CASE REPORTS

Disseminated fungal infection complicated with pulmonary haemorrhage in a case of acute myeloid leukaemia

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Abstract

Pulmonary haemorrhage is a common necropsy finding in acute leukaemia, however, it is rarely diagnosed during life. A man with acute myeloid leukaemia is reported who presented with disseminated fungal infection, anaemia, thrombocytopenia, and subconjunctival and petechial haemorrhages. During the course of the patient's illness, the chest infection was complicated with bilateral pulmonary haemorrhage. The diagnosis of pulmonary haemorrhage was based on characteristic clinical and radiological findings. The patient improved on treatment.

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A 52 year old man presented with the complaints of fever, cough, weakness, oral ulcers, painful swallowing, hoarseness of voice, and painful defecation of two weeks' duration. On examination, he was febrile and had severe pallor; his general condition was poor. Severe thrush was seen over the soft palate and oropharynx. There was generalised petechial rash on the skin along with right subconjunctival haemorrhage and proctitis. There was no organomegaly or peripheral lymphadenopathy.

On investigation, the blood haemoglobin concentration was 53 g/l, total leucocyte count $16.6 \times 10^9/l$, and platelet count $28.0 \times 10^9/l$. Peripheral blood smear revealed 90% myeloblasts. Cytochemistry was suggestive of acute myeloid leukemia (AML M2). Indirect laryngoscopy showed sloughing ulcers over the epiglottis. A chest radiograph was obtained (fig 1) and showed the presence of diffuse, poorly defined nodular interstitial opacities in both lungs. The transverse fissure was thickened. Based on these features, the diagnosis of acute myeloid leukaemia with disseminated fungal infection was made.

He was put on low dose cytosine arabinoside along with amphotericin B, ceftazidime, amikacin, and metronidazole. Daily transfusion of 200 ml of concentrated platelets was given for three days in view of thrombocytopenia and presence of petechial and subconjunctival haemorrhages. He received two units of blood transfusion in addition. There was mild

improvement in his general condition over a few days and he became afebrile. The oral thrush decreased and he was able to swallow semisolid food.

A further chest radiograph was obtained on the 19th day (fig 2) and this showed bilateral, segmental, asymmetric airspace consolidation. It was located in bilateral mid and lower zones and was more pronounced in the perihilar region. The periphery of the lungs were spared and a thick band of the aerated lung was seen separating the area of consolidation from cardiac silhouette. There was no dyspnoea or haemoptysis. The platelet count was $35.0 \times 10^9/l$ at this stage. Coagulation testing was not performed. Bronchoalveolar lavage was not performed because of his poor general condition and the presence of severe oral and pharyngeal thrush.

A third chest radiograph was obtained five days later (fig 3) and showed significant clearance of bilateral airspace consolidation. Chemotherapy and antimicrobial therapy were continued. The general condition and oral thrush improved further. Bone marrow biopsy performed on 37th day of admission confirmed complete remission. The haemogram became normal. He was subsequently discharged with an appointment for second consolidation chemotherapy but was lost to follow up.

Figure 1 Chest radiograph on presentation: diffuse, poorly defined, nodular opacities are seen in both lungs.

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Figure 2 Chest radiograph on 19th day: bilateral, segmental, asymmetric air space consolidation is seen. Peripheries of the lungs are characteristically spared.

Figure 3 Chest radiograph on 24th day: the air space consolidation shows significant resolution.

The radiographic differential diagnosis included diffuse pulmonary haemorrhage (DPH) and chest infection. In a patient with acute leukaemia and oral thrush, the diffuse abnormalities seen on the first chest radiograph should suggest the diagnosis of candida pneumonia.

In a patient with acute leukaemia and a chest infection, the sudden appearance of bilateral consolidation with characteristic features as seen in the second chest radiograph should suggest acute pulmonary haemorrhage as the most likely cause of consolidation. Clinical evidence of petechial haemorrhages, laboratory evidence of thrombocytopenia, and rapid resolution of the consolidation as seen on the third radiograph further substantiate this diagnosis. Segmental distribution of consolidation as well as its sudden appearance and rapid clearance

Box 1: Causes of diffuse pulmonary haemorrhage²

Immunocompetent host

- Antiglomerular basement membrane disease (Goodpasture's syndrome)
- Idiopathic glomerulonephritis
- Connective tissue disorders with systemic vasculitis: systemic lupus erythematosus, Wegener's granulomatosis, Henoch-Schönlein disease, rheumatoid disease
- Idiopathic pulmonary haemosiderosis
- Rare causes: blood dyscrasias, drugs, gases, tumours, trauma, necrotising pneumonia

Immunocompromised host

- Fat embolism
- Leukaemia
- Bone marrow transplant
- Idiopathic

make fungal pneumonia an unlikely cause of consolidation.

Discussion

DPH is a syndrome with few defining clinical and radiological features.¹ It is characterised by widespread haemorrhages from the microvasculature of the lung into the alveolar spaces. While uncommon, it can occur in a wide variety of clinical disorders. The usual causes are Goodpasture's syndrome, connective tissue disorders with vasculitis, and idiopathic pulmonary haemosiderosis among others (box 1).² It can also occur in variety of bleeding disorders including thrombocytopenia in the context of leukaemia.^{1 3 4} A triad of anaemia, haemoptysis, and diffuse alveolar consolidation on chest radiography strongly suggests DPH.^{1 4 5} As haemorrhages occur distal to the mucociliary escalator mechanism, many patients with DPH do not have haemoptysis.^{4 5} Even in absence of haemoptysis, DPH should be suspected on the basis of chest radiographs if the patient has one of the diseases known to be associated with pulmonary haemorrhage.⁵ Radiographic changes of the acute alveolar haemorrhage are the same regardless of the aetiology and consist of airspace consolidation.^{1 2}

Chest radiographs in DPH typically show the sudden appearance of diffuse alveolar filling pattern that ranges from patchy alveolar shadows to widespread confluent consolidation with air bronchogram.^{1 2 4 5} Initially the opacities may have an interstitial pattern but often progress to airspace consolidation as seen in our patient. The consolidation can be widespread or show a perihilar or mid to lower zone predominance and tends to be more pronounced centrally.^{2 5} It is usually bilateral and asymmetric but may be unilateral in distribution.^{1 3 4} The lung periphery, apices, and costophrenic angles are typically spared.^{4 5} As the blood is being absorbed into the

Box 2: Causes of pulmonary infiltrates seen on chest radiography in patients with leukaemia⁶

- Infection
- Haemorrhage
- Leukaemic involvement
- Drug reaction
- Opportunistic tumours (Richter's transformation)

interstitium, the consolidation clears rapidly, often within two or three days, either completely or partially, to leave a reticular pattern or ground glass haziness.^{2,4} Unless bleeding recurs, this interstitial opacities are also transient and clear completely within two weeks from the beginning of the episode.^{2,4} Computed tomography may be helpful and is indicated in patients with haemoptysis in whom a focal cause of haemorrhage such as bronchiectasis or tumour is suspected but it plays a limited part in patients with DPH.¹ The predominant findings on computed tomography are diffuse nodular opacities or ground glass haze.

The radiographic abnormalities are not specific for DPH since diffuse bilateral opacities can be caused by any substance filling the alveoli, for example oedema fluid (pulmonary oedema) or inflammatory exudate (pneumonia). Fortunately, the traditional clinical and radiographic criteria are present in most cases of DPH and the diagnosis can be made with some degree of confidence.⁵ When doubt exists or when treatment options would differ, trans-bronchial or open lung biopsy may be required to make the definitive diagnosis.^{1,5}

PULMONARY INFILTRATES IN LEUKAEMIA

The chest radiographs of patients with leukaemia can be difficult to interpret. These patients are often febrile and have impaired immunological and microbicidal defences as well as bleeding tendencies. The usual causes of pulmonary infiltrates in patients with leukaemia are infection and haemorrhage. Other conditions which need to be included in the differential diagnosis are leukaemic involvement, alveolar proteinosis, and adverse drug reactions (box 2).⁶ Although pulmonary leukaemic infiltrates are commonly found at necropsy, symptomatic pulmonary disease is uncommon. Alveolar proteinosis is uncommon but a well known cause of alveolar opacities in leukaemia and is thought to be a result of impaired phagocytosis by defective macrophages resulting in accumulation of cellular debris and phospholipids in alveoli.⁶ Rarely, pulmonary infiltrates can also occur as an adverse reactions to certain anticancer drugs such as cytosine arabinoside, busulfan, and methotrexate. A diagnosis of drug induced pulmonary disease requires exclusion of other causes and demonstration of histological features specific to the drug effect.⁶

Infection, particularly by opportunistic pathogens, is usually the first and most important consideration after the appearance of infil-

trates on chest radiographs of a leukaemic patient. Whereas common bacterial pathogens are responsible for most of the focal infiltrates, opportunistic organisms tend to produce more diffuse abnormalities.⁷ Bilateral and relatively uniform opacities are usually caused by pneumocystis, viruses, and disseminated fungal or mycobacterial infections. Pulmonary candidiasis may be suspected in presence of oral thrush.⁸ The usual radiographic appearance of candida pneumonia is of multiple nodular or patchy infiltrates in both lungs. These are usually poorly defined and do not follow a segmental distribution. Multiple nodular abscesses may be present occasionally.⁹ A diffuse, miliary, nodular pattern may also be seen.¹ In most patients, however, there are no specific features, partly because of high frequency of other coexisting infections, oedema and haemorrhages. Hence early institution of antifungal therapy based primarily on clinical grounds is recommended.⁹ Candida pneumonia is usually a part of disseminated candidiasis and has a poor prognosis.

The radiographic findings in aspergillus and mucoraceae pneumonia are also non-specific. They commonly produce solitary or multiple areas of pneumonia that slowly increase and may ultimately produce pulmonary infarction.^{1,4} Pulmonary infarction may be seen as a peripheral wedge shaped, pleural based area of consolidation. Viral infections produce interstitial infiltrates or bilateral extensive and diffuse airspace consolidation.

DPH IN LEUKAEMIA

Pulmonary haemorrhage is the most common cause of non-infectious pulmonary infiltrates in patients with leukaemia.⁷ Thrombocytopenia is universal in acute myeloid leukaemia and platelets also show abnormalities of morphology and function. Alveolar haemorrhage is often found at necropsy in patients with leukaemia.^{6,7} However, it is usually not suspected or diagnosed clinically before death because haemoptysis is absent in most patients and chest radiographs often have a non-specific appearance.^{6,10} Although DPH associated with thrombocytopenia alone does occur, it is more commonly a complication of diffuse alveolar damage caused by coexistent sepsis or thrombosis of blood vessels by invasive fungal infection.^{1,4}

The radiographic abnormalities of pulmonary haemorrhage in patients with leukaemia are usually bilateral. Initially the opacities may have interstitial pattern but often progress to bilateral airspace consolidation, which tends to clear rapidly.⁷ These typical radiographic findings are clearly exemplified in the present case. Radiographic changes of uncomplicated acute DPH in patients with leukaemia are the same as those from other causes.² However, most patients have non-specific appearance because of coexisting infection.^{1,2} The risk of uncontrolled bleeding makes invasive diagnostic procedures such as lung biopsy and bronchial brushing hazardous.¹⁰ The presence of increased haemosiderin content in the macrophages obtained by bronchoalveolar lavage may provide indirect evidence of intrapulmonary

haemorrhage.¹⁰ However this procedure may not be possible in patients with severe oropharyngeal thrush and the diagnosis may remain presumptive as in our patient. Although DPH occurring in an immunocompromised patient is often terminal,¹ prompt institution of treatment in our patient resulted in marked clinical and radiographic improvement.

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Primary haematogenous osteomyelitis of the patella: a rare cause for anterior knee pain in an adult

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Abstract

Acute osteomyelitis of the patella is a very rare condition, which commonly affects children between the ages of 5–15 years. Primary haematogenous osteomyelitis in an adult usually occurs in patients with associated risk factors like intravenous drug abuse, HIV infection, and trauma. This report discusses a similar condition in a 46 year old women with no associated predisposing risk factors. The rarity of this condition and its atypical presentation should be borne in mind while treating an adult patient with anterior knee pain. Point tenderness over the patella should alert a physician to the possibility of osteomyelitis of the patella. The value of bone scan and computed tomography in the early stages to help diagnose this condition has been stressed. The literature has been reviewed and discussed briefly.

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The atypical presentation, clinical signs, various investigative modalities, and the treatment of a case of acute primary haematogenous osteomyelitis involving the patella in a 46 year old women with no predisposing risk factors is discussed.

Case report

A 46 year old white woman was admitted under the physicians with complaints of insidious onset pain and swelling in the right knee and calf. There was no history of trauma. She was afebrile and otherwise healthy. On examination of the right leg, generalised tenderness in the leg was noted. However, specific tenderness was not looked for; 90 degrees of painless range of motion in the knee was present. The routine blood investigations and the radiographs of the knee were normal. As the calf was tender to palpation, a clinical diagnosis of deep

venous thrombosis was made, which was excluded by a venogram.

The pain around the knee persisted for six months subsequently, when she was referred to the orthopaedic team. Examination at this stage revealed specific tenderness over the patella and also a knee effusion. A raised erythrocyte sedimentation rate of 24 mm/hour was the only haematological abnormality. Blood culture grew *Staphylococcus epidermidis*, which was thought to be a skin contaminant. Radiographs at this stage revealed a possibility of a lytic lesion in the right patella (fig 1). The

Figure 1 Radiograph showing a possible lytic area in the patella.

Figure 2 Computed tomograms showing erosion of the right patella.

anterior knee pain was further investigated by a technetium bone scan, which showed a hot spot in the region of the right patella. Computed tomograms showed erosion of the patella and the clinical diagnosis of an infective pathology of the right patella was made (fig 2).

Surgery was offered to the patient both with a view to obtain a histological diagnosis and to offer a cure. Arthroscopy revealed an Outerbridge grade 2 change¹ in all the three compartments of the knee. Under the same anaesthetic the patellar erosion was curetted through a midline approach and the tissue sent for histological studies which confirmed the diagnosis of acute pyogenic osteomyelitis. Microbiology culture tests grew *Staphylococcus aureus*. However, the knee aspirate was sterile. The osteomyelitis was treated with intravenous cefuroxime for one week followed by five weeks of oral cephalosporin. The knee was splinted for six weeks in a cylinder cast. At her latest follow up at 18 months she had a painless range of 120 degrees of range of motion in the knee and radiologically the osteomyelitis had healed.

A search for any other infective focus in the body, which could be responsible for acute osteomyelitis of the patella in this patient, was negative.

Discussion

Isolated lesions of the patella are unusual. The list of pathological entities include trauma, degenerative diseases, primary or metastatic tumours, congenital defects, and cysts and infections.² Acute pyogenic haematogenous osteomyelitis of the patella is exceedingly rare in adults and in children under the age of 5 years. The rarity of the disease in children under the age of 5 years may be due to its cartilaginous nature and because of the fact that it has very little blood supply. Vascularisation proceeds with ossification reaching a maximum at 12 years and at 15 years the patella is ossified completely. After ossification the vascularity decreases. The incidence of haematogenous osteomyelitis of the patella is believed to correspond directly to the increased vascularity of the patella which is maximum between 5–15 years of age and hence it occurs commonly in

Learning points

- Acute haematogenous osteomyelitis of the patella usually affects children between the ages of 5–15 years. It is, however, exceedingly rare in adults. Five similar cases (excluding this one) in adults have been described in the literature, but all were associated with a predisposing risk factor like HIV infection, intravenous drug abuse, or trauma. Our patient was a healthy adult with no associated predisposing risk factors. We think this is the first report of its kind in the English literature.
- This condition should be included in the differential diagnosis for anterior knee pain in an adult patient.
- Awareness of this rare condition, which can occasionally baffle treating physicians and surgeons, is necessary and could help prevent delay in management.
- Early treatment by surgical debridement and administration of sensitive antibiotics ensures an optimal result and prevents the sequel of septic arthritis.
- Careful clinical examination is mandatory. Pinpoint tenderness over the patella can raise the index of suspicion for acute haematogenous osteomyelitis of the patella. This is probably the single most useful clinical sign. Raised infective haematological markers like C reactive protein and erythrocyte sedimentation rate would also raise the index of suspicion.
- Technetium bone scan and computed tomography are useful diagnostic tools and should be used where necessary.

this age group.^{3–6} This could also account for it being rare in adults where the vascularity is reduced. In adults a history of trauma is usually present in most of the cases. It is also often believed to be the sequel of a prepatellar bursitis.⁵ *S aureus* is perhaps the most common organism responsible for causing acute osteomyelitis of the patella.⁷ Tuberculous osteomyelitis is also an entity of which one should be aware, but it often tends to be multifocal.⁷

We could find five cases of acute pyogenic osteomyelitis of the patella in adults described in the literature, but all had an associated risk factor. The first patient was a 25 year old man who had pseudomonas osteomyelitis of the patella but he was an intravenous drug abuser.⁸ The second case was in an adult who was suffering from HIV.⁹ Brodie's abscess of the patella has also been described in a 24 year old man after a history of trauma.¹⁰ Pyogenic osteomyelitis has been described by Kochar and Srivastava in a 32 year old who had a history of trauma.⁷ The fifth case was recognised after a pathological fracture of the patella in a 57 year old patient with multiple myeloma.¹¹

The authors believe that this is the first reported case of primary acute haematogenous osteomyelitis of the patella without any predisposing risk factors. Routine plain radiographic evidence is not always of help because the patella is a sesamoid bone in the tendon of quadriceps femoris and is covered by thin lamina with no real periosteum. Periosteal elevation, which is one of the hallmarks of osteomyelitis, is hence absent in patellar infections.³ Pinpoint tenderness over the patella can raise the index of suspicion for acute haematogenous osteomyelitis of the patella. This is probably the single most useful clinical sign. Bone scan is a helpful diagnostic tool to localise the problem initially while computed tomography confirms the diagnosis. Though no associated septic focus was found in this case, a careful search to look for one should be made.

The articular cartilage in an adult is thinner than in the child; thus, articular involvement is more likely in the adult.⁹ Sympathetic effusion is often present and can result in a sterile aspirate as we had in this case. Early diagnosis and treatment is hence essential to prevent the eventual complication of septic arthritis.

The authors feel that osteomyelitis of the patella should be ruled out while treating a common condition like anterior knee pain in an adult for which a certain cause has not been

identified. This should be included as one of the rare causes for anterior knee pain in an adult. Careful clinical examination along with a raised erythrocyte sedimentation rate or C reactive protein can alert the treating physician of this rare condition, who can then use computed tomography to confirm the diagnosis. Only awareness of the existence of this condition can raise the index of suspicion in the treating physicians and thus avoid the delay in the diagnosis and management as we had in this patient.

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