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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 norepinephrine, 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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TABLE 1
Biochemical findings and sequential organ failure assessment score during the first week in the intensive care unit

Variable	D1	D2*	D3*	D4*	D5*	D6	D7	Normal range
Hemoglobin	11.0	6.7	7.0	4.2	6.6	8.2	7.6	13–16 g/dL
Hematocrit	34	28.1	19.3	10.9	16.4	22	20	37–49%
White blood cells	16,400	14,100	19,100	18,000	14,900	18,800	16,000	4,500–13,500/μL
Platelets	100	89	91	101	61	40	62	150–400 × 10^3/μL
C-reactive protein	11.9	30.8	82.5	69.4	39	46	34	< 5 mg/L
Ferritin	> 100,000	75,581	56,656	21,222	ND	ND	ND	30–400 ng/mL
Alanine aminotransferase	5,890	2,997	560	256	150	111	103	10–49 U/L
Aspartate aminotransferase	2,850	1,480	1,170	576	345	257	216	< 34 U/L
Lactate dehydrogenase	7,620	5,425	3,028	1,855	1,413	1,031	706	100–190 U/L
Total bilirubin	39.0	38.6	41.4	41.32	44.4	41.5	22.4	≤ 1.0 mg/dL
Direct bilirubin	23.0	23.9	25.8	26.87	29.6	28.0	15.8	≤ 0.7 mg/dL
Ammonia	258	ND	78	ND	ND	ND	ND	11–32 μmol/L
International normalized ratio	1.5	1.28	1.41	1.15	1.12	ND	1.0	0.95–1.12
Fibrinogen	141	106	205	210	334	ND	322	200–400 mg/dL
Factor V	144	115	80	103	120	157	164	62–139%
Urea	209	108	80	53	72	67	78	10–50 mg/dL
Creatinine	16.4	10.7	8.41	5.89	7.6	5.98	5.29	0.7–1.2 mg/dL
Sodium	136	139	135	134	134	135	135	135–145 mEq/L
Potassium	4.4	4.7	4.5	3.7	3.3	4.3	3.5	3.5–5.0 mEq/L
Bicarbonate	6.2	25	21	26	25.8	24	26	22–26 mmol/L
Lactate	118	23	37	21	11	11	10	4.5–14.4 mg/dL
Glucose	97	112	140	171	94	168	120	≤ 99 mg/dL
Amylase	297	765	719	676	661	470	452	< 125 U/L
Lipase	330	598	1,113	1,924	ND	458	335	8–78 U/L
Sequential organ failure assessment score	17	15	17	14	14	17	14	–

D = day; ND = no data.
* Days on which the patient underwent therapeutic plasma exchange.

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] The remarkable improvement observed in our patient, whose initial prognosis was dismal, is the cause for optimism regarding the potential role of TPE as a useful treatment in refractory cases of yellow fever.

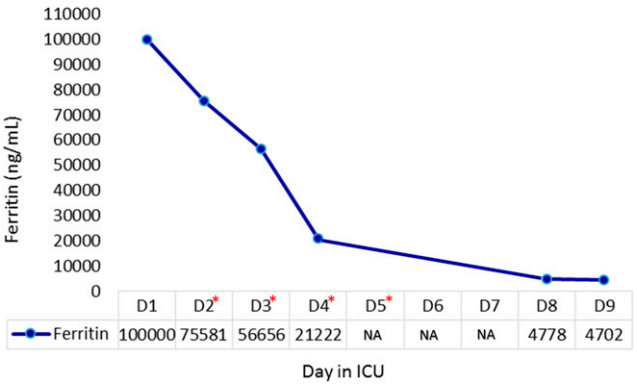

FIGURE 1. Time course of serum ferritin levels in the first day after intensive care unit (ICU) admission in a patient with yellow fever. *The patient underwent therapeutic plasma exchange on the second through the fifth days after admission. This figure appears in color at www.ajtmh.org.

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]

Involvement of the liver and kidneys, together with the potential increase in macrophage activity during infection with the yellow fever virus,[12,14] 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.[15–18] The potential role of ferritin in such derangement offers a rationale to consider therapeutic measures aimed at its clearance.[19,20]

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 behavior of ferritin mirrors its role as a sensitive biomarker of inflammation and liver/kidney damage, thus reflecting the clinical 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 severity) merits further study, as does the role of TPE in the management of cases such as the one presented here.

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