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Case report

The great imitator: Tuberculosis with lymphadenopathy and splenomegaly

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ABSTRACT

Tuberculosis (TB) is a leading infectious killer worldwide. Over two-thirds of new TB diagnoses in the United States occur among first-generation immigrants, especially within a year of migration. Hodgkin lymphoma (HL) accounts for a minority of lymphoma cases but presents similarly to disseminated or extrapulmonary TB. Clinical overlap between TB and HL increases patient risk of misdiagnosis. Concomitant presentation of both diseases is not uncommon but infrequently reported. We present a case of isoniazid-resistant TB with progressively worsening lymphadenopathy and splenomegaly despite appropriate TB treatment. The patient was diagnosed with HL following PET/CT and axillary lymph node biopsy.

Introduction

Tuberculosis (TB) is a leading infectious killer estimated to infect one-fourth of the world's population [1]. In the United States (US), more than two-thirds of active TB cases are diagnosed among first-generation immigrants, who are particularly vulnerable to infection within one year of migration. Screening of latent TB infection (LTBI) reduces the risk of progression to active disease; however, most patients with LTBI are unaware of their diagnosis and have not received preventive treatment [2,3].

Hodgkin lymphoma (HL) has a bimodal distribution, with the highest incidence among patients 20–40 years old, and accounts for 10% of new lymphoma cases in the US [4]. HL is characterized by supradiaphragmatic lymphadenopathy, systemic symptoms, and multinucleate giant cells or large mononuclear cells in an inflammatory background [4]. Concomitant presentation of TB and HL is infrequently reported and may lead to delayed recognition or misdiagnosis due to clinical overlap between TB and HL [5].

We present the case of a Hispanic patient who recently immigrated to the US, was diagnosed with TB, and developed worsening multifocal lymphadenopathy, splenomegaly, and fevers despite appropriate TB treatment.

Case Report

The patient was a 33-year-old male who immigrated to the US from Mexico two months prior to his initial presentation. He reported a one-month history of cough with fevers, chills, night sweats, fatigue, and unintentional weight loss of 20 pounds. Sputum studies showed 4 + acid-fast bacilli (AFB) with extensive bilateral lung involvement and right upper lobe cavitation on chest radiography, consistent with active TB. Computed tomography (CT) also showed right supraclavicular, axillary, hilar, and mediastinal lymphadenopathy, which was concerning for tuberculous lymphadenitis (TBL). *Mycobacterium tuberculosis* complex DNA was detected by PCR in sputum without *rpoB* gene mutation.

He was placed on rifampin (600 mg), isoniazid (INH, 300 mg), pyrazinamide (1000 mg), and ethambutol (800 mg), reporting good compliance, and was followed outpatient at the local TB Clinic. Susceptibility testing demonstrated INH resistance at 1.0 and 5.0 μg/mL, while genotype testing showed mutations in *inhA* and *katG*, so levofloxacin (750 mg) was substituted for INH. Sputum cultures converted to negative within two months of TB treatment. Repeat chest X-ray showed improved lung opacities.

The patient was readmitted four months into TB treatment due to a one-month history of progressive swelling in the right axilla and

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subsequent fevers. CT chest showed diffuse bilateral ground-glass opacification. Fused PET/CT of the abdomen and pelvis revealed splenomegaly with hypoenhancing lesions and diffuse peritoneal and retroperitoneal adenopathy (Fig. 1, A-B). Two excisional biopsies of the right axilla were performed and sent for cultures. Tissue samples were also sent for surgical pathology and flow cytometry.

AFB smears and cultures of multiple sputum, blood, and lymph node specimens were negative. Sputum MTB PCR was negative. Peripheral blood Karius test® was positive for EBV. Histopathological examination of an excisional right axillary lymph node biopsy revealed an atypical lymphoid infiltration composed of Reed-Sternberg cells (CD15 +, CD30 +) present in a polymorphous background of lymphocytes, plasma cells, histiocytes, and eosinophils. This resulted in the diagnosis of stage IV HL.

Following his diagnosis, our patient began therapy with 6 cycles of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD). He has tolerated chemotherapy well and has shown clinical improvement with decreased lymphadenopathy with ongoing treatment as of this manuscript (Fig. 1, C-D). Given the high burden of TB disease on presentation, low body weight, and active immunosuppression, the patient's TB treatment was extended to nine months.

Discussion

We present the case of a Hispanic patient who was diagnosed with INH-resistant TB within two months of immigration. He developed worsening lymphadenopathy, splenomegaly and fevers while on TB treatment, engendering a broad differential diagnosis. One initial consideration was worsening TB with progression of extrapulmonary TB disease (EPTB) due to treatment nonadherence, treatment failure, or development of multidrug-resistant (MDR) TB. However, the patient reported strict compliance with his TB treatment regimen, which was confirmed by the local county through a review of video directly observed therapy (VDOT) records. Poor gastrointestinal absorption of TB treatment was ruled out through high-performance liquid chromatography peak drug levels measured at 2 and 6 h after anti-TB drug administration (expected therapeutic levels: levofloxacin 8–12 μg/mL, rifampin 8–24 μg/mL, pyrazinamide 20–60 μg/mL, ethambutol 2–6 μg/mL) [6]. These facts in conjunction with the patient's negative sputum smears and absent growth following lymph node biopsy meant TB treatment failure, EPTB, and MDR-TB were less likely. Alternative diagnoses included a paradoxical response to TB treatment (e.g., immune reconstitution inflammatory syndrome, IRIS) or concomitant infectious or non-infectious processes. Excisional lymph node biopsy ultimately confirmed HL.

Like syphilis, TB has been called the great imitator as it masquerades as many other disease processes, including HL. The association between TB and HL is not uncommon and occurs at rates greater than those seen in the general population [5,7,8]. Kaplan et al. found that HL was the most reported malignancy among 201 TB cases [8]. Another study found that TB infection in lymphoma patients ranged from 11.9–14.6%, and male TB patients were particularly predisposed to lymphoma [9].

Overlapping clinical features of TB and HL may lead to misdiagnosis or delayed recognition of either disease [5]. This diagnostic dilemma has been known since 1926, when Herbert Fox found that one of Thomas Hodgkin's samples showed evidence of TB and not HL [10]. Despite a century of technological advancement, differentiating TB and HL remains a challenge. For example, FDG PET is unable to selectively identify TB from HL or other cancerous lesions because the radiotracer is absorbed by tumor cells and inflammatory or infectious lesions [11]. However, contrast-enhanced CT has clinical utility in that mediastinal lymph nodes in active TB often manifest as peripherally enhancing with a cystic necrotic center and multilocular appearance, whereas neoplastic (HL and non-HL) lymph nodes have a central and homogenous enhancement [12,13]. Anatomical distribution of lymphadenopathy may also provide clues in differentiating TB and lymphomas – a study showed that the right hilar region was more affected in patients with TB, whereas the para-aortic region was more frequently compromised by lymphomas [12,13]. Overall, radiographic imaging is useful but unable to provide a definitive diagnosis without supporting data.

Routine laboratory markers are also of limited utility, although serum lactate dehydrogenase (LDH) is more commonly elevated in lymphomas than TB pathology [14]. Diagnosis of TBL is incumbent upon fine-needle aspiration followed by microbial and cytological examinations, while a larger tissue sample, usually with an excisional biopsy of a target lymph node or mass, is necessary to exclude Hodgkin lymphoma [15]. Therefore, physicians caring for TB or HL patients should be cognizant of the association between the two diseases, and the possibility of concomitant processes should not be excluded, particularly in the setting of relapsing symptoms [5].

Simultaneous treatment with chemotherapy and anti-TB medication is suggested for patients with coexisting TB and HL, which has not been shown to increase patient risk of TB exacerbation [16]. First-line treatment options for patients newly diagnosed with stage III or IV HL have a high probability of cure and now include A+AVD, though some patients may still be successfully managed with doxorubicin, bleomycin, vinblastine, and dacarbazine or alternative regimens including immune checkpoint blockade [17]. Primary treatment of INH-resistant TB includes six months of rifampin, pyrazinamide, ethambutol, and levofloxacin [18].

This patient has many social determinants of health, including an undocumented status, low income, and low health literacy, which

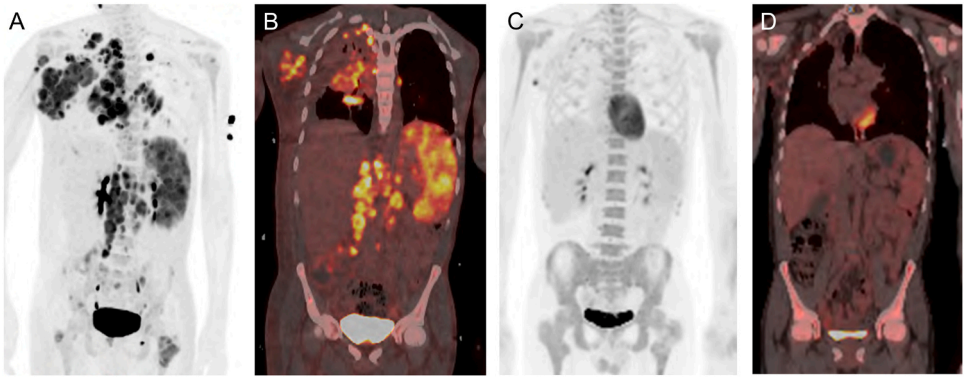

Fig. 1. FDG PET scan in July 2023 demonstrated tracer uptake in the cervical, supraclavicular, thoracic, abdominal, and pelvic lymph nodes as well as the spleen (A). Fused PET/CT showed FDG uptake bilaterally in the retroperitoneal lymph nodes and spleen (B). FDG PET and fused PET/CT scans in November 2023 with resolution of multifocal FDG avid lymphadenopathy and FDG avid splenic, osseous, and pulmonary/pleural lesions with a persistent FDG avid right axillary lymph node, suggestive of partial metabolic response (C-D).

highlights the social origins of TB disease [19]. More than two-thirds of active TB cases in the US are diagnosed among first-generation immigrants, which represents an enormous health disparity [20]. Studies indicate that immigrants are particularly vulnerable to TB disease within a year of arrival [21]. Screening and treatment of latent TB infection (LTBI) decreases the risk of progression to TB disease in 60 to 90% of cases [2]. However, about 90% of the 14 million people estimated to have LTBI in the US do not know about their LTBI diagnosis and have not received preventive TB treatment [3].

We report the case of a patient with INH-resistant TB who presented with fever, worsening lymphadenopathy and splenomegaly while on TB treatment. The initial differential diagnosis included progression of EPTB, development of MDR-TB, TB-IRIS, and concomitant infectious or non-infectious systemic processes. Following an axillary lymph node biopsy, he was diagnosed with HL. This case illustrates the clinical overlap between TB and HL and the inherent difficulty of differentiating them.

Ethical Approval Statement

HIPAA lists 18 information identifiers that, when paired with health information, become protected/personal health information. We have removed all such identifying details.

Consent

Our patient consented to the use of his medical record and clinical images for educational purposes upon hospital admission. We have retained a copy of this consent form and will provide it upon request.

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Authorship

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

CRediT authorship contribution statement

Moises A. Huaman: Writing – original draft, Supervision. **Bryan C. Hambley:** Writing – review & editing. **Kavya Patel:** Writing – review & editing. **Jared Vearrier:** Writing – review & editing. **Laura Victoria Medina Rodriguez:** Writing – original draft. **Ashton D. Hall:** Writing – original draft.

Conflict of Interest

M.A.H. reports contracts from Gilead Sciences, Insmed, and AN2 Therapeutics to the University of Cincinnati, outside of the presented work. All other authors have no potential conflicts of interest to disclose. We uploaded a COI form signed by all authors.

Declaration of Competing Interest

None.

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