Case Report

Aspergillus fumigatus tricuspid native valve endocarditis in a non-intravenous drug user

Antonios Vassiloyanakopoulos,[1] Matthew E. Falagas,[1,2,3] Maria Allamani[4] and Argyris Michalopoulos[2,5]

[1,4,5]Department of Medicine[1], Pathology Department[4] and Intensive Care Unit[5], Henry Dunant Hospital, Athens, Greece

[2]Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece

[3]Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

Correspondence
Argyris Michalopoulos
amichalopoulos@hol.gr

Received 3 November 2005
Accepted 30 December 2005

Invasive aspergillosis is an emerging infection mainly affecting immunocompromised patients. This report details a case of *Aspergillus fumigatus* tricuspid native valve endocarditis complicated by recurrent septic pulmonary emboli in a young, non-intravenous drug user. He was treated by surgical resection of the posterior leaflet of the tricuspid valve and the vegetations, as well as by valvuloplasty, which was followed by a combination of liposomal amphotericin B and voriconazole as acute-phase therapy and voriconazole alone as suppression therapy.

Case report

A 25-year-old man was admitted to hospital with fever, progressive dyspnoea, thoracic pain and bloody sputum. His past medical history was noteworthy for bronchial asthma, for which he had been receiving steroids for a period of 6 months (3 months systematically and 3 months inhaled) during the year prior to admission. In addition, he received antibiotics on six occasions for postulated respiratory infections during the year prior to admission. He also received warfarin 20 days prior to admission due to a suspected episode of pulmonary embolism.

Physical examination on admission revealed an elevated temperature (38·2 °C) and wheezing. Laboratory tests showed a white blood cell count of 22 700 cells mm^{-3} with 76·2 % neutrophils, a haematocrit value of 38·4 % and an erythrocyte sedimentation rate of 82 mm in the first hour. Chest X-rays and a CT scan showed several lesions of atelectasis in the right lower lobe and the presence of pleuritic fluid in the right thorax. Pulmonary scintigraphy did not show evidence of pulmonary embolism. A spiral thoracic CT scan showed multiple atelectatic lesions, especially in the right lower lobe, and therefore pulmonary embolism was ruled out.

He was admitted to our intensive care unit because his situation was deteriorating rapidly. Both thoracic and oesophageal echocardiography revealed a 1·5 cm lesion of the tricuspid valve associated with mild regurgitation of the valve, as well as mild pulmonary hypertension (Fig. 1). The finding of the valve vegetation was also confirmed with a heart MRI. Bronchoscopy was performed and showed a small amount of bloody bronchial secretions without other abnormal findings. Eight sets of blood specimens as well as sputum and bronchoalveolar lavage fluid specimens were obtained for culture.

The patient was thought to have right-side endocarditis, complicated with pulmonary septic emboli. Due to the severity of his condition, he received an antimicrobial regimen with a broad spectrum of activity. Specifically, he was treated empirically with vancomycin (1 g every 12 h), rifampicin (300 mg every 8 h), levofloxacin (400 mg every 24 h), gentamicin (80 mg every 8 h) and liposomal amphotericin B (3 mg kg^{-1} every 24 h) for 14 days. All blood and sputum cultures were negative. Serological tests for *Coxiella*, *Mycoplasma* and *Brucella* were also negative. The patient recovered quickly and was transferred from the intensive care unit to a regular hospital ward during the 4th day of hospitalization.

On the 14th day of hospitalization and while he was receiving the above-mentioned treatment, the patient complained again of fever (38·5 °C), chills, thoracic pain, dyspnoea and bloody sputum. He had leukocytosis, elevated levels of neutrophils and elevated markers of inflammation (erythrocyte sedimentation rate and C-reactive protein), while a thoracic CT scan showed an improvement in comparison with the previous scan. He was re-admitted to the intensive care unit. A resection of the posterior leaflet of the tricuspid valve and the vegetations, as well as valvuloplasty, was performed. He did not develop right heart failure post-operatively. Cultures of specimens from the valve vegetations produced *Aspergillus fumigatus* (Fig. 2).

Antifungal *in vitro* susceptibility tests were performed using a modified Clinical and Laboratory Standards Institute reference broth microdilution method (method M38-A; NCCLS, 1998). Amphotericin B, caspofungin and

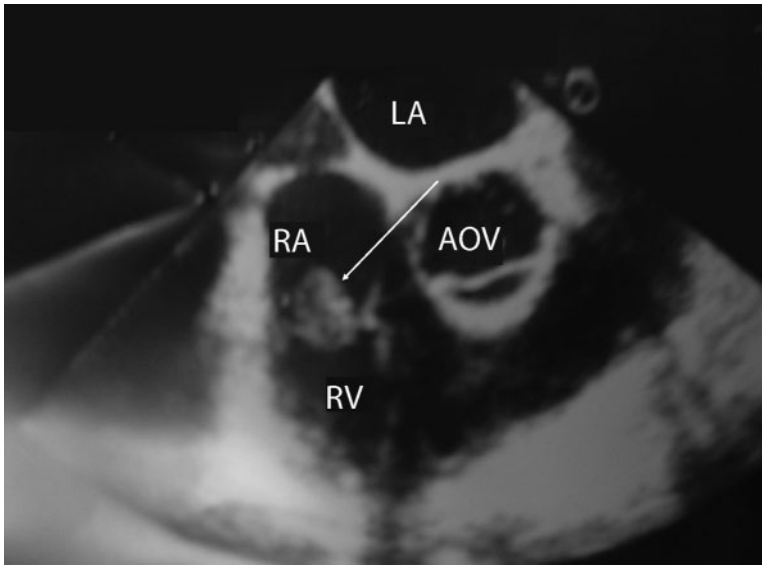

Fig. 1. Echocardiogram showing a large vegetation (arrow) of the tricuspid valve. AOV, Aortic valve; LA, left atrium; RA, right atrium; RV, right ventricle.

voriconazole exhibited good *in vitro* activity against the *A. fumigatus* isolate (MICs $<0{\cdot}06$ μg ml^{-1}). The patient received intravenous liposomal amphotericin B (3 mg kg^{-1} per day) and voriconazole (loading dose 6 mg kg^{-1}, followed by 4 mg kg^{-1} b.i.d.) post-operatively. All antibiotics were stopped. The patient recovered quickly and 6 weeks later was discharged on suppression treatment with *per os* voriconazole (200 mg b.i.d.). The patient remained on this dose for 6 months. The patient did not develop a recurrence of endocarditis or adverse drug effects during a 6 month follow-up period.

Discussion

Endocarditis due to fungal aetiology is an uncommon occurrence (Bayer & Scheld, 2000; Karchmer, 2000), but is considered to be the most severe form of infective endocarditis. Isolated native non-rheumatic fungal tricuspid valve endocarditis in the absence of intravenous drug addiction is even more rare (Pierrotti & Baddour, 2002). Although there are few data in the literature on *Aspergillus* endocarditis, it seems that *Aspergillus* species and all other fungi cause larger and more friable vegetations than bacteria.

Here, we have reported a case of tricuspid valve endocarditis due to *A. fumigatus*, which was treated successfully with combined surgical and medical therapy. Although we had echocardiographic evidence of endocarditis, all blood, sputum and bronchoalveolar lavage cultures were negative. However, having one major and three minor criteria, we had a definite diagnosis of endocarditis according to the modified Duke criteria (Li *et al.*, 2000). Negative blood cultures in endocarditis are common, implying fastidious pathogens or micro-organisms requiring a special environment for growth. *Aspergillus* is one of these pathogens. It has

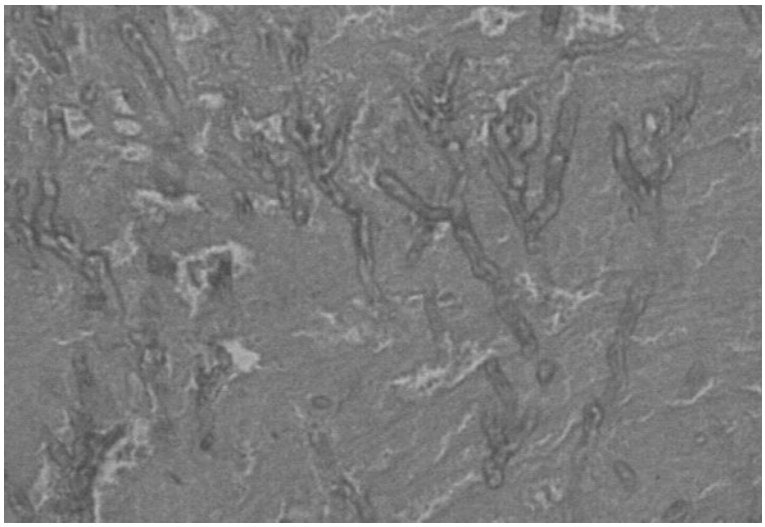

Fig. 2. Histological examination of the excised tissue of the tricuspid valve with evidence of invasive fungal infection (hyphae of *Aspergillus*).

been shown that blood cultures are negative in >50 % of patients with *Aspergillus* endocarditis (Rubinstein *et al.*, 1975).

The size of the valve vegetation, which was considered large for a typical case of bacterial endocarditis, the previous administration of steroids and multiple antibiotics and also the severity of the infection due to the septic embolic episodes led us to include an antifungal agent in our empiric therapeutic strategy. The fact that a new embolic episode occurred whilst the patient was under antimicrobial coverage convinced us that surgery was needed urgently. The septic emboli occurred despite the patient receiving liposomal amphotericin B. This may occur in cases of fungal endocarditis, as the friable and necrotic vegetations are not easily accessible to amphotericin B, which penetrates poorly into these vegetations. The presence of large vegetations favours septic embolic migration and usually makes medical treatment alone an unsatisfactory option (Abgueguen *et al.*, 2002). We believe that some of the postulated episodes of respiratory tract infection that occurred during the last months prior to the diagnosis of endocarditis were most likely due to recurrent septic emboli secondary to the cardiac infection, despite the fact that fungal endocarditis is considered an infection with a more acute course.

The combined medical and surgical approach that was undertaken in this patient was in accordance with the literature. Total tricuspid valvulectomy followed by antifungal treatment is the recommended management strategy for patients with tricuspid valve endocarditis. However, it should be emphasized that the procedure performed in our patient included resection of the posterior leaflet of the tricuspid valve and the vegetations, as well as valvuloplasty. The full resection of the vegetations ensured that all infected cardiac tissue was removed. This type of operation has the advantage of preserving part of the native valve, thus avoiding the severe tricuspid valve regurgitation that is a common post-operative problem after total tricuspid valvulectomy. *Aspergillus* species are the second most common fungi isolated from cardiac vegetations (25 %), whilst *Candida* accounts for 53 % and *Histoplasma* for 6 % of cases of fungal endocarditis. *A. fumigatus* is the most commonly isolated among the *Aspergillus* species. It should be noted that the incidence of invasive aspergillosis has increased during the last decade in various settings and patient populations (Chandrasekar *et al.*, 2001).

The effectiveness of combination antifungal therapy for invasive aspergillosis has elicited controversy and thus clearer data are needed. Concurrent use of amphotericin B and voriconazole could be a reliable combination, although many argue that there may be potential antagonism between these agents. However, the results of one recent study in patients with candidaemia suggest that the potential antagonism may not be an issue (Marr, 2004). In our patient, we preferred to give a combination of amphotericin B and voriconazole initially, followed by voriconazole alone, administered *per os* at home as suppression therapy. This was a difficult decision to make, as historically amphotericin B has been the 'gold standard' treatment for *Aspergillus* endocarditis, despite its known poor penetration into vegetations (Rubinstein *et al.*, 1974).

The role of the new echinocandins, such as caspofungin, which recently has been approved for salvage treatment of refractory *Aspergillus* infection, is important (Maschmeyer & Ruhnke, 2004). Caspofungin is at least as effective as amphotericin B in non-neutropenic patients with *Aspergillus* infection. A possible alternative approach could be the combination of voriconazole with caspofungin, which has led to promising results, although there has been very limited experience in patients with endocarditis (MacCallum *et al.*, 2005).

Prolonged suppressive therapy with antifungals is reasonable in patients in whom surgery cannot be performed to control the infection and because relapse is common after surgery and short-term antifungal treatment (Muehrcke *et al.*, 1995). In our patient, given his intact immune system, we preferred to administer a 6 month suppression therapy with voriconazole, which was well tolerated and was associated with a good outcome.

The prolonged administration of antibiotics and steroids could have played a role in the development of this infection in our patient, although endocarditis usually begins as a mechanical traumatic event of the valve.

In conclusion, *Aspergillus* endocarditis is a rare but emerging disease that it is difficult to diagnose and manage. A high suspicion index, early administration of proper antifungal agents and prompt surgical intervention are the steps needed to improve the prognosis of patients with this infection.

References

Abgueguen, P., Gouello, J. P., Pichard, E., Chabasse, D., Donal, E. & Alquier, P. (2002). *Candida* endocarditis: retrospective study in 12 patients. *Rev Med Interne* **23**, 30–40 (in French).

Bayer, A. S. & Scheld, M. (2000). Endocarditis and intravascular infections. In *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 5th edn, vol. 1, pp. 857–902. Edited by G. L. Mandell, J. E. Bennett & R. Dolin. Philadelphia, PA: Churchill Livingstone.

Chandrasekar, P. H., Cutright, J. L. & Manavathu, E. K. (2001). Aspergillus: rising frequency of clinical isolation and continued susceptibility to antifungal agents. *Diagn Microbiol Infect Dis* **41**, 211–214.

Karchmer, A. W. (2000). Infections of prosthetic valves and intravascular devices. In *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 5th edn, vol. 1, pp. 903–917. Edited by G. L. Mandell, J. E. Bennett & R. Dolin. Philadelphia, PA: Churchill Livingstone.

Li, J. S., Sexton, D. J., Mick, N., Nettles, R., Fowler, V. G., Jr, Ryan, T., Bashore, T. & Corey, G. R. (2000). Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* **30**, 633–638.

MacCallum, D. M., Whyte, J. A. & Odds, F. C. (2005). Efficacy of caspofungin and voriconazole combinations in experimental aspergillosis. *Antimicrob Agents Chemother* **49**, 3697–3701.

Marr, K. (2004). Combination antifungal therapy: where are we now and where are we going? *Oncology* **18** (Suppl. 7), S24–S29.

Maschmeyer, G. & Ruhnke, M. (2004). Update on antifungal treatment of invasive *Candida* and *Aspergillus* infections. *Mycoses* **47**, 263–276.

Muehrcke, D. D., Lytle, B. W. & Cosgrove, D. M., III (1995). Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. *Ann Thorac Surg* **60**, 538–543.

NCCLS (1998). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium-forming Filamentous Fungi: Proposed Standard*. NCCLS document M38-P. Wayne, PA: National Committee for Clinical Laboratory Standards.

Pierrotti, L. C. & Baddour, L. M. (2002). Fungal endocarditis, 1995–2000. *Chest* **122**, 302–310.

Rubinstein, E., Noriega, E. R., Simberkoff, M. S. & Rahal, J. J., Jr (1974). Tissue penetration of amphotericin B in *Candida* endocarditis. *Chest* **66**, 376.

Rubinstein, E., Noriega, E. R., Simberkoff, M. S., Holzman, R. & Rahal, J. J., Jr (1975). Fungal endocarditis: analysis of 24 cases and review of the literature. *Medicine* **54**, 331–334.