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Miliary tuberculosis presenting as a choroidal mass and a tuberculosis screening review

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ABSTRACT

Anti-tumor necrosis factor alpha (anti-TNF) therapy is a standard of care in the management of many inflammatory conditions. However, anti-TNF pharmaceuticals increases the risk of reactivating tuberculosis making screening for latent tuberculosis infection (LTBI) a requirement prior to initiating therapy. Case: A middle-aged male from China with a past medical history of LTBI and Crohn's disease, previously on infliximab, presented to the United States for a second opinion on his abdominal pain. He also reported new onset visual changes. Ophthalmology evaluation revealed a 4 cm choroid mass of his left eye and a CT scan of the abdomen showed diffuse lymphadenopathy and lesions in his liver, spleen, and lung. He was admitted for treatment of miliary tuberculosis. Discussion: Immunocompromised patients are a unique population that brings challenges to LTBI testing. Conclusion: Clinicians should know the most up to date screening tools for LTBI and diagnostic workup for active tuberculosis infection.

1. Introduction

Mycobacterium tuberculosis (TB) is a worldwide trepidation with about one third of the world's population being infected. The incidence of TB in the United States is 3.0 cases per 100,000 with 9,563 cases being reported in the U.S. for the year of 2015 [1]. There is a growing number of patients being treated with immunomodulators which increases their risk for latent tuberculosis infection (LTBI) activation. Anti-tumor necrosis factor alpha (anti-TNF) pharmaceuticals have shown significant success in multiple inflammatory disorders. These anti-TNF therapies increase risk of infection or reactivation of LTBI. Therefore, appropriate screening for latent and active tuberculosis is essential prior to initiation of anti-TNF therapy.

2. Case description

A middle-aged Chinese male with a known history of Crohn's disease was treated with nine doses of infliximab in China. He presented to the United States for a second opinion regarding his persistent abdominal pain. In China, his inflammatory bowel disease had resolved and was confirmed by colonoscopy, He had been started on azathioprine, but his symptoms worsened. Repeat colonoscopy showed recurrence of Crohn's disease. He was restarted on infliximab and the patient received four doses. Follow up colonoscopy revealed improvement in colonic mucosa on biopsy but again no resolution of his abdominal pain. He then noticed blurring of vision in the left eye which progressively worsened to loss of vision. Over a month period, his right eye developed visual changes. An ophthalmologist diagnosed a 4 cm choroid mass in the left eye and a normal right eye examination (Fig. 1A). Infliximab was discontinued and anti-tubercular treatment with ethambutol, isoniazid, rifampin and pyrazinamide was initiated in China. After two months of anti-tubercular therapy, he had clinical improvement of his abdominal symptoms, a decrease in size of the left eye choroid mass, and stabilization of his vision loss.

The patient sought a second opinion regarding Crohn's disease vs. intestinal tuberculosis at our institution. Computed tomography (CT) scans of the chest and abdomen showed multiple subcentimeter lesions in liver, spleen, lung, 4.5 cm mass on pole of left kidney and many subcentimeter lesions in both kidneys, diffuse colitis, hilar and mediastinal lymphadenopathy consistent with miliary tuberculosis (Fig. 1B–D). The patient was admitted to the hospital for further evaluation and treatment for miliary tuberculosis.

3. Discussion

This case describes a rare and life threatening complication, primary

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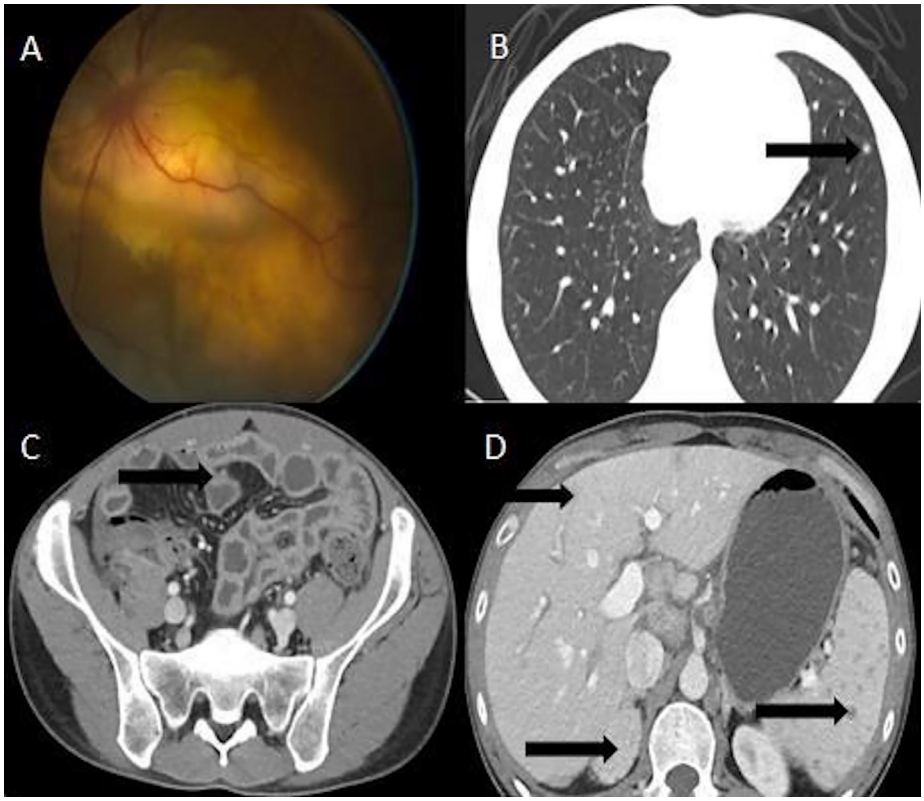

Fig. 1. (A) White choroidal mass, left eye. (B) Micronodule left lung base. (C) Diffuse bowel wall thickening. (D) Liver, Kidney and splenic lesions.

miliary TB, which presented as an eye choroidal mass after infliximab therapy. Miliary TB is an uncontrolled hematogenous spread of mycobacterium infection. Primary infection could involve multi-organ systems such as lung, liver, spleen, kidney, eye, and intestine, as in our case. The term miliary describes many tiny lesions that resemble small millet seeds. These tiny nodules can easily be missed on chest X-ray as 25–40% of cases have a normal chest x-ray early in the course [1]. In Western countries, the risk of TB reactivation while on infliximab for inflammatory bowel disease is low (0.52%), due to low prevalence of TB in these areas [2]. However, depending on the prevalence of TB in one's country and TNF antagonist used, the relative risk is increased up to 25 times; therefore, appropriate screening and exclusion of active TB is necessary before initiation of infliximab or any immunosuppressant agent [3].

Individuals who may be at higher risk of reactivating tuberculosis should be tested for latent tuberculosis infection (Fig. 2). These individuals include: health-care workers, previous exposure to someone with active TB disease, individuals from countries where TB is endemic (Asia, Africa, and Latin-America), and high risk settings (nursing homes, prisons, and homeless shelters). The two methods of screening for LTBI include the tuberculin skin test (TST) and Interferon-Gamma Release Assay (IGRAs). The TST and IGRAs provide data to the provider as to if the patient has been exposed to tuberculosis in the past or not. Neither provides information as to whether TB is in latency or active causing disease [4].

The TST was developed in the early 1900′s by Von Pirquet and Mantoux. By inoculating individuals with a purified protein derivative (PPD) a delayed type hypersensitivity reaction ensues as a result of the host's adaptive immunity. The interpretation of the result is structured by the host's response (induration diameter, not to be confused with erythema) and the risk stratification of the patient. A limitation to this screening modality is the test must be read in 48–72 h after inoculation, requiring the patient to return at a later date to be read by trained healthcare personnel. TST is considered positive when an induration

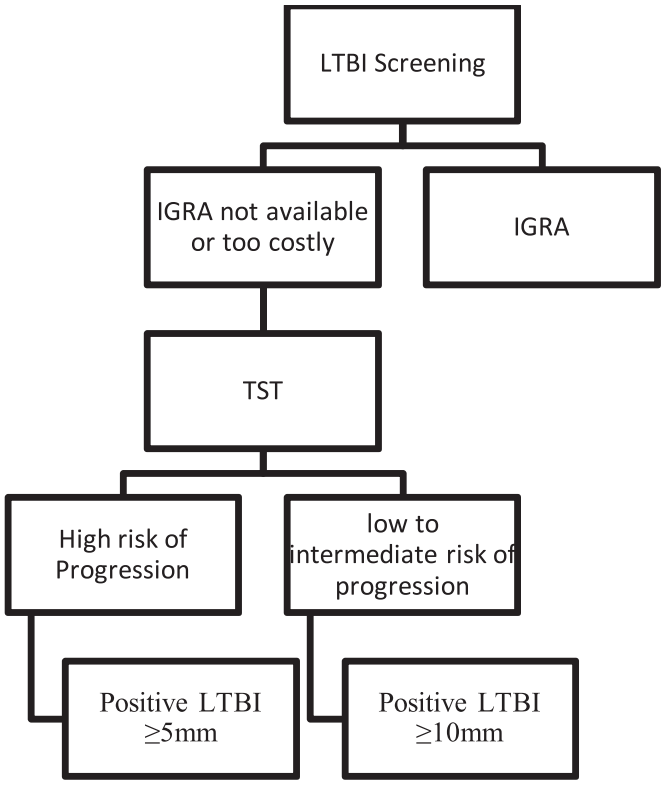

Fig. 2. Latent tuberculosis infection screening algorithm for immunocompetent patients likely to be infected.

diameter of 5 or more millimeters is reached for patients who are likely to be infected and high risk of progression including: HIV infected persons, a recent contact of a person with tuberculosis disease, patients

with organ transplants, or persons who are immunosuppressed; 10 or more millimeters for patients who are likely to be infected and have low to intermediate risk of progression which includes recent immigrants (< 5 years) from high prevalence countries, intravenous drug users, and healthcare workers [5].

After nearly a century, a new screening test, IGRA, for latent tuberculosis was approved by the FDA in 2001. The IGRAs detect sensitization to mycobacterium tuberculosis by measuring the interferon-γ release in response to antigens representing mycobacterium tuberculosis [6]. Since the first approval of the first IGRA, multiple generations of IGRAs have been approved with the two most widely available including the QuantiFERON-TB Gold-in-Tube (QFT-GIT) and T-SPOT TB test, approved in 2007 and 2008 respectively. The benefits of this screening modality includes: only one office visit required, results available in approximately 24 h, and the test may be used in individuals who have been previously vaccinated with BCG.

Patients who are immunosuppressed or who will initiate anti-TNF therapy are a unique population that brings about challenges to LTBI screening. Exposure to immunosuppressive therapy, such as anti-TNF and corticosteroids in inflammatory bowel disease patients, may cause false negative TST and QuantiFERON-TB in up to 30% of patients [7]. Screening should be initiated with a chest X-ray to determine if there are any abnormal TB-related findings such as cavitary or fibrotic lesions. If such lesions are found further work-up for active TB should be initiated and determine if appropriate LTBI treatment was completed. A normal chest x-ray should be followed by testing with IGRA testing [8]. There is currently not a good screening test for LTBI testing in patients with autoimmune inflammatory disease. The performance data in this group is limited [9]. Because of these high false negative results, some experts recommend a dual testing approach for patients on anti-TNF therapy to increase sensitivity by performing both TST and IGRA (Fig. 3). This dual screening may also be used for patients prior to initiating anti-TNF therapy in order to decrease false negative results

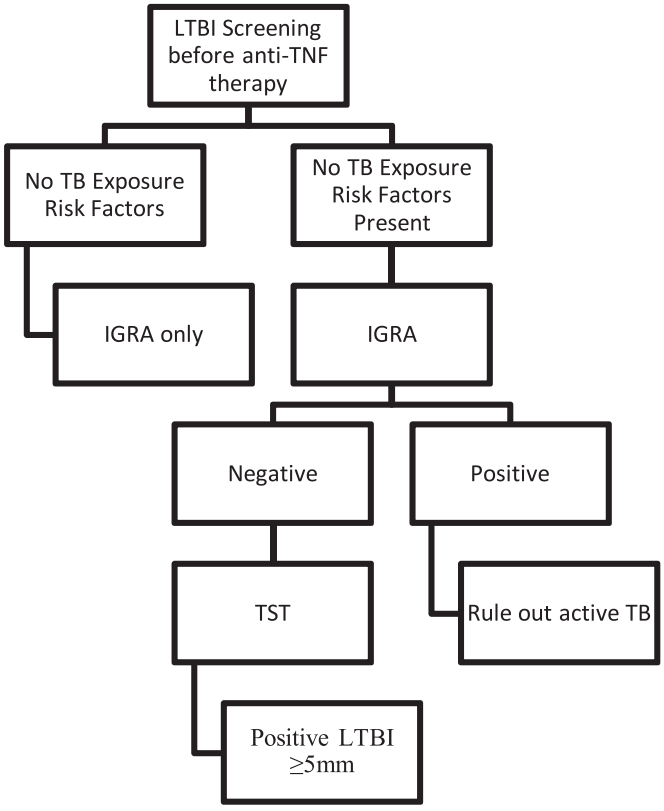

Fig. 3. Latent tuberculosis infection screening algorithm prior to initiated anti-TNF therapy.

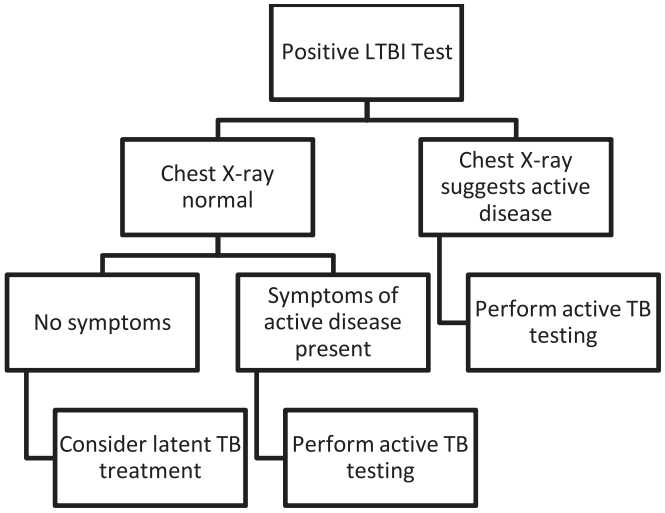

Fig. 4. Algorithm after positive latent tuberculosis testing.

[6,8]. If any of the LTBI screening modalities are positive then the patient is considered to have LTBI and warrant further testing to exclude active infection (Fig. 4). Extrapulmonary TB and disseminated TB are common presentations of reactivated TB after anti-TNF therapy. If clinical suspicion is high, then anti-TNF therapy should be discontinued and anti-tuberculosis therapy should be initiated without waiting for culture or biopsy results. These patients do not have typical signs and symptoms of pulmonary TB.

TST and IGRA screening modalities are just that, screening tests to determine if the individual has been infected with tuberculosis. These tests do not provide information as to the status of the infection, i.e. latent or active disease. All individuals with either positive TST or IGRA test without prior anti-tuberculosis therapy must undergo evaluation to determine the status of the infection. The next step in this clinical scenario would be to exclude active TB infection (Fig. 5) [11]. In order to exclude active TB, a chest x-ray is indicated. If the CXR is normal, no sputum cultures are indicated. If the CXR shows radiographic changes that could be consistent with a granulomatous disease, three sputum samples for acid fast bacilli smear microscopy on three different days with sputum cultures need to be obtained. Nucleic acid amplification testing of AFB smear positive specimens, if feasible, should be completed. Of course, the patient must be masked in public areas until results are known. Obtaining three sputum samples daily for three days increases the sensitivity and is the standard in the United States [10]. Because the AFB smear microscopy is known to have poor sensitivity (45–80%) it should be used with nucleic acid amplification test (NAAT) which can confirm positive mycobacterium TB in 50–80% of AFB negative specimens. Other benefits of NAAT include: a positive predictive value of >95% with AFB positive samples compared to a positive predictive value of 50–80% for AFB smear microscopy [12]. Interpreting the NAA testing results should be done in conjunction with the AFB smear microscopy results (Fig. 5) [11]. Despite the benefits that NAAT offers, its sensitivity is not optimum to exclude active tuberculosis in patients with AFB negative smears; only 50–80% of AFB smear-negative specimens that are culture positive are detected [11]. In the end, sputum culture remains the gold standard.

In conclusion, we present a patient from a highly endemic area for TB who received anti-TNF therapy in absence of exclusion of TB infection, not to mention the determination if he had latent or active disease. This case demonstrated the importance that all patients should be screened for TB prior to the initiation of anti-TNF therapy or immunosuppressive therapy. Once receiving anti-TNF therapy, patients should be monitored closely for signs and symptoms of active TB.

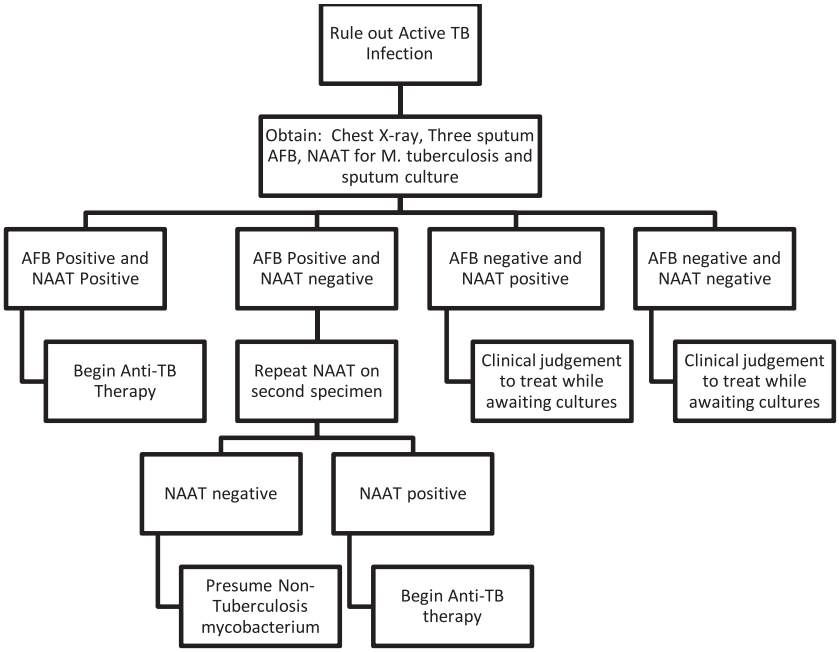

Fig. 5. Algorithm to rule out active tuberculosis infection.

4. Conflicts of interest

The authors declare that there are no conflicts of interest regarding publication of this paper.

References

[1] Bhalla AS, Goyal A, Guleria R, Gupta AK. Chest tuberculosis: Radiological review and imaging recommendations. Indian J Radiol Imaging 2015;25(3):213–25. https://doi.org/10.4103/0971-3026.161431.

[2] Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: a meta-analysis. Exp Ther Med 2016;12(3):1693–704. https://doi.org/10.3892/etm.2016.3548.

[3] Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2010;36(5):1185–206. Nov.

[4] CDC. Tuberculosis. https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm.

[5] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49. (No. RR-6. www.cdc.gov/MMWR/PDF/rr/rr4906.pdf.

[6] CDC. Updated Guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection. MMWR 2010;59. (No.RR-5. www.cdc.gov/MMWR/pdf/rr/rr5905.pdf.

[7] Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: A meta-analysis. Exp Ther Med 2016;12(3):1693–704. https://doi.org/10.3892/etm.2016.3548.

[8] Shim TS. Diagnosis and treatment of latent tuberculosis infection due to initiation of anti-TNF therapy. Tuberc Respir Dis (Seoul) 2014;76:261–8.

[9] Hsia Elizabeth, Schluger Neil, Cush JohnJ, et al. Interferon-gamma release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. Arthritis Rheum 2012;64(7):2068–77. July.

[10] Lewinsohn David, M. Michael, K. Leonard, Philip A. LoBue. et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017;64(2):111–5.

[11] CDC. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. MMWR 2009;58(01):7–10.

[12] Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess 2007;11:1–196.