Severe *Plasmodium malariae* Malaria in a Patient With Multiple Susceptibility Genes

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We present a case of severe malaria due to *Plasmodium malariae*. Genetic testing showed that the patient was homozygous for five important gene polymorphisms previously shown to be associated with increased susceptibility to, and/or severity of, severe sepsis. Our case suggests that *P. malariae* may cause life-threatening disease, and that disease severity may be linked, at least in part, to multiple susceptibility genes.

Case Report

We recently managed a healthy 27-year-old French soldier returning from a 4-mo mission in Ivory Coast. He reported taking doxycycline 100 mg/d regularly during his stay but stopped the drug 1 wk after returning to France. One month after the last doxycycline dose, he started experiencing fever and fatigue. At admission 2 wk later, he had hypotension (85/45 mm Hg), thrombocytopenia (72 \( \times \) 10\(^9\)/L), moderate renal failure (plasma creatinine, 152 \( \mu \)mol/L), moderate hepatic cytolysis (aspartate aminotransferase, 179 IU/L and alanine aminotransferase, 128 IU/L), systemic inflammation (C-reactive protein, 86 mg/L and procalcitonin, 23.3 ng/mL), and a normal chest X-ray. A blood smear was positive only for *Plasmodium malariae* (0.2% parasitemia). Severe malaria and leptoospirosis were suspected. Rapid fluid resuscitation, norepinephrine, intravenous quinine (loading dose, 1,400 mg over 4 h; then maintenance dose, 2,000 mg/d), and ceftriaxone were given. The patient became comatose and developed severe metabolic acidosis (lactate, 13 mmol/L; pH 6.97), requiring endotracheal mechanical ventilation. No other infections were identified by extensive microbiologic investigations including blood, cerebrospinal fluid, and urine cultures, and serological tests for hepatitis A, B, C, and E viruses, HIV, leptoospirosis, *Rickettsia conorii*, *Coxiella burnetti*, and hemorrhagic fever viruses (including West Nile and dengue viruses). Guidelines for treating severe falciparum malaria were followed, and the patient recovered fully. Nested polymerase chain reactions (PCRs) of the SSUrRNA gene with specific species primers were performed at the French Malaria Reference Center and were negative for both *Plasmodium falciparum* and *Plasmodium knowlesi* but positive for *P. malariae*.2 Nested PCRs with specific species primers followed by sequence analysis of the pLDH gene confirmed the diagnosis of *P. malariae*.3 PCR testing found no evidence of a simian malaria species such as *P. knowlesi*. Before admission, the patient received no curative antimalarial drug that might have cleared a *P. falciparum* infection already responsible for organ dysfunction, as confirmed by the military medical personnel and by plasma antimalarial drug assays. Nevertheless, we cannot definitively rule out a bacterial...
cointection because the first blood culture was drawn after administration of the first antimicrobial dose.

As severe malaria due to pure *P. malariae* infection is infrequent, genetic polymorphisms associated with severe sepsis were investigated. They include variants of genes for inflammation proteins [tumor necrosis factor (TNF), interleukin (IL)-6 and IL-10, macrophage migration inhibitory factor (MIF), angiotensin-converting enzyme (ACE), and catalase], genes for coagulation factors [plasminogen activator inhibitor (PAI)-1; fibrinogen; coagulation factors II, V, VII, and XIII], and genes for proteins involved in innate immunity [toll-like receptor (TLR)-2, TLR-4, TLR-5, mannos-binding lectin (MBL), IRAK-1, CD-14, toll interleukin-1 receptor-associated protein (TIRAP), and Nf-κB inhibitor (IκB)]. The patient was homozygous for five important gene polymorphisms previously shown to be associated with increased susceptibility to, and/or severity of, severe sepsis (*IRAK-1* rs1059703, *CD14* rs2569190, *TNF*-beta rs909253, *IL-6* rs1800795, and *MIF* rs755622). Interestingly, four of these five single-nucleotide polymorphisms were also present in a case of *P. malariae*-related multiple organ dysfunction syndrome reported recently in a French soldier also returning from Ivory Coast.4 Most of the evidence associating these polymorphisms with severe sepsis comes from Caucasians. Our patient was from the South Pacific Islands, suggesting that the deleterious consequences of these deletion variants may not be limited to one specific ethnic group.

Our case suggests that *P. malariae* may cause life-threatening disease, and that disease severity may be linked, at least in part, to multiple susceptibility genes. Further genetic polymorphism analyses in patients with severe *P. malariae*, *Plasmodium vivax*, or *Plasmodium ovale* infections and larger epidemiological studies are needed, however, to assess the relevance of these polymorphisms to malaria and/or secondary sepsis complicating malaria. Although *P. falciparum* is by far the greatest purveyor of severe or fatal malaria episodes, the two reported cases of severe *P. malariae*, together with reports of severe malaria due to *P. knowlesi*6 or *P. vivax*,6,7 indicate that *P. falciparum* is not the only malaria parasite responsible for life-threatening disease.

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Declaration of Interests

The authors state they have no conflicts of interest to declare.

References


