

An ironic case of liver infections: *Yersinia enterocolitis* in the setting of thalassemia

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Abstract

A 49 years old Vietnamese male with a history of thalassemia, presented with gastrointestinal symptoms and signs of hemolysis. He was diagnosed with *Yersinia enterocolitis*. *Yersinia* is a gram-negative rod that most frequently occurs in children especially during the winter months. In the current case, the bone marrow biopsy showed hemophagocytosis along with positive cultures for *Yersinia*. The microorganism likely triggered hemophagocytosis. This syndrome, also known as, hemophagocytic lymphohistiocytosis, is defined by fever for more than 7 d, cytopenia of two or more cell lines, hemophagocytosis, hepatitis, serum ferritin greater than 500, jaundice, lymphadenopathy, and hepatosplenomegaly. This disorder can be either familial or secondary to a strong immunologic activation. Both have an overwhelming activation of T-cells and macrophages.

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Key words: *Yersinia*; Enterocolitis; Bone marrow; Liver

biopsy; Thalassemia; Hemophagocytic lymphohistiocytosis

Core tip: In the current case, the bone marrow biopsy showed hemophagocytosis along with positive cultures for *Yersinia*. The microorganism likely triggered hemophagocytosis. This syndrome, also known as, hemophagocytic lymphohistiocytosis, is defined by fever for more than 7 d, cytopenia of two or more cell lines, hemophagocytosis, hepatitis, serum ferritin greater than 500, jaundice, lymphadenopathy, and hepatosplenomegaly. This disorder can be either familial or secondary to a strong immunologic activation. Both have an overwhelming activation of T-cells and macrophages.

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INTRODUCTION

Yersinia is a gram-negative rod that most frequently occurs in children especially during the winter months. Transmission is largely food and waterborne. Pigs are frequently colonized with strains that cause human illness. Incubation typically lasts 2-6 d followed by a diarrheal period that can last up to three weeks. Symptoms include nausea, vomiting, and abdominal pain. Most strains of *Yersinia* grow poorly in typical agar solutions because the bacteria lack a mechanism for the efficient uptake of iron. Individuals who have iron overload due to either primary or secondary hemochromatosis are at increased risk of infection, and are also at higher risk to develop severe infections. Complications of severe infection can include diffuse ulcerating ileitis and colitis, intussusception, perforation, toxic megacolon, cholangitis, mesenteric vein

thrombosis, and hemophagocytic lymphohistiocytosis. Post-infectious complications include erythema nodosum and reactive arthritis. Treatment, reserved only for severe systemic infections, should consist of a 3rd generation cephalosporin and gentamicin for 3 wk. Genetic studies on this patient showed a loss of three alpha globin genes indicating the presence of Hb H disease. This lack of alpha globin causes a relative increase in the number of beta globin chains which can aggregate to form unstable tetramers. The tetramers have abnormal oxygen dissociation curves reflected in poor delivery of oxygen to the periphery, as well as precipitation of the hemoglobin tetramers as Heinz bodies. These precipitants can induce phagocytosis of red blood cells and a chronic hemolytic anemia which in turn leads to an increase in serum hep-
cidin levels with resultant elevated iron transport across the gut mucosa. Over time, this leads to a systemic iron overload which can also be exacerbated iatrogenically by blood transfusions.

CASE REPORT

A 49-year-old Vietnamese male, with a history of malaria 27 years ago was well until 5 d prior to admission when he developed dark urine associated with fevers, chills, and night sweats. This was followed by non-bloody diarrhea, and right upper quadrant abdominal pain as well as nausea and non-bloody vomiting. He denied any IV drug abuse, sick contacts, or travel history. He drank alcohol socially, but not to excess. On physical exam, he had a temperature of 104.3 °C, Blood pressure of 102/59 mmHg, heart rate of 100 beats/min, and saturation of 92% on room air. Generally, he was pale, diaphoretic, and sclerae were icteric. Abdominal examination revealed some right upper quadrant tenderness, but no rebound or guarding, and no hepatosplenomegaly. He had no rashes or stigmata of chronic liver disease. His laboratory studies showed a hemoglobin of 6.1 (13.8-18.0) g/dL with an MCV of 58 (80-100) fL, a white cell count of 10.6 (4.8-10.5) 10³/μL, and a platelet count of 75 (150-400) 10³/μL. Aspartate aminotransferase and alanine aminotransferase were 168 and 160 (5-40 and 7-56) U/L, respectively with a total bilirubin of 3.3 (0.3-1.9) mg/dL, and a direct bilirubin of 1.1 (0-0.3) mg/dL. Haptoglobin was < 15 (41-165). A peripheral smear demonstrated marked anisopoikilocytosis with schistocytes and target cells. Iron saturation was initially normal, 29%, with a ferritin of 6148 (12-300) mg/dL. Subsequent testing revealed persistently high iron saturation, 80%, and ferritin levels > 1000 mg/dL. Glucose and electrolytes were normal. Computerized tomography (CT) of the abdomen showed a normal biliary tree, proximal ascending colon mural thickening with surrounding adenopathy and pericolic stranding as well as bilateral pleural effusions (Figure 1). Stool, blood, and bone marrow cultures were all positive for *Yersinia enterocolitica*. The patient was positive for HBsAg with a viral load of 270000 IU. Genetic testing revealed mutations of three alpha globin genes making a diagnosis of alpha thalassemia (Hb H). A liver biopsy showed 3+ iron in hepatocytes

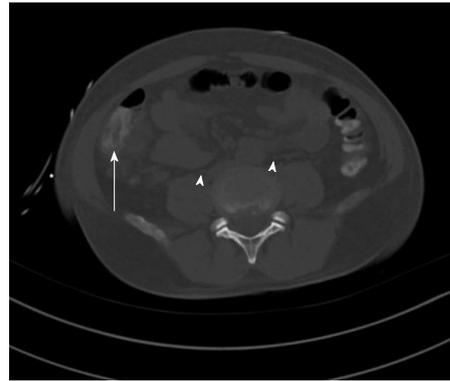


Figure 1 A computer tomography of the abdomen without contrast performed on the day of admission. There was moderate mural thickening of the proximal ascending colon (arrow) with surrounding adenopathy and mild pericolic stranding. Also visible are mesenteric, pericolic and retroperitoneal lymph nodes (arrowheads) with the largest measuring 1.6 cm in short axis in the right pericolic region.

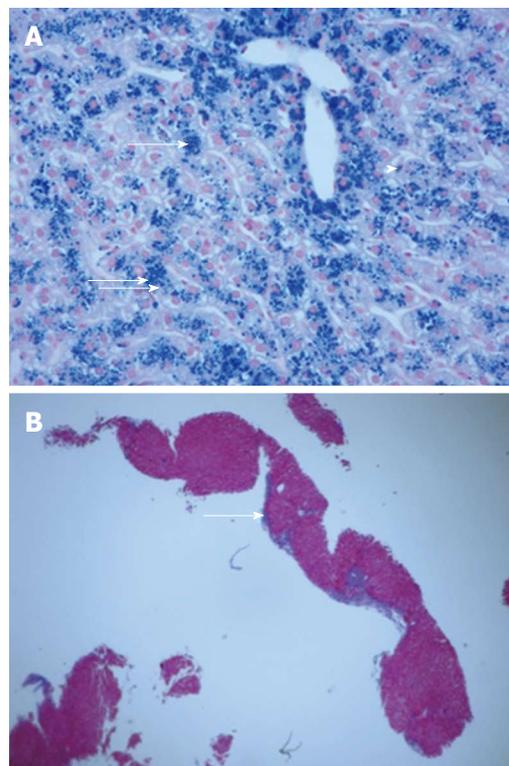


Figure 2 Liver biopsy. A: There is marked, 3+, accumulation of iron primarily in the hepatocytes (arrows), but also in Kupfer cells (arrow head), and bile duct epithelium in association with moderate lobular hepatitis (Prussian Blue stain for iron, × 400); B: There is increased fibrosis with focal portal-to-portal and occasional central-portal septum formation (arrow) indicating progression towards early cirrhosis (Masson Trichrome stain, × 40).

with a portal to central gradient (Figure 2A), and chronic inflammation with early septum formation (Figure 2B). Bone marrow biopsy revealed iron overload, and a granuloma (Figure 3A), and hemophagocytic lymphohistiocytosis (Figure 3B)^[1]. The patient was started on piperacillin/tazobactam/gentamicin and transfused to a hemoglobin level of 10 g/dL with rapid clinical improvement. He was discharged on a 3-wk course of oral ciprofloxacin, and a

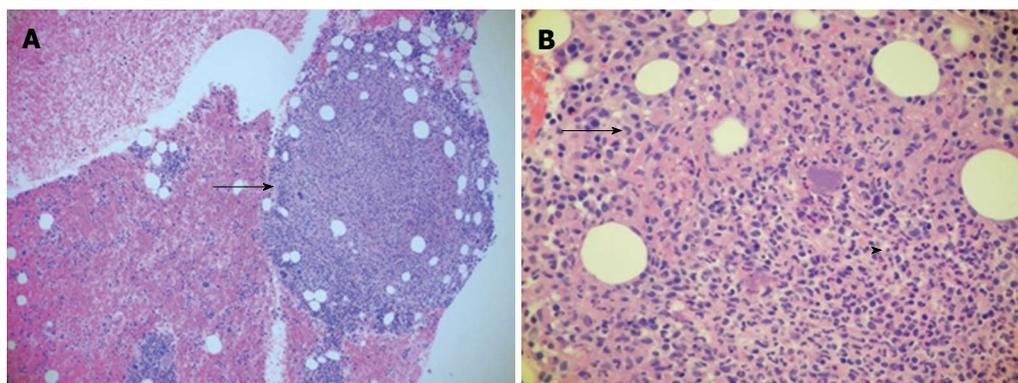


Figure 3 Bone marrow biopsy. A: A necrotizing granuloma (arrow) with trilineage maturation and markedly increased iron storage [hematoxylin and eosin (HE) stain, ×100]; B: An area of necrosis (arrowhead) with erythrophagocytosis typical, but not diagnostic of *Yersinia* infection (HE stain, ×400).

follow up CT of the abdomen showed resolution of the bowel thickening and disappearance of the fat stranding. In addition, he was treated with oral deferasirox (Exjade) and entecavir. His ferritin level decreased to 842 by 12 wk. His liver enzyme levels returned to normal, and his HBV viral load became undetectable.

DISCUSSION

In the current case, the bone marrow biopsy showed hemophagocytosis along with positive cultures for *Yersinia*. The microorganism likely triggered hemophagocytosis^[2]. This syndrome, also known as, hemophagocytic lymphohistiocytosis, is defined by: fever for more than 7 d, cytopenia of two or more cell lines, hemophagocytosis, hepatitis, serum ferritin greater than 500, jaundice, lymphadenopathy, and hepatosplenomegaly. This disorder can be either familial or secondary to a strong immunologic activation. Both have an overwhelming activation of T-cells and macrophages.

In this patient, the chronic anemia due to thalassemia, or anemia in combination with the hepatitis B caused a secondary hemochromatosis^[3]. This increased the risk of

Yersinia infection, and likely was responsible for the severity of the systemic infection^[4].

This patient will need iron chelation therapy and close monitoring for development of hepatocellular carcinoma because of the heightened risk with his coexisting HBV infection.

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