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CASE REPORT

Hemolytic anemia due to native valve subacute endocarditis with *Actinomyces israelii* infection

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Key Clinical Message

This case highlights the importance of considering infectious etiology in the management of hemolytic anemia. Hemolytic anemia associated with infectious endocarditis is rare. Actinomyces endocarditis is a rare occurrence and is very challenging to diagnose given the challenges to culture the organism.

Keywords

Anemia, cardiac actinomycosis, hemolysis, infective endocarditis.

Introduction

Hemolytic anemia (HA) is not a common presentation in infectious endocarditis (IE) and has only been reported in very few case reports. Hemolytic anemia associated with hypertrophic obstructive cardiomyopathy (HOCM) with left ventricular outflow tract (LVOT) obstruction was also reported, mostly with co-existing infectious endocarditis. Endocarditis caused by *Actinomyces* and related species is even more rare, occurring in <2% of reported cases [1]. Here we report a case of severe debilitating and transfusion-dependent HA occurring in an immunocompetent patient with hypertrophic obstructive cardiomyopathy (HOCM) with left ventricular outflow tract obstruction (LVOT) whose cause of anemia was only revealed after the discovery of subacute bacterial endocarditis due to *Actinomyces israelii* and a prolonged antibiotic treatment. This case highlights the importance of considering infectious causes in the management of hemolytic anemia especially in a patient who demonstrates cardiac anatomical deformities when persistent surveillance for subacute endocarditis is imperative.

Case Presentation

A 55-year-old female with a past medical history of asthma and chronic hepatitis B on Tenofovir was admitted to the hospital in November 2012 for complaints of malaise, 40 pounds (18 kgs) weight loss, shortness of breath, and cough. The patient denied fever, chills, or confusion. The patient was never admitted to the hospital and never had any surgical procedures. The patient denied tobacco, alcohol, or drug use and denied any significant family history. Vital signs upon presentation were within normal limits. The examination was within normal limits except for pallor. The patient did not have any signs of endocarditis including heart murmurs, Janeway lesions, osler nodules, splinter hemorrhages, and had

good oral hygiene. Initial laboratory findings showed normocytic normochromic anemia with hemoglobin (Hb) of 7.8 gm/dL (Baseline 12.7 gm/dL from July 2012), white blood cell of 7.8 Th/mm^3, and platelet count of 473 Th/mm^3. Renal function was within normal limits. Iron studies showed ferritin 266 ng/mL (12–150 ng/mL), iron 177, and TIBC 332 μg/dL. Reticulocyte percentage was 1.7% (0.5–1.5%). Coagulation studies, vitamin B12, and folate levels were within normal limits. Total and direct bilirubin were elevated at 2.1 and 0.4 mg/dL, respectively. LDH was 363 IU/L (87–201 IU/L), and haptoglobin was <8 mg/dL (30–200 mg/dL). Direct Coombs test was negative. HIV was negative, and quantiferon gold test for TB was negative. Hepatitis B viral load was 83,817 IU/mL (487,815 copies/mL). Parvovirus B19 IgM was negative, and its DNA was not detected. ESR was 54 mm/h (0–29 mm/h), and D-Dimer was 1800 mg/mL (<318 ng/mL). Chest X-ray showed an enlarged heart, obscuring the left hemidiaphragm and the cardiophrenic angles with a small left pleural effusion. Cardiac BNP was 855 pg/mL (<100 pg/mL). An echocardiogram in November 2012 showed normal ejection fraction 65%, moderate-to-severe left ventricular hypertrophy, and obliteration with the chordal systolic anterior motion of the mitral valve, moderate MR, and mild LVOT obstruction. The findings were consistent with hypertrophic obstructive cardiomyopathy with left ventricle outflow tract obstruction. Multiple blood cultures were negative for any growth. A CT of chest, abdomen, and pelvis was significant for marked left atrial and ventricular enlargement, hepatic steatosis, and splenomegaly. Bone marrow biopsy and aspirate showed mature trilineage hematopoiesis, mild plasmacytosis, and increased storage iron. Given the above parameters, the patient was diagnosed with hemolytic anemia with unknown etiology. The patient was discharged home and referred to hematology for further management of her symptomatic anemia in December 2012.

The patient continued to complain of shortness of breath, exertional chest pain, lethargy, and anorexia. Repeat Hb was 7.1 gm/dL and further decreased to 6.7 gm/dL. Upon further work-up, repeat reticulocyte count was <1%, and erythropoietin levels were >150 mIU/mL (4.1–19.5 mU/mL). G6PD was normal, urine hemosiderin was negative, Coombs test was negative, cold agglutinin was negative, and paroxysmal nocturnal hematuria screening was negative. Serum protein electrophoresis was normal. Peripheral smear showed scant schistocytes, but no spherocytes. Patient's lupus screen was mildly positive (mildly positive antinuclear antibody and soluble nucleoprotein antibody positive) and was started on a trial of steroid therapy for 4 weeks in an attempt to potentially treat lupus-induced anemia, which did not improve anemia. By this time, patient was progressively weaker and became transfusion-dependent requiring two units packed red blood cells (PRBC) every 2 weeks. In an attempt to assess whether Tenofovir was the etiology of anemia, it was held for 2 weeks, which did not improve her anemia. Repeat bone marrow biopsy in March 2013 showed a normal cellular marrow for her age along with the left shift of erythroid hyperplasia and reactive plasmacytosis, while another bone marrow in June 2013 showed mildly hypercellular marrow with erythroid hyperplasia and some dyspoiesis. A repeat echocardiogram in May 2013 showed moderate left ventricular diastolic dysfunction, moderate-to-severe aortic and mitral regurgitations, two small (5 mm) echogenic mobile masses on aortic valve suggestive of healed vegetations, and severe pulmonary hypertension. Multiple blood cultures were again negative for any growth. At this point, etiology for patient's anemia remained unclear. The patient was also sent to a transplant center for the evaluation of heart transplant for severe MR, AR regurgitations, and HOCM.

In July 2013, while she was being evaluated for a heart transplant, the patient developed recurrent night sweats and low-grade fever. A transesophageal echocardiogram showed severe left ventricular hypertrophy with an ejection fraction of >75% without any restrictive pattern; severe mitral, aortic regurgitation and small mobile components were visualized on the ventricular surfaces, presumably vegetations. Multiple blood cultures were drawn, and only one of them grew *A. Israelii*. The patient was started on intravenous Penicillin G 3 million units every four hours in July 2013 and was continued for 7 months followed by oral antibiotics for another 4 months. Four months after IV antibiotics were started; patient's Hb was consistently at 9–10 g/dL without transfusion. Hb was 6–7 g/dL chronically prior to antibiotics. Her last blood transfusion was in November 2013. Altogether, she received at least 45 units of PRBC. Her hemoglobin became completely normal in April 2014. At that time, ferritin level was 2983. Patient's symptoms improved, gained weight, appetite improved, and are able to walk 30 min without any symptoms. She did not get any cardiac surgery. She was started phlebotomy in July 2014. In June 2016, ferritin level was 808. In August 2016, MRI of the liver showed hepatomegaly, steatosis, and moderate iron deposition, while the heart had cardiomegaly with global LV hypertrophy, no evidence of iron deposition.

Discussion and Review of Literature

We have illustrated in this report a case of severe debilitating anemia in a patient with native valve subacute bacterial endocarditis with *A. israelii* infection, who has

severe MR and AR, as well as outflow obstruction consistent with HOCM. Anemia completely resolved after appropriate treatment for infectious endocarditis. The etiology of anemia in this case is most likely due to hemolysis based on the laboratory findings of elevation of LDH, decreased haptoglobin level, and the slight increase in indirect bilirubin. The mechanism of hemolysis is more likely to be mechanical sheering, as schistocytes were scant; less likely autoimmune hemolytic anemia as the Coombs tests was consistently negative and the patient did not respond to steroid treatment, which is a standard for autoimmune hemolytic anemia. Although hemolytic laboratory characteristics were met, repeat reticulocyte counts were low, which cast doubt in the consideration of additional mechanisms of anemia. This observation suggests that there could be a component of bone marrow suppression due to the bacteria or its toxins. Another potential explanation would be intramedullary ineffective hematopoiesis. Although the first bone marrow biopsy was completely unrevealing, the second and third bone marrow biopsy both showed erythroid hyperplasia, which is consistent with hemolysis. It seems that there is a good causal relationship of anemia due to *A. israelii* infection in the form of endocarditis and native valve vegetation.

Bacterial endocarditis associated with anemia is a rare presentation and has only been reported in a few case studies, and the mechanisms were postulated to be hemolytic anemia with normochromic and normocytic cells. Both mechanical hemolysis and autoimmune hemolysis have been described [2–4]. Hsuan-Li et al. reviewed six cases of hemolytic anemia secondary to endocarditis; in all the cases, there was the presence of fragmented erythrocytes suggestive of intravascular hemolysis [5]. Interestingly, multiple cases also demonstrated the co-existing immune-mediated mechanism, evidenced by the presence of spherocytes, splenomegaly, and a positive direct Coombs test [5]. It was hypothesized that vegetation on the valves can apply shearing stress on RBC leading to fragmentation similar to valve-related mechanical hemolytic anemia particularly prosthetic mitral valve regurgitation [5–7]. The infectious microorganisms may also cause the production of anti-erythrocyte antibodies by cross-reaction with erythrocyte antigens, or by modification of the antigenicity of erythrocyte antigens or by unmasking antigens that are not normally available [5]. Our case presentation was similar albeit with even more scant evidence.

Four cases of mechanical hemolytic anemia in patients with HOCM have been reported, and three of those cases also had infectious endocarditis in the presence of LVOT [8], and only one case demonstrated hemolytic anemia without endocarditis. In the case of HOCM with LVOT without endocarditis, there was marked obstruction to LVOT, and anemia improved from Hb 5.1 to 11.4 gm/dL after medical treatment with a beta blocker and a class Ia anti-arrhythmic medicine cibenzoline [8]. The fact that our patient recovered to have completely normal hemoglobin level after antibiotics treatment indicated that the etiology of her hemolytic anemia was more likely due to the sheer stress from the vegetation, or bone marrow suppression, rather than from the LVOT.

Infectious endocarditis is an uncommon complication of HOCM (1.4 per 1000 person-years) [9], the incidence is greater than community-acquired native-valve IE (1.7–6.2 per 100,000 person-years) [10], and its morbidity and mortality risk is high. The literature on IE in HCM is scant, but all cases have occurred when the left ventricular outflow is obstructed under resting conditions (≥30 mmHg) and had atrial dilatation (>50 mm) [9]. In our case, the flow velocity through LVOT was considered to be only mild.

Actinomycosis, originally described in 1878 by Israel, is non-spore-forming, strict, or facultative anaerobes with a variable cellular morphology, ranging from diphtheroidal to coccoid filaments. They are normal constituents of the oral flora within gingival crevices and tonsillar crypts and are particularly prevalent in periodontal pockets, dental plaques, and on carious teeth. Actinomycotic infections are commonly limited to the cervicofacial (50%), pulmonary (15%), and intra-abdominal (20%) areas [11]. Cardiac actinomycosis is relatively rare occurring in less than 2% of reported cases [1]. Endocarditis due to actinomycosis could be insidious, and 50% of the patients may not have any symptoms at the presentation based a large review of 181 cases [1]. Risk factors are noted to be extensive caries and underlying valvular heart disease, while one-third of the patients were not having any identifiable risk factors [12]. So far, only thirty cases of cardiac actinomycosis have been reported in the literature [13]. Although Actinomyces rarely causes endocarditis, there could be an additional component for the rarity of reported cases like difficulty in identifying the organism as like in one of the case reports where *A. israelii* endocarditis was misidentified as "Cornyebacteria Diptheroids" [14].

This case represents a rare occurrence of actinomycosis endocarditis in a patient with HOCM who developed severe anemia associated with the infection. In addition to be consistent with what was reported in the literature of the association of endocarditis with hemolytic anemia, this case also suggested bone marrow suppression. It is also the first case of association between actinomycosis and severe anemia. This case dragged for months after months without clear diagnosis, which highlights the importance of considering infectious causes for anemia in a patient with severe anemia of uncertain etiology after standard work-up. In a patient who demonstrates cardiac anatomical deformities, persistent surveillance for subacute endocarditis is also key and imperative.

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Authorship

ST: performed case review, data collection, and manuscript writing; YX: performed case selection and manuscript writing.

Conflict of Interest

None declared.

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