Disseminated tuberculosis following negative QuantiFERON-TB gold tests during infliximab therapy: Implications for screening of hidradenitis suppurativa

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Key words: directly observed therapy (DOT); disseminated tuberculosis; hidradenitis suppurativa (HS); infliximab therapy; latent tuberculosis; miliary tuberculosis; PPD screening; pulmonary tuberculosis; purified protein derivatives (PPDs); QuantiFERON-TB gold test; rifampin; isoniazid; pyrazinamide; ethambutol (RIPE); TNF-α inhibitors (TNFIs); tuberculosis (TB); tuberculosis screening; tumor necrosis factor-alpha (TNF-α).

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic relapsing skin condition that clinically manifests as painful swollen lesions, commonly located in intertriginous sites with an estimated prevalence of 0.05% to 4.1%.[1] Though the exact pathogenesis remains unclear, HS is believed to be secondary to deregulation of the local immune system which leads to follicular inflammation.[2] Tumor necrosis factor-alpha is one of the primary cytokines driving this vicious inflammatory process such that tumor necrosis factor-alpha inhibitors (TNFIs) have become mainstay treatment for moderate-to-severe disease.[3] Despite the significant benefits of TNFI therapy, there is particular concern about their association with an increased risk of life-threatening infections, specifically mycobacterial infections. Here, we describe a patient who developed disseminated tuberculosis (TB) while on infliximab therapy for HS, despite appropriate screening.

Abbreviations used:

HS:	hidradenitis suppurativa
PPDs:	purified protein derivatives
QFT-G:	QuantiFERON TB gold
TB:	Tuberculosis
TNF-α:	Tumor necrosis factor-alpha
TNFIs:	TNF-α inhibitors

CASE REPORT

A 38-year-old man with severe, extensive HS involving the groin and bilateral axillae failed several trials of antibiotics and 3 years of (2016-2019) subcutaneous adalimumab. Before commencing biologics, he was screened for potential risk factors for TB, revealing a history of incarceration in 2005. In fact, he had serial negative purified protein derivatives (PPDs) dating back to 2005 due to his incarceration, and his last 2 QuantiFERON TB gold (QFT-G) tests (December 2017 and January 2021) were additionally negative. He was started on infliximab in January 2021, with his HS improving on monthly infusion doses of 7.5 milligrams per kilogram for 6 months. Due to the COVID-19 pandemic and an uncomplicated SARS-CoV-2 infection, he missed 3 infusion sessions but followed up at the infusion center 3 months after his last infusion for treatment. He presented to the infusion center weak and emaciated, reporting a 2-week history of poor appetite and intermittent diarrhea. He denied respiratory symptoms, fever, or chills but noted night sweats for a few months. He was tachycardic and hypotensive, with significant weight loss of about 15 pounds from his original weight of 125 lbs 3 months ago. Skin examination was notable for active axillary,

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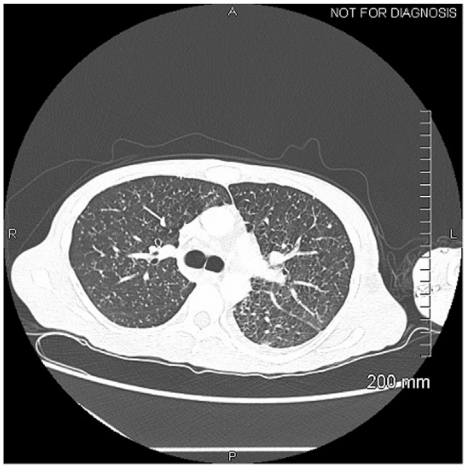

Fig 1. Disseminated TB involving the lungs in a miliary distribution in a 38-year-old male. Axial chest computed tomography image with contrast demonstrating diffuse fine nodularity throughout the lungs in a miliary distribution. *TB*, Tuberculosis.

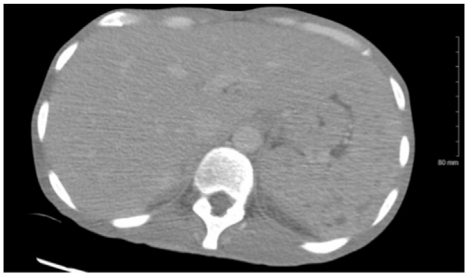

Fig 2. Disseminated TB with splenic involvement in a 38-year-old male. Axial abdomen/pelvis computed tomography image with contrast demonstrating hypoattenuating lesions throughout the splenic parenchyma suggestive of micro-abscesses on the axial view. *TB*, Tuberculosis.

inguinal, and gluteal HS with scarring and purulent drainage. A computed tomography scan of his chest (Fig 1) and abdomen (Fig 2) showed diffuse fine nodularity throughout the lungs in a miliary pattern, as well as subcarinal and hilar lymphadenopathy with hypoattenuating lesions throughout the splenic parenchyma, consistent with disseminated TB. Biologics were held. Rifampin, isoniazid, pyrazinamide, and ethambutol therapy through directly observed therapy monitoring commenced. On interview, the patient reported his cousin, with whom he lived at a young age, died of TB 20 years prior. When asked why this information was omitted upon initial questioning prior to starting biologics, he explained: "*I didn't like that cousin*."

Skin cultures from lesions isolated *Streptococcus agalactiae* and *Escherichia coli*, likely commensal flora. Blood and fungal cultures, as well as SARS-CoV-2 and HIV polymerase chain reactions, were all negative. Mycobacterium TB polymerase chain reactions of his HS lesions were negative as well. Symptomatic HS lesions were managed with local incision and drainage, antiseptic topical cream, and pain management. While undergoing rifampin, isoniazid, pyrazinamide, and ethambutol therapy, his HS therapy was limited to topical chlorhexidine wash, clindamycin lotion, and pain management.

DISCUSSION

TNFIs are the standard of care in the management of HS. However, this treatment represents an increased risk of reactivation of TB, with most cases[4] documented in the rheumatologic[5,6] and gastroenterological[6,7] literature. Specifically, there is a fourfold risk of mycobacterium infection with TNFIs.[8] Not all TNFIs are created equal, as infliximab and adalimumab carry a greater risk of TB reactivation than etanercept.[9] Table I gives a summary of published latent TB cases following TNFI therapy. Although screening for TB infection before initiation of TNFIs has been shown to markedly reduce the rates of TB reactivation, individual risk assessment during therapy remains a challenge. A recently published paper found that in 1335 TB cases, none of the cases had negative QFT-G and PPDs.[18] Although QFT-G has >99% specificity and 92% sensitivity as compared to 35% to 70% and 90%, respectively, for PPDs in certain settings,[19] our case illustrates the pitfalls of relying on PPDs and serial interferon-gamma releasing assays. Since sensitivity and specificity are independent of disease prevalence, likelihood ratios, negative, and positive predictive values are utilized. QTF-G is more specific than PPDs; however, both tests have excellent negative predictive values. Our case also illustrates the limitations in obtaining an adequate past medical history before initiating TNFI therapy. While our patient's past medical history did not involve systemic immunosuppression such as systemic steroids,[20] it was remarkable for incarceration and cohabitation with a relative with TB. These components of his history significantly increase the risk of TB exposure. Furthermore, the unfavorable sentiments about his relative highlight the biases that patients have that influence their willingness to share or withhold vital information. Thus, it is imperative to avoid assumptions about a patient's level of understanding regarding medical information and inquiry, such as risks of infectious exposure. Although the source of his TB exposure remains a mystery, we cannot discount his recent SARS-CoV-2 infection as a trigger for further immunosuppression or increasing his risk of new infections altogether.

Table I. Review of the literature on TB cases in patients on biologics

Study	Biologic used (%)	*N* of TB cases (%)	Country of the study
Sartori et al[10]	Adalimumab (62.8), infliximab (7), etanercept (23.2), certolizumab pegol (4.6), golimumab (2.3)	0.7 0.4 0.2 1.5 0.3	Brazil
López-Ferrer et al[11]	Adalimumab (100)	1.7	Spain
Cataño and Morales[12]	Adalimumab (38), ustekinumab (15), etanercept (41)	3	Colombia
Ergun et al[13]	Adalimumab (31), infliximab (44), etanercept (52)	1.1	Turkey
Chiu et al[14]	Adalimumab (62.8), infliximab (7), etanercept (23.2), certolizumab pegol (4.6), golimumab (2.3)	0.7	Taiwan
Lee et al[15]	Adalimumab (68.7), etanercept (31.3)	0.7	United States
Sánchez-Moya and Dauden[16]	Adalimumab (39), etanercept (39), ustekinumab (8)	0.5	Spain
Medina-Gil et al[17]	Adalimumab (24), etanercept (65), ustekinumab (6)	0.2	United States

Though it is possible our patient acquired a new primary TB infection since his last QFT-G, he was asymptomatic for months and the dissemination of his symptoms, the lack of a Ghon focus, and the presence of cavitary lesions support a latent TB etiology.[21]

Even with high specificity and sensitivity (>99% and 92%) and a positive predictive value 4 times greater than PPDs,[19] QFT-G results must serve as an adjunct to meticulous clinical investigations—not the denouement of screening in high-risk patients. Careful clinical evaluation and questioning regarding the common signs, symptoms, and high-risk exposures of TB may be valuable in stratifying patients at risk of TB infection and identifying patients on TNFI therapy who need more frequent TB screening or chest x-rays. There are limited data regarding the optimal time to recommence TNFIs following an active TB infection. Studies suggest that TNFIs are safe to restart in most patients who have been treated for latent TB with no relapses. However, there is no consensus regarding the optimal timing for restarting TNFIs. Screening results, albeit negative, are not the end but a means to an end. It is paramount for physicians to remain vigilant throughout the entirety of a treatment course regardless of negative screening tests and questionnaires. Physicians should be aware of the risk factors of active TB in patients on TNFIs and maintain a high index of suspicion, notwithstanding patient health literacy, to mitigate adverse sequelae in patients on TNFI therapy.

Conflicts of interest

None disclosed.

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