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Case report

Aspergillus endocarditis and myocarditis in a patient with the acquired immunodeficiency syndrome (AIDS)

A review of the literature

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Summary. We report the post-mortem findings of the case of a 31-year-old male who, through sexual contacts with a female drug addict, was found to be HIV-positive and developed the acquired immunodeficiency syndrome (AIDS) 2 years later. He was treated for various opportunistic infections over the next 7 years when he presented with cardiac abnormalities and multiple cerebral lesions which were responsible for his death. The results revealed *Aspergillus fumigatus* endocarditis and myocarditis with mycotic thromboembolic extension to the brain, spleen, kidney and pancreas. We review the literature of *Aspergillus* infection in patients with AIDS and more specifically cardiac involvement with this pathogen.

Key words: AIDS – Endocarditis – Myocarditis – *Aspergillus*

Introduction

The severe immunological abnormalities observed in patients with the acquired immunodeficiency syndrome (AIDS) predispose these patients to a wide range of opportunistic infections (e.g. *Pneumocystis carinii*, cytomegalovirus, bacteria and *Candida* (Armstrong 1987; Atkinson et al. 1984; Guarda et al. 1984; Hui et al. 1984; Rotterdam 1987.

Infection with *Aspergillus* spp. is uncommon in this condition and cardiac lesions are exceedingly rare (Cairns 1988; Henochowicz et al. 1985; Holmberg and Meyer 1986; Petito et al. 1986).

We describe the case of a patient with AIDS who presented with *Aspergillus* endocarditis, myocarditis and with involvement of other organ systems. We review the literature on the subject.

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Case report

A 31-year-old, non-homosexual male, known to have had sexual relationships with a female drug addict, was found to be HIV-positive in 1980. In 1982, generalized lymphadenopathy appeared and, in 1988, he observed nocturnal sweating with marked weight loss. Azydothymidine was started. A dry cough appeared in 1989 and a bronchoalveolar lavage revealed *P. carinii*. Sulphamethoxasole (9.6 g), pentamidine in aerosols (daily) and corticosteroids were started. Antibody to anti-envelope HIV antigens was positive, but antibodies to core antigen were negative; p24 antigen was positive at 19 pg/ml; lymphocytes were at 630/mm^3, CD4 at 12/mm^3 and CD8 at 44/mm^3. A proctitis (thought to be herpetic) was treated with acyclovir (4 × 800 mg/daily). He became cachectic, febrile at 38.2° C, with a heart rate of 102/min and blood pressure of 10/6 mmHg. A holosystolic murmur of 4/6 was now audible, radiating to the left shoulder. There was also a diastolic gallop.

Laboratory examination showed anaemia (10.4 g/100 ml), 7200 white cells with a normal distribution, but a lymphopenia of 13% and 26000 platelets. There was hypergammaglobulinaemia. The spinal fluid had 0.48 g/l proteins, 11 red cells, 2 white cells, of which 51% were polymorphonuclears, 37% lymphocytes and 10% monocytes. The culture was negative, as was the VDRL. Repeated blood cultures remained negative. A test for toxoplasmosis (IgG) was positive (titre 1/320).

Two-dimensional echocardiogram revealed mobile, globular masses in the left ventricular cavity at the level of the insertion of the mitral chordae to the postero-papillary muscle. A cerebral CT scan showed four annular hypodense lesions situated in the cortical region of the frontal lobes surrounded by an oedematous hollow.

A cocktail of treatment was initiated [Floxapen, Flucloxacillin (Beecham, United Kingdom); Rocephin, Cephalosporin (Roche, Switzerland); Flagyl, Metronidazole (Rhône-Poulenc, France); pyrimethamine, sulfadiazine, Leucovorin, Calcium folinate (Lederle, United States)] with some improvement but headaches accompanied with vomiting reappeared. He became confused and another CT scan showed several new lesions. He died the following day.

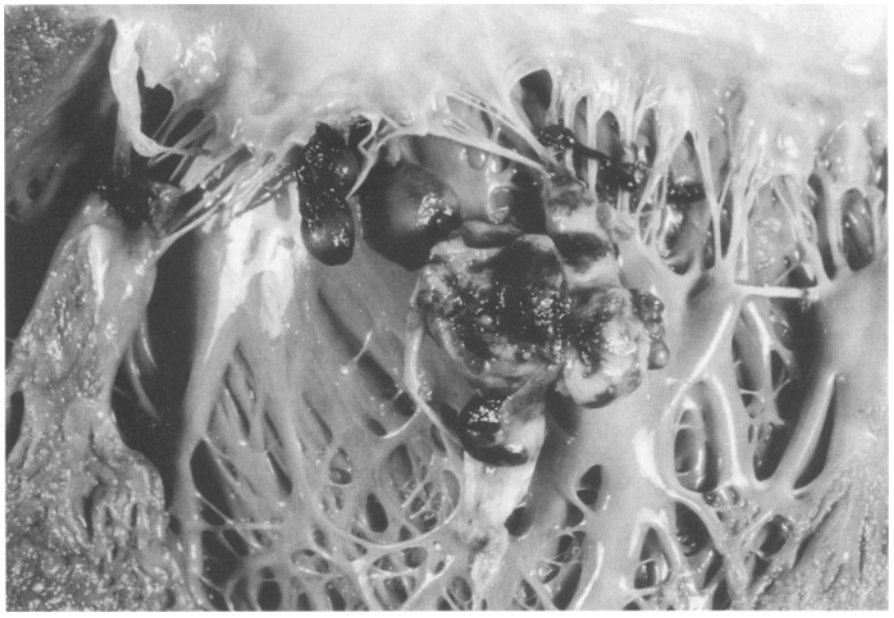

Fig. 1. Left ventricular cavity showing *Aspergillus* masses hanging from the septal leaflet of the mitral valve. Another mass infiltrates and partially destroys the posterior papillary muscle. The anterior papillary muscle is also involved

Materials and methods

The body was cachectic weighing 38 kg for a height of 180 cm. The heart was moderately dilated. The posterior papillary muscle of the left ventricle was partially replaced by a large, polylobular fungating reddish mass. Similar lesions were observed hanging from the edge of the anterior-medial and aortic side of the leaflet of the mitral valve. The upper portion of both anterior and posterior papillary muscles appeared necrotic, as well as at the insertions of the chordae (Fig. 1). The aortic, tricuspid and pulmonary valves appeared normal. The extramural coronary arteries were free of thrombus.

The lungs showed many consolidated areas, principally on the left. The left pleural cavity contained 600 cc straw-coloured fluid, the right 200 cc. The enlarged spleen presented an infarction (3 × 2 cm) at its inferior pole. A similar lesion (4 × 2 cm) was observed in the superior pole of the left kidney. The brain was swollen, covered by a thickened arachnoid showing a yellowish opaque exudate in places in the subarachnoid space.

The organs were fixed in 10% buffered formalin, dehydrated, embedded in paraffin wax, cut at 5 μm and stained with haematoxylin and eosin, elastic van Gieson periodic acid-Schiff (PAS), Gram, Grocott silver methenamine and Ziehl-Neelsen.

Coronal sections of the brain showed necrotic areas (1–4 cm) within the hemispheres and cerebellum occupying the cortex, white matter and basal nuclei. Sections from various regions were stained as above and, in addition, with PTAH, Mallory's phosphotungstic acid haematoxylin, Nissl and Luxol-van Gieson.

Results

Examination of the heart showed that the lesions of the posterior papillary muscle and those from the valvular leaflet were made up of necrotic tissue with bouquets of branching mycelia, positive with the PAS and Grocott stains but negative with the Gram stain. This, with their branching structure of about 45° and their spores, confirms the diagnosis of *Aspergillus* spp.

Multiple sections from the myocardium show numerous thromboemboli of intramural arteries accompanied by areas of necrosis with abscess formation and foci of *Aspergillus* myocarditis (Fig. 2a–d).

In the left kidney, a thrombus containing *Aspergillus* obliterated an intralobular artery with infarction of the corresponding area. Smaller peripheral vessels, including the glomerular capillaries in both kidneys, were occluded by thrombus containing *Aspergillus*. Similar lesions were observed in the spleen and pancreas. Post-mortem cultures grew *A. fumigatus*.

Lung sections were negative for *Aspergillus* spp., but showed chronic interstitial pneumonitis and in one area of the left lower lobe with a necrotic centre, surrounded by granulation tissue, *P. carinii* organisms were present.

The brain was studded with variable size abscesses infiltrated by *Aspergillus* invading the accompanying vessels; the latter were obliterated by mycotic thromboemboli with multiple infarcted areas (Fig. 3a). The pons and cerebellum were also involved. The right carotid artery showed a severe acute arteritis and was obliterated by a recent mycotic thromboembolus. A haemorrhage occupied the left caudate nucleus with perforation into the corresponding lateral ventricle. There was diffuse *Aspergillus* meningitis with extensive vascular involvement and frequent thrombus and mycotic aneurysms of the vessels (Fig. 3b).

Discussion

Patients with AIDS are susceptible to a wide variety of opportunistic infections (viruses, bacteria, protozoa and fungi) which may be the initial presenting clinical manifestation. The most prevalent offenders encountered either clinically or at post-mortem are cytomegalovirus, *P. carinii*, *Toxoplasma gondii* and *Candida albicans* among others (Armstrong 1987; Rotterdam 1987; Schrager 1988; Witt et al. 1987). Mycotic infections ap-

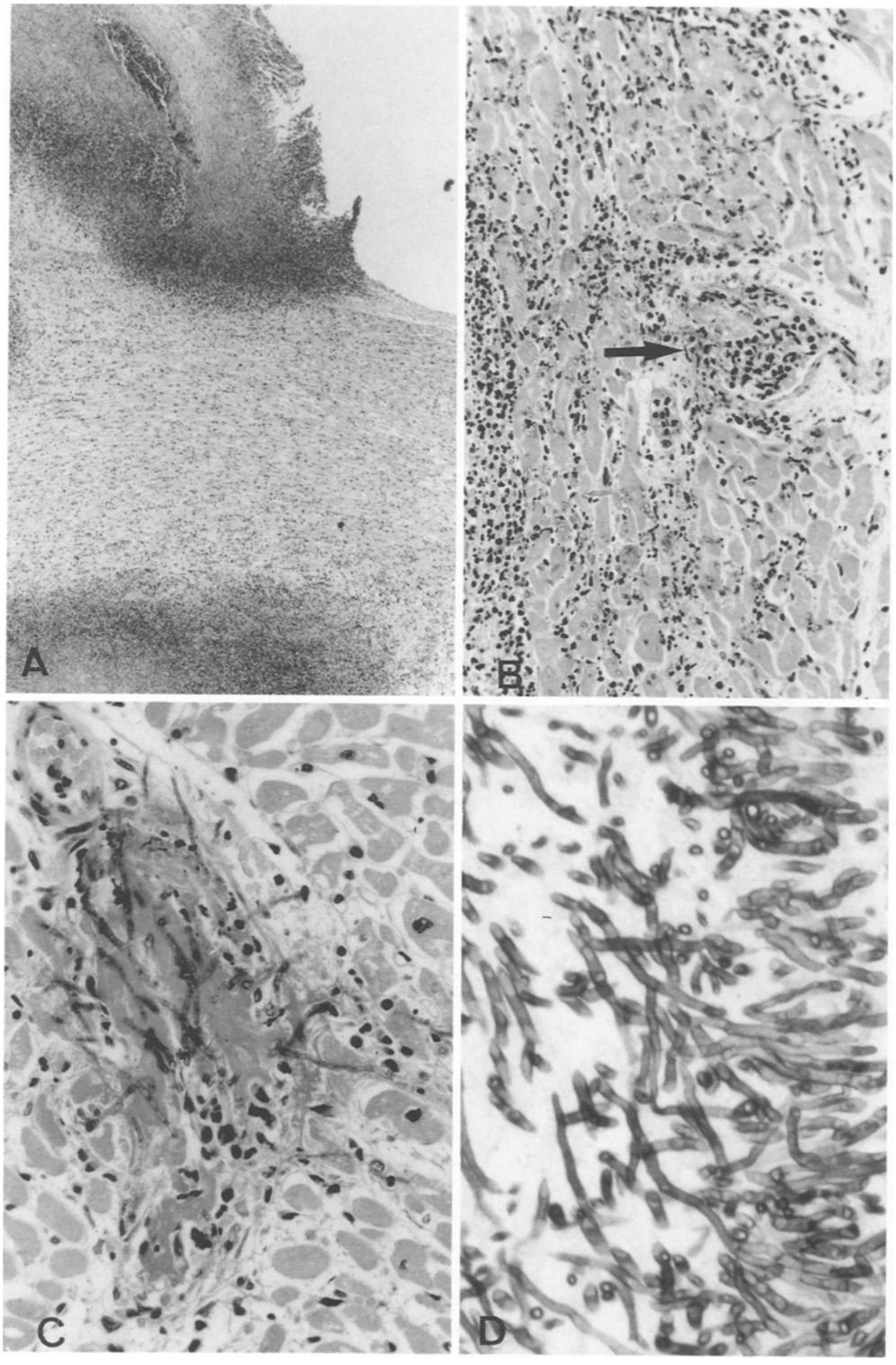

Fig. 2. **a** Section at the level of the posterior papillary muscle showing active fungating *Aspergillus fumigatus* endocarditis with scarring of the adjacent myocardium containing a mycotic abscess. H & E, ×25.
b Myocarditis containing mycotic elements with thrombosis and dilatation of the artery (↗) H & E, ×63.
c Thrombosis of peripheral myocardial vessel containing *Aspergillus* mycelia invading the vessel wall. H & E, ×160.
d *A. fumigatus* from valvular mass Grocott, ×400

pear to be on the increase generally, often in association with the use of chemotherapeutic agents for malignancies (e.g. haematological neoplastic diseases) and patients receiving immunosuppressive treatment in various clinical settings (Andersson et al. 1986; Hara et al. 1989; Laszewski et al. 1988; Rozo et al. 1983; Walsh and Hutchins 1979).

Clinically, diagnosis can be difficult and requires successive cultures of the fungus from collected samples (Guzman et al. 1987; Khardori 1989). Recently, new serological techniques for diagnosing invasive fungal infections have greatly improved the diagnostic sensitivity for clinical practice (Froudist et al. 1989; Repentigny 1989). Prolonged granulocytopenia is an important indi-

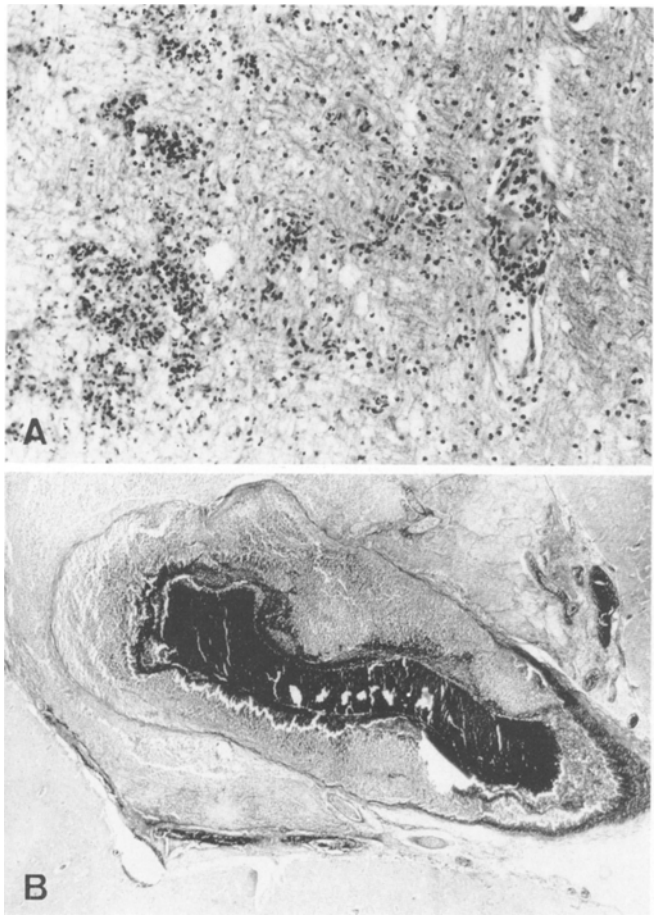

Fig. 3. a Multiple microabscesses of the brain with thrombosis of small vessel containing *Aspergillus* mycelia. Luxol van Gieson, ×160.
b Diffuse *Aspergillus* meningitis with extensive vascular thrombosis and mycotic aneurysms. Luxol van Gieson, ×16

cator when considering susceptible cases (Atkinson et al. 1984; Khardori 1989; Walsh and Hutchins 1979).

Although fungal infection with *Candida* is not an uncommon finding in patients with AIDS (Armstrong 1987; Cairns 1988; Holmberg and Meyer 1986; Reichert et al. 1983) infection due to *Aspergillus* is rare. The fungus has been reported more often in patients who have undergone organ transplantation, cardiac surgery or who have received immunosuppressive therapy over long periods. There is a high mortality rate (Andersson et al. 1986; Atkinson et al. 1984; Denning et al. 1989; Laszewski et al. 1988; Rozo et al. 1983; Walsh and Hutchins 1979).

In a review of 56 post-mortem examinations on patients dying with AIDS, Niedt and Schinella (1985) recorded 5 cases with lung involvement by *Aspergillus* which were not diagnosed during life. Seven cases were recorded by Petito et al. (1986) among 152 autopsies of AIDS patients. The organs involved were not specified. In other reports listing *Aspergillus* in AIDS patients, the lung was the primary site of infection. Amberson et al. (1985) found 2 cases among the 67 cases studied. Guarda et al. (1984) and Marchevsky et al. (1985) had 1 case each among the 13 and 70 patients studied respectively.

The case of Pervez et al. (1985) is of special interest in that there was extensive bronchial mucosal involvement without parenchymal invasion. We have seen 1 other case of invasive *Aspergillus* involving the lung among the 46 cases coming to post-mortem at our institution. Hui et al. (1984) had 1 cutaneous *Aspergillus* infection among their 12 cases.

In reviews dealing with the nervous system in AIDS 7 cases of *Aspergillus* infection have been reported but the other organs involved were not indicated (Anders et al. 1986; Gray et al. 1988; Lang et al. 1989; Levy et al. 1988) and some of these cases could be among those listed above.

Aspergillus endocarditis is very uncommon and Rozo et al. (1983) could find only 53 cases described in the literature in adding 5 of their own. All were associated with valve replacement or valvular surgery. Other authors have reported the infection in open heart surgery, long-term indwelling intravenous catheters, intravenous drug abuse and immunocompromised patients, including those with organ transplants (Abe et al. 1984; Atkinson et al. 1984; Laszewski et al. 1988). *Aspergillus* spp. have a wide distribution, including the normal microbial flora of the mouth and skin. They often reach the respiratory system and colonize the lower respiratory tract, giving rise to localized aspergilloma or invasive *Aspergillosis*. In our patient, numerous sections taken from various suspected areas of both lungs failed to show *Aspergillus* spp., but one of the well-defined nodules with a necrotic centre bordered by granulation tissue contained *P. carinii*.

To the best of our knowledge, only one other case of *Aspergillus* endocarditis with myocarditis in an AIDS patient has been documented (Henochowicz et al. 1985). The echocardiogram and gross specimen of that case were similar to those of our patient. Due to the rarity of the condition, the diagnosis was not entertained among the differential diagnoses. Non-bacterial thrombotic endocarditis and myocarditis have been reported by many authors who have studied cardiac lesions in patients with AIDS (Anderson et al. 1988; Baroldi et al. 1988; Cammarosano and Lewis 1985; Kaminski et al. 1988; Levy et al. 1989; Reilly et al. 1988). The non-specific myocarditis and other histological lesions observed in the hearts of many patients with AIDS are thought to contribute to the clinical cardiac abnormalities so often observed in these patients and could be responsible for the high morbidity and mortality among them (Anderson et al. 1988; Levy et al. 1989; Reilly et al. 1988).

Amphotericin B is the treatment of choice in this condition, but recent trials with itraconazole alone or in combination are promising (Denning et al. 1989).

However, one should be cautious, since Galgiani and Stevens (1977) have demonstrated the importance of prolonged follow-up in cases of fungal endocarditis, with adequate serological studies, in order to detect any persistent infection or relapse which may occur after apparently successful treatment.

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