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[Case Report] Challenging Detection of Latent Tuberculosis in a Patient Undergoing High-Dose Corticosteroid Therapy for Acute Hemolytic Anemia and Rhupus Arthropathy

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Acute autoimmune hemolytic anemia requires rapid stabilization, typically through the administration of high-dose corticosteroids. However, it is important to consider reactivation of latent infection and how immune suppression can interfere with molecular screening tools. In this case report, we present a patient with Rheumatoid Arthritis/Systemic Lupus Erythematosus experiencing severe autoimmune hemolytic anemia complicated by an unknown latent tuberculosis infection.

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Introduction

Activated tuberculosis in the setting of autoimmune disease often results in a clinical presentation that can be challenging to assess without a detailed patient history. Frequently, tuberculosis may cause auto-antibodies that overlap with autoimmune processes, whereas immunosuppression may cause false negative results for common Tb screenings. In this case presentation, we detail a challenging diagnosis of activated tuberculosis in the setting of an acute flare of

Rheumatoid Arthritis/Systemic Lupus Erythematosus Overlap Syndrome.

Case Presentation

A 53-year-old female with a long history (30+ years) of Rheumatoid Arthritis/Systemic Lupus Erythematosus (RA/SLE) Overlap Syndrome presented to her primary care provider with complaints of fatigue, dyspnea, weakness, and palpitations. Further history indicated significant weight loss (approximately 10 kg) over the last several months. She did not have cough, fevers, or chills. After performing laboratory examination, it was discovered the patient had critically low hemoglobin with suspicion for a hemolytic process (Initial Labs: Table 1). This was consistent with the patient's previous RA/SLE flares, with multiple hemolysis episodes resulting in hemoglobin levels of 4.0 mg/dl or lower. She was previously well-controlled prior to presentation, and was fully compliant with prednisone, methotrexate, and folic acid..

Table 1. Complete blood count

	Reference Range	Hosp. Day 0	Hosp. Day 2
WBC x10^3	4.30 - 11.10 10*3/µL	7.30	4.99
RBC x10^6	3.93 - 5.25 10*6/µL	1.90 (L)	1.64 (L)
HGB	11.6 - 15.0 g/dL	6.0 (L)	5.3 (L)
HCT	35.7 - 45.2 %	20.0 (L)	16.4 (L)
MCV	80.6 - 95.5 fL	105.3 (H)	100.0 (H)
MCH	25.9 - 32.8 pg	31.6	32.3
MCHC	31.6 - 35.1 g/dL	30.0 (L)	32.3
RDW-SD	39.0 - 49.9 fL	69.3 (H)	66.4 (H)
RDW-CV	12.0 - 15.5 %	19.7 (H)	20.2 (H)
PLT x10^3	166 - 358 10*3/µL	307	227
MPV	9.5 - 12.9 fL	9.0 (L)	8.8 (L)
NRBC /100 WBC	0.0 - 10.0 /100 WBCs	0.0	0.0
NRBC x10^3	Latest Units: 10*3/µL	<0.01	<0.01

The emergency department admitted this patient for further evaluation and management in the hospital, suspecting RA/SLE flare or occult malignancy.

Hospital Course

On presentation, the patient was found to have incompatible blood due to warm autoantibodies, precluding transfusion. On the second day of hospitalization, hemoglobin decreased to a nadir of 5.3 mg/dl. Rheumatological workup (Table 2) showed elevated IgM, positive rheumatoid factor, and anti-dsDNA, which was consistent with previous exams. Positive direct antiglobulin test was positive for IgG and C3, and a presumptive diagnosis of acute warm hemolytic anemia

complicating anemia of chronic disease was made. Following this diagnosis, the patient was given a single 125mg dose of methylprednisolone sodium succinate followed by high-dose oral prednisone (40mg/daily).

Table 2. Serology Results

	Reference Range	8 Mos. Pre-Admission	3 Mos. Pre-Admission	Hosp. Day 0
IGRA (TB-Gold)	Negative	Positive		Negative
ANA	Negative		Positive (A)	
ANA T,IFA	Unknown		1:320	
ANTI-CENTR	Negative	Negative		
ANTI-RNP	Negative		Negative	
ANTI-SMITH	Negative		Negative	
ANTI-SSA	Negative		Negative	
ANTI-SSB	Negative		Negative	
ANTI-DSDNA	0.0 - 4.0 IU/mL		21.0 (H)	
IgM	0.0 - 10.0 MPL			68.9 (H)
IgG	0.0 - 10.0 GPL			1.9
Anti-B2 Glycoprotein IgG	0.0 - 20.0 SGU			13.3
Anti-B2 Glycoprotein IgM	0.0 - 20.0 SMU			20.6 (H)
Anti-B2 Glycoprotein IgA	0.0 - 20.0 SAU			62.6 (H)
Anticardiolipin Antibody IgG	0.0 - 10.0 GPL			1.9
Anticardiolipin Antibody IgM	0.0 - 10.0 MPL			68.9 (H)
Anticardiolipin Antibody IgA	0.0 - 15.0 APL			4.3
CCP	0.0 - 20.0 U			22.1 (H)

Nevertheless, the patient continued to deteriorate, developing worsening fatigue, pre-syncope and palpitations despite steroid administration and stabilized hemoglobin. Other causes of acute decompensation were then considered. At this time, the treating team was informed of the positive IGRA two years prior and lack of follow-up treatment for latent TB. These records were previously unavailable to the team. Due to concern for TB re-activation, chest imaging was performed, along with repeat IGRA and infectious disease consult. While IGRA was negative, chest radiograph showed a small, laterally located lesion in the upper right lobe and focal consolidation of the upper left lobe (Figure 1). Isolation precautions were started, and empiric broad-spectrum antibacterial therapy was initiated for presumed pneumonia. CT imaging of the thorax showed necrotizing bronchopneumonia affecting the left upper lobe (Figure 2) with additional necrosis of the right middle lobe. Mild prominence of mediastinal lymph nodes was also appreciated. Additional tests for etiology included histoplasma antibodies, legionella urine antigen, as well as general mycology and bacteriology, however, antibody and culture tests were all initially negative. Repeat IGRA testing was negative. Furthermore, there was no evidence of neoplastic disease.

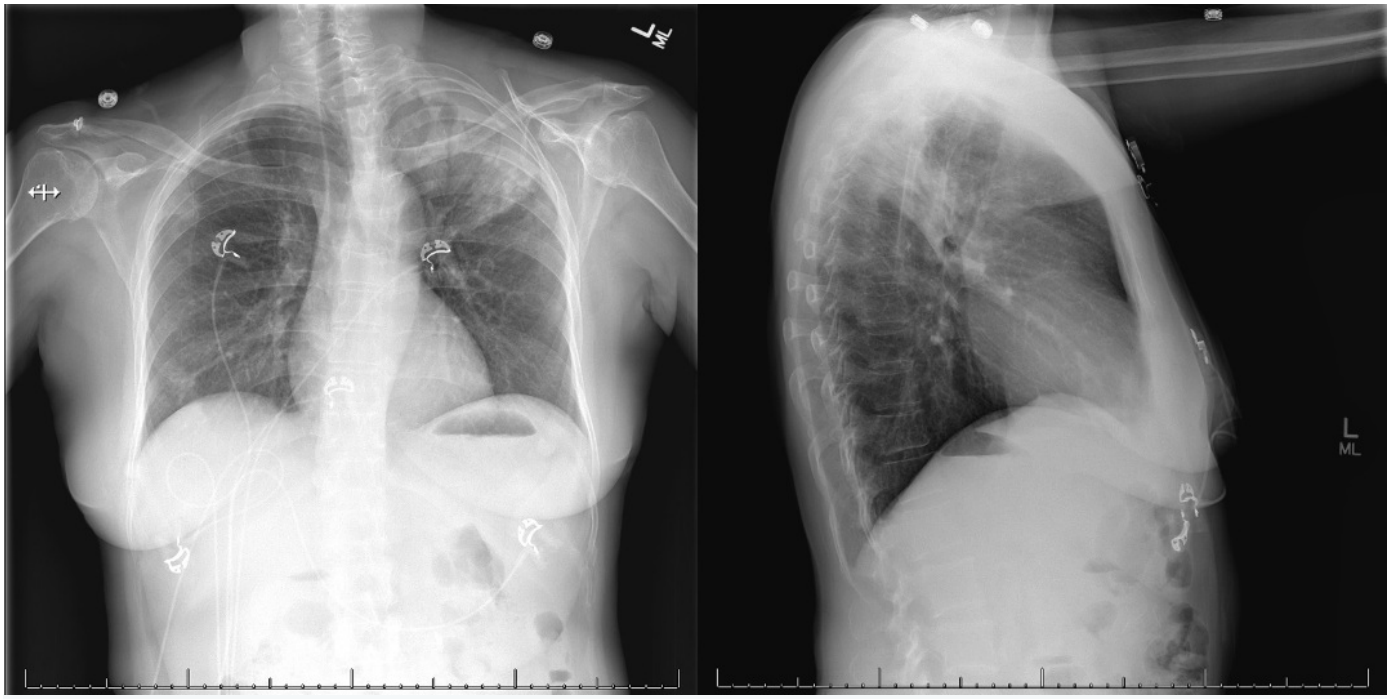

Figure 1. Chest X-ray PA and Lateral views showing consolidation and of the left upper lobe and small lateral lesion in the right upper lobe consistent with reactivation, apical TB.

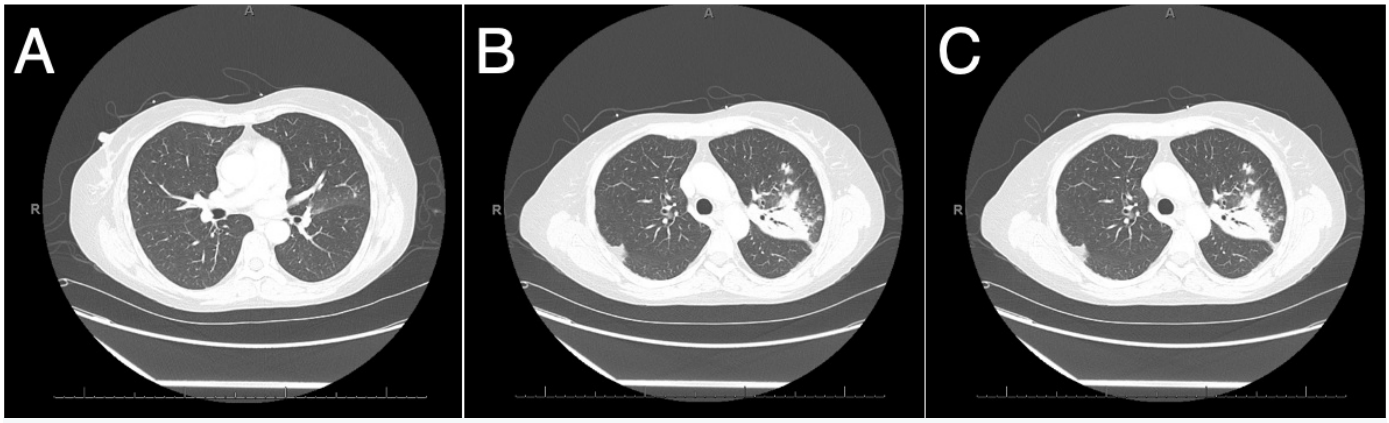

Figure 2. Coronal CT with contrast. A) Mildly prominent bilateral hilar and mediastinal lymph nodes, particularly in the subaortic region, up to 8 mm in short axis with prominent right rectropectoralis lymph node measuring 1.1 cm as per radiologist report. B) Upper left lobe consolidation with necrotizing bronchopneumonia. Additional consolidation in the periphery of the right middle lobe associated with tree-in-bud/branching nodular density. Additional milder nodes were found throughout the right upper lobe. C) Extensive consolidation of the left upper lobe with central areas of lucency. Additional branching of macronodular opacities are noted.

Because serologic testing was negative and sputum samples were unproductive despite sputum provocation with hypertonic saline, a bronchioalveolar lavage (BAL) was performed. The sample demonstrated 4+ acid-fast organisms. Follow up PCR testing of BAL sample was positive for *Mycobacterium tuberculosis* and rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) therapy was initiated.

The patient was discharged shortly thereafter, with complete resolution of anemia and great clinical improvement. Over the next 9 months, the patient had one episode of seronegative arthritis, and two additional episodes of AIHA. TB was well

controlled on RIPE therapy in these admissions, without evidence of reactivation.

Discussion

Here we present a complicated case of reactivation TB in a patient being treated for warm autoimmune hemolysis complicating anemia of chronic disease and RA/SLE overlap syndrome. To our knowledge, this is the first case discussion of reactivated TB complicated by RA/SLE overlap syndrome. The acuity and severity of her hemolytic anemia necessitated high-dose steroid therapy, which likely exacerbated her Tb reactivation. Further, corticosteroids are understood to frequently suppress interferon gamma release from macrophages, which caused delays in acquiring BAL for assessing Tb.

There are numerous reasons why this patient's presentation caused several challenges in identifying the underlying etiology of her decompensation. Given that the patient specifically denied any cough, and she presented first to a free clinic, initial clinical impressions favored her decompensation being secondary to malignancy (evidenced with extreme weight loss and fatigue) and/or autoimmune disease (as described above). The positive IGRA from several years ago was never addressed, which required confirmation with governmental bodies once identified. Further, the patient's presentation (outside of weight loss) was highly consistent with her previous presentations for RA/SLE flare, which likely created significant cognitive bias in her initial workup.

Pulmonary and extrapulmonary Tb are common complications in the treatment of autoimmune diseases.[1] While relatively rare in the United States (incidence of 2.7 cases per 100,000 persons in 2019)[2], Tb is one of the most common global etiologies of infectious disease, infecting approximately 1.7 billion people as of 2018 (~23% of the global population)[3]. Of those exposed, patients being treated for autoimmune conditions such as SLE or RA are particularly susceptible to active infection. Decreased production and secretion of interferon-gamma (IFN-γ) related to therapy with corticosteroids or TNF-a inhibitors (i.e., adalimumab) weakens phagocytotic response, facilitating TB re-activation[4][5][6]. Further, the high-dose immunosuppression blockades IFN-γ release by Th1 cells, reducing detection of latent TB infection (LTBI) by IGRA[4][5][6].

In the acute treatment of uncontrolled rheumatological conditions, high doses of corticosteroids or other immunosuppressants are often first-line agents[7]. However, in patients with latent TB infection, immunosuppression may only be appropriate where infection precautions are in place. In cases with unknown TB status, a cautious approach may be preferred, although guidelines for this specific clinical circumstance are primarily based on expert opinion rather than high-grade evidence. In our case, high-dose corticosteroid therapy for AIHA likely facilitated TB activation, leading to the development of necrotizing pneumonia and potentially exposing healthcare staff. Fortunately, there have been no healthcare-associated TB infections from this case, likely due to the absence of productive cough in the patient and the increased infection control interventions in place during the coronavirus pandemic.

Detection and treatment LTBI in immunocompromised patients is complicated and often controversial[8]. Currently, evidence and guidelines for detecting Tb in those with autoimmune processes are mixed, particularly with use of corticosteroids. However, guidelines for LTBI in other immunocompromised populations, such as those with solid organ

transplants, may be useful. These suggestions my vary but often recommend a two-stage screening approach using a Tuberculin skin test (TST, positive ≥5 mm) and IGRA[9][10]. However, in patients receiving inhibitors of TNF-a and related pathways, these tests are insufficient to rule out latent infection as TNF-a inhibitors significantly reduce these tests' negative predictive value[11].

Some studies suggest chest x-ray (CXR) may be useful as a screening tool where immunoassays are unreliable, however its utility in diagnosing latent infection is controversial[12]. Chest CT may also be useful following CXR situations, with the imaging modality detecting 89% of those with latent TB[12][13]. In general, IGRA should not be used alone as a screening or diagnostic tool in patients with suppressed Th1 T-cellimmune responses and should be interpreted with caution given their propensity for false-negative results in these settings[8]. While none of these tests are completely sensitive, combining TST, IGRA, CXR and CT may be indicated when attempting to rule out latent infection.

For high-risk immunocompromised individuals, in light of this case and in synthesis of the relevant guidelines, we recommend initial screening with, IGRA and CXR to increase sensitivity. If CXR is inconclusive or there is high clinical suspicion of LTBI, we then suggest to consider additional CT imaging. If CXR or CT are consistent with signs of latent TB infection (apical fibronodular lesions, calcified solitary nodule, calcified lymph nodes, or pleural thickening), it is important to obtain a clear patient history to rule out other granulomatous disease including histoplasma and sarcoidosis.

Patients should be treated according to national guidelines[14], if IGRA or TST is positive (TST, positive ≥5 mm) or if the patient has a history of untreated LTBI. In patients with negative IGRA/TST and positive imaging, consider treating those with high clinical suspicion of latent infection, including previous incarceration, known exposure, or time spent in TB endemic regions. Finally, consider treating anyone undergoing immunosuppressive therapy who has had prolonged contact with an individual with active TB regardless of immunoassay or imaging results.[10]

In patients with high clinical suspicion for LTBI with respiratory or systemic syndromes, preferred diagnostic strategies include lung imaging, sputum stains, MTB-PCR, and mycobacterial cultures as they are unaffected by systemic immunosuppression. Of these, MTB-PCR is likely the best choice, as highly specific results can be obtained within a matter of hours[15]. However, this test is only useful in ruling out active disease and should not be used to rule out LTBI. Finally, isolation precautions should be considered in patients undergoing immunosuppressive therapy with high clinical suspicion of LTBI despite negative IRGA.

Conclusion

This case represents an important opportunity to revisit mechanisms of Tb immune response and how they are impacted with immunosuppression, especially with corticosteroids. Molecular screening plays an important role in diagnosing LTBI and reactivation TB, but may be limited where patients are heavily immunosuppressed. Careful consideration of the mechanism behind these molecular tests, as well as thorough history-taking is important to effectively diagnose and treat TB in immunocompromised patients. Detection protocols should use TST, IGRA and chest imaging to increase sensitivity, as well as MCT-PCR to rule out active disease in patients with high clinical suspicion. Furthermore, TB protocols in

immunocompromised patients with high clinical suspicion should include airborne isolation and prophylaxis at presentation, even with negative IGRA.

Ethical Approval

There were no funders for this research, and the authors deny any conflict of interest that may have influenced the writing of this case report. Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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