

*Lesson of the week***Assessing the severity of malaria**

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Life threatening malaria may develop even in patients who appear relatively well at presentation

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Malaria caused by infection with *Plasmodium falciparum* kills over 1 million people a year.¹ In 2000, 1592 confirmed cases were reported to the United Kingdom's Malaria Reference Laboratory; 16 of these people died (John Williams, personal communication, 2002). Guidelines have been published to identify patients with poor prognostic signs.²⁻⁴ A recent study suggested that patients infected with *P falciparum* who present with uncomplicated disease may be treated safely outside hospital⁵; however, patients not uncommonly present without adverse signs but deteriorate over the next 24-48 hours despite apparently adequate treatment. This deterioration occurs because *P falciparum* undergoes repeated cycles of maturation approximately every 48 hours⁴: only the schizonts (mature forms) of the parasite sequester and cause pathology, while the trophozoites (immature forms) are relatively insensitive to antimalarial treatment.⁶ We present two cases from the Hospital for Tropical Diseases that illustrate why the severity of falciparum malaria may be underestimated at presentation.

Case reports**Case 1**

A 62 year old white man presented with a four day history of fever 19 days after returning from a two week holiday in Mozambique. He reported taking chloroquine 600 mg weekly and proguanil 200 mg daily as prophylaxis. On admission, he was febrile (38.4°C), with a pulse of 104 bpm, but examination was otherwise unremarkable. His blood film showed trophozoites and schizonts of *P falciparum* and parasitaemia of 2.9%. His haemoglobin was 12.2 g/dl (normal range 11.5-15.5 g/dl), white cell count $3.6 \times 10^9/l$ ($3.0 \times 10^9/l$ - $10.0 \times 10^9/l$), and platelets $20 \times 10^9/l$ ($150 \times 10^9/l$ - $400 \times 10^9/l$), and his concentrations of creatinine, electrolytes, and bilirubin and his chest radiographs were normal. Two hours after he was admitted to hospital, he became drowsy, confused, and dysphasic. His blood sugar concentration was 3.8 mmol/l, and he did not respond to a bolus injection of 50% glucose solution. He was transferred to the intensive care unit at our hospital and was treated with intravenous quinine. His subsequent course was complicated by acute lung injury that required ventilation, marked haemolysis (lowest haemoglobin 7.4 g/dl), thrombocytopenia (lowest platelet count $9 \times 10^9/l$), and a peak parasitaemia of 5.2%. The patient recovered fully and was discharged 10 days later.

Case 2

A 17 year old woman, who was born in Nigeria but had been resident in the United Kingdom for several years, presented with a two day history of fever and vomiting. She had returned from a three week visit to Nigeria two days earlier, for which she had taken no malarial

prophylaxis. She appeared well but was mildly jaundiced and had a temperature of 38.2°C and a pulse of 110 bpm. Examination was otherwise unremarkable. A blood film showed trophozoites of *P falciparum* and parasitaemia of 1.2%. Further investigations showed haemoglobin of 13.9 g/dl, white blood cell count $6.2 \times 10^9/l$, platelet count $60 \times 10^9/l$ (a normal finding in patients with malaria), and normal electrolytes and creatinine. Bilirubin was 84 $\mu\text{mol/l}$ (normal <17). A pregnancy test was negative, and a chest radiograph was normal. She was admitted and treated with oral quinine 600 mg every eight hours.

The next day the patient's clinical condition was unchanged, but her parasitaemia had increased to 30%. Her haemoglobin concentration had decreased to 10.9 g/dl and her platelet count to $35 \times 10^9/l$, while her bilirubin and creatinine concentrations had increased to 136 and 279 $\mu\text{mol/l}$. Her treatment was changed to intravenous quinine 600 mg every 12 hours, and she was transferred to the local intensive care unit. After 24 hours, the patient's score on the Glasgow coma scale had decreased to 11 from 15 (out of 15), and she was transferred to our hospital. Although the patient's parasitaemia had decreased to 0.2%, she developed metabolic acidosis and, within 24 hours, her Glasgow coma score decreased to 8 and she developed a fixed gaze palsy. Scans from computed tomography of her brain were unremarkable. She had to be intubated and ventilated for four days because of coma and needed haemofiltration for two days because of acute renal failure (peak creatinine 445 $\mu\text{mol/l}$). Her subsequent recovery was complicated by a ventilator associated pneumonia. She was discharged on day 10 after admission after making a full recovery.

Discussion

Patients who look well on presentation with most infectious diseases seldom deteriorate significantly once treatment is started. Malaria is much less easy to assess. The cases described were complicated variously by cerebral malaria, acute renal failure, marked haemolysis, metabolic acidosis, acute lung injury with respiratory failure, and progression to hyperparasitaemia despite appropriate chemotherapy. All are well known complications of *P falciparum* infection,¹ but the complicated course could not be predicted at presentation. The two cases are typical of patients seen at our hospital (and other tropical medicine units), who appear well and have few, or occasionally no, signs of severe disease at presentation but subsequently deteriorate despite treatment. If either of the cases described had been sent home from the emergency department to complete a course of oral treatment, the outcome probably would have been less favourable.

These cases illustrate three common pitfalls. Firstly, most doctors are aware that severe malaria can occur with low parasitaemia because the peripheral parasite count may not accurately reflect the total parasite load—many late stage parasites are sequestered in the kidneys, brain, and other organs.^{7,8} A significant increase in parasitaemia after starting treatment is common, however, because of the nature of the parasite's life cycle. A mature schizont of *P falciparum* contains 8-32 merozoites and within 48 hours of the mature schizont rupturing, each merozoite is capable of invading a fresh erythrocyte and developing into a mature schizont. The potential for a massive surge in parasitaemia, which may occur after therapy has started in patients with parasites of roughly the same age, is clear. Of the last 500 patients treated for falciparum malaria at our hospital, in the days after treatment was started, parasitaemia increased above the values at presentation in 119 (23.8%) cases; in several cases, parasitaemia increased several fold. This problem is compounded because the early ring stages of the parasite are less sensitive to conventional antimalarial drugs, including quinine, so sequestration can occur after treatment is started.

Secondly, a patient with *P falciparum* who seems well and whose haematological and biochemical investigations at presentation are normal or near normal can be deceptive. Complications of malaria in adults, especially renal failure and acute lung injury, can occur after several days when the number of parasites has decreased from baseline—or even when parasites have disappeared from the peripheral blood—and when the patient seems to be improving clinically in other ways.¹

Thirdly, patients and their doctors commonly assume that people brought up in regions in which malaria is endemic are likely to be immune to the disease. Immunity to malaria only occurs in some areas,

however, and it wanes if patients are not re-exposed constantly, so judging an individual's immunity from their history (or worse still their ethnicity) is foolhardy. Adults with malaria who grew up in parts of Africa where malaria is endemic are common in our intensive care unit. As it is not easy to judge the likely course of falciparum malaria reliably at presentation, it is prudent to admit to hospital all cases of infection with *P falciparum* that present in countries in which malaria is not endemic for at least the initial 48 hours of their management.

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Where worlds meet

On concluding the midday prayer, the imam turned to the congregation, which must have numbered over 100 people, and told them that he had, that morning, been informed that their friend and fellow worshipper was making good progress in hospital. Being a visitor to the area, I had no idea to whom he was referring and paid little attention to the progress report that followed. The imam's parting advice did, however, catch my notice: "There is, therefore, no need for you all to visit him today, and please pass this message on to your family and friends. Also, please remember that, when you do go, agree visiting timings among yourselves so you do not attend all together and cause unnecessary problems for the nurses and doctors."

As someone who knows first hand the central importance of supporting the ill and dying within the Islamic ethic, I fully appreciate the communal desire for regular visiting that may be present. My experiences of working on busy hospital wards, however, have also made me acutely aware of the logistical difficulties that may result from large visitor numbers and how these difficulties may be compounded if people visit outside of the designated visiting times (as many do). The failure to bridge such differences in perspectives effectively leads to misunderstanding and resentment, and I have, unfortunately, witnessed this often. But this need not be the case, for pluralism can—through mutual sharing of ideas, experiences, and aspirations—offer penetrating insights into the worlds inhabited by others. Respectful interaction also offers the potential for

learning new ways of making better sense of our own worlds and, in so doing, developing new ways of negotiating potential areas of conflict without necessarily compromising our values.

This small incident impressed me in many ways. I was moved by the concern so evidently on display for a fellow human in difficulty. The imam's advice was thoughtful and, I hoped, persuasive. Perhaps most impressive of all, however, was the recognition of the "behind the scenes" discussions and problem sharing that must have taken place. Inspired, I made a silent parting prayer for the wellbeing of the invisible actors and actresses who had momentarily been the centre of my thoughts, and through whose narrative I had once again been reminded of the need for, and power of, dialogue.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.