

CASE REPORTS

Disseminated *Mycobacterium avium* infection in a young woman with sickle cell disease and iatrogenic iron overload

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ABSTRACT

A 29-year-old woman with known sickle cell disease (SCD) and iatrogenic iron overload presented to the emergency department with a recurrent pain crisis and fever. Blood cultures obtained at a recent prior admission for the same complaints grew *M. avium*. Bone marrow biopsy revealed non-caseating granulomas, but stains for mycobacteria and fungi were negative. Disseminated non-tuberculous mycobacterial infections (NTMIs) occur almost exclusively in immunosuppressed patients. SCD is not considered a risk factor for the development of disseminated NTMIs, making diagnosis challenging in this population. However, a number of case reports describing disseminated NTMIs in patients with SCD have been published. This case adds to the current literature, suggesting SCD with iatrogenic iron overload is a possible risk factor for disseminated NTMIs. Potential mechanisms for this increased risk include 1) functional asplenia, 2) iatrogenic iron overload, 3) chronic indwelling central venous catheters, and 4) hydroxyurea use. Further investigation is required to describe the strength and mechanism of the relationship between SCD and disseminated NTMIs.

Key Words: Sickle cell disease, Iron overload, Disseminated mycobacterium avium, Immunocompromised state

1. INTRODUCTION

Sickle cell disease (SCD) is caused by a point mutation in the gene encoding the β chain of the hemoglobin molecule. Patients with homozygous mutations produce abnormal hemoglobin which polymerizes and causes a rigid deformity of the red blood cell. Deformed cells cannot efficiently flow through small vascular channels leading to infarction of tissues. Sickle cell disease is characterized by frequent infarction of tissues including brain, lung, liver, spleen, kidney, and bone marrow; the latter of which is responsible for

acute pain crises. Hemolysis of deformed intravascular erythrocytes results in anemia requiring frequent transfusions, ultimately leading to iatrogenic iron overload.^[1]

Disseminated non-tuberculous mycobacterial infections (NTMIs) were first described in 1907.^[2] The most common culprit is mycobacterium-avium complex.^[2] Disseminated NTMIs occur almost exclusively as opportunistic infections in the severely immunosuppressed, such as patients with acquired immunodeficiency syndrome (AIDS), primary im-

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munodeficiency disease, and those taking immunosuppressive medications.^[3] The interleukin 12 – interferon γ (IL12-IFN γ) pathway is critical to mycobacterial immunity. Primary and acquired immunodeficiencies involving the IL12-IFN γ pathway have been associated with disseminated NTMIs.^[4] SCD, however, is not considered a risk factor for the development of disseminated NTMIs; leading to low physician suspicion and making diagnosis difficult in this population.^[3] A handful of case reports describing disseminated NTMIs in patients with SCD were published between 2006 and 2017.^[5–9] This report adds to the current literature, suggesting that SCD with iatrogenic iron overload is a possible risk factor for disseminated NTMIs.

2. CASE PRESENTATION

A 29-year-old African American woman with known SCD (HbSS) presented to the emergency department with subjective fever, progressive weakness, dark urine, shortness of breath, and generalized pain for three weeks. She denied cough, chills, weight loss, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, dysuria, or any other symptoms. Her medical history included known SCD, complicated by iatrogenic iron overload. A chronic indwelling central venous catheter (CICVC) had been placed in 2016. A systolic murmur had been previously documented without evidence of structural abnormalities or endocarditis. One month prior to this presentation, the patient had been admitted to our hospital for sickle cell pain crisis and fever of unknown origin. Infectious work-up was negative at the time. Her home medications include cholecalciferol 2000 units daily, hydroxyurea (HU) 500 mg twice daily, folic acid 1mg daily, and hydrocodone-acetaminophen 10-325 mg as needed for pain.

Vital signs revealed tachycardia (107 beats per minute) and hypoxia (SpO₂ 85% on room air), requiring 4L O₂ via nasal cannula. Her blood pressure and temperature were normal. She was chronically ill appearing, thin, and in mild distress due to generalized pain. Conjunctival icterus and pallor were present. Cardiac exam revealed a regular rhythm and a faint systolic murmur. A CICVC was present in the chest wall. The rest of the physical examination was unremarkable.

2.1 Hospital Course

Pertinent laboratory tests on admission included total white blood cell count of 14,110/uL, absolute neutrophil count of 8,920/uL, hemoglobin 4.6 g/dL, reticulocyte count of 17.3%, and ferritin greater than 33,500 ng/mL. Acid fast bacilli (AFB) blood culture from the recent prior admission had turned positive for pan-susceptible *M. avium* four days prior to this admission.

The patient developed several episodes of fever during her hospitalization. Repeat blood and sputum cultures also grew *M. avium*. Human immunodeficiency virus (HIV) test was negative. Autoantibodies to interferon γ were absent. The Invitae primary immunodeficiency panel revealed variants of uncertain significance, but no mutations associated with immunodeficiency.

Computed tomography (CT) of the chest showed diffuse rounded peripheral and irregular ground-glass infiltrates predominantly in the lower lobes (Figure 1a). Peripheral blood smear showed microcytic and hypochromic red blood cells containing iron deposits (see Figure 1b). Bone marrow biopsy revealed markedly increased iron storage and frequent non-caseating granulomas (see Figure 1c-d). Bone-marrow staining and culture was negative for organisms including AFB.

2.2 Treatment

The patient was started on azithromycin, ethambutol, and rifampin. Her hospital course was complicated by continued hemolytic anemia and difficulty obtaining U-negative blood. She was discharged in stable condition on hospital day #20. The patient has subsequently been re-hospitalized for high fevers. AFB blood cultures persistently grew *M. avium* despite 3 months of appropriate treatment.

3. DISCUSSION

Disseminated NTMIs are challenging to diagnose, particularly in the absence of known immune dysfunction such as AIDS, IL12-IFN γ pathway dysfunction, or immunosuppressive medications. A review of 36 non-HIV cases showed the average time to diagnosis was 5.3 months.^[3] In our patient, the time to diagnosis was 10 weeks. Given the high mortality associated with this disease, high clinical suspicion is required to make a timely diagnosis and administer life-saving antimicrobial agents.^[3,4] A handful of case reports describing disseminated NTMIs in patients with SCD have been published.^[6–10] Our report adds to the current literature, suggesting that SCD with iatrogenic iron overload may be a risk factor for disseminated NTMIs. The mechanism of this risk is unclear. Some possible factors that may increase SCD patients' risk for mycobacterial infection include: functional asplenia, iatrogenic iron overload, CICVCs, HU use.

The spleen is the largest lymphoid organ in the body. It has numerous important functions including the regulation of inflammation, filtration and clearance from the blood, adaptive immunity, and innate immunity.^[11] As a result, asplenic patients suffer from more frequent and severe infections with encapsulated organisms and intra-erythrocytic parasites.^[11,12] SCD strongly affect the spleen both acutely

in the form of acute splenic sequestration crisis, and chronically in the form of progressive vasoocclusion and infarction.^[13,14] As a result, by age 6-8 years children with SCD have a non-functioning spleen.^[15] No association between asplenia and mycobacterial infections has been documented.

Iron is an essential trace element, and its sequestration is a key part of the innate immune system. In healthy patients, iron is permanently sequestered from mucosal surfaces, non-

transferrin bound iron is strongly regulated, and extracellular fluid is depleted of iron during inflammation or infection. These mechanisms inhibit microbial growth by limiting the availability of the essential element iron.^[16] Correspondingly, patients with iron overload are at increased risk of infection with a variety of organisms including *V. vulnificus*, *Y. enterocolitica*, *Y. pseudotuberculosis*, *L. monocytogenes*, and HIV.^[17-20]

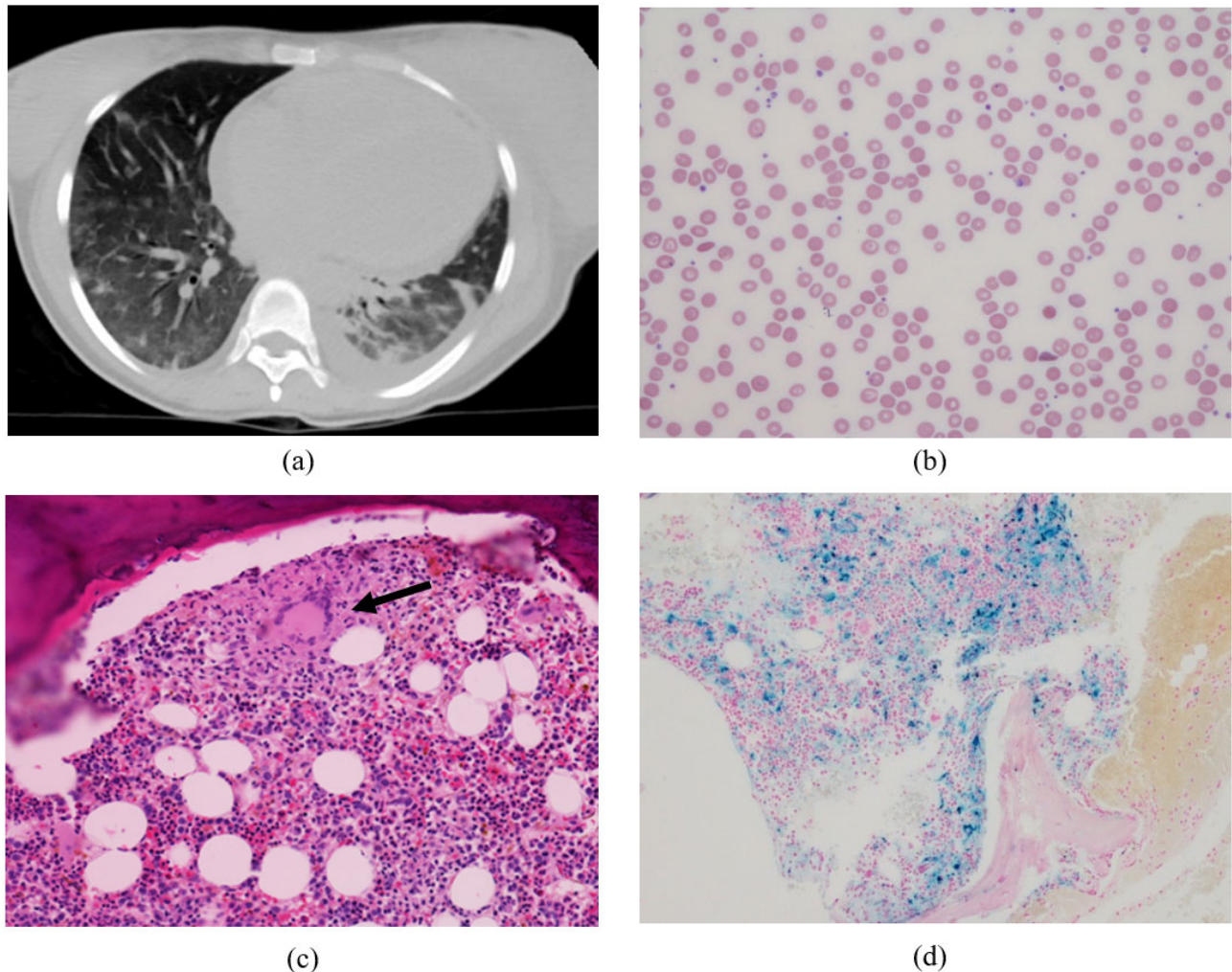


Figure 1. (a) CT image showing diffuse, rounded, peripheral and irregular ground-glass infiltrates predominantly in the lower lobes. (b) Wright-Giemsa stained peripheral blood smear showing microcytic and hypochromic red blood cells and target cells. Magnification $\times 400$. (c) Bone marrow biopsy showing non-caseating granuloma with Langerhan's type multinucleated giant cell (arrow). Magnification $\times 200$. (d) Prussian blue staining of bone marrow aspirate shows iron deposition.

Regarding mycobacterial infections specifically, a post-hoc analysis of 714 individuals from southern Africa showed that those with severe iron overload were 17 times more likely to die from tuberculosis.^[21] The mechanism of iron overload in the aforementioned study was increased dietary ingestion, and the prevalence of sickle cell disease was not reported. It

remains to be seen if these results can be generalized to other mycobacterial infections.

CICVCs are used in SCD to facilitate chronic transfusions and acute management. CICVCs increase the risk of blood stream infections (BSIs).^[22] This risk seems to be magnified

in SCD patients. In a study of 47 SCD patients, CICVCs were the source of BSIs in 41% of patients, compared with 11% in the general population.^[22] Regarding mycobacterial infections specifically, a small study of 16 patients suggested that CICVCs increase the risk for blood-stream NTMIs.^[10] The same study also suggested that the presence of SCD was a risk factor for NTMIs independent of CICVCs.^[10]

HU is used in SCD because of its ability to increase fetal hemoglobin levels by incompletely understood mechanisms.^[23] HU is a cytotoxic drug that can rarely cause myelosuppression. However, there is no evidence of increased infection risk or clinical immunosuppression with long-term use.^[23–25]

Other mechanisms by which SCD patients may be susceptible to infections have been described, though the clinical significance of these findings is unclear.^[26–29] Further investigation is required to describe the exact strength and mechanism of the relationship between SCD and disseminated NTMIs.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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