

Glucose-6-Phosphate Dehydrogenase Deficiency: Possible Determinant for a Fulminant Course of Israeli Spotted Fever

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Israeli spotted fever, caused by a local variant of *Rickettsia conorii*, differs antigenically and clinically from the classical form of Mediterranean spotted fever (Boutonneuse fever). Both Mediterranean spotted fever and Rocky Mountain spotted fever have been known to be more lethal in patients with glucose-6-phosphate dehydrogenase deficiency. We describe the first case of the Israeli variant of Mediterranean spotted fever, which occurred in a patient with the local variant of G6PD deficiency and was characterized by a fulminant complicated course.

Case Description

A 35-year-old man, born in Israel to parents of Iraqi origin, was admitted to the hospital with high fever, fatigue and headache of 4 days duration. The patient owned three dogs that were kept in his yard.

During the first 3 days of hospitalization and no medications, high fever, headache and fatigue persisted. On the following day a maculopapular rash appeared that involved his abdomen, chest and upper extremities, including the palms. The patient became irritable, lethargic and then lapsed into coma. This was followed by acute renal failure, hepatic insufficiency, hemolysis, tachypnea and respiratory failure that required intubation and assisted ventilation. Hemodialysis was started and blood transfusions were administered. On admission to the intensive care unit, the patient had slightly elevated creatinine (1.6 mg/dl) and elevated liver transaminases (SGOT 142 U/L, SGPT 117 U/L). Fragmented cells were not seen in the blood smear. Chloramphenicol 3 g/day i.v. was initiated, but when G6PD deficiency became known it was switched after 24 hours to ofloxacin 400 mg/day. Following a week of treatment with ofloxacin, with no clinical improvement, a worsening jaundice (total bilirubin 35 mg/dl,

direct 24 mg/dl) and renal failure (creatinine 10.8 mg/dl), antibiotic treatment was completely withdrawn.

All blood, urine, cerebrospinal fluid and sputum cultures obtained prior to therapy were sterile. Tests for hepatitis B surface antigen and antinuclear factor were negative. Indirect immunofluorescence tests for *Leptospira* and *Rickettsia* were initially negative but *Rickettsia* immunofluorescent antibody converted 3 weeks later from negative to highly positive (>1:1248) (both immunoglobulin G and M). The patient's status and laboratory findings gradually improved from the 11th hospital day onwards and he was discharged, feeling well, on the 25th hospital day with normal bilirubin and a creatinine value of 4.5 mg/dl.

Comment

Mediterranean spotted fever, caused by *R. conorii*, clinically resembles Rocky Mountain spotted fever, although it is usually a more benign disease with a milder course. Israeli *R. conorii* isolates were recently shown

G6PD = glucose-6-phosphate dehydrogenase

to be genetically different, as a group, from the European *R. conorii* reference strain [1]. Israeli spotted fever also differs from Mediterranean spotted fever by being clinically milder and consistently missing the tache noire at the site of the tick bite. A multi-system involvement due to a generalized vasculitis is characteristic for all rickettsial spotted fevers and is manifested by a purpuric maculopapular rash, myalgia, conjunctivitis and hepatomegaly accompanied by high fever and headache. Israeli spotted fever may run a sub-clinical course, although severe and fatal forms have recently been more frequently reported [2].

G6PD deficiency has been demonstrated to be among the predisposing factors for the severe course of Rocky Mountain spotted fever, while in Mediterranean spotted fever the association of G6PD deficiency and a severe course of the infection is still debated [3]. The fulminant course of Mediterranean spotted fever is characterized by renal failure (80%) and hepatic (60%), cardiovascular and respiratory involvement (both 50%). It is unknown however whether these complications are due to an interaction between G6PD deficiency and rickettsial infection, or due to the interaction of G6PD deficiency and the antibiotics given for spotted fever.

A variant of G6PD deficiency (G6PD Mediterranean, with a markedly reduced catalytic activity) is widespread in Israel among Jews of Iraqi and Persian origin, as is Israeli spotted fever. The apparent lack of documented fulminant cases of Israeli

spotted fever associated with G6PD deficiency in this population is an enigma. It may be because physicians are unaware of this link and do not evaluate G6PD status in such patients with a severe course of Israeli spotted fever. As our case illustrates, fulminant Israeli spotted fever, especially in the setting of G6PD deficiency, may present a diagnostic difficulty. The diagnosis is hampered by misleading clinical presentation, the inability to isolate the microorganism, and the fact that specific antibodies are virtually always absent at the initial stages of the disease.

The issue of therapy for such patients is also controversial. In our patient tetracycline, the drug of choice for rickettsial diseases, was not administered due to the patient's hepatic failure. A second-line agent, chloramphenicol, was started but when G6PD deficiency became known this treatment was switched to ofloxacin. Quinolone compounds are active against rickettsiae, and there have been a few reports of successful therapy with these compounds [4]. However, our patient's condition deteriorated even further on one week of ofloxacin treatment and it was discontinued; 24 hours after ofloxacin withdrawal the patient showed a rapid clinical and laboratory improvement. Hemolysis in G6PD-deficient patients treated with nalidixic acid, a closely related quinolone, is well documented. To date however, ofloxacin has not been reported to cause hemolysis in G6PD-deficient individuals. Furthermore, *in vitro* experiments did not disclose a liaison between G6PD

deficiency and hemolysis induced by ofloxacin [5]. Thus, the association between ofloxacin withdrawal and improvement of the patient's condition may have been coincidental. Furthermore, improvement may have resulted from the one week therapy.

In conclusion, we described a fulminant case of Israeli spotted fever in a patient with G6PD deficiency unresponsive to treatment. We assume the complicated course of the infection is due to G6PD deficiency. The appropriate treatment strategy for such patients remains unknown.

References

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I cannot forecast to you the action of Russia. It is a riddle wrapped in a mystery inside an enigma.

Sir Winston Churchill, British Prime Minister (1874-1965)