CD20-negative diffuse large B-cell lymphoma presenting with lactic acidosis

To the Editor: A 61-year-old man presented with acute onset confusion and one month of persistent fevers. Review of systems revealed abdominal distension and anasarca, weight loss, diarrhea, and poor oral intake. Laboratory workup showed acute kidney injury (creatinine 1.48 mg/dL) and pancytopenia (WBC 2.6 $\times$ 10^9/L, hemoglobin 11.5 g/dL, platelets 109 $\times$ 10^9/L). He also had transaminitis (AST 105 IU/L, ALT 56 IU/L, alkaline phosphatase 131 IU/L), normal bilirubin level, profound hypoalbuminemia (albumin 1.4 g/dL), and elevated lactate of 4.9 mEq/L. HIV and viral hepatitis serologies were negative. Extensive workup including paracentesis and stool cultures was unrevealing. Computed tomography (CT) scans showed no lymphadenopathy, hepatosplenomegaly, or discrete masses. On day 4 of admission the patient experienced diarrhea with blood clots, developed ventricular tachycardia, and died. Histopathology revealed large malignant cells diffusely involving extranodal sites: heart, epicardium, peripancreatic tissue, liver, subserosa of the digestive tract, and pituitary gland (Fig. 1). Immunohistochemical staining was negative for CD20 but positive for CD45 and CD79a providing evidence of B-cell lineage. T-cell markers CD3, CD4, and CD8 were negative. The malignant cells did not express CD5, CD10, CD138, CD30, CD15, IRF4/MUM1, EBV LMP1, HHV8 LANA, cyclin D1, MYC, or anaplastic lymphoma kinase (ALK). Ki-67 expression was 50%. These findings were consistent with stage IV CD20− diffuse large B-cell lymphoma (DLBCL).

As the spectrum of CD20− DLBCL continues to evolve, specific entities have been described. Plasmablastic lymphoma (PBL) is associated with HIV and Epstein-Barr virus (EBV) co-infection with median survival of 12 months [1]. Based on a recent study, PBL is the most common CD20− DLBCL subtype, accounting for 75% of the cases [2]. PBL cells usually express plasma cell markers CD138 or IRF4/MUM1 with Ki67 >90%. Primary effusion lymphoma (PEL) is associated with co-infection by HIV, EBV, and HHV8, and presents as pleural, peritoneal and/or pericardial effusion without mass or lymphadenopathy. Survival is poor at 9 months [3]. HHV8-positive DLBCL arising from multicentric Castleman disease (MCD) presents in the setting of HIV infection and is associated with poor survival [4]. ALK+ DLBCL presents with nodal and extranodal involvement, malignant cells express ALK and patients have median survival of 20 months [5]. ALK+ DLBCL is not associated with viral infections [6]. Our patient did not meet criteria for PBL, PEL, HHV8+ DLBCL arising from MCD or ALK+ DLBCL. Our patient also presented with type B1 lactic acidosis since there was no evidence of hypoperfusion in the setting of malignancy. Type B lactic acidosis is rare in hematologic malignancies and often goes unrecognized, and is a marker of poor prognosis [7,8]. A report showed that with appropriate chemotherapy, a portion of patients could obtain a survival benefit [9]. We present a patient with CD20− DLBCL with diffuse extranodal disease but no discrete masses who presented with type B1 lactic acidosis. Such association is rare and we have not found similar reports in the literature. Our patient did not meet criteria for well-described CD20− DLBCL subtypes, and suggests that the spectrum of CD20− DLBCL continues evolving. Given the poor prognosis of these lymphomas and lack of benefit from anti-CD20 therapy, the development of new therapies is warranted.

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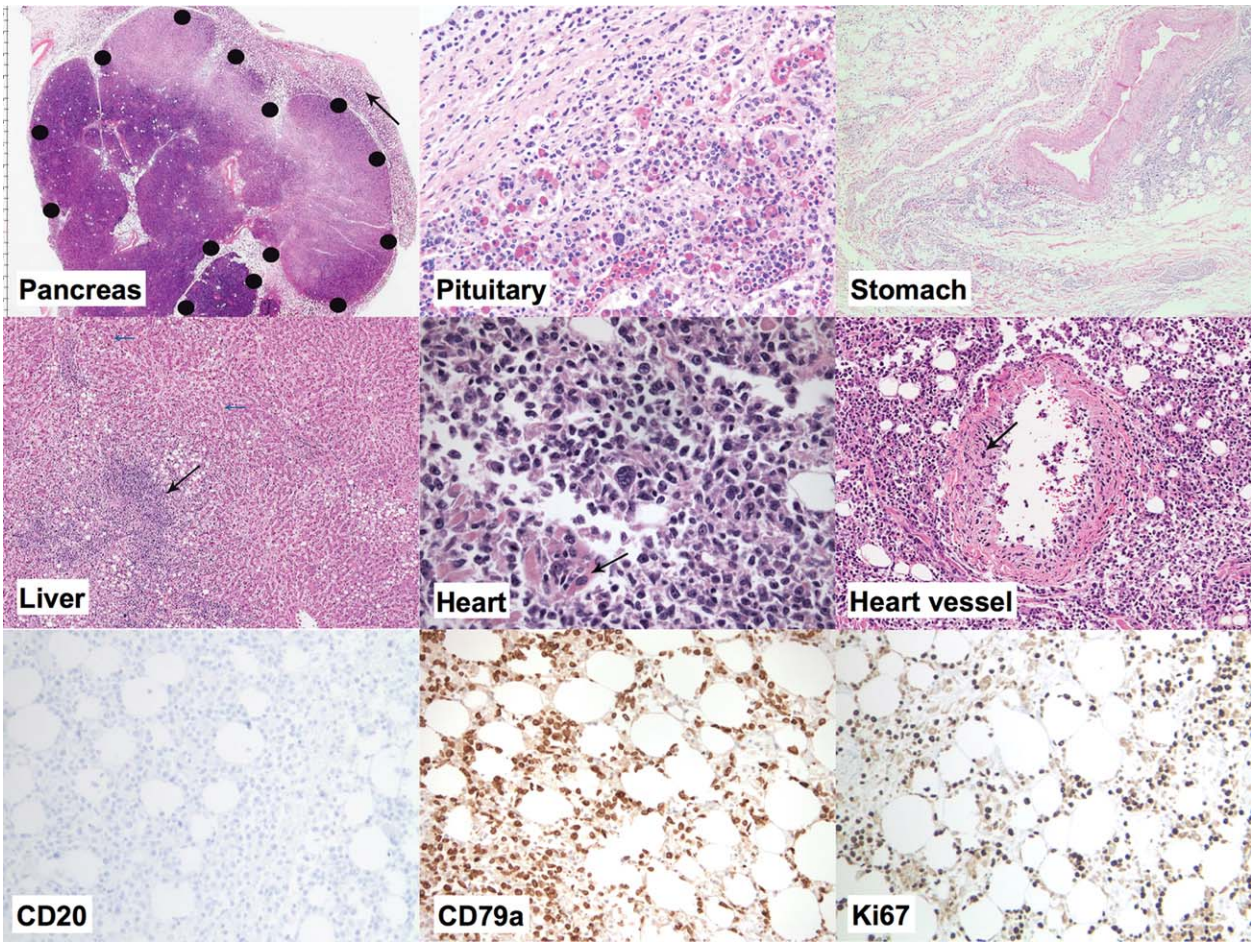

Figure 1. Pancreas is outlined by dots while the arrow shows tumor in the peripancreatic fat. Section of the pituitary shows similar morphology of cells intermixed with cells of the pituitary and surrounding fibrous tissue. Submucosa of the stomach shows infiltration around a vessel. Liver section shows an infiltrate (arrow) with non-neoplastic liver to the right. Tumor cells range in size from medium size to large lymphocytes including multinucleated forms. Heart with tumor infiltrating the right atrium and tumor cells infiltrating a vessel wall (arrow). Immunohistochemical profile shows lack of CD20 expression, positivity for CD79a, and Ki-67 expression in 50% of cells.

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Hepatitis E infection in a patient with transfusion-dependent β thalassemia

To the Editor: The clinical course of transfusion-dependent β thalassemia is frequently complicated by liver disease resulting from infection with hepatitis C virus (HCV), biliary pigment stones, tissue iron overload, and/or iron chelator toxicity. We report an unusual case of acute hepatitis in a patient with β-thalassemia intermedia following infection with hepatitis E virus (HEV). Although HEV is endemic in many developing regions of the world and exhibits high seropositivity rates even in industrialized countries, it has not previously been associated with liver dysfunction in patients with thalassemic conditions.

A 61-year-old man of Mediterranean descent was referred to our practice for the evaluation of anemia and splenomegaly, which had been noted prior to endoscopic retrograde cholangiopancreatography (ERCP) for acute choledocolithiasis. The patient stated a history of easy fatigue and splenic enlargement that dated to early adulthood, but had never been formally evaluated or empirically treated. Physical examination was remarkable for short stature, mild frontal bossing, and painless enlargement of the liver and spleen. Hematological studies revealed hemoglobin 7.5 g/dL, hematocrit 22%, MCV 75 fL, MCH 26 pg, white blood cell count 3.0 × 10^3/μL, and platelets 53 × 10^3/μL; a hemolysate comprising 88.1% HbA, 5.2% HbA2, and 6.7% HbF; and ferritin 1,361 ng/mL. Molecular studies demonstrated double heterozygosity for the c.17_18delCT and c.-151C→T β-globin gene mutations, confirming a diagnosis of β-thalassemia intermedia. Baseline (post-ERCP) liver function tests revealed total bilirubin 6.9 mg/dL, direct bilirubin 3.1 mg/dL, aspartate aminotransferase (AST) 82 U/L, and alanine aminotransferase (ALT) 119 U/L. Liver iron concentration (LIC) was estimated as 3.8 mg/g dry weight by liver R2 MRI (Ferriscan) analysis. Serological tests were positive for HCV antibody and antigen, but negative for surface antibodies against both hepatitis A virus (HAV) and hepatitis B virus (HBV).

The patient initiated regular therapeutic red-cell transfusions and oral deferasirox (Exjade; 20 mg/kg/day) and reported rapid improvements in both fatigue and splenomegaly. Following 4 months of therapy, though, the patient developed non-focal abdominal discomfort, decreased appetite, and worsening jaundice; he denied any new medications (including acetaminophen) or alcohol consumption. Laboratory analyses revealed deteriorating liver function tests that continued to worsen even after deferasirox was discontinued (Fig. 1). Serological tests for HAV, HBV, and HCV were unchanged from baseline; the LIC was modestly elevated at 5.5 mg/g dry weight. Serological studies for HEV were positive for IgM and negative for IgG, consistent with acute infection.

HEV infection typically manifests as a mild and self-limited liver inflammation that rarely progresses to either a fulminant or a chronic condition; contemporary studies cite seroprevalence rates of 6.25% in industrialized countries [1] and higher rates elsewhere [2]. Although commonly transmitted by human fecal–oral contamination, HEV circulates in both domestic animals and in wild game and can be contracted by consuming raw or undercooked meat products [3,4]. HEV can also be transmitted through exposure to infected blood products [5], with donor viremia rates estimated between 0.03% and 1.5%

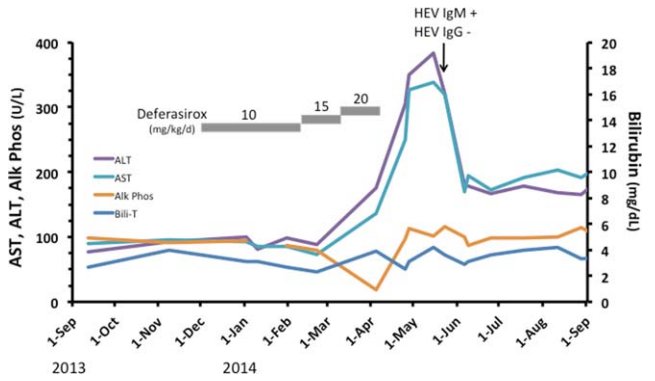

Figure 1. Course of acute Hepatitis E infection in thalassemia. Laboratory values are shown for ALT, AST, and alkaline phosphatase (left axis); and for total bilirubin (right axis). The dose of deferasirox (Exjade) is indicated in mg/kg/day. The results of serological studies for HEV IgM and IgG are illustrated.

in non-endemic and endemic populations, respectively [6–8]. Importantly, nearly half of the recipients of HEV-infected blood will develop clinically relevant infection [7]. The expectation that patients with transfusion-dependent β thalassemia will display high seropositivity rates for HEV, though, is not supported by the literature [9–11], possibly reflecting study groups that are both small in size and that are not stratified for the number of blood-product exposures.

The present case emphasizes the importance of considering HEV as a cause of acute hepatic inflammation in patients with transfusion-dependent β thalassemia whose presentations are inconsistent with other, more common etiologies. The acuity of the inflammatory process in our patient was unlikely to reflect exacerbations in HCV- or iron-related processes; and our suspicions for deferasirox toxicity were proved false when the patient's liver function continued to deteriorate following its discontinuation. We subsequently considered the possibilities that the patient had contracted HEV either through leisure activities (he hunts and consumes wild game) or through HEV-contaminated donor red blood cells, and proved the diagnosis with IgM-positive, IgG-negative HEV serologies. The route of transmission, though, remains a mystery, as neither samples of game, nor blood segments from donor erythrocyte units, were available for post-transfusion viral analyses. Although there is no approved antiviral therapy for HEV infection, accurate diagnosis provided reassurance that the disease would likely be self-limited in this patient and would not require significant long-term changes to a transfusion and chelation strategy that was highly effective in treating his thalassemic condition.

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