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CASE REPORT

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Invasive aspergillosis in solid-organ transplantation: report of eight cases and review of the literature

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Abstract Invasive fungal infections are life-threatening complications in solid-organ transplantation. Although the rate of fungal infections in transplant recipients is lower than that of other infections, the mortality rate is higher. The most frequent fungi isolated from these kinds of infections are *Candida spp.* and *Aspergillus spp.* We retrospectively evaluated the clinical and laboratory findings in eight patients who were treated for invasive aspergillosis (IA) at our center. This report describes these cases and discusses the relevant literature.

Keywords Invasive aspergillosis · Solid-organ transplantation · Fungal infection

Introduction

Organ transplantation has become one of the main therapy options for many acute and chronic diseases. The increase in transplantations has meant greater numbers of immunocompromised patients and higher rates of infection-related morbidity and mortality. The rate of invasive fungal infection in transplant recipients is lower than the rates of viral and bacterial infections, but mortality is higher in patients with fungal disease [23]. *Candida spp.* and *Aspergillus spp.* infections are the two most common types of fungal disease in transplant recipients, and the latter infection is associated with high mortality [4, 19, 26]. Risk factors for invasive aspergillosis (IA), such as acute rejection, graft dysfunction, intensive immunosuppressive therapy, OKT3 treatment, long-term antibiotic use, and creatinine level at the time of diagnosis have been reported [12, 16, 17, 22]. Construction activity was also reported to be a risk factor for immunocompromised patients [35]. We retrospectively assessed the clinical and laboratory findings in eight patients who were treated for IA at our center. This report describes these cases and discusses the relevant literature.

Case reports

Patients with IA were identified by review of clinical charts, autopsy, biopsy, and microbiological records between 1998 and 2001. Eight (four liver and four kidney recipients) of 207 transplant

recipients (27 liver and 180 kidney recipients) were diagnosed with IA. The following criteria were used for case definitions: definitive IA was defined as histological evidence of *aspergillus* hyphae upon autopsy or biopsy with tissue destruction and/or tissue invasion; autopsy suggestive of aspergillosis with cultures yielding *Aspergillus spp.*; and probable IA was defined as a clinical history suggestive of IA associated with microbiological identification of *Aspergillus spp.* [11, 17]. Although the diagnosis was made in the initial post-transplant period in six patients and at subsequent admission in two, all cases were accepted as nosocomial aspergillosis. All the affected patients were male, and their mean age was 38 years (range 22–55 years). Two of the renal grafts came from living donors and the other two were from cadavers. Three of the hepatic transplants were from cadaveric donors and one was from a live donor. The recipients' immunosuppressive protocols included various combinations of prednisolone, cyclosporine, mycophenolate mofetil, azathioprine and tacrolimus. For the patients whose protocol included cyclosporine (5 mg/kg), dose adjustment was performed according to blood levels of the drug. Four of the eight patients developed acute rejection and were treated with high-dose pulse steroid therapy and OKT3. All eight patients received fluconazole as antifungal prophylaxis, acyclovir as antiviral prophylaxis, and trimethoprim-sulfamethoxazole as antimicrobial prophylaxis. Dose adjustment of cyclosporine was needed in some patients when they were given fluconazole.

The mean time from transplantation to diagnosis was 24 days (range 15–34 days). The risk factors for the development of the disease were: acute rejection ($n=4$), long-term antibiotic therapy ($n=4$), OKT3 treatment ($n=3$), thrombocytopenia ($n=3$), and re-transplantation ($n=1$). Prior to being diagnosed with IA, four of the patients had been on wide-spectrum antibiotic therapy for 5–21 days. Also, between 1998 and 2001 reconstruction of some parts of the hospital wards was continued. The clinical symptoms were fever, cough, and dyspnea, which are typical for pulmonary IA, in four patients (one of them had unexplained diarrhea); fever and purulent secretion in one; abnormal oxygen saturation in one; and fever in one patient. One of the patients had no signs revealing IA.

Upon radiological examination (chest X-ray), six patients showed pneumonic infiltration, one had cavitation and infiltration, and one showed nodular infiltration. Thoracic computed tomography (CT) revealed nodular infiltration and cavitation in three patients, and infiltration and consolidation in the other three patients. In two patients CT was not performed. None of the patients had the 'halo sign', which is characteristic for IA.

Death occurred in six patients (four liver, two kidney recipients). Duration between symptoms and death was 2–29 days (mean 15.4 days).

Microbiological studies of sputum (in six patients) and broncho–alveolar lavage (BAL) fluid (in five patients) were performed in patients whose clinical and radiological findings were suggestive of IA. Definitive diagnosis was based on isolation of *Aspergillus fumigatus* from cultures of BAL fluid and sputum in two patients, bronchial biopsy in one, and autopsy findings in five. In one of the autopsy cases, a tentative pre-mortem diagnosis was also made by tracheal aspiration.

The four patients who were diagnosed with aspergillosis, pre-mortem, were treated with liposomal amphotericin B (5 mg/kg per day) after a mean stay of 4 days from the beginning of the symptoms. Two patients with clinical and laboratory findings that were highly suggestive of IA were empirically treated with amphotericin B (3 mg/kg per day), and the diagnosis was confirmed postmortem. Two of the five patients who were diagnosed at autopsy did not receive pre-mortem antifungal therapy. One of the remaining two patients was discharged after 21 days of amphotericin B and 14 days of itraconazole therapy. The other individuals received 21 days of amphotericin B therapy only. Immunosuppressive drug doses were reduced in patients who were started on antifungal therapy for IA.

Table 1 summarizes the patients' demographic features and details surrounding transplantation. Table 2 lists the clinical and laboratory findings and the outcome of the eight cases. Table 3 summarizes therapy and the outcome of the eight cases.

Discussion and review of the literature

Fungi of the genus *Aspergillus* are ubiquitous saprophytes that can cause several distinct clinical entities, including allergic bronchopulmonary disease and invasive tissue conditions. IA is the most frequent life-threatening fungal infection. This disease is common in immunosuppressed patients, particularly in solid-organ transplant recipients [7]. The frequency of IA varies according to the transplanted organ, with rates of 1–4.5% in liver recipients, 0.5–2.2% in kidney recipients, and 18% in lung or lung–heart recipients [1, 11, 17]. The differences in these figures relate to the technical aspects of the transplantation procedures and the need for comparatively less immunosuppression in renal-graft recipients [12]. The IA rates in our total 207 cases were 2.2% for kidney and 14.8% for liver recipients.

Spore inhalation is the main route by which *Aspergillus* infections are contracted, and the risk of infection has been linked to the concentration of conidia in the patient's ambient air. Since hospital construction causes diffusion into the atmosphere of fungal spores from normally closed reservoirs, cases of aspergillosis may increase dramatically [24, 35]. Although the lungs are the primary port of entry, the organism may also enter the body through the sinuses or the skin. After tissue infection develops, the general pattern of progression is invasion of blood vessels, tissue infarction, hemorrhage, and dissemination [12]. The pathogenesis of fungal infections in solid-organ recipients is not completely understood. In non-immunosuppressed individuals, macrophages inhibit the germination of inhaled spores and neutrophils damage the hyphae. Considering this, it seems likely that neutropenia and/or neutrophil and macrophage dysfunction lead to IA in solid-organ recipients [14]. Several factors are thought to contribute to IA in transplant recipients. In liver recipients, a well-functioning allograft is considered to be the key defense against dissemination of *Aspergillus*. Thrombocytes, which secrete cytokines and various growth factors, are also important in the prevention of invasive fungal infection. A below-normal thrombocyte count, which is seen in some patients with allograft dysfunction, is reported to be a leading risk factor for IA [3]. Other known risk factors in liver-transplant recipients are the duration of surgery, creatinine level at the time of diagnosis, long-term antibiotic use, multiple blood transfusions, acute rejection, concomitant cytomegalovirus infection, and OKT3 treatment [12, 16, 17]. Research has shown that OKT3 interferes with receptors in

Table 1 Demographic features and type of transplantation (*Tx*) of IA cases

Patient	Age (years)	Type of Tx	Type of donor	Immuno suppression	Acute rejection	Rejection therapy	Time of IA after Tx	Risk factors
KE	43	Renal	Cadaver	Prednisone[a], azathioprine (150 mg/day), cyclosporine[b]	No (mean creatinine level: 5.2 mg/dl, CyA: 264 ng/ml)	–	21st day	–
KB	53	Renal	Cadaver	Cyclosporine[b], tacrolimus (0.01–0.015 mg/kg)	Yes	OKT3 (5 mg/day) and prednisone (total: 6 g)	23rd day	Acute rejection, OKT3 therapy, antibiotic therapy, thrombocytopenia
MC	32	Renal	Live	Mycophenolate mofetil (1.5 g/day), cyclosporine[b], prednisone[a]	Yes	OKT3 (5 mg/day) and prednisone (total: 2.5 g)	26th day	Acute rejection, OKT3 therapy
AC	30	Hepatic	Cadaver	Cyclosporine[b], prednisone[a]	No (mean AST: 140 U/l, ALT: 67.5 U/l, CyA: 304 ng/ml)	–	28th day	–
MB	41	Hepatic	Cadaver	Cyclosporine[b], prednisone[a]	No (mean AST: 133 U/l, ALT: 100 U/l, CyA: 53.3 ng/ml)	–	28th day	Antibiotic therapy, thrombocytopenia
FÖ	55	Hepatic	Cadaver	Cyclosporine[b], prednisone[a]	No (mean ALT: 115 U/l, AST: 146 U/l, CyA: 198 ng/ml)	–	34th day	Antibiotic therapy
FA	28	Renal	Live	Cyclosporine[b], prednisone[a], azathioprine (150 mg/day)	Yes	Prednisone (total: 5 g)	17th day	Acute rejection
VS	22	Hepatic	Live	Mycophenolate mofetil (1.5 g/day), tacrolimus, pulse prednisolone	Yes	Prednisone (total: 4.5 g), OKT3 (5 mg/day)	15th day	Acute rejection, re-transplantation, antibiotic therapy, thrombocytopenia

[a]1.5 mg/kg, dose tapered within 2 weeks with maintenance dose 10 mg per day
[b]5 mg/kg
CyA cyclosporine

Table 2 Clinical features and laboratory findings of invasive aspergillosis cases

Patient	Clinical manifestations	Chest roentgenogram findings	Thoracal CT	Definite diagnosis
KE	Productive cough, fever, dyspnea, diarrhea	Bilateral homogeneous pneumonic infiltration	Bilateral disseminated consolidation	Autopsy
KB	Abnormal oxygen saturation	Bilateral nodular pneumonic infiltration	Multiple patchy consolidation	Bronchial biopsy
MC	Fever, productive cough, dyspnea	Pneumonic infiltration in right lung	Bilateral nodular infiltration and cavitation	Sputum culture and BAL culture
AC	Fever, cough, dyspnea	Pneumonic infiltration	No information	Autopsy
MB	No signs	Pneumonic infiltration in right lung	Pneumonic infiltration in right lung	Autopsy
FÖ	Fever	Pneumonic infiltration in left lung	No information	Autopsy
FA	Fever, cough, dyspnea	Bilateral pneumonic infiltration	Bilateral nodule and cavitation	Sputum culture
VS	Fever and purulent secretion	Heterogeneous infiltration in left lung andcavitation	Bilateral cavitation	Autopsy and tracheal aspiration culture

Table 3 Patients' antifungal therapy and outcome

Patient	Duration between symptoms and therapy	Duration between therapy and death	Therapy	Outcome
KE	1 day	2 days	Empirical liposomal amphotericin B (3 mg/kg)	Died
KB	2 days	5 days	Liposomal amphotericin B (5 mg/kg)	Died
MC	3 days	–	Liposomal amphotericin B (5 mg/kg)	Cured
AC	No therapy	No therapy	No therapy	Died
MB	5 days	4 days	First fluconazole (400 mg/day) empirically, then liposomal amphotericin B (3 mg/kg)	Died
FÖ	No therapy	No therapy	No therapy	Died
FA	3 days	–	Liposomal amphotericin B (5 mg/kg), then maintenance therapy with itraconazole (200 mg/day)	Cured
VS	12 days	3 days	Liposomal amphotericin B (5 mg/kg)	Died

circulating T lymphocytes, thus impairing the function of these cells. Thus, this agent is considered to be an independent risk factor for IA.

Compared with the risk in other transplantation patients, the IA risk in kidney recipients is comparatively low. Dialysis is a major reason for this, since patients are generally in better condition pre-operatively and since this treatment provides an alternative to immunosuppressive therapy in cases of allograft failure [22]. Intensive immunosuppressive therapy and renal failure necessitating hemodialysis have been noted as risk factors for IA [22].

Six of our liver and kidney recipients had risk factors defined in previous studies, such as pulse steroid and OKT3 treatment, antibiotic use, organ failure, re-transplantation, and thrombocytopenia, but the number of cases in each category was too low for statistical analysis. Although the number of patients was small, there was no difference, regarding the risk factors, between those who survived and those who died. Besides, it is interesting to note that in two patients no risk factors were determined at all. These data remind us that reconstruction activity may be the only predisposing factor for infection in this patient group if other risk factors are not established. IA typically develops within the first 12 months after transplantation and is most often seen within 3 months. The interval may be as short as 2–4 weeks in liver recipients [4, 22, 26, 29, 36]. In our patients, IA developed a mean 24 days after transplantation (range 15–34 days). This disease is observed in different clinical forms. Acute or chronic invasive pulmonary aspergillosis is the most common type [13, 19, 29]. Tracheobronchitis (seen mostly in patients with acquired immunodeficiency syndrome), acute invasive rhinosinusitis, and disseminated disease with invasion of the brain or other organs (eye, heart, kidney), are forms of IA that are rarely seen [18]. *Aspergillus*-induced osteomyelitis, surgical-site infection, and peritonitis, have all been reported in transplant recipients [29]. Although the symptoms differ according to the organ that is invaded, non-specific symptoms such as fever, weight loss, and fatigue, are common. Dry cough and fever are observed in pulmonary disease [11, 13, 18]. In high-risk patients, fever that does not respond to broad-spectrum antimicrobial therapy should alert the physician to the possibility of IA. All our patients were defined as having invasive pulmonary aspergillosis. Fever was the first sign in seven of our eight cases. In five patients clinical findings were correlated with IA, while one patient had no clinical symptoms and two patients had only fever and abnormal oxygen saturation.

Since the clinical signs of IA are non-specific and often non-existent, radiological and laboratory evaluation are key diagnostic tools. The findings on plain chest films of affected transplant recipients vary, comprising diffuse bilateral disease, diffuse shadowing, or nodular shadows and cavitation [11, 19, 36]. Plain radiographs are usually not diagnostic in these individuals. High-resolution CT (HRCT) scans are very valuable for making an early diagnosis, and this modality is considered the first diagnostic step when IA is suspected [2, 15, 33]. CT is also useful for demonstrating rhinosinusitis and involvement of other tissues, such as cerebral aspergillosis and skeletal invasion [18]. Another benefit of this technique is that it can be used to guide biopsy procedures. In addition to plain radiographs and CT, a few reports have noted that radionuclide scans with indium-111-labeled IgG demonstrate early *Aspergillus spp.* infection in immunocompromised patients [21]. Regarding our patients, the plain chest films all showed different pathological findings. Although the 'halo sign' and 'air crescent sign' are characteristic for IA in neutropenic patients, these images are not commonly seen in solid-organ transplant recipients. Although the scans revealed three separate patterns (nodules only, nodules and cavitation, and bronchopneumonia), in our patients it was also remarkable that a 'halo sign' was not detected in any case, as previously mentioned in the literature [22].

Diagnosis of IA based on microbiological examination of respiratory secretions remains controversial. Some reports suggest that positive cultures from high-risk

patients should be considered to be diagnostic [17, 37, 38]. On the other hand, laboratory contamination can be confused with colonization of *Aspergillus spp.* in the respiratory tract [17]. Also, sensitivity rates of cultures obtained from non-sterile materials are not high. Different series have reported varying culture positivity rates. Studies performed on patients at high risk of contracting IA have demonstrated 42–75% and 52–62% positivity in sputum and BAL cultures, respectively [13, 30]. Two of our six patients had positive sputum cultures, and only one positive culture was detected in BAL fluids obtained from five patients. These data reveal a low culture positivity rate, similar to the literature [13, 32].

It is recommended that culturing be done on sterile materials such as BAL fluid, lung material obtained by percutaneous biopsy, or aspirates collected by radiologically guided methods [18]. In their investigation of transplant recipients, Brown et al. found a strong correlation between IA and two or more colonies on a culture, and found a similar association between IA and positive cultures of materials from different sites. Using these criteria, they reported the specificity and sensitivity of culturing as 75% and 93%, respectively [1]. The evidence indicates that nasal surveillance cultures are valuable for early diagnosis of IA in patients with leukemia, but not in transplant recipients [9].

In solid-organ recipients, it appears that surveillance by serological testing may be more helpful. Latex agglutination and ELISA can demonstrate the circulating galactomannan antigen of *Aspergillus spp.* ELISA is positive 2–3 weeks earlier than latex agglutination, and the reported ranges of sensitivity and specificity are 50–90% and 81–93%, respectively [22]. It is claimed that testing twice or three times weekly after transplantation assists early diagnosis, and testing of serum galactomannan levels is also used in the follow-up of transplant recipients [18, 31].

Amphotericin B (1–1.5 mg/kg per day) is the standard therapy for IA, but the optimum duration of treatment remains controversial. It is recommended that clinical outcome, not total dose, be the main criterion for discontinuing therapy. Treatment should be continued until the clinical and radiological signs resolve, cultures become negative, and predisposing factors are eliminated [30]. Success with therapy ranges from 20–83%, depending on the stage of the disease, function of the allograft, and intensity of immunosuppressive therapy [5, 30]. The outcome is better in heart or kidney recipients than in liver or bone marrow recipients [18]. If renal dysfunction develops or the patient is on another nephrotoxic drug (aminoglycoside, cyclosporine, or others), it is recommended that lipid-associated preparations of amphotericin B be used [20, 27, 34]. There are conflicting reports on treatment with higher-than-conventional doses of amphotericin B [10]. Itraconazole has also proven effective against *Aspergillus spp.*, but data are limited regarding the use of this drug in transplant patients. The consensus is that it should be used for maintenance therapy in individuals who respond to amphotericin B [8, 12, 30]. We used 5 mg/kg per day liposomal amphotericin B in our four culture- and biopsy-proven cases. Empirical treatment with amphotericin B (3 mg/kg per day) was initiated in two clinically suspect cases. The other two patients did not receive this drug. Patients who were discharged shortly after transplantation responded well to the therapy, but among patients who had surgical and metabolic problems and prolonged hospitalization (and who might therefore have been exposed to more fungal spores), mortality was high. Recent reports on new antifungal agents such as voriconazole, echinocandin, and pneumocandin have indicated that they are effective in treating IA [6, 25]. In addition to antifungal therapy, surgical intervention has also been shown to improve outcome [2, 36]. Antifungal prophylaxis in transplant recipients remains controversial. Although itraconazole has in vitro activity against *Aspergillus*, poor bioavailability and absorption of the drug make it difficult to achieve adequate serum concentrations. Liposomal amphotericin B (3–5 mg/kg per day) was recommended for high-risk liver-transplant recipients for 4 weeks [28].

Despite the advances that have been made in treatment, mortality in patients with IA remains high. The reported rates for transplant recipients range from 40–92% [1, 29, 36]. The mortality rates in our group were in line with this, with 100% in the liver recipients and 50% in the renal patients. Duration between symptoms and therapy did not differ among those that survived and those who died (mean: 5 and 3 days, respectively).

In conclusion, clinical and microbiological findings might be inadequate for the diagnosis of IA. In our small series we observed that HRCT was more important than clinical and microbiological findings as a diagnostic tool. However, for high-risk patients such as transplant patients, more sensitive diagnostic methods are needed. Periodic detection of serum galactomannan in high-risk patients may be a promising diagnostic tool in the coming years.

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