CASE REPORTS

Native valve Aspergillus endocarditis in two patients with aplastic anaemia

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Abstract

Native valve fungal endocarditis is an uncommon disease with a high mortality rate. We present the clinical features, histological findings and outcome of 2 patients with native valve Aspergillus endocarditis. Both patients had aplastic anaemia as a predisposing disease. The diagnosis was made by Duke’s criteria in 1 case and by histology in the other. Surgery was precluded owing to profound thrombocytopenia. Both patients had fatal outcome despite administration of liposomal amphotericin B.

Introduction

Aspergillus causes several distinct syndromes in both immunocompetent and immunocompromized patients. The particular form of aspergillosis that develops is determined by the immune status of the host. Invasive pulmonary aspergillosis occurs mainly in severely immunosuppressed persons. Although widespread dissemination of the organism occurs and may affect any organ, native valve endocarditis due to Aspergillus is uncommon [1]. In this report we present the clinical features and outcome of 2 patients with aplastic anaemia whose clinical course was complicated with native valve Aspergillus endocarditis.

Case reports

Case 1

A 17-year-old white, male student was admitted to the hospital because of jaundice, increased transaminases (AST 868 IU/l, ALT 259 IU/l), and bilirubin (total 6.47 mg/dl, direct 5.01 mg/dl). The patient had had mild epigastric pain for 3 d before his admission. His past medical history was free and he denied use of alcohol, tobacco or recreational drugs. No other people in his environment, either at school or at home, had similar symptoms. On physical examination he was lean, in no acute distress, with jaundice of the skin and conjunctivae, small painless enlargement of neck lymph nodes and palpable liver and spleen. His vital signs were normal. His laboratory examinations showed: white blood cells count 5600 cells/mm3 (neutrophils 66%, lymphocytes 21%, monocytes 12%, eosinophils 0.4%), haemoglobin 16.1 g/dl, platelets 242,000/mm3, sedimentation rate 5 mm/h, prothrombin time 17.3 s, glucose 4.1 mmol/l, urea 3.3 mmol/l, creatinine 64 mmol/l, AST 1481 IU/l, ALT 1646 IU/l, total bilirubin 13 mg/dl, direct bilirubin 9.3 mg/dl, alkaline phosphatase 221 IU/l, γ-GT 47 IU/l (5–45), total protein 64 g/l (68–87), albumin 44 g/l (34–53), IgM anti-HAV Ab (−), HBsAg (−), anti-HBcAb (−), anti-HCV Ab (−), HIV (−), antinuclear antibodies (−), Mantoux (−), chest X-ray: normal. An upper abdominal ultrasound showed increased dimensions of the liver, with homogeneous echogenicity, non-calculous cholecystitis and no dilation of the biliary tract. The hepatocellular damage was further investigated by HCV-RNA, HBV-DNA antibodies against various viruses (EBV, HSV, CMV, Coxsackie, parvo B19), antibodies against Leptospira and Leishmania,
and levels of copper of blood and urine. All the tests were negative.

During hospitalization the transaminases and bilirubin increased, but there were no signs of hepatic encephalopathy. Two weeks after admission the patient started to be febrile (38.5°C). The work-up did not reveal a site of infection and the patient was treated empirically with ceftriaxone for 5 d. Three weeks after admission aplastic anaemia developed, with initial small decrease of white cells and haematocrit, but abrupt and rapid decrease of platelets. The patient was treated with immunoglobulin, with no results. His haematological status deteriorated (WBC 500 cells/mm³, neutrophils 55%, Hgb 8 g/dl, Plt <10,000/mm³) and he was treated with anti-lymphocytic serum, cyclosporin and growth factors. He also received small doses of corticosteroids for a short period of time. His growth factors. He also received small doses of corticosteroids for a short period of time. His aplastic anaemia showed some signs of improvement with anti-lymphocytic serum, cyclosporin and growth factors. He also received small doses of corticosteroids for a short period of time. His aplastic anaemia showed some signs of improvement (transaminases and prothrombin time returned to normal and only the increased bilirubin remained). However, fever developed and the patient was treated with imipenem, vancomycin and amikacin. A chest X-ray showed a consolidation at the lower lobe of the right lung. Two nodular lesions, 1 on each lung, with halo sign, were seen on CT scan, as well as a large pleural effusion on the right side.

The patient was still neutropenic and febrile and a diagnosis of possible aspergillosis was made. He was treated with liposomal amphotericin B (AmBisome) for 1 month (7 mg/kg, total dose 9 g) but he remained febrile. He also received empirical treatment for tuberculosi for 2 weeks, but it was discontinued because he did not respond. During his treatment with AmBisome he continued imipenem and vancomycin. Haemothorax developed as a result of a pleural tap, and, possibly due to injury to the liver, bleeding in the abdominal cavity, which necessitated surgical treatment. The white and red cell counts improved, but the platelets remained low (<30,000/mm³). The fever persisted and an open lung biopsy was performed. The histology of the nodular lesion of the right lung confirmed the diagnosis of invasive aspergillosis. A few d later haemorrhage in the right hemithorax was noted and the patient was re-operated. He was admitted to the intensive care unit.

A cardiac ultrasound revealed a vegetation of the mitral valve and the diagnosis of fungal endocarditis was made. The patient remained febrile and, additionally, an embolus on the right cerebral artery produced a large haemorrhagic infarct as well as subarachnoid haemorrhage. Caspofungin (MK-0991) was given to the patient on a compassionate basis, but he expired 1 week later due to respiratory failure.

Case 2

A 31-y-old white female, with a free past medical history, was admitted to the hospital because of a recent history of bleeding of the gums and bruising. She presented the first signs of her disease, petechiae and ecchymoses, 3 months before admission, while 10 d earlier, bleeding from the nose and oral mucosa were added.

On physical examination, the patient was an obese woman in no acute distress, afebrile, but pale, with several petechiae and ecchymoses. Examination of the head, eyes, ears, nose and throat revealed epistaxis and mucosal bleeding. There were no conjunctival or retinal lesions, or adenopathy. On examination of the chest her lungs were clear to auscultation and her heart was normal. Examination of the abdomen and extremities was unremarkable, except for several bruises on her limbs. Neurological examination revealed no focal deficits. Her laboratory tests included a haematocrit of 28%, WBC of 3100 cells/mm³ and a platelet count of 9000/mm³. The ESR was 100 mm and blood chemistry was within normal range.

Bone marrow examination confirmed the diagnosis of aplastic anaemia. Chest radiography and ECG were normal. The patient received initially gamma-globulin and high doses of steroids (methylprednisolone) and subsequently growth factors (erythropoietin and GM-CSF) and androgens, but her haematological status remained unchanged.

On d 20 of her hospitalization, CT scans of the chest and abdomen were performed, because of a low grade fever (37.5°C–37.9°C), and they were normal. Empirical treatment with amoxicillin and then with amoxicillin-clavulanate was given for 10 d. The patient continued to receive treatment for her aplastic anaemia and remained afebrile.

On d 80 of hospitalization, while afebrile, she complained of pain at the right upper quadrant of the abdomen, radiating to the right shoulder. Neurological examination revealed mild weakness of the right upper limb. A chest CT scan showed multiple nodular lesions bilaterally, while a brain CT scan showed small ring-shaped lesions. Fine needle aspiration of the lung lesions was performed twice, but produced no results. She was started on imipenem-cilastatin and cotrimoxazole on the presumptive diagnosis of nocardiosis. About a week later her neurological condition deteriorated and she developed left hemiparesis. Three nodules were noted on the skin of her limbs. One of the skin
nodules was excised for biopsy and culture. The direct microscopic examination, after preparation with KOH 20%, showed septate hyphae and the culture of the skin tissue yielded Aspergillus fumigatus. A. fumigatus was also isolated from the nasal cavity, although no signs of local inflammation were present.

Treatment with AmBisome was started (5 mg/kg). The patient started to have a fever and it was not clear whether this was related to AmBisome. A chest X-ray showed pleural fluid in addition to the previous lesions, as well as an increase of the dimensions of the heart. On d 20 of treatment with AmBisome the patient started to have dyspnoea and tachycardia. On auscultation, a faint systolic murmur was noted. A heart ultrasound revealed vegetations of the mitral and aortic valves.

10 d later worsening of the neurological condition was observed and 20 d later the patient’s temperature increased to 39°C.

The patient received a total of 17 g of AmBisome and itraconazole for 69 d (initially 800 mg daily and later 200 mg daily due to hepatotoxicity). Surgery was precluded due to profound and unresponsive thrombocytopenia. Despite treatment, the patient died, after 6 months of hospitalization, because of brain haemorrhage.

On post mortem examination, multiple mural, yellow-grey, necrotic lesions, up to 0.6 cm in diameter, were found on the epicardium, myocardium and endocardium. The mitral and aortic valves were covered by similar, cauliflower-like vegetations. A large frontal subdural haematoma was found. Multiple thromboembolic lesions, associated with areas of haemorrhagic infarction, were found on the cortex, as well as the parenchyma of the basal brain areas and of the cerebellum, while extensive subarachnoid haemorrhage was noted. Similar emboli were present in the upper lobe of the left lung, the left kidney, the spleen and the intestine. Microscopic examination of the vegetations and several sections of all the affected organs revealed typical branching septate hyphae, consistent with Aspergillus.

**Discussion**

Fungal endocarditis is an uncommon complication of prosthetic valve surgery, drug addiction, indwelling catheters and immunosuppression [1,2]. The incidence of endocarditis due to Aspergillus species has increased since the 1960s, mainly because of the greater frequency of cardiac valve replacement surgery [1–9]. Aspergillus endocarditis in native valves remains uncommon. In 2000, Gumbo et al. [10] reported 3 such cases and reviewed 58 other adult patients reported in the English language literature. Four additional cases have since been published [11–13]. The majority of such cases have occurred in immunocompromized patients.

We present here 2 cases of patients with aplastic anaemia, complicated by invasive aspergillosis that involved the heart. In the first patient the aplastic anaemia was a result of non A-E hepatitis.

Both patients had invasive pulmonary aspergillosis that progressed to widespread dissemination and resulted in endocarditis. Factors predisposing to Aspergillus endocarditis are those that predispose to invasive disease [17]. Patients with haematological malignancies who receive chemotherapy, patients who receive large or prolonged doses of corticosteroids, and patients who are on antilymphocytic therapy have an increased risk for Aspergillus infection [10]. In Gumbo’s review some patients had anergic skin reactions to trichophyton and mumps skin tests, suggesting that T-lymphocyte defects may be important in invasive Aspergillus infections. According to Woods et al. [18], who reviewed the medical literature and documented 28 cases of Aspergillus endocarditis in patients without prior cardiac surgery, the most common predisposing factors were steroid therapy (55%), followed by prolonged antibiotic treatment (31%), haematological malignancy (28%) and cytotoxic therapy (28%). Another potential risk factor is the long-term presence of intravascular catheters, particularly those that enter the right side of the heart [2,19,20]. Our patients had no past history of cardiac surgery or any pre-existing valvular abnormalities, which are critical for the development of fungal endocarditis [21]. However, it can be argued that since Aspergillus is angioinvasive, the mechanism of endocarditis might be different. Both patients had immunosuppression due to their aplastic anaemia and they both received broad-spectrum antibiotics. In addition, the first patient received anti-lymphocytic serum and cyclosporin and the second, large doses of steroids. The role of cyclosporin in fungal infections remains ambiguous. There are reports of cases where it was a predisposing factor to Aspergillus infection [22], but there is also increasing evidence that cyclosporin acts synergistically with antifungal agents, both in vitro and in vivo [23,24].

In a review of 270 cases of fungal endocarditis [25], the most common clinical manifestations were fever (74%), changing or new heart murmurs (50%) and symptoms due to major peripheral embolizations (48%). Fever ranked high among the earliest presenting symptoms, often accompanied by cytokine-mediated phenomena, such as chills, sweats and fatigue. 26% of patients had prominent central neurological presentations. It has been noted by several authors [10,18] that the classical signs of
endocarditis (Osler nodes, splinter haemorrhages, Roth spots, and glomerulonephritis) are seen much more rarely in fungal endocarditis. In the first case described here fever was the main symptom, while in the second case the patient was afebrile. In this patient, the initial symptoms, which were subsequently attributed to Aspergillus, were due to emboli of the central nervous system. In both cases, it is not clear whether the endocarditis was the initial source of Aspergillus, or whether it followed the lung infiltration. The diagnosis of Aspergillus endocarditis in the first patient was made according to Duke's criteria [26], based on the finding of vegetations on the echocardiogram (major criterion) and the presence of continuing fever and embolic haemorrhagic brain infarct (minor criteria). However, these criteria refer to bacterial endocarditis and might not apply to fungal endocarditis. Although blood cultures are always negative in Aspergillus endocarditis they should always be performed to exclude other concomitant causes of endocarditis. In the second case, the demonstration of septate branched fungal elements in the skin biopsy and isolation of Aspergillus fumigatus from the skin culture, while blood cultures were negative, as well as the findings on ultrasound, led to the diagnosis. The presence of distinctive skin lesions as a diagnostic clue to fungaemia is highlighted [25]. Newer diagnostic techniques, such as serology and molecular tests (PCR) may help establish the diagnosis earlier [27].

In Aspergillus endocarditis, internal organs such as the brain, lungs, kidneys and mesentery, are often infiltrated. Neurological manifestations, secondary to cerebral embolization, occur in up to 30% of cases [10]. In our case, neurological complications predominated and finally became fatal. The mortality rate of Aspergillus endocarditis is about 95% [10]. It appears that survival of patients with Aspergillus endocarditis is very low and is always related to the early diagnosis and surgical valve replacement [10,18]. In our cases surgical treatment was impossible because of severe thrombocytopenia.

Although the need for surgical replacement of the infected valve is well documented, the optimal antifungal chemotherapy has yet to be established [28]. Our patients were treated with a liposomal preparation of amphotericin B (AmBisome). In the first case, AmBisome was changed to caspofungin, but the patient survived only for a week thereafter. The second patient who received combination of liposomal amphotericin B with oral itraconazole survived for 79 d. On post mortem examination, multiple mycotic emboli were found in most internal organs. Involvement of the epicardium, myocardium and endocardium, with vegetations on the mitral and aortic valves, was found. The presence of septate hyphae on several organs proved that the fungus survived despite aggressive antifungal chemotherapy.

References


Enhanced chickenpox exanthema in vaccine injection site

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Abstract
Exacerbation of viral exanthema has been described after different types of aggression. We report a case of enhanced chickenpox exanthema occurring in the vaccination site of an otherwise healthy boy. Specific local inflammatory modifications may explain the increased number of varicella skin lesions on the site of a previous vaccine-induced inflammation.

Case report
A healthy 19-month-old boy presented at our paediatric office on 23 April 2004 for a skin rash with fever (38.2°C). The parents reported that their child had no significant past medical history and that his immunizations were up-to-date, but that he was in contact on 8 April with an index case of varicella. On 14 April, he had received an intramuscular booster dose of DTPaIPV-Hib vaccine in the right deltoid, according to the French immunization schedule. Local swelling (3 to 4 cm in diameter), redness and pain were present at the injection site during the subsequent 4 d. These local inflammatory reactions were not associated with fever and disappeared progressively. On 21 April, vesicular skin lesions appeared and located preferentially on the right shoulder (Figure 1), exactly at the site of the vaccine-induced local reactions. The vesicles were all at the same stage of development. A diagnosis of varicella was established based on the skin lesions and the positive history. Fever disappeared 2 d after the appearance of the exanthema, no new lesions occurred, and recovery was complete.

Discussion
The exacerbation of viral exanthema has been described following various stimuli. With regard to chickenpox atopic dermatitis, sunburn and diaper rash have been associated with a greater density of vesicles at the site of inflammation [1–3]. Different hypotheses have been given to explain the focalization of lesions at the site of skin inflammation. Local inflammation could be associated with increased local blood flow and capillary permeability, resulting in a higher dissemination of viral particles to the surrounding skin, to changes of the local temperature enhancing viral replication, to blunting of the