A CASE OF FATAL PLASMODIUM FALCIPARUM MALARIA COMPlicated BY ACUTE DENGUE FEVER IN EAST TIMOR

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Abstract. A case is reported of a seven-year-old girl who had concurrent infections with Plasmodium falciparum malaria and dengue in a remote area of East Timor. The diagnosis of malaria was delayed because of two false-negative results with malaria rapid diagnosis test cards. Diagnosis was eventually made on microscopic examination of the patient’s blood. Despite treatment, the patient subsequently died. This case serves as a reminder of the fallibility of rapid diagnostic tests, and the importance of examining the patient’s blood microscopically if malaria is suspected.

INTRODUCTION

Malaria and dengue are diseases that have significant worldwide mortality and morbidity. It is estimated that more than 100 million people are infected with malaria, causing more than a million deaths per year, and 50–100 million people are infected with dengue, including 500,000 cases of dengue hemorrhagic fever per year.1,2

In East Timor, malaria and dengue are transmitted by Anopheles and Aedes mosquitoes, respectively. Both diseases are endemic in this country. According to the Indonesian Ministry of Health 1998 Health Profile, 11.1% of all deaths in East Timor in 1998 were from malaria, and in 2000 malaria accounted for 18.3% of all medical presentations.3 Dengue case numbers are impossible to quantify because of the lack of diagnostic tests available to the civilian population in East Timor at the time of this case study.

CASE REPORT

A seven-year-old girl came to a clinic in East Timor with her father. She had fever and a headache. She had been sick for three days. Her associated symptoms were fatigue, anorexia, nausea, and occasional vomiting. Her headache was generalized, without neck stiffness or photophobia.

Clinical examination revealed a flushed, small girl, with a temperature of 39.1°C, a heart rate of 130 beats/minute, and oxygen saturations of 98% on room air. Mucosal membranes were dry, and skin turgor appeared reduced. She had an inflamed pharynx and a palpable liver. All other examination results were unremarkable. A tourniquet test result was positive, but no other rash was observed.

Results of initial investigations are shown in Table 1. Rapid tests were performed for malaria (Malaria P.f/P.v™; AMRAD-ICT, Sydney, New South Wales, Australia) and dengue (Dengue Duo IgM and IgG Rapid Strip™; Panbio Sinnamon Park, Queensland, Australia). Results were negative for Plasmodium falciparum and P. vivax, and positive for IgM antibody to dengue. A diagnosis of acute dengue fever was made, with mild dehydration. Microscopy was not performed based on the results of the rapid tests and the presumptive diagnosis of dengue fever.

She was treated with intravenous crystalloid, oral paracetamol, and intravenous ceftriaxone (500 mg, to treat possible meningococcal infection). She was admitted to the clinic overnight pending transfer to the district hospital in the morning. During the night, her temperature increased to 41.3°C, and she became delirious. Repeated blood samples were taken, the results of which are shown in Table 2.

A generalized tonic-clonic seizure then occurred. Her blood glucose level was 70.3 mg/dL (3.9 mmol/L). She was treated with intravenous midazolam, 1.5 mg, and intubated with succinylcholine, 40 mg, and thiopentone, 100 mg. A morphine/midazolam infusion maintained sedation. Thick and thin blood films were prepared, which showed P. falciparum parasitemia greater than 30%. She was immediately treated with intravenous quinine, 350 mg, over a four-hour period.

Within an hour, her oxygen saturations decreased to 88% on 100% oxygen (via an endotracheal tube). Chest auscultation showed crackles globally, with poor air entry. An electrocardiograph showed no significant arrhythmia or ischemia. A chest radiograph showed bilateral infiltrates consistent with acute pulmonary edema. She was treated with diuretics and ventilatory pressure support.

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Over the next 30 minutes, her blood pressure became unstable, and she became peripherally shutdown. Inotropic support (adrenaline, 2 μg/minute) was started and increased to 10 μg/minute without success. Carotid pulses were then lost and cardiac monitoring showed pulseless electrical activity. Cardiopulmonary resuscitation was started and continued for 20 minutes without restoration of circulation. Resuscitation was ceased two hours after the initial seizure.

DISCUSSION

This case demonstrates several important features, including diagnosis of malaria and dengue on clinical, pathologic, and serologic grounds, the importance of thick and thin blood films, and the rapidity with which infection with *P. falciparum* can become fatal. It would be expected that coexisting malaria and dengue infection would be common in an area where both illnesses are endemic. However, there is little published evidence regarding dual malaria and dengue infection despite both diseases being co-endemic in many parts of the world, including East Timor. In differentiating between these illnesses, Shirlcliffe and others state that “dengue virus infection should be considered in all febrile travellers who have recently returned from areas where the disease is endemic and in whom tests for malaria are negative.” Others investigators have suggested that the number of negative test results for malaria is the best indicator of dengue infection in febrile patients in some areas. To add to the potential for mistaken diagnosis, confusion between dengue and malaria has been described in areas of Indonesia, with most febrile illnesses being labeled “malaria”. The most common features of dengue are fever (100%), myalgia (79%), rash (74%), headache (68%), nausea (37%), and diarrhea (37%). In children, dengue fever is generally asymptomatic or a mild, undifferentiated fever with malaise, irritability, pharyngeal injection, and rash. Less common findings include lymphadenopathy, sore throat, cough, hyperesthesia, photophobia, and delirium. Hepatomegaly can occur. Leukopenia and neutropenia are typical in the acute stage; thrombocytopenia develops in one-third to half of the patients. In serologically confirmed clinically overt dengue infections, the tourniquet test had a sensitivity of 41.6%, a specificity of 94.4%, and positive and negative predictive values of 98.3% and 17.3% respectively.

Similarly, malaria produces fever, headache, malaise, abdominal discomfort, vomiting and other flu-like symptoms. Hepatomegaly is common. Anemia, neutropenia, and leukopenia are typical. Complicated falciparum malaria can produce altered level of consciousness, renal failure, hypotensive shock, and death. Differentiating malaria from dengue based on purely clinical grounds can be difficult. Compared with those with malaria, patients with dengue are significantly more likely to have myalgia and a temperature < 39°C. Compared with other febrile illnesses, dengue fever is 18 times more likely if fever and leukopenia are present, 71 times more likely if fever and rash are present, and 230 times more likely if fever, rash, and leukopenia are present. It is also difficult to confirm either disease in baseline pathology tests; specialized testing based on serologic analysis is required for dengue, and detection of *Plasmodium* proteins is required for malaria.

Rapid tests for dengue have a sensitivity of 73–100% for detection of IgM antibody to dengue. The Panbio rapid test has a sensitivity of 73–100%, but there is a significant rate of cross-reactivity to other arboviruses, such as Japanese encephalitis virus and West Nile virus. Other tests may have similar or higher sensitivity and specificity, but some lack the portability and simplicity of rapid tests described.

Rapid diagnostic tests for *P. falciparum* show a sensitivity of 79.3–98% and a specificity of 98.4–100%. The Panbio and AMRAD ICT tests for *P. falciparum* malaria show a sensitivity of 92–100%. This is because the sensitivity of these tests is proportional to parasitemia, and at parasite levels of < 100/μL the sensitivity is only 11–40%. They are also much less sensitive and specific for diagnosis of *P. vivax* infection. Rapid tests for malaria are easy to learn and perform and have lower rates of error in interpretation compared with microscopy. They have also been shown to be more cost effective than microscopy in remote areas.

Of concern is the occasional failure of the ICT (and other rapid tests) to detect high parasite densities. Failure to detect both *P. falciparum* and *P. vivax* has been demonstrated when parasite densities exceeded 5,000/μL of blood. Absence of the histidine-rich protein 2 (HRP-2) gene in some malaria parasites has been described, leading to negative test results that depend on expression of HRP-2. This may have occurred in our case.

When dealing with a disease that is potentially fatal, diagnostic confidence by the user is very important, particularly when the disease is curable if treated early. Over-confidence in a test that has less than 100% sensitivity can lead to devastating consequences, as demonstrated. There are suggestions in the literature that rapid point-of-care tests may replace microscopy, or at least allow diagnosis in remote areas without microscopic resources. These tests may be useful in outbreak investigation and complex medical emergencies, but should only be considered an adjunct to microscopic diagnosis.

Examination of thick blood films for detection of malaria parasites has an operator-dependent sensitivity of 80–90%. This compares favorably with the ICT rapid test described earlier. There have been no studies examining combined microscopy and rapid diagnostic tests versus either separately. In experienced hands, microscopy can detect lower parasite counts than ICT rapid tests and it is still considered the gold standard test. However, the availability of microscopy is limited by training, experience, equipment cost, maintenance, and power (light source).

This case demonstrates the rapidity with which *P. falciparum* malaria can progress to become fatal. Although this patient had been sick for only a few days, the time from first presentation to death without treatment was approximately seven hours. The time from first cerebral symptoms to death was only a few hours.

Malaria and dengue infection can coexist in the same patient. Although causing quite similar symptoms and signs, the treatment of these two illnesses is different. It is important to diagnose *P. falciparum* malaria because it can be rapidly fatal if untreated. Although the sensitivity and specificity for rapid diagnostic tests are high, they are not infallible. Any suspicion of malaria in disease-endemic areas must be excluded with
microscopy if it is available, regardless of whether rapid test results are negative.

It will be important in the future to improve the sensitivity and specificity of rapid tests for malaria. Enhancing their performance so that these assays can differentiate species, monitor response to therapy, and determine quantitative parasite density remains a desirable goal.35

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REFERENCES


