Fever and shock in a child: How 'good' is a good blood test?

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CASE PRESENTATION

A 12-year-old girl presented with a history of intermittent fever (38.3°C to 40°C) for 10 days that was not associated with chills and rigours, and was relieved by antipyretics. She also had nonbilious and nonprojectile vomiting (seven days), shortness of breath (four days) and watery diarrhea (two days). At the beginning of her illness, she was treated with a complete course of oral chloroquine by a general practitioner.

In the pediatric emergency room, she presented with a heart rate of 136 beats/min, a respiratory rate of 56 breaths/min, a temperature of 37.8°C, a blood pressure of 60/30 mmHg and a capillary filling time of 5 s to 6 s. Shock resuscitation measures were initiated with intravenous normal saline (20 mL/kg bolus) and dopamine 5 µg/kg/min. She developed ventricular fibrillation, which was cardioverted. After cardiac arrest, she was intubated and transferred to the intensive care unit. Two hours later, she started bleeding from the nasogastric tube and endotracheal tube. A chest radiograph revealed bilateral lung opacities suggestive of intraparenchymal bleeding. The other significant clinical findings included icterus, cervical and inguinal lymphadenopathy, soft tender hepatomegaly, moderate splenomegaly and an absence of focal neurological deficits and meningeal signs.

In the intensive care unit, her hemodynamics improved (heart rate of 100 beats/min, blood pressure of 90/60 mmHg) with fluid resuscitation (60 mL/kg of normal saline titrated to a central venous pressure of 8 cm H₂O to 10 cm H₂O) and inotropic support (dopamine 15 µg/kg/min, adrenaline 0.15 µg/kg/min and noradrenaline 0.2 µg/kg/min). She also received three units each of fresh frozen plasma (200 mL) and platelet concentrates (50 mL). Empirical antibiotic therapy with ceftriaxone, cloxacillin and metronidazole was started along with dexamethasone. However, she remained unresponsive (E₁V₁M₁ on the Glasgow coma scale [GCS]). Her pupils were bilaterally dilated 5 mm and sluggishly reacted to light. An immediate cerebrospinal fluid analysis was deferred due to underlying coagulopathy and considering the absence of meningeal signs on presentation.

The serial hematological and biochemical parameters are shown in Table 1. Urinalysis confirmed hematuria without proteinuria or casts. Blood smear examination for malaria was performed every 6 h according to the institutional protocol. A septic screen (blood, urine and tracheal aspirate cultures) did not show any growth. A hepatitis work-up for both infective and autoimmune etiologies (ie, hepatitis B surface antigen, hepatitis A immunoglobulin M, hepatitis C serology,

antineutrophil cytoplasmic antibody, and liver kidney microsome antibodies). Both the Widal test for enteric fever and the dengue serology test were negative. An immunochromatographic assay for falciparum malaria based on the histidine-rich protein 2 (HRP-2) antigen (ParaSight-F, Becton, Dickinson and Company, USA) was also negative on admission. Ultrasound examination of the abdomen confirmed hepatosplenomegaly with moderate ascites. The ascitic fluid analysis was suggestive of an exudate (protein of 6.3 g/dL), and predominantly contained lymphocytes. As well, on the second day of admission, an additional five units of platelet concentrates and three units of fresh frozen plasma were transfused to control bleeding from the nasogastric and endotracheal tubes. Bone marrow and lymph node biopsy were planned for the next day.

What is the probable diagnosis?

TABLE 1
Laboratory findings during the patient's stay in the intensive care unit

	Day 1	Day 2	Day 3*	Day 4	Day 5
Hemoglobin (g/L)	104	114	92	74	103
WBC ($\times 10^9/L$)	45	31	16.5	7	9.8
DC (P:L)	89:10	88:11	80:17	80:16	70:23
Platelet count (per mL)	47,000	50,000	60,000	79,000	125,000
PT (control 10 s)	17	17	13	13	12
aPTT (control 30 s)	58	39	34	32	29
Fibrinogen (µmol/L)	5.3	5.8	8.8	8.4	8.8
D-dimer	+ve	+ve	+ve	+ve	-ve
Serum albumin (g/dL)	3.2	3.0	2.8	2.7	2.8
Serum globulin (g/dL)	3.0	2.8	2.6	3.0	2.7
Total bilirubin (µmol/L)	80.3	63.2	23.9	12.0	12.0
Direct bilirubin (µmol/L)	12.0	12.0	13.7	6.8	6.8
AST (U/L)	665	635	61	64	20
ALT (U/L)	191	189	51	55	19
Alkaline phosphatase (U/L)	27	27	12	14	6
Blood urea (mmol/L)	11.3	20.6	11.6	7.9	5.8
Serum creatinine (µmol/L)	159	114	80	62	62
Serum sodium (mmol/L)	133	138	140	136	141
Serum potassium (mmol/L)	3.3	3.2	4.0	3.9	3.5
Malaria blood smear	-ve	-ve	+ve	-ve	-ve

*All investigations after patient received the loading dose and two subsequent doses of quinine. ALT Alanine aminotransferase; aPTT Activated partial thromboplastin time; AST Aspartate aminotransferase; DC Differential count; L Lymphocytes; P Polymorphonuclear leukocytes; PT Prothrombin time; WBC Total white blood cell volume; +ve Positive; -ve Negative

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DIAGNOSIS

Differential diagnoses were enteric fever, dengue hemorrhagic fever, severe falciparum malaria or a hematological malignancy. On day 3, one of the serial microscopic blood smears showed ring forms of *Plasmodium falciparum* with a parasitemia rate of 2%. Intravenous quinine (20 mg/kg loading dose, followed by 10 mg/kg every 8 h) was then started with frequent blood sugar and continuous electrocardiographic monitoring. Over the next 12 h, hepatosplenomegaly and lymphadenopathy resolved. Her general condition started improving and she was gradually weaned off all inotropes. All laboratory investigations normalized within the next 48 h except for hemoglobin (75 g/L), which prompted transfusion of one unit of blood.

However, her neurological status did not show any marked improvement ($E_1V_1M_2$ on the GCS). The diameter of her right pupil was 3 mm (with brisk pupillary response), while the diameter of her left pupil was 5 mm (sluggishly reacting to light). Computed tomography revealed diffuse brain edema with a faint hypodense area in the right frontotemporal region suggestive of evolving infarction. Mannitol and furosemide were also started to reduce cerebral edema. Over the next 24 h, her GCS score improved to $E_3V_7M_5$ and her pupils were bilaterally equal and reactive to light. After four days of quinine therapy, she was fully conscious, and she was weaned off the ventilator and transferred to the pediatric ward. After completion of a seven-day course of quinine, she was discharged from the hospital with no neurological deficits.

DISCUSSION

The clinical picture of malaria is often unpredictable and misleading. In children, severe malaria can manifest itself as impaired level of consciousness (35%), convulsions (26%), respiratory distress (42%), jaundice (23%), severe anemia with a hemoglobin level of less than 50 g/L (20%), acidosis with a pH of less than 7.25 (21%), hypoglycemia (15%), prostration (9%), severe intravascular hemolysis and macroscopic hematuria (5%), cardiovascular collapse (3%), renal failure (3%), disseminated intravascular coagulation (3%) or pulmonary edema and acute respiratory distress syndrome (1%); hence, severe malaria can be misdiagnosed unless there is a high degree of clinical suspicion (1). Early diagnosis and treatment of malaria can further be delayed when laboratory investigations fail to confirm the clinical suspicion.

In our patient, the predominant gastrointestinal symptoms (vomiting and diarrhea) along with the paralytic ileus, moderate ascites and hepatosplenomegaly, prior treatment with chloroquine and increased white blood cell count led to initial suspicion of enteric fever. A negative Widal test in the second week of illness and an absence of clinical improvement despite enteric fever therapy was highly suggestive of an alternative diagnosis. Dengue fever, septicemia and hepatitis were also excluded. Although the initial work-up for malaria was also negative (ParaSight-F test and blood film microscopy), a high degree of clinical suspicion and serial microscopy helped us arrive at the diagnosis.

Presently, the gold standard for diagnosing malaria is blood film microscopy (thick films to detect parasitemia and thin films to identify the species). During microscopy, the diagnosis may be missed due to faulty staining technique, incorrect buffer pH, inexperienced technicians or prior partial treatment (2). Occasionally, mixed infections (eg, *Plasmodium vivax*,

Plasmodium malariae and *P falciparum*) can lead to misdiagnosis on slide examination, which can delay appropriate therapy. Furthermore, people may have asymptomatic parasitemia in endemic areas. Hence, the demonstration of malarial parasites in blood films should not stop an active search for other causes of infections, septicemia or encephalopathy.

To address the problems stated above, immunochromatographic tests were developed. They are based on the detection of either the HRP-2 antigen or the parasite lactate dehydrogenase (pLDH) antigen (OptiMAL test, Flow Inc, USA) (3). Their main advantages are bedside availability even in the absence of an experienced microscopist, rapidity (10 min to 15 min), and as an aid in assessing the response to treatment.

Both ParaSight-F and ICT Malaria Pf are designed to diagnose only a single malarial species – *P falciparum*. Because falciparum infections are the most virulent, these tests are claimed to have a high negative predictive value in suspected cases of severe malaria. However, in cases of mixed plasmodium infections in children (ie, vivax and falciparum), ParaSight-F was found to be only 25% sensitive for the detection of *P falciparum* (4).

Recently, the ParaSight F+V assay was created as an improvement on the ParaSight-F test format by incorporating a monoclonal antibody directed against *P vivax*-specific antigen. The ICT Malaria Pf/Pv test was also developed along the same lines. However, at parasite densities of less than 500/μL, the ParaSight F+V and ICT Malaria Pf/Pv tests showed sensitivities of only 23% and 55%, respectively (5,6), and were of limited utility in diagnosing *P vivax*.

The OptiMAL test uses a dipstick coated with monoclonal antibodies against the intracellular metabolic enzyme pLDH for rapid detection of malaria. It has a sensitivity of 84% to 94% and a specificity of 99% to 100% (7,8). Unlike HRP-2 antigen-based tests, the OptiMAL test can also differentiate malarial parasite species based on their antigenic differences in pLDH isoforms. In comparison with ParaSight-F and ICT Malaria Pf, OptiMAL is also more sensitive for the detection of *P falciparum* (9,10). However, the main disadvantages of the OptiMAL test are poor reliability at low levels of parasitemia (less than 0.01%), and the occasional inability to distinguish between *P vivax* and *P falciparum* due to cross-reactivity of antigens in the pan-specific band.

A study in Myanmar (11) interestingly found batch quality variations in the OptiMAL and ICT Malaria Pf/Pv tests, resulting in their unacceptably poor performance in comparison with microscopy. The sensitivities reported in that study for the detection of *P falciparum* and non-*P falciparum* parasites were 86.2% and 2.9% for ICT Malaria Pf/Pv, respectively, and 42.6% and 47.1% for OptiMAL, respectively.

In the light of present evidence, we conclude that immunochromatographic studies cannot replace Giemsa-stained microscopy in the timely diagnosis of malaria, but should be considered as an adjunct to microscopy. Partially treated malaria can pose a serious diagnostic dilemma to the clinician due to the low level of peripheral parasitemia. Fortunately, most serious falciparum infections have a high level of peripheral parasitemia (higher than 5%), which can be easily detected in peripheral smears (1). In rare instances of severe falciparum infections, such as in our case, the parasite can remain sequestered in the liver, spleen and maybe even the brain with low peripheral parasitemia and may avoid

detection in a single blood smear examination. A high degree of clinical suspicion and serial microscopy is beneficial in this setting for timely diagnosis and the initiation of appropriate treatment.

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