A deadly thorn prick

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Introduction

Infection is a leading cause of morbidity and mortality among haemodialysis patients. Some of the risk factors specific to this population include repeated access to the blood stream through venous cannulation for dialysis as well as a higher prevalent usage of prosthetic materials like haemodialysis catheters and arteriovenous grafts. In addition, defects in immunity and phagocytosis also contribute to the increased risk of infection. Both iron overload [1] and its treatment, desferrioxamine (DFO), predispose haemodialysis patients to infections [2, 3]. We describe here a fatal case of Cunninghamella bertholletiae infection in a haemodialysis patient with transfusional iron overload while receiving DFO.

Case history

A 59-year-old man was admitted with fever and shortness of breath. He had a complex past medical history. He underwent deceased donor renal transplant in 1989 for end-stage renal disease secondary to chronic gout and interstitial nephritis. He developed chronic allograft nephropathy in 1996 and was reinitiated on haemodialysis in 1997. Four years later, he had coronary artery bypass grafting and prosthetic aortic valve replacement. His international normalized ratio (INR) was maintained between 3 and 4 on warfarin. The renal allograft was removed in 2002 because of graft pyelonephritis. He did not have diabetes. Two years later, his anaemia became refractory to high-dose darbepoetin therapy (200 μg IV a week). Bone marrow examination showed relatively reduced erythropoiesis with mild dyserythropoiesis. Iron stores were increased. No cytogenetic abnormalities were detected in the marrow. He required 3–4 units of packed red cell transfusion a week for more than a year to keep his haemoglobin >80 g/L. As a consequence of repeated blood transfusions, he developed haemosiderosis with a serum ferritin of 2400 μg/L (normal range 15–150 μg/L) and transferrin saturation of 100% (range 15–50%). He received IV DFO at a dose of 50 mg/kg each dialysis session for 6 months before the current presentation.

Three weeks prior to the final admission, he developed fever and swelling of the left calf following a thorn prick injury. He had received oral ampicillin and ciprofloxacin for 10 days prior to the current admission, but there was little improvement in his clinical state. On admission, he had high-grade fever (38°C), left-sided pleuritic chest pain and hypoxia. Salient investigations included: C-reactive protein 250 mg/L (0–5 mg/L), haemoglobin 83 g/L (130–150 g/L), D-dimer 0.22 mg/dL (range 0.00–0.25 mg/dL), INR 6.7 and erythrocyte sedimentation rate 92 mm/h (0–30 mm/h). Repeated cultures of urine and blood were sterile. Chest X-ray showed an enlarged heart with a left mid-zone infiltrate. Ultrasound of the injured left calf revealed a hypoechoic region measuring 1.3 × 1.0 × 0.4 cm in the subcutaneous tissue. There was no post-acoustic shadowing to suggest a collection and this was reported to be consistent with a scar. A contrast-enhanced computerized tomogram of the chest revealed an elongated tubular filling defect within the pulmonary artery to the left lower lobe with some patchy air space changes without pleural effusion, suggesting pulmonary thromboembolism, later confirmed by a computed tomography (CT) pulmonary angiogram. Transoesophageal echocardiogram showed moderate left ventricular dysfunction and did not reveal any vegetation. On admission, he was initiated on IV vancomycin and meropenem in renal modified doses.

The patient deteriorated over the next 3 days despite broad spectrum IV antibiotics with worsening hypoxia, left-sided consolidation and pleural effusion. Bronchoalveolar lavage (BAL) showed the growth of Acinetobacter. Despite intravenous meropenem, he developed multiorgan failure requiring inotropic support and mechanical ventilation. A repeat CT pulmonary angiogram did not show any fresh pulmonary embolism, but showed worsening lung opacification.

The patient underwent left lower lobectomy for worsening sepsis. Meanwhile, cultures from the BAL fluid grew Cunninghamella, later identified both on the histopathology of resected lung and in the pulmonary thrombus. IV amphotericin was commenced once culture
results were obtained. Microscopy of resected lung revealed extensive infarction with many organizing thromboemboli in arteries of varying calibre. The affected blood vessels showed focal transmural necrosis with marked suppuration along with irregularly branching fungal elements (Figures 1 and 2). The patient suffered neurological deterioration subsequently with a CT scan of the head revealing multiple acute infarcts involving both the frontal and parietal lobes. The patient died a week later despite treatment with amphotericin B and broad-spectrum antibiotics.

Discussion

Iron overload, evidenced by high ferritin levels in excess of 650 μg/L, has been observed in up to 15% of the dialysis population [4, 5]. Dialysis patients with iron overload are at increased risk of infection and infections contribute significantly to mortality of the dialysis patients. Boelaert et al. [1] observed a 3-fold increase in infection in patients with serum ferritin >1000 μg/L. Incidence of infection in dialysis patients ranges between 0.9 and 3.5 episodes per 100 patient-months. Vascular-related infections cause up to one-third of these infections. Galic et al. [6] observed a higher incidence of sepsis in patients with serum ferritin in excess of 500 μg/L. In this study, the incidence of vascular access-related infection was also higher in those with higher ferritin levels.

Iron chelating therapy is indicated in patients requiring long-term red-cell transfusion such as patients with sickle cell disease and thalassaemia major. However, indications for iron chelating therapy in long-term dialysis patients are limited to those with poor response to erythropoietin requiring repeated blood transfusion. Three preparations are currently available for transfusional iron overload, intravenous DFO, oral deferasirox and oral deferiprone. A detailed discussion of the individual agents is beyond the scope of this article, but the reader is referred to a recent excellent review on this subject [7]. DFO is the preferred agent in patients with established cardiac failure.

Cunninghamella infection

Among fungi, organisms belonging to the order Mucorales (class Zygomycetes) cause life-threatening opportunistic infections in predisposed hosts. The order Mucorales includes genera Mucor and Cunninghamella [8, 9]. Cunninghamella bertholletiae is the only pathogenic species among Cunninghamella and disseminated infection of this species has been previously described in a renal transplant recipient [10]. Risk factors for development of disease include diabetes mellitus, malignancy, solid-organ transplantation, immunosuppressive therapy, iron overload state and DFO therapy [9, 11]. Pathologically, the fungal hyphae invade blood vessels and form mycotic thrombus within the vessels leading to infarction of tissues.

Infection occurs either by inhalation of sporangio- phores or secondary to direct inoculation by penetrating trauma. The clinical manifestations are varied and include rhino cerebral, pulmonary, cutaneous, abdominopelvic, isolated gastric and disseminated forms.

A striking association was noted in the 1980s between the use of DFO therapy for aluminium/iron overload and development of mucormycosis. Boelaert et al. [2] initiated an international registry and reported 59 cases of mucormycosis in dialysis patients. Mucormycosis was disseminated in 44%, rhino cerebral in 31% and other forms in 25%. Antemortem diagnosis was made in only one-fifth of patients. As to be expected, the organism was cultured only in 36% of cases. The outcome was dismal in most of these patients, with a mortality of >85%, and most patients died within 3 weeks of diagnosis. This cohort of dialysis patients was distinct in that the conventional risk factors for development of opportunistic fungal infection such as diabetes mellitus, liver disease, splenectomy, neutropaenia or immunosuppressive therapy were not seen in over 70% of that population. Of note, almost 80% of these patients were being treated with DFO at the time of development of fungal infection.

Several factors have been proposed for the pathogenic effect of DFO in the development of mucormycosis. Iron is a growth factor required for the growth of many microorganisms. Siderophores are synthesized by microbes for the uptake and transfer of essential iron from the

Fig. 1. Thromboembolus in a small pulmonary artery. H&E ×400.

Fig. 2. Irregular branching fungi within arterial thromboemboli. Grocott stain ×600.
surrounding media and host. Mucor are non-siderophore producing organisms. Van Cutsem et al. [12] proposed that DFO acts as a siderophore for mucor. DFO combines with iron to form ferroxamine. This complex functions as a siderophore for the organism and helps in transfer of iron, needed for its growth, into the fungal cell.

Ferroxamine is normally excreted by the kidneys. Pharmacokinetic changes in renal failure lead to prolonged circulation in patients with renal failure compared with those with normal renal function. This also increases the risk of mucormycosis in dialysis patients [13].

The role of iron overload in development of mucormycosis has been debated earlier. Mucormycosis has been noted in bone marrow transplant recipients with iron overload, not exposed to DFO treatment and in anephric patients with transfusional iron overload [13]. These observations have given credence to iron overload as a possible risk factor for developing mucormycosis. Iron adversely affects the phagocytic, chemotactic and bactericidal capacity of neutrophils and monocytes [14]. Iron overload also inhibits the activity of natural killer cells and macrophages. Normally, iron is bound to high-affinity proteins like transferrin and the amount of free iron for microorganisms is very low. Following exogenous administration of large amounts of iron secondary to repeated transfusion, serum transferrin is highly saturated and there is an excess of non-transferrin-bound serum iron.

A few microorganisms (Klebsiella, Salmonella typhimurium, Yersinia and Vibrio vulnificus) have the ability to take up iron from ferroxamine and this accentuates both in vitro growth and pathogenicity of these organisms. Iron overload was a major risk factor in an outbreak of Yersinia in one dialysis population [2]. These observations underline the importance of iron overload in predisposing to infection.

DFO, widely used before in the dialysis population for aluminium and iron overload, is less commonly used now. The advent of erythropoiesis-stimulating agents and the resultant decrease in transfusion requirement has limited iron overload to a very select group. Similarly, the sparing use of aluminium-based phosphate binders and better water treatment facilities have virtually eliminated aluminium overload from the Western world. Both oral preparations, deferasirox and deferiprone, are non-siderophores and may be used as an alternative to DFO in dialysis patients in view of the infectious risks associated with DFO.

Our patient initially developed a septic thrombus and later pulmonary embolism despite adequate anticoagulation with warfarin. Uraemia, iron overload and DFO therapy contributed to systemic fungal dissemination in our patient. Typically, the infection caused angioinvasion and a hemorrhagic infarct of the lung, as evidenced in our case by the growth of C. bertholletiae in both the thrombus and resected lung specimens. The clinical presentation was compatible with descriptions in the literature, with fever unresponsive to antibacterial therapy, pleuritic chest pain and dyspnoea. The terminal neurological signs and lesions on cerebral CT suggest brain involvement secondary to the haemorrhagic spread.

Early diagnosis is critical in successful management of this infection, but this is rare in view of the poor isolation of Mucor by culture. Histological examination of biopsied tissue is the preferred method of diagnosis. Invasion seen on histopathology with special stains combined with a high level of suspicion is needed to confirm the diagnosis.

In patients with pulmonary involvement, diagnostic yield with BAL is less than with a lung biopsy [10] and hence early biopsy of lung lesions should be considered. Polymerase chain reaction assays, targeting 18S ribosomal DNA in the blood, may become a diagnostic tool of the future to identify these organisms [15].

Antifungal therapy with amphotericin B, surgery, and correction of the underlying predisposing condition all form important components of therapy. Prognosis is better with combined medical and surgical therapy than with either alone [16].

In summary, we describe a fatal, disseminated infection due to Cunninghamella in a dialysis patient with iron overload on DFO therapy. Despite an early diagnosis combined with surgical removal of the infected lobe of lung and use of amphotericin B, the patient succumbed to the infection, underlining the catastrophic nature of this illness.

Chelating therapy with DFO in dialysis patients is fraught with side-effects and hence iron and aluminium overload should be prevented in this population. Decisions about DFO therapy in dialysis patients require careful consideration of all the options including the possibility of using an oral chelating agent. A high index of suspicion of mucormycosis in a patient presenting with infection while receiving DFO therapy should help to improve the outcome of this disease.

Teaching points

1. Iron overload occurs in up to 15% of dialysis patients, and these patients are at increased risk of infection.
2. Mucormycosis is an uncommon, often fatal infection in haemodialysis population, and should be suspected in appropriate clinical settings on a background of iron overload and IV DFO therapy.
3. Use of IV DFO to treat transfusional overload should be limited to exceptional cases only. It is advisable to use the lowest possible dose (5–10 mg/kg/week). Administering the drug 8 h before dialysis optimizes iron chelation and allows dialysis to remove chelates quickly from circulation, reducing the risk of infection.
4. Oral deferasirox, a non-siderophore, should be considered as an effective alternative to DFO therapy in treatment of iron overload in haemodialysis patients and this drug does not predispose to mucormycosis.

Conflict of interest statement. None declared.

References


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