Severe Yellow Fever and Extreme Hyperferritinemia Managed with Therapeutic Plasma Exchange

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Abstract. A 43-year-old man was admitted to the intensive care unit and diagnosed with yellow fever. He presented with refractory bleeding, extreme hyperferritinemia, and multiple organ dysfunction syndrome, requiring renal replacement therapy, mechanical ventilation, and treatment with vasoactive drugs. Because the bleeding did not respond to fresh-frozen plasma administration, the patient received therapeutic plasma exchange, which was accompanied by a marked improvement of the clinical and biochemical parameters, including a significant decline in serum ferritin levels.

INTRODUCTION

Yellow fever is an endemic mosquito-borne viral infection of humans and nonhuman primates in the tropical regions of Africa and South America, currently being a leading cause of hemorrhagic fever-related mortality in those regions.1,2 Infection with the yellow fever virus can result in disseminated disease that is typically characterized by a sudden onset of fever and prostration, the more severe form of yellow fever being associated with hepatic, renal, and myocardial failure, as well as with hemorrhagic diathesis and shock.1,2 The mortality rates associated with yellow fever in South America have been reported to be as high as 60%.2 There is as yet no specific pharmacological treatment for yellow fever. For individuals infected with the yellow fever virus, the treatment remains limited to symptomatic and supportive care, which produces unsatisfactory results in those with the most severe presentations.3,4 Here, we describe a case of multiple organ failure and refractory bleeding in a patient with yellow fever, in whom the disease was successfully managed with therapeutic plasma exchange (TPE).

CASE REPORT

A 43-year-old male rural worker, who had not been vaccinated against yellow fever, presented with a 7-day history of fever, headache, myalgia, malaise, and nausea, together with a 3-day history of abdominal pain, jaundice, and anuria. The patient lived and worked on a peach palm (Bactris gasipaes) farm in the south of the Brazilian state of São Paulo, where there was an ongoing outbreak of yellow fever, and he had not traveled recently. He was admitted to the intensive care unit (ICU). At ICU admission, blood samples were collected and sent for diagnostic tests. The diagnostic hypothesis of yellow fever was confirmed by real-time polymerase chain reaction and serologic testing with immunoglobulin M antibody–capture ELISA (MAC-ELISA; Centers for Disease Control and Prevention, Atlanta, GA).5,6 The patient tested negative for dengue (MAC-ELISA; Centers for Disease Control and Prevention) and viral hepatitis A, B, and C (by electrochemiluminescence). At admission, he was conscious but disoriented, with a heart rate of 64 bpm, blood pressure of 128/97 (103) mmHg, respiratory rate of 12 bpm, peripheral oxygen saturation on room air of 91%, axillary temperature of 36°C, ecchymoses on the arms, gingival bleeding, asterixis (flapping tremor), and anuria. Soon after ICU admission, he presented generalized tonic–clonic seizures, which were controlled with midazolam, and he was intubated because mechanical ventilation was necessary. He also evolved to hypotension, requiring saline infusion, as well as administration of sodium bicarbonate and noradrenaline, to maintain the target mean arterial pressure of 65 mmHg. Blood was drawn for laboratory tests (Table 1), and he was started on renal replacement therapy (hemodialysis). He subsequently developed massive bleeding through the nasogastric tube and from the puncture sites. The bleeding was refractory to fresh-frozen plasma infusion and required packed red cell transfusion. Therefore, beginning on day 2 after ICU admission, he was submitted to TPE once daily for four consecutive days, with no fixed time interval between the sessions—at a rate of 1 L/h. Plasma was removed and replaced with an equivalent volume of fresh-frozen plasma; the total volume of plasma exchanged was 3 L/day. On the third day of TPE, the spontaneous bleeding decreased, and the vasoactive drugs were discontinued on the following day. The blood tests performed at admission had also revealed hyperferritinemia, and there was a progressive decline in ferritin levels from the first TPE session onward (Figure 1), just as there were improvements in most of the biochemical parameters and in the sequential organ failure assessment score (Table 1). The patient was extubated on day 8 and showed no subsequent bleeding. He was discharged from ICU 40 days after admission.

DISCUSSION

Hepatic failure and renal failure are hallmarks of severe, life-threatening yellow fever, as is bleeding diathesis. In a retrospective cohort study of patients with yellow fever, Tuboi et al.1 found that the following factors were associated with higher mortality in their univariate analysis: male gender; age > 40 years; jaundice; serum aspartate aminotransferase > 1,200 IU/L; alanine aminotransferase > 1,500 IU/L; total bilirubin > 7.0 mg/dL; direct bilirubin > 5.0 mg/dL; and blood urea nitrogen > 100 mg/dL. Those authors reported that elevated aspartate aminotransferase and jaundice both remained independently associated with higher mortality in their multivariate analysis. In the case presented here, the patient had all of those risk factors at admission, subsequently evolving to shock, metabolic acidosis, hyperlactatemia, and refractory bleeding, which are indicative of a grim prognosis.

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The potential role of TPE as a useful treatment in refractory cases of yellow fever.

Another remarkable finding in the case presented here was the extremely high level of ferritin (> 100,000 ng/mL [normal range 30–400 ng/mL]) at ICU admission. Although hyperferritinemia has been reported in other viral hemorrhagic fevers, such as dengue and Ebola,9,10 this is, to our knowledge, the first time it has been reported in yellow fever. The pathogenesis of the hyperferritinemia in our patient was probably multifactorial. Hepatocytes, Kupffer cells, proximal tubular renal cells, and macrophages have all been shown to secrete ferritin in response to injury.11,12 The extremely high level of ferritin (> 100,000 ng/mL [normal range 30–400 ng/mL]) at ICU admission. Although hyperferritinemia has been reported in other viral hemorrhagic fevers, such as dengue and Ebola,9,10 this is, to our knowledge, the first time it has been reported in yellow fever. The pathogenesis of the hyperferritinemia in our patient was probably multifactorial. Hepatocytes, Kupffer cells, proximal tubular renal cells, and macrophages have all been shown to secrete ferritin in response to injury.11,12 Ferritin under various in vivo and in vitro conditions,11 and it is noteworthy that our patient presented with severe hepatic and renal injury. Cultured cells have also been shown to release ferritin into surrounding media when grown in the presence of interleukin 1 beta or tumor necrosis factor alpha,11 cytokines that are known to be elevated during infection with the yellow fever virus.12,13

Involvement of the liver and kidneys, together with the potential increase in macrophage activity during infection with the yellow fever virus,12,13 suggests that ferritin could be a biomarker of severity and prognosis and that the determination of ferritin levels could be a practical tool to monitor disease progression in YF. In addition, ferritin plays a role in the pathogenesis of inflammatory diseases by modulating the innate immune response and lymphocyte function. In humans, T and B lymphocytes bind ferritin, directly eliciting an immunosuppressive effect through impairment of T-cell proliferation, B-cell maturation, and immunoglobulin production. Severe lymphocyte impairment is a characteristic of severe YF in humans and in experimentally infected macaques.15–17 The potential role of ferritin in such a phenomenon offers a rationale to consider therapeutic measures aimed at its clearance.18,19

In the present case of yellow fever virus infection, the initial support therapies for the acute hepatic and renal failure included hemodialysis, transfusion of packed red cells, and infusion of fresh-frozen plasma. However, the administration of the blood products failed to control the bleeding. Our decision to use TPE, in which the patient plasma is replaced with fresh plasma, was based on previous reports of its successful use in patients with fulminant hepatic failure.7,8 In this context, TPE has been shown to increase survival by providing significant improvements in multiple clinical parameters, such as liver enzymes, renal function, lactate (as a marker of tissue injury), and the model for end-stage liver disease score.7,8 Another remarkable finding in the case presented here was the extremely high level of ferritin (> 100,000 ng/mL [normal range 30–400 ng/mL]) at ICU admission. Although hyperferritinemia has been reported in other viral hemorrhagic fevers, such as dengue and Ebola,9,10 this is, to our knowledge, the first time it has been reported in yellow fever. The pathogenesis of the hyperferritinemia in our patient was probably multifactorial. Hepatocytes, Kupffer cells, proximal tubular renal cells, and macrophages have all been shown to secrete ferritin under various in vivo and in vitro conditions,11 and it is noteworthy that our patient presented with severe hepatic and renal injury. Cultured cells have also been shown to release ferritin into surrounding media when grown in the presence of interleukin 1 beta or tumor necrosis factor alpha,11 cytokines that are known to be elevated during infection with the yellow fever virus.12,13
In the case presented here, the post-TPE improvement in synthetic and metabolic liver function was clinically evident and eventually resulted in normalization of the international normalized ratio and effective control of the bleeding diathesis. That improvement was accompanied by a progressive decrease in the plasma ferritin levels. It remains unclear whether this kinetic improvement, or whether the removal of ferritin by TPE played a role in bringing about that improvement. The role of ferritin (in the pathogenesis of disease and as a biomarker of normalized ratio and effective control of the bleeding diathesis. That eventually resulted in normalization of the international normalized synthetic and metabolic liver function was clinically evident and management of cases such as the one presented here.

REFERENCES