Fatal Invasive Aspergillosis Complicating Severe Plasmodium falciparum Malaria

We report the first 2 cases of fatal invasive aspergillosis complicating severe malaria. In 2 nonimmune European adults without underlying disease, death was directly ascribable to invasive aspergillosis. We believe that transient malaria-induced immunosuppression allowed massive growth and overwhelming dissemination of preexisting Aspergillus colonization.

We report the first 2 cases of invasive aspergillosis complicating severe Plasmodium falciparum malaria and discuss the pathogenic mechanisms underlying this association. We searched MEDLINE for studies published from 1968 through 1999 that mention “malaria,” “falciparum” or “plasmodium” and “aspergillosis” or “A. fumigatus.”

From 1987 through 1998, 205 patients were admitted to our intensive care unit (ICU) for imported falciparum malaria. The overall mortality rate was 7.3% (15 deaths). In 2 nonimmune European patients, death was directly ascribable to invasive aspergillosis.

Patient 1, a 40-year-old man, was hospitalized in China in 1987 because of fever and jaundice and received a 3-day course of iv corticosteroids for suspected hepatitis. Three days later, because of impaired consciousness (Glasgow coma score [GCS], 12), the decision was made to repatriate the patient. When he arrived in France 2 days later, he was referred to our ICU because of severe malaria with 19% parasitemia, rousable coma (GCS, 11), acute renal failure, and disseminated intravascular coagulation. A chest radiograph showed an alveolar infiltrate in the right upper lobe. The patient’s condition improved slowly with quinine infusion, antibiotics, mechanical ventilation, and hemodialysis. The parasitemia abated within 72 h, and neurologic disorders and pneumonia resolved. On day 12, he rapidly developed unrousable coma (GCS, 5), flaccid tetraplegia, and shock. A cerebral CT scan showed hemorrhagic infarction of the cerebellum and brain. The patient died 4 days later in a deep coma. Autopsy revealed invasive aspergillosis with ulcerated mitral endocarditis and fungal abscesses in the myocardium and lungs (figure 1). The biopsy of a cutaneous lesion yielded Aspergillus fumigatus.

In 1997, patient 2, a 32-year-old man, returned from a trip to Gabon. He had been given oral cefuroxime by his physician for suspected acute sinusitis. Four days later he was hospitalized through the emergency room of our hospital because of fever and jaundice. P. falciparum parasitemia was 48%. A quinine infusion was started and the patient was referred to our ICU. Over the following 24 h his condition worsened rapidly, and he developed unrousable coma (GCS, 5), partial seizures, shock, acidosis, acute renal failure, and acute respiratory distress syndrome. Upon intubation of the patient, macroscopic evidence of esophageal mycosis was noted. Specific tests excluded HIV infection or primary infection. Despite supportive care and parasite clearance within 72 h, his neurologic status failed to improve. On day 3, a bronchoalveolar lavage yielded Aspergillus nidulans and Candida albicans. Intraocular amphotericin B (1 mg/kg/d) was started. On day 5, a tracheal aspirate yielded Pseudomonas aeruginosa, Staphylococcus aureus, and A. fumigatus. Aztreonam and ciprofloxacin therapy was instituted and amphotericin was discontinued, as fungal presence was thought to be a colonization. On day 11, cardiac arrest occurred and resuscitation efforts failed. Autopsy disclosed disseminated aspergillosis with cerebral and pulmonary fungal abscesses.

Fungal infection is thought to be uncommon during severe malaria [1, 2]. In our cases, coincidental occurrence of aspergillosis and malaria is very unlikely because invasive aspergillosis is extremely rare in healthy patients [3]. The absence of a coincident aspergillosis outbreak in our ICU and the short time from admission to aspergillosis onset militate against ICU-
acquired aspergillosis. Invasive aspergillosis usually occurs in patients with severe immunosuppression due, for instance, to hematologic malignancies with prolonged neutropenia, transplantation, AIDS, or immunosuppressive agents (especially if combined with steroids) [3]. None of our patients had a previous history of immunosuppression or significant health problems. In neither patient did the neutrophil count fall below 1500 cells/μL. Patient 1 received corticosteroids, but the duration of the treatment was too short to result in a substantial risk of aspergillosis. Patient 2 received antibiotics before admission. This may have promoted the growth of fungi, as suggested by the macroscopic evidence of esophageal mycosis and the early demonstration of *Aspergillus* in the bronchoalveolar lavage fluid. In both patients, mechanical ventilation may have disseminated *Aspergillus* to the lower respiratory tract.

Falciparum malaria is associated with impairments in cell-mediated and humoral immunity. Schwarzer et al. [4] have reported decreased splenic macrophage phagocytosis during acute malaria as a consequence of massive phagocytosis of red blood cells, and have demonstrated expression of the HLA class II antigens, CD54 and CD11c, is impaired by human monocytes loaded with hemozoin [5]. Abnormalities in antigen presentation may contribute to the immune function impairment. Circulating malarial antigens induce transient nonspecific T cell depression in acute malaria with massive parasite invasion [6]. In addition, cytokine network dysregulation and transient humoral impairment have been documented [1]. Finally, there is in vitro evidence that neutrophil function may be altered by chloroquine, mefloquine, and amodiaquine [7].

In our patients, we believe that transient malaria-induced immunosuppression allowed massive growth and overwhelming dissemination of preexisting *Aspergillus* colonization. The risk of aspergillosis may be underestimated during severe malaria because of the absence of previously reported cases, the difficulty of the diagnosis, and the small number of fatal malaria cases investigated by total body autopsy. Not only bacteria but also *Aspergillus* and other fungi should be looked for early in patients with unexplained worsening of severe falciparum malaria, and specific treatment should be considered.

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References

Disseminated Mucormycosis Due to \textit{Saksenaea vasiformis} in an Immunocompetent Adult

A case of disseminated infection due to \textit{Saksenaea vasiformis} in a previously well adult male is presented. The clinical presentation was that of septic shock with a distinctive rash. At postmortem, endocarditis and widespread dissemination were evident.

Mucormycosis is an uncommon illness usually associated with immunosuppression or diabetes mellitus. Most reported cases of infection due to \textit{Saksenaea vasiformis} have been subcutaneous or rhinocerebral. We describe a case of disseminated mucormycosis due to \textit{S. vasiformis} in a previously healthy adult.

A 59-year-old man was transferred to our institution because of a 6-week history of malaise, headache, arthralgias, and cough. Three days before presentation, he had developed truncal skin lesions over a course of minutes. These lesions were initially raised, slightly erythematous, and 10 mm in diameter. Over 24 h they enlarged to several centimeters in diameter with a purple center, but they were without ulceration or surface vesiculation. The following day, the patient presented with severe dyspnea, fever, and the skin lesions, and therapy with ceftriaxone and roxithromycin was instituted. During the next 48 h, his condition deteriorated; there was renal and respiratory failure.

The patient’s medical history included hypertension, esophageal reflux, mild asthma, and a 3-year history of idiopathic mild diarrhea. Long-standing medications were trandalopril, omeprazole, fluticasone, and salbutamol. His hobbies included orchid farming and opal mining.

On admission to the hospital, the patient was drowsy with signs of sepsis. Blood evaluation showed acute renal failure. A skin biopsy revealed mild superficial chronic inflammation without evidence of vasculitis and was otherwise nondiagnostic. Transesophageal echocardiography suggested endocarditis with thickening of the aortic valve and mobile strands in the ascending aorta. He was started on therapy with amphotericin B, ceftazidime, amikacin, and vancomycin. Over the ensuing hours his condition deteriorated without evidence of valvular regurgitation or myocardial rupture. The patient died 24 h after admission to our unit or ~12 h after the commencement of amphotericin.

Postmortem examination revealed disseminated mucormycosis with endocarditis involving the mitral valve, bronchopneumonia, and pulmonary emboli; all sites contained large numbers of mycelia. Mycelia were also identified in skin and thyroid; bowel involvement was not evident.

Culture of the premortem skin biopsy yielded a zygomycete after 48 h incubation at 37°C and at room temperature on Sabouraud dextrose agar. The organism sporulated slowly, but was identified as \textit{S. vasiformis} by sporangia production on Czapek-Dox agar (Difco, Detroit). All postmortem samples were culture negative. The identification was confirmed at a reference laboratory.

\textit{S. vasiformis} is a soil fungus in the class Zygomyces, order Mucorales. It is associated with warm climates and has been isolated in the United States, Central America, Israel, and India [1]. There are 7 previous reports of \textit{S. vasiformis} infection in Australia in patients with localized subcutaneous infections [1–3]. There have been 24 cases of \textit{S. vasiformis} infection reported in the world literature of which only 2 had disseminated infection; one of these was immunocompromised [4], and the other was a child from Iraq who presented with a 5-week history of necrotic skin lesions, fever, and bronchopneumonia [5].

We assume our patient was infected by inhalation, which resulted in pneumonia and hematogenous dissemination to the endocardium and to other organs. The source of infection is likely to have been a heavy airborne inoculum that was encountered either while underground or while gardening. Postmortem serum immunoglobulin analysis revealed an IgG1 level of 3.06 g/L (normal range, 4.9–11.4 g/L) with normal levels of other immunoglobulins. A small free κ light chain was detected. Even with the possibility of an occult immunodeficient state, his presentation with disseminated \textit{S. vasiformis} infection is unusual.

Hyphae were seen but not cultured from other anatomical sites at postmortem. It is well described that there is a low culture positivity rate in invasive fungal diseases, possibly because of the predominance of mycelia rather than sporangia in...