HIV-associated Hodgkin Lymphoma with a Granulomatous Bone Marrow Biopsy: A Case Report

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Abstract The incidence of HIV-associated Hodgkin lymphoma has risen during the era of combined antiretroviral therapy (ART) despite the proven, protective effects of ART as treatment for HIV. The clinical presentation of Hodgkin Lymphoma may also resemble disseminated mycobacterial infection - in symptoms, laboratory findings, and even bone marrow biopsy. This is a case report of a patient with HIV who was suspected to have disseminated mycobacterial infection after a first bone marrow biopsy showed granulomatous inflammation and was later found to have HIV-associated Hodgkin lymphoma on a repeat biopsy.

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1. Introduction

A bone marrow biopsy revealing granulomas is not a common finding; estimated incidence ranges from 0.2 to 3.3% of all biopsies performed [1]. Such a finding can be attributed to several different diseases of the marrow, including infection (most common), sarcoidosis, malignancy, and therapy-induced granulomas. These diseases often have overlapping symptoms and presentations thus requiring a high degree of suspicion and consideration for the other etiologies amongst the differential diagnosis. Fever and anemia are the most common symptoms accompanying a bone marrow biopsy with granulomas.

Hodgkin lymphoma is a malignancy of lymphocytes that is characterized by a mixture of inflammatory cells that often include epithelioid histiocytes. A cluster of histiocytes have the potential to form necrotizing non-caseating granulomas. While several studies have shown that up to nine percent of Hodgkin lymphoma can be accompanied by non-caseating granulomas, this finding can make for a difficult diagnosis, especially when there are overlapping symptoms with mycobacterial infection and sarcoidosis [2]. Moreover, a patient with immunosuppression can add another element of complexity, prompting the question of whether the laboratory findings are part of the syndrome or merely a component of the host's underlying disease. Here, we present a case of a patient with human immunodeficiency virus, whose bone marrow biopsy revealed granulomas, with repeat biopsy showing HIV-associated Hodgkin lymphoma.

2. Case Presentation

A 46-year-old male presented to the emergency department with fever, shortness of breath, myalgias, and general malaise for three days. He had a past medical history of HIV (current CD4 count 125/33%, viral load 107), end-stage renal disease on hemodialysis, and was admitted two months prior for hypoxic respiratory failure secondary to COVID-19 which was treated with five days of hydroxychloroquine and azithromycin as part of a clinical trial. His home medications included dolutegravir/rilpivirine, darunavir/cobicistat, atovaquone, and mirtazapine. He emigrated to the United States nine years prior, had worked for a healthcare facility in his native country, and was working as a chicken farmer in Maryland USA until he became ill five months prior to admission. He has no toxic habits, reported to be heterosexual and had one child.

Vital signs upon presentation to the hospital were as follows: temperature 103 F, blood pressure 153/77 mmHg, heart rate 115 bpm, respiratory rate of 24, oxygen saturation 96% on room air. On physical exam, he was alert and oriented, cachectic, had scleral icterus, normal heart sounds, and lungs clear to auscultation. His laboratory findings were notable for pancytopenia (WBC 2.3, Hb/Hct 3.7/14, Plt 70), elevated transaminases

(AST/ALT 136/186), hyperbilirubinemia (total bilirubin 3.3, direct bilirubin 2), and a procalcitonin of 65.5. The calculated reticulocyte index (0.96) indicated a hypo-proliferative marrow. CT of the head was negative for acute pathology. CT of the chest, abdomen, and pelvis showed bilateral ground glass opacities (consistent with history of COVID-19), pleural effusions, pulmonary edema, hepatic venous congestion, ascites, and hepatosplenomegaly consistent with fluid overload. The patient was admitted for sepsis, multifocal pneumonia, and severe pancytopenia in an immunocompromised host. He was started on vancomycin, piperacillin-tazobactam, azithromycin, and atovaquone for broad-spectrum antibiotic coverage.

An extensive infectious workup was negative for COVID-19 (SARS-COV2 PCR negative, IgG positive) hepatitis A (IgM negative, IgG positive), hepatitis B (viral load), hepatitis C (viral load), syphilis (RPR), tuberculosis (QuantiFERON gold), cryptococcus (serum antigen), aspergillus (antigen), histoplasma (antibody and urine antigen), HSV (DNA-PCR), and CMV (antibody). ACE level was normal. Cerebrospinal fluid was negative for organisms and daily blood cultures showed no growth.

The bilirubin continued to climb (peak of 24) with concern for drug-induced liver injury and antiretrovirals were stopped, later to be restarted on a new regimen of tenofovir disoproxil fumarate, emtricitabine, and dolutegravir. A liver biopsy was performed and showed poorly formed, mainly portal granulomas that were negative for mycobacteria on acid-fast stain. A bone marrow biopsy was performed and showed that the marrow was hypercellular and replaced by granulomatous inflammation (Figure 1). Stains for acid-fast bacilli were also negative. His thrombocytopenia, anemia, elevated LDH, decreased haptoglobin, schistocytes on blood smear, and low ADAMTS13 level raised concern for thrombotic thrombocytopenic purpura (TTP) and three days of exchange transfusion were performed.

The patient was followed by multiple services (hepatology, hematology/oncology, infectious disease, and cardiology) and the consensus working diagnosis was disseminated mycobacterial infection; he was started on rifabutin (later switched to rifampin due to worsening cholestatic pattern of liver injury), isoniazid, pyrazinamide, ethambutol, levofloxacin, and azithromycin. Liver function initially normalized with the new regimen but then worsened. Persistent fevers, pancytopenia, and imaging on CT scan showing worsening ascites and pleural effusions led to a suspicion of immune reconstitution inflammatory syndrome (IRIS). The pleural fluid was exudative on thoracentesis and had an adenosine deaminase level of 13 U/L (tuberculosis mean 92.1 U/L, typically above 45 U/L; lymphoma mean 64.3 U/L). The anti-mycobacterial agents were all stopped, and prednisone was started along with micafungin for empiric fungal coverage.
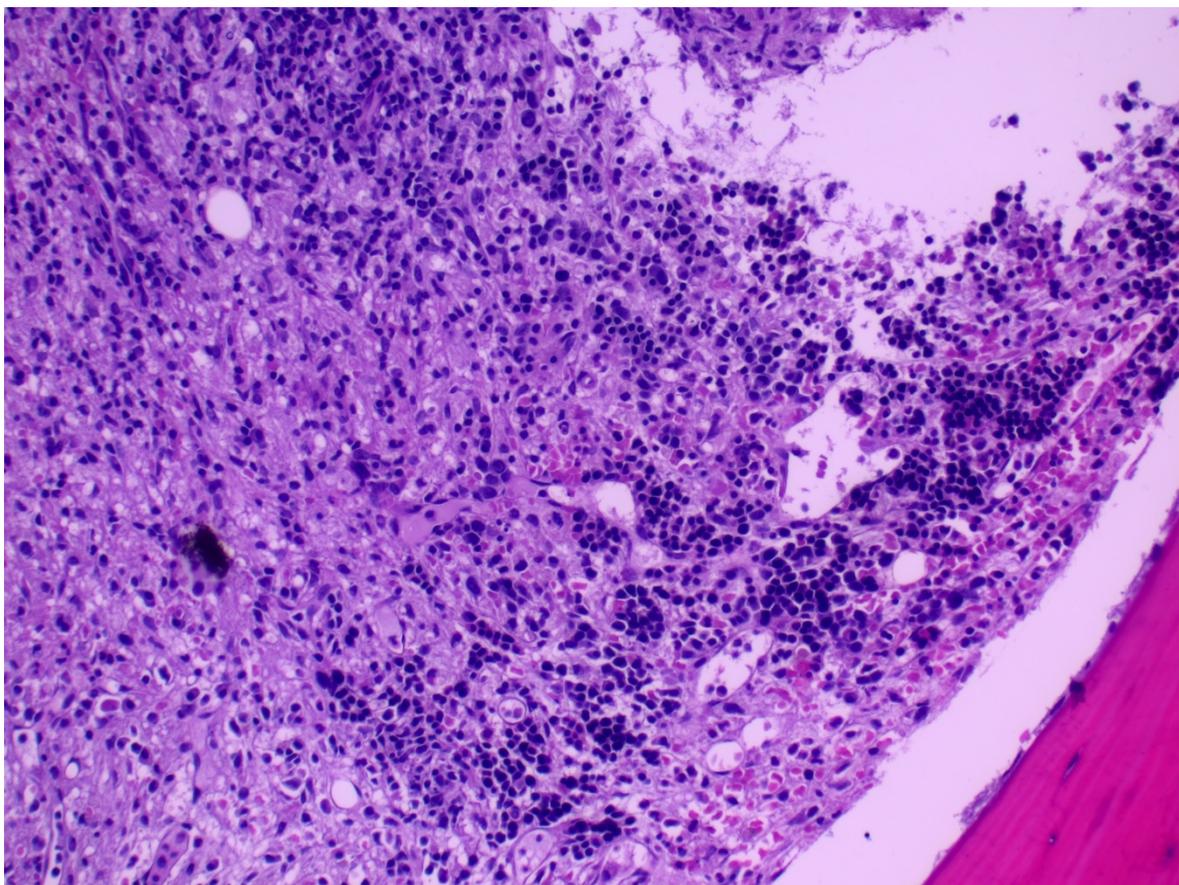
Figure 1 H&E x200: bone marrow biopsy showing subtotal replaced of the cellularity by sheets of granulomatous inflammation (consists of pink granular areas interspersed with small lymphoid cells). Only small residual pockets of trilinear hematopiesis are present. Few early erythroid and myeloid cells are identified.
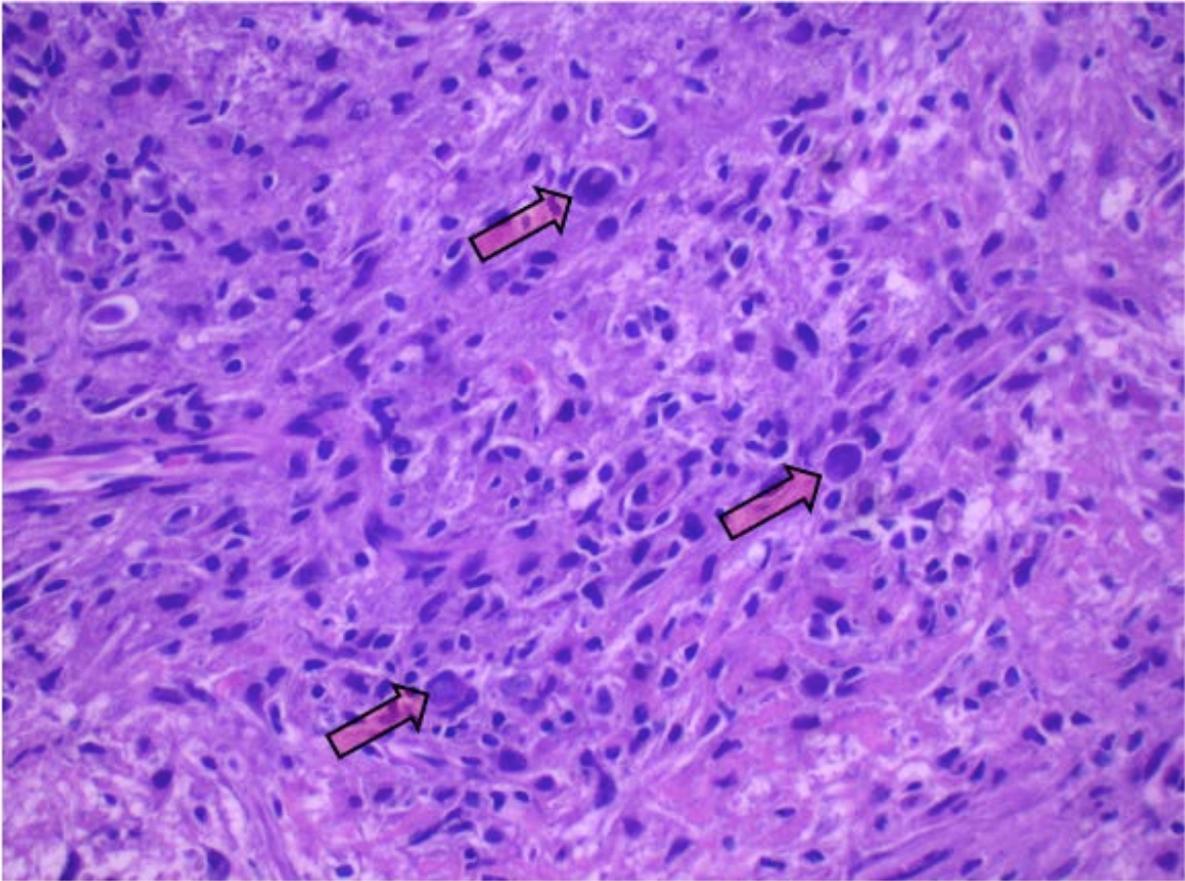
Figure 2 H&E x200: bone marrow biopsy showing extensive fibrosis with infiltrative small lymphocytes, plasma cells, rare eosinophils and rare large atypical cells (black arrows). The background shows small lymphocytes (mostly T cells according to flow cytometric analysis).
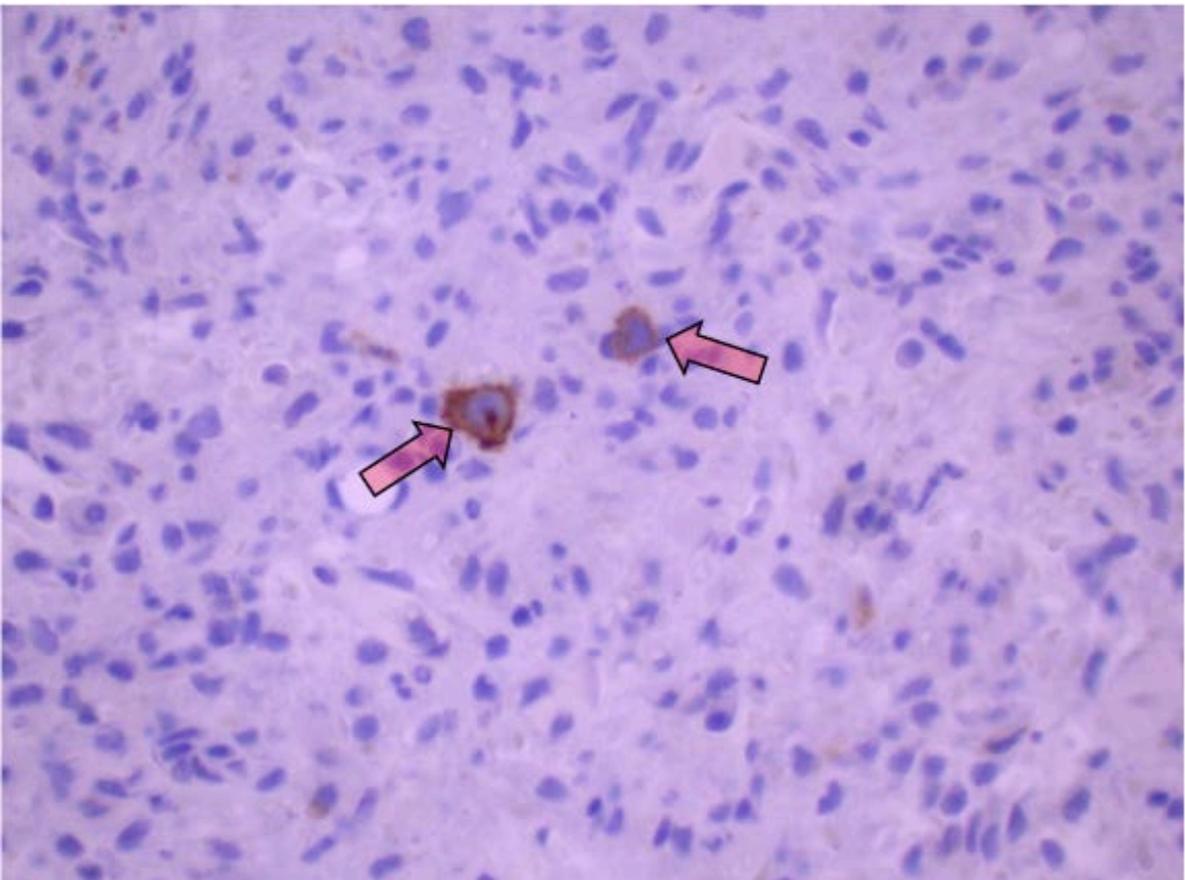
Figure 3 CD30 x 400: bone marrow immunohistochemical staining of CD30 showing membrane and paranuclear (golgi zone) of the large atypical cells (black arrows).
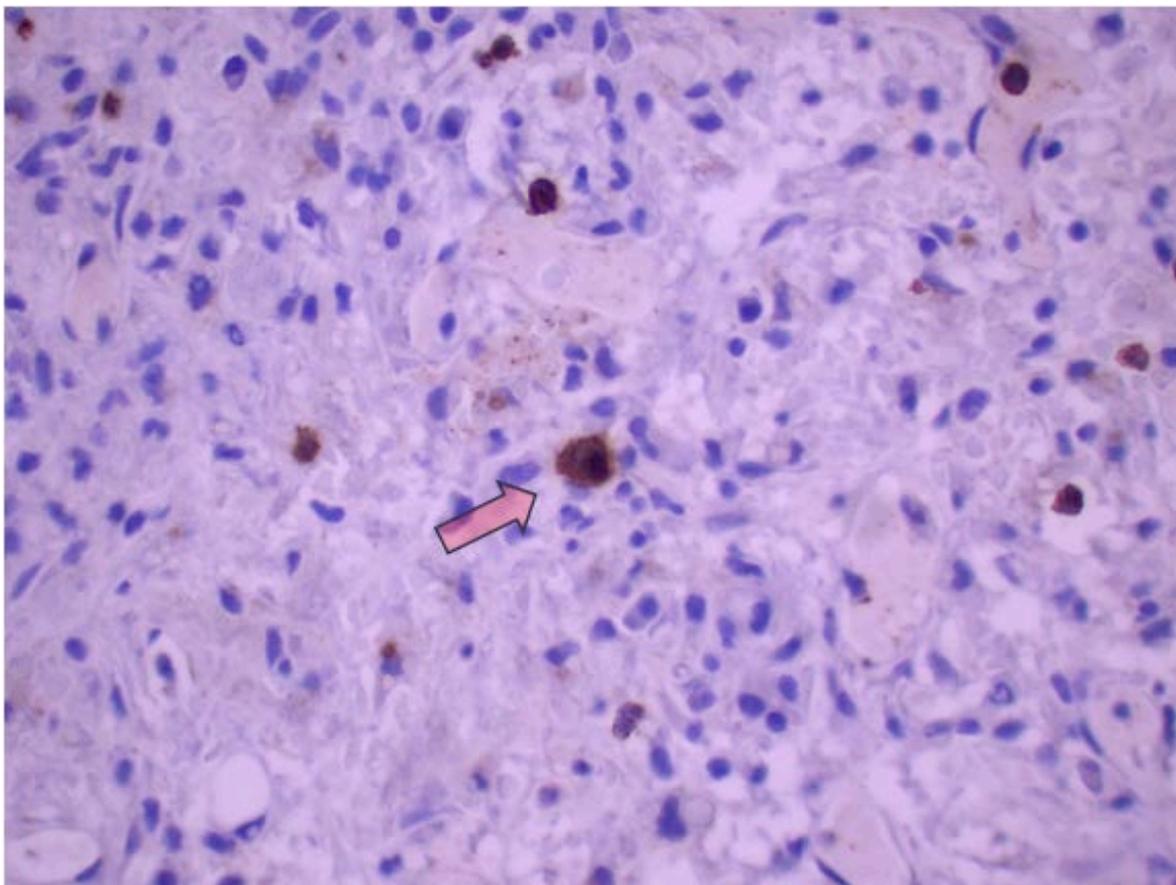
Figure 4 CD15 x 400: bone marrow immunohistochemical staining of CD15 showing membrane and paranuclear (Golgi zone) positivity in the large atypical cells (black arrow).

A second bone marrow biopsy was performed; it showed scattered large CD30+ and CD15+ cells in a fibrous background with small lymphocytes and plasma cells consistent with a diagnosis of Hodgkin lymphoma (Figure 2 - Figure 4). He developed neutropenic fever while waiting to initiate chemotherapy and was given vancomycin and cefepime for four days with negative blood cultures. Six cycles of chemotherapy with adriamycin, vinblastine, and dacarbazine were initiated. The CBC after the first cycle markedly improved with a WBC 11.52, Hb/Hct 6.9/21.2, Plt 23. Serial echocardiograms performed after two cycles of chemotherapy revealed a decline in left ventricular ejection fraction to 35 percent. The patient was subsequently switched to brentuximab vedontin and nivolumab as a new regimen in the setting of chemotherapy-induced cardiotoxicity.

3. Discussion

Hodgkin lymphoma is a hematopoietic neoplasm that arises from germinal center or post-germinal center B-cells. The tumor histopathology is composed of characteristic multinucleated giant cells or large mononuclear cells in an inflammatory background referred to as Hodgkin and Reed-Sternberg cells [11].

The disease is typically curable regardless of the stage at presentation. Treatment involves the use of multiple chemotherapy agents and/or localized radiation for most patients and high-intensity treatment for a minority of patients who are not cured by initial chemo-radiotherapy.

However, it is important to recognize that standard therapeutic approaches to HL should be modified for subpopulations, including immune-compromised HIV patients [3].

Up to nine percent of cases of Hodgkin lymphoma may have granuloma formation [3]. Epithelioid cell granulomas are a focal collection of inflammatory giant cells, macrophages, mononuclear cells and fibroblasts with or without caseous necrosis in the center. These granulomas can form at the primary site of tumor, at distant organs or draining lymph nodes (without evidence of malignancy) [13,14], or in advance of the onset of the primary malignancy. Multiple possible mechanisms have been postulated for granuloma formation in the setting of malignancy. Common causes include tumor-related sarcoid reaction or sarcoid-like lymphadenopathy; associated infections caused by bacteria (such as mycobacteria), fungi and protozoa; and a foreign body reaction due to tumor necrosis and sarcoidosis [12]. However, in the majority of cases no definite cause is identified, subsequently leading to difficulty in treatment.

The era of combined antiretroviral therapy has led to a shift in the landscape of malignancies associated with HIV and AIDS. AIDS-defining cancers like Kaposi sarcoma and non-Hodgkin lymphoma have seen an overall decrease in incidence, while the incidence of Hodgkin lymphoma, a non-AIDS-defining cancer, has risen despite the overall highly beneficial effects of ART [1]. The risk of Hodgkin lymphoma is estimated to be five to ten times higher than the risk for the general population. Despite the rise in cases, HIV-associated Hodgkin lymphoma can still

be a difficult diagnosis to make, especially when the clinical presentation overlaps with that of a disseminated mycobacterial infection.

HIV-associated Hodgkin lymphoma typically presents at a median age in the mid-30s after a median time from HIV diagnosis of approximately 7.5 years [6]. About one quarter of patients will have a prior AIDS diagnosis at the time their cancer is diagnosed, and most will be diagnosed while receiving ART. The median CD4 count at diagnosis of Hodgkin lymphoma is approximately 240 cells/µL. The most common histology is mixed cellularity in about half of patients, followed by nodal sclerotic in one quarter and lymphocyte depleted in one tenth [6]. Hodgkin lymphoma with formation of epithelioid cell granuloma is much less common but has been the subject of several large case series [1].

People living with HIV are at an increased risk of developing HL; this risk remains elevated despite modern antiretroviral therapy. However, patients with a CD4 count greater than 100 and on combined ART have much higher rates of remission and improved overall survival compared with patients with untreated HIV [1]. In contrast to Hodgkin lymphoma in the general population, HIV-associated Hodgkin lymphoma differs in that it is nearly always associated with Epstein-Barr virus and more often presents with higher risk features of advanced disease, "B" symptoms, and extra-nodal involvement [1]. The underlying mechanism of granuloma formation in HL remains unknown. Recent studies suggest a few pathophysiological mechanisms including: an inflammatory response by T-helper cells to tumor antigens; [1] a delayed hypersensitivity reaction related to cytokines and/or byproducts of tumor cell obliteration; [1] and the uninterrupted stimulation of tumor antigen, which can result in tissue fibrosis and ultimately granuloma development. Notably, there is conflicting opinion whether the local immune response with granuloma formation represents a more favorable or worse prognosis [1,2].

This case report is an illustration of both the complexity of diagnosing Hodgkin lymphoma with a granulomatous bone marrow biopsy and overcoming anchoring bias when it comes to diagnosis and treatment in the setting of an immunocompromised host. The consensus etiology for nearly two months was disseminated mycobacterial infection. Persistent fevers, worsening liver function, and continued pancytopenia raised questions about the many empiric treatments including drug-induced liver injury, immune reconstitution inflammatory syndrome, and resistant pathogens. Revisiting the consensus diagnosis and surmounting one's own cognitive dissonance can be the key to revealing the true causal pathology.

Acknowledgments

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