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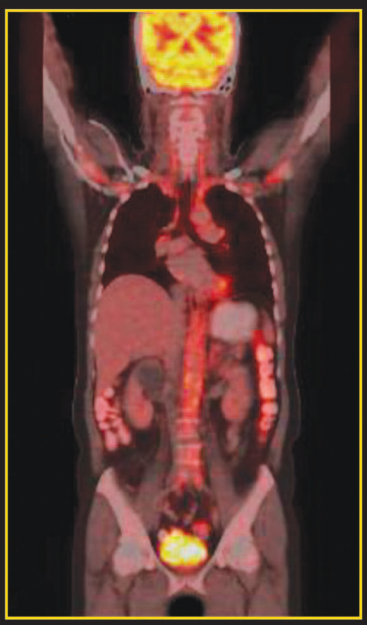
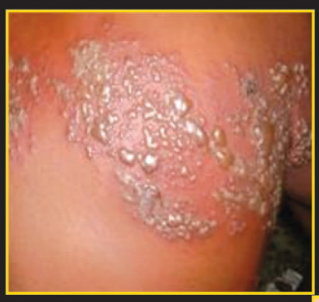
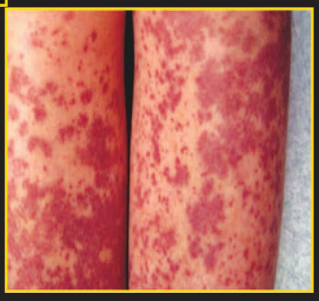
CASE STUDIES IN INTERNAL MEDICINE







Atul Kakar • Atul Gogia

Foreword
SP Byotra

Case Studies in
Internal Medicine

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Internal Medicine

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Foreword
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Foreword

It gives me great pleasure to write the foreword of *Case Studies in Internal Medicine*.

Internal Medicine is the mother of all medical subspecialties. The wide variety of complex medical cases seen in Internal Medicine is a challenging task. This book gives an insight about management of these complex cases which a physician or internist may not be able to address at peripheral level, however, the knowledge about them helps to refer the patient to the concerned doctor.

To be able to analytically assess medical problems, approach to a differential diagnosis and thereby formulate a diagnostic and treatment plan are the challenges in Internal Medicine, which bring about excitement in practising this specialty.

This book on *Cases in Internal Medicine* is written from the perspective of how to approach common medical conditions, by authors who have extensive training and experience in diagnosing and managing those diseases. The book promises to fill a major void in this area of diagnostic approach in clinical cases.

The editors and the contributors must be lauded for producing a useful book for postgraduates and practising clinicians in general.

I extend my very best wishes for the success of this book.

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Preface

There are many books on Internal Medicine, but not many have a case–based teaching approach.

Theoretical knowledge and factual information do add to our clinical acumen but a case-based approach and differential diagnosis discussion greatly helps the clinicians in their day-to-day patient management. Patient care depends upon many factors in which foremost is training and knowledge of the concerned doctor. This book would help the physicians what to do next if they have symptoms in their patients.

This book has been designed to be of use to postgraduates and physicians in their daily practice. The book covers unusual cases in Internal Medicine with emphasis on approach to various common clinical symptomatology and presentations.

Atul Kakar
Atul Gogia

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Contents

CASE

Joint Pain, Rash and Fever 1

HISTORY

A 32-year-old female presented to us with complaints of purpuric rashes over the lower limbs and swelling of small joints of hands for 1 month. Rash was papular in nature, non-itchy, red colored (Figure 1.1). Provisional diagnosis of? Urticarial vasculitis?? Systemic lupus erythematosus was made and she was investigated accordingly. There was pancytopenia with raised ESR (68 mm in 1st hour), antinuclear antibody was positive, serum creatinine—0.87 mg/dL. Her anti-ds-DNA was >1000 IU/mL. Serum C3 and C4 were 274 mg/L (970–1576 mg/L) and 35 mg/L (162–445 mg/L) respectively. Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) were negative. Urine routine examination was normal. She was finally diagnosed as a case of systemic lupus erythematosus. She was initially given tapering dose of methylprednisolone, azathioprine, hydroxychloroquine along with other supportive treatment. She responded to the above treatment and followed therapy for 1 year. Thereafter she stopped the treatment and no follow-up was available for next 1 year.

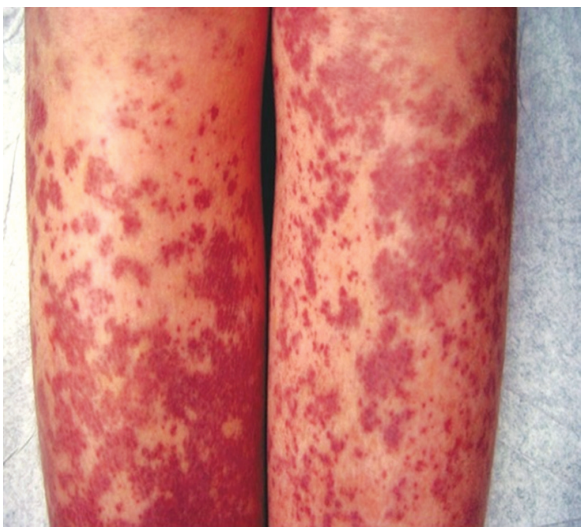


Figure 1.1 Rash of lower limbs

1. How do you diagnose urticarial vasculitis?

Ans. Urticarial vasculitis is characterized by skin lesions that appear as erythematosus wheals resembling urticarial rash. Skin biopsy is the definitive modality for diagnosis which is consistent with leukocytoclastic vasculitis along with low or normal serum complement levels. Lesions are generally painful and itchy.

2. What are the diagnostic criteria for systemic lupus erythematosus?

Ans. Systemic lupus erythematosus (SLE) was classified according to 1982 American College of Rheumatology (ACR) which includes malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, antinuclear antibody. For diagnosis of SLE 4 out of 11 criteria had to be met.

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC), an International clinical research group, revised the ACR classification criteria. The classification is given below, according to this classification 4 criteria (atleast 1 clinical and 1 immunologic) or biopsy proven lupus nephritis with positive antinuclear antibodies (ANA) or anti-ds-DNA are needed for diagnosis (Table 1.1).

Table 1.1 Systemic Lupus International Collaborating Clinics

Immunologic criteria	*Clinical criteria*
• Antinuclear antibody (ANA) • Anti-ds-DNA • Anti–Smith (Sm) • Antiphospholipid antibody • Low complement levels • Direct coombs test	• Acute cutaneous lupus • Chronic cutaneous lupus • Oral or nasal ulcers • Non-scarring alopecia • Arthritis • Serositis • Renal disorder • Neurologic disorder • Hemolytic anemia • Leukopenia • Thrombocytopenia

FURTHER HISTORY

After 1 year, she presented with complaints of breathlessness [New York Heart Association (NYHA) class IV] and pedal edema. On general examination, her blood pressure was 200/110 mm Hg. Laboratory investigations showed hemoglobin—8.3 gm/dL, total leukocyte count—4000/uL, platelet counts—2.5 lakh/uL, erythrocyte sedimentation rate (ESR)—20 mm in 1st hour, and serum creatinine—2.84 mg/dL. Her ds-DNA was very high (3200 IU/L) and complement levels were low and had significant 24 hours urine protein (2269 mg/day). Kidney biopsy showed diffuse proliferative glomerulonephritis (stage–IV). Echocardiography showed moderate mitral regurgitation (MR) and ejection fraction—23%. She was given intravenous methyl prednisolone for 3 days and subsequently given mycophenolate mofetil 1.5 gm/day, hydroxychloroquine 200 mg/day, diuretic therapy, anti-hypertensive and hematinics for anemia. She was closely followed and her medicines were modified accordingly.

3. What are the parameters monitored for disease activity in lupus patient?

Ans. Disease activity is monitored both clinically along with laboratory investigations. Clinically, patient may complain of persistent joint pains, joint swellings, fever and rash. Investigations like raised ESR, C-reactive protein (CRP), low complement levels are helpful for disease monitoring. Anti-ds-DNA rise may precede other markers and even before patient has any clinical features of systemic lupus erythematosus.

4. What is the WHO classification for lupus nephritis?

Ans. It is important to have kidney biopsy as it is useful in prognosis and treatment guidance. All patients with lupus nephritis should receive hydroxychloroquine, unless contraindicated.[1] Glucocorticoids with other immunosuppressant is used for class III/IV disease. Patients class I/II nephritis do not require immunosuppressive therapy (Table 1.2).

Table 1.2 WHO classification for lupus nephritis

Class I	Minimal mesangial	Normal glomeruli with mesangial deposits
Class II	Mesangial proliferation	Mesangial cell proliferation with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary or extracapillary proliferation with focal subendothelial immune deposits
Class IV	Diffuse nephritis	Diffuse endocapillary or extracapillary proliferation with diffuse subendothelial immune deposits. This class is further divided into (IV-S) diffuse segmental or (IV-G) diffuse global
Class V	Membranous nephritis	Basement membranes is thickened with diffuse subepithelial immune deposits
Class VI	Sclerotic nephritis	Sclerosis of > 90% of all glomerular capillaries

FURTHER ADMISSION

She was maintaining well on prednisolone 5 mg/day, hydroxychloroquinine 200 mg/day, mycophenolate mofetil 1500 mg/day, when she developed low grade fever for 2 months. She also complained of headache which was dull aching and on and off. There were no other eye and ENT complaints. On general examination, she had mild pallor and was febrile (100.4°F). Systemic examination was unremarkable. Investigations revealed hemoglobin—8.9 gm/dL, total leukocyte count—9200/uL, platelet count—2.76 lakh/uL, ESR—65 mm, serum creatinine—1.79 mg/dL. Liver function test was normal. Urine examination showed proteinuria. Blood and urine cultures were sterile. Imaging (chest radiograph, abdominal ultrasound, MRI brain, non-contrast enhanced CT thorax and abdomen) was normal. HIV was negative. Anti-ds-DNA was negative. Serum C3 and C4 were normal. Serum CRP was normal. Lumbar puncture was planned for headache, but patient refused for the same. Bone marrow aspiration was reported as cellular marrow with myeloid hyperplasia along with evidence

of fungal spores and hyphae on biopsy (Figure 1.2). Bone marrow culture grew *Cryptococcus neoformans* (Figure 1.3). The steroid dose was decreased and the patient was started on injectable amphotericin along with fluconazole. By 7th day, patient became afebrile and was discharged with the advice to continue amphotericin injections along with oral fluconazole.

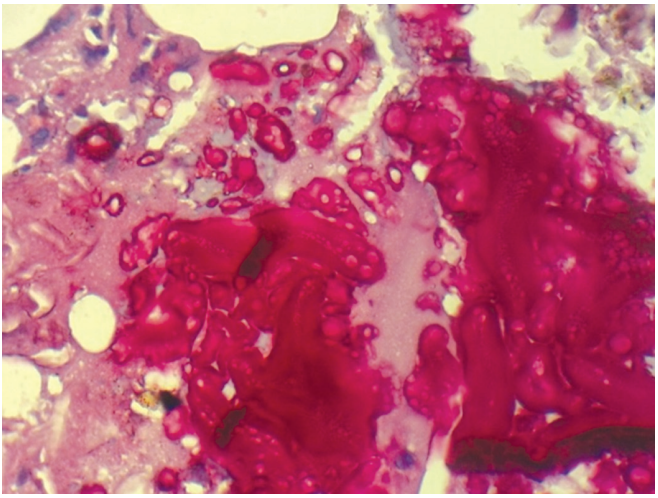


Figure 1.2 Bone marrow biopsy showing trilineage hematopoiesis with presence of fungal spores and hyphae

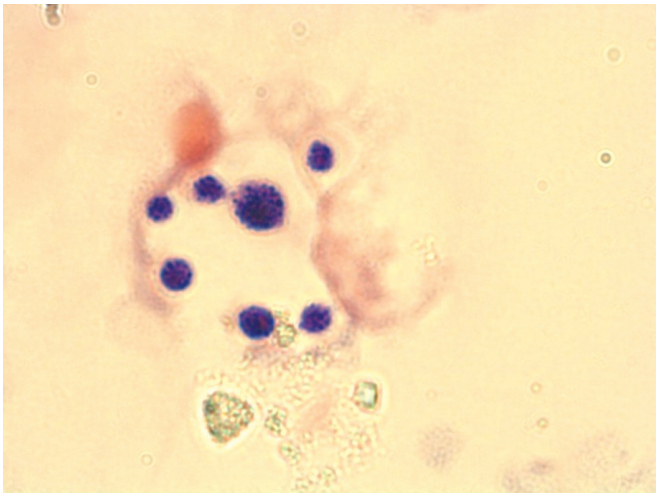


Figure 1.3 Bone marrow culture on Grams stain showing *Cryptococcus neoformans*

5. What is the importance of headache in systemic lupus erythematosus?

Ans. Headache can be neuropsychiatric manifestation of lupus cerebritis. Any patient who is immunocompromised and complains of fever with headache, lumbar puncture must be done to rule out infection.

6. What is the incidence of infection in patients on Disease-Modifying Antirheumatic Drugs (DMARDs) used in SLE?

Ans. Patients with SLE are prone to infection of the central nervous system, lungs, urinary tract and skin. During the course of the disease, approximately half of patients will have at least one infection. Infections in SLE patients are related to immunologic defects caused by the disease itself or by the immunosuppressive therapy.[1] Use of corticosteroids, high disease activity, organ dysfunction and use other immunosuppressants, are the strongest risk factors for the development of an infection in SLE. In many series, infection is reported as the leading cause of death in SLE patients. Among fungus, the most lethal species reported is *Cryptococcus* species (100% mortality), followed by *Aspergillus* (80%) and *Candida* (44.4%).[2]

7. How do we diagnose cryptococcal infection?

Ans. For diagnosis of cryptococcal meningoencephalitis lumbar puncture is a must. The opening pressure should be measured, along with India ink evaluation, cryptococcal antigen testing, fungal culture, and routine spinal fluid studies. The diagnosis is established definitively by culturing the organism from anybody fluid. High cerebrospinal fluid (CSF) cryptococcal antigen level is considered poor prognosis in patients. Level of antigen decreases following antifungal therapy and can be used to monitor therapy effectiveness.[3]

8. How to treat cryptococccal infection?

Ans. Treatment is divided in two phases:[3,4]

1. Induction phase
2. Maintenance consolidation phase.

Induction phase

Treatment consists of combination of two drugs for 2 weeks:

- Amphotericin B + flucytosine
- Amphotericin B + fluconazole
- Amphotericin B short course (5–7 days) + high dose fluconazole
- Fluconazole high dose + flucytosine, when amphotericin B is not available
- Fluconazole high dose alone, when amphotericin B is not available.

Consolidation phase treatment

Treatment consists of 8 weeks of fluconazole therapy:

- Fluconazole 400 to 800 mg/day.
- Fluconazole 800 mg/day after induction treatment with short course amphotericin.

Some of common side effects of amphotericin includes nephrotoxicity (can be lessened with liposomal amphotericin), electrolyte imbalance (hypokalemia, hypomagnesemia), hepatotoxicity and cardiac arrhythmia.

FINAL DIAGNOSIS

Cryptococcal fungemia, systemic lupus erythematosus with lupus nephritis (class IV), hypertension, anemia.

LEARNING POINTS

- The organism *Cryptococcus* can disseminate particularly in immuno-compromised patients without eliciting systemic symptoms.
- It is necessary to maintain balance between dose of corticosteroid and immunosuppressants to control disease activity and infection in such cases.

REFERENCES

1. Tsakonas E, Joseph L, Esdaile JM, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus. 1998;7(2):80-5.
2. Gluck T, Muller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases; 2008
3. Antinori S, Radice A, Galimberti L. The role of cryptococcal antigen assay in diagnosis and monitoring of cryptococcal meningitis; 2005.
4. *www.whqlibdoc.who.int/publications/2011/9789241502979 eng.pdf.*

CASE

Patient with Rash, Cough and Fever

2

HISTORY

A 46-year-old male presented to us with complaints of fever for 15 days, cough for 10 days and rash for 7 days. Fever was low grade, continuous in nature, not associated with chills and rigors. Cough was dry in nature. There was history of malar rash and rash over sun exposed parts of the body. There was history of weight loss around 6 kg in last 2 months. There was no history of any systemic complaints.

EXAMINATION

On physical examination, patient was febrile (100°F) and had malar red erythematosus rash, non-itchy and multiple, discrete, non-tender lymph nodes in bilateral axillary region largest being 2 × 2 cm in diameter. There was thickening of skin around distal extremities and there was synovitis at multiple PIP joints. No other lymph nodes were palpable. Systemic examination was unremarkable. Initial laboratory investigations are tabulated (Table 2.1).

Table 2.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	11.3 gm/dL	13–17 gm/dL
Total leukocyte count	5500/uL	4,000–10,000/uL
Platelet count	1.09 lakh/uL	1.5–4.5 lakh/uL
ESR	25 mm	<11 mm
BUN/S creatinine	14.6/0.63 mg/dL	5–23/0.6–1.3 mg/dL
AST/ALT	77/31 IU/L	0–40/0–34 IU
C-reative protein (CRP)	34 mg/L	<6 mg/L
Anti-nuclear antibody (ANA)	Positive (2 +)	
Anti-ds-DNA	>10,000 IU	
Anti-SS-A	Positive (3+)	
Anti-SS-B	Positive (2+)	
Anti-U1-RNP	Positive (+)	
Anti-Sm	Positive (+)	
c-ANCA	Negative	
p-ANCA	Negative	
Serum C3/C4 levels	403/77 mg/L	970–1576/162–445

Creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) both were elevated in our patient. HRCT chest scan was suggestive of interstitial lung disease. Twenty four hour urine was 668.2 mg/dL. He was given steroid pulse therapy (methylprednisolone 500 mg) for 3 days. Following pulse therapy he was started on oral steroids, azathioprine along with hydroxychloroquinine. By 6th day of therapy he became afebrile; appetite increased and was discharged with advice to continue therapy.

1. What is mixed connective tissue disorder?

Ans. About 25 to 50 percent of patients referred to tertiary rheumatology centers do not carry a diagnosis of a clearly defined rheumatic disease or present with features of two or more rheumatic diseases. These patients are classified as having either undifferentiated connective tissue disease or overlap-syndrome.

Mixed connective tissue disease (MCTD), however, should not be confused with undifferentiated connective tissue disease or overlap syndrome. It is a distinct clinical entity that manifests as a mixture of certain clinical features also seen in other rheumatic diseases. Mixed connective tissue disorder was earlier called as Sharp's syndrome. It was described in 1972 by Sharp and his colleagues with features of SLE, systemic sclerosis, and polymyositis (Figure 2.1). High titers of anti-U1-RNP autoantibodies further defined this disease.[1] In early stages, patients often present with one of the following features: Raynaud's phenomenon, puffy fingers of the hands, sclerodactyly, arthralgias, arthritis, myalgias, myositis and malaise.

In our case there was sclerodactyly and skin thickening which was limited to distal limbs as seen in scleroderma. He had classical malar rash which was photosensitive and high titres of anti ds-DNA as seen in lupus. Interstitial lung disease is seen in 1% of patients with mixed connective tissue disorder.

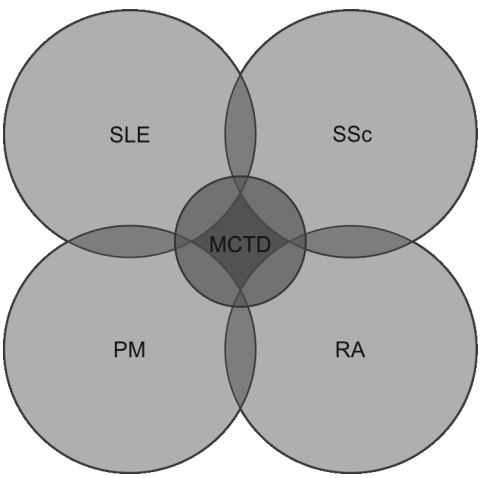


Figure 2.1 Overlap syndrome (*Abbreviations:* SLE—Systemic lupus erythematosus; SSc—Systemic sclerosis; RA—Rheumatoid arthritis; PM—Polymyositis; MCTD—Mixed connective tissue disease)

2. What is overlap syndrome?

Ans. Up to 25% of patients with rheumatologic diseases fulfill the classification criteria for more than one rheumatic disease and are consequently diagnosed as having overlap syndrome combinations of coexisting rheumatic diseases. These patients are treated according to underlying, specific rheumatic diseases.

3. What is the classification of mixed connective tissue disorder?

Ans. Table 2.2 gives Kasukawa's criteria for diagnosing mixed connective tissue disorder. Diagnosis of mixed connective tissue disorder requires ≥ 1 common symptom plus ≥ 1 symptom of the mentioned signs of ≥ 2 of the defined connective tissue diseases SLE, systemic sclerosis and polymyositis plus the serologic criterion.

Many physicians have augured if mixed connective tissue disease (MCTD) as a distinct disease entity? However due to association with certain HLA types, high titers of IgG anti-U1-RNP antibodies and specific clinical manifestations MCTD is a separate disease.

Table 2.2 Kasukawa's criteria for classification of mixed connective tissue disorders

Common symptoms	*Symptoms of SLE, SSc and PM*	*Serologic criterion*
• Raynaud's phenomenon • Swollen fingers	• *Systemic lupus erythematosus (SLE)* – Polyarthritis – Adenopathies – Malar rash – Serositis – Leukopenia and/or thrombocytopenia • *Systemic sclerosis* – Sclerodactyly – Pulmonary fibrosis and/or restrictive changes and/or reduced diffusing capacity of the lung for carbon monoxide (DLCO) – Esophageal hypomobility or dilatation • *Polymyositis* – Muscle weakness – Elevated muscle enzymes – Myogenic changes in electromyogenic (EMG)	• Anti-U1RNP antibodies

4. What are the clinical features of mixed connective tissue disorder?

Ans. It is predominant in females with a ratio of 9:1 to 16:1. The mean age of onset is 28 to 37 years, but mixed tissue connective disorder can manifest at virtually any age.

The earliest clinical symptoms of mixed connective tissue disorder are usually non-specific. At this stage of the disease, patients often suffer from malaise, myalgias, arthralgias, Raynaud's phenomenon and low grade fever. In later stages of the disease, a set of five cardinal signs should lead to the suspicion of MCTD:

- The presence of high titers of anti-U1-RNP-autoantibodies, in particular IgG antibodies that recognize the 68 kDa protein of the U1-RNP-complex.
- The lack of severe kidney and CNS-involvement
- Severe arthritis and the presence of RF
- Pulmonary arterial hypertension (PAH)
- Raynaud's phenomenon in association with puffy hands.

5. What is the prognosis of mixed connective tissue disorder?

Ans. Mixed connective tissue disorder is a connective tissue disease with good prognosis and an excellent response to corticosteroids. Renal and CNS-manifestations are a major cause of morbidity and mortality in SLE, are very low in mixed tissue connective disorder. Nevertheless, the incidence of pulmonary artery hypertension, which shortens life span significantly, is high in MCTD. In general, the prognosis of MCTD is better than that of SLE and diffuse systemic sclerosis.[2] In many patients, the disease follows a benign course and goes into remission. Other patients show an aggressive disease course and may only have a partial response to the treatment with immunosuppressive therapies.

6. What is the treatment of mixed connective tissue disorder?

Ans. The therapy for mixed connective tissue disorder should be same as initiated for components of connective tissue. More than 50% patients have favorable course and more than 80% having 10 year survival rate.

Oral corticosteroids in doses of 1 mg/kg/d or intravenous pulses of high dose-steroids in severe cases as well as cyclophosphamide is indicated for active alveolitis and interstitial lung disease. Imatinib mesylate might also be effective in treating active alveolitis associated with MCTD, as shown in a patient with progressive and refractory alveolitis and lung fibrosis.

FINAL DIAGNOSIS

Mixed connective tissue disorder.

LEARNING POINTS

- Patients presenting with features of rheumatologic diseases, who do not fulfill the criteria for a defined rheumatic disease, are diagnosed as having undifferentiated connective tissue disease.
- Patients with overlap-syndromes fulfill the criteria for two or more rheumatologic diseases.
- Mixed connective tissue disease share several features of systemic lupus erythematosus, systemic sclerosis, polymyositis and rheumatoid arthritis.
- Specific genetic, serologic and clinical features, support the concept of mixed connective tissue disease as a separate clinical entity.
- Anti-U1-RNP-antibodies directed against U1-RNP are essential for the diagnosis of mixed connective tissue disease.

REFERENCES

1. Tomsic M, Ferlan-Marolt V, Kveder T, et al. Mixed connective tissue disease associated with autoimmune hepatitis and thyroiditis. Ann Rheum Dis 1992;51(4):544-6.
2. Burdt MA, Hoffman RW, Deutscher SL, et al. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. Arthritis Rheum 1999; 42(5):899-909.

CASE

Cough and Fever along with Pain Abdomen

3

HISTORY

A 56-year-old female was admitted with complaints of fever with cough for 1 month. Fever was low-grade, more in evening with maximum upto 100°F. There was no history of weight loss or decreased appetite. Cough was non-productive and more on lying down. There was no history of breathlessness. Examination was unremarkable. She was investigated for above complaints. Complete blood counts were normal; proinflammatory markers (ESR, CRP) were elevated. Chest X-ray showed mediastinal widening. Contrast CT scan thorax revealed homogenous enlarged lymph node. There was no necrosis in lymph node or parenchymal involvement. Mantoux test was positive. She was started empirically on four drug anti-tubercular therapy after she refused for a histopathological examination from the lymph nodes. Three weeks later, she returned with pain abdomen and recurrent episodes of vomiting. There was no history of addiction.

1. What are the important causes of mediastinal lymphadenopathy?

Ans. Mediastinal adenopathy is commonly seen in tuberculosis, lymphoma (Hodgkin's and non-Hodgkin's), bronchogenic carcinoma, HIV, sarcoidosis and leukemia (lymphoblastic). Other causes are histoplasmosis, Wegener's granulomatosis, cytomegalovirus (CMV), SLE and other miscellaneous causes.

2. What are the important causes of vomiting/pain abdomen in patient on anti-tubercular drugs?

Ans. The important causes of vomiting in patient taking anti-tubercular drugs:

- Drug-induced hepatitis. Isonicotinylhydrazine (INH) and rifampicin together is the most common cause, followed by INH alone, pyrazinamide alone. The causes of hepatitis are INH + rifampicin > INH alone > pyrazinamide > rifampicin > ethionamide. The hepatitis is not very common in children, but common among patients above 35 years and alcoholics. If liver function test (LFT) is 3 to 5 times more than the normal, one should discontinue the hepatotoxic drugs.[1]
- Gastritis.
- Intestinal Koch leading to intestinal obstruction.
- Due to TB meningitis/Tuberculoma—due to raised intracranial pressure.

FURTHER HISTORY

On examination, patient had BP—100/70 mm of Hg, PR—98/min. Per abdomen-diffuse tenderness, bowel sound sluggish. Systemic examination of chest, cardiovascular and nervous system was unremarkable. Investigation revealed, hemoglobin—10.2 gm%, total leukocyte count (TLC)—12,600/cumm with polymorphic leukocytosis (P–87%), Albumin—2.3 gm%, amylase—1046 IU/L (16–108), lipase 298 IU/L (23–300), renal function test (RFT)—normal, serum calcium—10.2 gm/dL (8.5–10.4), sodium—132 mg%, potassium—4 mg%, urine—no abnormality detected (NAD), serum alkaline phosphate—112 IU, serum triglycerides—normal.

3. What is the cause of pain abdomen?

Ans. The cause of pain abdomen is acute pancreatitis as amylase was elevated more than three times.

4. What is the etiology for this condition?

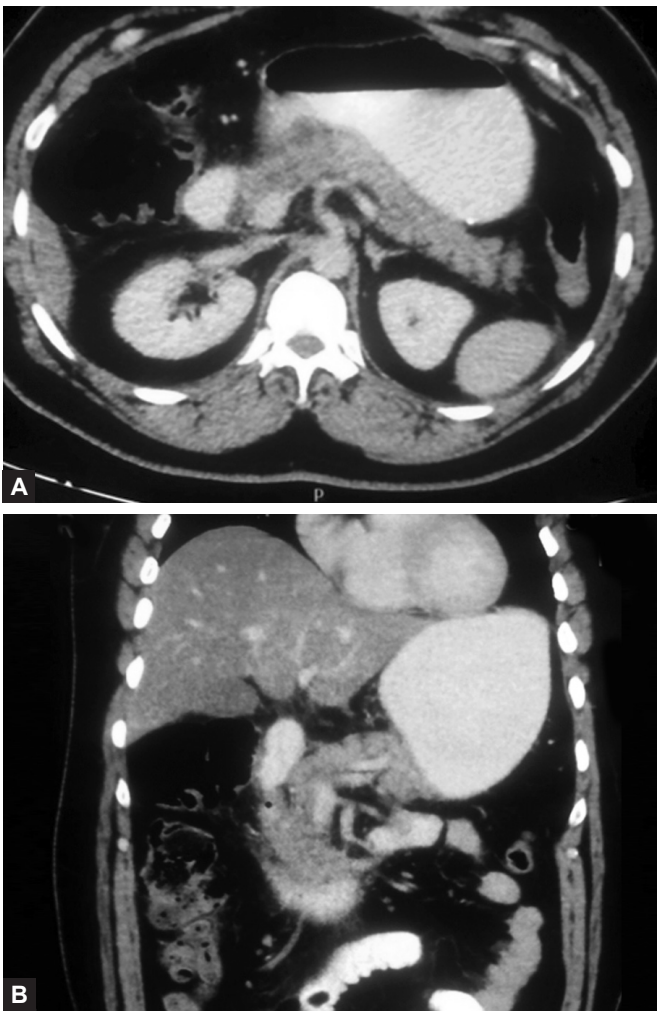
Ans. Hypercalcemia is the likely etiology for acute pancreatitis in our patient. Although the calcium levels are within normal range but in presence of low albumin the corrected calcium is high. For every 1 gm/dL drop in serum albumin, serum calcium decreases by 0.8 mg/dL. The hypercalcemia can be divided into mild (10.5–11.9 mg/dL), moderate (12–13.9 mg/dL) or severe (>14 mg/dL). Acute shift of calcium from bone to extracellular space is the cause of hypercalcemia. Important causes of hypercalcemia are parathyroid adenoma or ectopic production from cancers like bronchogenic carcinoma and hypernephroma. Metastatic malignancy, multiple myeloma, excess intake of calcium/vitamin D are other causes.

5. How will you correct the electrolyte abnormality?

Ans. Forced diuretics with 0.9% NaCl and furosemide (5–10 mg/hr) helps in calciuresis. Biphosphonates, e.g. pamidronate (15–60 mg) as infusion or in divided doses over 2 to 4 days, maximum of 90 mg/dL is also indicated. Calcitonin 3 to 4 IU/kg IV initially followed by upto 8 IU subcutaneous (SC) 6 to 8 hr is useful. Steroids are useful in malignancy induced hypercalcemia. The effect may take time to develop. Calcium free dialysis is highly effective in lowering serum calcium levels.

FURTHER WORK-UP

CT scan done (Figures 3.1A and B) showed bulky pancreas with fatty infiltration. There was no pancreatic calcification. Hypercalcemia was corrected by injection calcitonin, IV saline-diuretic. Pancreatitis took 12 days to settle. Angiotensin-converting enzymes (ACE) levels were elevated—152 IU/L (8–52). Parathyroid hormone (PTH)—10 ng/L (12–82). Endoscopic ultrasound (EUS) guided biopsy revealed non-caseating granuloma. No necrosis or acid-fast bacilli (AFB) was seen. Patient was started on hydroxychloroquine and low-dose steroids. Angiotensin-converting enzyme (ACE) levels came down gradually. After one year of follow-up patient is doing well.



Figures 3.1A and B Bulky pancreas with fatty infiltration

FINAL DIAGNOSIS

Sarcoidosis presenting as hypercalcemia and acute pancreatitis.

LEARNING POINTS

- Sarcoidosis is a multisystem disease with unknown etiology.
- Lung involvement can be variable, from asymptomatic (30–60%) to respiratory failure, interstitial lung disease, hilar lymphadenopathy, fibrotic lung disease and bronchiectasis.
- Acute hypercalcemia due to sarcoidosis is a rare cause of pancreatitis.[2]

- Histopathologically, non-caseating granulomas are the cause of pancreatitis.
- Eye (anterior uveitis) and skin (granulomatous lesion) are two common extra-pulmonary involvement sites.
- Hypercalcemia has been described in sarcoidosis. Hypercalcemia can lead to nephrolithiasis and renal dysfunction. The cause of hypercalcemia is due to increased intestinal absorption. The enzyme 1 alpha hydroxylase in activated macrophages of granulomas converts 25,OH vitamin D to 1,25 dihydroxy vitamin D.
- Therapy is indicated for sarcoidosis for hypercalcemia, ocular, neural, and cardiac sarcoidosis. Arthritis usually responds to NSAID's. Pulmonary asymptomatic sarcoidosis is not treated. Corticosteroids are given for moderate to severe pulmonary involvement. Hydroxychloroquine and methotrexate are steroid sparing agents.

REFERENCES

1. Obrien RJ. Hepatoxic reaction to anti tubercular drugs: adjustments to therapeutic regimen. JAMA 1991;265:3323.
2. Gaur S. Sarcoidosis presenting as hypercalcaemic pancreatitis. The Internet Journal of Academic Physician Assistants. 1999;2.

CASE

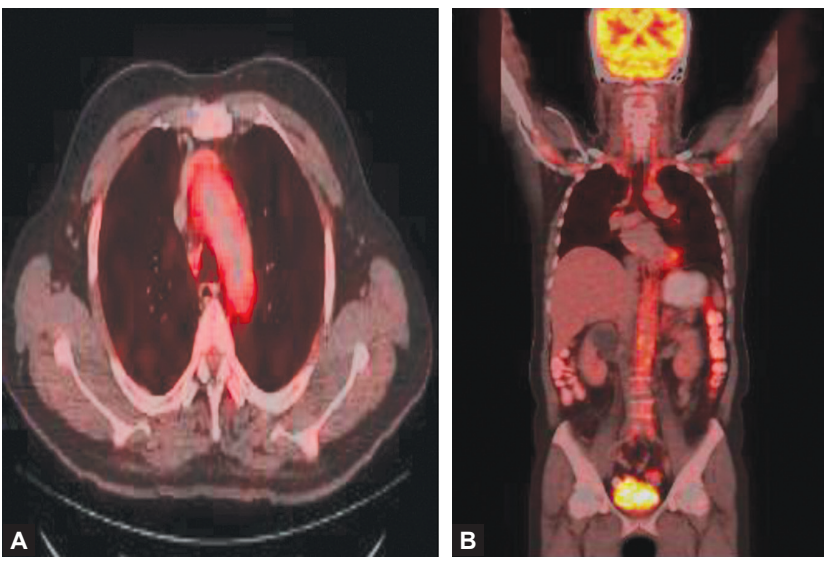
Pyrexia of Unknown Origin 4

HISTORY

A 26-year-old female patient presented with low grade fever of 3 months duration with evening rise of temperature. There was no other complains. There was no significant past, personal and family history. She had earlier taken multiple courses of antibiotics and antimalarials.

On physical examination, the patient was febrile—38°C with normal blood pressure. All peripheral pulses were palpable and there were no bruits. Systemic examinations was non-contributory. Routine investigations revealed raised ESR (96 mm), and CRP (32 mg/dL). Mantoux test and QuantiFERON gold test were negative for tuberculosis. Repeatedly blood and urine cultures were negative. Radiological tests (X-ray chest, USG abdomen and CT scan chest and abdomen) were non-contributory. Collagen markers (ANA, anti-CCP, RF, p-ANCA and c-ANCA), hepatitis B and C, and HIV were found to be negative.

In view of persistently high ESR a trial of antitubercular treatment was given. After 4 weeks of therapy patient showed no signs of improvement. PET-CT was done to rule out mitotic pathology (Figures 4.1A and B). Corticosteroids were



Figures 4.1A and B PET-CT sections showing increased uptake in aorta and its branches

added in the dose of 1 mg/kg body weight and patient showed dramatic response within a week.

Patient became asymptomatic and dose of corticosteroids was tapered off gradually.

1. What is the diagnosis?

Ans. PET-CT showed markedly abnormal uptake of 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) in the aortic arch, carotid arteries and abdominal aorta, suggestive of Takayasu arteritis.

Takayasu arteritis (TA) is a cause of pyrexia of unknown origin due to large vessels vasculitis. It is also called "aortic arch syndrome", "non-specific aortoarteritis" and the "pulseless disease. It has a predilection for the aorta, its major branches as well as the coronary and pulmonary arteries.[1]

Takayasu's arteritis is a disease that afflicts young women and often goes unrecognized because its clinical signs and symptoms are so non-specific, particularly during the acute (prepulseless) phase. Later, an occlusive (pulseless) phase ensues and is associated with CNS complications in up to 10% of patients angiography is considered as the gold standard to identify the disease.

2. What is the use of FDG-PET scan in early diagnosis and treatment of Takayasu's arteritis.

Ans. The principal advantage of PET or PET-CT is in the diagnosis of early pre-stenotic disease, an event that can be missed by intra-arterial angiography. PET or PET-CT can diagnose early TA during diagnostic work-up of other causes of pyrexia of unknown origin. Reduction in PET uptake at the site of aortitis has been correlated with both clinical improvement with therapy and reduction in aortic wall thickness.[2]

With the availability of 18F-FDG-PET, early diagnosis of disease can be made even when the pulses are palpable as was seen in our case. Besides assessing the disease activity, response to therapy can also be assessed using PET-CT. In TA, abnormal 18F-FDG-PET uptake is seen in the wall of large vessels (> 4 mm), if vascular inflammation is present. PET is proving to be a sensitive and specific means through which vascular wall inflammation can be detected. In a prospective study, (18)F-FDG PET achieved a sensitivity of 92%, specificity of 100%, and negative and positive predictive values of 85% and 100% respectively in the initial assessment of active vasculitis in TA.

3. What are the limitations of PET scan?

Ans. Limitations of PET scans are, significant radiation exposure, it is expensive and available in relatively few centers. It lacks histological confirmation in TA. It is yet to be universally accepted method for quantification of FDG uptake. Another limitations seen in older population is it detects atherosclerosis, although the vascular distribution is distinct from TA. Thus PET-CT scan is a non-invasive test which helps not only in early diagnosis, but also to assess response to therapy.

4. How do you classify Takayasu disease?

Ans. For purposes of classification, the patient should have at least 3 of these 6 criteria.[3] The presence of any 3 or more criteria yields a sensitivity of 90.5%

and a specificity of 97.8%. BP = blood pressure (systolic; difference between arms) (Table 4.1).

Takayasu arteritis has been classified into five types. Table 4.2 gives angiographic classification of Takayasu disease.

Table 4.1 1990 criteria for the classification of Takayasu arteritis

• Age at disease onset < 40 years Development of symptoms or findings related to Takayasu arteritis at age less than or equal to 40 years
• Claudication of extremities Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
• Decreased brachial artery pulse Decreased pulsation of 1 or both brachial arteries
• BP difference >10 mm Hg Difference of >10 mm Hg in systolic blood pressure between arms
• Bruit over subclavian arteries or aorta Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
• Arteriogram abnormality

Table 4.2 Angiographic classification of Takayasu disease

Type I	Branches of aortic arch
Type IIa	Ascending aorta, aortic arch and its branches
Type IIb	Type Iia plus thoracic descending aorta
Type III	Thoracic descending aorta, abdominal aorta, renal arteries or a combination
Type IV	Abdominal aorta, renal arteries or both
Type V	Entire aorta and its branches

5. What are complications of Takayasu's disease?

Ans. Complications of Takayasu's disease include:

- Hypertension (45–69%)
- Stroke/TIA (5–9%)
- Seizures
- Myocarditis/pericarditis
- Congestive cardiac failure
- Aortic regurgitation
- Pulmonary artery hypertension
- Abdominal aortic aneurysm
- Claudication
- Visual disturbance/glaucoma

The major principle complications like retinopathy, secondary arterial hypertension, aortic value regurgitation, and aneurysm formation, determine the prognosis. The main cause of death in patients with complicated disease is cerebrovascular accident and heart failure.

6. What is the treatment of Takayasu disease?

Ans. Treatment of takayasu arteritis depends on the disease activity and the complications that develop. The major group of drugs are:

- Corticosteroids
- Immunosuppressant (sometimes)
- Antihypertensives
- Angioplasty or bypass grafts may be necessary once irreversible arterial stenosis has occurred.

Corticosteroids: They are the mainstay of therapy for active Takayasu arteritis. Oral corticosteroids are started at 1 mg/kg daily or divided twice daily and tapered over weeks to months as symptoms subside. Long-term, low-dose corticosteroid therapy may be required. Side effects should be monitored regularly.

IL-6 receptor inhibitor-IL-6 is now being implicated as a major component in the proinflammatory process of large-vessel vasculitis. Tocilizumab is being increasingly used for the arteritis.

B-cell depletion: Rituximab, a chimeric IgG1 antibody that binds to CD20 expressed on the surface of B-cells has shown to improve clinical signs and symptoms of Takayasu arteritis. It is believed that B-cells have an antibody-independent effect, which may modulate regulatory T-cell immune reactions against foreign and self-antigens.

Cytotoxic agents: Cytotoxic agents are used for patients whose disease is steroid resistant or relapsing. These agents are usually continued for at least 1 year after remission and are then tapered to discontinuation. Methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide are among the drugs used in Takayasu arteritis.

Anti-tumor necrosis factor agents—adjunctive treatment with anti-TNF agents was effective in patients with active, relapsing Takayasu arteritis despite treatment with steroids and multiple other immunosuppressive agents. The initial dose of etanercept was 25 mg twice weekly; infliximab given at 3 mg/kg initially and at 2 weeks, 6 weeks, and then every 8 weeks thereafter.

Cardiovascular procedures: Bypass graft surgery is the procedure with the best long-term patency rate. Angioplasty and stenting have been used to treat recurrent stenosis

FINAL DIAGNOSIS

Aortoarteritis (Takayasu disease type 2b)

LEARNING POINTS

- Most commonly affected territories: the aorta and its branches, subclavian (85–88%), carotids (37–54%), abdominal aorta, renal artery (25–63%)
- Women are affected more than men

- The aortoarteritis or Takayasu disease, has two phases (i) inflammatory which has symptoms of fever, arthralgia, weight loss and fatigue and (ii) stenotic phase which is pulse less stage and has symptoms of claudication
- PET-CT can be useful to diagnosis early cases and also monitoring response to therapy.

REFERENCES

1. Wu W, Chaer RA. Nonarteriosclerotic vascular disease. Surg Clin North Am. 2013;93:833-75,
2. Schmidt WA. Imaging in vasculitis. Best Pract Res Clin Rheumatol. 2013 ;27(1):107-18.
3. IWen D, Du X, Ma CS. Takayasu arteritis: diagnosis, treatment and prognosis. Int Rev Immunol. 2012;31(6):462-73.

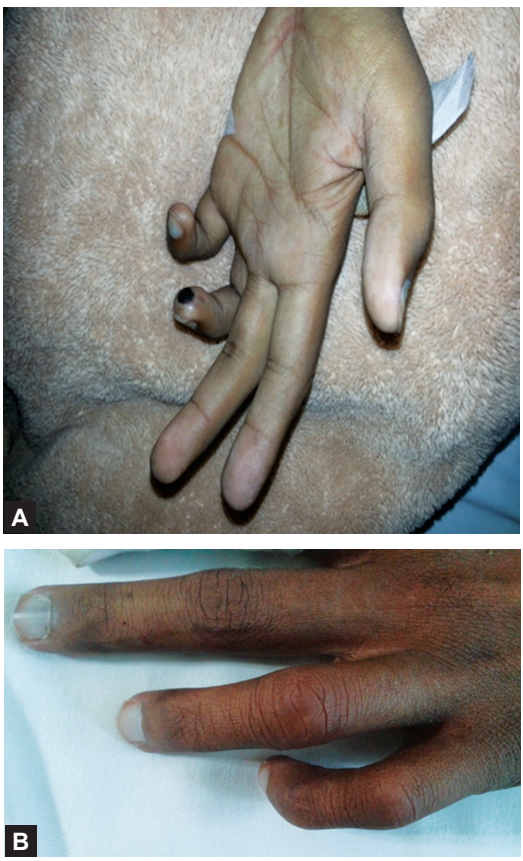
CASE

Bloody Sputum in Patient with Claw Hand

5

HISTORY

A 28-year-old male presented to us with complaints of fever for 2 months and generalized weakness for 2 days. Fever was high grade associated with chills with no diurnal variation. He had developed left hand weakness and deformity suggestive of claw hand (Figures 5.1A and B), two years back and he was diagnosed



Figures 5.1A and B Claw hand

as a case of borderline tuberculoid leprosy on clinical basis. He received multi-drug therapy for one year (Dapsone 100 mg/day, Rifamipicin 600 mg/month, Clofazimine 100 mg/day and Dexamethasone).

On general examination, there was significant pallor and bilateral pitting edema. Skin was dry and ichthyotic. There was left side claw hand with no thenar muscle atrophy. Systemic examination was unremarkable.

On day 2, of hospital stay patient developed sudden onset breathlessness. He desaturated and his chest radiograph (Figure 5.2) worsened with bilateral infiltrates more on right side. Non-contrast enhanced CT was undertaken which showed bilateral infiltrates with mild pleural effusion with possibility of infection or diffuse alveolar hemorrhage (Figure 5.3). As his condition worsened he was intubated. Postintubation bronchoscopy was undertaken and it showed frank

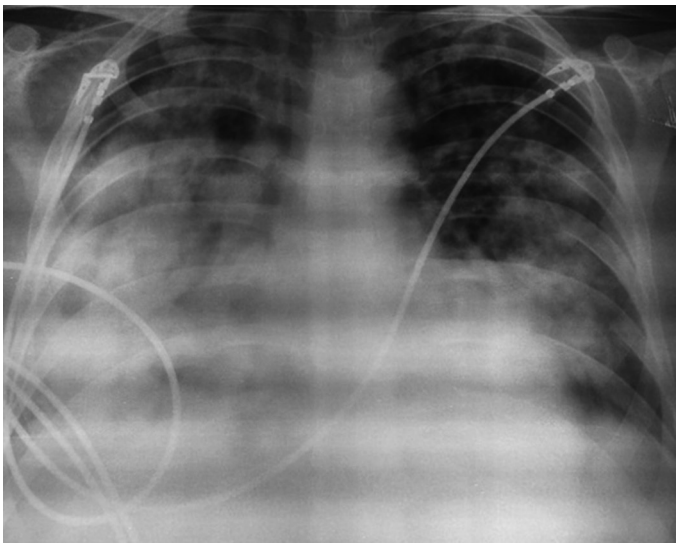


Figure 5.2 Bilateral diffuse haziness in both lung fields

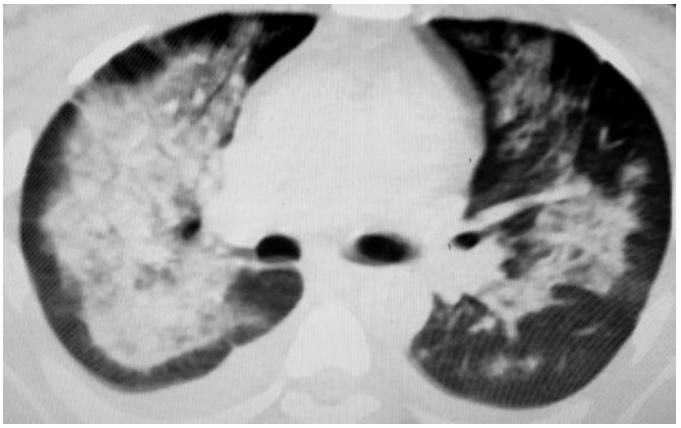


Figure 5.3 Diffuse alveolar hemorrhage

Table 5.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	6 gm/dL	13–17 gm/dL
Total leukocyte count	2,100/uL	4,000–10,000/uL
Platelet count	44,000/uL	1.5–4.5 lakh/uL
ESR	72 mm	<13 mm
BUN/S. creatinine	13/0.9 mg/dL	5–23/0.6–1.3 mg/dL
Corrected reticulocyte count	4.2%	1%
Total/Direct bilirubin	1.3/0.7 mg/dL	0.2–1/0–0.2 mg/dL

blood in lungs. He was given intravenous steroids, broad spectrum antibiotics along with other supportive measures. Echocardiography showed ejection fraction of 34%. Bronchoalveolar lavage (BAL) culture grew *S. pneumoniae*. By 3rd day, he was clinically better and got extubated.

Laboratory investigations done are given in Table 5.1. Complete blood counts revealed pancytopenia. Anemia profile was suggestive of anemia of chronic disease.

FURTHER MANAGEMENT

Viral serologies (HIV, HBsAg, anti-HCV) were negative. Coomb's test was negative. CRP was positive. Patient was transfused blood products to give him symptomatic relief. Anti-nuclear antibody was negative. C-ANCA, P-ANCA was negative. Nerve conduction velocity of limbs showed asymmetrical sensory nerve involvement in upper limbs. Urine routine showed proteinuria (+2). Creatinine kinase was 40 IU/mL (132 IU/mL). Twenty-four hours urine protein was 1700 mg. Serum C3/C4 levels were normal. Kidney biopsy was done which showed amyloid deposits (Congo red stain-positive). Bone marrow aspiration and biopsy showed reactive cellular bone marrow. Muscle and sural nerve biopsy was done which were normal. Anti-cardiolipin and lupus anticoagulant antibodies were negative. By 14th day, he was discharged with advice to continue oral Colchicine (1.2 mg/day).

1. What are the types of leprosy?

Ans. World Health Organization has classified it into 2 groups according proliferation of bacteria, i.e. paucibacillary and multibacillary. It can also be classified into indeterminate leprosy, tuberculoid leprosy, borderline tuberculoid, borderline, borderline lepromatous, lepromatous, histoid leprosy.[1]

2. What is the prevalence of leprosy in India?

Ans. The prevalence in India has reduced over years, 8.9/10,000 in 2000 to 1.1/10,000 in 2010 0.69/100007. The cases of leprosy are not uniformly distributed but tend to cluster in certain localities or villages. While the country as a whole has eliminated leprosy, two States, Bihar and Chhattisgarh are yet to achieve elimination.

3. What is the treatment of leprosy?

Ans. WHO recommendations for the treatment of leprosy are given in Table 5.2.[2]

Table 5.2 Treatment of leprosy

Types of leprosy	*Drugs administered*	*Duration of treatment*
Paucibacillary	Dapsone 100 mg/day Rifampicin 600 mg once a month	6 months
Multibacillary	Dapsone 100 mg/day Rifampicin 600 mg once a month Clofazimine 50 mg/day and 300 mg once a month	12 months
Single lesion paucibacillary	Rifampicin 600 mg Ofloxacin 400 mg Minocycline 100 mg	Single dose

4. What is diffuse pulmonary hemorrhage?

Ans. Diffuse alveolar hemorrhage (DAH) refers to the bleeding into alveolar spaces. It is characterized clinically by the presence of hemoptysis, falling hemoglobin, diffuse pulmonary infiltrates on chest radiograph and hypoxemic respiratory failure on blood gas analysis. Various differential diagnoses include pulmonary edema, pulmonary alveolar proteinosis, bronchopneumonia, alveolar carcinoma. Pulmonary infections are rarely reported in association with diffuse alveolar hemorrhage. In immunocompromised patients, it is mainly caused by cytomegalovirus, adenovirus, aspergillosis, *Mycoplasma*, *Legionella*, and *Strongyloides*. In immunocompetent patients, it is usually caused by influenza A (H1N1), dengue, leptospirosis, malaria, and *Staphylococcus aureus* infection.[3]

5. What is the management of diffuse alveolar hemorrhage?

Ans. The foremost step in evaluation is history taking. Patient usually complains of cough, dyspnea and hemoptysis. On examination, patient usually has crackles on chest examination. Oral and nasal cavity must be properly looked for collagen vascular disorders. Laboratory reports show anemia, raised ESR. Renal functions and urine microscopy to be done. Chest radiograph shows diffuse infiltrates. The diagnosis is best established by bronchoscopy. The next step is establishing the cause of hemorrhage. The tests which are helpful are anti-nuclear antibody (ANA), antiglomerular basement membrane antibody, antineutrophil cytoplasmic antibody (ANCA) levels, serum complement levels, anti-double-stranded DNA, and antiphospholipid antibodies. If still the cause cannot be established then surgical biopsy of lung should be considered which can reveal pulmonary capillaritis, bland pulmonary hemorrhage and diffuse alveolar damage.

6. What is the treatment of diffuse alveolar hemorrhage?

Ans. Corticosteroids and immunosuppressive agents remain the gold standard for treatment. Besides corticosteroids, other immunosuppressive drugs such as cyclophosphamide, azathioprine, mycophenolate mofetil, and etanercept may be used in diffuse alveolar hemorrhage, in severe cases and

in steroid failure cases in setting of autoimmune etiology. In presence of autoimmune etiology plasmapheresis may be useful. Role of recombinant-activated human factor VII is still controversial.

7. What are the causes of secondary amyloidosis?

Ans. Amyloidosis is a clinical condition characterized by a disorder of protein structure, resulting in the formation and deposition of insoluble fibrillary proteins (amyloid) in extracellular spaces of organs and tissues, resulting in damage to organ. It is of 2 types, primary and secondary. Secondary amyloidosis occurs secondary to chronic inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, tuberculosis, bronchiectasis, osteomyelitis, and drug addiction.

8. What is the management of secondary amyloidosis?

Ans. There is no specific test for its detection. The biopsy of suspected organ is stained with congo red. The stained tissue gives green birefringence under polarized light. No specific therapies are available for its management. The treatment involves correcting the basic underlying disease. Colchicine is useful in familial Mediterranean fever cases only. Eprodisate is a new drug and awaiting Food and Drug Administration (FDA) approval and delays renal progression.

FINAL DIAGNOSIS

Leprosy with diffuse alveolar hemorrhage due to *S. pneumoniae* with renal amyloidosis.

LEARNING POINTS

- Leprosy (or Hansen's disease) is one of the oldest and notorious, but least understood diseases of man.
- In India, most common type of leprosy is borderline tuberculoid.[4]
- Diffuse alveolar hemorrhage can occur due to infection or autoimmune disease.
- It presents as acute, life-threatening event, and repeated episodes can lead to organizing pneumonia, collagen deposition in small airways, and, ultimately, fibrosis.
- Secondary amyloidosis is a rare disorder.

REFERENCES

1. James William D, Berger Timothy G, et al. Andrews' Diseases of the Skin: Clinical dermatology. Saunders Elsevier 2006.
2. *www.who.int/medicinedocs/en/d/jh2988e/5.html.*
3. Bruno Hochheger, Edson Marchiori, Felipe Mussi von Ranke, Glaucia Zanetti. Infectious diseases causing diffuse alveolar hemorrhage in immunocompetent patients: a state of the art review. Epub 2012.
4. Adarsh Lata Singh, SJ Vagha, Amit Agrawal, SR Joharapurkar, Brij Raj Singh. Current scenario of leprosy at tertiary care level hospital of rural central India. Indian Journal of Dermatology, Venereology and Leprology. 2009;75(5):520-2.

CASE

Jaundice in Patient with Fever

6

HISTORY

A 57-year-old male presented to us with complaints of decrease in appetite, fever and swelling of feet for 2 months. Fever was high grade, intermittent with chills. Swelling of feet was followed by facial swelling and decreased urine output. There had been history of orthopnea and weight loss of 8 kg in 2 months. On general examination, patient had pallor, deep icterus and bilateral pitting edema but no lymphadenopathy. He had tachypnea, blood pressure—100/60 mm Hg, pulse—102/min. Systemic examination revealed hepatosplenomegaly. Laboratory investigations are tabulated (Table 6.1).

All viral markers [Hepatitis B, Hepatitis C, HIV, Epstein-Barr virus (EBV) and cytomegalovirus (CMV)] were negative. Blood sugars were normal, reticulocyte count was 7.7%, scrub typhus and leptospira serology were negative. Thyroid profile was normal. Anemia profile was suggestive of iron deficiency anemia.

Table 6.1 Values of laboratory investigations

Parameter	*Patient's value*	*Normal range*
Hemoglobin	9.3 gm/dL	13–17 gm/dL
Total leukocyte count	6300/uL	4000–10000/uL
Platelet count	1 lakh	1.5 lakh–4.5 lakh/uL
Erythrocyte sedimentation rate (ESR)	25	<13 mm
Blood urea nitrogen (BUN)/S. creatinine	18/0.99	5–23/0.6–1.3 mg/dL
Total/Direct bilirubin	5.8/3.6 mg/dL	0.2–1.0/0–0.2 mg/dL
Aspartate aminotransferase/Alanine transaminase (AST/ALT)	184/656 IU/L	35/42 IU/L
Serum alkaline phosphatase	380 IU/L	<112 IU/L
International normalized ratio (INR)	2.26	
Lactate dehydrogenase (LDH)	567	180 IU

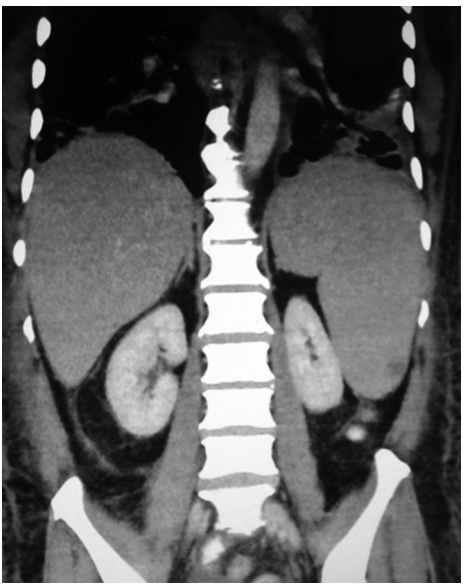


Figure 6.1 Hepatosplenomegaly

Contrast enhanced CT thorax and abdomen showed enlarged right deep cervical, mediastinal lymph nodes with patchy bilateral consolidation, bilateral pleural effusion, hepatosplenomegaly and periportal lymphadenopathy (Figure 6.1). Echocardiography showed mild concentric left ventricular hypertrophy (LVH) with ejection fraction 60%. Serum lactate dehydrogenase (S. LDH)—567 IU/mL, glucose-6-phosphate dehydrogenase (G-6-PD) levels were normal.

1. What is differential diagnosis of painless jaundice?

Ans. Painless jaundice presenting along with constitutional symptoms (fever, weight loss, appetite loss) usually points towards carcinoma of pancreatic head or ampulla of Vater. Examination of such patient may reveal a palpable gallbladder (Courvoisier's sign).

Jaundice may also be a feature of advanced gastric carcinoma. Many patients with carcinoma of stomach may have ascites and metastases to bone, liver, brain and lungs. Weight loss will be present and patient will be icteric along with palpable lump in abdomen. Palpable left supraclavicular node should alert the physician about gastric cancer in this setting (Virchow's node).

Other causes of painless jaundice are Hodgkin's lymphoma, large cell lymphoma, T cell lymphoma, Burkitt lymphoma, extramedullary plasmacytoma of pancreas and drug induced hepatitis. Jaundice in patients can be due to direct liver involvement, extrahepatic obstruction or combination of two.

FURTHER MANAGEMENT

Anti-nuclear antibody (ANA) and extractable nuclear antigen (ENA) profile were negative. For tissue biopsy, we debated whether to do bone marrow aspiration or transjugular liver biopsy. However in view of low platelet counts and deranged INR, we decided to do bone marrow biopsy. Bone marrow aspiration and biopsy had features of diffuse large B-cell lymphoma. Bone marrow flow cytometry was positive for B-cell markers. By the 3rd day of admission his jaundice deepened (total/direct bilirubin 29.83/21.2 mg/dL); INR worsened in spite of all supportive measures. He could not be given chemotherapy as his liver parameters were severely deranged. By 5th day he died inspite of all supportive measures.

2. What is diffuse large B-cell lymphoma?

Ans. Diffuse large B-cell lymphoma is a common malignant cancer of B lymphocytes. The B-cell lymphocytes are larger than normal and fail to undergo apoptosis and they proliferate at a rapid rate. Majority of patients are diagnosed in 7th or 8th decade with male: female ratio of 1.3:1.

3. What are the causes of jaundice in a patient of lymphoma?

Ans. Obstructive jaundice is a rare presentation of non-Hodgkin's lymphoma. Jaundice in patients of lymphoma can be because of liver infiltration by lymphoma cells, obstruction by lymph node at porta and periportal area, due to sepsis or infections like CMV. Diffuse large B-cell lymphoma can produce obstructive jaundice due to biliary stricture. The incidence of jaundice due to biliary stricture is nearly 3 times. There is poor prognosis in case of biliary obstruction by lymphoma. Jaundice is usually a late presentation but occasionally can be an early presentation in cases of lymphoma. Doxorubicin containing chemotherapy is important in management of lymphoma, but its use should be delayed for initial cycles in patients with jaundice. The role of stenting in patients to relieve obstructive jaundice is only in patients with cholangitis.

4. What is the staging in diffuse large B-cell lymphoma (DLBCL)?

Ans. World Health Organization (WHO)/Revised European-American Lymphoma (REAL) classification[1]

- DLBCL, not otherwise specified (NOS):
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary DLBCL of the central nervous system (CNS)
  - Primary cutaneous DLBCL—large cell type
  - Epstein-Barr virus (EBV)—positive DLBCL of the elderly
  - Germinal center B-cell (GCB)—DLBCL
  - Activated B-cell (ABC)—DLBCL
- DLBCL associated with chronic inflammation:
  - Primary mediastinal lymphoma
  - Intravascular large B-cell lymphoma
  - Anaplastic lymphoma kinase (ALK)—positive large B-cell lymphoma (Table 6.2)

Table 6.2 Cotswolds modification of Ann Arbor staging system

Stage	*Area of Involvement*
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk > 10 cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss > 10%, fever, drenching night sweats

5. What are the risk factors in diffuse large B-cell lymphoma?

Ans. Risk stratification is done according to international prognositic index.[2] Risk factors are given in Table 6.3 and each factor is given 1 point.

Risk categorization according to total score*:*

- Low (0 or 1)
- Low-intermediate (2)
- High-intermediate (3)
- High (4 or 5).

Serum LDH is raised in 50% of patients with constitutional symptoms. A high LDH level indicates tumor bulk. Raised levels in presence of hyperbilirubinemia, jaundice do not always indicate hemolysis but tumor bulk.

Table 6.3 Poor prognostic markers of lymphoma

Age >60 years
Elevated LDH
Ann Arbor stage III or IV
>2 extranodal sites of disease
Eastern Cooperative Oncology Group (ECOG) performance status >2

6. What is the prognosis of diffuse large B-cell lymphoma?

Ans. The most common chemotherapy regimen given is R-CHOP. The patients having low-risk have a complete response rate of 87% and a 5-year survival rate of 73%, as compared to complete response rate of 44% and a 5-year survival rate of 26% in the high-risk group.[3]

FINAL DIAGNOSIS

Diffuse large B-cell lymphoma presenting as obstructive jaundice.

LEARNING POINTS

- Obstructive jaundice is a rare presentation of non-Hodgkin's lymphoma.
- Biliary drainage is indicated only in presence of infectious complication.
- High LDH in a patient with diffuse large B-cell lymphoma carries poor prognosis.

REFERENCES

1. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009. pp. 523-31.
2. A predictive model for aggressive non-Hodgkin's lymphoma. The International non-Hodgkin's lymphoma prognostic factors project. N Engl J Med. 1993; 329(14):987-94.
3. *www.emedicine.medscape.com/article/202969-overview#aw2aab6b2b5.*

CASE

Shortness of Breath and Abdominal Distension

7

HISTORY

A 21-year-old female presented to us with complaints of abdominal distension for 3 months which has increased rapidly in last 20 days followed by swelling of feet. It was associated with orthopnea. There had been history of loss of appetite along with loss of weight around 6 kg in 2 months. There was no history of fever, jaundice, chest pain, decreased urine output.

EXAMINATION

On general examination, patient had blood pressure—110/50 mm Hg, pulse—120/min, respiratory rate—24/min, jugular venous pressure (JVP) was raised. On abdominal examination, umbilicus was everted, flanks were full, shifting dullness was present, bowel sounds were heard. On respiratory system examination, there were decreased breath sounds in bilateral infrascapular region. Rest of systemic examination was unremarkable.

INVESTIGATION

Ascitic fluid was drained and sent for analysis. Values of laboratory investigations are given in Table 7.1. Liver and renal function tests were normal. ECG was

Table 7.1 Values of laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	11.9 gm/dL	13–17 gm/dL
Total leukocyte count	6,000/uL	4,000–10,000/uL
Platelet count	1.85 lakh/uL	1.5–4.5 lakh/uL
ESR	71 mm	<13 mm
Pericardial fluid—Cell count	295 (95% lymphocytic)	–
Protein/albumin	3.5/1.2 gm/dL	
pH	Alkaline	
Stains (gram, fungal, AFB stain)	Negative	
Adenosine deaminase	25.6	<24 uL
Routine culture and sensitivity	Sterile	

normal. Chest radiograph showed widening of mediastinum, enlarged cardiac Silhouette, and bilateral pleural effusion (Figure 7.1). HIV, HBsAg, anti-HCV were negative.

Mantoux test was positive. Echocardiography showed global hypokinesia, ejection fraction—32%, dilated inferior vena cava. Contrast enhanced CT thorax and abdomen revealed a large lobulated peripherally enhancing mass lesion involving the superior and anterior mediastinum most likely nodal in origin with diffuse pericardial thickening, bilateral pleural effusion and peripherally enhancing nodes in the periportal, portocaval region (Figure 7.2). Thyroid profile

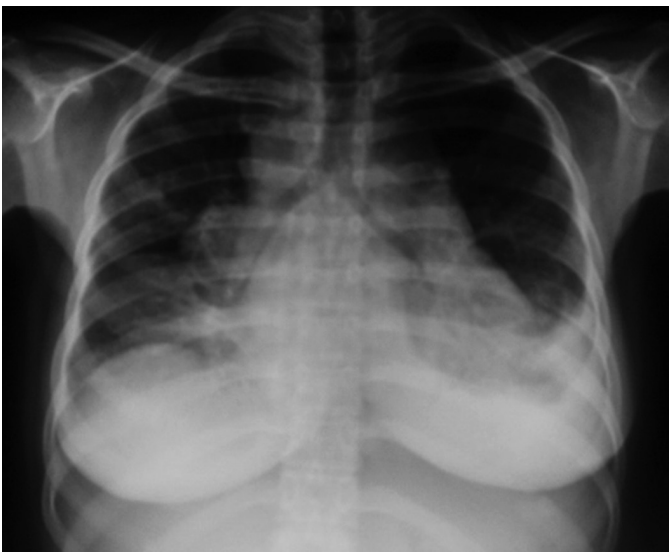


Figure 7.1 Mediastinal widening, bilateral pleural effusion and cardiomegaly

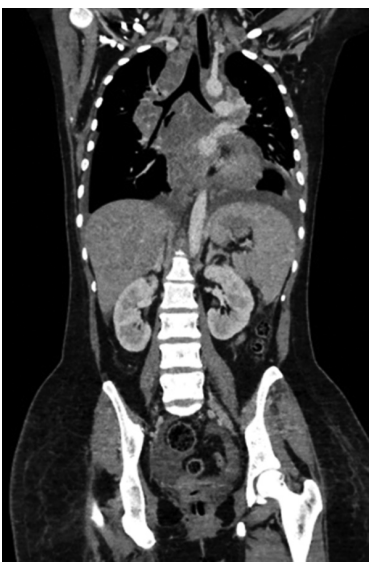


Figure 7.2 CT film showing diffuse thickened pericardium with left pleural effusion

was normal. Patient was advised to undergo pericardiectomy which she refused. Endoscopic ultrasound guided lymph node fine needle aspiration cytology (FNAC) revealed granulomatous lymphadenitis with necrosis and features suggestive of tuberculosis. Subsequently, she was given 4 drugs antitubercular treatment along with steroids.

1. What is constrictive pericarditis?

Ans. Constrictive pericarditis is a clinical condition due to fibrosis of the pericardium resulting in loss of elasticity of pericardial sac. It can be due to infections (tuberculosis, fungal like *Aspergillus*, *Candida*, parasitic, viruses like coxsackie, adenovirus and echovirus), radiation, postcardiac surgery, uremia, connective tissue disorders like scleroderma, systemic lupus erythematosus, trauma, drugs like methysergide, etc.

2. What are its clinical features?

Ans. In the Mayo Clinic series, 67% of patients presented with symptoms of heart failure (HF), 8% with chest pain, 6% with abdominal symptoms, 4% with atrial arrhythmia, and only 5% with symptoms of cardiac tamponade.[1] Patient presents with fatigability, tachycardia, orthopnea, fever, palpitations, diaphoresis and chest pain. On examination, patient always have elevated jugular venous pressure, 50% have pericardial knock and in severe cases have Kussmaul's sign, peripheral edema, ascites, pulsatile hepatomegaly and pleural effusion.[2] The differential diagnosis include cardiomyopathy (restrictive, hypertrophic or dilated), cardiac tamponade.

3. How do you differentiate between constrictive pericarditis and cardiac tamponade?

Ans. Pulsus paradoxsus, electrical alternans and pericardial effusion may be seen in cardiac tamponade whereas pericardial knock and thickened pericardium seen in constrictive pericarditis.

4. How do you manage constrictive pericarditis?

Ans. Various diagnostic modalities include electrocardiography, chest radiograph, echocardiography, CT thorax, MRI heart, right sided heart catheterization, pericardial biopsy. Patient should be advised low salt diet along with fluid restriction. The definitive modality is pericardiectomy. Medical therapy is not of much help, diuretic have to be used cautiously to decongest lungs. In case of prominent inflammatory component NSAIDs, corticosteroids and colchicine is beneficial.[3] In case tuberculosis is the cause, antitubercular drugs along with steroids are given.

FINAL DIAGNOSIS

Constrictive pericarditis due to tuberculosis.

LEARNING POINTS

- In India, the most common cause of constrictive pericarditis is tuberculosis.
- Renal failure, connective tissue disorders and post surgery are other important causes of this condition.

- Kussmaul's sign is an important JVP finding in patient's with constrictive pericarditis.
- Pericardectomy is the treatment of choice for patient's with constrictive pericarditis.
- Differential diagnosis of constrictive pericarditis includes—pericardial effusion and cardiac tamponade.

REFERENCES

1. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation 1999; 100:1380.
2. Maisch B, Seferovi PM, Risti AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary. The task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology. Eur Heart J 2004;25:587.
3. Imazio M, Antonio B, Roberto C, Ferrua S, Belli R, Maestroni S, et al. Colchicine treatment for recurrent pericarditis (CORP): a randomized trial. Ann Intern Med. 2011;155(7):128.

CASE

Cough and Chest Pain

8

HISTORY

A 60-year-old male a diagnosed case of immune thrombocytopenic purpura on steroids presented to us with complaints of left sided chest pain for 3 days. Pain was increasing on deep inspiration, non-radiating, no relation with posture. There was no history of fever or breathlessness. On general examination, he had fever (38°C), tachypnea (22/min), tachycardia (110/min). Systemic examination was unremarkable.

1. **What is the differential diagnosis of left-sided chest pain?**

Ans. The chest pain could arise from cardiopulmonary, musculoskeletal or gastrointestinal causes. The cardiac causes include angina, myocarditis and hypertrophic cardiomyopathy. The pulmonary causes for pain are asthma, pleuritis, pneumonia/lung abscess, pulmonary embolism, and pulmonary hypertension. The gastrointestinal causes are gastric reflux, peptic ulcer, and pancreatitits. Other causes include rib fracture, muscle strain, shingles, and costochondritis.

FURTHER MANAGEMENT

Laboratory investigations revealed hemoglobin—12 g/dL, total leukocyte count—10500/uL, platelet count—36000/uL, erythrocyte sedimentation rate (ESR)—71 mm. Liver and renal function tests were normal. Electrocardiography was normal. Chest radiograph showed cavity in left lower zone (Figure 8.1). Patient was given antibiotics along with other supportive treatment. HbA_{1c} was 13.2%. Fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) were 250 and 340 mg/dL. Contrast enhanced CT thorax showed pleural based heterogeneously enhancing mass lesion with internal cavity breakdown with associated parenchymal opacity in the surrounding lung parenchyma in the lingular segment of left lung, cavitatory nodular lesion in the right lower lobe and subcentimeter nodule in the superior segment of left lower lobe and upper lobe of the right lung. ELISA for HIV was negative. Antinuclear antibodies (ANA) was negative. Sputum examination on kinyoun stain showed nocardia (Figure 8.2). Patient was empirically given Cotrimoxazole. Later, sensitivity report revealed nocardia resistant to cotrimoxazole. So, imipenem was initiated. Minimal dose of steroid to prevent disease relapse was maintained and to treat nocardia antibiotics were continued. Patient continued to have fever, the dose of prednisolone

was maintained between 10 and 15 mg/day and platelet counts were between 12000 and 15000/uL. The patient required platelet apheresis. It was decided to give single dose of intravenous immunoglobin (IVIg) (1 gm/kg) over 24 hours to increase the platelet counts. Post-infusion, platelets started increasing and by 7th day platelet counts were 57000 to 60000/uL. By 2nd week, platelet counts were more than 1 lakh/cumm. Antibiotic was continued and patient made steady improvement and chest radiograph done after 6 months was better (Figure 8.3).

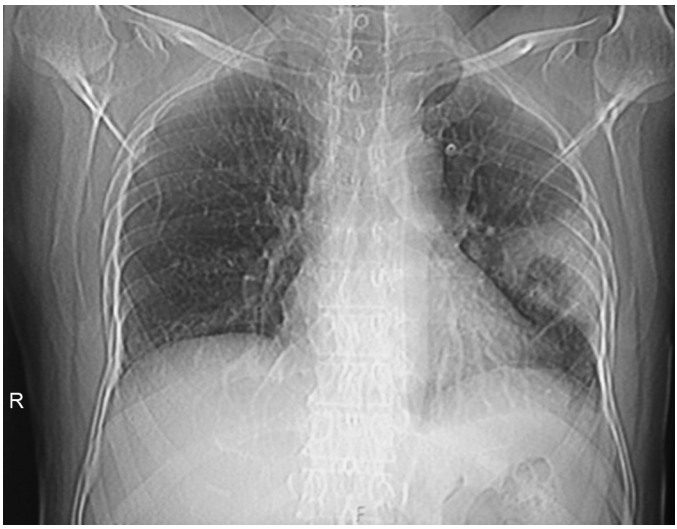


Figure 8.1 Pre-treatment—thick-walled cavitary lesion in left lower zone

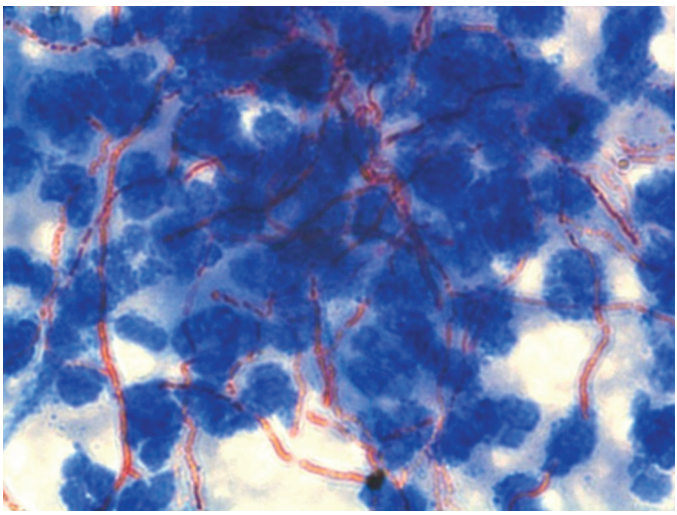


Figure 8.2 Kinyoun stain showing nocardiosis

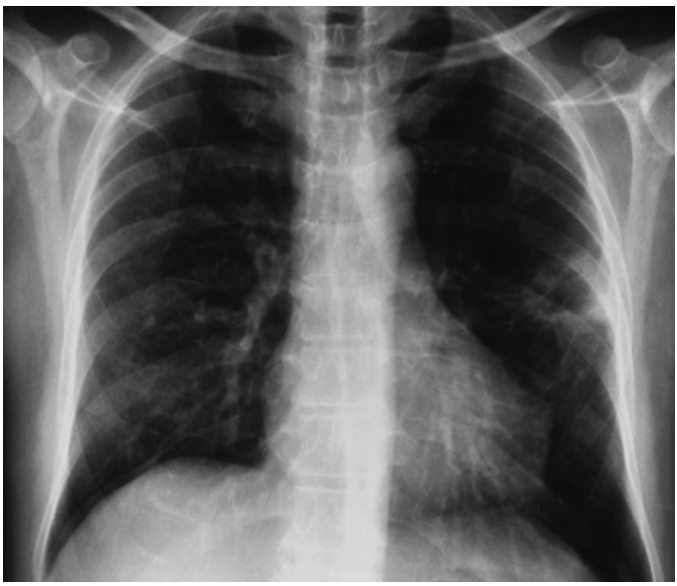


Figure 8.3 Post-treatment—clearing of cavitary lesion

2. How is nocardia transmitted and diagnosed?

Ans. Nocardia is a bacterial infection. The common mode of transmission is inhalation of organisms. This is normally found in soil. Other routes include traumatic introduction, especially in the jaw, direct inoculation through wounds.[1] The diagnosis of nocardiosis is usually difficult. Grams staining of body fluid is required which show grams positive branching organism. Other stains which are used are kinyoun stain, and Ziehl–Neelsen stain. The gold standard is culture but it grows slowly. The infection occurs commonly in immunocompromised host like diabetes, cancer, HIV/AIDS, ethanolic, post-bone marrow or solid organ transplant and patient taking steroids.

3. What are the antibiotics effective in nocardiosis?

Ans. Co-trimoxazole is the first line therapy for nocardiosis. However, in recent review, 42% isolated were resistant to co-trimoxazole.[2] Alternative parenteral therapies include imipenem, meropenem, third-generation cephalosporins, and amikacin. Oral therapy includes linezolid, minocycline and amoxicillin/clavulanate. For serious infections, combination therapy is been recommended.[3] The treatment should also include surgical drainage of abscess and excision of necrotic tissue.

4. How long to treat the infection?

Ans. The usual consensus regarding duration of treatment is given in following Table 8.1.

Table 8.1 Duration of therapy for nocardiosis

Disease	*Duration*
• Pulmonary or systemic	
– Intact host defences	6–12 months
– Immunocompromised	12 months
• CNS disease	6-12 months
• Skin disease	2 months
• Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
• Keratitis	*Topical*: Until apparent cure *Systemic*: Until 2–4 months after apparent cure

FINAL DIAGNOSIS

Chronic immune thrombocytopenic purpura with pulmonary nocardiosis.

LEARNING POINTS

- Nocardia is a bacteria commonly found in soil.
- It commonly affects lung, brain and skin.
- Prolonged therapy 6 to 12 months is undertaken.
- IVIG can be given to tide over acute period for immune thrombocytopenic purpura in presence of infection.

REFERENCES

1. *www.emedicine.medscape.com/article/224123.*
2. Uhde KB, et al. Antimicrobial-resistant nocardia isolates. United States. 1995-2004. Clin Infect Dis. 2010;51:1445.
3. Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc. 2012; 87(4):403-7.

CASE

Patients with Diarrhea and Lower Limb Weakness

9

HISTORY

A 38-year-old female presented to casualty with diffuse watery diarrhea for one day duration. Diarrhea was watery multiple episodes in last 24 hours, with no blood or mucous. There was no associated abdominal pain or vomiting. Patient had adequate urine output. There was no history of any medication intake or any chronic illness. On examination, there was presence of significant dehydration. Arterial blood gas analysis (ABGA) done in emergency room revealed pH^- 7.32, pCO_2^- 32, pO_2^- 75, HCO_3^- 18, Anion gap-10.

1. How do you interpret the ABGA?

Ans. As the pH is low it is acidosis (Normal pH^- 7.35–7.45). Second step is to decide the primary process, as bicarbonate is low (Normal 22–26 meq/L), it is metabolic acidosis. The next step is to find out compensation. Due to low pCO_2 (Normal 35–45 mm Hg), it is compensatory respiratory alkalosis. The metabolic acidosis in this lady is due to bicarbonate loss from lower gastrointestinal tract.

2. What are the common causes of diarrhea in adults?

Ans. Diarrhea is described as more than 3 or more loose stools. The causes can be due to virus such as rotavirus or norovirus, bacterial infection such as *Campylobacter*, *Clostridium difficile*, *E. coli*, *Salmonella* and *Shigella*. Parasitic infection like *Giardia* can also cause diarrhea. Certain non-infectious conditions anxiety, food allergy, excess coffee, alcohol, antibiotics, laxative abuse can also cause diarrhea.

FURTHER HISTORY

Two weeks later, patient noticed there was weakness and heaviness in lower limbs. She found difficulty in walking over next one day and also to turn sides in bed. On examination, power in lower limb was NMRC Grade 4. Deep tendon reflexes in lower limbs were absent and so was the plantar response. Investigations like complete blood counts, electrolytes, liver and renal functions were non-contributory.

3. What is the diagnosis in this patient?

Ans. In view of symmetrical weakness that involves lower limb and rapidly ascends to trunk the diagnosis is acute inflammatory demyelinating

polyneuropathy (AIDP). It is a form of Guillain-Barré syndrome (GBS). The disease is usually triggered by an infection of *Campylobacter jejuni* (most common—32%) prior (1–4 weeks) to this episode.

Cerebral spinal fluid (CSF) examination and nerve conduction velocity helps in diagnosis. In CSF, the findings are albuminocytological dissociation, i.e. there is increase in protein levels in CSF without accompany increase in the cell count. Nerve conduction velocity will show conduction block, prolonged distal latencies, conduction slowing, F and H reflex may be prolonged or absent.

4. What are the common clinical features of Guillain-Barré syndrome?

Ans. Typical Guillain-Barré syndrome has motor neuropathy involving distal lower limb, symmetrical weakness, ascending paralysis with reduced or absent reflexes.

Five other variants have been described in addition to acute inflammatory demyelinating polyneuropathy (AIDP), Miller-Fisher syndrome (ophthalmoplegia, ataxia, areflexia).[1] Acute motor axonal neuropathy (Chinese paralytic syndrome), acute motor sensory axonal neuropathy, acute pan autonomic neuropathy and Bickerstaff's brain encephalitis variant.

Sensory involvement is seen is more than 50% cases, autonomic nervous system in 65% subjects, pain in 2/3rd cases, cranial nerve involvement in half the cases and respiratory weakness in 1/3rd cases. Patient should be monitored for respiratory muscle weakness and spirometry should be done frequently.

5. What are the differential diagnosis for this condition?

Ans. The differential diagnosis includes disorders of neuromuscular transmission like Botulism and myasthenia gravis, acute peripheral neuropathy due to heavy metal toxicity, nutritional neuropathy, vasculitic neuropathy, metabolic myopathies, multiple sclerosis, cauda equina and Conus Medullaris syndromes and chronic inflammatory demyelinating polyradiculoneuropathy.

6. How do we treat Guillain-Barré syndrome?

Ans. Plasma exchange and intravenous immune globulin (IVIG) have proven effective for Guillain-Barré syndrome (GBS).[2] They may decrease autoantibody production and increase solubilization and removal of immune complexes. Both have been shown to shorten recovery time by as much as 50%. IVIG is easier to administer and has fewer complications than plasma exchange. The cost and efficacy of each are comparable. Steroid as a monotherapy has no role in treatment.

FINAL DIAGNOSIS

Post-diarrheal acute inflammatory demyelinating polyneuropathy.

LEARNING POINTS

- Guillain-Barré syndrome is progressive, symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes.
- It is major cause of acute neuromuscular paralysis in the Western world.
- GBS usually is associated with an antecedent infection.
- Meta-analysis concluded that IVIG is as effective as plasma exchange in hastening recovery from GBS in patients.

REFERENCES

1. Dimachkie MM, Barohn RJ. Guillain-Barré syndrome and variants. Neurol Clin. 2013;31:491-510.
2. Van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). Presse Med. 2013;42:193-201.

CASE

Patient with Fracture and Altered Sensorium

10

HISTORY

A 54-year-old male presented with generalized weakness and reduced appetite since last one year. He also noticed weight loss of about 5 kg in last 3 months. There was history of altered sensorium since last 5 days. There was no history of fever, cough, pain abdomen, loose motions or any altered sensorium. History of increased urinary frequency present. Patient had mid shaft fracture tibia right side 3 years back and was on calcium and vitamin supplementations. There was no history of diabetes mellitus, hypertension or any other chronic disease.

EXAMINATION

On physical examination, patient was disoriented, restless and moving all four limbs. Oral thrush was present. BP 150/80 mm Hg, PR 82/min. Severe pallor was present. Rest of the systemic examination was within normal limits. Investigations as available in Table 10.1.

Table 10.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	9.6 gm/dL	13–17 gm/dL
TLC	4,800/cumm	4,000–10,000/uL
Platelet counts	2.03 lakh	1.5–4.5 lakh
ESR	55 mm	<11 mm
BUN	25 mg/dL	5–23 mg/dL
S. creatinine	3.5 mg/dL	0.6–1.3 mg/dL
Uric acid	7.5 mg/dL	4–5 mg/dL
Serum Ca/phosphorus	13.3/3.5 mg/dL	9–11/2.5–4.5 mg/dL
Serum Na/K	137/3.0 meq/dL	135–145/3.5–5 mg/dL
Serum bilirubin (T)	0.60 mg/dL	0.2–1 mg/dL
Serum protein/albumin	5.4/3.4 mg/dL	6–8.3/3.4–5.4 mg/dL
Serum glutamic oxaloacetic transaminase (SGOT)/ Serum glutamic pyruvic transaminase (SGPT)/ Alkaline phosphatase (ALP)	23/14/58 IU/L	0–40/0–34 IU/L

Thyroid profile, blood sugar, urine normal.
USG abdomen: Enlarged prostate (33.8 gm).
Chest X-ray: No abnormality detected (NAD).
ELISA for HIV: Negative

1. What are the differential diagnosis in this case?

Ans. This patient had anemia with elevated ESR, high serum creatinine and serum calcium. The differential diagnosis includes:

- Multiple myeloma
- Drug induced hypercalcemia
- Malignancy associated hypercalcemia.

FURTHER INVESTIGATIONS

Twenty-four hours urinary protein—1,020 mg/24 hr, 24 hr creatinine clearance—13.9 mL/min, 24 hr urine creatinine—741.2 mg/24 hr, parathyroid hormone (PTH)—45.8 ng/L (18–51 ng/mL), 25–OH vitamin D 150 ng/mL (14–42 ng/mL). Bone marrow aspiration to rule out myeloma was non-contributory (plasma cell 3%). Uroflowmetry was suggestive of obstructive pattern. Non-contrast computerized tomography (NCCT) abdomen was normal.

2. What is the cause of acute renal failure in this patient?

Ans. The cause is hypervitaminosis D which leads to hypercalcemia and acute renal failure.

3. What are the causes of hypercalcemia?

Ans. The causes of hypercalcemia can be remembered with pneumonic VITAMINS TRAP, i.e. **V**itamin A & D, **I**mmobilization, **T**hyrotoxicosis, **A**ddison's disease, **M**ilk alkali syndrome, **I**nflammatory disorders, **N**eoplastic disease, **S**arcoidosis, **T**hiazides, **R**habdomyolysis, **A**IDS, **P**aget's disease, **P**arentral nutrition and **P**arathyroid disease.

Excessive PTH production

- Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
- Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
- Ectopic PTH secretion (very rare)
- Inactivating mutations in the calcium sensing receptors (CaSR) [Familial hypocalciuric hypercalcemia (FHH)]
- Alterations in CaSR function (lithium therapy).

Hypercalcemia of malignancy

- Overproduction of parathyroid hormone-related peptide (PTHrP) (many solid tumors)
- Lytic skeletal metastases (breast, myeloma).

Excessive $1,25(OH)_2D$ production[1,2]

- Granulomatous disease (sarcoidosis, tuberculosis, silicosis)
- Lymphomas
- Vitamin D intoxication.

Primary increase in bone resorption
- Hyperthyroidism
- Immobilization.

Excessive calcium intake
- Milk-alkali syndrome
- Total parenteral nutrition.

Other causes
- Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
- Medications (thiazides, vitamin A, antiestrogens).

4. How will you manage hypercalcemia?

Ans.
- Emergency management
  - Normal saline—2–3L over 3–6 hrs
  - Furosemide—40–100 mg IV every 2–4 hrs
  - Pamidronate—90 mg IV over 24 hrs
  - Mithramycin—25 mcg/kg IV every 3–4 days
  - Calcitonin—4 MRC units/kg S/C every 12 hrs
  - Hydrocortisone—1 mg/kg every 6 hrs
  - Prednisolone—40–80 mg/day
  - Hemo/peritoneal dialysis—Calcium free
- Non-emergency treatment
  - Adequate fluid intake
  - Withdrawal of drugs causing hypercalcemia
  - Restriction of oral calcium
  - Mobilization if possible.

FINAL DIAGNOSIS

Hypervitaminosis D leading to hypercalcemia and acute renal failure with benign prostatic hyperplasia with hypertension.

LEARNING POINTS

- Normal range of vitamin D is 14–42 ng/mL, hypervitaminosis D occurs when the level goes above 72 ng/mL.
- Majority of cases of hypervitaminosis D are iatrogenic.
- Overdose should be suspected in patients presenting with polyuria, polydipsia, vomiting, azotemia or encephalopathy in the emergency room.
- Injectable form of vitamin D is beneficial to treat patients with rickets and also in patients with malabsorption.

REFERENCES

1. Billoo AG, Murtaza G, Memon MA, et al. J Coll. Comparison of oral versus injectable vitamin D for the treatment of nutritional vitamin D deficiency rickets. Physicians Surg Pak. 2009;19(7):428-31.
2. *http://www.japi.org/january_2009/R-1.html]a review of over 50 studies of 25(OH)D.*

CASE

11 Obese Patient with Multiple Ulcers

HISTORY

A 40-year-old phenotypic female presented to us with complaints of lower back pain and generalized weakness for one year. There was history of easy bruisability, bone pains along with poor healing of wounds present over both forearms and weight gain. She had history of primary amenorrhea and she had been taking medicines for the same.

EXAMINATION

On general examination, she had cushingoid face (Figure 11.1), thin paper like skin, buffalo hump over nape of neck, and purple striae over anterior abdominal wall (Figures 11.2A and B). Her blood pressure was 120/90 mm Hg, pulse was 90 beats/min. Her arm span was 140 cm and height was 160 cm. Her body mass index was 36.6 kg/m^2 (morbidly obese). There were multiple irregular ulcers with clear margins and surrounding induration on bilateral forearms and hands

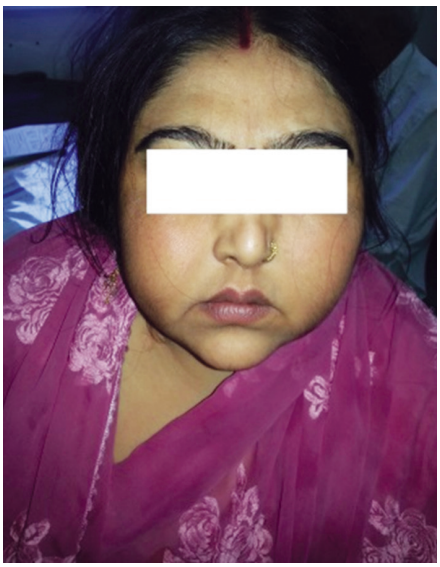
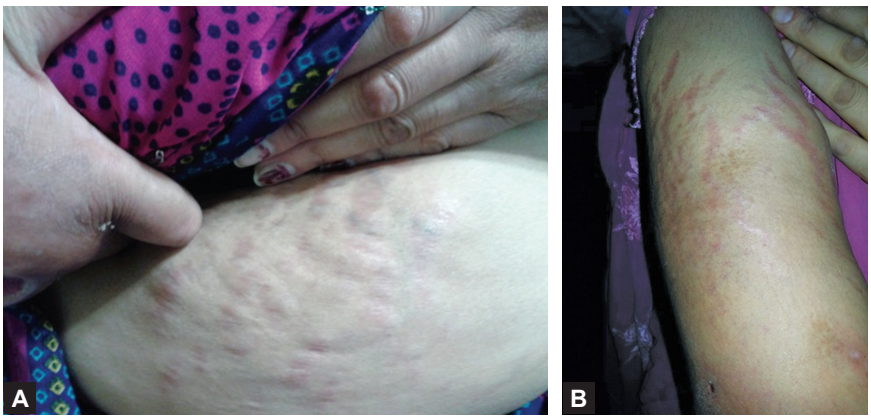
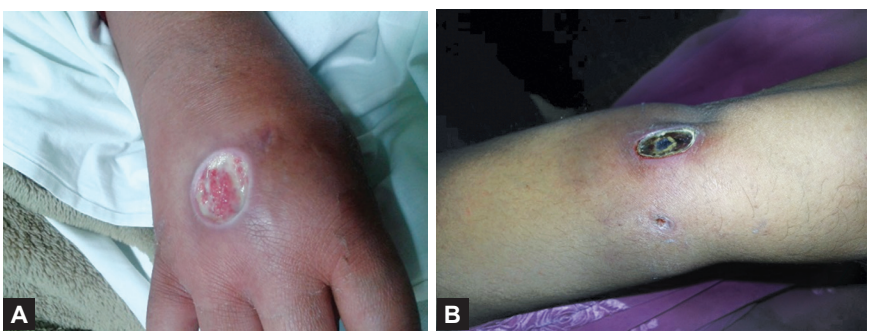


Figure 11.1 Moon like face



Figures 11.2A and B Striae over abdomen and arms



Figures 11.3A and B Non-healing ulcer over left hand and left forearm

(Figures 11.3A and B). Her secondary sexual features (breasts, pubic and axillary hair) were developed. Genitourinary system examination revealed short vagina. Rest of systemic examination was unremarkable.

Again, we intrigued her about the medicines she was taking, this time she accepted that she had been taking oral steroids for amenorrhea since 20 years. She had developed severe backache in thoracic region for last few years. So, she had been taking injection pentazocine in forearms for pain and was feeling better with no pain in back. Laboratory investigations are tabulated in Table 11.1.

Anemia profile was suggestive of iron deficiency. Pus culture was sterile. Serum cortisol at 6 AM and 4 PM were low, 5 mg/dL (6–28 mg/dL) and 1.3 mg/dL (2–12 mg/dL), both respectively and were consistent with exogenous corticosteriod administration. MRI spine done for backache showed fracture at D7, 8 vertebrae with no cord compression. Ultrasound abdomen showed absent uterus. Her hormonal profile depicted in Table 11.2.

Dual-energy X-ray absorptiometry (DEXA) scan revealed T score –3.7. Her karyotypic analysis revealed 46XX chromosome constitution. She was given calcium supplements, recombinant PTH for osteoporosis, surgical debridement

Table 11.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	11.8 gm/dL	11–15 gm/dL
Total leukocyte count	11,500/uL	4,000–10,000/uL
Platelet count	2.17 lakh/uL	1.5–4.5 lakh/uL
Blood urea nitrogen (BUN)/ S. creatinine	13/0.56 mg/dL	5–23/0.6–1.3 mg/dL
AST/ALT	75/81 IU/L	0–40/0–34 IU/L
Glycosylated hemoglobin	4.5%	< 6%

Table 11.2 Hormonal profile

Parameters	*Patient's value*	*Normal range*
Serum estradiol	20.6 pg/mL	0–30 pg/mL
Serum follicle-stimulating hormone (FSH)	39.3 mIU/mL	16.7–113.6 IU/L
Serum luteinizing hormone (LH)	16.5 mIU/mL	1–20 IU/L
Serum testosterone	0.09 ng/mL	0.1–1 ng/mL
Serum adrenocortico-tropic hormone (ACTH)	6 pg/mL	9–52 pg/mL
Thyroid profile	Normal	
Lipid profile	Normal	

of ulcers with skin grafting was done consequently and for spine fracture, she was advised to take maximum bed rest and not to lift heavy loads. She was counselled about Mayer-Rokitansky-Hauser syndrome, which resulted in primary amenorrhea in her.

1. What are the conditions leading to absent uterus?

Ans. Failure of Müllerian duct to develop results in missing uterus called Müllerian agenesis, i.e. Mayer-Rokitansky-Hauser syndrome. The incidence of this syndrome varies from 1 in 4,000 to 5,000 female births. The women with Müllerian agenesis have normal 46XX karyotype, with normal external genitalia with functional ovary with primary amenorrhea. In addition, there is agenesis of fallopian tubes and upper 2/3rd of vagina. In presence of functional ovary they produce estrogen normally so secondary characters are normal. Thus, development of breasts, vulvar structure and pubic hair are like female.

The other condition with absent uterus is Turner's syndrome. It is characterized by phenotypic female, 45X0, short stature, broad chest, low hair line, webbed neck, amenorrhea, sterility, hypothyroidism, visual and hearing problems.

2. What are the characteristic features of exogenous Cushing's syndrome?

Ans. Exogenous Cushing's syndrome occurs once a person takes glucocorticoid such as prednisolone or dexamethasone for a long-time. The patient has moon like face, obesity, purple striae (they are ½ inch or more wide and present on abdomen, thigh and breasts), easy bruising, backache due to osteoporosis, buffalo hump, hirsutism, depression, hypertension, hyperglycemia and acropathy. The hormonal assay will reveal low ACTH, low cortisol. Table 11.3 distinguishes the two types of Cushing's syndrome.

Table 11.3 Exogenous v/s endogenous Cushing's syndrome

	Exogenous Cushing's syndrome	*Endogenous Cushing's syndrome*
Cause	Due to self/ prescribed corticosteroid for condition like asthma, SLE, rheumatoid arthritis	Due to pituitary adenoma (produce ACTH) or adrenal gland hyperplasia, adenoma or carcinoma (produce excess cortisol) or ectopic ACTH source (small cell carcinoma, neuroendocrine tumor)
Incidence	Much more	1-2/1,00,000 population
Serum cortisol	Low (except when prednisolone which cross reacts with immunosuppressants)	High
ACTH level	Undetectable	Undetectable-adrenal tumor Detectable-pituitary or ectopic source

3. What are the current guidelines for prevention of glucocorticoid induced osteoporosis?

Ans. Glucocorticoids are widely prescribed and one of the most misused drug to treat a number of diseases. The long-term therapy with oral glucocorticoids is associated with a significant increase in fracture risk at the hip and spine. The dose greater is the risk of fracture. There is increased fracture risk even at 7.5 mg/day or even less dose of prednisolone. Fracture risk decreases steeply after stopping the glucocorticoid intake.

All patients on glucocorticosteroid should receive calcium and vitamin D supplements. Maximum loss in bone mass occurs in initial months of starting the glucocorticoid. Individuals greater than aged 65 years or aged less than 65 years but are at risk for fracture should be advised to start bone protective therapy before starting glucocorticoids without going for bone density scan. People aged < 65 years who intend to use glucocorticoids for more than 3 months should have their bone density measured before initiating glucocorticoids.[1] If T score is above zero only reassurance is to be given to patient, if T score is between 0 and –1.5, bone densitometry to be repeated after 1 to 3 years and no medicines are required and if T score is –1.5 or less than patient has to be given bone protective measures before starting glucocorticoids. Good nutrition, adequate dietary calcium intake, regular exercise should be encouraged. Alcohol and tobacco abstinence should be advised. Various treatment options available are bisphosphonates (alendronate, zolendronic acid,

etidronate), calcitonin, calcitriol, hormone replacement therapy in post-menopausal women and recombinant parathyroid hormone (PTH).[2]

4. What are the characteristics of pentazocine induced ulcer?

Ans. Pentazocine is a non-narcotic, addicting analgesic. It is easily available in the Indian market. Clinically, patient presents with irregular ulcers with surrounding induration, hyperpigmentation from thrombophlebitis, scars along veins.[3] Ulcers are usually present over easily accessible portion of the body like thigh, arm and abdomen as the patient injects them due to addiction. Various causes of discharging sinuses are scrofuloderma, atypical mycobacterial infection, mycetoma, hidradenitis suppurativa.

FINAL DIAGNOSIS

Mayer-Rokitansky-Hauser syndrome, exogenous-Cushing syndrome with pentazocine induced ulcers, drug induced osteoporosis.

LEARNING POINTS

- In Mayer-Rokitansky-Hauser syndrome women are born with normal ovary and normal external genitalia but without uterus, fallopian tubes and upper 2/3rd of vagina.
- Corticosteroids are used for multiple inflammatory and autoimmune conditions in medicine.
- Overnight low dose dexamethasone suppression or 24 urinary free cortisol are screening test for suspected cushing disease.
- Any patient receiving corticosteroids for more than 3 months should receive bone protective treatment for osteoporosis.
- Pentazocine induced ulcers are chronic non-healing ulcers.

REFERENCES

1. Heffernan MP, Saag KG, Robinson JK, et al. Prevention of osteoporosis associated with chronic glucocorticoid therapy. JAMA. 2006;295(11):1300.
2. *www.nhslothian.scot.nhs.uk/Services/A-Z/DiabetesService/Information HealthProfessionals/MUHEndocrineManagementProtocols/014_gluco.pdf.Aaccessed at 14/1/2014 at 16:00 pm.*
3. Bhateja G, Subodh BN, Grover S, et al. Cutaneous complications with parenteral pentazocine dependence. 2006.

CASE

12 Backache with Limb Weakness

HISTORY

A 54-year-old male presented with lower back pain for 6 years duration and restriction of neck movements for last 2 years. All these complaints were progressive in nature and at the time of presentation he had severe pain and stiffness at cervical, thoracic and lumbar joints. There was no history of fever, pain radiating to lower limbs or any trauma. He had a past history of diabetis mellitus since last 8 years which was poorly controlled on hypoglycemics.

EXAMINATION

On examination, there was flexed posture of neck with Schober's test positive. He was referred as a case of ankylosing spondylitis for biological therapy. His blood investigations showed CBC—normal, ESR—20, human leukocyte antigen (HLA) B27—negative.

Cervical X-ray as shown in Figures 12.1A and B, thoracic X-ray shown in Figure 12.2 and lumbosacral spine shown in Figure 12.3.

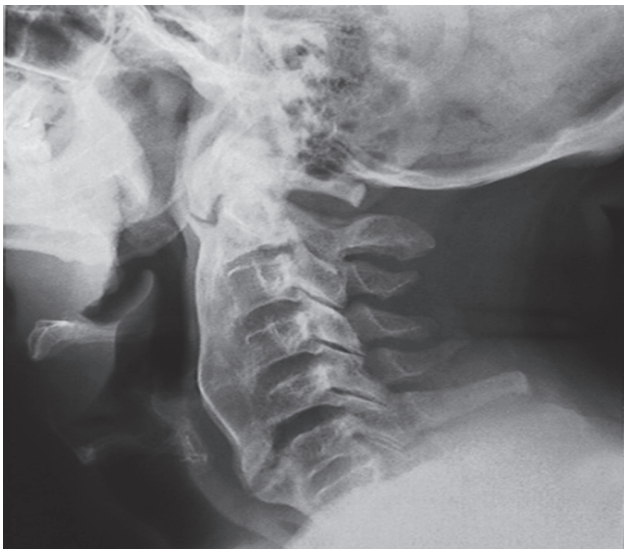


Figure 12.1A Cervical spine, lateral view

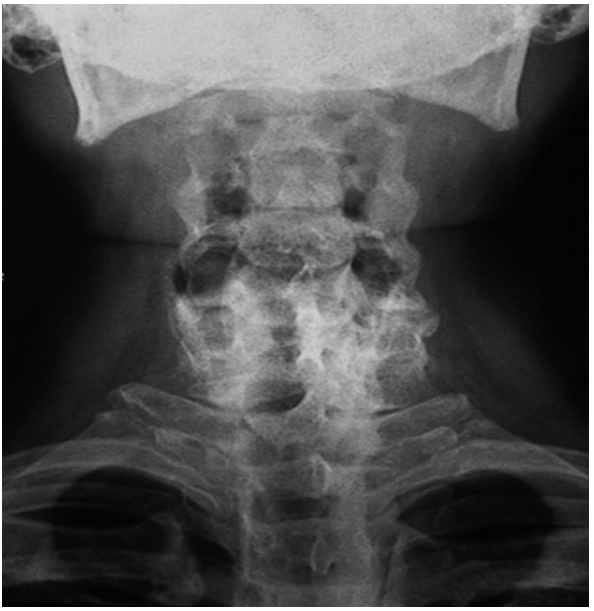


Figure 12.1B X-ray cervical, anteroposterior (AP) view

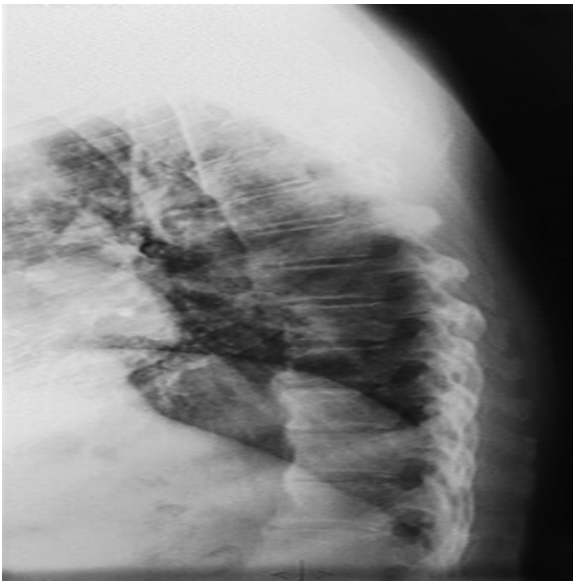


Figure 12.2 X-ray thoracic spine, lateral view

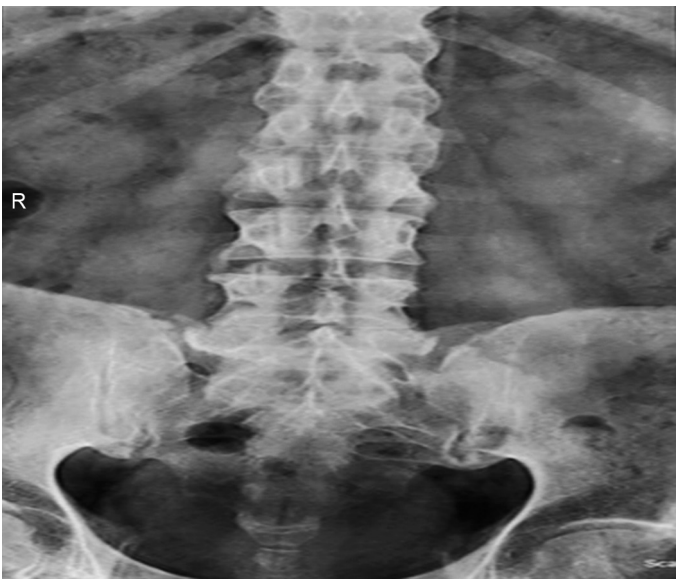


Figure 12.3 X-ray lumbosacral spine, AP view

1. What are the possibilities in this patient?

Ans. There is a typical flowing wax appearance suggestive of diffuse idiopathic skeletal hyperostosis in view of anterior and posterior longitudinal ligament thickening. This condition is also called as Forestier's disease. Ankylosing spondylitis was ruled out as there were no syndesmophytes, no reduction in vertebral spaces, no bamboo like calcification and HLA B27: negative. DISH is associated with DM, type 1 (39%) is more common than type 2 (13%).

FURTHER HISTORY

Since the patient had severe pain, it was decided to give pamidronate which is biphosphonate. Biphosphonates prevent further calcification and provide analgesia. Sugars were controlled with insulin. On the same day in the evening patient complained of difficulty in moving his all four limbs. On examination patient had acute flaccid paralysis.

2. What is the pathogenesis of quadriparesis in this patient?

Ans. There could be two possibilities:

1. Diffuse idiopathic skeletal hyperostosis causing compressive myelopathy leading to spinal shock.
2. Severe electrolyte disturbance.

FURTHER WORK-UP

His serum electrolytes were send immediately, which showed severe hypokalemia (1.8 meq/L). He was diagnosed as periodic paralysis due to hypokalemia.

3. What is periodic paralysis?

Ans. Periodic paralysis is a group of rare genetic disorders associated with channelopathy leading to weakness and paralysis or even death in some cases. Some patients have their first attack within minutes of birth, but a few do not have symptoms until they are in their 60s or 70s. Attacks can last only a few moments or go on for days, depending on the type of periodic paralysis the person has. Some forms of periodic paralysis include muscle stiffness or rigidity as part of the attacks.[1,2]

The common types of periodic parylsis are:

- Hypokalemic periodic paralysis
- Thyrotoxic periodic paralysis
- Hyperkalemic periodic paralysis
- Normokalemic periodic paralysis
- Paramyotonia congenita
- Potassium aggravated myotonias.

4. How will you treat hypokalemic periodic paralysis?

Ans. The treatment of hypokalemic periodic paralysis is:

- If potassium < 2 mmol or ECG abnormalities or muscle weakness/ paralysis, give up to 40 mmol/h of KCl (in saline).
- If potassium > 2 mmol/L and no ECG abnormalities, give up to 10 mmol/h IV KCl.
- Monitor serum or blood potassium, serum Mg^{2+}, ECG.
- Total body potassium replacement (150–300 mmol/L for every 1 mmol decrease in serum potassium) to be given over 3 to 4 days.
- After deficits are corrected, place on maintenance potassium to cover ongoing losses.

5. What are the know complications of DISH?

Ans. The known complications are:

- Stridor
- Dysphagia
- Severe backache
- Dysphonia
- Arthopathy
- Myelopathy
- Neruogenic claudication

6. How will you differentiate DISH from ankylosing spondylitis?

Ans. Table gives important clinical and radiological features to differentiation the two conditions.

	DISH	*Ankylosing spondylitis*
Clinical		
Age	>50 years	<40 years
Pain	Asymptomatic/–+	Symptomatic++
Limitation of chest expansion	+/–	++
Radiographic		
Sacroiliac (SI) joint erosion	–	++
Anterior longitudinal ligament (ALL) ossification	++	+/–
Posterior longitudinal ligament (PLL) ossification	+	?
Syndesmophytes	–	++

FINAL DIAGNOSIS

Type 2 diabetes mellitus with diffuse idiopathic skeletal hyperostosis (DISH) with hypokalemic periodic paralysis.

LEARNING POINTS

- Symptoms of DISH include intermittent back pain and particularly stiffness of the back, especially in the area from below the neck to the middle of the back.
- Diffuse idiopathic skeletal hyperostosis is uncommon in patients younger than 50 years of age.
- The principal manifestation of DISH is ligamentous ossification of the anterolateral aspect of the spinal column.
- DISH patients were more likely to report a history of diabetes mellitus.

REFERENCES

1. Jurkatt-Rott K, Lehmann-Horn F. Genotype-phenotype correlation and therapeutic rationale in hyperkalemic periodic paralysis. Neurotherapeutics. 2007;4:216-24.
2. Kim JB. Channelopathies. Korean J Pediatr. 2014;57(1):1-18.

CASE

13

Orbital Cellulitis in an Immunocompromised Person

HISTORY

A 64-year-old male with poorly controlled diabetes mellitus presented to us with complaints of moderate grade fever, lethargy, right periorbital pain and swelling in left eyelid for 7 days. Pain and swelling have worsened over 7 days. There is no history of trauma or blurred vision.

EXAMINATION

Patient had tachycardia, temperature of 39°C. There was no pallor, icterus, lymphadenopathy. There was right periorbital swelling and erythema, conjunctival congestion, vision was normal and blackish necrosis over the right side of nose. Respiratory, abdominal and cardiovascular systems were within normal limits.

INVESTIGATIONS

For the above problems, patient was investigated (Table 13.1).

Table 13.1 Laboratory work-up

Parameters	*Measured values*	*Normal range*
Hemoglobin	10.8 gm%	13–16 gm%
WBC	31,500/cumm (87% neutrophils)	4,000–10,000/cumm
Platelets	1.98 lakh	1.5–4 lakh
Random blood sugar	634 mg/dL	
Fasting blood sugar	299 mg/dL	100
S. creatinine	1.6 mg/dL	0.4–1.3 mg/dL
Blood sugar PP	345 mg/dL	160
HbA_{1c}	10.9%	6.5%

Urine ketones and serum ketones were negative, there was no acidosis on blood gas examination.

FURTHER WORK-UP

Patient was started on broadspectrum intravenous antibiotics, sugars were controlled with insulin. Despite the above treatment, his fever persisted and orbital swelling increased. He developed proptosis with blindness of right eye. He also developed thick nasal discharge. Patient underwent CT scan of paranasal sinuses which showed bilateral maxillary, ethmoid sinusitis with exophthalmos with right mastoiditis with orbital fat infiltration. Patient underwent functional endoscopic sinus surgery which showed gross necrosis in maxillary sinus with invasion of sinus wall (Figure 13.1). Patient was started on Liposomal Amphotericin B, in a dose of 3 mg/kg. Microbiological examination of specimen showed non-septate hyphae branching at right angles (Figure 13.2). His cultures were negative.

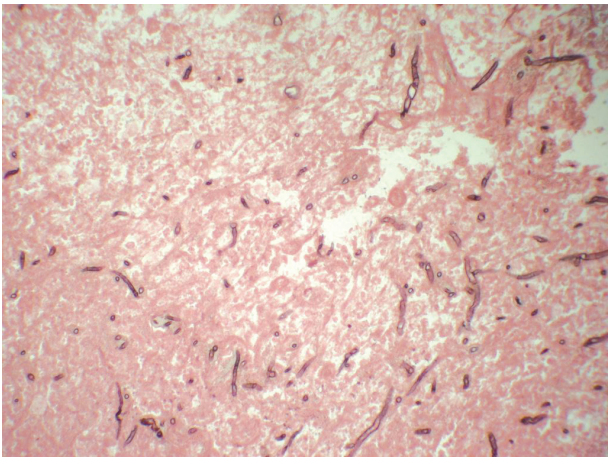


Figure 13.1 Endoscopic picture showing necrosis in middle turbinate

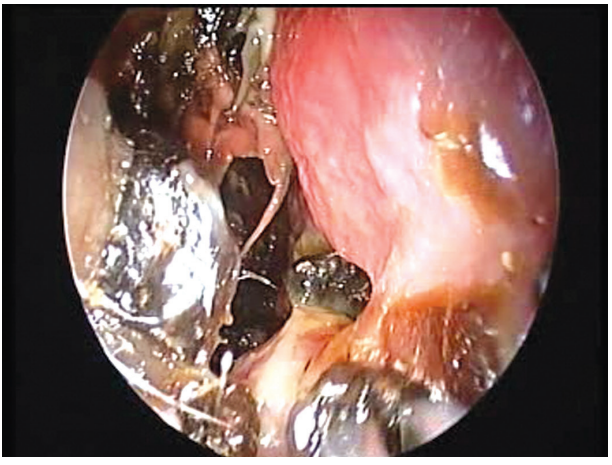


Figure 13.2 Hematoxylin and eosin stain showing septate fungal hyphae

Patient underwent extensive surgical debridment with inferior and middle turbinate. Patient improved clinically, however, he lost vision of his right eye.

1. What are the types of mucormycosis?

Ans. Mucormycosis is an emerging angio-invasive infection caused by the ubiquitous filamentous fungi of the Mucorales order of the class of Zygomycetes.

Mucormycosis has emerged as the third most common invasive mycosis in order of importance after candidiasis and aspergillosis. Mucormycosis remains a major threat in patients with diabetes mellitus.

Based on anatomic localization, mucormycosis can be classified as one of six forms:

1. Rhinocerebral
2. Pulmonary
3. Cutaneous
4. Gastrointestinal
5. Disseminated
6. Uncommon presentations like endocarditis, peritonitis.

2. When to suspect mucormycosis?

Ans. The most important conditions predisposing to mucormycosis are:

- Malignant hematological disease with or without stem cell transplantation prolonged and severe neutropenia
- Poorly controlled diabetes mellitus with or without diabetic ketoacidosis
- Iron overload
- Major trauma
- Prolonged use of corticosteroids
- Illicit intravenous drug use
- Neonatal prematurity
- Malnourishment.

3. What are the causative organism causing mucormycosis?

Ans. The Mucorales species most often recovered from clinical specimens are those of the genera *Rhizopus* (the most common genus associated with mucormycosis), *Lichtheimia* (formerly known as *Absidia* and *Mycocladus*), and *Mucor*.

4. What are the clinical manifestations of mucormycosis?

Ans. The clinical hallmark of invasive mucormycosis is tissue necrosis resulting from angio-invasion and subsequent thrombosis. In most cases, the infection is rapidly progressive and results in death unless underlying risk factors (i.e. metabolic acidosis) are corrected and aggressive treatment with anti-fungal agents and surgical excision is instituted.

PULMONARY MUCORMYCOSIS

Pulmonary mucormycosis occurs most often in neutropenic patients with cancer. The overall mortality rate in patients with pulmonary mucormycosis is high (76%); it is even higher in severely immunosuppressed patients. The clinical features of pulmonary mucormycosis are non-specific and cannot be easily distinguished from those of pulmonary aspergillosis. Patients usually present with prolonged high-grade fever (>38°C) that is unresponsive to broadspectrum antibiotics.

Nonproductive cough is a common symptom, whereas hemoptysis, pleuritic chest pain, and dyspnea are less common. Pulmonary mucormycosis may invade lung-adjacent organs, such as the mediastinum, pericardium, and chest wall.

RHINOCEREBRAL MUCORMYCOSIS

Rhinocerebral mucormycosis (ROCM) is the most common form of mucormycosis in patients with diabetes mellitus. The infection develops after inhalation of fungal sporangiospores into the paranasal sinuses. The infection may then rapidly extend into adjacent tissues. Upon germination, the invading fungus may spread inferiorly to invade the palate, posteriorly to invade the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to invade the brain. The initial symptoms of ROCM are consistent with those of sinusitis and periorbital cellulitis and include eye and/or facial pain and facial numbness followed by blurry vision. Signs and symptoms that suggest mucormycosis in susceptible individuals include multiple cranial nerve palsies, unilateral periorbital facial pain, orbital inflammation, eyelid edema, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss. A black necrotic eschar is the hallmark of mucormycosis.

CUTANEOUS MUCORMYCOSIS

Cutaneous mucormycosis results from direct inoculation of fungal spores in the skin, which may lead to disseminated disease. Depending on the extent of the infection, cutaneous mucormycosis is classified as localized when it affects only the skin or subcutaneous tissue; deep extension when it invades muscle, tendons, or bone; and disseminated when it involves other noncontiguous organs. The clinical manifestations of cutaneous mucormycosis vary. The typical presentation of cutaneous mucormycosis is a necrotic eschar accompanied by surrounding erythema and induration.

GASTROINTESTINAL MUCORMYCOSIS

Gastrointestinal mucormycosis is uncommon and seldom diagnosed in living patients. Only 25% of gastrointestinal mucormycosis cases are diagnosed antemortem, and authors have reported the disease mainly in premature neonates, malnourished children, diabetes mellitus, or a history of corticosteroid use. Gastrointestinal mucormycosis is acquired by ingestion of pathogens in foods such as fermented milk and dried bread products. Gastrointestinal mucormycosis can occur in any part of the alimentary system, but the stomach is most commonly affected, followed by the colon and ileum. Neutropenic fever, typhlitis, and hematochezia also can occur in neutropenic patients. Diagnosis of gastrointestinal mucormycosis is usually delayed, because its nonspecific presentation requires a high degree of suspicion.

DISSEMINATED MUCORMYCOSIS

Mucormycosis in one organ can spread hematogenously to other organs. The organ most commonly associated with dissemination is the lung. Dissemination

also occurs from the alimentary tract, burns, and extensive cutaneous lesions. Although the brain is a common site of spread, metastatic lesions may also be found in the liver, spleen, heart, and other organs. Patients with iron overload (especially those receiving desferoxamine), profound immunosuppression and acute leukemia are the classic groups at risk for disseminated mucormycosis]. The symptoms and evolution of disseminated mucormycosis vary widely, reflecting the host as well as the location and degree of vascular invasion and tissue infarction in the affected organs.

UNCOMMON FORMS OF MUCORMYCOSIS

Other less common or unusual focal forms of mucormycosis include endocarditis, osteomyelitis, peritonitis, and pyelonephritis. Specifically, mucormycosis is a rare cause of prosthetic or native valve endocarditis. Intravenous drug use is the typical risk factor.

5. How to treat mucormycosis?

Ans. Patients with mucormycosis should be treated in a tertiary referral center. Correction of the underlying abnormality and prompt institution of liposomal amphotericin B therapy and surgical resection are critical.

MEDICAL MANAGEMENT

Diabetic ketoacidosis requires insulin, correction of acidosis with sodium bicarbonate, and rehydration

- Neutropenia in association with hematologic malignancy and its treatment should be reversed, if possible, with the use of colony-stimulating factors and the withdrawal of cytotoxic chemotherapy
- Wean glucocorticosteroids and other immunosuppressive drugs
- Interrupt desferoxamine therapy; hydroxypyridine chelating agents may be substituted for desferoxamine.

ANTI-FUNGALS

In current practice, amphotericin is the sole antifungal agent licensed by the US Food and Drug Administration (US-FDA) for the primary therapy of mucormycosis. Antifungal treatment options consist of lipid formulations of amphotericin B, amphotericin B deoxycholate, or posaconazole. First-line treatment is with an amphotericin derivative, preferably with liposomal amphotericin.

Lipid preparations of amphotericin B are used at 3 to 5 mg/kg/day. It is known to cause nephrotoxicity hence monitoring of the renal function of patients taking amphotericin B is required; doubling of serum creatinine over the baseline levels is an indication reducing the dose and careful monitoring and repletion of serum electrolytes (e.g. potassium, phosphorus, magnesium) should be performed when administering any formulation of amphotericin B.

Posaconazole, a triazole, is currently considered a second-line drug for treatment of mucormycosis and the typical dose is 400 mg twice daily (total of 800 mg/d). Administration with a high-fat meal/food and acidic beverages enhances absorption of the drug. It is shown to have variable response. Posaconazole has also been used as sequential therapy after the initial administration and control of the disease with liposomal amphotericin B.

Other azoles (e.g. fluconazole, voriconazole) have not shown significant activity against mucormycosis fungi.

SURGICAL MANAGEMENT

Debridement of necrotic tissue in combination with medical therapy is mandatory for patient survival. In rhinocerebral disease, surgical care includes drainage of the sinuses and may require excision of the orbital contents and involved brain. Excision of pulmonary lesions if they are localized to a single lobe; excision of cutaneous lesions entirely; and resection of any GI masses.

ADJUNCTIVE THERAPIES

Hyperbaric oxygen therapy after surgical debridement are used, especially in cases of cutaneous disease and rhino-cerebral disease. It is not currently approved. High oxygen concentrations may improve neutrophil function, inhibit the growth of Mucorales, and improve wound healing.

Colony-stimulating factors have been used to enhance immune responses, specifically in neutropenic patients, as have interferon-gamma and white blood cell transfusions.

FINAL DIAGNOSIS

Rhino-sinus Mucormycosis with orbital invasion in a diabetic patient with uncontrolled sugars.

LEARNING POINTS

- Mucormycosis refers to several different diseases caused by infection with fungi in the order of Mucorales.
- Rhizopus species are the most common causative organisms.
- Most mucormycosis infections are life-threatening, and risk factors, such as diabetic ketoacidosis and neutropenia are present in most cases.
- Rhinocerebral, pulmonary and cutaneous varieties are most common forms.
- Successful mucormycosis treatment requires correction of the underlying risk factor(s), anti-fungal therapy with liposomal amphotericin B, and aggressive surgery.

BIBLIOGRAPHY

1. Bigby TD, Serota MD, Tierney LM, Matthay MM. Clinical spectrum of pulmonary mucormycosis. Chest. 1986;89:435-9.
2. Hay RJ. Liposomal amphotericin B, AmBisome. J Infect. 1994;28(1):35-43.
3. Losee JE, Selber J, Vega S, Hall C, Scott G, Serletti JM. Primary cutaneous mucormycosis: Guide to surgical management. Ann Plast Surg. 2002;49:385-90.
4. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13:236-301.
5. Tedder M, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg. 1994;57: 1044-50.

CASE

14 Muscle Pain and Fever

HISTORY

A 54-year-old gentleman was presented with fever and swelling in right upper thigh for 10 days. Fever was high grade, associated with chills and rigors, intermittent, decreased with antipyretics and no evening rise. Swelling in right upper thigh was painful and overlying skin was indurated. Patient denied history of joint pain or swelling, rash, discharge from swelling, burning micturition, vomiting, diarrhea, chest pain, cough or hemoptysis, breathlessness, altered behavior, abnormal movements of limbs. There was no history of local trauma either. Patient had past history of bilateral varicose veins for 10 years; hypertension and coronary artery disease for 5 years. His bladder and bowel habits were normal. There was no history of alcoholism or substance abuse.

EXAMINATION

Patient's physical examination revealed blood pressure—130/90 mm Hg, heart rate—98 beats/min, body temperature 38.8°C and respiratory rate 16 breaths/min. Pallor was present. A swelling was noted over right upper thigh inner aspect, which was tender, firm, mobile, 2 to 3 cm in size with overlying skin indurated and erythematosus. No erythema, joint tenderness, or restricted movements were present. Bilateral varicose veins were seen which were more prominent on right leg. Systemic examination was noncontributory. Investigations are tabulated (Table 14.1).

Table 14.1 Initial work-up

Parameters	*Patient's value*	*Normal range*
Hemoglobin	9.5 gm/dL	12–16 gm/dL
Total leukocyte count	19,000/cumm	4,000–10,000/cumm
ESR	34 mm/1st hour	0–10 mm/1st hr
Fasting blood sugar	98 mg/dL	70–100 mg/dL
Lactate dehydrogenase	378 IU/L	230–460 IU/L
AST/ALT	76/82 IU/L	0–42/0–60 IU/L
Creatinine phosphokinase	456 IU/L	22–195 IU/L

Contd...

Contd...

Parameters	*Patient's value*	*Normal range*
Urine culture	Sterile	
Blood culture	Sterile	
HIV antibody test	Nonreactive	
Chest X-ray	Normal	
Ultrasound Doppler-Lower limbs	Patient deep vein system	

1. What are the causes of elevated creatinine phosphokinase level?

Ans. There are many causes of rise in level of creatinine phosphokinase enzyme. Among them drugs is the most common cause of raised creatinine kinase level encountered by physicians in their practice. Drugs commonly implicated are statins, fibrate, antimalarial (chloroquine, hydroxychloroquine), antiretroviral (zidovudine), immunosuppressants (glucocorticoids, TNF-alpha inhibitors), colchicine and cocaine. Other common causes are myocardial infarction, myocarditis, traumatic muscle injury, muscular dystrophy, rhabdomyolysis, myositis, polymyositis, dermatomysitis, hypothyroidism, malignant hyperthermia, cerebral infarction, convulsions and tetanus.

FURTHER HISTORY

CT scan of right thigh was performed which showed muscles of right thigh were bulky in size with thrombosis of right common femoral, superficial femoral and great saphenous vein and a soft tissue density nodule was noted at medial aspect of right thigh. CT-guided fine needle aspiration cytology (FNAC) of the thigh nodule was done which revealed many polymorphonuclear cells and Grams negative bacilli. The culture yielded *Salmonella typhi* (Figure 14.1) sensitive to ceftriaxone and ciprofloxacin. Widal test showed

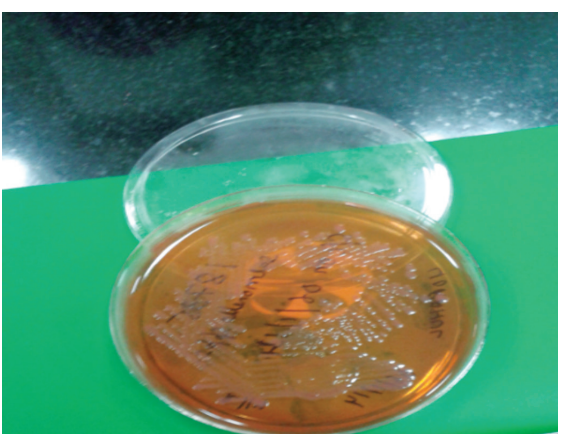


Figure 14.1 *Salmonella typhi* growth

TO titer 1:320 and TH titer 1:640. He received intravenous ceftriaxone (2 gm every 12 hours and ofloxacin 200 mg every 12 hours for 10 days) and low molecular weight heparin (enoxaparin 0.6 mg every 12 hours) and Patient's fever settled in next 10 days.

2. What is tropical pyomyositis?

Ans. Tropical pyomyositis is a bacterial infection of skeletal muscles resulting in abscess formation. It is most common in tropical regions, but can also occur in temperate zones. The most common organism implicated is *Staphylococcus aureus* in 75% of cases followed by streptococci in 4 to 16% of cases.[1] Rarely *Salmonella*, *Citrobacter*, anaerobes and *Mycobacterium* is implicated.[2,3] History of trauma to affected muscle is present in 20 to 50% of cases.[4] The two most common underlying conditions are diabetes and HIV. Commonly involved muscles are quadriceps, iliopsoas, glutei, pectoralis major, serratus anterior, biceps, gastrocnemius, abdominal and spinal muscles.[5] In our patient, pus grew *Salmonella typhi*, which is very rarely reported for this clinical picture.

3. What are the differential diagnoses?

Ans. Tropical pyomyositis is a great masquerader. Its differential diagnosis includes septic arthritis, muscle hematoma, osteomyelitis, trichinosis, osteosarcoma, deep vein thrombosis, and polymyositis.

4. How pyomyositis is diagnosed?

Ans. Aspiration of pus from the muscle or muscle biopsy with culture and tissue staining in case of absence of macroabscesses is the gold standard for diagnosis. Hypoechoic area with increase in muscle bulk is seen on ultrasound. Computed tomography or MRI is the best imaging techniques for early diagnosis. Computed tomography reveals low attenuation areas with loss of muscle planes and a surrounding rim of contrast enhancement as characteristic of pyomyositis. MRI shows hyperintense rim on T1 weighted images with peripheral enhancement on gadolinium DTPA scan. Serum levels of muscle enzymes are either normal or slightly raised.

5. How would you treat pyomyositis?

Ans. Surgical debridement along with antistaphylococcal beta-lactamase resistant penicillin (cloxacillin) intravenously is the preliminary recommended treatment. Penicillin is the drug of choice for penicillin susceptible *Staphylococcus*. For methicillin resistant *Staphylococcus*, vancomycin is a suitable alternative.

If group A *Streptococcus* is isolated from the pus, treatment should be changed to crystalline penicillin. For Grams negative bacilli, addition of an aminoglycoside should be considered along with cephalosporins.

For HIV infection and immunosuppressed patients, broad spectrum empirical antibiotics against Grams positive, Grams negative and anaerobic organism should be given. In addition to antistaphylococcal antibiotics, patient should also get aminoglycosides and clindamycin.

Secondary spread of metastatic infection from involved muscles usually requires four to six weeks of high dose antimicrobial therapy intravenously. Otherwise, treatment should be continued till wound is clean, the leukocyte count become normal, and the patient is afebrile for at least a week.

FINAL DIAGNOSIS

Tropical pyomyositis due to *Salmonella typhi*.

LEARNING POINTS

- Infection of the muscle is a rare cause of elevated creatinine kinase level
- *Staphylococcus* is the most common organism causing pyomyositis
- Trauma, diabetes and HIV infection are the most common underlying conditions
- CT scan or MRI scan are the best imaging modalities for early diagnosis
- Management includes drainage of abscess and intravenous antibiotics.

REFERENCES

1. Christin L, Sarosi GA. Pyomyositis in North America: case reports and review. Clin Infect Dis. 1992;15:668-77.
2. Minami K, Sakiyama M, Suzuki H, et al. Pyomyositis of the vastus medialis muscle associated with *Salmonella enteritidis* in a child. Pediatr Radiol. 2003;33:492-4.
3. Mootsikapun P, Mahakkanukrauh A, Suwannaroj S, et al. Tuberculous pyomyositis. J Med Assoc Thai. 2003;86:477-81.
4. Hall RL, Callaghan JJ, Moloney E, et al. Pyomyositis in a temperate climate, presentation, diagnosis and treatment. J Bone Joint Surg Am. 1990;72:1244.
5. Ashken MH, Cotton RE. Tropical skeletal muscle abscesses (pyomyositis tropicans). Br J Surg. 1963;50:846-52.

CASE

15 Fever, Rashes and Breathlessness

HISTORY

A 20-year-old female who was diagnosed at district hospital as tubercular pleural effusion. She was started on anti-tubercular drugs and referred to us with complaints of persistent fever, rashes and breathlessness for 25 days. Her fever was of low grade, intermittent, with no chills, rigors or diurnal variation. Breathlessness progressed in severity over the time. She gave significant past history of seizure disorder since childhood and was on carbamazepine since 10 years. She denied history of abdominal distention, joints pain or altered bowel and bladder habits.

EXAMINATION

Her physical examination revealed blood pressure 120/70 mm Hg, pulse 86 beats per minute, temperature 38°C. Breath sounds were decreased on left base of lung. Maculopapular rash over back of trunk and lower extremities were noted (Figure 15.1). Cardiovascular and abdomen examinations were normal.

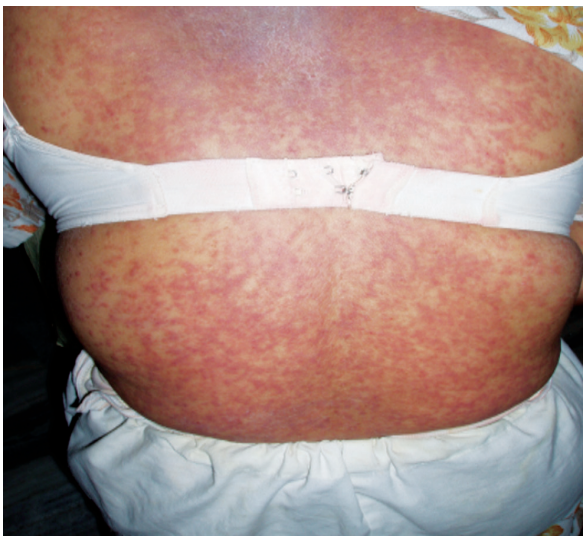


Figure 15.1 Extensive maculopapular rashes over back)

Table 15.1 Investigations chart

Parameters	*Patient's value*	*Normal range*
Hemoglobin	10 gm/dL	13–17 gm/dL
Total leukocyte count	2,200 cumm	4,000–10,000/uL
Differential leukocyte count (DLC)	N67, L13, E20	–
ESR	75 mm/1st hour	< 11 mm
Total bilirubin	1.2 mg/dL	0.1–1 mg/dL
Total protein/albumin	6.6/3.6 mg/dL	6–8.3/3.4–5.4 mg/dL
AST/ALT/gamma-glutamyl transferase (GGT)	252/133/114 IU/L	0–40/0–34 IU/L
Serum creatinine	0.8 mg/dL	0.6–1.3 mg/dL
Vitamin B_{12} and folic acid	Normal	–

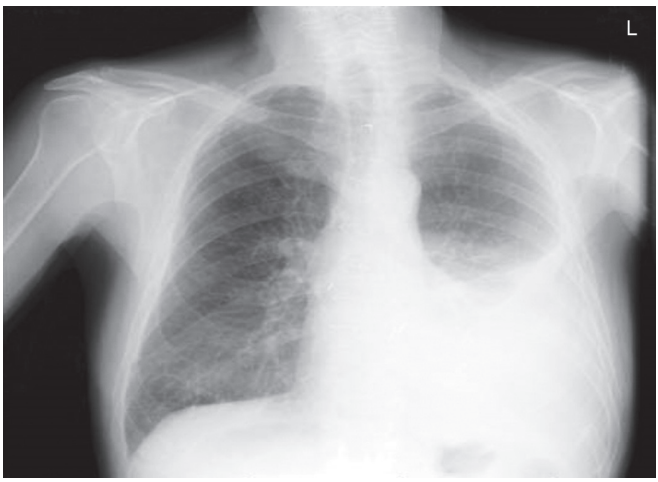


Figure 15.2 Chest X-ray showing left pleural effusion

Investigations are shown in Table 15.1. Chest X-ray done showed moderate left pleural effusion as shown in Figure 15.2.

FURTHER FOLLOW-UP

Bone marrow aspiration and biopsy were performed which showed maturation arrest probably drug induced. Mantoux and Quantiferon TB gold tests were negative. Her antinuclear antibodies were positive (homogeneous pattern) and Extractable nuclear antigens came positive for anti-histone antibodies while anti-ds-DNA was negative. Complement C3 and C4 were in normal range. Twenty-four hours urinary protein was high (592 mg/24 hours). Serum carbamazepine assay was 23.3 mcg/mL (therapeutic normal range: 4–12 mcg/mL) which was high. CECT thorax and abdomen revealed left pleural effusion and pleural thickening. Left pleural fluid analysis showed exudative fluid, negative for AFB, Grams and KOH stain. Adenosine deaminase (ADA) of pleural fluid was normal.

1. What is the diagnosis?

Ans. This patient had rash, exudative pleural effusion, leukopenia, eosinophilia, bone marrow–maturation arrest, ANA and anti-histone positive, anti-ds-DNA negative and high carbamazepine drug level. This was suggestive of carbamazepine induced lupus erythematosus.

TREATMENT OFFERED

Her carbamazepine and anti-tubercular drugs were stopped with immediate effect. She was started on oral prednisolone 40 mg per day which was tapered off at later stage. Her anticonvulsant drugs were changed to oral levetiracetam 500 mg thrice daily along with clobazam 10 mg–5 mg–20 mg. With above line of management her fever and pleural effusion got relieved. One year of follow-up visits showed that she is doing fine.

2. What is drug-induced lupus erythematosus?

Ans. Drug induced lupus is a variant of systemic lupus erythematosus that resolves within days to months following withdrawal of that culprit drug in a patient with no underlying immune system dysfunction. It is generally equally common in males and females and more common in older population.[1,2] It usually develops within 7 to 21 days after a drug is started. It can arise months to years after exposure to drugs prescribed to treat various medical conditions. Most common drugs implicated are procainamide, hydralazine and quinidine. However, drugs like carbamazepine, isoniazid, propylthiouracil methyldopa, diltiazem, minocycline, sulfasalazine, phenytoin, lithium and hydrochlorothiazide have low propensity towards causing lupus erythematosus.[3]

For proper diagnosis, the following factors should be preliminary confirmed:

- The patient has 1 or more clinical symptoms of SLE (arthralgias, lymphadenopathy, rashes, fever)
- The patient had no history of SLE before starting the culprit drug
- Antinuclear antibodies are present
- The drug was taken anytime from 3 weeks to 2 years prior to the appearance of symptoms
- Clinical improvement is rapid when the drug is discontinued, whereas antinuclear antibodies and other serological markers slowly decrease towards normal levels.

3. What are the clinical features of drug induced lupus erythematosus?

Ans. Most patients with drug induced lupus erythematosus have one or more symptoms of SLE, such as joint pain, rash, fever, lymphadenopathy with no previous history of autoimmune disease. Rashes are usually maculopapular and photosensitive. Butterfly rash across the bridge of nose and cheek can also occur. As many as 90% of patients can have severe, noninflammatory joint pain but sometime, synovitis can present. Approximately, 50% patients have constitutional symptoms like fever, weight loss and fatigue. In general, absence of involvement of central nervous and renal system indicates toward drug induced lupus than SLE.

Extracutaneous physical findings are splenomegaly, hepatomegaly, pleurisy, fever and cerebritis, nephritis and episcleritis are rare.

Although differentiating drug induced lupus from SLE may be difficult. Table 15.2 gives difference between SLE and drug induced lupus erythematosus (DILE).

Table 15.2 Differences between SLE and DILE

Findings	*SLE*	*DILE*
Clinical		
Age of onset	20–30 years	50–70 years
Race affected	Black more than white	White more than black
M:F	1:9	1:1
Renal and CNS involvement	Very often	Rare
Laboratory		
Antihistone antibodies	50%	> 95%
Anti-ds-DNA	80%	Anti-ss-DNA present
C3/C4 levels	Decrease	Normal
ANA	>95%	>95%
Immunofluorescence	Granular deposition of IgG at dermatoepidermal junction	Same as SLE
Histopathology	Lymphohistiocytic interface dermatitis	Same as SLE

4. How will you treat drug induced lupus?

Ans. Symptoms of drug induced lupus erythematosus generally disappear within weeks of stopping the culprit drug; however, residual antibodies may persist for extended periods after discontinuance of the identified causative agent. Low doses of systemic corticosteroids may be prescribed for short periods if the symptoms of DILE are severe regular monitoring of anti-ss-DNA, anti-ds-DNA, anti-histone antibody levels, serum complement levels, and urinalysis findings are recommended. Continue to monitor cardiac, renal, and pulmonary function if any of these were initially involved.

FINAL DIAGNOSIS

Carbamazepine induced lupus erythematosus.

LEARNING POINTS

- The drug induced lupus erythematosus is a rare entity
- Most common implicated drugs are procainamide and hydralazine
- Renal and CNS involvement rarely occur
- Antihistone antibodies are often found positive
- Withdrawal of culprit drug and low dose systemic corticosteroids is the prescribed treatment.

REFERENCES

1. Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. Ann NY Acad Sci. 2007; 1108:166.
2. Vasoo S. Drug-induced lupus: an update. Lupus. 2006;15:757.
3. Fritzler MJ. Drugs recently associated with lupus syndromes. Lupus. 1994;3(6):455-9.

CASE

Severe Pain Abdomen with Rash

16

HISTORY

A 27-year-old, male presented with complaints of history of high-grade fever for 5 days along with worsening abdominal pain for 2 days. Fever was high-grade, continuous, associated with chills and rigors. There was history of headache and retro-orbital pain with severe myalgias. Pain abdomen was in the epigastric region. It had worsened over 2 days, was radiating to back and, was associated with nausea and vomiting. He also had abdominal distension and complained of reddish rash all over the body. There was no history of alcohol intake, abdominal surgery or other chronic illness. There was no bleeding from any site.

EXAMINATION

Patient was dehydrated, febrile with tachycardia and tachypnea. There was icterus. No pallor, cyanosis lymphadenopathy was seen. Blanching macular rash was present all over the body. No petechiae or purpura were seen. Blood pressure was 90/60 mm Hg. Abdomen was distended, umbilicus was everted with diffuse tenderness and guarding. Bowel sounds were sluggish. There was decreased air entry in chest. Cardiovascular and central nervous systems were within normal limits (Figure 16.1). Table 16.1 enumerates investigation for this patient.

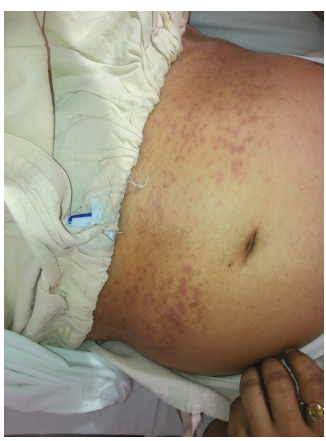


Figure 16.1 Maculopapular rash over abdomen

Table 16.1 Initial laboratory investigation

Parameters	*Patient's value*	*Normal range*
Hemoglobin	9.9 gm%	13–16 gm%
WBC	3,600 cumm	4,000–10,000 cumm
Platelets	30,000	1.5–4 lakh
Bilirubin (T)/(D)	5.3/3.3 mg/dL	0.1–1.2 mg/dL
AST/ALT	51/104 IU/L	5–40/7–56 IU/L
S. protein/Albumin	4.7/2.3 gm	5.6–8.5/3.5–5.5 gm/dL
Amylase/Lipase	506/808	<100 IU/< 50 IU
Blood glucose	303 mg/dL	<140 mg/dL
S. creatinine	1.7 mg/dL	0.6–1.3 mg/dL
S. calcium	7.2 mg/dL	9–11 mg/dL
S. triglyceride	117 mg/dL	80–150 mg/dL
Na/K	132/2.8 mEq/dL	135–145 /3.5–5.5
USG abdomen	Bulky pancreas	

1. What is the diagnosis?

Ans. Patient had abdominal pain and elevated amylase and lipase suggestive of acute pancreatitis and in addition had exanthematous fever etiology of this was under investigation.

FURTHER WORK-UP

Patient underwent contrast-enhanced CT of abdomen which was suggestive of reduced parenchymal enhancement of pancreas with heterogeneous enhancement and air mottled lucency in the body and tail of pancreas and in peripancreatic region suggestive of emphysematous pancreatitis (Figures 16.2 and 16.3).

His viral markers (HBsAg/Anti-HCV/CMV) were negative. Blood and urine cultures were sterile. His dengue antigen and serology (NS1 antigen and IgM) were positive. Malarial serology was negative. Patient was admitted in the ICU and managed with non-invasive ventilation, antibiotics, IV fluids and other supportive treatment. Platelets were monitored and transfused as required. Nasojejunal (NJ) tube was inserted and nutrition was managed with NJ feed. Patient continued to have high-grade fever and developed dyspnea. Repeat CT scan was done which showed emphysematous pancreatitis with collection in lesser sac. The X-ray showed bilateral pleural effusion. Thoracocentesis showed transudative fluid. Patient underwent pancreatic necrosectomy and peritoneal fluid revealed *Klebseilla* which was managed according to culture and sensitivity report. Postoperatively patient gradually improved.

2. What are the causes of pancreatitis?

Ans. Gallstone disease and alcohol consumption are the most common causes of pancreatitis. The important causes are as follows:

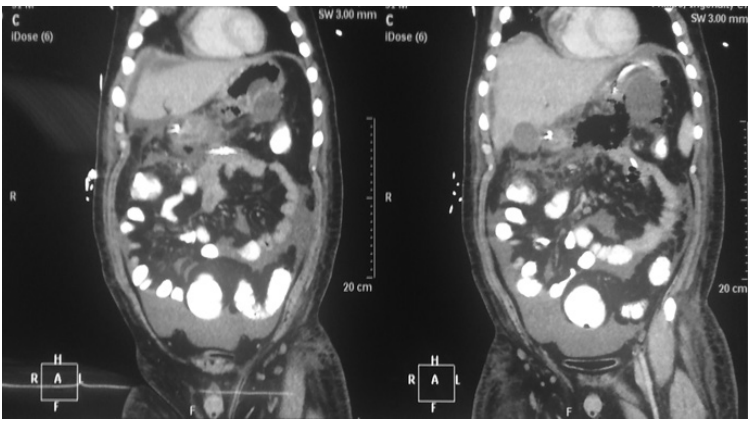


Figure 16.2 CT scan of abdomen depicting air-mottled lucency in pancreas

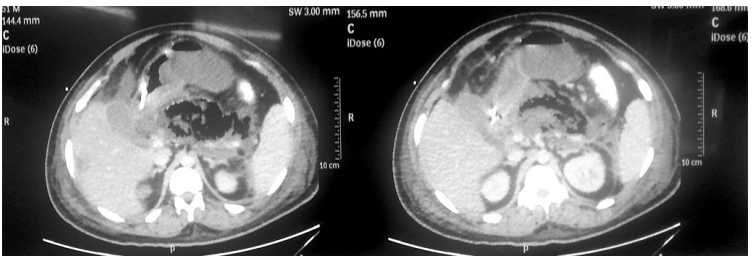


Figure 16.3 Emphysematous pancreatitis

- *Common causes*:
  - Gallstones
  - Alcohol
  - Hypertriglyceridemia
  - Endoscopic retrograde cholangiopancreatography (ERCP)
  - Blunt trauma
  - Drugs—azathioprine, sulphonamides, estrogens, tetracycline, valporic acid, anti-retroviral drugs
  - Postoperative
  - Sphincter of Oddi dysfunction
- *Rare causes*:
  - Connective tissue disorders
  - Hypercalcemia
  - Periampullary diverticulum
  - Pancreatic malignancy
  - Cystic fibrosis
  - Infections (Mumps, CMV, dengue, echovirus)

3. What are the clinical manifestations of dengue fever?

Ans. Dengue is caused by four flavivirus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4). Unfortunately, the incidence of dengue fever (DF) and dengue hemorrhagic fever (DHF) has increased thirty-fold globally over the last few

decades. In India, unplanned urbanization and migration of population from rural to urban areas with lack of proper sanitation facilities are important factors resulting in increased burden of dengue in recent times. Dengue can present as classical dengue fever or dengue hemorrhagic fever or dengue shock syndrome.

Classical dengue: All ages are susceptible to dengue fever. It is characterized by incubation of 3–10 days. The onset is sudden with chills and high fever, intense headache, myalgias joint pains, and retro-orbital pain. There is accompanying rash in 80% patients, which is diffuse maculopapular or scarlatiniform with flushing, mottling or fleeting pin point eruptions on the face, neck and chest seen on 3rd or 4th day. It may be accompanied by itching.

Dengue hemorrhagic fever (DHF): It is a severe form of dengue, caused by infection with more than one dengue virus. Dengue shock syndrome is a more severe form of the disease characterized by shock and hemoconcentration. DHF is characterized by four major clinical features: high fever, hemorrhagic phenomenon, hepatomegaly and signs of impending circulatory failure (postural hypotension, resting tachycardia, sweating). Laboratory manifestations show significant thrombocytopenia with hemoconcentration. The patients with excessive plasma leakage and hemoconcentration are called dengue shock syndrome.

The disease may sometimes present as acute acalculous cholecystitis, hepatitis, edematous gallbladder wall on ultrasonography, serositis involving pleural and abdominal cavity, fulminant hepatic failure, splenic rupture, acute renal failure or neurological manifestations including intracranial bleeding, seizures and myelitis.

4. What is Ranson's criteria for pancreatitits?

Ans. To determine the prognosis, the Ranson's criteria is commonly used:

At time of diagnosis	*In 48 hours*
Age > 55 years	Decreased hematocrit > 10%
Leukocyte > 16,000/mm^3	Decreased blood urea nitrogen (BUN) > 5 mg/dL
Glucose > 200 mg/dL	Calcium < 8 mg/dL
LDH > 350 IU/L	PO_2 < 60 mm Hg
AST > 250 U/L	Base deficit > 4 mEq/L

5. Can dengue fever cause pancreatitis?

Ans. Pancreatitis associated with dengue fever is rare. We excluded common causes of acute pancreatitis in our patient by history, laboratory examination and imaging. There are very few reported cases of dengue infection complicated with acute pancreatitis. The diagnosis of acute pancreatitis depends on elevated serum amylase and lipase greater than three times the upper limit of normal after excluding perforation and infarction. The average time to diagnose pancreatitis in dengue fever is 7 days. The principal hemorrhagic phenomena of dengue fever include epistaxis, gum bleeding and mucosal bleeding from gastrointestinal tract, these could be hemorrhagic gastritis, gastric or duodenal ulcer. Therapy

for acute pancreatitis in dengue fever is not different from those without dengue infection. It is important to monitor the fluid status and replace fluid deficiency timely because of fluid sequestration, in third space, caused by both pancreatitis and dengue hemorrhagic fever.

6. What is the timing for pancreatic necrosis?

Ans. The first 2 weeks after onset of symptoms are characterized by systemic inflammatory response syndrome (SIRS). Pancreatic necrosis develops in first four days after onset of symptoms to its full extent. Infection in pancreatic necrosis develops most frequently in 2nd and 3rd week. Infection of pancreatic necrosis is the major risk factor of sepsis-related multiorgan dysfunction and main life-threatening complication in later phase of acute pancreatitis.

Treatment of acute pancreatitis in early phase is solely conservative. The development of infection of necrosis is main determinant of mortality and morbidity in late phase of severe pancreatitis. The indication of surgery in pancreatic necrosis is infected necrosis, non-improving sterile necrosis or rapidly progressive multiple organ dysfunction syndrome (MODS). The accepted time for surgery in severe pancreatitis is as late as possible and ideally postponed four weeks after onset of symptoms. The rationale for late surgery is the ease of identifying well demarcated necrotic tissue from viable parenchyma and thus limiting the extent of surgery to pure debridement. This approach decreases the risk of bleeding and minimizes the surgery related loss of vital tissue which leads to surgery induced endocrine and exocrine pancreatic insufficiency.

FINAL DIAGNOSIS

Dengue fever with emphysematous pancreatitis.

LEARNING POINTS

- Dengue fever is an arboviral infection which is a major public health problem in subtropical and tropical countries.
- Dengue fever may present with atypical manifestations.
- Acute pancreatitis is underdiagnosed in dengue fever due to delayed diagnosis with consequent normalization of amylase and lipase.
- Management of acute pancreatitis due to dengue fever remains same as of non-infected pancreatitis.

BIBLIOGRAPHY

1. Dezieland DJ, Doolas A. Pancreatic abscess and pancreatic necrosis: current concepts and controversies. Problems in General Surgery. 1990;7(3):415-27.
2. Sharma SK, Gupta BS, Devpura G, Agarwal A, Anand S. Pulmonary haemorrhage syndrome associated with dengue haemorrhagic fever. JAPI. 2007;55:729-30.
3. Widdison L, Karanjia ND. Pancreatic infection complicating acute pancreatitis. British Journal of Surgery. 1993;80(2):148-54.
4. World Health Organization. Regional office for South-East Asia [homepage on Internet]. New Delhi: Trend of Dengue cases and CFR in SEAR Countries. c2009 [cited 2009 October 23].

CASE

17 Right-sided Weakness and Rash

HISTORY

A 22-year-old female was admitted with complaints of sudden onset of weakness of right side of body for two hours. Her weakness started simultaneously in both right upper and lower limbs and she also confirmed deviation of angle of mouth at the same time. On further questioning, she gave history of rash on and off on hands and feet for 3 months and limping of left lower limb which started two months ago. She had been investigated outside for rashes and limping and was informed that she had allergic rashes and limping is due to nerve weakness for which she was given intravenous steroids. Although her limping improved completely after therapy, rashes persisted. She denied loss of consciousness, abnormal movements of limbs, unusual sensations over body, chest pain, palpitation, breathlessness, abdominal pain, decreased urine output or abnormal bowel movements.

EXAMINATION

Physical examination revealed blood pressure 130/68 mm Hg; pulse 74 beats/minute, regular, normal in character and temperature 37°C. Papular rashes were noted over hands and feet (Figure 17.1). She was conscious and oriented. Muscle power was 3/5 on right sided limbs and deep tendon reflexes were hyporesponsive

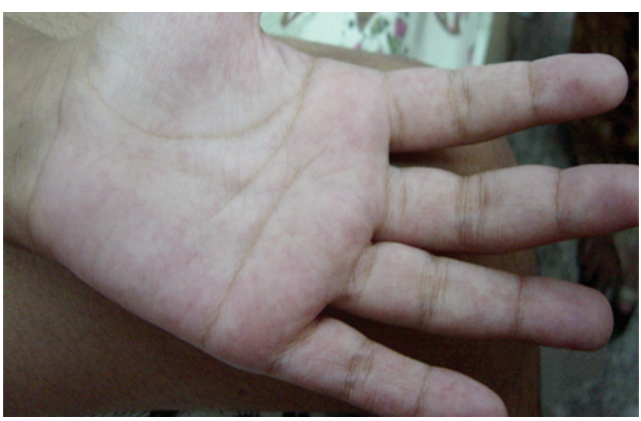


Figure 17.1 Papular rashes over left palm

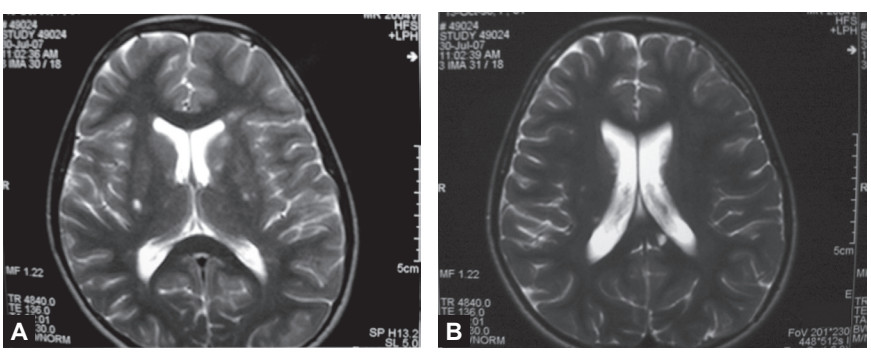
Table 17.1 Initial laboratory work-up

Laboratory tests	*Results*	*Normal range*
Hemoglobin	11.9 gm/dL	12–16 gm/dL
Total leukocyte count	9,500 cumm	4,000–10,000 cumm
Platelet	2.33 lakh cumm	1.5–4.5 lakh cumm
ESR	20 mm/1st hour	0-10 mm/1st hour
AST/ALT/GGT	33/42/46 IU/L	0-42/0-60/0-64 IU/L
S. creatinine	0.8 mg/dL	0.6–1.2 mg/dL
CPK	3,892	22–195 IU/L
Urine R/M	Normal	
HIV antibody	Non-reactive	
Blood culture (3 samples)	Sterile	
Urine culture	Sterile	

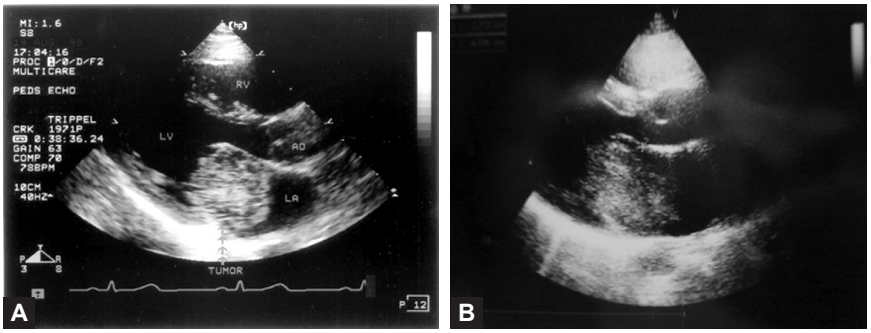
in both right upper and lower limbs. Extensor plantar reflex was noted on right side. Ophthalmoscopic examination was within normal limit. There was no organomegaly on abdominal examination. Chest and cardiovascular examination were normal. Investigations are charted in Table 17.1.

FURTHER WORK-UP

Her chest X-ray was normal. Ultrasound abdomen revealed scar on superior pole of right kidney. MRI brain was consistent with left middle cerebral territory infarct. Her ANA, anti-dsDNA antibody, complement levels, anti-phospholipid antibodies, and antiproteinase 3 were negative. Nerve conduction study revealed left median motor axonal involvement and left sural sensory involvement with chronic neurologic changes. Figures 17.2A and B show infarct in left middle cerebral artery (MCA) territory.



Figures 17.2A and B Infarct in left middle cerebral artery territory



Figures 17.3A and B 2D echocardiogram showing left axial myxoma

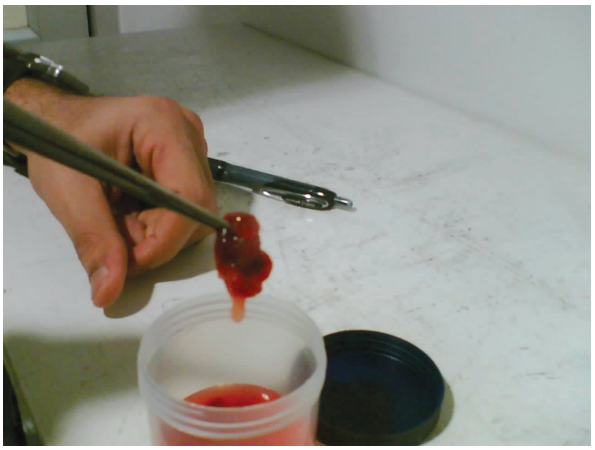


Figure 17.4 Specimen of left atrial myxoma

This patient had purpuric rashes, myalgia and arthralgia, brain infarct, neuropathy, with negative autoimmune profile. 2D echocardiogram done showed left atrial myxoma (Figures 17.3A and B).

She was immediately started on low molecular weight heparin, anticonvulsant, along with other supportive management following confirmation of infarct on MRI scan. Patient showed improvement in neurological status in the subsequent week. She was operated for left atrial myxoma at a later stage (Figure 17.4). Histopathology confirmed the diagnosis and her follow-up echocardiogram showed no cardiac abnormality.

1. **What are the sources of cardioembolic stroke?**

Ans. Cardiogenic emboli accounts for 20% of acute stroke. Sources of cardioembolic embolisms are valvular disease, left atrial thrombi, left ventricular thrombi, cardiac tumors and paradoxical emboli.

Left atrial thrombi: The leading cause of cardioembolic stroke is atrial fibrillation, especially in elderly cohort. Formally, associated with rheumatic disease, atrial fibrillation is now more commonly attributed to

hypertension and ischemic heart disease.[1] Atrial flutter is another source of left atrial thrombi leading to embolic stroke.

Valvular diseases: Mitral stenosis, infective endocarditis, prosthetic valve, marantic endocarditis, aortic stenosis, bicuspid aortic valve and inflammatory valvulitis are major risk factor for cardioembolic stroke.

Left ventricular thrombi: Myocardial infarction, ischemic heart disease and cardiomyopathy contribute to cardioembolic stroke.

Cardiac tumors: Atrial myxomas, cardiac sarcomas and metastatic disease are linked with cardioembolic stroke.

Paradoxical emboli: Paradoxical emboli are rare causes of embolic stroke where emboli arise from right sided circulation with subsequent passage through patent foramen ovale, atrial and ventricular septal defect.[2]

2. What is the basic work-up in a patient with cardioembolic stroke?

Ans. Emergency neuroimaging is essential for confirming the diagnosis of stroke. Non-contrast CT scanning is the most commonly used imaging for evaluation of patient with acute stroke. MRI scan can provide structural details as well as it can also detect early cerebral edema. Carotid duplex is one of the most useful tests in evaluation of patient with stroke. Not only carotid duplex can demonstrate the cause of emboli but also, it helps to stratify the patients for early medical management or for carotid intervention, if carotid stenosis is present. Digital subtraction angiography is the definite method for detecting vascular lesions including stenosis, occlusions, and aneurysms.

Extensive laboratory testing is not usually required for making decision for fibrinolysis. Testing is limited to complete blood counts, coagulation profile, basic biochemistry and blood glucose level.

3. What is atrial myxoma?

Ans. Atrial myxomas are most common primary heart tumors. They are more common in females in sporadic cases and they have been reported in patients aged 3 to 83 years. Approximately, 75 to 85% atrial myxomas occur in left atrial cavity and most of them are solitary and pedunculated. Around 10% cases are familial and transmitted in autosomal dominant mode.

4. What are the symptoms of left atrial myxoma?

Ans. Symptoms are produced by mechanical interference with cardiac function or by embolization. Embolization occurs in 30 to 40% of patients with left atrial myxoma. Left atrial myxoma produce symptoms when it weighs more than 70 gm or at least 13 cm wide. Surgical resection of myxoma is the treatment of choice but it can recur especially in familial cases.

Symptoms of left atrial myxoma are:

- Shortness of breath, palpitation
- Fever
- Weight loss
- Joint pains
- Raynaud's phenomenon
- Embolism to brain, eye, limb
- Syncope

Complications such as pulmonary edema, arrhythmia, stroke and cerebral aneurysm have been reported. Sudden deaths have been reported due to right atrial myxoma. Rare case reports of right atrial myxoma causing neuropathy and also rash over hands as in our case have been reported.

FINAL DIAGNOSIS

Left atrial myxoma with embolic episodes.

LEARNING POINTS

- Myxomas are the common type of primary heart tumors.
- "Tumor Plop" is audible sound as the mass passes through AV valve.
- Embolic symptoms are seen in up to 40% of cases.
- Myxoma may mimic vasculitis due to its constitutional symptoms.
- Surgically a resection of myxoma is the treatment of choice.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.
2. Arboix A, Alio J. Acute cardioembolic cerebral infarction: answers to clinical questions. Curr Cardiol Rev. 2012;8(1):54-67.

CASE

Recurrent Episode of Purpuric Rash

18

HISTORY

A 36-year-old male, presented in year 2000 with a purpuric rash all over the body. There was no history of any drug ingestion or fever prior to this episode. He was diagnosed a case of immune thrombocytopenic purpura (ITP). Test for HIV, Hepatitis C and ANA were negative. A bone marrow aspiration and biopsy was done at the time of diagnosis and it showed cellular marrow with megakaryocytic prominence. He was given steroid pulse therapy followed by oral steroids. He was lost to follow-up for next 1 year.

Next time, he presented to us in 2002 with complaints of recurrent petechial hemorrhages and excessive bruising. He had taken oral glucocorticoids for 9 months last time and then left. Platelet counts were 15,000 cumm that time (Table 18.1). With a diagnosis of relapse of this illness he was given methyl prednisolone pulse therapy (500 mg/d for 3 days) followed by tapering oral glucocorticoids for about 3 months, with which there was initial improvement in his condition. He was doing well for about 9 months, after which there was a recurrence of ITP symptoms in 2004.

EXAMINATION

On clinical examination, patient was alert and conscious. His pulse was 80 beats/min and blood pressure was 130/80 mm Hg. There was no pallor,

Table 18.1 Values of laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	14.4 gm/dL	13–17 gm/dL
Total leukocyte count	6,100/uL	4,000–10,000/uL
Platelet count	15,000/uL	1.5–4.5 lakh/uL
Erythrocyte sedimentation rate (ESR)	4 mm	<13 mm
Blood urea nitrogen (BUN)/S. creatinine	18.1/0.9 mg/dL	5–23/0.6–1.3 mg/dL
Asparate aminotransferase (AST)/alanine aminotransferase (ALT)	20/30 IU/L	0–40/0–34 IU
Peripheral smear	Severe thrombo-cytopenia, no abnormal cell	

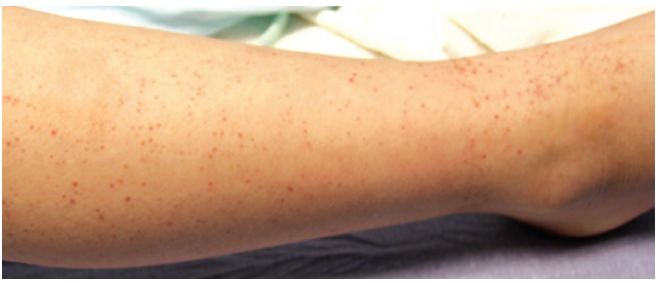


Figure 18.1 Petechial hemorrhagic rash

cyanosis and edema. There were petechial hemorrhages all over his body (Figure 18.1). Systemic examination was unremarkable.

FURTHER HISTORY

Patient was given steroid pulse therapy, which failed. He was given multiple platelet apheresis. He was vaccinated pneumococcal, meningococcal and influenza and subsequently given intravenous immunoglobulin. After this there was steady increase of platelets for three weeks and then there was a falling trend. The patient underwent splenectomy in early part of 2006 as he had multiple episodes of minor bleeds and he was unable to sustain platelet counts.

The patient did well for 1 year after which he started having purpuric rash again. The platelet count had fallen to 11,000/uL. Ultrasound of abdomen did not reveal any enlarged spleen. As platelet counts didn't improve, technetium labeled RBC scan was done which showed an accessory spleen in the sub-diaphragmatic region of left hypochondrium. Laparoscopically removal of accessory spleen was done in 2007.

However, this also did not help to improve his condition. The patient had another episode of relapse this time in the form of ecchymotic patches all over the body. The patient was started on rituximab infusions. A total of 4 infusions, once every week in the dose of 500 mg/intravenously of rituximab were given. The patient showed a gradual improvement in his condition. At the end of 6 weeks, his platelet counts had gone up to 80,000 cells/uL.

He was followed up regularly for a period of 24 months, his platelet count increased and were in the range of 40 to 90,000 cells/uL.

1. What are the causes of thrombocytopenia?

Ans. Thrombocytopenia can occur because of damage to bone marrow, destruction of platelets in blood circulation, phagocytosis in spleen or combination of above causes.[1]

The causative conditions that don't allow bone marrow to manufacture platelets are leukemia, lymphoma, chemotherapy or radiotherapy for cancer treatment, aplastic anemia, toxins exposure (pesticides, arsenic, benzene), medicines (chloramphenicol, NSAIDs, etc.), alcohol, viruses (chicken pox, mumps, rubella, parvovirus, Epstein-Barr virus), vitamin B_{12} or folate deficiency and certain rare inherited conditions (Wiskott-Aldrich, May-Hegglin syndromes).

Destruction of platelets occur in autoimmune conditions (ITP, SLE), infections (bacterial sepsis, mononucleosis), pregnancy, intravascular thrombosis and with use of medicines (vancomycin, rifampin, heparin).

Enlarged spleen as seen in chronic liver disease, myelofibrosis causes thrombocytopenia.

2. How do we diagnose immune thrombocytopenia purpura (ITP)?

Ans. The diagnosis of ITP is based on history, physical examination and complete blood counts.

- *History:* Isolated bleeding symptoms consistent with thrombocytopenia without constitutional symptoms
- *Physical examination:* Bleeding symptoms in the absence of palpable liver, spleen or lymph nodes
- *Complete blood count:* Isolated thrombocytopenia (platelet count <100 $\times 10^9$/L). Anemia only if due to significant bleeding—otherwise normal WBC counts
- *Peripheral blood smear:* Normal smear with no abnormal cells.

3. When should bone marrow examination be done in ITP?

Ans. Marrow is unnecessary in patients with the typical features of ITP. The presence of abnormalities in the history, physical examination, or the complete blood count and peripheral blood smear should be further investigated, with a bone marrow examination or other appropriate investigations, before the diagnosis of ITP is made.

4. What is refractory immune thrombocytopenia purpura?

Ans. The International Working Group defines immune thrombocytopenia purpura as newly diagnose acute if it is less than 3 months from diagnosis, persistent if it is 3 to 12 months from diagnosis or chronic if it is lasting for more than 12 months.[2] Refractory ITP is defined as the presence of severe ITP occurring after splenectomy.

5. What are the clinical features of immune thrombocytopenia purpura?

Ans. Often, thrombocytopenia is asymptomatic and is picked up on routine investigations. Mild thrombocytopenia doesn't cause any problem. Moderate to severe thrombocytopenia can present with petechiae or purpura. Purpuras are purple, brown, and red bruises. Petechiae are small red or purple dots on skin. ITP can also present with prolonged or heavy bleeding from minor cuts, spontaneous bleeding from nose, mouth or abnormal heavy menstrual bleeding. Internal bleeding is usually more severe and serious as patient doesn't manifest till its massive or has damaged the organ.

6. What is the treatment of immune thrombocytopenia purpura?

Ans. According to recent ASH (American Society of Haematological guidelines), patients with platelet counts greater than 50,000/uL don't require treatment. Treatment is indicated only with platelet counts less than 30,000/uL or with significant mucous membrane bleeding (or presence of risk factors as hypertension) and platelet counts less than 50,000/uL.

First-line treatment includes observation, corticosteroids, IVIg, or anti-D immunoglobulin (anti-D). Anti-D should be used with caution because of severe hemolysis. It is, therefore, not advised in patients with bleeding causing a decline in hemoglobin, or those with evidence of autoimmune hemolysis. Table 18.2 gives some special consideration for adults ITP.

Initial therapy should be with high dose glucocorticoids or IVIg (1 gm/kg) therapy.[3,4]

In patients with ITP and intact spleen with Rh antigen positive Rho immunoglobulin (RhIG) offers comparable efficacy.[5]

Next approach should be splenectomy in failure cases. Before splenectomy is done, patient should be vaccinated with pneumococcal vaccine, influenza vaccine and meningococcal vaccine. Splenectomy is often appropriate if platelet counts remain below 30,000 after 4 to 6 weeks of medical treatment.

If still patient doesn't respond rituximab, azathioprine, danazol can be tried. Nowadays, thrombopoietin receptor agonist (Eltrombopag) is also available for patients with chronic ITP.

Table 18.2 Special consideration for adults ITP (American Society of Hematology, 2011 evidence-based practice guideline)

- Treat patients with a platelet count < 30 x10^9/L
- Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg.
- IVIg may be used along with corticosteroids if a more rapid increase in platelet count is required.
- Either IVIg (1 gm/kg for one dose) or anti-D (in appropriate patients) may be used as a first-line treatment if corticosteroids are contraindicated.

FINAL DIAGNOSIS

Resistant immune thrombocytopenic purpura.

LEARNING POINTS

For resistant ITP following can be considered:

- *Splenectomy:* Recommended for adults who have failed corticosteroid therapy, with similar efficacy with open or laparoscopic procedures.
- *Rituximab:* May be considered for patients with risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy.
- *Thrombopoietin receptor agonists:* Recommended after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy.

REFERENCES

1. *www.mayoclinic.org/diseases-conditions/thrombocytopenia/basics/causes/con-20027170. Accessed on 13/1/2014 at 12:00PM.*
2. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113(11):2386-93.
3. Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. Blood. 2007;109(4):1401-7.
4. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet. 1981;1(8232):1228-31.
5. Sandler SG. Treating immune thrombocytopenic purpura and preventing Rh alloimmunization using intravenous rho (D) immune globulin. Transfus Med Rev. 2001;15(1):67-76.

CASE

19

High Grade Fever with Pneumonia

HISTORY

A 25-year-old male, presented with complaints of high grade continuous fever for 10 days associated with chills. He also complained of myalgia and throbbing headache along with cough and mucoid colored sputum. There was no breathlessness. He was being treated outside with intravenous antibiotics with no relief of symptoms. Patient was referred to us because of persistent fever and cough. Chest X-ray was showing right basal pneumonia (Figure 19.1). He gave history of trekking in jungle 2 weeks back. There was no history suggestive of insect bite.

EXAMINATION

Patient was febrile with temperature of 103°F. There was tachycardia and tachypnea. There was conjunctival congestion with left inguinal non-tender lymphadenopathy (1.5 × 1.5 cm). There was no pallor, jaundice or edema. There was decreased air entry on the right side basal region.

Local examination: There was an eschar in the form of a small painless ulcer with scab on the lower back (Figure 19.2). Generalized macular patches.

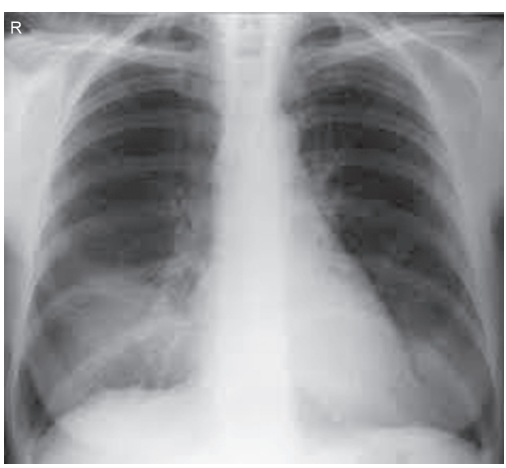


Figure 19.1 X-ray (chest) PA showing right-sided LZ pneumonias

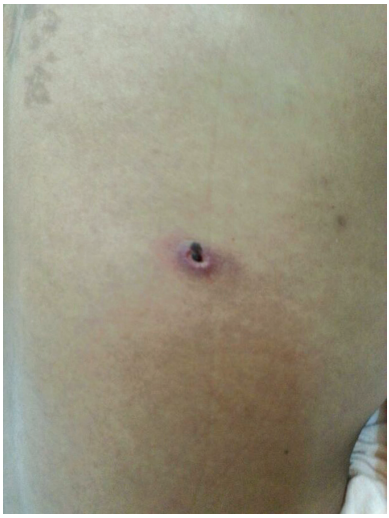


Figure 19.2 Eschar on lower back measuring 12 mm

INVESTIGATIONS

For high grade fever and other systemic complaints patient was investigated (Table 19.1).

Table 19.1 Value of laboratory investigation

Parameters	*Patient's value*	*Normal value*
Hemoglobin	10.5 gm%	13–16 gm%
WBC	12,400/cumm (50% neutrophils)	4,000–10,000/cumm
Platelet	30,000 uL	1.5–4 lakh
ESR	38 mm	0–8 mm
Total bilirubin	1.7 mg/dL	0.1–1 mg/dL
Serum creatinine	0.68 mg/dL	0.6–1.3 mg/dL
Total protein/albumin	5.6/2.5	6–8.3/3.4–5.4 mg/dL
AST/ALT	155/138	0–40/0–34 IU/L

Other Investigations

- Blood and urine culture—sterile
- Dengue (IgM and NS1Ag)—negative
- Malaria (peripheral smear)—negative
- Mycoplasma serology—negative
- Leptospira serology—negative
- Scrub typhus (IgM)—positive
- *Weil-Felix agglutination test:* Titers of 1:640 to Proteus OX-K antigen.

1. **How do we diagnose scrub typhus?**

Ans. Scrub typhus is an acute, febrile, infectious illness that is caused by *Orientia tsutsugamushi* (previously *Rickettsia tsutsugamushi*). The name is derived from the type of vegetation (i.e. terrain between woods and clearings) that harbors the vector. The diagnosis is suggestive by clinical features and supported by serology.[1]

CLINICAL DIAGNOSIS

After incubation period of 6 to 21 days the onset of disease is manifested by high grade fever, intense generalized headache, diffuse myalgias. History of travel to endemic areas is often present. History of chigger bite is mostly unnoticed as it is painless and in many patients rash and an eschar at the site of the chigger (larval stage of trombiculid mite) bite goes unnoticed.

Physical findings includes an chigger bite mark in most cases called eschar. Eschar is pathognomic of scrub typhus. It begins initially as a small papule at the site of infection which enlarges followed by central necrosis and scab formation with erythematosuss halo, which is called eschar. It is often seen on the trunk but can occur on face, neck and perineum. Bites are often found at sites where skin surfaces meet clothes, such as the axilla, groin, neck, waist, and inguinal area. Other physical findings includes regional or generalized tender lymphadenopathy, macular rash and conjuctival congestion.[1]

LABORATORY DIAGNOSIS

- *Blood counts:* Normal WBC or leukocytosis may be seen. Thrombocytopenia may occur.
- *Liver function tests:* Elevated transaminases may be seen in 75 to 95% of patients. Hypoalbuminemia occurs in about half the cases. Hyperbilirubinemia is not uncommon.
- *Renal function tests:* Creatinine may be elevated in severe cases.
- *Chest X-ray:* It may reveal pneumonitis, pleural effusion or bilateral infiltrates.
- *Ultrasound abdomen:* It may reveal liver or spleen enlargement.

Serology

Serologic testing for antibodies is the investigation of choice. The immunofluorescent assay (IFA) is the gold standard test for diagnosis. Indirect immunoperoxidase is a modification of the standard IFA that can be used with a light microscope and results are comparable to IFA. Infection is confirmed by 4 fold rise in titers between acute and convalescent serum samples. A single high titer with classic clinical features is considered a probable case.

Other tests include, ELISA for detection of IgM and IgG against *O. tsutsugamushi.* ELISA assays are sensitive and specific and yield quicker results. PCR (polymerase chain reaction) for *O. tsutsugamushi* can be used in skin rash biopsies and lymph node biopsies.

The Weil-Felix OX-K strain agglutination reaction can be used to aid in diagnosis of scrub typhus. It is cheapest and easily available test. However, this test lack sensitive and specific.

2. What are the complications of scrub typhus?

Ans. Complications of scrub typhus are as follows:

Pulmonary: Pulmonary involvement is a well-documented complication of scrub typhus infection. Interstitial pneumonia with or without vasculitis is the most common complication. Acute respiratory distress syndrome may develop in scrub typhus.

Cardiac: Cardiomegaly, which may be due to myocardial or pericardial involvement and is usually reversible. Complications such as palpitations and ventricular ectopics are rare during the acute phase of scrub typhus and developed usually during the second or third week of illness in untreated patients.

Abdominal: Scrub typhus also may involve other abdominal organs. It may cause gastrointestinal hemorrhage and acute renal failure. Splenic enlargement and gallbladder wall thickening are also reported.

Central nervous system: May cause meningoencephalitis. Other include tremors, nervousness, slurred speech, nuchal rigidity, or deafness during, the second week of the disease.

Hematological: Patients may present with disseminated intravascular coagulation (DIC). Patients with scrub typhus often exhibit leucopenia.

3. What are the risk factors for acquiring scrub typhus?

Ans. Behavioral factors have association with scrub typhus during an autumn epidemic season. Taking a rest directly on the grass, working in short sleeves, working with bare hands, and squatting to defecate or urinate posed the highest risks. Most cases in India are acquired through agricultural exposure. Travel activities like trekking, camping and rafting in endemic area is also associated with scrub typhus.[2]

4. How do we manage Scrub typhus?

Ans. Treatment should be inituated early in course of disease, based on presumptive diagnosis, to reduce mortality and morbidity.

- Doxycycline is the drug of choice.[3]
- The recommended treatment duration is 7 to 14 days. Treatment for less than a week is initially curative but may be followed by relapse.
- In case of small children and pregnant women, azithromycin is the drug of choice. It has been shown to have comparable efficacy when compared to doxycycline in a small trial.
- Rifampicin has also been used as an alternative drug. Importantly, it should not be used alone because of the risk of resistance. It has been used in combination with azithromycin.
- A combination therapy with doxycycline and rifampicin should be used in areas where there is poor response to doxycycline alone.[3]
- Antibiotic therapy brings about prompt disappearance of the fever and dramatic clinical improvement. Rapid defervescence after antibiotic treatment is so characteristic feature of scrub typhus.
- Meticulous supportive management is necessary to abort progression to DIC and septic shock.[4]

FINAL DIAGNOSIS

Scrub typhus with right basal pneumonia.

LEARNING POINTS

- Scrub typhus is a re-emerging disease in India.
- It is an important cause of community acquired undifferentiated febrile illness in India.
- It has to be considered in the differential diagnosis of sepsis and multiorgan dysfunction syndrome.
- Search for an eschar in hidden areas of body can give clue for this disease.
- Diagnosis is done by IgM scrub typhus ELISA.
- Doxycycline is the drug of choice.

REFERENCES

1. Saah AJ. *Orientia tsutsugamushi* (scrub typhus). In: Mandell GL, Bennett JE, Dolin R, (Eds). Principles and practice of infectious disease, 5th edn. Philadelphia, PA: Churchill Livingstone, 2000. pp. 2056-57.
2. Sharma PK, Ramakrishnan R, Hutin YJ, et al. Scrub typhus in Darjeeling, India: opportunities for simple, practical prevention measures. Trans R Soc Trop Med Hyg. 2009.pp.1153-8.
3. Watt G, Chouriyagune C, Ruangweerayud R, Watcharapichat P, Phulsuksombati D, Jongsakul K, et al. Scrub typhus infections poorly responsive to antibiotics in Northern Thailand. Lancet. 1996;348(9020):86-9.
4. Watt G, Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis Oct. 2003;16(5):429-36.

CASE

Fever with Splenomegaly 20

HISTORY

A 54-year-old male resident of Bihar, India, came with the chief complaints of fever, cough, weakness, loss of appetite and 4 kg weight loss since the last 20 days. Fever was associated with chills and rigor, and it was intermittent in nature. He also gave history of yellowish minimum expectoration. There was no history of hemoptysis, yellowish discoloration of sclera, pain abdomen, vomiting, pruritus, dysuria, breathlessness, altered sensorium, headache, rash, photosensitivity or joint pains. No significant history in the past.

EXAMINATION

On general physical examination, patient was febrile (102°F); there was no lymphadenopathy, icterus, pallor and edema. Pulse-96/min, BP-100/70 mm Hg, RR-18/min. Systemic examination revealed bilateral crepitations in infra-mammary, infra-axillary and infra-scapular area and a firm non-tender spleen enlarged 6 cm below costal margin. There were no signs of meningeal irritation and cardiovascular examination was within normal limits. Since he was a resident of area endemic for kala-azar and differential of leishmaniasis was also kept. Initial investigations were done to known cause of fever (Table 20.1).

FURTHER WORK-UP

Contrast CT chest and abdomen revealed bilateral pleural thickening with abdominal lymphadenopathy (10–15 mm) and moderate splenomegaly. Bone marrow aspiration showed reactive changes. Interleukin-6 (IL-6) and C-reactive protein (CRP) were raised, serum ferritin and lipid profile were within normal limits. K 39 antigen was negative. His anti-nuclear antibody (ANA), ANA profile, C-anti-neutrophil cytoplasmic antibodies (C-ANCA), p-ANCA, immunoglobin profile was normal. 2D-echocardiography was normal.

An ultrasound-guided splenic biopsy was finally done to confirm the cause of splenomegaly and it showed granulomatous changes (Figure 20.1). So, the final diagnosis of tuberculosis of spleen was made. Patient was started on category 1 (2H3R3Z3E3/4H3 R3), anti-tubercular therapy to which he favorably responded.

Table 20.1 Values of laboratory parameters

Parameters	*Patient's value*	*Normal range*
Hemoglobin	9.6 gm/dL	13–15 gm/dL
Total leukocyte count	4.8/cumm	4–10/cumm
Platelets	1.08 lakh	1.5–4.5 lakh
Erythrocyte sedimentation rate (ESR)	110 mm	<20 mm
Proteins/Albumin	6.3/2.4 gm/dL	6.5–7.5/3.5–4.5 gm/dL
SGOT/SGPT	66/36 IU	0–40/0–34 IU/L
Alkaline phosphatase	227 IU	<112 IU
Gamma-glutamyl transferase	122 IU	
Mantoux test	Negative	
HIV	Negative	
Urine (routine/microscopy)	Trace proteins	
Renal function test	Normal	
Chest X-ray	Bilateral pleural thickening	
Ultrasound	Splenomegaly	
Blood (culture/sensitivity)	Sterile	

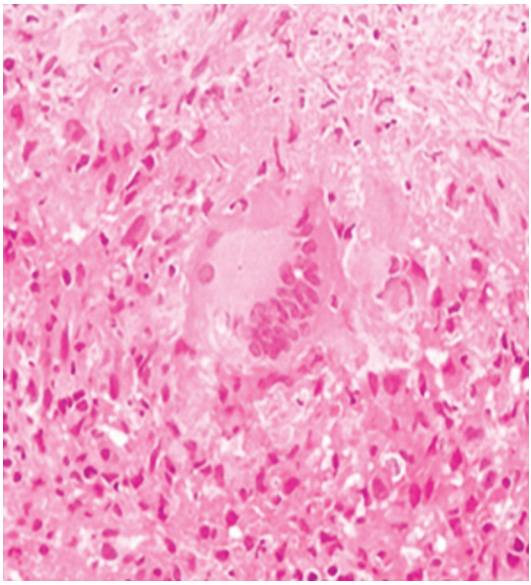


Figure 20.1 Focal granulomatous inflammation showing multinucleated giant cells

1. What are the types of splenic tuberculosis?

Ans. Splenic tuberculosis is one of the rare manifestations of extra-pulmonary tuberculosis. It was earlier known to occur in the form of splenic abscess in the setting of immunodeficiency. However, in the recent past, there has been an increase in the reported cases. It can occur as a part of disseminated or isolated splenic tuberculosis. Hematogenous spread is responsible for the disseminated variety.[1] There are five types of pathomorphological classifications for splenic tuberculosis:

1. Miliary tuberculosis
2. Nodular tuberculosis
3. Tuberculosis spleen abscess
4. Calcific tuberculosis
5. Mixed type tuberculosis[2]

2. What is the differential diagnosis of splenic mass lesion?

Ans. The differential diagnoses of splenic masses lesion are splenic lymphoma, splenic abscess, splenic carcinoma, calcified granuloma, splenic infarction, metastases, echinococcal cysts and hemangioma. Splenic abscess should be considered in patients presenting with fever of undetermined origin and abdominal pain; although splenic infarction can have a similar clinical appearance. Lymphoma may also present with fever of unknown origin and pain over spleen suggesting a primary presentation localized to spleen though it may involve multiple sites.

3. What is the clinical spectra of splenic tuberculosis?

Ans. Diagnosis of isolated splenic tuberculosis is difficult and often delayed because of vague clinical presentations. There are no specific symptoms for establishing the diagnosis of splenic tuberculosis. Fever (75%), anorexia (50%), and weight loss (10%) are common presentations apart from other symptoms such as pain abdomen (62%).[3]

Most of the patients show normochromic or hypochromic normocytic anemia of chronic disease. Other manifestations may be leukemoid reactions, myelofibrotic changes, polycythemia and pancytopenia.[4] Thrombocytosis is the usually a reactive change.[5] Tuberculosis presenting as immune thrombocytopenia in adults is rare. It occurs as a part of pancytopenia.[6] Recovery from the hematological abnormality with anti-tuberculous treatment confirms that the hematological disorder has arisen secondary to the infection. This warrants a peripheral smear and bone marrow examination before attributing the hematological disorder to tuberculosis.[7]

4. What is the role of splenectomy?

Ans. Whenever pre-operative diagnosis of tuberculosis is not possible, splenectomy can be done, it is diagnostic as well as therapeutic. Surgery may be appropriate in subjects having rupture of the spleen, or if the anti-tubercular treatment fails.

FINAL DIAGNOSIS

Isolated splenic tuberculosis in immunocompetent host.

LEARNING POINTS

- Diagnosis of isolated splenic tuberculosis requires a high index of suspicion.
- It is a treatable condition of spleen enlargement with standard line of anti-tubercular therapy.
- CT is the preferred imaging modality, as not only does CT reveal the presence of a splenic abnormality but it gives an indication of its nature, the site for possible biopsy or drainage and follow-up after treatment.
- Diagnosis remains microbiological/histopathological confirmation of the tuberculous lesion in the splenic specimen obtained by fine needle aspiration or biopsy or after splenectomy.

REFERENCES

1. Gupta PP, Fotedar S, Agarwal D, et al. Tuberculosis of spleen presenting with pyrexia of unknown origin in a non-immunocompromised woman. Lung India. 2008; 25(1): 22-4.
2. Zhan F, Wang CJ, Lin JZ, Zhong PJ, Qiu WZ, Lin HH, et al. Isolated splenic tuberculosis: a case report. World J Gastrointest Pathophysiol. 2010;1(3):109-11.
3. Dixit R, Arya MK, Panjabi M, et al. Clinical profile of patients having splenic involvement in tuberculosis. Indian J Tuberc. 2010;57(1):25-30.
4. Singh B, Ramdial PK, Royeppen E, et al. Isolated splenic tuberculosis. Trop Doct. 2005;35:48.
5. Hunt BJ, Andrews V, Pettingale RW. The significance of pancytopenia in miliary tuberculosis. Postgrad Med J. 1987;63:801-4.
6. Al-Majed SA, Al-Momen AK, Al-Kassimi FA, et al. Tuberculosis presenting as immune thrombocytopenic purpura. Acta Haematol. 1995;94:135-8.
7. Cooper W. Pancytopenia associated with disseminated tuberculosis. Ann Int Med. 1959;50:1497-501.

CASE

21

Painful Swelling of Joints in a Patient with Rheumatoid Arthritis

HISTORY

A 34-years-old married male was admitted with complaints of painful swelling of left ankle since two months and fever on and off, since the same duration associated with cough and expectoration. He had pain in the knees as well but it was mild and not associated with swelling and joint restriction. He was a known case of rheumatoid arthritis diagnosed one year back on methotrexate and sulphasalazine but had left all medication for 2 months. He was a known diabetic on irregular medication. He had history of frequent alcohol consumption and he was a chronic smoker. There was no history of trauma, loose motions, dysuria, loss of weight, loss of appetite yellowish or discoloration of sclera.

EXAMINATION

On examination, he had swollen left proximal inter-phalangeal joint of third digit, left ankle joint was swollen, extremely tender with restricted joint mobility and left knee joint had mild effusion. Patient was febrile, pulse—108/min, BP—110/70, there was pallor, no icterus, cyanosis, clubbing, edema and lymphadenopathy. Chest examination revealed bilateral rhonchi. On the basis of history and examination, our differentials were limited to disease activity/septic arthritis of left ankle joint. Initial investigations are tabulated in Table 21.1.

Table 21.1 Initial investigations

Parameters	*Patient's value*	*Normal value*
Hemoglobin	11.2	13–17 gm/dL
Total leukocyte count (TLC)	11.1	4000–10000/UL
Platelet	1.80 lakh	1.5–4.5 lakh/uL
Erythrocyte sedimentation rate (ESR)	97	<11 mm
Creatinine	0.5 mg/dL	0.6–1.3 mg/dL
Albumin	2.2 mg/dL	3.4–5.4 gm/dL
HbA_{1c}	8.8 %	<6%
C-reactive protein (CRP)	263	Negative
Sputum	No definite organism	-
Uric acid	7.2 mg/dL	4–5.2 mg/dL
Chest X-ray	Increased bronchovascular markings	-
Blood (culture/sensitivity)	Negative	-
Venous Doppler	Bilateral lower limb normal flow	-

FURTHER WORK-UP

He was given a single dose of steroid, antibiotics and pain medication. His fever worsten, he was initially having intermittent fever, and it progressed to continuous fever. Pain in the left ankle became unbearable and he required sedative analgesia. X-ray of left ankle joint was non-contributory and HIV antibodies was negative. MRI of the joint was suggestive of collection with increased echogenecity (Figure 21.1). Joint cavity became tense and surgical drainage of the joint was done via arthroscopic approach. Suction drainage drained thick pus. Drain was irrigated on a regular basis. Grams stain of pus showed many polymorphonuclear cells and few Grams positive cocci and it was negative for fungus and acid-fast bacilli. Pus culture grew *Streptococcus pneumoniae* sensitive to penicillin, ceftriaxone, clindamycin, vancomycin, erythromycin, linezolid, cotrimoxazole, and levofloxacin (Figure 21.2).

On 3rd day postdrainage, patient had tachypnea and oxygen saturation dropped on room air. On auscultation, he had bilateral crepitations, repeat X-ray of chest revealed bilateral in homogeneous infiltrates.

Urgent contrast-enhanced computed tomography (CECT) chest was done to know the cause of breathless and to rule out pulmonary embolism. The scan which showed right upper lobe and lower lobe consolidation with subcentimeter mediastinal lymph nodes (Figure 21.3). Bronchoscopic lavage and endobronchial ultrasound FNA was noncontributory. He received 4 weeks of intravenous antibiotic therapy and was discharged on oral antibiotics for 2 weeks.

1. What are the common organisms causing arthritis?

Ans. *Staphylococcus* and *Streptococcus* are the most common isolates.[1] Grams negative bacilli account for 10 to 20% of cases. Ten percent of nongonococcal arthritis has polymicrobial infection. *Haemophilus influenzae* causes very few cases postvaccination era. Septic arthritis secondary to infectious cause can be due to *Shigella*, *Salmonella*, *Campylobacter* and *Yersinia* species.[2]

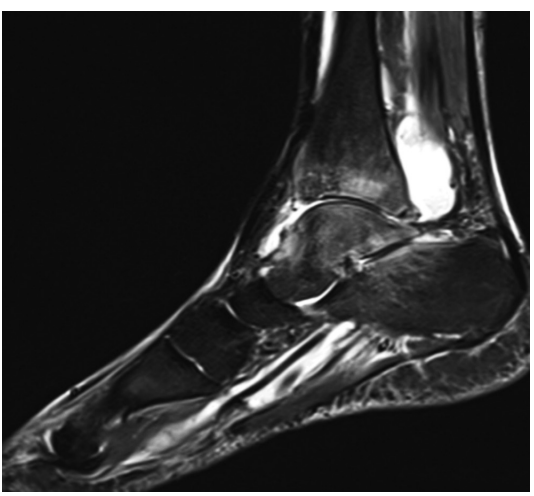


Figure 21.1 MRI pus collection left ankle joint

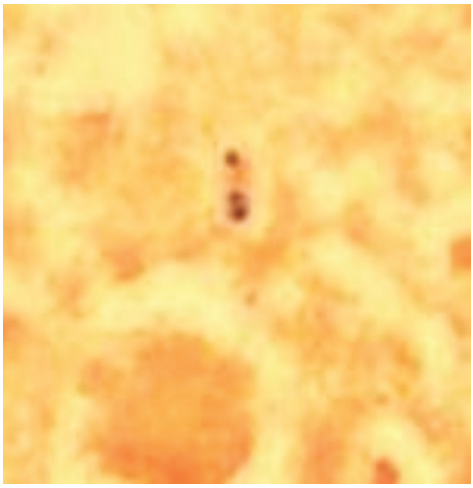


Figure 21.2 Grams positive pus

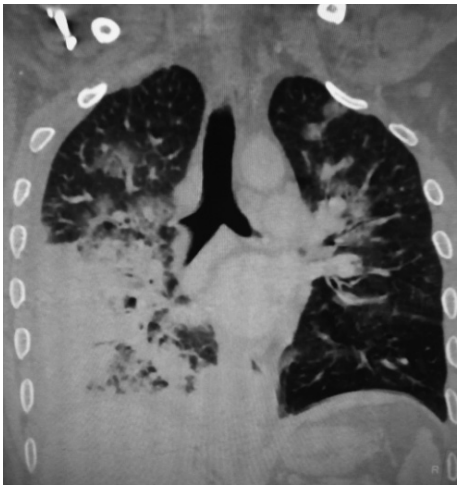


Figure 21.3 Large pneumonia on right side of chest

2. What are the predisposing factors for septic arthritis?

Ans. Patients with rheumatoid arthritis have two-fold higher incidence for injection as compared to normal population. Other clinical situations are immunocompromised status, drugs such as, corticosteroids (four-fold, dose dependent increase), diabetes mellitus, malignancy, IV drug abuse (Grams negative arthritis).

Other conditions are autoimmune conditions, complement deficiency and sexual risk behavior. Atypical joint infection, including the sternoclavicular, costochondral, and sacroiliac joints, may be common in intravenous drug users.[1] The risk with low dose methotrexate for infection is low but the biological therapy can escalate the risk of infection in a given patient.

3. How do we diagnose septic arthritis?

Ans. Table 21.2 gives diagnostic clue for diagnosis of septic arthritis. Fever has been found to be a poor indicator of septic arthritis as only 50% of patients may fever. The definition of an infected joint remains positive bacterial culture test and synovial fluid analysis.

Table 21.2 Diagnosis of septic arthritis

History	Recent onset fever, malaise, joint pain, risk factors
Examination	Warmth, swelling and decreased range of motion in the involved joint
Synovial fluid analysis	• Synovial culture and Grams stain • Leukocyte counts in excess of 50,000/mm^3 • Glucose level 40 mg/dL or less than half that seen in the serum • High concentration of lactate • 90% polymorphonuclear leukocytes • Lack of bifringent crystals
Cultures	Blood cultures are positive in 50% of cases, sputum and urine cultures to know the primary source
Hematology	Elevated erythrocyte sedimentation rate, C-reactive protein levels, peripheral leukocyte levels

4. Discuss the medical management of septic arthritis?

Ans. Acute nongonococcal septic arthritis is a medical emergency. Rapid and aggressive treatments are critical to ensure a good prognosis. Antibiotics need to be adjusted based on culture and sensitivity results, monitoring of synovial fluid leukocyte counts and cultures.

The usual course of therapy for nongonococcal arthritis is 2 weeks. For arthritis due to *H. influenzae* or *Streptococcus*, due to *S. aureus* or Grams negative bacilli, antibiotic therapy should be given for 4 to 6 weeks.[2] In case of *Staphylococcus aureus* treatment is with intravenous penicillinase resistant penicillin. In case of methicillin resistant *Staphylococcus aureus* vancomycin and linezolid are the drugs of choice.

Streptococcus species, penicillin G is used. If the Grams stain is negative, an extended spectrum or broad-spectrum cephalosporin or semisynthetic penicillin is appropriate.

Ceftriaxone is antibiotic of choice in sexually active adults.[1]

5. What is the role of surgery in septic arthritis?

Ans. Adequate drainage of joint is important to prevent the joint from damage. If the cell count and the polymorphonuclear percentage decreases with each aspiration, it should be continued along with antimicrobial therapy in the first week. Persistence of effusion beyond a week warrants arthroscopic lavage or open drainage. It is also useful in case of multiple loculated pockets. It allows visualization of joint space and debridement. Open drainage is required for deep joints like hip, abscess with multiloculated spaces. Decompression arthrotomy is required in case of neuropathy and compromised blood supply. Some negative prognostic indicators are immunosuppressive state, joint deformity and extremes of age. Nasal

carriage of organisms is the most important risk factor for surgical site infection.

In the acute phase of diseases, patient is adviced rest and optimal joint position. Following the acute phase, early physical therapy and aggressive mobilization should be done. Splint is required to maintain joint position. Hip joint should be in neutral rotation in abduction, knee in full extension, elbow in flexion at 90° and forearm in neutral rotation. Recurrence rates of infection are up to 60% in rheumatoid arthritis. A permanent reduction in joint function is seen in approximately 40% of patients with gonococcal septic arthritis. The outcome is poor in case of virulent organisms such as superantigen-producing *S. aureus* and *Grams negative bacilli*. Patients who present with nongonococcal polyarticular involvement have a high mortality.

6. How do we manage prosthetic joint infections?

Ans. The prevalence of infection after total knee or hip arthroplasty is estimated to be approximately 1 to 2%. If the infection is in less than 3 months, the most common organism is *Staphylococcus epidermidis*. Late infection is caused by hematogenous seeding. Implant removal is necessary in later stage of joint space infections. Early onset prosthetic joint infections is treated with antibiotics and debridement.

FINAL DIAGNOSIS

Streptococcal arthritis with bilateral pneumonia in rheumatoid arthritis patient with multiple risk factors.

LEARNING POINTS

- Classically, septic joint presents as monoarthritis, in this patient oligoarthritis was presentation which let to delay in diagnosis.
- Rheumatoid arthritis and diabetes are the risk factor for sepsis and this should always be considered in a patient with rheumatoid who reports a “flare” in just one or two adjacent joints.
- If the diagnosis is strongly suspected, the patient requires immediate admission and treatment for sepsis pending the results of synovial fluid and blood cultures.
- Septic arthritis is a medical emergency.

REFERENCES

1. Mark E Shirtliff, Jon T Mader. Acute Septic Arthritis. Clinical microbiology reviews, 2002. pp. 527-44.
2. John L Zeller, Cassio Lynm, Richard M Glass. JAMA, April 4, 2007-Vol 297, No. 13.
3. Masatoshi Hayashi, Toshihisa Kojima, Koji Funahashi, et al. Pneumococcal polyarticular septic arthritis after a single infusion of infliximab in a rheumatoid arthritis patient: a case report. Journal of Medical Case Reports. 2012;6:81.

CASE

Dry Mouth with Pain Abdomen

22

HISTORY

A 51-year-old female was admitted with complaints of pain upper abdomen, fever for 1 day and recurrent episodes of vomiting for 2 months. Patient was diagnosed to have rheumatoid arthritis 2 years back. Six months prior to admission, she had bilateral swelling of parotid glands with dryness of mouth. The episode of parotitis were managed symptomatically with antibiotics and anti-inflammatory drugs. There was history of gritty sensation and dryness of eyes. Schirmer's test done 6 months back was negative.

Her arthritis was well controlled and she occasionally required rofecoxib for pain in the joints. Due to repeated vomiting, she was on injectable methotrexate 12.5 mg/week for two months prior to admission. Liver function tests, blood urea and ultrasound abdomen done repeatedly were reported as normal.

One day prior to admission, she complained of pain in right upper abdomen and high grade fever with chills. Pain was non-colicky and non-radiating. She used to have feeling of heaviness in the abdomen specially after meals associated with occasional vomiting. The vomiting was thought to be self induced by a local practitioner. She gave no history of any referred pain or significant weight loss.

EXAMINATION

Patient was febrile with temperature 38°C, toxic and had an anxious look. Pulse rate was 102/min with blood pressure 130/80 mm Hg. Chest and cardiovascular (CVS) examinations were normal. Abdomen was soft with tenderness in the right hypochondrium and thump sign was positive. Musculoskeletal examination showed no synovitis or swelling of any joints.

1. What could be the cause of dry mouth in patient with arthritis?

Ans. Dry mouth has many causes like medication (antihistamines, antidepressants, diuretics), systemic diseases (diabetes, anemia, rheumatoid arthritis, stroke, mumps, Sjögren's syndrome postcancer and radiation. In a arthritis patient, it is usually due to Sjögren's syndrome. It needs to be investigated if the disease is primary or secondary Sjögren's syndrome. Sjögren's syndrome is a chronic autoimmune disease in which the body's white cells destroy the exocrine glands, specifically the salivary and lacrimal glands, that produce saliva and tears.[1]

2. What are the organs commonly involved in Sjögern's syndrome?

Ans. Eye and mouth are the most common two sites of involvement, however, joint, skin, kidneys can also involved. Involvement of lungs, intestine and vasculitis is rare.

INVESTIGATIONS

Hemoglobin–10.5 gm/dL, total leukocyte count 2,000/mm^3, differential count neutrophils 57%, lymphocytes 38%, eosinophils 2%, monocytes 7%, ESR 59 mm/1st hr and platelet count 1.59 × 10^9/L. Liver function test, blood sugar, ECG and chest X-ray were normal. Ultrasound done one week prior to admission was normal. Plain CT abdomen showed multiple hypodense liver lesions and bilateral renal calculi.

The biochemical findings were blood urea nitrogen–11.8 mg/dL, serum creatinine 0.6 mg/dL, sodium 136 mEq/L, potassium 2 mEq/L, chloride 112 mEq/L, calcium 7.2 mg/dL, uric acid 4.2 mg/dL, urinary pH 7.5, urinary sodium 437 (N–40–220 mmol/L/d), urinary potassium 108 (N–25–100 mmol/L/d), ABG–pH–7.28, PO_2–98 mm Hg, PCO_2–28 mm Hg, HCO_3–10.

Serum parathyroid hormone level was normal. CT guided needle aspiration from lesions in the liver revealed typical anchovy sauce aspirate. Grams stain of the aspirate showed no organism, no trophozoites or malignant cells. Rheumatoid factor was positive (1024 IU/mL), ANA (Hep-2) was positive (speckled pattern, titer 1:80) and anti-Ro and anti-La were positive. Serology for *Entamoeba histolytic* was positive. DEXA scan showed T score of – 2.21. Repeat TLC after 3 days was 7,200/cumm. Lip biopsy was suggested to patient but she refused for the same.

Oral ammonium chloride loading test was performed. Ammonium chloride 0.1 mg/kg was given and blood and urine pH measured over the next 6 hours. Though systemic acidosis worsened, urine pH did not fall below 5.5.

Patient was treated with calcium and potassium supplements (KCL) and bicarbonate salts and injection metronidazole for liver abscess. Six months after discharge, she is maintaining normal levels of electrolytes.

3. How will you explain the electrolyte abnormalities in this patient?

Ans. Our patient had recurrent vomiting for 2 months which could well explain hypokalemia but the arterial blood gas analysis showed metabolic acidosis which could not be explained by vomiting alone. The anion gap was calculated using the formula, [Na+K] – [Cl+HCO_3] and for our patient was normal. The diagnosis of distal renal tubular acidosis (type 1) was made as patient had hypokalemia, hyperchloremic metabolic acidosis with normal anion gap, inability to lower the urinary pH below 5.5, osteopenia and nephrolithiasis. The other abnormal investigations in our patient were hypokalemia, hypocalcemia, hypouricemia, hypophosphatemia suggesting presentation of Fanconi's syndrome.

4. What is the renal involvement in patient with to primary Sjögren's syndrome?

Ans. Renal involvement due to primary Sjögren's syndrome is usually in the form of distal renal tubular acidosis. The frequency of renal involvement in Sjögren's syndrome varies from 5 to 67%. Proximal renal tubular acidosis

is rarely described and only a few cases of Fanconi's syndrome have been reported with primary Sjögren's syndrome. We had this case of distal and proximal renal tubular acidosis in a patient who had initially been treated as rheumatoid arthritis but was later diagnosed as a case of primary Sjögren's syndrome.[2]

The diagnosis of proximal renal tubular acidosis (type 2) was made as patient had hyperchloremic metabolic acidosis with features of Fanconi's syndrome. Our patient had combination of distal and proximal renal tubular acidosis which is very rare in Sjögren's syndrome.

The renal involvement in patient's with Sjögren's syndrome is due to tubulo-interstitial involvement.[3] Some studies have revealed immune mediated glomerulonephritis. Interstitial nephritis is early feature of this condition where as glomerular involvement is late and unusual feature in Sjögren's syndrome.[4] In patient's of primary Sjögren's syndrome with glomerular involvement, possibility of associated connective tissue disorder like systemic lupus erythematosus needs to be ruled out.[5] Renal involvement may precede the onset of sicca symptoms.[5]

In a published study in 60 patients of primary Sjögren's syndrome the following renal laboratory tests were performed in all patients: electrolytes in serum and in 24 hours urine, creatinine in serum and in 24 hours urine, venous pH and HCO_3, urinalysis, urinary osmolality, urine pH and urine culture. A water deprivation test was performed in patients with morning urine osmolalities below the reference values, oral ammonium chloride loading test was performed when urine pH was above 5.5 and renal biopsy done in patients with renal involvement.[5] In this study, 27% patients had laboratory evidence of tubular/glomerular dysfunction, creatinine clearance was decreased in 13%, Frank distal tubular acidosis was seen in 5%, hypokalemia in 7% and pathological proteinuria in 20%. Renal biopsies in 9% patient showed tubulointerstitial nephritis.

Renal tubular acidosis is a non-uremic condition where kidneys are unable to maintain acid–base balance. Normally, kidney excretes acids into urine returning bicarbonate into blood to maintain acid–base balance. The kidneys in this condition fail to produce acidic urine. Cellular immunity is predominantly involved in the pathophysiology of interstitial nephritis in Sjögren's syndrome which is evident by diffuse infiltration of plasma cells and CD4 positive T lymphocytes. Patients of proximal renal tubular acidosis have multiple defects in proximal tubular function, including defective reabsorption of glucose, calcium, phosphate, citrate, uric acid, lysozymes, light chain immunoglobulins and amino acids.

Interstitial nephritis in primary Sjögren's syndrome is usually asymptomatic. Some patients may present with growth retardation, weakness, hypokalemic quadriparesis, cardiac arrhythmias or sudden death. Other clinical presentations are renal stones, nephrocalcinosis and compromised renal functions, renal rickets and osteomalacia.[3]

5. What could be reason of leukopenia in this patient?

Ans. On admission, patient had leukopenia which improved subsequently. There is no relation between primary Sjögren's syndrome and liver abscess but less than 5% patient on methotrexate may develop leukopenia. Low

dose methotrexate can be associated with opportunistic infections as like nocardia, *Pneumocystis carinii, Cryptococcus*, herpes zoster.[6] The risk factors for this drug toxicity include renal insufficiency, folic acid deficiency, acute infection such as parvovirus, dosing error and use of concomitant drugs causing leukopenia.

6. What is the indications for aspiration of liver abscess?

Ans. Amebic liver abscess is caused by *Entamoeba histolytica.* Majority of liver abscess can be managed by metronidazole or tinidazole, however, few patients listed below will benefit from aspiration. Needle aspiration is simpler and potentially safer than catheter drainage. The main indications are:

- Larger abscess more than 10 cm
- Abscess impending rupture
- Left lobe abscess
- Abscess with negative serology.

FINAL DIAGNOSIS

Hypokalemic periodic paralysis proximal and distal renal tubular acidosis and amebic liver abscess in primary Sjögren's syndrome.

LEARNING POINTS

- Primary Sjögren's syndrome is a disease of middle aged female.
- Rheumatoid arthritis closely mimics primary Sjögren's syndrome.
- The differentiating features from rheumatoid arthritis are no erosions on radiography, normal C-reactive protein (CRP), marked hypergammaglobulinemia, absence of extra-glandular involvement such as lymphadenopathy, renal involvement and Raynaud's phenomenon and presence of SS-A and SS-B antibodies.
- The clinical profile of our patient like symptoms of xerophthalmia and xerostomia with autoantibody profile (high rheumatoid factor levels, positive SS-A and SS-B) with renal tubular acidosis suggests diagnosis of primary Sjögren's syndrome.

REFERENCES

1. Misra R, Hissaria P, Tandon V, et al. Primary Sjögren's syndrome: Rarity in India. J Assoc Phy India. 2003;51:859-62.
2. Bridoux F, Kyndt R, Abbou-Ayache R, et al. Proximal tubular dysfunction in primary Sjögren's syndrome : A clinicopathological study of 2 cases. Clin Nephrol. 2004;61:434-9.
3. Goules A, Masouridi S, Tzioufas AG, et al. Clinically significant and biopsy documented renal involvement in primary Sjögren's syndrome. Medicine (Baltimore). 2000;79:241-9.
4. Skopouli FN, Dafni U, Loannidis JPA. Clinical evolution, morbidity and mortality of primary Sjögren's syndrome: a retrospective study 5-53 years after the presentation of urolithiasis. J Intern Med. 1996;239:483-8.
5. Bossini N, Silvoldi S, Franceschini F, et al. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Neph dial Transplant. 2001;16: 2328-36.
6. Weinblatt ME. Toxicity of low dose methotrexate in rheumatoid arthritis. J Rheumatol. 1985;12:35.

CASE

Chronic Diarrhea and Weight Loss

23

HISTORY

A 52-year-old gentleman admitted with complaint of loose stools and decrease appetite of 3 months duration. There were 15 to 20 episodes of loose stools per day, not mixed with mucus or blood. History of significant weight loss was also present. He denied complaint of fever, cough, breathlessness, ear discharge, abdominal pain, abdominal distension, burning micturition, decrease urine output, abnormal behavior, abnormal movements of limbs, yellowish discoloration of eyes or swelling of limbs. He was a chronic alcoholic and was involved in homosexual activities. There was history of rash over back and arm, 2 months back.

EXAMINATION

Physical examination revealed blood pressure 110/70 mm Hg, pulse 86 beats per minute, temperature 37.2°C. The patient was cachexic and had significant pallor. Mild dehydration was also present. There were markers of healed herpes zoster (Figure 23.1). There was no icterus or lymphadenopathy. Abdomen examination

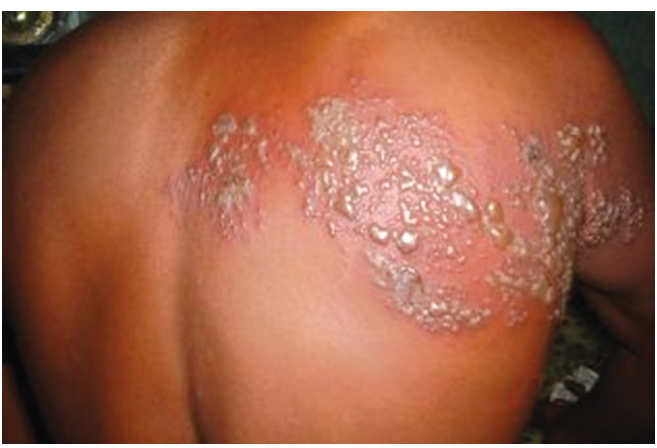


Figure 23.1 Multi-dermatomal herpes zoster infections

showed no hepatosplenomegaly. Chest, cardiovascular and nervous system examinations were inconclusive.

INITIAL WORK-UP

The patient's stool culture was sterile but Kinyoun's stain on stool sample showed oocysts of *Cryptosporidium*. Table 23.1 shows patients CD4 cell counts, viral load and other parameters. He was started on 3 drugs anti-retroviral therapy: emtricitabine, efavirenz and tenofovir, intravenous fluid, along with nitazoxanide for cryptosporidial infection. The patient's general condition improved in 5 days and he got discharged from the hospital on combination of antiretroviral therapy cotrimoxazole tablets.

Table 23.1 Laboratory investigations for initial admission

Laboratory tests	*Patient's value*	*Reference range*
Hemoglobin	7.2 gm/dL	12–16 mg/dL
Total leukocyte count	3,800/cumm	4,000–10,000/cumm
Platelet count	1.44 lakh/cumm	1.5–4.5 lakh cumm
S. creatinine	0.75 mg/dL	0.6–1.2 mg/dL
Sodium/potassium	141/4 mEq/L	132–148/3.5–5.5 mEq/L
AST/ALT/ALP	57/47/465 IU/L	0–42/0–60/0–64 IU/L
Albumin	2.8 gm/dL	3.5–5 gm/dL
LDH	216 IU/L	91–180 IU/L
HIV-I (ELISA)	Positive	–
CD4 count	53/cumm	500–1,500/cumm
HIV viral load	1.7 lakh copies/mL	–
HbsAg	Non-reactive	–
Anti-HCV	Non-reactive	–
Chest X-ray	No abnormality detected	–
Contrast CT chest and abdomen	Normal	–

FURTHER ADMISSION

This patient developed high-grade fever, rashes, cough and breathlessness, 3 days after his discharge from the hospital. Papular rashes were present all over the body. Oral thrush was evident. Repeat CECT thorax showed bilateral upper lobe ground glass opacities and 1 to 2 cm mediastinal lymph nodes with no central necrosis. Bronchoscopy was performed and bronchoalveolar lavage along with mediastinal lymph node biopsy was done. Oocysts of *Pneumocystis jiroveci* were found on immunofluorescence test on BAL, while *Mycobacterium avium* complex was isolated after 7 days of incubation of bronchial washing specimen on rapid AFB culture (Figure 23.2). Upper GI endoscopy was suggestive of esophageal candidiasis. Biopsy grew *Candida albicans*. He was started on oral

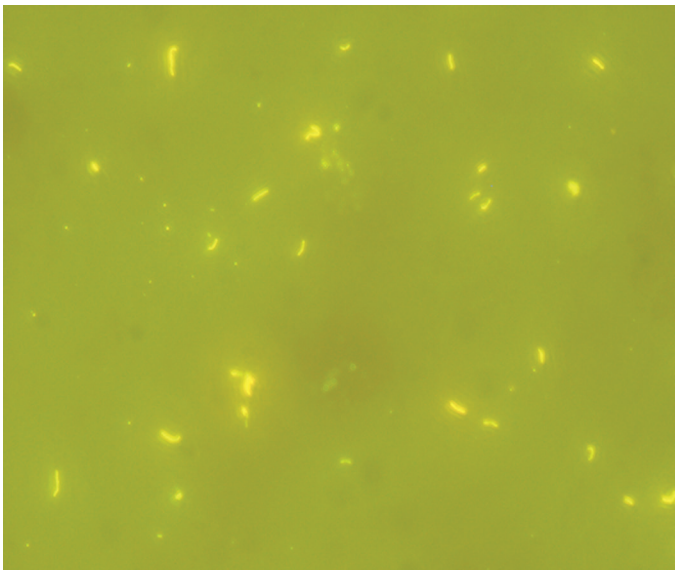


Figure 23.2 *Mycobacterium avium* complex

clarithromycin, ethambutol for *Mycobacterium avium* complex. Oral fluconazole for oral candidiasis. Trimethoprim and sulfamethoxazole was started for *Pneumocystis jiroveci*, along with small dose oral prednisolone for macular rash which was later tapered off completely over 5 days period.

1. What is the diagnosis for this patient?

Ans. This 52-year-old male is homosexual and has had infections like herpes zoster, chronic diarrhea, thrush and *Mycobactrium avium* disease. In addition he has low CD-4 cell counts and very high viral load suggesting the diagnosis of *acquired immunodeficiency syndrome* (AIDS).

Antibodies to HIV proteins may be detected by various methodologies; the current standards are enzyme-linked immunosorbent assays (ELISAs) for screening and Western blot (WB) for confirmation, but WB is a expensive test. A second/third ELISA based on different antigens and a different test principle compared with the first ELISA could be used as an alternative to the WB assay for confirmation of human immunodeficiency virus (HIV) antibodies as was done in our patient.

Thus, alternative HIV testing strategies that do not require use of the Western blot approach are done in resource constrain settings. Three strategies are proposed which are given below:

1. Strategy I, sera are tested for HIV antibody using an enzyme-linked immunosorbent assay (ELISA)/rapid/simple (ERS) test.
2. Strategy II, sera reactive in an initial ERS test are retested using a second ERS test
3. Strategy III involves retesting with a third ERS test all sera reactive in two previous ERS tests. Where the objective is identification of asymptomatic HIV-infected individuals, strategy III is proposed where HIV prevalences

in the study population are < or = 10%, and strategy II at prevalences > 10%. Strategy II is recommended where the diagnosis of HIV-related disease requires HIV testing.

The serological identification of antibodies to human immunodeficiency virus (HIV) in blood is the most widely used method to diagnose HIV infection. Recently, however, the use of oral fluid samples for the detection of antibodies to HIV has been suggested as an alternative.

2. What is the clinical stage of this patient?

Ans. This patient is in WHO stage 4 disease due to extensive esophageal candidiasis and chronic diarrhea due to *cryptosporidiosis*. The absolute CD4 cell in healthy adults who are HIV-negative is between 500 and 1,200 CD4 cells/cubic millimeter of blood. CD4 cell counts correlated with WHO stage of disease. Patients progress to AIDS (acquired immunodeficiency syndrome) when their CD4 cell counts drops below 200 cells/microliter. Individuals who have CD4 cell counts below 200 are at the greatest risk of developing opportunistic infections because there is no longer cell-mediated immunity.

The stage of the disease is classified as per WHO (Table 23.2).

Table 23.2 WHO clinical staging of HIV/AIDS for adults/ adolescents with confirmed HIV infection

Clinical stage 1
• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2
• Moderate unexplained weight loss • Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrheic dermatitis • Fungal nail infections
Clinical stage 3
• Unexplained severe weight loss • Unexplained chronic diarrhea • Unexplained persistent fever) • Persistent oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe bacterial infections • Bone or joint infection, meningitis or bacteremia • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anemia • Chronic thrombocytopenia (<50 × 109/ liter)

Contd...

Contd...

Clinical stage 4

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection
- Esophageal candidiasis
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extra-pulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis
- Recurrent non-typhoidal *Salmonella bacteraemia*
- Lymphoma
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

3. What are the indications of starting antiretroviral therapy in HIV patients?

Ans. Revised DHMS guidelines indicate that treatment should be given to any one with CD4 cell count <500 cell/mm^3 or with any CE cell count with HIV associated nephropathies (HIVAN), neuropathy, pregnancy, hepatitis B coinfection.

WHO guidelines (2013) are based on CD4 cell counts and stage of disease.

WHO guidelines

Clinical	**CD4 count available**
Stage I or II	Antiretroviral therapy if CD4 < 500/cumm
Stage III or IV	Antiretroviral therapy regardless of CD4 count

WHO also recommends ART with active tuberculosis, hepatitis B, co-infection, serodiscordant couples and pregnancy.

Highly active antiretroviral therapy is the initial regimen prescribed for an ART naïve patient when the patient fulfils clinical and laboratory criteria to start ART. Current NACO treatment guidelines for first-line ART recommends two classes of drugs for initial treatment, i.e. 2 NRTI + 1 NNRTI.

4. What is immune reconstitution inflammatory syndrome (IRIS)?

Ans. Immune reconstitution inflammatory syndrome (IRIS) refers to inflammatory reactions occurring at the site of pre-existing infection owing to reconstitution of immune system in HIV infected patients following

the initiation of antiretroviral therapy (ART). Up to 10 to 30% patients responding to ART manifest, immune reconstitution inflammatory syndrome. Commonly IRIS occurs in with tuberculosis, *Cryptococcus* and *Cytomegalovirus*.

General IRIS case definition proposed by Robertson, et al. (2006)

Required criterion

- Worsening symptoms of inflammation/infection
- Temporal relationship with starting antiretroviral treatment.
- Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease.
- >1 $\log_{10}$ decresed in plasma HIV load.

Supportive criterion

- Increased in CD4+ cell count of > 25 cells/uL
- Biopsy demostrating well-formed granulomatous inflammation or unusually exuberant inflammatory response.

It may be possible to avoid IRIS by treating identified opportunistic infections that have an effective antimicrobial therapy for one or two months prior to initiation of ART thereby reducing the microbial burden when ART is initiated.

Diagnosis requires two major criteria (A+B) or major criterion (A) plus two minor criteria to be fulfilled.

Major criteria

- Atypical presentation of opportunistic infections or tumors in patients responding to ART, manifested by any of the following:
  - Localized disease
  - Exaggerated inflammatory reaction
  - Atypical inflammatory response in affected tissues
  - Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treamtent toxicity and new diagnoses.
- Decrease in plasma HIV RNA level >1 $\log_{10}$ copies/mL.

Minor criteria

- Increase in CD4 count after ART
- Increase in an immune response specific to the relevant pathogen
- Spontaneous resolution of disease with continuation of ART.

5. What is primary and secondary prophylaxis of opportunistic infections?

Ans. Primary and secondary prophylaxis of opportunistic infections as shown in Tables 23.3 and 23.4.

Table 23.3 Primary prophylaxis of opportunistic infections

Agent	*CD4 count/cumm*	*Drugs*
Pneumocystis jiroveci	< 200/cumm	Cotrimoxazole double strength once daily
Mycobacterium avium complex	< 50 cumm	Azithromycin 1.2 gm once a week or clarithromycin 500 mg twice daily

Table 23.4 Secondary prophylaxis of opportunistic infections

Agent	*Drugs*
Cytomegalovirus	Valganciclovir 900 mg once daily
Cryptococcosis	Fluconazole 100–200 mg orally daily

Prophylaxis should be continued for the patient's lifetime unless multiple drug therapy for *Mycobacterium avium* complex becomes necessary because of the development of *Mycobacterium avium* complex disease.[1]

Primary prophylaxis may be ceased once the CD4 count is over 200/cumm for over 6 months. Secondary prophylaxis may be stopped when CD4 count is more than 100/cumm for more than 6 months while patient is on ART.

6. What is the management of *Mycobacterium avium* complex (MAC)?

Ans. MAC is a late complication of HIV infection, occurring predominantly in patients with CD4 count of < 50/cumm. The diagnosis is made by culture or involved tissue. The finding of two consecutive sputum sample positive of MAC is highly suggestive of pulmonary infection. Culture may take two weeks to turn positive. The therapy consists of a macrolide, usually clarithromycin, with ethambutol. Some physicians add third drug from among rifabutin, ciprofloxacin or amikacin in patients with extensive disease. Most patients who ultimately respond show substantial clinical improvement in the first 4 to 6 weeks of therapy. Elimination of the organisms from blood cultures may take somewhat longer, often requiring 4 to 12 weeks.[2]

FINAL DIAGNOSIS

HIV-acquired immunodeficiency syndrome with opportunistic infection:

- *Mycobacterium avium* complex
- *Pneumocystis jiroveci*
- Cryptosporidiosis
- Candidiasis
- Herpes zoster

LEARNING POINTS

- In India, the most common way to acquire HIV/AIDS is homosexual route.
- In patients living with HIV/AIDS (PLHA), tuberculosis and candidiasis are two opportunistic infections.
- Patients with CD4 cell count less than 50/cumm are more likely to have CMV, atypical mycobacteriosis
- New onset of symptoms within a few weeks of initiation of ART is called IRIS.

REFERENCES

1. *http://www.cdc.gov/mmwr/preview/mmwrhtml/00021272.htm.*
2. Medical management of HIV infection. International Edition 2010. Barlett JG (Ed), Durham NC.

CASE

Drowsiness in Elderly Patient

24

HISTORY

A 72-year-old gentleman had come with history of progressive decrease in movements, increased stiffness of limbs for 6 months; impaired thought process and memory and abnormal behavior for 1½ months; drowsiness for 2 weeks which had worsened over last 2 days. His past history was significant for urinary complaints for which he underwent transurethral resection of prostate. He was also a follow-up case of dilated cardiomyopathy and was on digoxin, anti platelets and vasodilators. There was no history of alcoholism, head trauma, loss of consciousness, abnormal movement of limbs, and weakness of limbs. Family history was non-contributory.

EXAMINATION

Physical examination revealed blood pressure 124/68 mm Hg, pulse 74 beats/minute, temperature 37°C. On CNS examination, he was drowsy but arousable on day 1 and not responding to oral commands but was responding to painful stimuli. Marked rigidity was present in all 4 limbs. Deep tendon reflexes were hypo responsive and bilateral plantar reflexes were flexors. Pupils were equal in size and reacting to light. Corneal and jaw reflexes were normal. Muscle power and sensory system could not be assessed. Cardiovascular, respiratory and gastrointestinal systems were inconclusive. He was admitted in intensive care unit with working diagnosis of septicemia or metabolic encephalopathy. Table 24.1 showing initial blood investigations.

INITIAL WORK-UP

Patient was admitted in intensive care unit with above complaints and investigated for drowsiness.

Table 24.1 Laboratory investigations

Laboratory tests	*Values*	*Reference range*
Hemoglobin	9.4 gm/dL	12–16 mg/dL
Total leukocyte count	9.2 cumm	4,000–10,000 cumm
ESR	50 mm/1st hour	0–10 mm/1st hour
Serum creatinine	1.16 mg/dL	0.6–1.2 mg/dL

Contd...

Contd...

Laboratory tests	*Values*	*Reference range*
AST/ALT/GGT/ALP	30/31/26/79 IU/L	0–42/0–60/0–64/39–117 IU/L
Albumin	2.7 gm/dL	3.5–5 gm/dL
Serum calcium/phosphorus	5.3/8.5 mg/dL	8.2–10.4/2.5–4.6 mg/dL
Ionized calcium	1.2 mg/dL	4.5–5.3 mg/dL
Sodium/potassium	148/4.1 mEq/L	132–148/3.5–5.5 mEq/L
Magnesium	1.4 mg/dL	1.7–2.7 mg/dL
Vitamin D assay	23 ng/mL	> 20 ng/mL
S. parathormone	9.9 pg/mL	12–72 pg/mL

FURTHER WORK-UP

The patient's metabolic profile revealed corrected serum calcium 6 mg/dL (reference range—8.4–10.2 mg/dL), ionized calcium 1.2 mg/dL (4.5–5.3 mg/dL), serum magnesium 1.4 mg/dL (1.7–2.7 mg/dL) serum phosphorous level 8.5 mg/dL (2.5–4.6 mg/dL). Serum sodium and potassium levels were in normal limit. 24 hours urine calcium was 23 mg/day (100–300/day). He was started on calcium gluconate 10%, 10 mL thrice a day, magnesium sulphate 2 gm twice a day, intravenously along with phosphate binders. CT scan of the head revealed presence of bilateral calcification of the basal ganglia (Figure 24.1).

In addition, other factors causing hypocalcemia like hypovitaminosis-D and hypoparathyroidism were ruled out by assaying vitamin D (23 ng/mL;

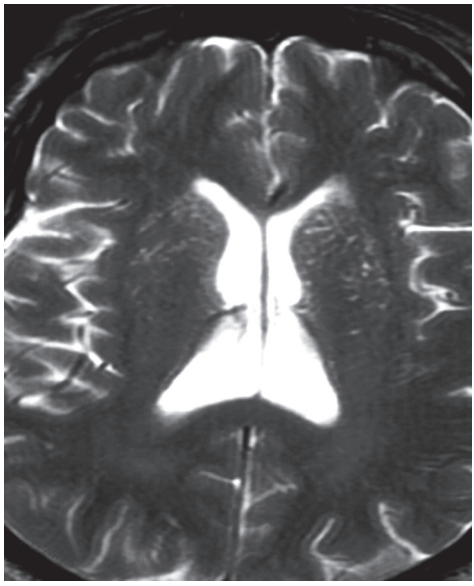


Figure 24.1 Bilateral calcification in basal ganglia

< 20 ng/mL) and parathormone level (9.9 pg/mL; 12–72 pg/mL). Toxoplasmosis, an important cause of cerebral calcification was precluded with IgM and IgG toxoplasma antibody tests. Rapid plasma regain was also non-reactive. Digoxin level was found in sub optimal range (0.7 ng/dL). Urine and blood culture were sterile. All viral markers as well as chest X-ray were normal.

Following correction of calcium and phosphate levels patient became fully conscious and responded well to oral command.

1. What is the diagnosis for this patient?

Ans. This patient had progressive Parkinson's like and neuropsychiatric symptoms over the period, parathyroid disturbance, absence of focus of infection and symmetrical basal ganglia calcification. Thus, the final diagnosis is idiopathic basal ganglia calcification or also known as Fahr's disease.

2. What is Fahr's disease?

Ans. It is a rare inherited or sporadic neurological disorder first described by German Neurologist Karl Theodor Fahr in 1930.[1] It is characterized by abnormal deposition of calcium in areas of the brain that control movements including basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum, subcortical white matter and hippocampus.[2] Most cases present with extrapyramidal symptoms first but may present with neuropsychiatric symptoms, cerebellar dysfunction, speech abnormality or with dementia.[3]

3. What are the diagnostic criteria for Fahr's disease?

Ans. The diagnostic criteria are:

- Bilateral calcification of basal ganglia visualized by neuroimaging, beside this may present in other region of the brain.
- Progressive neurological dysfunction, which generally includes a movement disorder and or neuropsychiatric manifestation at fourth or fifth decade but onset can occurs during childhood period.
- Absence of alternative metabolic, toxic, infectious or traumatic cause.
- A family history consistent with autosomal dominant inheritance.

4. What are the radiological diagnostic tests?

Ans. The radiological tests which can be done are:

- *Computed tomography:* It is a preferred imaging method for diagnosing cerebral calcification. The most frequent affected area is lenticular nucleus especially the internal globus pallidus while cerebellar gyri, brainstem, centrum semi-ovale, and subcortical white matter may also affected. Calcification in the putamen, thalami, caudate, and dentate nuclei are also common.
- *MRI scan:* It shows calcified areas in the basal ganglia seen as low intensity signal on a T2 image and low or high intensity signals on a T1 weighted plate.[4]
- *X-ray skull:* It can occasionally shows calcification which appears as clusters of punctuate densities symmetrically distributed above sella turcica and lateral to midline.[5]

5. What is the etiology of Fahr's disease?

Ans. Endocrine problem particularly parathyroid disturbance is commonly associated with Fahr's disease. These abnormalities include idiopathic hypoparathyroidism, secondary hypoparathyroidism, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism and hyper-parathyroidism. The most common abnormality found is idiopathic hypoparathyroidism (23.3%) characterized by the absence, fatty replacement or atrophy of the parathyroid glands. Secondary hypoparathyroidism (15.3%) occur post-thyroidectomy as a complication of surgery. Pseudohypoparathyroidism is a condition associated primarily with resistance to the parathyroid hormone and the term pseudo-pseudohypoparathyroidism is used to describe a condition where the individual has the phenotypic appearance of pseudohypothyroidism type 1a, whereas biochemically normal.[5,6] Vitamin D has an important role in calcium metabolism and has been implicated in the patient of Fahr's disease.[6]

6. What are the clinical features?

Ans. The clinical features of Fahr's disease are:

Neurological features: A variety of neurological symptoms and signs are associated with Fahr's disease. Spasticity, gait disturbance, chorea, tremors, myoclonus, transient ischemic attacks, orthostatic hypotension may occur. Losses of consciousness and seizures have been reported. Papilledema of intracranial hypertension, pleocytosis of CSF, paroxysmal choreoathetosis have been reported.

Movement disorder: A spectrum of symptoms including clumsiness, fatigability, unsteady gait, slow or slurred speech, dysarthria, dysphagia, involuntary movements may occur in patient of Fahr's disease.

Neuropsychiatric symptoms: These range from mild difficulty with concentration and memory to changes in personality or behaviors to psychosis to dementia.

7. What is the management of Fahr's disease?

Ans. There are various treatment modalities to date which have been tried in an attempt to achieve remission or at least stabilization. Pharmacological treatment should be used to improve anxiety, depression, and to improve dystonia. Oxybutynin is used for urinary incontinence and antiepileptics are used for seizures.[5] Correction of calcium and phosphate levels may improve movement disorders. Clonazepam and atypical antipsychotic also offer an advantage in treating patients with Fahr's disease.[6]

LEARNING POINTS

- Fahr's disease is a rare neurological disorder characterized by abnormal deposition of calcium in various brain areas.
- It usually present with clumsiness, fatigability, unsteady gait, slow or slurred speech, dysarthria, dysphagia, involuntary movements.

- CT scan is preferred diagnostic modality which shows bilateral basal ganglia calcification.
- There is no cure for Fahr's disease. The available treatment is directed symptomatic control.

REFERENCES

1. Fahr T. Idiopathische verkalkung der hirngefässe. Zentrabl Allg Pathol. 1930;8:129-33.
2. Ahad MA, Bala C, Karim S. Fahr's syndrome. Bangladesh Medical Journal Khulna. 2013;8:33-5.
3. Chiu H, Lam L, Shum P, Li K. Idiopathic calcification of the basal ganglia. Postgraduate medical journal. 1993;8(807):68-70.
4. Kobari M, Nogawa S, Sugimoto Y, Fukuuchi Y. Familial idiopathic brain calcification with autosomal dominant inheritance. Neurology. 1997;8(3):645-9.
5. Sobrid SH MJ, Geschwind DH. Familial Idiopathic Basal Ganglia Calcification: GeneReviews™ [Internet] Seattle (WA): University of Washington, Seattle; 2004. Updated 2007 Sep 20.
6. Lauterbach EC. Psychiatric management in neurological disease. American psychiatric press; 2005.

CASE

Violent Cough with Dysphagia

25

HISTORY

A 31-year-old male presented to us with complaints of violent coughing for past 10 days, difficulty in swallowing for past 10 days, vomiting for 7 days and low grade fever for 4 days. Cough was productive with copious amount of yellowish colored sputum. Dysphagia was more for liquids and was associated with severe violent coughing so much so that he had to stop eating. He also complained of nausea, vomiting and decreased for 3 weeks. Patient was apparently well 2 months back when he was started on empirical. Anti-tuberculous treatment on the basis of mediastinal lymphadenopathy, positive Mantoux test and constitutional symptoms.

EXAMINATION

On examination, the patient had tachycardia with temperature of 99.6°F. There was no pallor, icterus, lymphadenopathy or pedal edema. There were coarse crepitations in both inter scapular and basal region (left > right). Abdomen and cardiovascular examination were normal. The investigations are tabulated (Table 25.1).

INVESTIGATIONS

Table 25.1 Laboratory results

Parameters	*Patient's value*	*Normal range*
Hemoglobin	12.4 gm%	13–16 gm%
WBC	5,500 cumm	4,000-10,000 cumm
Platelets	2.51 lakh	1.5–4 lakh
Erythrocyte sedimentation rate (ESR)	45 mm/hr	0–10 mm/hr
T. bilirubin	0.4 mg/dL	0.3–1 mg/dL
Aspartate aminotransferase/Alanine aminotransferase (AST/ALT)	434/338 IU	0–40/0–37 IU
T. protein/Albumin	6.2/3.2	6.6–8.7/3.5–5.0 gm/dL
S. creatinine	0.2 mg/dL	0.6–1.3 mg/dL

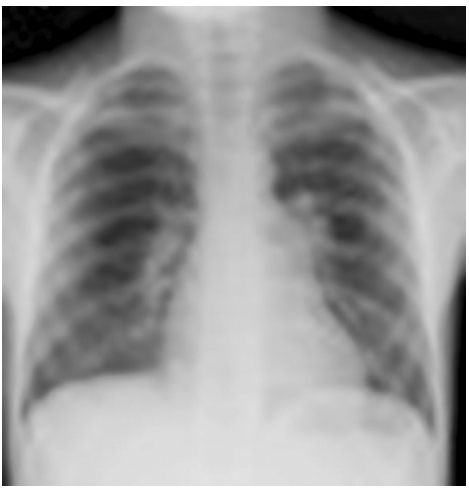


Figure 25.1 Chest radiograph showing bilateral hilar lymphadenopathy

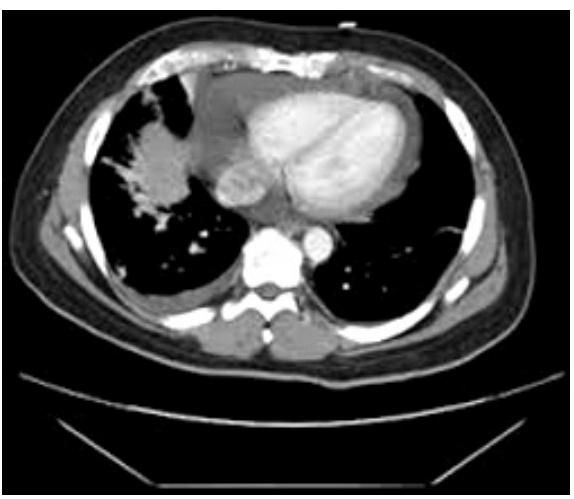


Figure 25.2 CT scan of thorax with administration of oral contrast confirming the fistulous tract extending from mid esophagus into the left main stem bronchus

Chest radiograph was suggestive of bilateral hilar lymphadenopathy (Figure 25.1). Sputum examination was negative for acid-fast bacilli (AFB). He was tested negative for HIV. With suspicion of bronchoesophageal fistulae (BOF), a computed tomography of thorax with administration of oral contrast was done. This was suggestive of enlarged necrotic mediastinal lymph nodes with tracheo-esophageal fistula extending into mid esophagus into left main stem bronchus with nodular and ground glass lesions in infero-lingular segment and basal segment of left lower lobe (Figure 25.2). Angiotensin-converting enzyme (ACE) levels were within normal limits. An endoscopic ultrasound was done which

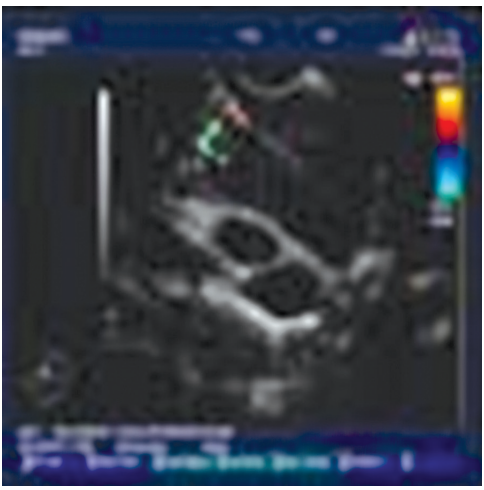


Figure 25.3 Endoscopic ultrasound showing enlarged lymphadenopathy with fistulous connection

confirmed the level of fistula (Figure 25.3). On Ziehl-Neelsen (ZN) staining, it was found to be acid-fast bacilli positive.

1. When to suspect tracheoesophageal fistula?

Ans. Tracheoesophageal fistula (TEF) is a congenital or acquired communication between the trachea and esophagus. It is extremely rare and poses a challenge to the clinician for accurate diagnosis. Any patient presenting with combination of lymphadenopathy and paroxysm of cough with ingestion should alert the possibility of tracheoesophageal fistula. TEFs often lead to severe and fatal pulmonary complications.

FURTHER TREATMENT

Patient was started on modified antitubercular treatment (ethambutol, pyrazinamide, levofloxacin) and a nasogastric tube was inserted and Ryle's tube feed was started. A self-expanding plastic stent was put in mid esophagus endoscopically. Patient gradually improved. His liver function improved and antitubercular treatment (ATT) was restarted.

2. What are the clinical features of tracheoesophageal fistula?

Ans. The common symptom is uncontrolled coughing after swallowing, often worse with carbonated drinks.[1] Other features which should raise suspicions of an acquired TEF are: history of trauma, malignancy or ingestion of caustic substances; chest pain; hemoptysis; shortness of breath; dysphagia; hoarseness; pyrexia of unknown origin; repeated respiratory tract infections; and pneumonia.

3. What are the causes of tracheoesophageal fistula in adults?

Ans. The important causes of tracheoesophageal fistula are infections, malignancy and foreign body.[2,3] Table 25.2 gives causes tracheoesophageal fistula.

Table 25.2 Causes of acquired tracheoesophageal fistulae (TOF)

• Intrathoracic malignancy
• Infections – Tuberculosis – Fungal – Actinomycosis – Histoplasmosis – Syphilis – Bacterial
• Trauma – Foreign body ingestion – Instrumentation – Crushing/operative trauma – Chemical burns
• Miscellaneous–esophageal diverticulosis

4. What is the best diagnostic modality for TEF?

Ans. A chest X-ray will demonstrate the effects of repeated soiling with basal infiltrates and extent of white out revealing its severity. Barium swallow will demonstrate the defect in 70% of lesions. Endoscopy is the best diagnostic modality available for diagnosis of tracheoesophageal fistula. Esophagoscopy will enable the diagnosis of tumors and fistula's. Flexible or rigid bronchoscopy identifies TEF orifice better on posterior memebranous wall and facilitates biopsies.[4]

5. How do you treat TEF?

Ans. It is depending on the cause of tracheoesophageal fistula. Malignancy is the most common cause of acquired TEF, 70 to 80% TEF is attributable to esophageal tumors. Of the non-malignant fistula, endotracheal cuff-related trauma in patients subjected to prolonged mechanical ventilation remains most common cause. The aim of treatment is to minimize further aspiration, prevent and treat pulmonary infections. Surgery remains the definitive treatment.[5] Esophageal stenting remains an important tool for treatment of variety of benign and malignant esophageal conditions. Benign conditions include refractory strictures, tracheoesophageal fistulae, iatrogenic perforation and leaks. Inoperable esophageal malignancies like inoperable esophageal cancer, gastroesophageal junction cancer, gastric cardia cancer for palliative treatment. Stents are made from metal alloy compounds and durable polymers. There is recent development of self expanding plastic stents (SEPS) and self expanding metal stents (SEMS). These are safe and cost effective. Being minimally invasive they improve the quality of life of patients who would otherwise face a possibly morbid surgical procedure or have multiple comorbidities.[6]

FINAL DIAGNOSIS

Mediastinal tubercular lymphadenopathy, tracheoesophageal fistula, anti-tuberculous treatment induced hepatitis.

LEARNING POINTS

- Tracheoesophageal fistula is rare clinical entity.
- Esophageal malignancy remains the most common cause.
- Any patient with paroxysms of cough with ingestion of food should raise the suspicion.
- Endoscopy is the best modality for diagnosis.
- Surgery and esophageal stenting are the treatment options.

REFERENCES

1. Vasquez RE, Landay M, Kilman WJ, et al. Benign esophagorespiratory fistulas in adults. Radiology. 1988;167:93.
2. Braimbridge MV, Keith HI. Oesophagobronchial fistula in the adult. Thorax. 1965;20:226-33.
3. Hutchin P, Lindskog GE. Acquired esophagobronchial fistula of infectious origin. J Thorac Cardiovasc Surg. 1964;48:1-12.
4. Pecora DV. Tuberculous fistula of the esophagus. J Thorac Surg. 1958;36:53.
5. Jenkinson DL, Bate LC. Esophagobronchial fistula through an esophageal diverticulum. AM J Roentgenol. 1951;66:236.
6. Lee JH, Shin DH, Kand KW, et al. The medical treatment of a tuberculous tracheo-esophageal fistula. Tuber Lung Dis. 1992;73:177-9.

CASE

Throat Pain in a Young Patient

26

HISTORY

A 24-year-old female presented to us with complaints of fever and throat pain for 3 weeks. Fever was moderate grade associated with bodyache. She complained of pain in throat which was radiating to left ear along with slight dysphagia. Patient was treated outside with 2 courses of antibiotics. She was investigated outside which revealed normal white cell count and normal X-ray chest. Patient underwent upper gastrointestinal (GI) endoscopy fore dysphagia, which was normal.

EXAMINATION

Patient was febrile with temperature of 101°F. There was no pallor, icterus, lymphadenopathy. Ear, nose and throat (ENT) examination was within normal limits. Chest, cardiovascular and abdominal examination were within normal limits.

Neck Examination

Tender thyroid gland.

INVESTIGATIONS

Investigations (Table 26.1) as charted.

Table 26.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	11.5 gm%	12–15 gm%
WBC	14,300 cumm	4,000–10,000 cumm
Platelet	3 lakh	1.5–4 lakh
TSH/TF3/FT4	0.002/1.659/2.781	0.02–5 mIU/L/0.2–0.5 ng/dL/0.7–1.8 ng/dL
ESR	111 mm	10–20 mm
Antithyroid peroxidase antibodies	Positive	
Antithyroglobulin antibodies	Positive	

Patient underwent thyroid scan which showed decreased uptake (Figure 26.1) suggestive of thyroiditis.

Figure 26.1 Thyroid scan showing diffuse decrease uptake

1. What are the causes of throat pain with fever?

Ans.
- Pharyngitis (Viral, *Streptococcus*)
- Tonsillitis, laryngitis
- Infectious mononucleosis
- Adenoiditis
- Influenza
- Lymphadenitis
- Thyroiditis

2. How to classify thyroiditis?

Ans. Thyroiditis can be classified on the basis of duration and onset of disease:

Acute:
- *Bacterial infection: Staphylococcus*, *Streptococcus*
- *Fungal infection: Aspergillus*, *Candida*, *Histoplasma*
- Radiation thyroiditis
- Amiodarone

Subacute:
- Viral thyroiditis
- Postpartum thyroiditis
- Mycobacterial infection

Chronic:
- *Autoimmunity:* Focal, Hashimoto's,[1] atrophic
- Riedel's thyroiditis
- *Parasitic thyroiditis:* Cysticercosis, *Echinococcus*
- Traumatic

3. How does thyroiditis present?

Ans. **Acute thyroiditis:** A history of acute illness, including fever, chills, neck pain, sore throat, hoarseness, and dysphagia, is common.[2] Neck pain is frequently unilateral and radiates to the mandible, ears, or occiput. Neck flexion reduces the severity of the pain. The pain worsens with neck hyperextension.[3]

Subacute thyroiditis: Neck tenderness and swelling may occur. Occasionally, the initial symptoms are those of hyperthyroidism. Systemic symptoms such as weakness, fatigue, malaise, and fever are usually low grade.

Chronic thyroiditis is observed in the following three patterns:

1. *Goiter that is usually diffuse and non-tender:* Systemic illness is not evident. The thyroid gland is frequently 2 to 3 times its normal size and may be larger.
2. *Symptoms of hypothyroidism:* Signs of hypothyroidism including constipation, lethargy, cold intolerance, menstrual irregularities.
3. *Symptoms of hyperthyroidism:* These may include poor attention span, hyperactivity, restlessness, heat intolerance, or loose stools.

4. How to manage thyroiditis?

Ans. Acute thyroiditis: Acute thyroiditis requires immediate parenteral antibiotic therapy before abscess formation begins. For initial antibiotic therapy should cover Grams positive cocci and the anaerobes that are the usual causes of the disease.[4]

Subacute thyroiditis: Subacute thyroiditis is self-limiting; therefore, the goals of treatment are to relieve discomfort and to control the abnormal thyroid function. The discomfort can usually be relieved with nonsteroidal anti-inflammatory drugs (NSAIDs) or large dose of aspirin. If this treatment is inadequate or if patient has marked local or systemic symptoms, glucocorticoids should be given. The usual starting is 40 to 60 mg prednisone, the dose is gradually tapered over 6 to 8 weeks.

Propranolol can be used to reduce signs and symptoms of hyperthyroidism. Low-dose levothyroxine may be necessary in some patients who develop hypothyroidism.

Chronic autoimmune thyroiditis: Treatment for chronic thyroiditis depends on the results of the thyroid function tests. Patients with overt hypothyroidism who have high thyroid-stimulating hormone (TSH) and low free T4 levels require treatment with levothyroxine. TSH levels should be monitored and the dose should be adjusted to maintain levels within the reference range.[5]

FINAL DIAGNOSIS

Subacute thyroiditis presenting as prolonged pyrexia.

LEARNING POINTS

- The broad category of thyroiditis includes the following inflammatory diseases of the thyroid gland:
  - Acute thyroiditis
  - Subacute thyroiditis
  - Chronic thyroiditis
- Patients with autoimmune thyroiditis frequently develop hypothyroidism and require lifelong treatment.

REFERENCES

1. Iacovelli P, Sinagra JL, Vidolin AP, et al. Relevance of thyroiditis and of other autoimmune diseases in children with vitiligo. Dermatology. 2005;210(1):26-30.
2. Fisher DA, Greueters A. Thyroid disorders in childhood and adolescence. In: Sperling MA. Pediatric Endocrinology, 3rd edn. Philadelphia, PA: Sunders Elevier. 2008. pp. 227-53.
3. Demirbilek H, Kandemir N, Gonc EN, et al. Hashimoto's thyroiditis in children and adolescents: a retrospective study on clinical, epidemiological and laboratory properties of the disease. J Pediatr Endocrinol Metab. 2007;20(11):1199-205.
4. Fava A, Oliverio R, Giuliano S, et al. Clinical evolution of autoimmune thyroiditis in children and adolescents. Thyroid. Feb 18 2009.
5. Sattar N, Lazare F, Kacer M, et al. Celiac disease in children, adolescents, and young adults with autoimmune thyroid disease. J Pediatr. 2011;158(2):272-5.e1.

CASE

Polyarthritis in Middle-aged Person

27

HISTORY

A 48-year-old male presented with multiple joint pains, small and large joints for 2 years. The pain has increased for last two weeks. The patient's movement is restricted to bed due to severe agonizing pain (VAS-90 mm). There is stiffness of joint which remains throughout the day. Patient was a known case of hypertension and dyslipidemia. There was no history of fever, weight loss, backache, severe fatigue photosensitivity, alopecia oral and genital ulcers.

EXAMINATION

On examination, patient has asymmetric joint involvement. There was swelling of 2nd and 3rd distal interphalangeal (DIP) joint with swelling of 1st metacarpal. There was ulceration over 3rd digit with whitish chalky material coming out (Figure 27.1). Swelling of left ankle joint, bilateral knee swelling left > right. BP–140/90 and systemic examination was unremarkable. Figures 27.2 to 27.4 show tophi at various different joints.

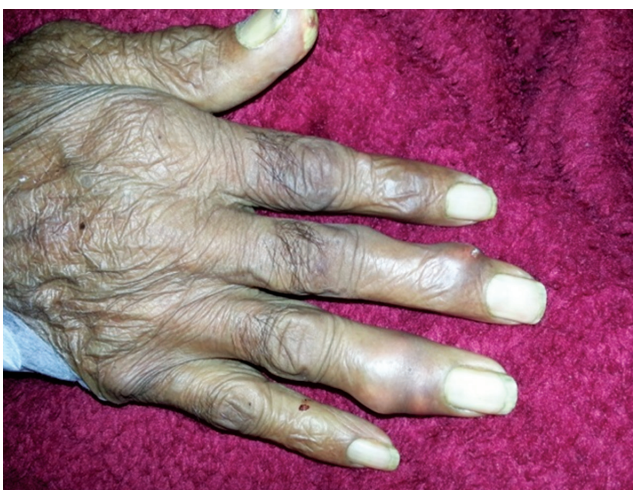


Figure 27.1 Tophi with chalky material over the distal interphalangeal (DIP) joints

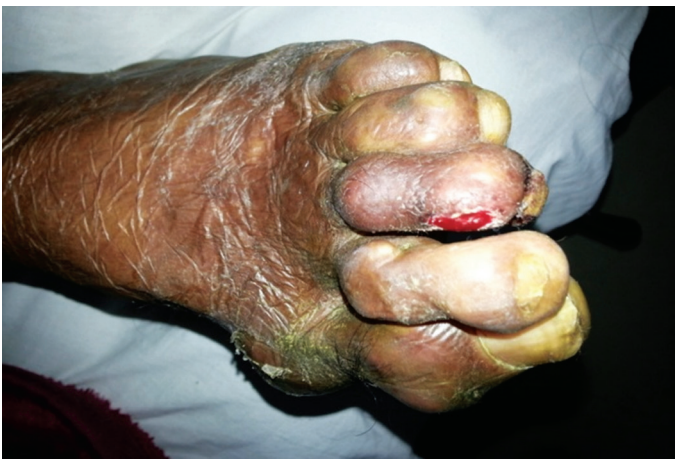


Figure 27.2 Tophi with ulcerations over DIP joints of left foot

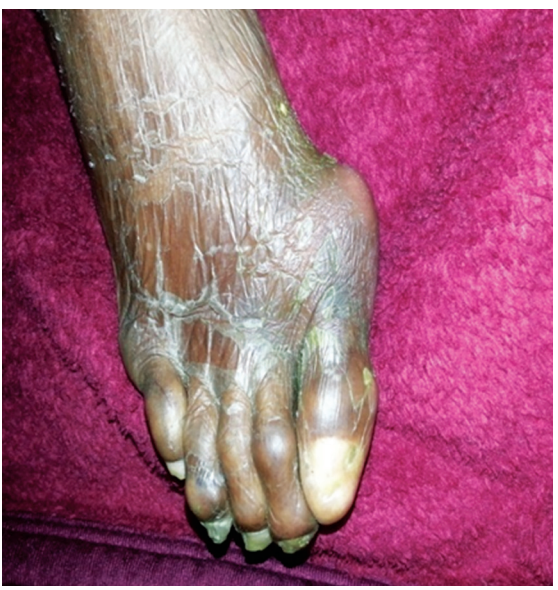


Figure 27.3 Tophi of first metatarsophalangeal (MTP) and proximal interphalangeal (PIP) joints

INVESTIGATIONS

Complete blood count (CBC) was normal, uric acid–5.3 mg/dL, liver function test (LFT), and renal function test (RFT)–normal, blood sugar was normal. X-ray foot revealed erosion with sclerotic margins and overlying soft tissue fullness (Figure 27.5). Human leukocyte antigen (HLA) B27 was negative.

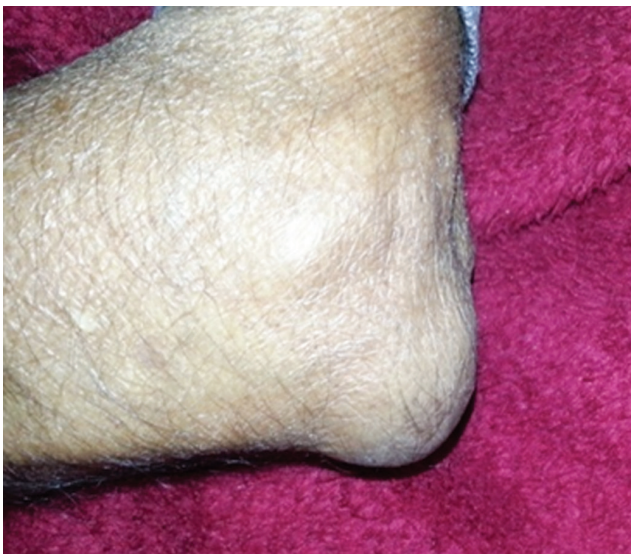


Figure 27.4 Tophus collection over elbow joint

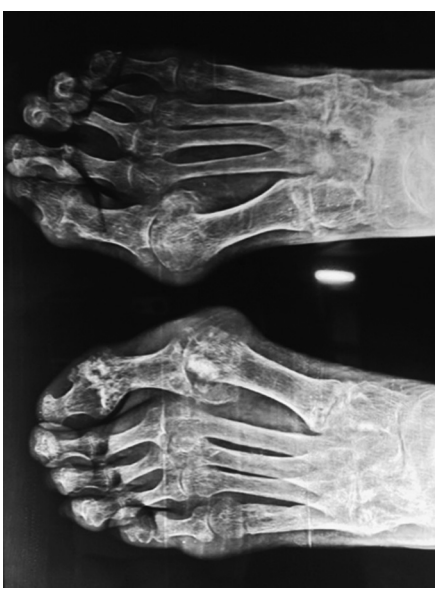


Figure 27.5 X-ray of foot showing erosions with over hanging margins

1. **How do you approach a patient with joint problem to reach to a diagnosis?**

Ans. The first step is to know, if the history is suggestive of inflammatory or non-inflammatory joint pain. Prolonged early morning stiffness of more than 30 minutes is suggestive of an inflammatory pathology. In our case, the stiffness was present throughout the day suggestive of an inflammatory process. The next step to analyze from history and clinical examination, the

number of joints involved. In this case, more than 4 joints were affected, thus making it as polyarthritis. The next step is to ascertain the duration of disease: acute, subacute or chronic. In the above case, it was chronic as history was more than 6 months. Now coming to the pattern of the disease, it is chronic, asymmetrical polyarthritis without any backache or skin and eye involvement. Flow chart 27.1 shows the approach to a patient with joint pain. Table 27.1 gives the difference between inflammed and damaged joints.

Flow chart 27.1 Approach to a patient with musculoskeletal complaints

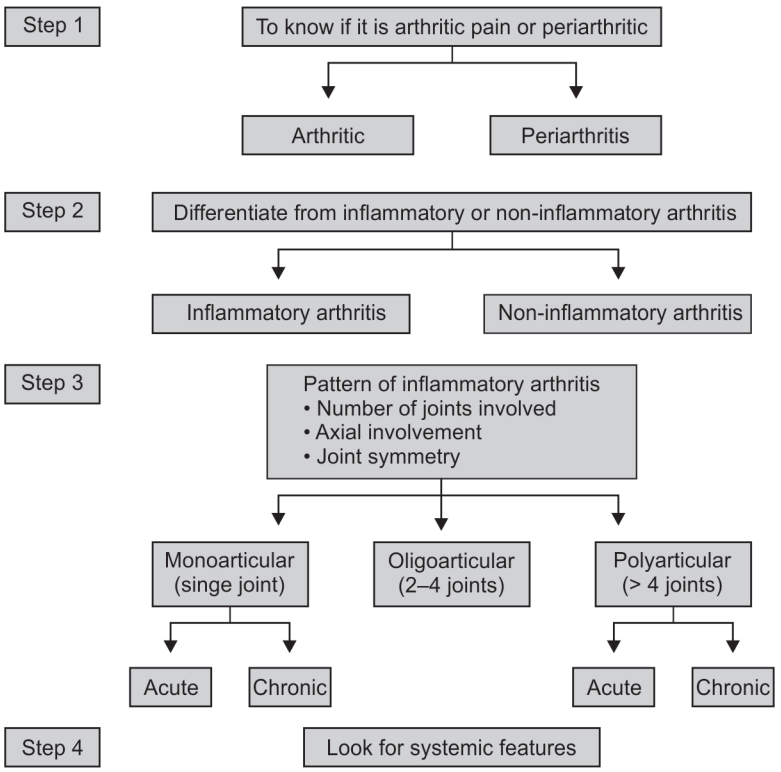


Table 27.1 Difference between inflammed and damaged joints

	Inflammed joints	*Damaged joints*
Early morning stiffness	More than 30 minutes	Usually less than 30 minutes
Stiffness inactivity	Prolonged	Brief
Increased warmth	+	–
Capsular soft tissue swelling	+	–
Effusion	+++	+/–
Coarse crepitus	–	+++
Malalignment/deformity	–	+/–

2. What are the risk factors for gout?

Ans. A typical patient of gout is an obese middle aged man consuming alcohol regularly. Males usually exhibit a rise of serum uric acid levels from puberty, a reason for higher preponderance in males. Females exhibit little change in serum uric acid concentrations until menopause, when uric acid levels rise and reach values equal to that of men.

An association between alcohol consumption and gout has been recognized long ago. The risk varies depending on the type of alcohol ingested. Beer, which is purine rich, carries the highest risk. Diet rich in meat and sea food carries high-risk of gout whereas intake of dairy foods lower the serum urate levels.

Drugs may precipitate acute gout by affecting serum urate levels. Drugs causing gout by increasing urate levels are diuretics, intravenous heparin, cyclosporine.

Other risk factors include trauma, hemorrhage, protein therapy, and infections.

3. What is the classical presentation of gout?

Ans. The basic pattern of clinical gout begins with acute attacks of intensely painful arthritis. The first attack is usually monoarticular and associated with few constitutional symptoms. Attacks occurring later are associated with polyarticular, long lasting, slow and incomplete resolution. Usually, a single joint is involved in 85 to 90% of first attacks, with first MTP joint being the most common site. The initial attack is polyarticular only in 3 to 14% of cases. Ninety percent of monoarticular gout involve great toe. Next in the order are ankles, heels, knees, wrists, fingers and elbows. Acute attacks rarely affects shoulders, hips, spine, sacroiliac joints, sternoclavicular joints or temporomandibular joints. Acute gout affecting up to three sites occurs in one-third of cases and occurrence of four or more sites simultaneously is a rarity.[1]

In most patients, the initial attack occurs with explosive suddenness and commonly begins at night after the individual had gone to sleep. Within a few hours, the affected becomes dusky red, hot, swollen and extremely tender. Systemic signs of inflammation like fever, leukocytosis and elevated ESR can occur. Radiographs usually show only soft tissue swelling during early stages.

The course of untreated gout is variable. Mild attacks subside in several hours to a day or two. But severe attacks may last days to weeks. The skin over the joint desquamates as erythema subsides. With resolution, patient enters inter critical period.

The term "intercritical gout" has been applied to the periods between gouty attacks. Some patients never have a second attack. However, most patients suffer a second attack in 6 to 24 months. Radiological changes may occur in intercritical period also even though there are no signs of tophi. Aspiration of synovial fluid is a useful adjunct to diagnose gout in intercritical period.[1] The frequency of gouty attacks usually increases overtime in untreated patients. Later attacks are less explosive in onset, polyarticular, more severe and lasts longer, resolve more slowly progressing into a chronic and crippling phase of arthritis.

4. What is chronic tophaceous gout?

Ans. After a series of acute gouty attacks with intercritical period, individual enters the chronic phase, which is characterized by polyarticular presentation, increased symptom tolerance and absence of pain free intercritical period. This stage of gout is easily confused with arthritis of other types. The time from initial attack to beginning of chronicity is highly variable. Ten years after the first attack, about half are free of tophi with the other half having minimal tophi. Twenty years after first attack, 28% are free of tophi and 2% have severe crippling disease.[2]

The rate of formation of tophi correlates with both the degree and duration of hyperuricemia. A chronic inability to eliminate hyperuricemia leads to expanding urate pool, deposition of urate crystals in cartilage, synovium, tendons, soft tissues and elsewhere. Tophi are rare in first attack of gout. They are more likely in gout secondary to myeloproliferative diseases, juvenile gout occurring in metabolic diseases like glycogen storage diseases.

Tophi can occur in a variety of locations producing irregular, asymmetric, moderately discrete tumescence of involved joint. Tophi also involve cartilage (anthelix of pinna), bursae (olecranon bursa), tendons (Achilles tendon). Tophi themselves are painless but acute inflammation around them causes pain and eventual destruction causing bizarre deformities. Tense shiny skin over the tophus may ulcerate, extrude white chalky material. Secondary infection of tophi is rare.

Radiographic changes, particularly erosions with sclerotic margins and overhanging edges of bone occur with development of tophi.[2] These may be difficult to distinguish erosions of other causes but the presence of an overhanging bony ridge is strong evidence of gout. USG, MRI can demonstrate images but CT provides the most specific evidence of tophi.

5. How do we confirm the diagnosis?

Ans. Demonstration of negatively birefringent needle shaped monosodium urate (MSU) crystal is suggestive of crystal. MSU crystal can often be demonstrated in 1st MTP and knee joint. According to American College of Rheumatology, criteria used for a presumptive diagnosis include a triad of acute monoarticular arthritis, hyperuricemia, dramatic response to colchicine therapy.

6. How do we manage asymptomatic hyperuricemia?

Ans. The presence of hyperuricemia in the absence of typical clinical picture of gout is not always an indication for antihyperuricemic therapy. Rather, the presence of asymptomatic hyperuricemia indicates the presence of a previously unsuspected disorder which should be investigated and treated like metabolic syndrome. Thus, the common practice is not to treat asymptomatic hyperuricemia until symptoms develop. The only indication to treat asymptomatic hyperuricemia is uric acid more than 10 mg/dL or in a patient who is receiving chemotherapy.[3]

7. How to manage acute gouty arthritis?

Ans. The attack of acute gout can be successfully terminated by early initiation of treatment. The drugs of choice are colchicines, NSAIDs corticosteroids. But the timing of initiation is more important than choice of treatment.[4]

Colchicine: Colchicine is the traditional first line drug for the treatment of suspected acute gout. An oral dose 0.5 mg can be given hourly until GI side effects like nausea, vomiting, diarrhea develop. The recent trend is to give 0.5 mg every 4 to 6 hrs.

NSAIDs: For a case of an established gout, NSAIDs are the preferred first-line treatment. An oral dose of 25 mg four times a day is a starting low dose regimen. The doses can be increased to 50 to 75 mg initial dose followed by 50 mg every 6 to 8 hours with a maximum dose of 200 mg in the first 24 hours. The treatment should be continued for the next 24 hours to prevent relapse. The drugs include naproxen, fenoprofen, ibuprofen, piroxicam, ketoprofen, and ketorolac.

Corticosteroids, both oral and parenteral are required in high doses. A dose of 20 to 60 mg prednisolone per day may be required. Withdrawal of steroids may cause rebound attacks.

Prophylaxis with low dose colchicines or NSAIDs is used to prevent relapse. Prophylaxis is used until there are no attacks for 3 to 6 months and serum urate levels are well in normal limits.

FINAL DIAGNOSIS

Acute polyarticular tophaceous gout.

LEARNING POINTS

Crystal synovitis has the following characteristics:

- Very rapid onset of pain and swelling—at its worst within just 6 to 24 hours.
- Very severe pain—often described as "worst ever".
- Marked tenderness—often unable to bear clothes or bedsheets touching the overlying skin.
- Often florid synovitis with a tense effusion, adjacent soft tissue swelling and overlying erythema (especially gout).
- *Chronic polyarticular gout* may have a similar pattern of distribution as generalized OA. However, almost invariably this is preceded by a period of recurrent monoarthritis in the past.

REFERENCES

1. Burns CM, Wortmann RL. Clinical features and treatment of Gout. In: Firestein GS, Budd RC, Gabriel SE, et al. (Eds). Kelley's textbook of rheumatology, 9th edn. Philadelphia, Pa: Saunders Elsevier. 2012;95.
2. Ar'ev AL, Kunitskaia NA, Kozina LS. Gout and hyperuricemia today: prevalence, risk factors, features in the elderly. Adv Gerontol. 2012;25(3):540-4.
3. Khanna D, Fitzgerald JD, Khanna PP, et al. American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care & Research. 2012;64(10):1431-46.
4. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: A systematic review. Semin Arthritis Rheum. 2014.

CASE

Ringing in Ears in Young Man

28

HISTORY

Mr SK 24-year-old student presented with complaint of ringing in both ears for last 3 months. There was no positional variation and the symptoms were progressively getting bad and he was unable to sleep. There was no history of trauma and addictions. He also occasionally had headache. General physical examination including ENT checkup was unremarkable. Audiometry was normal. Investigations done are tabulated (Table 28.1).

Table 28.1 Laboratory investigations

Parameters	*Patient's value*	*Normal range*
Hemoglobin	19.5 gm/dL	13.0–17.0
TLC	9.8 thousand/uL	4.0–10.0
Platelet count	154 thousand/uL	150–450
Packed cell volume (PCV)	57.2%	40.0–50.0
RBC	6.79 milli/uL	4.50–5.50
MCH	28.7 pg	26.7–31.7
MCV	84.2 fL	83.0–101.0
MCHC	34.1 gm/dL	31.5–34.5
RDW	14.1%	11.6–14.0
DLC	N60, L27	N40–80%, L20–40%

1. What is the likely diagnosis?

Ans. A young person with tinnitus with elevated hemogloblin and packed cell volume (PCV) should be investigated for polycythemia.

FURTHER MANAGEMENT

He underwent other tests like arterial blood gas analysis, serum erythropoietin levels 7.1 mIU/mL (4.3–29.0), *BCR–ABL* gene was negative. RT–PCR for JAK-2 was positive (V617F mutation), LFT and RFT were normal, USG abdomen normal, Chest X-ray normal, MRI head and angiography were normal.

2. What is erythropoietin?

Ans. Erythropoietin (EPO) is a glycoprotein hormone that regulated erythropoiesis. EPO levels in anemia are primarily determined by the degree of anaemia and not by any specific effect of underlying illness on the production of EPO. Morning values are higher than afternoon levels due to the diurnal rhythm of EPO secretion.[1]

Increased levels

- Anemias including aplastic anemia
- *Secondary polycythemia:* High attitude hypoxia, chronic obstructive pulmonary disease, pulmonary fibrosis
- *EPO producing tumors:* Cerebellar hemangioblastoma, pheochromocytoma, renal tumors.
- Pregnancy
- Polycystic kidney disease
- Moderate bleeding in a normal individual.

Decreased levels

- Primary polycythemia
- Anemias secondary to inflammation, rheumatoid arthritis and neoplasms
- Renal failure.

Uses

- To differentiate primary from secondary polycythemia
- To detect recurrence of erythropoietin producing tumors.

3. What is the final diagnosis?

Ans. Polycythemia vera is the final diagnosis. It is a clonal disorder which results in increase in red cell production independent of stimulation by erythropoietin.[2] Polycythemia vera is clubbed as chronic myeloproliferative disorders. Tyrosine kinase Janus kinase-2 (JAK-2) mutation is found in 90 to 95% of polycythemia vera. According to WHO, the diagnostic criteria for polycythemia vera requires 2 major and 1 minor or 1 major with atleast 2 minor criteria (Table 28.2).

Table 28.2 WHO diagnosis for polycythemia vera (2008)

Major criteria	
Hemoglobin	> 18.5 gm/dL in men > 16.5 gm/dL in women
Or other evidence of increase in red cell volume, i.e. unexplained sustained increase in Hb of atleast 2 gm/dL to > 17 gm/dL in men or > 15 gm/dL in women or elevated red cell mass > 25% above normal. The other major criteria is presence of JAK-2 V617F mutation	
Minor criteria	
Bone marrow biopsy showing hypercellularity for age with trilineage proliferation, low serum EPO levels and endogenous erythroid colony formation	

4. What can be clinical presentation of polycythemia vera?

Ans. Many patients of PV are asymtomatic and are diagnosed during routine blood counts. Up to 50% patients have non-specific complaints like weight loss, sweating, headache, visual complaints, fatigue related to low blood

flow due to increased velocity. Other symptoms included generalized pruritus after warm bath, venous and arterial thromboembolic events (major cause of morbidity and mortality), TIA, myocardial infarction, DVT, pulmonary embolism, Budd-Chiari syndrome, peripheral vascular disease.

5. What are secondary causes of polycythemia?

Ans. The most common cause of secondary polycythemia is cigarette smoking. Other causes are elevated EPO due to renal cell carcinoma, hepatocellular carcinoma, uterine fibroid, high altitude chronic hypoxic lung disease, sleep apnea, androgens and kidney transplant.

6. What are principles of management of polycythemia vera?

Ans. Phlebotomy should be considered in all patients with target hematocrit less than 45%. It is one of the fastest way to get hematocrit to normal. Usually 500 mL of blood is removed every 1 to 2 days till hematocrit is less than 45%. Low dose aspirin is given to all patients. The dose is 75 to 100 mg/day except if counts are inadequate. Hydroxyurea should be given to high risk polycythemia vera (age > 65 years, prior thrombosis). A starting dose of 1000–1500 mg/d is installed. Myelosuppression is the main toxicity. The dose should be titrated to ensure that WBC count is higher than 3×10^9/L. Hyperuricemia can be treated with allopurinol. Oral JAK-2 inhibitor (Ruxolitinib) is under investigation. Patient should be instructed to stop smoking, control hypertension and diabetes which are also risk for thrombosis.[3]

FINAL DIAGNOSIS

Polycythemia vera.

LEARNING POINTS

- Secondary polycythemia is more common and is commonly due to smoking, chronic obstructive lung disease, high altitude or tumors (Renal cell cacinoma).
- All patients with polycythemia should have JAK-2 mutation + erythropoietin testing.
- Polycythemia increases risk of thrombosis.
- Aspirin, phlebotomy and hydroxyurea are main stay of therapy.

REFERENCES

1. McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30(6):447-59.
2. Michiels JJ, De Raeve H, Hebeda K, et al. WHO bone marrow features and European clinical, molecular, and pathological (ECMP) criteria for the diagnosis of myeloproliferative disorders. Leuk Res. 2007;31(8):1031-8.
3. Michiels JJ. Institute and Foundation Group, Education Thrombocythemia Vera Study Group FO, Ewg Mpn TA. Physiopathology, Etiologic Factors, Diagnosis, and Course of Polycythemia Vera as Related to Therapy According to William Dameshek, 1940-1950. Turk J Haematol. 2013;30(2):102-110.

CASE

Backache in Elderly Patients

29

HISTORY

A 75-year-old, female patient known case of hypertension and interstitial lung disease (ILD), on steroids for many years presented with complaints of severe pain in lower back for 5 days. Pain was worsened over last 5 days, it was radiating to left thigh till knees. There was no postural variation and pain was aggravated by sitting and coughing and relieved by lying supine, no bowel and bladder involvement. She had no history of recent trauma or fever.

EXAMINATION

Her physical examination revealed blood pressure of 140/90 mm Hg, pulse of 88/min. Chest had bilateral fine crepts. CNS power—left hip flexion 3/5, tone—bilateral normal, sensory—decreased sensation to touch and pin prick at L2/L3 level. Deep tendon reflexes (DTR) normal, straight leg raising test was limited to 40° on left side, tenderness at L2/L3 level on the left side.

1. **What is the probable diagnosis?**

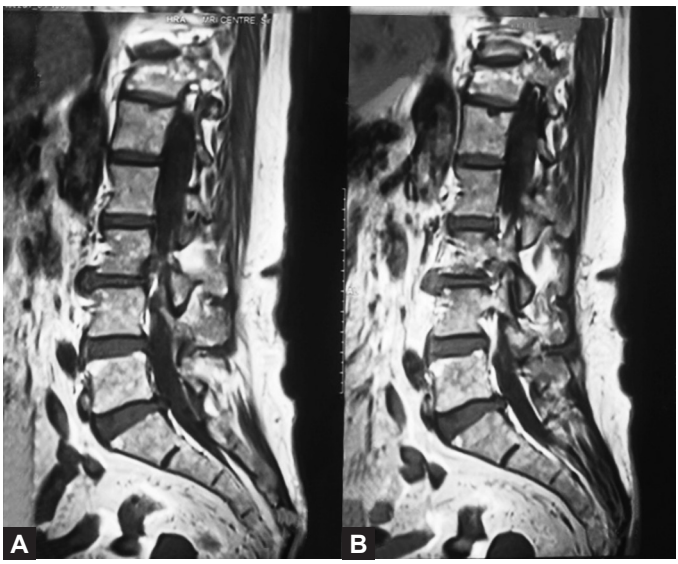
Ans. As the patient was a known case of ILD for past 6 years and on steroids, with local tenderness at L2/L3 level, a diagnosis of ILD, hypertension, steroid-induced osteoporotic fracture with L2/L3 radiculopathy was made and further work-up was done.

FURTHER WORK-UP

Patient underwent MRI spine which showed lumbar spondylosis with an extruded disc lying posteriorly to L3 vertebral body and compressing the thecal sac with left neural recess component (Figures 29.1A and B).

Her routine hematological and biochemical profile (serum alkaline phosphatase, vitamin D, calcium and phosphorus) was within normal limits.

Patient underwent dual energy X-ray absorptiometry (DEXA) scan which showed T-score of –2.5 in lumbar spine and –1.5 in hip. Her fracture risk assessment tool (FRAX) score (major fracture) was 12% and fracture risk (FRISK) score 4.8.



Figures 29.1A and B Extruded disc L3 level

TREATMENT OFFERED

Patient was treated conservatively with intravenous analgesics and other treatment for symptomatic relieve, she was given zoledronic acid (5 mg) intravenous. She showed improvement on the above line of treatment.

2. What are the causes of ILD?

Ans. In most cases ILD, the cause is not known, i.e. idiopathic. Other important causes[1,2] of ILD are :

- *Occupational:* Coal, asbestos, silica.
- *Environmental:* Fumes, gases.
- *Drugs:* Nitrofurantoin, bleomycin, amiodarone, chemotherapy drugs, radiation exposure.
- *Connective tissue diseases:* Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis, systemic sclerosis, Sjögren's syndrome, polymyositis.
- *Pulmonary hemorrhages syndromes:* Good Pastures syndromes, pulmonary hemosiderosis.
- *Gastrointestinal:* Crohn's disease, primary biliary cirrhosis, ulcerative colitis.
- *Inherited:* Tuberous sclerosis, pulmonary Langerhans cell histiocytosis, pulmonary alveolar proteinosis, Gaucher's disease.
- *Rare:* Amyloidosis, eosinophilic pneumonia.

3. What are the causes of low backache?

Ans. Low backache can be divided into inflammatory and mechanical causes:[3]

- *Inflammatory:*
  - Spondylosis
  - Arthritis

  - Atlantoaxial joint disease (e.g. RA)
  - Sacroiliitis
  - Reactive arthritis
  - Vertebral osteomyelitis
  - Septic disc (discitis)
  - Lumbar arachnoiditis
  - Arthropathy
- *Mechanical:*
  - Strain
  - Fractures
  - Trauma
  - Metabolic—osteoporosis, osteosclerosis
- Neoplasms—metastatic, hematologic, primary bone tumors
- Postural
- Vascular—abdominal aortic aneurysm, vertebral artery dissection
- Referred pain from viscera.

4. What are the features of inflammatory back pain ?

Ans. Typically, inflammatory back pain:

- Starts before the age of fourty
- Has been present over 3 months (i.e it is chronic)
- Has come over slowly over time
- Is worse in the mornings
- Causes stiffness in the mornings more than 30 mins
- Improves with exercise and worse with rest
- Improves with anti-inflammatory medication
- Can wake patient from sleep
- Can cause pain in the buttocks

5. What are the predisposing factors for osteoporosis?

Ans. Predisposing factors for osteoporosis can be modifiable and non-modifiable

Non-modifiable

- Female sex
- Advanced age
- Caucasian and Asian ethnicity
- Previous history of fractures
- Family history of osteoporosis
- Early menopause
- Dementia

Modifiable

- Low calcium intake
- Physical inactivity
- Smoking
- Alcoholism
- Recurrent falls
- Low body weight

6. What is FRAX score ?

Ans. The FRAX tool has been developed by World Health Organization (WHO) to evaluate fracture risk of patients. WHO FRAX algorithm, which uses

clinical risk factors, bone mineral density, and country-specific fracture and mortality data to quantify patient's 10-year probability of a hip or major osteoporotic fracture. Included in this are risk factors which comprise of femoral neck bone mineral density, prior fractures, parental hip fracture history, age, gender, body mass index, ethnicity, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis.[4] FRAX was developed by the WHO to be applicable to both postmenopausal women and men aged 40 to 90 years; the National Osteoporosis Foundation Clinician's Guide focuses on its utility in postmenopausal women and men aged >50 years. It is validated to be used in untreated patients only. The current National Osteoporosis Foundation Guide recommends treating patients with FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture, to reduce their fracture risk. Additional risk factors such as frequent falls, not represented in FRAX, warrant individual clinical judgment. FRAX has the potential to demystify fracture risk assessment in primary care for patients with low bone density, directing clinical fracture prevention strategies to those who can benefit most.

FRAX calculation tool: The calculator (available online at *http://www.shef.ac.uk/FRAX/tool.jsp?locationvalue=9*) also can risk adjust for various ethnic groups.

7. When do we measure bone mass?

Ans. Clinical guidelines have been developed for the use of bone densitometry in clinical practice. The original National Osteoporosis Foundation Guidelines recommend bone mass measurements in postmenopausal women, assuming they have one or more risk factors for osteoporosis in addition to age, sex, and estrogen deficiency (Table 29.1). The guidelines further recommend that bone mass measurement be considered in all women by age 65.

Table 29.1 Food and Drug Administration (FDA) approved indication for BMD test

• Estrogen-deficient women at clinical risk of osteoporosis
• Vertebral abnormalities on X-ray suggestive of osteoporosis (osteopenia, fracture)
• Glucocorticoid treatment equivalent to 7.5 mg of prednisone or duration of therapy more than 3 months
• Primary hyperthyroidism

8. What is the management of acute disc prolapse?

Ans. Resumption of normal activity as much as possible is usually the best activity recommendation.[5]

Acetaminophen and NSAIDs are appropriate for pain relief, although severe pain may require short courses of opioid analgesics.

Epidural glucocorticoid injections have a role in providing temporary symptom relief for sciatica due to a herniated disc.

Surgical intervention is indicated for patients who have progressive motor weakness, demonstrated on clinical examination or who have evidence of the cauda equina syndrome or spinal cord compression, generally suggested by bowel or bladder dysfunction, diminished sensation

in a saddle distribution, a sensory level, bilateral leg weakness, or bilateral leg spasticity.[6]

Surgery is also an important option for patients who have disabling radicular pain despite optimal conservative treatment or patients with no relief after 6 to 8 weeks of conservative treatment.

The usual surgical procedure is a partial hemilaminectomy with excision of the prolapsed disc.

FINAL DIAGNOSIS

Interstitial lung disease with acute disc prolapse (L3) with osteoporosis.

LEARNING POINTS

- Red Flag signs of low backache are pain in age <20 or >55 years, stiffness or rest pain (inflammatory backpain), thoracic pain, history of cancers, history of immunosuppressive, weight loss or neurological defects.
- Backpain due to root compression occurs usually between 30 and 50 years, about 70% resolve within 30%.
- Bed rest (1–2 days) and paracetamol and initial therapy for acute disc surgery is indicated for cauda equina syndrome, progressive neurological deficit and neuropathy.
- Lumbar canal stenosis presents as stiffness on walking and decrease on lying down. Surgical decompression is done if there is leg pain rather than backpain or stenosis is focal.
- Glucocorticosteroid-induced osteoporosis (G10) is major concern in patients requiring long-term steroids. All patients for prevention of G10 should receive calcium, vitamin D and bisphosphonate.

REFERENCES

1. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994;150(4):967-72.
2. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157(4 Pt 1):1301-15.
3. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine. 2009;34(10):1078-93.
4. Ettinger B, et al. Updated fracture incidence rates for the US version of FRAX. Osteoporos Int. 2010;21(1):25-33.
5. Jani P, Battaglia M, Naesch E, Hammerle G, Eser P, et al. A randomised controlled trial of spinal manipulative therapy in acute low back pain. Ann Rheum Dis. 2009;68:1420-7.
6. Bhangle SD, et al. Back pain made simple: An approach based on principles and evidence. Cleve Clin J Med. 2009;76:393.

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