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

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Abstract

In this report, we discuss how autoimmune conditions and associated immunocompromise may impact diagnostic utility of molecular screening tools for mycobacterial infection. Imaging, molecular screening, and clinical judgment are required to rule out disease in the immunocompromised, especially in an acute setting.

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Case Report

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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.

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.

Objective

This study was done to elucidate the complex interactions between immune-dysfunction and latent tuberculosis infection in an acutely ill patient.

Background

In this report, we discuss how autoimmune conditions and associated immunocompromise may impact diagnostic utility of molecular screening tools for mycobacterial infection. Imaging, molecular screening and clinical judgement are required to rule out disease in the immunocompromised, especially in an acute setting.¹ ².

Case Report

A 53-year-old Spanish speaking female with a past medical history of Rheumatoid Arthritis/Systemic Lupus Erythematosus (RA/SLE) Overlap Syndrome with subsequent chronic polyarthritis presented to the emergency room after routine labs showed severe anemia (Initial Labs: Table 1). The patient had previous episodes of autoimmune-hemolytic anemia resulting in hemoglobin levels of 4.0 mg/dl or lower. Therapy at the time of evaluation included prednisone 5 mg every other day at home, methotrexate 200 mg/week, and folic acid 1 mg daily to treat RA/SLE overlap syndrome. She reported increasing fatigue over the past few days without joint pain, cough, fever, chills, or any other constitutional symptoms; however, she noted recent weight loss.

Notably, the patient had a positive interferon gamma release assay ([IGRA], QuantiFERON Gold) screening two years prior (Table 2) that had not been addressed. The patient immigrated from Honduras, a tuberculosis (TB)-endemic region, three years prior. She did not recall having received vaccination against TB nor ever receiving therapy for latent TB. She had no previous incarcerations, or hospitalizations related to tuberculosis.

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 panel (Table 2) showed elevated IgM, positive rheumatoid factor, and anti-dsDNA. 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).

Nevertheless, the patient continued to deteriorate, developing worsening fatigue, pre-syncope and palpitations despite steroid administration and stabilized hemoglobin. At this time, the treating team was informed of the positive IGRA two years prior and lack of follow-up treatment for latent TB. 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. Furthermore, there was no evidence of
neoplastic disease.

Because serologic testing was negative and sputum samples were unproductive despite sputum induction
with hypertonic saline, a bronchoalveolar 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. Over the next 9 months, the patient had one episode of seronegative arthritis, and two
additional episodes AIHA. TB was well controlled on RIPE therapy in these admissions, without evidence
or 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. As far as we know, this is
the first case of reactivation TB complicated by RA/SLE overlap syndrome. The acuity and severity of her
hemolytic anemia necessitated high-dose pulse-steroid therapy, with the unfortunate result of facilitating TB
reactivation. IGRA assays performed while the patient was on immunsuppressive therapy were negative,
and possible reactivation TB was not considered until high-dose corticosteroid therapy began.

Pulmonary and extrapulmonary TB are common complications in the treatment of autoimmune diseases.3
While relatively rare in the United States (incidence of 2.7 cases per 100,000 persons in 2019)4, 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)5. 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-activation1,6,7. Further, the high-dose immunosuppression
blockades IFN-γ release by Th1 cells, reducing detection of latent TB infection (LTBI) by IGRA1,6,7.

In the acute treatment of uncontrolled rheumatological conditions, high doses of corticosteroids or other
immunosuppressants are often first-line agents8. However, in patients with latent TB infection, immuno-
suppression 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
lacking. In our case, high-dose corticosteroid therapy for AIHA likely facilitated TB activation, leading to
the development of necrotizing pneumonia and potentially exposing the healthcare staff. Fortunately, there
have been no healthcare-associated TB infections to date, 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 controversial9.
Currently, there are no clear universally accepted guidelines for TB detection and screening in those being
treated for autoimmune conditions with corticosteroids. However, guidelines for LTBI in other immuno-
compromised populations, such as those with solid organ transplants, may be useful. These suggestions
may vary but often recommend a two-stage screening approach using a Tuberculin skin test (TST, positive
[≥5 mm] and IGRA10,11. 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 value12.

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 controversial13. Further chest CT (CCT) may also be
useful following CXR situations, with the imaging modality detecting 89% of those with latent TB13,14. In
general, IGRA should not be used alone as a screening or diagnostic tool in patients with suppressed Th1-immune responses and should be interpreted with caution given their propensity for false-negative results in these settings. While none of these tests are 100% sensitive, combining TST, IGRA, CXR and CT may be indicated when attempting to rule out latent infection.

For high-risk immunocompromised individuals we recommend screening with, IGRA, TST and CXR to increase sensitivity. If CXR is inconclusive or there is high clinical suspicion of LTBI consider additional chest CT imaging. If CXR or CT come back with signs of latent TB infection (apical fibronodular lesions, calcified solitary nodule, calcified lymph nodes, or pleural thickening), it is important to get a clear patient history to evaluate other granulomatous disease including histoplasma and sarcoidosis.

Consider treating patients using national guidelines, 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.

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. 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 IGRA.

Conclusion

Molecular screening plays an important role in diagnosing LTBI and reactivation TB. However, careful understanding of the mechanism behind these molecular tests, as well as thorough interview/chart review 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.

References


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