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Successful Treatment of Disseminated Aspergillosis in a Leukemic Child

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The incidence of severe fungal infections in the immunocompromised patient with malignancies has increased in recent years. This appears to be associated to the profound periods of immunosuppression and the extended use of broad spectrum antibiotics. *Aspergillosis* is the second most common fungal infection reported in the immunocompromised cancer patients. In patients with advanced immunosupression, the mortality due to invasive aspergillosis approaches 100% despite treatment with antifungal agents. Reports of complete or partial response to echinocandins are well demonstrated in adults, but very limited in the pediatric population. This report describes the case of a child with relapsed acute lymphoblastic leukemia (ALL) who developed cutaneous aspergillosis and subsequent multiorgan dissemination during therapeutic induction and was treated successfuly with caspofungin acetate.

Key words: Aspergillus, Acute lymphocytic leukemia, Antifungal

This is the case of an eleven year old female with a 30 day history of persistent fever and otitis media during treatment with oral antibiotics. The initial laboratory findings included pancytopenia with blast cells in the peripheral smear. The diagnosis of high risk β cell acute lymphoblastic leukemia (ALL) was made based on physical exam, bone marrow cell morphology, cytogenetics, and surface markers, B antigen positive 79%. As induction therapy, the received vincristine (V), adriamycin (A), l-asparaginase (L-ASP), prednisone (P), and intrathecal (IT) cytarabine/methotrexate (ARA-C/MTX) achieving complete remission in consolidation was initiated with V, A, P, L-ASP, and 6-mercaptopurine (6-MP). Three months after her diagnosis, she had a new onset of generalized bone pain, sore throat, abdominal pain, and fever. Physical examination was unremarkable although the laboratory tests showed significant neutropenia (absolute neutrophil count less than 500 / mm^3) and high lactate dehydrogenase (LDH: 1,603u/l). Bone marrow aspirate revealed more than 25% immature cells. She was initiated on IV *ceftazidime* and *fluconazole* after appropriate cultures and radiographs were obtained. Her chest radiograph (CXR) and cultures (blood, urine and throat) yielded negative results at 72 hours after therapy was initiated.

As re-induction, she received ARA-C, adriamycin and IT ARA-C/MTX. After 7 days of antibiotics she persisted with fever and developed watery diarrhea. Blood, urine and stool cultures were obtained and ceftazidime was substituted by *imipenem*. All her cultures were reported as negative. On her 16th hospital day, a small erythematous pin-point lesion was noticed at the superior malleolar area of the left ankle and IV clindamycin was added to her antimicrobial treatment. She persisted febrile so imipenem was discontinued and IV ciprofloxacin and co-trimoxazole was started. Despite antimicrobial therapy, fever persisted, her skin lesion expanded and within 4 days evolved into an ulcer with an erythematous halo (3.5 x 2 cm) with a central necrotic nodule measuring 2x2 cm (Figure 1). Cultures were again obtained from blood, urine, stool and

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the skin lesion. Within 48 hours the skin culture yielded *Aspergillus species* and amphotericin B (Ampho. B) at 1mg/kg/day was initiated. All other cultures were reported negative and chest films showed no abnormalities. M mode and 2D echocardiogram were obtained, showing no evidence of vegetations, fungal growth, or pericardial

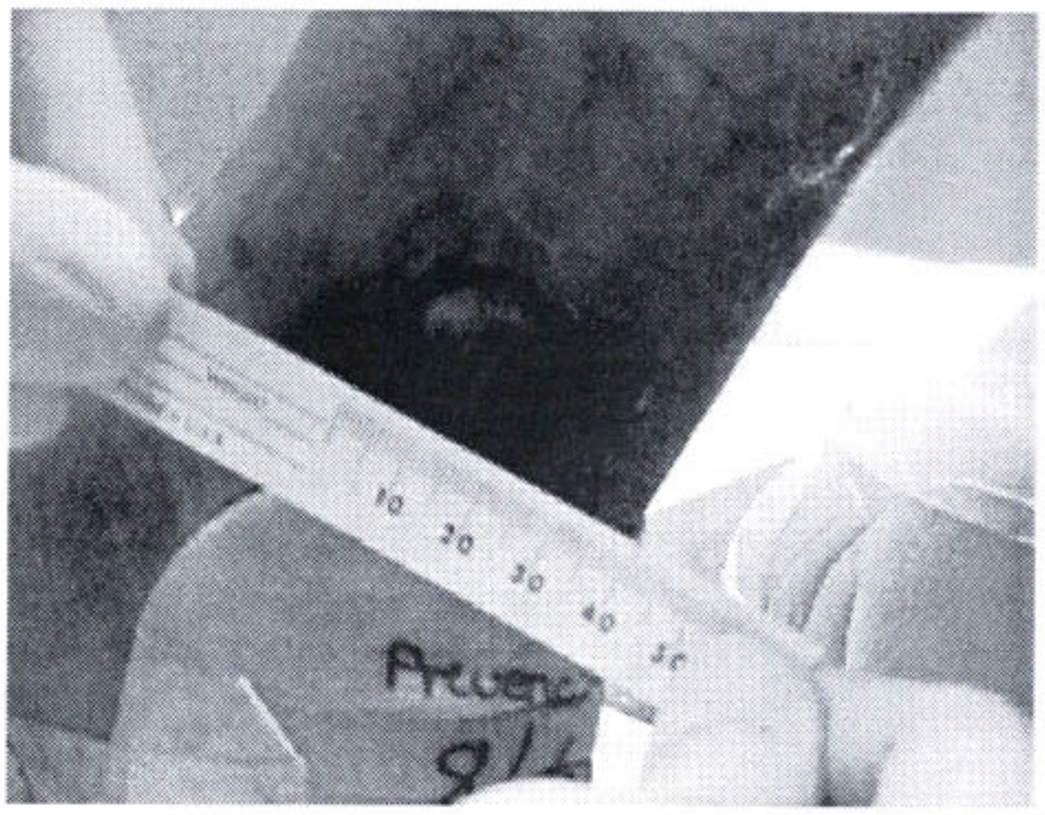

Figure 1. Ulcerated skin lesion with necrotic tissue material on the left lower extremity

effusion. Abdominopelvic computer tomography (CT) scan revealed no evidence of abscess or fungal invasion. All cultures, including cerebrospinal fluid yielded no growth for fungi or bacteria. Fine needle aspiration of the skin nodule revealed numerous invading fungal hyphae and the culture of tissue confirmed a deep seated infection with *Aspergillus species.* On her 25th hospital day, she developed acute neurologic deterioration consisting of lethargy (Glasgow coma scale 9/15) and focal seizures. A head CT scan with contrast revealed multiple, deep, white matter hypodensities with areas of non-specific edema (Figure 2). Left and right parietal cortical lesions suggestive of cortical infarcts were identified. Since the lesion did not correspond to a typical vascular territory, a vasculitis secondary to *Aspergillus species* was suspected. A brain magnetic resonance image (MRI) identified multifocal lesions involving the subcortical gray matter and periventricular white matter without evidence of intracraneal hemorrhage (Figure 3). On day 29, she developed melena, hematemesis, hypertension, pancreatitis and acute renal insufficiency. Her bone marrow biopsy was hypocellular. Amphotericin B was substituted for liposomal amphotericin B (5 mg/kg/day). On her 32nd hospital day she developed unexplained tachypnea and her respiratory status rapidly deteriorated demanding respiratory support, her chest film was normal. In view of the degenerating condition, amikacin was added to her treatment and liposomal amphotericin B was replaced with

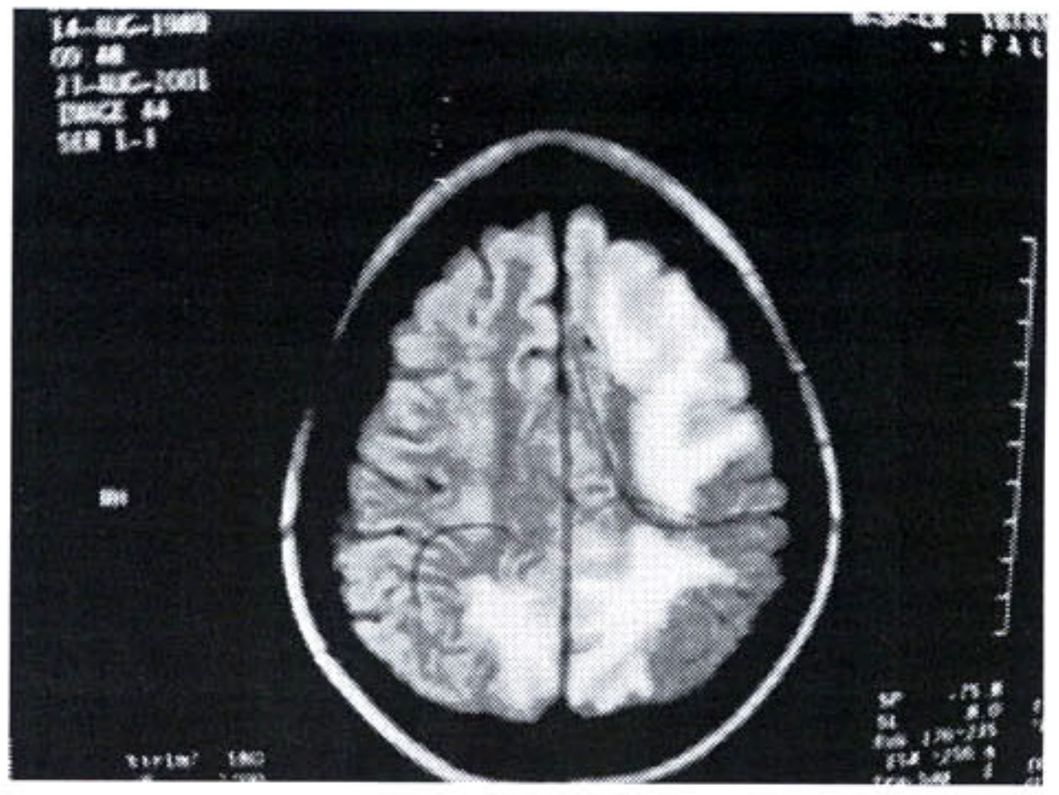

Figure 2 . Magnetic resonance image of brain revealing multiple deep white matter hypodensities with areas of edema

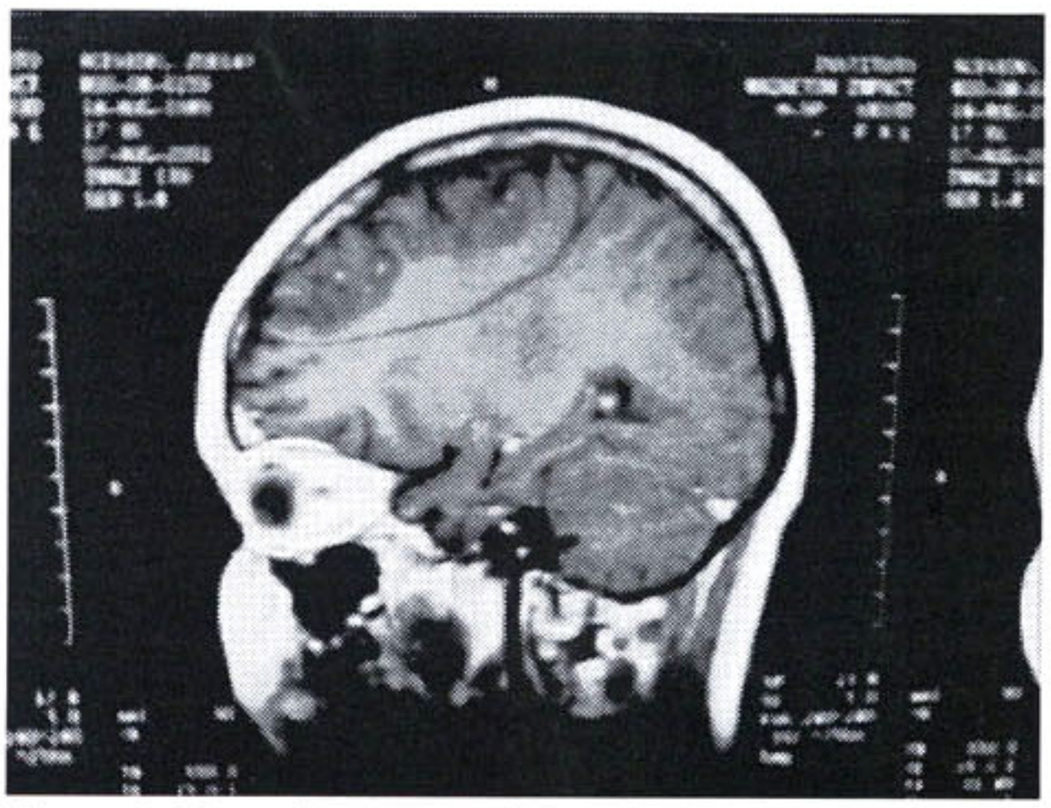

Figure 3. Magnetic resonance image obtained before treatment depicting the lesion of subcortical matter without evidence of hemorrhage

Echinocandin (caspofungin acetate) at a dose of 50mg following a loading dose of 70mg, for suspected refractory *Aspergillus* infection. On day 36, she defervessed, regained consciousness and her renal, pancreatic and respiratory functions normalized. A bone gallium scan confirmed the presence of osteomyelitis at the left distal tibia and fibula, as well as over the distal femur. On the 44th hospital day, her respiratory status again deteriorated and IV pentamidine was added. A bronchoalveolar lavage was not possible due to her clinical condition. The chest CT scan showed patchy ground-glass opacities over both lungs and the echocardiogram ruled out cardiac disease as a possible etiology for deterioration. A follow-up brain MRI showed progression of the previously described lesion with associated edema and subacute hemorrhage at the left parietal convexity. Her bone marrow aspirate was hypocellular with a diffuse infiltrate of immature cells.

On day 61, a follow-up chest CT scan showed marked interval worsening with bilateral alveolar infiltrates. Head CT scan showed improvement in the multifocal hypodensities although a new fronto-parietal subdural hematoma was noticed. The left ankle ulcer at the time showed clean borders without evidence of necrosis but her respiratory status progressively deteriorated and died on her 66th hospital day in bone marrow relapse. Autopsy revealed an intracraneal *dura mater* hemorrhage. The vessels at the circle of Willis, brainstem and cerebellum showed no abnormalities. The brain cortex was uniform without changes in white matter, basal ganglia, or thalamic nuclei. Cerebral histological examination showed marked infiltration of atypical mononuclear cells. No hyphae were identified. There were bilateral multifocal hemorrhagic pulmonary lesions without evidence of fungal invasion. Marked edema with hyaline membrane formation was seen, compatible with adult respiratory distress syndrome (ARDS). Left leg skin ulcer showed inflammatory reaction without evident growth of *Aspergillus species* (Figure 4) and the bone marrow aspirate revealed immature lymphoblasts.

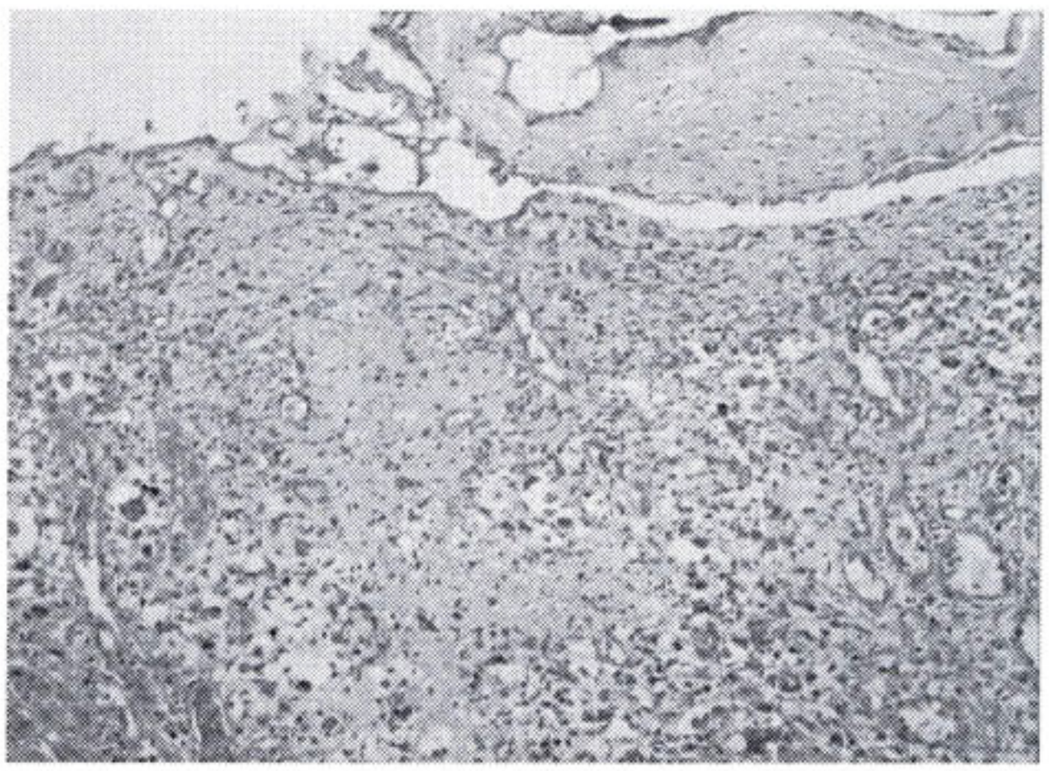

Figure 4. Periodic acid shift stain of ulcerated area showing abundant macrophages with PAS positive material, but no evidence of fungi

Discussion

Invasive *aspergillosis* is an increasing predicament in patients with advanced immunosuppression. The greater number of affected patients and those at highest risk of invasive aspergillosis are children with acute leukemias with chemotherapy-associated neutropenia (4). The status of the underlying neoplastic process plays an important role in the mortality associated with invasive fungal infections. Patients with invasive fungal infections, whose malignant etiology was unknown or was not in remission, have a six-fold or greater mortality rate than those in complete remission (5).

In spite of accessible antifungal treatment, the mortality associated with disseminated aspergillosis reached nearly 100% in the past. It remains over 65% with currently available antifungal agents (13). No definitive treatment plan has been outlined and the mainstay of treatment has been amphotericin B but response to amphotericin B alone has been reported as less than 25%, being even lower for neutropenic patients. Other combination of drugs has been used with different variable results, therefore establishing an appropriate treatment plan continues to be a major concern to physicians.

The lungs are frequently the primary focus of *Aspergillus species* infection from which hematogenous dissemination results (6). Primary cutaneous aspergillosis is uncommon and satisfactory response depends on the absence of other simultaneous infection foci (7). Central nervous system (CNS) is the most prevalent site for disseminated aspergillosis. Such patients usually present with lethargy, coma, or focal neurological signs (8). The evolution of CNS aspergillosis in the immunocompromised host is almost always fatal in all cases despite surgical and medical treatment (3). As with CNS aspergillosis, osteomyelitis primarily develops from hematogenous dissemination or by contiguous spread (9).

Our report describes a distinct case of a child with relapsed ALL and invasive aspergillosis. In our patient, *Aspergillus species* involved multiple sites and featured a rather unusual organ distribution. Both amphotericin B and liposomal amphotericin B given at controversial high doses failed to control the infection. Both were poorly tolerated and resulted in additional toxicity due to the patients abnormal renal and pancreatic function, *Caspofungin* was well tolerated and did not cause additional toxicity. There was a clear improvement in her clinical, laboratory, and radiographic findings once caspofungin was initiated which suggested a response of her disseminated aspergillus infection.

The definitive diagnosis of aspergillosis is often difficult since it depends on the growth of *Aspergillus* from a sterile body site. It often requires invasive procedure such as open biopsy or bronchoalveolar lavage to yield a histological diagnosis. Such invasive procedures also carry an increment in mortality risk in neutropenic patients. In the immunocompromised host, antibody detection of *Aspergillus* has not been useful (10) and assays for antigen and metabolic detection are still experimental (11,12).

We were able to isolate *Aspergillus species* by biopsy and superficial cultures of the cutaneous lesion. As her clinical condition and organ involvement deteriorated, we

were highly suspicious of *Aspergillus species* as the responsible pathogen. CT scan and MRI were useful studies for following the course of disease.

The methods of therapy for disseminated aspergillosis are not well defined. Once there is CNS, bone, and eye invasion, medical treatment has been rarely successful. This is primarily due to propensity of the organism to invade or occlude blood vessels and consequently prevent adequate drug delivery at high concentrations.

Caspofungin acetate is the first of a new class of antifungal agents, the echinocandins, that have fungicide activity against a wide range of pathogens including *Aspergillus*, *Candida*, and *Histoplasmosis species* (13,14). Complete or partial response to caspofungin was seen in 41% of immunocompromised adults with invasive aspergillosis (15), however, the experience in the pediatric population has not been sufficiently studied. Subsequent to the initiation of caspofungin acetate, our patient exhibited a clinical improvement documented by physical, laboratory and radiographic findings and there was no evidence of *Aspergillus*. There was no evidence of disseminated aspergillosis by the autopsy findings. Adult RDS secondary to progressive ALL was identified as the cause of her death. Even though she did not survive, this report appears to be the first documented case of successful treatment of disseminated aspergillosis in an immunocompromised pediatric patient with relapsed ALL. We conclude that caspofungin acetate was effective and better tolerated than amphotericin B and should be considered in the managment of pediatric patients with disseminated aspergillosis refractory to amphotericin B.

Resumen

La incidencia de infecciones micóticas severas en pacientes con malignidades o inmunosuprimidos a causa del tratamiento con agentes quimioterapéuticos ha aumentado en los últimos años. Este aumento en incidencia parece estar asociado a los profundos períodos de immunosupresión y al uso prolongado de antibióticos de amplio espectro. La aspergilosis es la segunda infección más común en pacientes de cáncer immunosuprimidos por la quimioterapia. En pacientes con un grado de inmunosupresión severa la mortalidad asociada a la aspergilosis invasiva se acerca al 100% aún habiendo recibido tratamiento con agentes antimicóticos. Los estudios sobre la eficacia de las equinocandinas son, en su mayoría, en pacientes adultos, pero son muy limitados en pacientes pediátricos. Este informe describe el caso de una paciente con leucemia linfoblástica en relapso que desarrolló aspergilosis cutánea y diseminación generalizada durante el tratamiento de re-inducción que fue tratada con éxito usando acetato de caspofungina.

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