Aspergillus fumigatus endocarditis in a pediatric liver transplant recipient: Favorable outcome without cardiac surgery


Abstract: Transplant recipients are very susceptible to invasive aspergillosis, which increases mortality rate. Disseminated aspergillosis in the liver transplant recipient can affect virtually any organ and endocarditis is often lethal despite cardiac surgery and antifungal therapy. We report the case of an eight-month-old girl who presented with Aspergillus fumigatus endocarditis 18 days after liver transplantation that was successfully treated by a combination of antifungal drugs associated to a low dosage of immunosuppressive therapy.

Aspergillus endocarditis is uncommon but usually occurs in patients after cardiac surgery and also in immunocompromised patients without prior cardiac surgery (1–14). In the majority of cases, diagnosis is made postmortem (3, 5, 7). Transplant recipients are very susceptible to invasive aspergillosis, which increases mortality rate (1–4, 6, 7, 9, 10). Disseminated aspergillosis in the liver transplant recipient can affect virtually any organ but mainly affects the brain, eye, and heart. Endocarditis is often lethal despite antifungal therapy and cardiac surgery (1–14). We report the case of an eight-month-old girl who presented with Aspergillus fumigatus endocarditis 18 days after LT that was successfully treated by a combination of antifungal drugs associated to a low dosage of immunosuppressive therapy.

Case report

An eight-month-old girl without heart disease and with normal pretransplantation and early post-transplantation Doppler echocardiograms underwent LT for biliary atresia. Initial immunosuppressive regimen consisted of intravenous basiliximab and oral tacrolimus. Initial immunosuppressive regimen consisted of intravenous basiliximab and oral tacrolimus. Bacterial infection prophylaxis included intravenous ticarcillin and clavulanate until day 3 post-LT. Fungal infection prophylaxis with fluconazole was started at the time of surgery and continued thereafter. On day 18 after LT, the child presented with unexplained dyspnea and pulse...

Abbreviations: CT, computed tomography; GGT, gamma-glutamyl transferase; LT, liver transplantation; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.
oxymetry showed oxygen saturation below 85%. Chest radiographs and CT scan showed atelectatic lesions of the right lung. *Aspergillus fumigatus* was identified in routine tracheal aspiration fluid culture (9). Both antigenemia [galactomannan testing; 3.6 ng/mL, (n < 0.5 ng/mL)] and real-time blood PCR for *Aspergillus* were positive on two independent analyses (4, 14–17). A whole body CT scan did not show other lesions. Fungal and bacterial blood cultures were sterile. These data were compatible with the diagnosis of probable invasive aspergillosis (18). Antifungalogram showed *Aspergillus* species sensitivity to voriconazole, caspofungin and amphotericin B. As the child was asymptomatic, only voriconazole treatment (200 mg twice daily = 45 mg/kg/day, per o.s.) was initiated on day 20 after LT, with the goal to achieve therapeutic trough blood concentration ranging from 0.8 to 2.2 mg/L (19).

Figure 1 summarizes course of *Aspergillus* antigenemia and blood PCR during antifungal therapy. On day 60 after LT, high fever was noticed, but all blood cultures were again sterile. Three mm size vegetations localized on chordae and papillary muscle of the mitral valve, without any functional consequence, were revealed by transthoracic Doppler echocardiogram (Fig. 2a). In this context, echocardiographic images were consistent with the diagnosis of *Aspergillus* endocarditis (8). There was no sign of embolic spreading and heart murmur was normal. Caspofungin (1 mg/kg/day, intravenous) was added to voriconazole therapy, to get a synergic effect (8, 20–22). Cardiac surgery was considered too hazardous by expert surgeons and therefore rejected. Four days later, the child had a pleural effusion. Pleural fluid culture was negative for bacterial and fungal species as well as urine culture. On day 78 after LT, serum GGT activity increased, and a liver biopsy was performed. Histology showed minimal signs of biliary obstruction and no sign of rejection. Liver sample culture was sterile. On day 92 after LT, the patient remained febrile but blood cultures were sterile. *Aspergillus* antigenemia was still positive (>6 ng/mL) as well as blood PCR. Doppler echocardiogram showed worsening of endocardial lesions with 9 to 19 mm size vegetations localized on chordae and papillary muscle of the mitral valve and on the left side of interventricular septal endocardium (Fig. 2b), 3 mm size vegetations of the left lateral ventricular wall, and 3 mm size vegetations of the apical right ventricular endocardium. Cardiac surgery was again considered but rejected by expert surgeons. Intravenous amphotericin B (3 mg/kg/day, intravenous) was added to the two other

**Fig. 1.** Evolution after liver transplantation of *Aspergillus* antigenemia (Ag) and real time blood PCR under antifungal therapy in the reported patient with *Aspergillus* endocarditis.

**Fig. 2.** Transthoracic apical modified four-chamber Doppler echocardiography (left parasternal long axis view): (a) At diagnosis of *Aspergillus* endocarditis (Day 60 post-liver transplantation). Presence of 3 mm size vegetations of the mitral valve apparatus (arrow); (b) On day 92 post-liver transplantation. Presence of 9 to 19 mm size vegetations of the mitral valve apparatus, and on the left side of interventricular septal endocardium (arrow). RA, right ventricle; LA, left atrium; LV, left ventricle.
antifungal medications and tacrolimus dosage was decreased to obtain trough blood concentration of 3 ng/mL. On day 122 after LT, immunosuppression was stopped because endocardial lesions did not improve. Following these changes in the treatment regimen, the patient’s condition improved dramatically, with progressive fever disappearance. On day 150 post-LT, *Aspergillus* PCR became negative whereas *Aspergillus* antigenemia remained positive (6 ng/mL). Echocardiographic lesions decreased in size but did not disappear and became similar to initial lesions, without any functional consequence. Because of a new increase in serum GGT activity, liver biopsy was repeated. Histological aspect was similar. Abdominal ultrasonography was normal as well as MRI cholangiography. *Aspergillus* antigenemia was still positive (6 ng/mL) while blood PCR remained negative. Therefore, the hypothesis of a false positive antigenemia because of caspofungin and/or amphotericin B treatment was now considered. Indeed, these drugs may contain some galactomannan and *Aspergillus* antigen testing is based on immunodetection of galactomannan species (23). For this reason, these two medications were stopped but oral voriconazole was continued under therapeutic blood concentration survey. Over the three next months, *Aspergillus* antigenemia and serum GGT activity progressively decreased and eventually were found to be negative (<0.5 ng/mL) and normal on day 300 after LT, respectively. Treatment regimen was limited to oral voriconazole (150 mg twice daily) under therapeutic blood concentration monitoring. Very low dose of tacrolimus 0.1 mg/day was reintroduced on day 260 after LT, as blood PCR remained negative and *Aspergillus* antigenemia decreased. Trough tacrolimus blood concentrations <4 ng/mL were maintained and serum liver tests remained normal. Twenty months after LT, the patient is doing well under voriconazole (100 mg twice daily), blood PCR and *Aspergillus* antigenemia are negative and liver biology is normal. Last echocardiogram shows decreased size vegetations (1–2 mm) and normal heart function.

**Discussion**

Invasive aspergillosis is a feared complication in immunocompromised patients (1–4, 6, 7, 9–11, 15). *Aspergillus* endocarditis is often lethal in transplant recipients and is rarely diagnosed antemortem (1, 3, 7). When diagnosis is established antemortem, antifungal therapy and cardiac surgery, a potentially devastating procedure in this context, represent therapeutic tools that are often ineffective (1, 3, 5, 7, 8, 10, 12, 13). Mortality rate in patients with *Aspergillus* endocarditis is higher than 80% (1, 2, 5, 14). We report a case of mitral valve and left ventricular wall endocarditis probably due to *Aspergillus fumigatus*, diagnosed after LT in an eight-month-old girl, and successfully treated using triple and prolonged antifungal therapy together with a low dosage of immunosuppressive therapy.

It is often difficult to establish a definitive diagnosis of invasive aspergillosis in immunocompromised patient. The most common clinical sign is a prolonged and unexplained fever (1–3, 5, 7, 8, 18). Although the finding of *Aspergillus* in culture is highly predictive of invasive aspergillosis and indicates initiation of antifungal therapy, in many transplant recipients with invasive aspergillosis, *Aspergillus* is rarely identified in culture of affected site sample before death (9, 18). In addition, fungal blood culture is often negative (8). In this context, positive *Aspergillus* antigenemia is highly predictive of invasive aspergillosis, but false positive results have been reported, because some drugs or food may contain galactomannan (1, 4, 14, 15, 23). Blood PCR for *Aspergillus* species is much more specific than antigenemia and when positive, makes the diagnosis of aspergillosis very likely (16, 17). In the case reported here, the diagnosis of probable invasive aspergillosis was based on the following arguments and published criteria (18): (i) identification of fungal species in tracheal fluid culture; (ii) several positive antigenemia and blood PCR test results; (iii) occurrence of endocardial lesions compatible with the diagnosis of *Aspergillus* endocarditis, a well known complication of aspergillosis; (iv) repeated negativity of these parameters and favorable outcome following antifungal therapy. When a diagnosis of aspergillosis is likely or established in an immunocompromised patient, repeated transthoracic echocardiography must be performed to detect endocarditis, especially in a patient with prolonged and unexplained fever (1, 3). In our patient, diagnosis could be made earlier if Doppler echocardiogram had been performed between D18 and D60 post-transplantation. Endocardial lesions can be detected by transthoracic echocardiography in 78% of patients with *Aspergillus* endocarditis (3). Alternative imaging modalities for *Aspergillus* endocarditis detection are transesophageal echocardiography, which may have a higher sensitivity than transthoracic echocardiography, and cardiac MRI (3, 7, 8, 13).

The best therapeutic option for patients with *Aspergillus* endocarditis remains unclear. Most
authors recommend a combination of surgical and medical therapy (1, 3, 5, 8, 11–13). Very few immunocompromised patients have survived thanks to antifungal therapy alone (2, 3, 10). Nevertheless, surgery is considered dangerous because it is aimed at removing endocardial lesions and to replace native valves, with high risk of valve infection recurrence and embolic spreading (1, 12). The indication of cardiac surgery was disapproved in our patient because she presented with no sign of heart dysfunction. Successful medical treatment might depend on three factors: early diagnosis, combination antifungal therapy, and reduction of immunosuppression. In the present case, outcome was favorable with triple antifungal therapy together with immunosuppression regimen discontinuation. Whether the synergy of antifungal drugs, as recently suggested, or immunosuppression discontinuation, or more likely combination of both was the determinant factor of infectious process control remains unknown (8, 13, 18, 20–22). Since echocardiogram follow-up still showed endocardial lesions, voriconazole therapy was maintained despite negative antigenemia and blood PCR. In this situation, the proper duration and dosage of antifungal therapy is not clearly defined (8, 18, 19, 22). It is not known whether endocardial lesions correspond to residual and potentially active lesions or to scar tissue. In this view, endocardiac biopsy of the lesions could be helpful, but represents a high risk procedure. It is postulated that if absence of active lesions was confirmed, this could theoretically allow the discontinuation of antifungal therapy. In our patient, remaining endocardial lesions were not proven to correspond to scar lesions. Since adverse events because of voriconazole therapy under blood concentration monitoring were not identified, we decided to maintain oral antifungal therapy with progressive decrease of drug dosage and blood PCR monitoring. This empirical strategy might be justified and reasonable in immunocompromised patients to avoid a relapse, but more data are needed. Although native valve Aspergillus endocarditis is often lethal in transplant recipients, the present report shows that in a pediatric liver transplant recipient with probable Aspergillus endocarditis and antifungal combination therapy, long term survival without cardiac surgery is possible.

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