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Successful management of central nervous system *Scedosporium apiospermum* infection after haematopoietic stem cell transplantation for aplastic anaemia

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Abstract

Immunosuppressed patients are at high risk for opportunistic infection. Here we report a central nervous system *Scedosporium apiospermum* infection after allogeneic stem cell transplantation for severe aplastic anaemia, successfully treated and cured with Voriconazole. Early diagnosis and treatment of opportunistic infection is challenging but crucial for a good outcome.

Keywords

Scedosporium apiospermum; allogeneic stem cell transplantation; opportunistic infection; central nervous system infection

Introduction

Patients undergoing allogeneic Hematopoietic Stem Cell Transplantation (HSCT) are at increased risk of Invasive Fungal Infections (IFI), which are associated with a high mortality rate. Several risk factors for the occurrence of IFI after HSCT have been reported. Among the pre-transplant factors: a European Group for Blood and Marrow Transplantation (EMBT) risk score > 2 and a prior history of IFI or diabetes mellitus are significant predictors. Among the post-transplant factors: grade III-IV acute graft versus host disease (aGVHD), extensive chronic GVHD (ecGVHD), post-transplant lymphoproliferative disorders (PTLD), corticosteroid therapy (≥ 2 mg/kg/d prednisolone equivalents), quantifiable Cytomegalovirus (CMV) DNA, CMV disease and lymphopenia (≤ 300 /mm^3) are associated with increased risks of invasive mold infections [1,2].

Invasive aspergillosis is the most common mold infection. However, there has been an increased

incidence of less common non-Aspergillus mold infections including *Zygomycetes*, *Fusarium spp*. and *Scedosporium spp* [3].

Scedosporium apiospermum, once considered the asexual form of *Pseudoallescheria boydii*, is a filamentous fungus found world-wide in soil, sewage, and polluted waters [4].

Previously considered exceedingly rare, *Scedosporium apiospermum* is increasingly reported as a cause of opportunistic infection, as use of corticosteroids, immunosuppressive agents, antineoplastics, and broad-spectrum antibiotics have become more widespread [5].

Furthermore, it is thought that increased use of antifungals in immunocompromised patients with agents that have activity against *Candida spp*. and *Aspergillus fumigatus*, but only modest or no activity against *Scedosporium* (e.g. amphotericin B and echinocandins), may exert a selective pressure and contribute to the increased incidence of *Scedosporium infections* [6].

Scedosporium apiospermum infections most commonly occur in the paranasal sinuses, lungs, skin, soft tissue, central nervous system and bones, but disseminated disease is also common and often fatal [4].

Case Presentation

We report the case of a 48-year-old previously fit woman admitted to our hospital for asthenia, fatigue, and epistaxis and bruising, the patient had lived in a rural area of East Europe. She had no concomitant comorbidities. On physical examination, no alterations were found and vital signs were normal. Laboratory tests showed hyporegenerative anaemia (Hb 8.9 g/dl, reticulocyte count 30,000/mm^3), severe thrombocytopenia (platelets 10 x 10^9/L) and moderate neutropenia (617/mm^3).

Acute leukaemia, viral infections (HIV, HCV, HBV, HHV-6 and Parvovirus B-19) and autoimmune diseases (antinuclear, anti-ENA, anti-DNA antibodies) were excluded. Findings of bone marrow (BM) aspirate and biopsy (marrow cellularity < 5%, presence of a lymphocytic infiltrate 10% and immunophenotyping showing lack of CD34 positive elements) were consistent with non-severe Aplastic Anaemia (AA) [7].

Three months after diagnosis, due to the worsening of the blood counts, a combination of steroids, plus Cyclosporine A (CsA), has been administered without response.

Therefore, she was given a second line therapy with rabbit anti-thymocyte globulin (thymoglobulin) without response. Due to disease's refractoriness and considering the lack of a matched related donor, a year later she underwent an allogeneic HSCT from a matched unrelated donor (MUD). The pre-transplant BM biopsy showed marrow cellularity < 1% with severe iron overload. She received peripheral blood stem cells HSCT from a 9/10 compatible male donor; the graft contained 8.57 x 10^6/kg total nucleated cells. The conditioning consisted on total body irradiation (200 cGy), Cyclophosphamide (300 mg/m^2) and Fludarabine (30 mg/m^2) [8].

The GVHD prophylaxis consisted on Sanofi® thymoglobulin (3.75 mg/kg on days -4 and -3); CsA 2 mg/kg starting on day -3; Methotrexate 15.9 mg on d +2, and 12.7 mg on days +3, +6. She achieved haematologic recovery at d +15 for neutrophils > 500/mm^3, d +14 for platelets > 20.000/mm^3 and had full donor chimerism at d +30 without signs of GVHD.

The post-transplant course was complicated by CMV reactivation (644 copies/ml), successfully treated with Valganciclovir, and by transient iatrogenic hypertension. Bi-weekly microbiological monitoring showed an oral colonization from multiresistant *Pseudomonas Aeruginosa* and borderline value for serum Galactomannan (index 0.5).

Few days after transplantation, she developed left migraine with ipsilateral back-eye pain with neither fever, nor chills. Both brain magnetic resonance (MR) and head Computed Tomography (CT) scan showed a diffuse opacification of paranasal sinuses (Figure 1), mainly in the sphenoid sinus; the symptoms spontaneously improved therefore the patient was discharged.

A BM biopsy performed at day +30 revealed variable cellularity (20%) with notable increase of iron stores. The clinical follow-up confirmed the haematological recovery and afterward she developed stage I, grade I, cutaneous GVHD treated with topical steroids; an Epstein Barr Virus (EBV) reactivation (735 copies/ml) required treatment with Rituximab 375 mg/m^2 weekly for 4 weeks. At a subsequent clinical follow-up, she reported a flare of the migraine, with a left-sided headache that had transient, partial relief with non-steroidal anti-inflammatory drugs (NSAIDs). Despite the CT scan revealed an improvement of the sinus inflammation, the headache gradually worsened until the vision in the left eye became blurred with conjunctival hyperemia. Upon suspicion of *Toxoplasma gondii* retinitis, the Consultant Ophthalmologist started administration of intra-vitreal steroids and Clindamycin with transient benefit.

However, fifteen days later she was re-admitted to hospital for worsening headache, irradiated to the occipital area, and weakness in the right hemisoma. Lumbar puncture was performed: Tests on cerebrospinal fluid were negative for bacterial pathogens as well as *Toxoplasma gondii*, CMV, EBV, Varicella Zoster Virus, Herpes Simplex Virus 1-2. A new MR revealed a complete occlusion of the intracranial tract of left internal carotid artery, with likely infectious material localized in the left lateral cerebral fissure (Figure 2).

A chest CT scan showed a nodule with initial excavation in the right superior pulmonary lobe (Figure 3).

The clinical and radiological pictures were suggestive of tuberculosis; therefore, she immediately started antitubercular therapy with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. However, since the Mantoux and Quantiferon tests resulted negative, a second lumbar puncture has been done, showing a cloudy spinal fluid, suggestive of an acute bacterial meningitis; however, the culture microbiological research for bacteria and fungi, specific Gram's stain and acid-fast stain were negative; polymerase chain reaction for tuberculosis was also negative.

Based on these findings anti-tubercular therapy was stopped as well immunosuppressive therapy with CsA.

An empirical broad-spectrum antimicrobial therapy with Meropenem/Linezolid and Amphotericin B was started and few days later, the patient underwent surgical biopsy of the sphenoid sinus. The biopsy showed acute and chronic inflammation of the respiratory mucosa, periodic acid–Schiff and Grocott staining highlighted several broad septate fungal hyphae. Cultural analysis of pathological specimens revealed the presence of *Scedosporium apiospermum* (Figure 4, A & B).

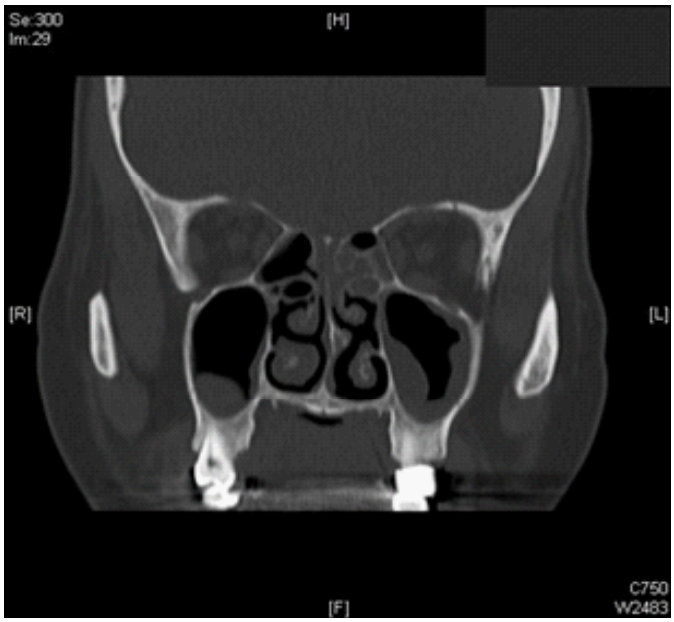

Figure 1: Diffuse opacification of paranasal sinuses as shown in the CT.

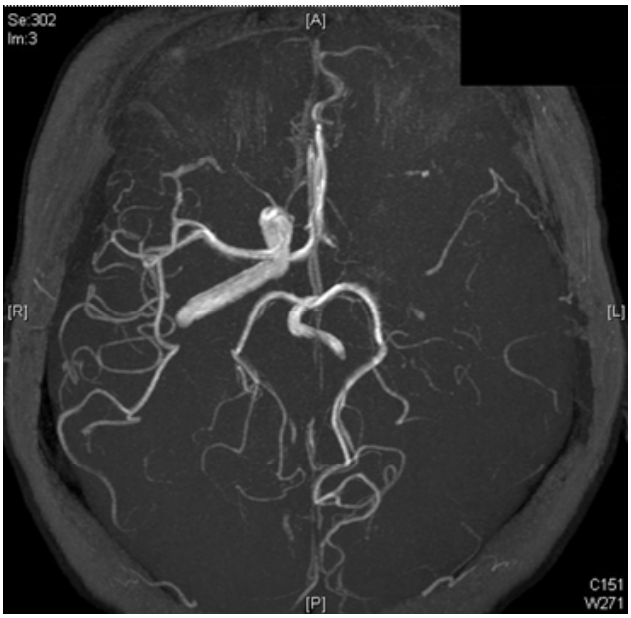

Figure 2: CT scan showing complete occlusion of the intracranial tract of the left internal carotid artery.

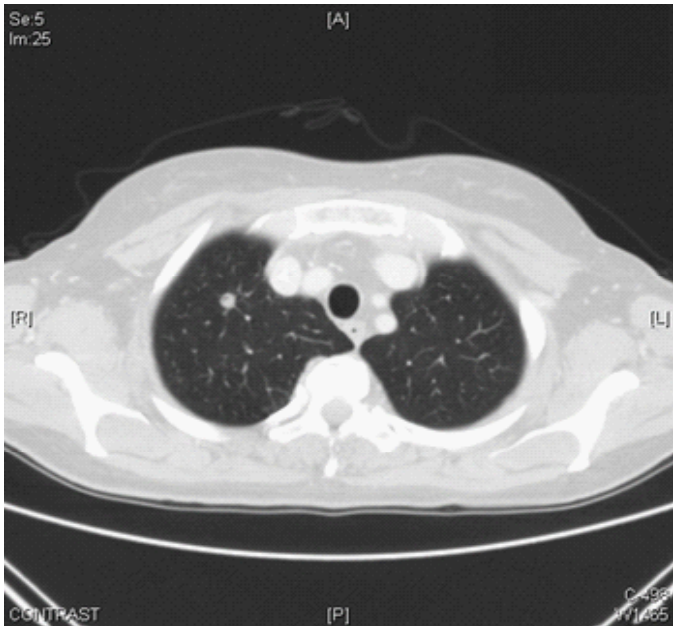

Figure 3: CT scan showing nodule in the right superior pulmonary lobe.

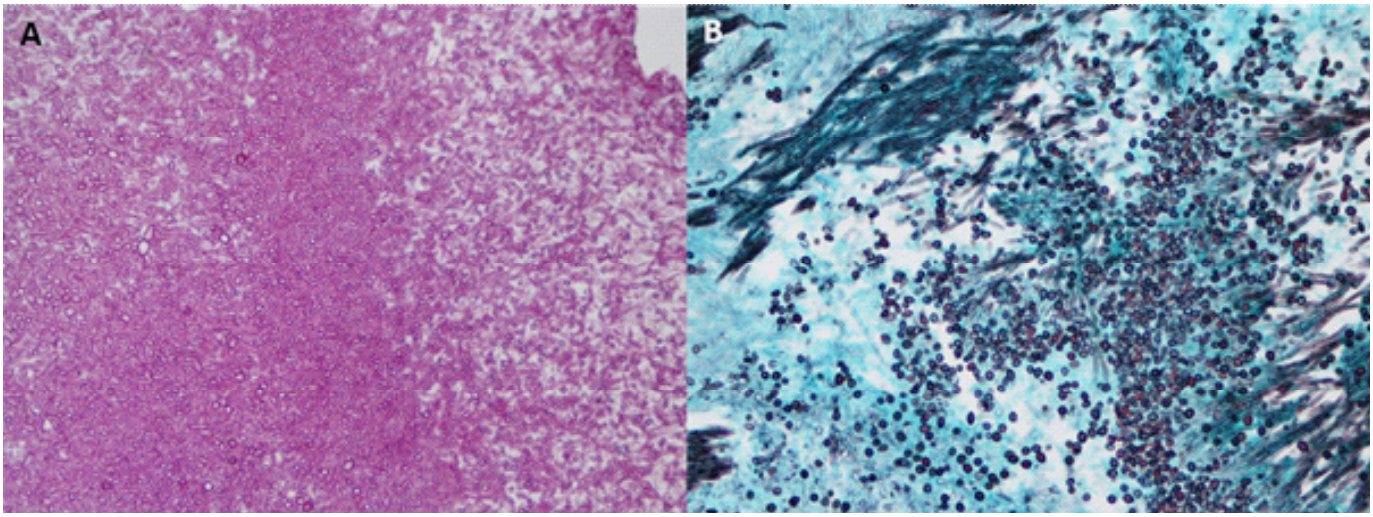

Figure 4: Periodic acid-Schiff (A) and Grocott (B) stain of the sphenoid sinus biopsy.

Based on these findings, Voriconazole intravenous therapy at 400 mg initial loading dose was started and then continued at 200 mg/day intravenously. Few days later the patient developed neutropenia (neutrophils 720/µl), which normalized after Granulocyte Colony-Stimulating Factor administration; BM biopsy showed 60% marrow cellularity, with increased iron stores, and reactive lymphocytic infiltrate.

Ten days later, she developed aphasia and right hemiparesis; a brain angio-MR showed new lesions associated with abnormality of left internal carotid artery lumen and complete left choroid detachment. Nevertheless, after two weeks of Voriconazole, a significant clinical improvement was observed: aphasia and hemiparesis disappeared, while the blindness in the left eye persisted unchanged. The patient was discharged, with oral Voriconazole at 400 mg/day, without any adverse events. The antifungal therapy has been continued for 8 months without major toxicities.

At the last follow-up, the patient did not show any neurological symptoms, except for the permanent left eye blindness. The haematological reconstitution was complete and stable with complete chimerism.

Discussion & Conclusion

Aplastic Anaemia refractory to immunosuppressive treatment is still challenging to treat and has a significant mortality, often caused by severe infections; these patients are particularly prone to develop opportunistic infections, particularly IFI, which are facilitated by several concomitant risk factors, such as prolonged and profound immunosuppression, iatrogenic diabetes and iron overload.

In these patients, allogeneic HSCT has high transplant-related mortality (TRM) and the prognosis of IFI is affected by the post-HSCT time of recovery [9,10].

Diagnosis of IFI should always be based on the criteria of the revised consensus of the EORTC/MSG (European Organisation for the Research and Treatment of Cancer and Mycoses Study Group) and the ECIL (European Conference of Infections in Leukemia) recommendations [11].

Although *Aspergillus spp*. remains the main pathogen in IFI, other less common moulds such as *Zygomycetes*, *Fusarium spp*., and *Scedosporium spp*. have become increasingly prevalent among immunosuppressed patients [12,13]. In particular, *Scedosporium apiospermum* is a virulent pathogen, which clinically and histologically may resemble aspergillosis, in which invasion of blood vessels leading to infarction is very common. *Scedosporium apiospermum* often causes sinus-pulmonary disease, endophthalmitis, and dissemination to the central nervous system infection [14-16]. This pathogen is generally resistant to Amphotericin B, while it responds to Voriconazole and, when feasible, to surgical resection of the localized lesions [3,17].

This case-report confirms that the risk of IFI is a relevant complication in patients treated with HSCT for AA, probably not only because of the prolonged neutropenia, but also because of the association of other risk factors such as the long term immunosuppressive therapy, including ATG and the iron overload. Moreover, a CNS opportunistic infection in immunosuppressed patient should always be kept in the list of differential diagnosis. The early diagnosis of CNS opportunistic infections remains challenging, but in our patient, the prompt initiation of treatment was extremely effective and successful.

Key Clinical Message

Long-term immunosuppressed patients are at high risk of opportunistic infections. Moreover, due to an impaired immune response, the signs and symptoms may be atypical. This case shows very well how important is a good multi-disciplinary approach to diagnose such a rare condition.

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