Invasive Aspergillosis After Transplantation

R. Guillemain, V. Lavarde, C. Amrein, P. Chevalier, A. Guinvarc'h, and D. Glotz

The increased number of organs transplanted with the use of new immunosuppressive agents has caused an increased incidence of invasive aspergillosis (IA) after transplantation. At Broussais Hospital, from 1968 to 1993 we performed 1045 renal transplants, and from 1984 to 1993 we performed 249 heart transplants and 45 heart-lung and/or lung transplants. The incidence of IA was 0.5% for renal transplants, 4.5% for heart transplants, and 18% for heart-lung and/or lung transplants.

Patients and Methods

The diagnosis of IA was based on the following criteria: confirmed IA in cases of positive biopsies or autopsies; probable IA when radiological pulmonary abnormalities were present with positive bronchoalveolar lavage (BAL); and possible IA when clinical signs were associated with positive and repeated cultures of sputum, endotracheal aspirates, and bronchial sampling (BS). All patients receiving thoracic transplantation after January 1989 had a prophylactic nasal solution of amphotericin B at a concentration of 1 mg/mL four times daily. This therapy was associated with amphotericin B aerosol at a dose of 20 mg/d for heart transplant recipients and increased to 40 mg/d if leucopenia was present and up to 100 mg/d for lung transplant recipients. This prophylactic treatment was maintained throughout the entire hospitalization.

Risk factors included those favoring aspergillus colonization (cystic fibrosis, tobacco use), neutropenia (<500 granulocytes/mm²), intense immunosuppressive therapy, obliterans bronchiolitis, lymphoma, and other infectious pulmonary complications. Finally, the existence of interior hospital construction work was also assessed. The search for preoperative aspergillosis colonization was systematic. Sputum cultures and aspergillus antibody detection by electroosyneresis and hemagglutination were undertaken, especially in patients with cystic fibrosis. The diagnosis of postoperative infection was based on direct examination and cultures of the different aspirates (sputum, BS, BAL). These tests were systematic for heart and lung transplant recipients, whereas for renal transplant patients the tests were decided on according to the individual clinical course. The detection of aspergillus antigen was performed by latex agglutination (Pastorex aspergillus) simultaneously on both blood and BAL supernatant.

Results

Incidence

Twenty-four cases of aspergillosis were diagnosed from 1989 to 1993 on 23 patients. These included five patients with renal transplants, 11 with heart transplants, and eight with heart-lung and/or lung transplants. The site of aspergillosis was pulmonary in 95.8% (23 of 24) and ocular in 8.3% (2 of 24), with a secondary cerebral localization; of these, only 21 cases were explored (18 males and two females). Ages ranged from 18 to 67, with a mean age of 45 years.

Effect of Antimycotic Prophylaxis

Two hundred and thirty-one cardiac transplant recipients benefited from antimycotic prophylaxis. The efficacy of prophylactic aerosol and spray amphotericin B was excellent. One case of IA was observed in 107 patients with the aforementioned therapy, whereas seven cases were observed in 115 patients without prophylactic therapy (P = 0.001). The risk factors observed were as follows: (1) immunosuppressive therapy, either primary for patients at high immunological risk or secondary for the treatment of rejection (61%, 13 of 21); (2) neutropenia (19%, 4 of 21); (3) intercurrent infection, especially cytomegalovirus (CMV) (28.5%, 6 of 21); (4) chemotherapy for lymphoma (14%, 3 of 21); and (5) hospital construction (36.3%, 8 of 21). Preoperative aspergillosis colonization in patients with cystic fibrosis and obliterans bronchiolitis increased the incidence of IA but was not significant.

Diagnosis

Fever and pulmonary manifestations (cough and dyspnea) were present in 95.5% of cases. Chest X-rays demonstrated in 86% of patients three different types of images: (1) an interstitial syndrome (56%, 12 of 21); (2) nodular opacities (23%, 5 of 21); and (3) cavitary lesions (9.5%, 2 of 21). The isolation of the pathogenic agent was always obtained from living tissues. Histological examination was positive in 23% of cases (5 of 21); BAL was positive in 57% of cases (12 of 21). Of these last 12 cases, 66% (8 of 12) had preceding positive sputum cultures. In two cases of aspergillosis suspected by BAL, the diagnosis was confirmed by an open lung biopsy. In one of the patients with ocular aspergillosis, the diagnosis was established by puncture of the vitreous humor. Serological diagnosis was of no aid in immunodepressed patients: Antiaspergillus antibodies were positive in only one case, and soluble aspergillus antigen was positive in only 50% of cases with positive BAL cultures.

Treatment

Intravenous amphotericin B was used in 78% of patients (17 of 21). The following modes of administration were utilized: (1) amphotericin B (AB) in D5W at a dose of 1.2 mg/kg for an average duration of 11 days (1 to 42 days) in 64% of patients (11 of 17); (2) AB in intralipid 10% at a

From the Department of Cardiovascular Surgery, Broussais Hospital, Paris, France.

Address reprint requests to Romain Guillemain, Department of Cardiovascular Surgery, Broussais Hospital, 96, Rue Didot, 75014 Paris, France.

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Although the recent increase in IA has been demonstrated, the diagnosis essentially relies on BAL, whose indications are realized figure. This rate does not reflect the new diagnostic methodology. The clinical diagnosis, which is often difficult, can be simplified if one considers all possible pulmonary infections in transplant recipients as aspergillus in origin. In fact, clinical, radiological, and scan studies are nonspecific, and the diagnosis essentially relies on BAL, whose indications should be extended. BAL permits isolation of the pathogen in 75% to 100% of cases. Infection is certain if aspergillus filaments are present. The isolation of the fungus solely by culture is usually difficult to interpret, especially when other pathogens are present. In these cases, further studies are necessary (eventually fine-needle biopsy and/or open lung biopsy). The isolation of aspergillus in sputum or nasal aspirates is insufficient and imposes limitations on BAL. The diagnosis of extrapulmonary localizations is more difficult and is often done during autopsy. Serological tests are useless in immunosuppressed patients; the detection of aspergillus antigen is disappointing and without interest when compared to direct examination and culture.

The mortality of IA in organ transplant patients is considerable; from 50% to 100%. An earlier diagnosis probably enhances survival. New antifungal agents active against aspergillus will also influence prognosis. Prophylactic therapy of aspergillus risk is based on environmental protection: laminar flow (very expensive) or an air filtration system (HEPA) whose efficacy is proven. Other prophylactic measures were proposed, and interesting results were noted with local amphotericin B by spray or aerosol. At our hospital, we use both amphotericin B nasal sprays and aerosols with a good efficacy. The incidence of nosocomial aspergillus decreased from 6% before prophylactic therapy to 0.9% under prophylactic treatment in heart transplant recipients. The tolerance was good, and there was no systemic level of amphotericin B.

Treatment of IA relies on two antifungal agents: amphotericin B and itraconazole. Their efficacy depends on the localization and extension of the infection. Amphotericin B in liquid deoxycholate solution has been the treatment of reference for a long time in aspergillosis infections. Unfortunately, its high toxicity rarely permits the maintenance of efficient posologies by transplanted patients because of simultaneous administration of nephrotoxic drugs like cyclosporine (CyA). The mortality of this infection is still high under amphotericin B, with an average of 75% to 100%. The addition of Fluconazol or Rifampicin does not change the prognosis. To raise the efficacy and diminish the toxicity of this molecule, several vectorisation attempts of amphotericin B have been tried under colloidal or liposomal amphotericin B. If, at an equal posology, the greater efficacy of liposomal amphotericin B (Ambisome) has not yet been demonstrated in controlled studies, its toxicity is certainly lower than that in solution. Its low general and nephrological toxicity allows much higher daily intakes, thus achieving 10 times larger total doses. These high posologies are probably responsible for the drug's greater efficacy, which has been reported by different authors. Itraconazole has a high antifungal activity against aspergillus and good tissue diffusion. The clinical success of this molecule is convincing, although no randomised survey is available. However, one must be careful when using this molecule because it presents a metabolic interaction with CyA which, even if lower than for ketoconazole, can be responsible for an important increase of CyA plasmatic concentrations. On the contrary, there seems to be an uncontrolled increase in IA....
interaction between oral CyA and itraconazole metabolism, which is responsible for a decrease of plasmatic levels and for difficulties in equilibrating the posologies of each drug. The urgency of IA treatment for immunodepressed patients is impeded by the long plasmatic equilibration of itraconazole (around 15 to 21 days), which is postponed by the coadministration of CyA. In our practice, we begin the antymycotic treatment by liposomal amphotericin B at a posology of 5 to 7 mg/kg until infectious clinical signs disappear and X-rays or scan images improve. The switch to itraconazole is then achieved with an increasing posology adapted to plasmatic dosages. In case of aspergillar isolation with no gravity sign like systematic positive BAL after lung transplantation, we immediately begin the treatment, with itraconazole covering the period of plasmatic level equilibration by amphotericin B. CyA posologies for these patients usually range from 400 to 1600 mg/d but can reach 2400 mg/d. In nonvital organ transplantation (kidney or pancreas), immunosuppression should be diminished and, if possible, stopped. Eventually, surgical reduction of the aspergillar inoculum must be tried as often as possible (for instance, in nodular pulmonary forms and local abscesses).

CONCLUSION

The increasing number and diversification of organ transplantations as well as the use of more powerful immunosuppressive agents are responsible for an increase of aspergillosis. Even with progress in the treatment of aspergillar infection due to the introduction of new antymycotics in therapeutics, the mortality rate is still high and the best treatment for this infection is prophylactic. A good evaluation of aspergillar risk and appropriate isolation measures will decrease the incidence of aspergillosis.

REFERENCES

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