

CASE REPORT

Aspergillus endocarditis in chronic granulomatous disease

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We report the first case, to our knowledge, of *Aspergillus* endocarditis in chronic granulomatous disease in a patient who also had an atrial septal defect. A diagnosis was made on culture of the organism from the mass despite extensive prior investigation. The presence of distinctive skin lesions as a diagnostic clue of fungaemia is highlighted. Possible advances in diagnosis by detection of fungal cell wall components and in prophylaxis by use of itraconazole are referred to. We conclude that fungal endocarditis should be considered in this condition, especially in the presence of a structural heart defect. □ *Aspergillus*, chronic granulomatous disease, endocarditis

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Chronic granulomatous disease (CGD) is a condition characterized by an absent respiratory burst in phagocytic cells. This causes impaired killing of ingested organisms, especially *Aspergillus*, *Staphylococci* and *Escherichia coli*. Approximately two-thirds of cases are inherited in an X-linked manner, and one-third are autosomal recessive (1). Classically, infection occurs in the skin, lymph nodes and lungs. We present the first recorded case of *Aspergillus* endocarditis in CGD.

Case report

A 3-year-old girl, born to consanguineous parents, had suffered unexplained fevers, cough and failure to thrive since birth. Over this period chest radiographs had demonstrated changing areas of consolidation. Apart from her generally debilitated state the only findings of note were a heart murmur, which was due to a small atrial septal defect (ASD), and hepatosplenomegaly. A diagnosis of tuberculosis had been made because of a borderline positive Mantoux test; however, there was no improvement with anti-tuberculous treatment.

The presence of sterile granulomas in a liver biopsy raised an initial suspicion of CGD, which was confirmed by demonstrating defective neutrophil reduction of nitroblue tetrazolium. Further investigation showed the absence of the 67 kDa cytoplasmic factor, which is essential for the activation of the NADPH oxidase system.

Despite prophylactic trimethoprim and having prolonged courses of other antibiotics for exacerbations, recurrent fever and weight loss continued. Blood

cultures and fungal antibody titres were repeatedly negative, and it was felt that a bone marrow transplant was indicated. Prior closure of her ASD was recommended to prevent paradoxical emboli during transplant.

At operation there was marked pericarditis, and a mass was felt in the lateral wall of the right atrium. This appeared to be inoperable, and the procedure was abandoned. Biopsies from the mass and the pericardium showed granulomas, but fungal and bacterial cultures were negative. Treatment for bacterial endocarditis was started without any improvement.

Four weeks later, a raised, tender erythematous lesion was noted over her occiput at a site of possible trauma. This gradually enlarged, and sterile altered blood was aspirated. A second similar lesion was noted on the left side of her head. She then experienced several episodes of amurosis fugax, presumably resulting from paradoxical emboli. At this stage echocardiography showed the mass to be larger and more friable. Removal of the mass was felt imperative to resolve the infection and prevent further emboli.

The mass virtually filled the right atrium, and resection required removal and reconstruction of the entire free right atrial wall. Staining and culture of the mass demonstrated *Aspergillus nidulans*. The same organism was subsequently grown from the second skin lesion and from the sternotomy wound.

Amphotericin and γ -interferon were started. Two weeks later the mass had recurred and was obstructing the superior venae cavae. Despite this anti-fungal treatment, blood cultures grew *A. nidulans*, and 24 days postoperatively she died. A post-mortem was declined.

Discussion

Infective endocarditis in CGD is very uncommon and, to the best of our knowledge, this is the first recorded case of *Aspergillus* endocarditis in this condition. Fungal endocarditis, though a rare disease, is most frequently recognized as a complication of open heart surgery, especially in association with prosthetic valves (2). In these cases the organism is generally thought to have been introduced at operation. Less often, *Aspergillus* endocarditis has been noted in immunosuppressed conditions such as haematological malignancies and post-transplantation, in which the lungs are felt to be the initial site of infection (3). Risk factors are noted to be multiple or prolonged courses of antibiotics, corticosteroids and chemotherapy.

Aspergillus species are most frequently introduced via the respiratory tract. Although we were never able to demonstrate a primary site of infection, and repeat cough swabs were negative on fungal culture, frequent chest radiography changes could indicate a primary pulmonary focus.

Diagnosis of an invasive or systemic fungal infection can be extremely difficult, as this case demonstrates. Culture and antibody titres have a low sensitivity (2, 4), and biopsy is often the most reliable procedure (5). Repeated chest radiography changes that are either unresponsive or only partially responsive to antibacterial treatment are suggestive. In the absence of a reliable test there must be a high index of suspicion and a low threshold for starting treatment. This case demonstrates the importance of awareness that cutaneous manifestations are frequently the first specific clinical indicator of fungaemia in children. Often they occur at sites of minor trauma, possibly due to stasis of *Aspergillus*-laden blood. They are "tender, erythematous macules or vesicles which frequently progress to necrotic eschars" (6).

The importance of fungal infections in CGD and other states of compromised immunity demands new stratagems in detection and prevention. The identification of characteristic fungal cell wall components is a relatively new approach which may provide a sensitive and specific diagnostic test allowing earlier intervention (7). Several prophylactic regimes have been tried with generally poor results; however, some success has recently been reported with itraconazole (8). Such

advances will hopefully improve the outlook for such patients.

The decision to perform a bone marrow transplant was taken because of the lack of progress with standard treatments. This procedure carries a 10–20% mortality, and the risk is increased in actively infected cases (9). In those few cases where it is felt to be indicated there should be vigorous attempts to exclude fungal and other infections.

Aspergillus is responsible for most deaths in CGD (10). There should be increased awareness of the significance of these skin lesions as their recognition and biopsy may enable a diagnosis to be made. Unusual sites of infection should be considered, and in the presence of cardiac defects or embolic phenomena, endocarditis should be sought.

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