CASE REPORT

Invasive aspergillosis of the central nervous system after allogeneic stem cell transplantation

João F. Lacerda*, Carlos Martins, José A. Carmo, F. Lourenço, M. Moura Guedes, Paulo Sequeira, J.M.F. Lacerda

Hematology, Neurosurgery and Radiology Services, Hospital de Santa Maria, University of Lisbon, Lisbon, Portugal

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Abstract

Central nervous system aspergillosis is a rare infectious complication in patients submitted to allogeneic stem cell transplantation. When it arises, this infection appears early post-transplant and most patients present with multiple central nervous system lesions. We report the clinical case of a 52 year old woman with IgGk multiple myeloma in relapse after a matched related allogeneic bone marrow transplant, who presented with a large central nervous system Aspergillus lesion 11 months post-transplant in the setting of acute graft vs. host disease developing after the infusion of donor leucocytes. Although liposomal amphotericin B was promptly instituted, the patient died 1 week after the diagnosis.

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Invasive fungal infections are an important cause of morbidity and mortality in patients submitted to stem cell transplantation (SCT).1 The spectrum of fungal infections in the stem cell transplantation setting is changing, and an increased incidence of Aspergillus and other filamentous fungi, as well as Candida non-albicans species, has been observed.2,3 Despite the efforts for an early diagnosis and the availability of powerful antifungal agents, patients with documented invasive aspergillosis (IA) have a dismal prognosis and a very high mortality rate.4,6 Although the most frequent localization of proven IA in patients submitted to allogeneic SCT is the lung, infection of the central nervous system (CNS) has been described, arising in less than 3% of all allogeneic stem cell transplant recipients.7 We report the clinical case of a patient with graft-vs.-host disease (GVHD) following a donor leucocyte infusion for the treatment of multiple myeloma in relapse after an allogeneic SCT, who developed a large single CNS Aspergillus lesion.

Case report

A 52 year old female with IgGk multiple myeloma primary resistant to VAD chemotherapy (vincristine, doxorubicin and dexamethasone) was
submitted to an allogeneic SCT from her HLA-matched sister in January 2001. In June of the same year, she had evidence of relapse of the multiple myeloma, with an increased paraprotein level (IgG 31.7 g/l and k light chain 7.25 g/l). Between July and August of 2001, the ongoing post-transplant immunosuppression was discontinued in an attempt to induce a graft vs. myeloma effect. Unfortunately, the disease progressed and in September 2001 the paraprotein level had increased to 42.1 g/l. At this time, with the aim of attaining complete remission of the disease by the induction of an alloreactive effect, the patient received one infusion of donor whole blood containing $8 \times 10^6$ CD3+ cells/kg of body weight, as adoptive immunotherapy. In the subsequent weeks, a significant improvement of the disease was documented. However, in October 2001 the patient developed acute skin GVHD, for which prednisolone was started. In November 2001, although there was a regression of the skin rash, the patient presented with moderate diarrhoea, suggestive of intestinal GVHD, for which she was admitted. In addition to the steroid treatment, she was started on cyclosporine A and mycophenolate mofetil. In the meantime, all evidence of multiple myeloma had subsided. At this time, the patient also presented with an asymptomatic cytomegalovirus (CMV) infection, which regressed with the association of ganciclovir and foscarnet. In November and December of 2001, due to persistent fever without a site of infection, a course of broad-spectrum intravenous antibiotics and a 14 day-course of 5 mg/kg liposomal amphotericin B were administered. At this time there was no clinical, laboratory or radiologic evidence of fungal infection. After this treatment, prophylactic oral fluconazol was initiated. Four weeks later, in January of 2002, the patient presented with confusion and a declining level of consciousness. The CAT scan of the brain showed a large left parietal lobe lesion, which, on MRI, had low intensity in T1 and a ring enhanced by contrast (Fig. 1(Panel A)). In T2, the lesion had increased signal, a central necrotic area and a low intensity ring (Fig. 1(Panel B)). There was surrounding oedema and lateral ventricle compression, with no evidence of obstruction. The patient underwent surgery and the diagnosis of aspergillosis was obtained histologically. Although liposomal amphotericin B was re-started, the patient died 7 days after surgery.

Discussion

This clinical case illustrates a rare and severe complication of allogeneic stem cell transplantation.

According to published series, the incidence of CNS aspergillosis in recipients of allogeneic stem cell transplants ranges from 0.5 to 3%,$^7,^8$ probably depending on several factors such as: the age, diagnosis and other characteristics of the patient, the type of donor (related vs. unrelated), the degree of HLA-matching between donor and recipient, the type of graft infused (conventional vs. T-cell depleted), the conditioning regimen, and GVHD prophylaxis and treatment protocols.$^9,^{10}$

Our patient had several well identified risk factors for the development of invasive
aspergillosis: she was an older patient treated for an hematologic malignancy in relapse after an allogeneic SCT, developed GVHD which needed treatment with triple immunosuppression including high-dose steroids, and had concurrent opportunistic infections such as CMV. Marr et al. also identified the patients with multiple myeloma as being at the highest risk for invasive aspergillosis, while patients with chronic myeloid leukaemia had the lowest risk for this complication, and patients with other hematologic malignancies had an intermediate risk.

The median time post-transplant for the diagnosis of invasive aspergillosis is approximately 3 months. In our case, the presentation of CNS aspergillosis occurred 11 months post-transplant, which is considered very late for this complication. This was determined by the emergence of GVHD only after the administration of donor leucocytes as treatment of multiple myeloma in relapse post-transplant. The patient had to be treated with immunosuppressive agents, further increasing the risk for this complication. If the patient had not relapsed, she would no longer be at risk for invasive aspergillosis. Therefore, in allogeneic stem cell transplantation, we clearly have a second period of risk for this type of infectious complication, determined by the relapse of the disease, the therapeutic options available and their complications, all concurring for an increased immunosupression of the patient this late after transplant.

Our case report is also very unusual due to the fact that CNS aspergillosis presented as a large single lesion of the parenchyma in a patient with no prior history of cranial disease or surgery. After a thorough examination of the lungs and abdomen, this was the only site of infection. More than 75% of the patients developing CNS invasive aspergillosis present with multiple lesions, consistent with multiple areas of infarction. The differential diagnosis in this clinical setting is between aspergillosis, toxoplasmosis and post-transplant donor B-cell derived Epstein–Barr virus associated lymphoma. In our case, the diagnosis was performed only after surgery. Some authors have suggested the value of determining the Aspergillus galactomannan titer in the cerebrospinal fluid. We did not perform that test.

Despite the existence of powerful broad-spectrum anti-fungal drugs, the prognosis of proven invasive aspergillosis in allogeneic stem cell transplant recipients continues to be very poor. In a review of the literature, over 90% of the patients died. Shortly before the diagnosis of CNS aspergillosis our patient had completed a full course of liposomal amphotericin B for fever unresponsive to intravenous broad-spectrum antibiotics. At that time, we had no evidence of systemic or localized Aspergillus infection. It is well known that Aspergillus has a significant growth capacity and that large lesions can develop in a relatively short period of time. That appears to have been the case in our patient, in whom the CNS lesion probably developed in the 4 weeks that elapsed after the discontinuation of amphotericin B. During this time, she received prophylactic oral fluconazol, which is not active against Aspergillus species. Interestingly, the patient was always housed in a high-efficiency particulate air-filtered positive-pressure airflow room during that time, and there were no other documented cases of aspergillosis in our unit. However, the patient was not isolated, her visits, including house staff, did not wear mask and gowns, and our hospital had persistent construction ongoing at that time.

Finally, this clinical case further emphasizes the need for prompt diagnosis of invasive aspergillosis in stem cell transplant recipients so that early treatment is instituted in order to cure more patients with this difficult infectious complication post-transplant.

References


