Minireview: invasive fungal infection complicating acute Plasmodium falciparum malaria

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Summary Malaria is the most important parasitic infection in people, affecting 5–10% of the world’s population with more than two million deaths a year. Whereas invasive bacterial infections are not uncommon during severe Plasmodium falciparum malaria, only a few cases of opportunistic fungal infections have been reported. Here, we present a fatal case of disseminated hyalohyphomycosis associated with acute P. falciparum malaria in a non-immune traveller, review the cases reported in the literature and discuss the theoretical foundations for the increased susceptibility of non-immune individuals with severe P. falciparum malaria to opportunistic fungal infections. Apart from the availability of free iron as sequelae of massive haemolysis, tissue damage, acidosis and measures of advanced life support, patients with complicated P. falciparum malaria also are profoundly immunosuppressed by the organism’s interaction with innate and adaptive host immune mechanisms.

Key words: Aspergillosis, zygomycosis, candidiasis, malaria, Plasmodium falciparum.

Introduction Malaria is the most deadly parasitic infection in people worldwide, and is a significant problem in non-immune travellers returning from endemic areas.1 Not considering the inconsistent reporting in many countries, there have been a total of 77 683 reported malaria cases imported into Europe over the period 1985–1995.2 In Germany, from 1993 to 1996, 85 subjects died of Plasmodium falciparum malaria with a striking age dependency: in the age group of 65 years and older, almost every fifth patient had a lethal course.3 While more recent data indicate a decline in both number of imported malaria cases4,5 and attributable mortality,5 these trends may be temporal and do not abrogate the continuous threat arising from P. falciparum malaria to non-immune individuals.6

Apart from the sequelae of haemolysis and complications of organ failure that result from the interaction between the parasite and the microcirculation, severely ill patients with complicated P. falciparum malaria also are profoundly immunosuppressed by the organism7 and susceptible to infection through measures of intensive care medicine.8 During the past decade, cases of invasive fungal infections associated with complicated P. falciparum malaria in non-immune individuals have emerged in the literature.9–12 In the following, we report on a fatal case of disseminated hyalohyphomycosis in a patient recovering from complicated P. falciparum malaria, review the cases reported in the literature and discuss factors that put patients with imported malaria tropica at risk to develop invasive mycoses.

Case report The patient was a 32-year-old woman who had been travelling for 14 days in Thailand. Eleven days after her return to Europe, in immediate temporal relationship to
the discontinuation of anti-malarial chemoprophylaxis with chloroquine, the patient developed fever, cough and abdominal symptoms, interpreted as influenza-like viral infection by her primary physician. Eight days later, after progressive worsening of her general status, the patient was emergently admitted to a peripheral hospital with circulatory collapse. The peripheral blood smear on admission showed almost 100% infected erythrocytes, and laboratory parameters were indicative of marked haemolysis, consumption coagulopathy, thrombocytopenia and compensated renal insufficiency. The patient was somnolent and hypotensive, but there was no evidence of respiratory compromise apart from a productive cough with purulent discharge. Therapy with chloroquin was started and supportive therapy with broad-spectrum antibiotics and dexamethasone instituted. For reasons of a lack of significant reduction in parasitaemia after 2 days, the patient was started on quinine and mefloquine and was transferred to the university hospital. This change in antiparasitic chemotherapy was followed by the prompt clearance of parasites from the peripheral blood smear within 48 h, marked clinical improvement, reversal of somnolence, and mobilisation out of bed. Five days after admission, however, the patient developed moderate dyspnoea and was placed on supplemental oxygen. On the next day, the patient had an acute respiratory and cardiac arrest because of aspiration of necrotic material from the trachea, but was successfully resuscitated. The patient was placed on mechanical ventilation and had progressive pulmonary insufficiency with radiographic findings compatible with acute respiratory distress syndrome (ARDS), leading to pulmonary air leak, cardiac decompensation and death on the 10th day in hospital.

At autopsy, there was no evidence of vital parasites in smear and tissue sections (Fig. 1). The respiratory tract revealed severe purulent pseudomembranous tracheobronchitis, extensive bilateral necrotizing pneumonia with abundant presence of septate hyphae, marked pulmonary oedema, amorphous hyaline material lining the alveolar septa and beginning interstitial fibrosis, suggestive of advanced ARDS. In the left upper lung lobe, a caseous granuloma with giant cells and acid-fast rods was found, consistent with reactivated tuberculosis. The heart showed global dilatation of both ventricles. Brain, kidney and myocardium revealed numerous small abscesses containing septate hyphae. Small blood vessels were gorged with erythrocytes with occasional diapedesis and microthrombi. There was a mild interstitial nephritis with mild proliferation of mesangial cells and scattered fatty necroses of the pancreas. Sections of the brain showed mild cerebral oedema and occasional small perivascular haemorrhages. Cultures taken from blood and sputum during lifetime all remained sterile. As there had been no clinical suggestion of invasive fungal infection, no antifungal therapy had been given.

Discussion
Whereas invasive bacterial infections such as bronchopneumonia and bacteremia are frequent during both natural course\(^1^3,14\) and intensive care management\(^6\) of severe \(P. falciparum\) malaria, only a few cases of invasive opportunistic fungal infections have been reported.\(^9^\)\(^12^,15^\)\(^18\)

Including the case presented here, invasive pulmonary hyalohyphomycosis has been reported in sufficient detail in six non-immune patients with severe imported \(P. falciparum\) malaria,\(^9^\)\(^12\) including one case with concomitant isolation of \(Absidia\) spp.\(^11\) and four cases with dissemination beyond the respiratory tract\(^9^\)\(^10\) (Table 1). Although diagnosed and treated during lifetime in four patients, the infection was ultimately fatal in all but one.\(^12\) At presentation, the parasite count ranged from 10 to 100% and all patients had clinical signs and symptoms associated with hyperparasitaemia and multiorgan failure: pulmonary infiltrates were present in three patients. All patients were previously healthy individuals and between 26 and 58 years of age. None was neutropenic and only two patients had received a short course of corticosteroids. All patients had marked haemolysis, three were reported to have metabolic acidosis, and four developed acute respiratory distress syndrome during hospitalisation. A majority of patients had cleared the parasites from the bloodstream within 72 h. Clinical signs and symptoms associated with development of invasive mould infection were persisting or new fever despite parasite clearance, new or changing pulmonary infiltrates, haemoptysis and persistent, worsening or new neurological signs.\(^9^\)\(^12\)

Additional reports of opportunistic fungal infections associated with \(P. falciparum\) malaria include a single case of candidaemia and two cases of cryptococcal meningoencephalitis.\(^16^\)\(^18\) Invasive candidiasis has been reported in a non-immune, previously healthy 47-year-old male patient with acute \(P. falciparum\) malaria who presented with a parasite count of 24%, shock and multiorgan failure following a 1 week history of fever and flu-like symptoms. Following parasite clearance and initial clinical improvement, the patient developed signs of sepsis on the third day in hospital. Blood cultures taken on admission and on follow up ultimately grew \(Candida albicans\). The patient received treatment with amphotericin B plus flucytosine and made an
uneventful recovery. Candidaemia in this case was clearly not catheter-associated as the organism was detected in the blood prior to catheterisation.18 Whereas cryptococcal meningoencephalitis has not been reported in conjunction with imported *P. falciparum* malaria, there are two published cases in paediatric patients from endemic areas, including a successfully treated 15-year-old boy with nephrotic syndrome and corticosteroid therapy16 and a fatal case in a previously healthy 2-year-old boy.17 The clinical manifestations of cryptococcal meningoencephalitis and cerebral malaria can be very similar and, analogous to the frequent association of intensive care and candidaemia,19 concurrent cerebral cryptococcosis and *P. falciparum* malaria may be more common as reflected by these two reports,14 particularly in HIV-infected individuals from sub-saharan Africa or Southeast Asia.

Host defence against opportunistic fungi requires an organised interplay of intact mucocutaneous barriers, functional polymorphonuclear leucocytes and monocytes, and cell-mediated immunity.20–22 The theoretical foundation for the susceptibility of non-immune individuals with severe *P. falciparum* malaria to invasive opportunistic fungal infections is complex and may involve several mechanisms. Apart from immunosuppressive effects of antimalarial drugs, the availability of free iron as sequelae of marked haemolysis, tissue damage and -acidosis through the interaction of the parasite with the microcirculation and measures of advanced life support in the intensive care unit, patients with complicated *P. falciparum* malaria also are profoundly immunosuppressed by the organism’s interference with innate cellular and adaptive cell-mediated immunity.

Mortality of *P. falciparum* infection in non-immune individuals directly correlates with the extent of parasitaemia at presentation.23 Historical data indicate that once the fraction of parasitized erythrocytes exceeds

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**Figure 1** Microscopic pathology of hyahyphomycosis in severe *Plasmodium falciparum* malaria. Haematoxylin-eosin, ×100 (a, e), ×200 (b, c), ×400 (d, f). (a) Lung: Necrotizing pneumonia with abundant presence of septate hyphae, amorphous hyaline material lining the alveolar septa and beginning interstitial fibrosis (arrow), suggestive of advanced ARDS. (b) Brain: small abscesses containing septate hyphae (arrow). (c) Myocardium: septate hyphae in close proximity to a blood vessel (arrow). (d) Kidney: septate hyphae within autolytic kidney tissue (arrow). (e) Trachea: necrotizing purulent tracheitis as sequelae of altered microcirculation during heavy parasitaemia. (f) Liver: Hae-moxin-laden Kupffer cells resulting from phagocytosis of Haemoxin-laden erythrocytes. Note the absence of parasites in all tissue sections.
10%, the case fatality rate may be as high as 72%.\textsuperscript{23–27} Whereas the destruction and removal of red blood cells is usually not immediately life-threatening, outcome is determined by profound and complex disturbances of the microcirculation that ultimately lead to hypoxia and acidosis of dependent tissues and multiorgan failure.\textsuperscript{1,28} In this scenario, hypoxia of mucosal membranes may lead to breakdown in mucosal barriers, allowing for the invasion of fungal elements in both the respiratory and alimentary tract. Fungal growth and establishment of infection is further enhanced by tissue acidosis and red blood cell lysis, that both procure free iron, which not only promotes growth and virulence of opportunistic fungi but also impairs T- and phagocytic cell functions.\textsuperscript{29–34} Indeed, iron tissue overload has recently been shown to be independently associated with invasive aspergillosis in patients with haematological malignancies or allogeneic blood stem cell transplantation\textsuperscript{35} and with invasive fungal infections following liver transplantation.\textsuperscript{36} Vice versa, iron chelation was highly effective as treatment for experimental disseminated candidiasis\textsuperscript{14} and mucormycosis,\textsuperscript{32} supporting the notion of iron as important growth factor and/or immunosuppressant in invasive fungal infections.

Phagocytosis by polymorphonuclear leucocytes and macrophages is the mainstay in host defence against opportunistic fungal pathogens.\textsuperscript{20–22} However, there is growing evidence that the adaptive immune system is not only active against \emph{Cryptococcus neoformans} but also has an important role in the host-response to invasive \emph{Candida-} and \emph{Aspergillus} infection.\textsuperscript{21,37,38} Alterations in adaptive immunity during acute malaria have been observed early on in mice and humans, including impaired phagocytosis and intracellular killing by monocytes and macrophages; a reduction in the number of T-lymphocytes, the proportion of T-helper cells, and functional impairment of T-lymphocyte responses to antigen stimulation.\textsuperscript{7,39–42} More recent, important insights include the observation of an inhibition of the maturation of dendritic cells and their capacity to stimulate T-cells by the parasite\textsuperscript{43} and the recognition of a predominantly TH2-type immune response in malaria\textsuperscript{44} that may depress the host immune system particularly against opportunistic fungi.\textsuperscript{45} There is now convincing evidence from \textit{in vitro} and \textit{in vivo} studies that the malaria parasite pigment Haemoglobin impairs dendritic cell, monocyte/macrophage and T-cell function, and that it is a key factor in the suppression of adaptive immune responses to parasite- and other antigens during acute blood stage malaria.\textsuperscript{46–48} Haemoglobin consists of aggregates of insoluble polymers and is released together with other cell debris when the mature blood-stage forms of the parasite cause red blood cells to rupture.\textsuperscript{47} It is rapidly taken up by monocytes, macrophages and dendritic cells, and reacts with membrane phospholipids, generating biologically active hydroxy-polyunsaturated fatty acids.\textsuperscript{49} Haemoglobin inhibits monocyte and macrophage functions such as phagocytosis, activation by inflammatory cytokines,

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<tr>
<th>Table 1</th>
<th>Hyalohyphomycosis complicating acute \emph{Plasmodium falciparum} malaria</th>
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<tbody>
<tr>
<td>Case 1\textsuperscript{9}</td>
<td>Case 2\textsuperscript{2}</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>None</td>
</tr>
<tr>
<td>Age/gender</td>
<td>40/\textit{m}</td>
</tr>
<tr>
<td>Fungal species</td>
<td>\emph{Aspergillus} \textit{fumigatus} \emph{A. fumigatus} \emph{A. nidulans}</td>
</tr>
<tr>
<td>Anatomic site (s)</td>
<td>Lung, heart, brain, skin</td>
</tr>
<tr>
<td>Treatment</td>
<td>AMB</td>
</tr>
<tr>
<td>Outcome</td>
<td>Fatal</td>
</tr>
<tr>
<td>Initial parasite count (%)</td>
<td>19</td>
</tr>
<tr>
<td>Time to parasite clearance (h)</td>
<td>72</td>
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<tr>
<td>Multiorgan failure</td>
<td>Yes</td>
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<tr>
<td>Pulmonary infiltrates</td>
<td>Yes</td>
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<tr>
<td>ARDS</td>
<td>No</td>
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<tr>
<td>Haemolysis</td>
<td>Yes</td>
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<tr>
<td>Acidosis</td>
<td>n.r.</td>
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<tr>
<td>Neutropaenia</td>
<td>No</td>
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<tr>
<td>Steroid treatment</td>
<td>Yes</td>
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AMB, amphotericin B; VCZ, voriconazole; ARDS, acute respiratory distress syndrome; n.r., not reported; n/a, data not available.
generation of the oxidative burst and antigen presenta-
tion as well as the differentiation of monocytes to dendritic cells, dendritic cell maturation and primary and secondary T-cell responses. These broadly immunosuppressive effects not only provide a survival advantage to the parasite but may also contribute to an increased susceptibility to opportunistic fungal pathogens.

Treatment with anti-inflammatory glucocorticoster-
oids, as administered in the case presented here for unknown reasons at the referring institution, has been shown to prolong coma in cerebral malaria and to increase the rate of nosocomial pneumonia and gastrointestinal bleeding and is therefore not recommended as supportive treatment in cerebral malaria. In a recent case-control study in the ICU setting, corticosteroid use was associated with an increased rate of infection, increased ventilator time, and increased length of stay in the unit. Given their additional potent and broad-ranging immunosuppressive effects, the risks and benefits of corticosteroids need to be particularly carefully evaluated in patients with complicated P. falciparum malaria. In contrast to glucocorticosteroids, however, immunosuppressive effects of antimalarial drugs are less well characterised. A notable exception is chloroquine which has been shown to interfere with the production of pro-inflammatory cytokines and various T-cell functions and to have immunosuppressive applications in marrow transplantation and autoimmune disorders.

In conclusion, while larger epidemiological data are lacking, anecdotal evidence suggests that non-immune patients with severe P. falciparum malaria are susceptible to opportunistic fungal infections. The availability of free iron as a result of massive haemolysis, tissue damage and acidosis through the interaction of the parasite with the microcirculation, measures of advanced life support, as well as the organism’s interference with innate cellular and specific cell-mediated immunity all provide a plausible foundation for an association between severe P. falciparum malaria and invasive fungal infections.

Conflict of interest

All authors report no financial support and/or conflicts of interest.

References


