

## INVASIVE *Aspergillus flavus* SINUSITIS: CASE REPORT IN A PATIENT WITH BIPHENOTYPIC ACUTE LEUKEMIA

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### SUMMARY

Here we report a case of invasive pansinusitis with proptosis of the right eye caused by *Aspergillus flavus* in an immunocompromised patient with acute biphenotypic leukemia without aggressive therapy response.

**KEYWORDS:** Leukemia; *Aspergillus flavus*; Invasive sinusitis.

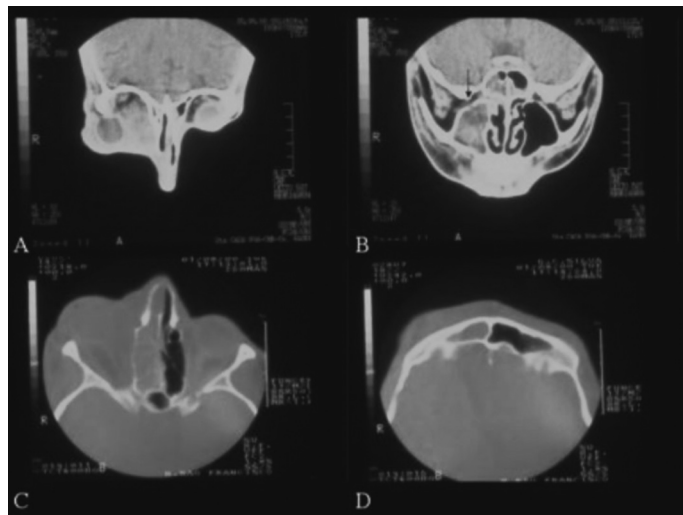
A 17-year-old white man was diagnosed with acute biphenotypic leukemia and underwent chemotherapy with cytarabine, idarubicin and etoposide (7+3+5) followed by high dose cytarabine. After an initial complete remission of short duration he relapsed and underwent a second course of induction chemotherapy with metoxantrone and etoposide without response. The patient was pancytopenic and with persistence of blasts; biphenotypic acute leukemia (lineages myeloid and T-lymphoid) demonstrated in a bone marrow biopsy.

He was being treated for febrile neutropenia when developed a fever of 39 °C and headache. Physical examination showed edema, hyperemia and proptosis in the right eye with periorbital swelling laterally. Computed tomography (CT) scan of the head revealed opacification of the right maxillary, ethmoidal, sphenoidal and frontal sinuses. Bone erosion was also observed in the medial wall of the right maxillary sinus (Fig. 1). Lung CT scan revealed no abnormalities.

Drained material of the right maxillary sinus was examined and revealed narrow, hyaline, septate hyphae elements, and characteristic dichotomous branching. Fungal culture yielded *Aspergillus flavus*. Microscopic examination of the biopsy obtained from the sinus mucosa showed chronic inflammation and invasion of the submucosa with numerous fungal hyphae consistent with *Aspergillus* (Fig. 2).

Although precipitating antibody to *A. flavus* antigens was negative, the diagnostic was confirmed by the positivity in two serum galactomannan immunoassay, latex agglutination (Pastorex *Aspergillus*, Sanofi Diagnostic Pasteur) and sandwich enzyme immunoassay (ELISA, 1.34) test (Platelia *Aspergillus*, BioRad, France).

The patient was receiving amphotericin B at a dose of 1 mg/kg/day since two months before the diagnosis of *Aspergillus* sinusitis, due to an



**Fig. 1** - CT scan of the head showing opacification of the right maxillary, ethmoidal, sphenoidal and frontal sinuses (A, B, C and D), bone erosion in the medial wall of the right maxillary sinus (B), and proptosis of the right eye (A).

episode of candidemia. After the definitive diagnostic of fungal sinusitis, itraconazole (200 mg/daily) was associated to the therapy and surgical procedure was indicated (rhinosinusectomy). However, this aggressive treatment was unsuccessful, leukemia and fungal infection progressed, clinical status deteriorated and the patient showed neurological signs leading to death.

Fungal sinusitis, commonly caused by the genus *Aspergillus*, is frequently described in immunocompetent patients and in AIDS patients as a chronic indolent invasive sinusitis, characterized by a granulomatous

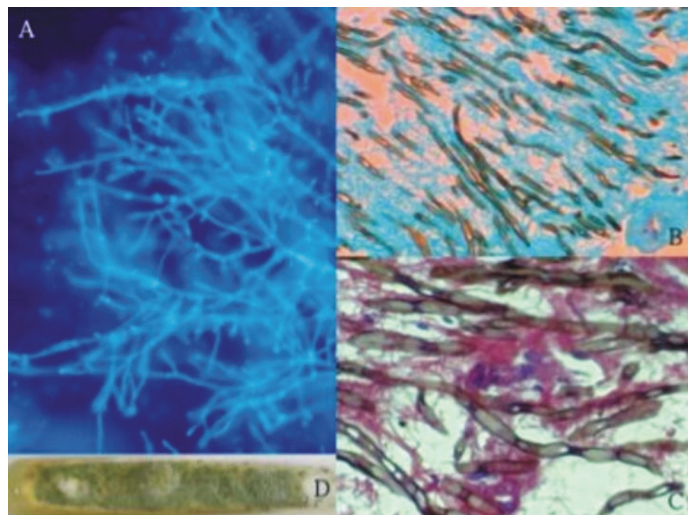
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**Fig. 2** - Microscopic examination of a sinus mucosa biopsy with calcofluor white (A), with Gomori Methenamine silver stain (B) and with combination of stains Gomori Methenamine Silver and Hematoxylin & Eosin (C) showing septate and dichotomous branching hyphae characteristic of *Aspergillus*. Sabouraud agar dextrose with *A. flavus* (D).

response. In neutropenic patients, as observed in our report, the presentation of an *Aspergillus* sinusitis is a fulminant invasive disease where rapidly progressive, gangrenous mucoperiosteitis is frequently fatal<sup>1,4,5,10</sup>.

Biphenotypic acute leukemia is an uncommon type of leukemia, which probably arises in a multipotent progenitor cell with capability of differentiating along both myeloid and lymphoid lineages<sup>3</sup>. Reports of sinusitis by *A. flavus* in patients with leukemia as described here were already observed with concomitant invasive pulmonary aspergillosis<sup>6</sup>, as well as rhinosinusitis presentation<sup>9</sup>. In fact, in the largest series of fungal sinusitis described in the literature, *A. flavus* was the main etiologic agent, representing 65% (11/17) of all cases<sup>2</sup>.

Early diagnosis plays a great role in the treatment efficacy of fulminant sinusitis. Therapy is based in surgical remotion of the damaged tissue associated with antifungal therapy, where amphotericin B is the drug of choice<sup>1</sup>. Despite this aggressive treatment the outcome death is common, mainly due to the great period between the beginning of the disease and the therapy start, which permit the infection progress to a severe clinical form. Thus, in a series of five rhinocerebral mycosis cases, four patients died in spite of the amphotericin B therapy<sup>7</sup>, as well as in the largest series of fungal sinusitis where nine from the 17 patients evolved to death<sup>2</sup>. On the other hand, the development of a severe *Aspergillus* infection in a patient receiving a fungicide drug, amphotericin B as showed in our report, is very uncommon, since this antifungal should prevent the fungal growth and consequently reappearance of the disease. However, a very

similar case was described in the literature<sup>8</sup> suggesting that only the antifungal chemotherapy is not efficient in the control of a fungal infection in neutropenic patients. Both reports emphasized the need of preventive measures as ventilation systems with high efficiency particulate airtype filters in rooms of patients included in a risk group<sup>7,8</sup>.

## RESUMO

### Sinusite invasiva por *Aspergillus flavus*: relato de um caso associado a leucemia aguda bifenotípica

Descreve-se um caso de pansinusite invasiva com proptose do globo ocular direito causado por *Aspergillus flavus* em um paciente imunossuprimido com leucemia aguda bifenotípica sem resposta a terapia agressiva.

## REFERENCES

1. CARPENTIER, J.P.; RAMAMURTHY, L.; DENNING, D.W. & TAYLOR, P.H. - An algorithmic approach to *Aspergillus* sinusitis. **J. Laryngol. Otol.**, **108**: 314-318, 1994.
2. IWEN, P.C.; RUPP, M.E. & HINRICHS, S.H. - Invasive mold sinusitis: 17 cases in immunocompromised patients and review of the literature. **Clin. infect. Dis.**, **24**: 1178-1184, 1997.
3. MATUTES, E.; MORILLA, R.; FARAHAT, N. *et al.* - Definition of acute biphenotypic leukemia. **Haematologica**, **82**: 64-66, 1997.
4. MEDEIROS, A.K.A.; BARROS, A.A.P.; MEDEIROS, F.S. *et al.* - Sinusite fúngica crônica indolente. **J. bras. Med.**, **90**: 25-28, 2006.
5. MEYER, R.D.; GAULTIER, C.R.; YAMASHITA, J.T. *et al.* - Fungal sinusitis in patients with AIDS: report of 4 cases and review of the literature. **Medicine (Baltimore)**, **73**: 69-78, 1994.
6. PAUKSENS, K. & OBERG, G. - Concomitant invasive pulmonary aspergillosis and *Aspergillus* sinusitis in a patient with acute leukemia. **Acta Biomed.**, **77**(suppl. 4): 23-25, 2006.
7. SCHMIDT, J.M. & POUBLON, R.M.L. - Rhinocerebral mycosis in immunocompromised patients. A case report and review of the literature. **Rhinol. J.**, **36**: 90-93, 1998.
8. SWERDLOW, B. & DERESINKI, S. - Development of *Aspergillus* sinusitis in a patient receiving amphotericin B. Treatment with granulocyte transfusions. **Amer. J. Med.**, **76**: 162-166, 1984.
9. TALBOT, G.H.; HUANG, A. & PROVENCHER, M. - Invasive *Aspergillus* rhinosinusitis in patients with acute leukemia. **Rev. infect. Dis.**, **13**: 219-232, 1991.
10. TEH, W.; MATTI, B.S.; MARISIDDAIAH, H. & MINAMOTO, G.Y. - *Aspergillus* sinusitis in patients with AIDS: report of three cases and review. **Clin. infect. Dis.**, **21**: 529-535, 1995.

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