

## ***Scedosporium apiospermum* SINUSITIS AFTER BONE MARROW TRANSPLANTATION: REPORT OF A CASE**

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### SUMMARY

A forty-year-old man underwent an allogeneic BMT from his HLA identical sister. GvHD prophylaxis was done with cyclosporine (CyA), methotrexate and prednisone (PDN). On day +90 extensive GvHD was noted and higher doses of immunosuppressive drugs alternating CyA with PDN were initiated. Patient's follow-up was complicated by intermittent episodes of leukopenia and monthly episodes of sinusitis or pneumonia. One year after BMT, the patient developed hoarseness and nasal voice. No etiologic agent could be identified on a biopsy sample of the vocal chord. Upon tapering the doses of immunosuppressive drugs, the patient had worsening of chronic GvHD and was reintroduced on high doses of cyclosporine alternating with prednisone on day +550. Three months later, GvHD remained out of control and the patient was started on azathioprine. On day +700, hoarseness and nasal voice recurred. Another biopsy of the left vocal chord failed to demonstrate infection. Episodes of sinusitis became more frequent and azathioprine was withheld 3 months after it was started. One month later, the patient had bloody nasal discharge and surgical drainage of maxillary sinuses was performed. Histopathology showed hyphae and cultures grew *Scedosporium apiospermum*. Itraconazole 800 mg/day was initiated. The patient developed progressive respiratory failure and died 15 days later.

**KEYWORDS:** *Scedosporium apiospermum*; Bone marrow transplantation; Sinusitis.

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### INTRODUCTION

*Scedosporium apiospermum* is a fungal pathogen that occasionally causes soft tissue infection such as mycetoma and more recently reported to cause invasive disease in immunocompromised patients. This fungus was first isolated in 1911 from a mycetoma patient, in Italy. *S. apiospermum* and *Pseudallescheria boydii* were accepted as different agents of mycetoma until 1944 when EMMONS revealed that *Scedosporium apiospermum* was the anamorph (asexual state) of *Pseudoallescheria boydii*<sup>6</sup>.

The comprehension of the full spectrum of clinical disease due to this fungus is still incomplete because of the infrequency of this infection. The lower respiratory tract or the sinuses are predominantly involved, suggesting that the portal of entry appears to be the inhalation of fungal conidia<sup>1,2</sup>. Disseminated infection, lung, cerebral, thyroid or liver abscess, osteomyelitis, endocarditis, meningitis, endophthalmitis and sporothrichosis-like skin infection due to *Scedosporium* and *Pseudallescheria* have also been reported in immunocompromised hosts<sup>3,5,7,10,11</sup>.

Since the infection may be indistinguishable from *Aspergillus* infection, precise diagnosis is essential to guide therapy, because *Scedosporium* is resistant to most antifungal agents, including Amphotericin B.

### CASE REPORT

A forty-year old man with CML was admitted to the BMT unit to undergo an allogeneic transplant from his HLA identical sister. The conditioning regimen included busulfan and melphalan. Graft versus host disease (GvHD) prophylaxis was initiated with cyclosporine (CyA), methylprednisolone and methotrexate. Upon tapering the immunosuppressive drugs, the patient developed extensive GvHD on day +104 and higher doses of CyA alternating with prednisone were initiated according to a 40-week treatment protocol. Concurrently, the patient became febrile, neutropenic, blood cultures grew *E. coli*, sinusitis was diagnosed and ceftazidime was started. Since that, the patient's follow-up was complicated by intermittent episodes of leukopenia and monthly episodes of sinusitis or pneumonia. One year after BMT, the patient developed hoarseness

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Fig. 1 - Microscopic morphology of *Scedosporium apiospermum*. Pyriform conidia (anneloconidia) produced terminally or laterally on the conidiogenous hyphae. (1000x)

and nasal voice. No etiologic agent could be identified on a biopsy sample of the vocal chord. On day +550, high doses of CyA plus prednisone were reintroduced because of worsening of chronic GvHD. Three months later, GvHD remained out of control, recurrent episodes of infection were observed and the immunosuppressive regimen was switched to azathioprine. Nasal voice and hoarseness recurred on day +700, but a second biopsy of the left vocal chord failed to demonstrate infection. Episodes of sinusitis became more frequent and azathioprine was withheld 3 months after it was started. One month later, while receiving Amphotericin B, empirically introduced during an episode of febrile neutropenia, the patient had bloody nasal discharge and surgical drainage of maxillary sinuses was performed. Amphotericin doses were adjusted to treat a suspected *Aspergillus* sinusitis. However, histopathologic findings showed invasive fungal sinusitis and cultures grew *Scedosporium apiospermum*. The specimens were inoculated on Sabouraud's 2% dextrose agar and the isolates were identified on the basis of the macroscopic and microscopic morphology (Figure 1). In vitro susceptibilities to amphotericin or the azoles were not determined. Amphotericin B was withheld and itraconazole 800 mg/day was initiated. The patient developed progressive respiratory failure and died 15 days later. The autopsy revealed bacterial sepsis as the cause of death and confirmed *Scedosporium* sinusitis but no fungal elements were seen in other organs.

## DISCUSSION

As bacterial infections have become better controlled in the immunocompromised patient, fungi have emerged as an important cause of morbidity and mortality. *Candida* and *Aspergillus* species remain the most frequently isolated fungi; however, a number of less common but potentially devastating agents such as *Fusarium*, *Trichosporon* and *Scedosporium* species, have been increasingly reported<sup>4,9,11</sup>. The distinction between *S. apiospermum* infection and aspergillosis is subtle. Both fungi are angioinvasive and produce hyphae. Although some epidemiological aspects may suggest the etiologic agent, most investigators agree that culture is essential for differentiation<sup>3,5</sup>. In the present case, fungal sinusitis was aggressively investigated.

Whenever the patient had an episode of sinusitis that did not respond to antibiotic therapy, cultures of the secretion obtained by surgical drainage of the sinuses were performed, in an attempt to early detection of fungal infection. However, fungal sinusitis had never been diagnosed until the last episode. One month before *Scedosporium apiospermum* was isolated, cultures of the sinuses secretion obtained by maxillary puncture grew *S. aureus*. This fact suggests a short period between colonization and tissue invasion by the fungus, as observed in experimental infection in rabbits and in mice<sup>6</sup>.

The fact that *Aspergillus* species and *S. apiospermum* cannot be distinguished by histopathologic findings suggests that histologic diagnosis of *Aspergillus* infection may be misleading and the incidence of *S. apiospermum* infection may be underestimated. In neutropenic patients, the presence of a wedge shaped infiltrate with the halo sign on chest CT scan is accepted by most investigators as strongly suggestive of pulmonary aspergillosis. However, patients that do not respond to Amphotericin B therapy for a presumed aspergillosis may have in fact, an infection caused by an uncommon fungus resistant to Amphotericin B. Reports have documented the resistance of *Scedosporium* and *Pseudallescheria* species to Amphotericin B and their sensitivity to the imidazoles<sup>7,8</sup>. Although the incidence of invasive aspergillosis is much higher than *Scedosporium apiospermum* infection in immunocompromised patients, rapid and precise diagnosis is necessary to guide therapy.

In the setting of allogeneic BMT, major risk factors for fungal infection such as granulocytopenia, multiple antibiotic therapy, the use of corticosteroids and indwelling catheters, are usually present. Moreover, the presence of chronic GvHD increases the risk of fungal infection since it is immunosuppressive *per se*, it can induce leukopenia, and higher doses of corticosteroids are necessary to control GvHD. In the present case, the basis of all the complications observed was an uncontrolled GvHD. Consequently, the patient had intermittent episodes of neutropenia. Once febrile, broad spectrum antibiotic therapy had to be initiated. At the same time, higher doses of corticosteroids had to be used and the management of the infectious episodes and the GvHD became increasingly arduous. If the present case reflects a trend towards uncommon and multidrug-resistant fungal infections, then new antifungal and immunosuppressive drugs for controlling GvHD urge to be developed.

## RESUMO

### Sinusite por *Scedosporium apiospermum* após transplante de medula óssea: relato de um caso

Paciente portador de leucemia mielóide crônica, com irmã HLA-compatível foi submetido a transplante alogênico de medula óssea. No dia +90 pós-TMO foi diagnosticado doença do enxerto contra o hospedeiro (DECH) extensa e iniciado protocolo alternado de imunossupressão com altas doses de ciclosporina A e prednisona. O seguimento ambulatorial foi complicado, com granulocitopenia intermitente e quadros frequentes de sinusite e pneumonia. Um ano após o transplante, o paciente apresentou rouquidão e voz anasalada. Foi realizada uma biópsia de corda vocal mas nenhum agente infeccioso pode ser identificado. Na diminuição das doses das drogas imunossupressoras, houve piora da DECH crônica e foi reiniciado esquema de doses altas no dia +550. Três meses após, permanecendo o quadro de DECH fora do controle, foi tentado imunossupressão com azatioprina sem sucesso. Novo episódio de rouquidão foi observado no dia

+700, mas nenhum agente pode ser identificado em nova biópsia de corda vocal. Após um mês, o paciente apresentou secreção nasal sanguinolenta e foi realizada uma raspagem cirúrgica dos seios maxilares. *Scedosporium apiospermum* foi identificado nas culturas iniciando-se itraconazol na dose de 800 mg/dia. O paciente desenvolveu falência respiratória progressiva e foi a óbito em 15 dias.

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