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ASPERGILLOSIS IN IMMUNOCOMPROMISED CHILDREN WITH ACUTE MYELOID LEUKEMIA AND BONE MARROW APLASIA. REPORT OF TWO CASES

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SUMMARY

Two cases of Aspergillosis in immunocompromised children are reported. Both were caused by *Aspergillus flavus*. Early diagnosis and treatment led to the remission of the process. One patient had acute myeloid leukemia; the fungus was isolated from the blood. The other patient with bone marrow aplasia, presented an invasive aspergillosis of the paranasal sinuses with dissemination of fungal infection; the diagnosis was obtained by histology and culture of biopsied tissue from a palatal ulceration.

KEYWORDS: Aspergillosis; *Aspergillus flavus*; Leukemia; Bone marrow aplasia.

INTRODUCTION

The different species of *Aspergillus* are currently identified on the basis of "conidial head" color and of conidiophore morphology. On these basis, KWON-CHUNG & BENNETT [7] present a key for identification of *Aspergillus spp.* commonly isolated from human lesions.

Cases of aspergillosis have been more and more frequent in immunocompromised patients, with the most varied clinical manifestations, may be caused by one or by different species of *Aspergillus*. These fungi are found in soil and in plant debris and their propagula are inhaled and invade abnormal host through nasal, sinusal or tracheobronchial mucosa or the alveoli.

According to YOUNG et al. [20], 42% of patients infected with *Aspergillus flavus* present lesions of the palate or epiglottis. Invasive aspergillosis may be a cause of death in immunocompromised patients with collagen diseases, sarcoidosis, and severe blood diseases, and in transplanted patients treated with immunosuppressive drugs. When an early diagnosis of aspergillosis is made, prolonged treatment with itraconazole can produce satisfactory results, as reported by LOEUILLE et al. [9].

In the present paper we report *A. flavus* aspergillosis in two children with acute myeloid leukemia and bone marrow aplasia, respectively.

CASE REPORT

Case 1

A.T.S., a 14-year old girl was admitted to the Onco-

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Hematology Service of the Children's Institute complaining of fatigue and ecchymoses throughout her body. Bone marrow aspirative puncture revealed type M2 acute myeloid leukemia. A chemotherapy schedule was started according to the LNLA-1-86 protocol (Onco-Hematology Unit/May 1986), with administration of arabinosyl-cytosine (ARAC), daunomycin, dexamethasone and vincristine. After remission, the patient was discharged with a centrally implanted venous catheter for the administration of chemotherapy for 60 weeks using the same protocol.

Four months later, readmitted for receiving high doses of ARAC, the patients presented episodes of fever accompanied by perioral cyanosis. Empirical antibiotic treatment was then started with clindamycin (1200 mg/m^2) and amicacin (800 mg/m^2). *Pseudomonas paucimobilis* was isolated from blood cultures; ceftazidine (125 mg/kg) was introduced and clindamycin was discontinued. On the tenth day of this schedule, the patient presented again elevated fever peaks and diffuse myalgia.

An echocardiogram showed absence of vegetations and the catheter was removed because of the persistence of fever. *Aspergillus flavus* was isolated from blood cultures (2 times). The patient was treated with amphotericin B (1 mg/kg/day) for 21 days, when the blood cultures were negatives. For maintenance of antifungal therapy, the patient received itraconazol (3mg/kg/day), a drug with recognized action against *A. flavus* with relative absence of side effects.

The patient had a very good course, with no infectious relapses, and should complete her chemotherapy schedule within 10 weeks.

Case 2

F.F.L., an 8-year old girl was referred to the Onco-Hematology Service with a history of ecchymoses and gingival bleeding of 3 months duration, having already received 5 blood transfusions due to intense anemia. She reported contact with the insecticide Baygon about one year before and sporadic ingestion of dipyrone. Laboratory examination revealed bone marrow aplasia probably induced by the insecticide. The child had been taking prednisone (PRED, 30 mg/kg/day) and, in addition to intense anemia with limb ecchymoses and petechiae, she presented diffuse bone rarefaction of the entire skeleton.

The patient was admitted with fever and epistaxis. Blood culture revealed the growth of *Serratia marcescens*. She was treated with amicacin and discharged without fever. Fifteen days later she was readmitted with bronchopneumonia and a pleural hemorrhage, also presenting bleeding gums. She was again submitted to broad-spectrum antibiotic treatment despite negative cultures of blood, pulmonary secretion and urine.

A bone marrow biopsy showed maintenance of aplasia and treatment with methylprednisolone was started. The patient continued to have fever and developed frontal headache, photophobia, lumbar and right shoulder pain, as severe nasal obstruction. Roentgenogram of the facial sinuses demonstrated right maxillary sinusitis. Successive blood cultures showed the growth of *Klebsiella pneumoniae* and *Enterobacter sp.*

Despite the antibiotic treatment (vancomycin, ceftazidine and amicacin), fever continued and an ulcer of approximately 2.5 x 5.0 cm appeared on the hard palate and became deeper, with rapid loss of tissue. Because of the continued fever and bone marrow aplasia, we introduced amphotericin B and rhGMCSF (recombinant human granulocyte macrophage colony stimulating factor) and discontinued corticoid treatment.

Cultures of the palatal biopsy were positive for *Aspergillus flavus*. Histological examination of the palate biopsy documented the diagnosis of aspergillosis. The palatal lesion evolved to necrosis of the uvula and of the tonsil pillars, and partial peripheral paralysis was observed clinically. Computerized skull tomography showed intense bone erosion.

Despite the treatment, there was no bone marrow recovery and the child started to present worsened general condition and was transferred to the Intensive Therapy Unit. She continued to have fever and developed renal failure, neurological worsening with anisocoria and signs of decerebration, and multiple organ failure. Three days after admission into the ITU the patient died. Up to the time of death, the child had received 19 days of treatment with amphotericin B (Figs. 1, 2 and 3).

DISCUSSION

Aspergillosis is the designation of a group of diseases caused by fungus of the genus *Aspergillus*. Pathologic process includes: 1) toxicity due to ingestion of contaminated foods; 2) allergy and sequelae to the

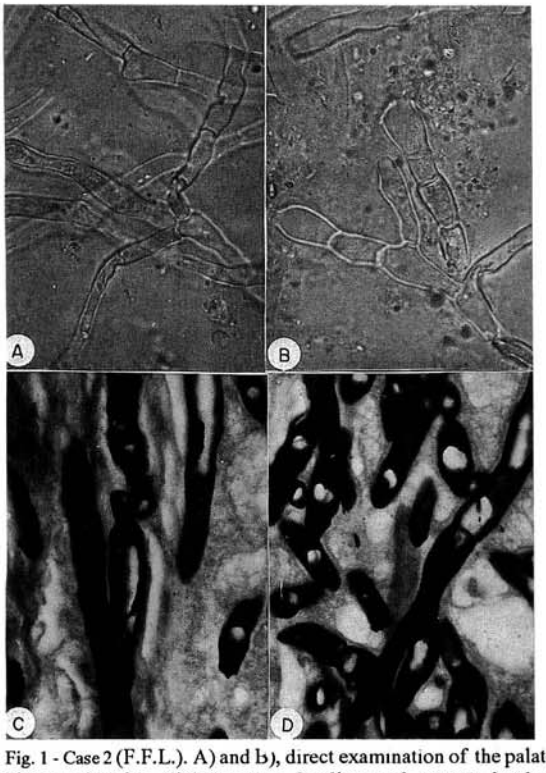

Fig. 1 - Case 2 (F.F.L.). A) and b), direct examination of the palate biopsy showing dichotomous, hyaline and septate hyphae suggestive of *Aspergillus sp.* C) and D), tissue section stained by Gomori-Grocott showing dichotomous branching hypha septate C, and swollen, hyphae in D.400X.

presence of conidia or transient growth of the organism in body orifices; 3) colonization without extension in preformed cavities and debilitated tissues; 4) invasive, inflammatory, granulomatous, necrotizing disease of lungs and other organs; 5) systemic and fatal disseminated disease. The type of disease depends on the local or general physiologic state of the host, as the etiologic agents are ubiquitous and opportunistic. The spectrum of human infection also includes otomycosis, mycotic keratitis and rarely mycetoma (RIPPON [17]).

Cases of invasive aspergillosis are being observed at increasing frequency among immunocompromised patients. MUSIAL et al. [16], pointed out that various species of *Aspergillus* could be detected in these patients; *A. fumigatus* being the most frequent, followed by *A. flavus*, *A. niger* and *A. terreus*.

In the immunocompromised host, *Aspergillus spp.* commonly produce an acute pneumonia which is usually fatal. Patients with acute leukemia, those receiving highdose corticosteroid or cytotoxic drug therapy, or those who have recently undergone bone marrow transplantation with functional or absolute neutropenia are most often afflicted.

Often *Aspergillus spp.* disseminate from the lungs, to the brain, liver, kidney, heart, skin, and rarely to the gastrointestinal tract. Localized infection may also occur in the immunocompromised host, especially in the facial sinuses often with contiguous spread to the brain to produce rhinocerebral aspergillosis. Disseminated aspergillosis most often occurs in patient with granulocytopenia.

BODEY et al. [2], in an international survey of autopsies of patients with neoplasias from countries in Europe, Japan and Canada, observed that the fungal infections habitually occurring in these patients (especially those with leukemia), are aspergillosis and candidiasis.

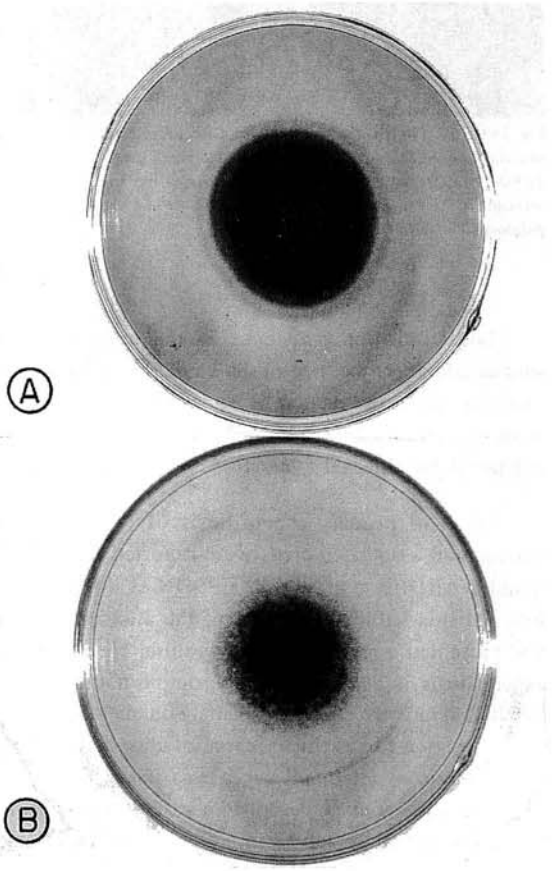

Fig. 2 - Case 2 (F.F.L.). *Aspergillus* of the *flavus* group. A) Giant colony on agar malt after 7 days at room temperature. B) On Czapek agar under the same conditions as described above.

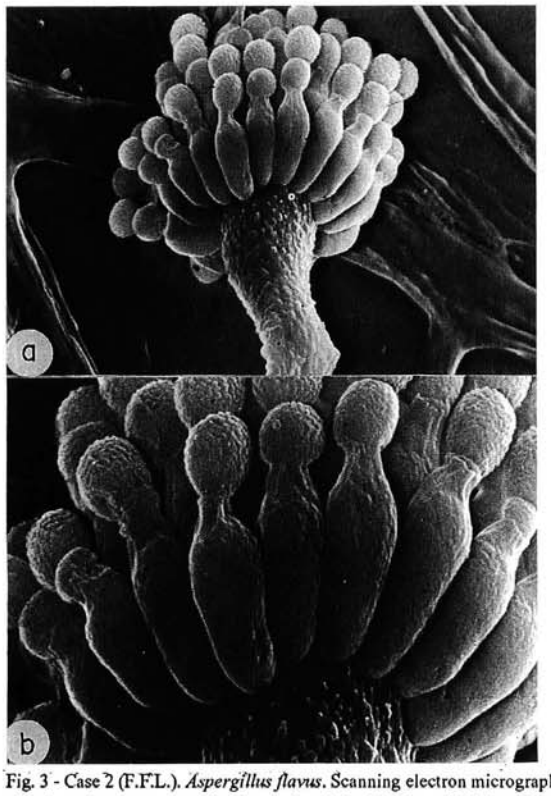

Fig. 3 - Case 2 (F.F.L.). *Aspergillus flavus*. Scanning electron micrograph showing: a(verrucose conidiophore and vesicle, phialids and phialoconidia. 2000X. b) Enlarged detail of the phialids originating from the vesicle, arranged in a row in the shape of flasks, and globose and slightly verrucose phialoconidia. 4960X.

Local infection may arise in the orbit or nasal sinuses and affect the base of the brain. These infections cause extensive destruction of facial tissues. The diagnosis can usually be established readly by biopsy and culture of the infected material. [3]

Cases of primary aspergillosis of the paranasal sinuses and associated areas were reported by HORA [5], and WARDER et al. [21]. AXELSSON et al. [1] reported four patients with aspergillosis of the maxillary sinus and presented a review of the literature. Nasal orbital aspergillosis is a rare disease throughout the world, but it is relatively common in the Sudan. MILOSEV et al. [14] reviewed seventeen cases of this disease and the etiologic agent in all cases was *Aspergillus flavus*. WELLER et al. [22], described a case of aspergillosis by *A. flavus* with involvement of the right maxillary, ethmoid sinuses and orbit. MARTINSON et al. [11], related case of aspergilloma of the ethmoid by *Aspergillus flavus*. LACAZ et al. [8], registered a case of orbital aspergillosis due to *A. flavus* with a progressive proptosis of right eye with impairment of right infravergence.

McGILL et al. [12] reported four cases of fulminant aspergillosis of the nose and paranasal sinuses, a new clinical entity occurring in individuals with depressed immunological responses. It is marked by a rapid malignant course, requiring early recognition, agressive surgery and chemotherapy. Clinical manifestations include a rapidly progressive gangrenous muco-periostitis advancing relenthessly to destruction of the nasal cavity and the paranasal sinuses within a few days. The recent emergence of this form of aspergillosis appears to be directly related to the increased intensity of chemotherapy and immunosuppression in the treatment of neoplastic diseases. Control of this disease process requires aggressive therapy. This may include radical sinus ablation, debridement of nasal structures, chemotherapy and possible correction of immunological deficits, i.e., bone marrow transplantation. SWERDLOW & DERESINSKI [19] related a case of a fulminant sinusitis due to *A. flavus* that developed in a patient with acute leukemia. SAAH et al. [18] observed 8 cases of rhinocerebral aspergillosis in 423 patients undergoing bone marrow transplantation. The responsible fungal pathogens were *A. flavus* in 7 patients and *A. quadrilineatus* in 1 patient.

LOWE & BRADLEY [10] described *A. fumigatus* infection due to primary infection of the ethmoid sinus affected brain and orbit of an otherwise healthy elderly woman.

MILROY et al., [15] reported aspergillosis of the nose and paranasal sinuses caused by *A. fumigatus*.

Cases of sinusitis induced by *A. fumigatus* have been described in patients with AIDS (GEISSMANN et al. [4]).

Pulmonary aspergillosis is relatively common in recipients of bone marrow transplants and patients with AIDS, and some investigators have recommended the use of amphotericin B (KEMPER et al. [6]).

In the cases reported here, *A. flavus* cultures were isolated from circulating blood and from palate lesions, and the evidence lead us to believe that early treatment with itraconazole and amphotericin B may be of benefit to the patients.

RESUMO

Aspergilose em crianças imunocomprometidas com leucemia mielóide aguda e aplasia de medula óssea. Registro de 2 casos.

No presente trabalho são registrados dois casos de aspergilose em crianças imunocomprometidas. O estudo micológico completo identificou *Aspergillus flavus* como agente dos dois processos. A presença cada vez mais frequente da aspergilose invasiva deve-se ao número crescente de pacientes imunocomprometidos, muitos com hemopatias graves submetidos à quimioterapia. O diagnóstico precoce em um dos casos possibilitou remissão do processo.

Tratava-se de paciente com leucemia mielóide aguda, tendo sido isolado o fungo do sangue circulante. O segundo caso evoluiu para óbito, com infecção fúngica generalizada.

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