ELSEVIER

Aspergillus Infection in Immunocompromised Patients

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SYSTEMIC FUNGAL INFECTIONS, particularly with candida and aspergillus, remain an important issue in immunosuppressed patients, especially those with neutropenia, those undergoing solid organ transplantation, and those with HIV infection. The diagnosis of aspergillosis depends upon clinical judgment and is difficult without tissue biopsy and histologic confirmation.[1] Many patients have multiple simultaneous viral, bacterial, and other opportunistic infections.[2,3] Intact neutrophil and macrophage functions are the most important factors for successful treatment. Corticosteroids suppress monocyte and macrophage function against aspergillus hyphae, and cyclosporin inhibits interferon gamma, which in turn is responsible for macrophage activation. Successful treatment depends on three factors: early diagnosis, aggressive antifungal treatment, and ability to reduce immunosuppressive therapy.[4] The cornerstone of treatment is medical-intravenous amphotericin.[1,5] The objective of our study was to present our experiences with aspergillus infections in immunocompromised patients.

PATIENTS AND METHODS

In the period between January 1987 and January 1999, sixteen immunocompromised patients with aspergillus infection were found, 10 men and 6 women, aged 22 to 64 years. Kidney transplant recipients, patients with hematologic malignancy, and patients with systemic vasculitis were included in the observed group. They were treated with steroids, antineoplastic agents, and cytoxan. Aspergillus was found by different diagnostic procedures: with isolation and culture from bronchoalveolar lavage (BAL); by bronchial, transbronchial, skin biopsies; from transureteral prostatic resection; and in two patients by autopsy. Computed tomography (CT) scan was the main noninvasive diagnostic procedure in pulmonary aspergillosis. Routine light microscopy was performed on buffered neutral formalin-fixed material, cut to 5 μm slices. The latter were stained routinely by hematoxylin-eosin and additionally with PAS and Grocott silver staining.

RESULTS AND DISCUSSION

Sixteen patients with aspergillosis included seven patients with kidney graft, seven patients with hematologic malignancy, and two patients with systemic vasculitis. Ten patients were neutropenic when diagnosis of aspergillosis was made, and two patients had diabetes mellitus as concomitant disease. Four patients had systemic angioinvasive aspergillosis, seven patients had only pulmonary involvement, and two patients had skin aspergillosis or aspergillus prostatic abscesses.

Kidney transplant recipients, on low-dose steroids and cyclosporin, developed aspergillosis 2 to 40 months after transplantation. Three patients presented with localized forms and four patients with systemic angioinvasive aspergillosis.

Cutaneous aspergillosis developed 40 months after transplantation in one patient. He was treated with liposomal amphotericin and cured. Skin involvement is usually direct implantation following trauma.[6]

Prostatic aspergillosis was found 2 months after the second renal transplantation in a patient suffering from hip pains. Prostatic abscesses with aspergillus were found. The treatment was prostatic surgical resection and amphotericin.

Pulmonary aspergilloma was found in a patient 23 months after medical treatment of proteus mirabilis and enterobacter lung abscesses. The patient, treated with amphotericin, is still alive after three relapses of the disease.

Systemic angioinvasive aspergillosis was detected in two patients. First clinical signs, suggesting the infection, appeared 2 and 3 months after transplantation. Diagnosis of aspergillosis was suspected after 17 and 28 days of these clinical signs. Treatment with amphotericin began. But the diagnosis was definitely confirmed 28 and 32 days after the first clinical signs. In two other patients diagnosis was made postmortem. Two patients were neutropenic because of herpes zoster infection and therapy with antilymphocyte globulin. In all patients multiple simultaneous viral, bacterial, and mycotic infections were found.

Patient A was a 56-year-old woman who developed zoster infection 2 months posttransplant. She was treated with aciclovir and, because of additional pulmonary infiltrates, with antibiotics. Her immunosupression therapy was unchanged. She remained febrile despite treatment and died 1 month after with clinical picture of cerebrovascular accident. On autopsy, aspergillotic lesions were found in the brain and lungs.

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Patient B was a 40-year-old man who had two episodes of acute cellular rejection in the first month after transplantation. He was unsuccessfully treated with steroid pulses and mono- and polyclonal antibodies. Meanwhile, he developed pseudomonas sepsis from femoral phlegmon. Graftectomy was urgently done because of untreatable rejection. He died 14 days later, and autopsy revealed systemic aspergillosis, affecting the brain, the lungs, and the heart. Additional synchronous cytomegalic and actinomycotic lung infections were also detected.

Patient C was a 49-year-old man with escherichia coli urosepsis, diagnosed in the second posttransplant month. Despite adequate antibiotic treatment, he remained febrile, and chest X-ray showed pulmonary infiltrates, and a week later, lung abscess was revealed. Aspergillus, pneumocystis, pseudomonas, and enterobacter were isolated from sputum and draining abscessus. Steroids were excluded, and the therapy with liposomal amphotericin was introduced. The patient died 13 days later with the clinical picture of disseminated aspergillosis, and autopsy revealed aspergillosis in the brain, lungs, heart, kidney, in adrenal glands, thyroid, pancreas, and spleen.

Patient D was a 43-year-old man who was admitted three months posttransplant because of suspected infection. Chest X-ray revealed nodular pulmonary infiltrates, and the patient was treated for suspected tuberculosis. At first, he did not allow aggressive diagnostic procedures. Bronchoscopy, BAL, and transbronchial biopsy were performed 4 weeks later. Aspergillus was found in BAL and in the lung tissue. At the same time, the patient complained about pain and visual changes in right eye. Fundoscopic examination revealed fungal endophthalmitis. This infection usually has a poor prognosis.[7] The patient was treated with systemic and intravitreal amphotericin in cumulative doses of 3200 mg. He was discharged 4 weeks later, markedly improved, on the therapy with itraconasol. Ten days later, he became febrile again, and keratitis of the left eye was diagnosed. The therapy with steroids and cyclosporin was stopped and amphotericin was introduced again. Despite therapy, aspergillosis progressed. In follow-up, we diagnosed fungal endocarditis with fungal embolisms to the brain and the right brachial artery. Discontinuation of immunosuppressive drugs caused acute rejection, and graftectomy had to be performed urgently. Finally, he revealed symptoms of an acute abdomen and on laparatomy, hemorrhagic intestinal infarction was found. The patient died 5 months after diagnosis of aspergillosis. Cumulative dose of amphotericin was 7230 mg. On autopsy, aspergillosis of the brain, heart, native kidneys, lung, and intestinum was found.

Seven patients were treated because of invasive aspergillosis. When risk factors for invasive fungal infections were present, the diagnosis of aspergillosis was based particularly on CT chest scan and subsequently BAL when necessary and when galactomannan antigenemia in peripheral blood was found. Adequate amphotericin therapeutic response also confirmed the diagnosis. At the time polymerase chain reaction-based aspergillus diagnostics was not available at our center. Three of seven patients were diagnosed with acute myeloblastic leukemia (AML), two of seven with acute lymphoblastic leukemia (ALL), one with advanced chronic lymphatic leukemia, and one with chronic myelomonocytic leukemia (MDS4). All seven patients had pulmonary aspergillosis with highly aspergillus-specific CT chest scan with one or more focal nodules or consolidations with distinctive halos around. Galactomannan antigen, determined by ELISA, was positive in four of seven patients. Patients were treated with conventional amphotericin or its liposomal form in case of hepatic or renal failure. In four of seven patients we observed clinical improvement and regression of pulmonary infiltrates on chest X-ray after amphotericin treatment. Two patients died because of progressive pulmonary aspergillosis during the treatment of acute leukemia, and one because of advanced CLL with progressive pulmonary aspergillosis confirmed at autopsy. Four of seven patients are still alive. Two of them have chemotherapy-resistant acute leukemia, and they are receiving itraconazol prophylaxis. Prophylaxis is effective in one patient and only partially effective in the second, who had an outbreak of hemoptoe, reversible to amphotericin retreatment. Two patients are doing well. The first one is 1 year after allogeneic bone marrow transplant, with normal leukocyte count, without antifungal prophylaxis. The second, with ALL in remission, is still on chemotherapy maintenance treatment and is receiving itraconazol prophylaxis, 400 mg daily.

In all our patients with aspergillosis well-known risk factors for invasive fungal infections were present. They were severely neutropenic with neutrophil count below 500×10^6/L for more than 3 weeks; some of them also received immunosuppressive therapy. We observed a significant increase of invasive aspergillosis incidence in the year 1999 due to some minor reconstruction works performed in our hospital unit.

Two patients with systemic vasculitis, ANCA-positive, treated with steroids and cytoxan, one of them neutropenic, developed aspergillotic tracheobronchitis. Steroids and cytoxan were excluded, and the therapy with liposomal amphotericin was induced. Both patients recovered. Aspergillosis relapsed 6 months and 2 years later, respectively, and was successfully treated again with liposomal amphotericin and/or itraconasol.

The majority of our patients presented with abnormal pulmonary chest radiography. Ten of 16 patients had neutropenia. Invasive aspergillosis was found in 11 cases. Concomitant infections were present in all patients with systemic disease. Antemortem diagnosis was confirmed in 13 of 16 patients. Mortality from aspergillus infection is high in our group: 7 of 16 patients died, all patients with disseminated disease (100%), and three of seven patients with hematologic malignancy.

We conclude that aspergillus infections continue to be an important cause of morbidity and mortality in immunocompromised patients. A high index of suspicion, prompt diagnosis, and early antifungal therapy are needed. Reduc-

tion or discontinuation of immunosuppressive drugs timely is very important.

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