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Case Report

Pitfalls of a Negative Tuberculin Skin Test When Used as a Screening Modality for Latent Tuberculosis Prior to Adalimumab Therapy: A Case Report

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Abstract

Adalimumab (ADA) is a tumor necrosis factor (TNF) inhibitor commonly used in inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease due to its immunosuppressive effect through TNF alpha blockade. However, this treatment presents with the risk of contracting opportunistic infections like Tuberculosis (TB) that may be missed during initial screening. We discuss a case of an extrapulmonary miliary TB presenting 11 months after starting Adalimumab for treatment of Crohn's disease, despite negative screening with tuberculin skin testing (TST). We discuss the appropriate screening modality to reduce false-negative latent TB screening prior to starting TNF inhibitors for patients diagnosed with Crohn's disease.

Keywords: Adalimumab; Anti-tumor Necrosis Factor α; Miliary Tuberculosis; Extrapulmonary Tuberculosis; Crohn's Disease; Interferon-γ Release Assays

Case Report

This is the case of a 19 year-old male patient who presented with a 4-week history of fever, night sweats and nonproductive cough associated with severe diarrhea and abdominal pain of 3 months duration. One year prior to admission, he was diagnosed with Crohn's disease that involved the terminal ileum and ileocecal valve, respectively. Due to these findings, the patient was started on adalimumab (Amjevita) 40mg every 2 weeks for the last 11 months. He showed clinical improvement of his Crohn's disease on Adalimumab with reduction in ulcerations as was evident by a follow-up colonoscopy. Before beginning treatment, the patient was screened for tuberculosis with a tuberculin skin test (TST) which was negative. However, a chest X-ray and interferon-gamma release assays (IGRA) had not been done. He had no risk factors for tuberculosis except for his current disease treatment on Adalimumab.

Upon admission to the hospital, his temperature was 38.9 °C, heart rate 107/min, respiratory rate 12/min and blood pressure 110/75 mm Hg. His physical examination was normal except for one left sided supraclavicular lymphadenopathy. Laboratory analysis revealed elevated CRP (146.2 mg/L. Normal:0-5) and ESR (69 mm/hr. Normal:0-20), WBC count of 5.7 ×1000/c (Normal:4000-11000) with 72% neutrophils (Normal:40-65) and 17% lymphocytes (Normal:25-40), elevated LDH (360 IU/L. Normal:140-271), elevated GGT (53 IU/L. Normal:8-37) but normal alanine aminotransferase (28 UI/L. Normal 10-60) and normal aspartate aminotransferase (30 UI/L. Normal:10-42), a microcytic anemia (Hb 11.2 g/dl and MCV 57 fl) and iron levels 7 µg/dL (Normal:65-175) in favor of an iron deficiency anemia. All other parameters were normal. He was screened for Brucella (negative), EBV IgM (negative) and IgG (positive: 56.4), and widal test (negative). CT of chest revealed sub-centimetric bilateral lung nodules with absent consolidations and no enlarged mediastinal lymph nodes. Abdominal CT revealed soft tissue lesion (23 x 17 mm) localized in left para-aortic area consistent with adenopathy. There were also multiple enlarged retroperitoneal and mesenteric lymph nodes, the largest measuring 2.5 x 2 cm. He had omental and mesenteric thickening with findings of pelvic free fluid, however there was no hepatosplenomegaly (figures 1 and 2).

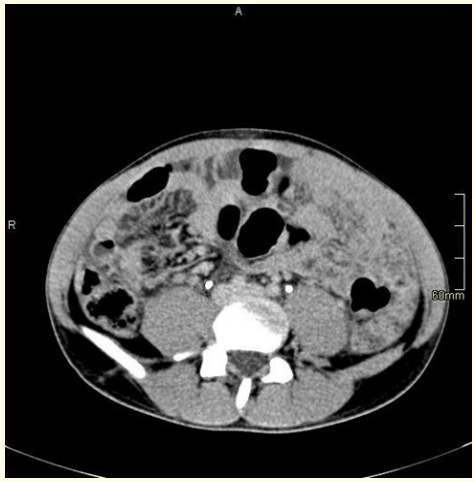

Figure 1: Abdominal CT after IV contrast administration revealing multiple enlarged mesenteric lymph nodes with omental and mesenteric thickening.

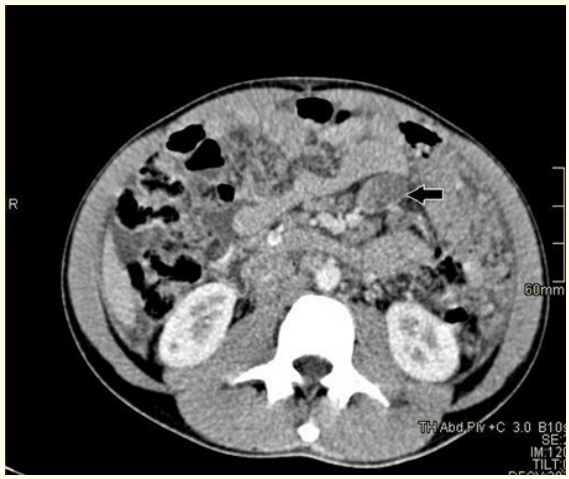

Figure 2: Abdominal CT scan after IV contrast administration acquired in portal phase, showing a 27.5 x 18.5 mm soft tissue density mass, marked by arrow, located in the left mesenteric area, consistent with an adenopathy. Free fluid in the subhepatic space.

These findings were conducive to investigate possible tuberculosis reactivation secondary to anti-TNF treatment, despite negative TB screening prior to treatment. Hence, QuantiFERON (IGRA) test was done which yielded a positive result. Additionally, a peritoneal biopsy was obtained which revealed noncaseating granulomas suggestive of tuberculosis. Hence, a PCR analysis was done on the biopsy which confirmed the presence of Mycobacterium Tuberculosis.

Therapeutic intervention

The clinical and histological findings indicate the diagnosis of military tuberculosis involving the lungs and abdomen with no neurological spread. As a result, anti-TNF treatment was stopped and the patient was started on a standard anti-tuberculosis therapy. He showed significant improvement with a decrease of CRP to 20 mg/L and ESR to 24 mm/hr after 1 month of therapy.

Discussion

The usage of anti-TNF therapy has revolutionized the treatment of inflammatory bowel diseases. TNF alpha is a pro-inflammatory cytokine which helps maintain granuloma integrity. Adalimumab blocks the activity of interferon alpha and hastens immune dysregulation. Such immune dysregulation is thought to play a key role in both reactivation of latent TB and developing primary TB infection. The tuberculosis infection seen in our patient may be due to reactivation of latent TB missed during initial screening, or due to acquiring novel TB infection, as patients on anti-TNF treatment are

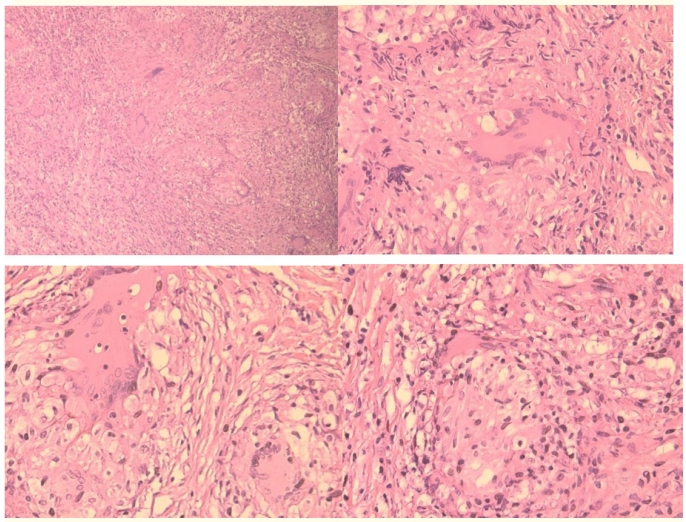

Figure 3: Granulomatous inflammation, composed of epithelioid histiocytes with varied number of multinucleated giant cells and lymphocytes. No evidence of necrosis. Stain: H&E, Power 100 and 400.

immunocompromised and vulnerable even in low risk settings. According to a study undergone by Kang., *et al*. IBD patients with TB secondary to anti-TNF treatment followed-up after one year had an incidence of TB infection 14 times greater than the overall population, despite screening and adequate management [2]. The average period expected to develop tuberculosis (TB) after Adalimumab (ADA) treatment according to a metanalysis of 128 articles and 130,000 patients was 7 months with 75% of cases occurring within 15 months, signifying that most TB cases arise within a long-term period between 1 to 1.5 years of anti-TNF therapy [3]. In patients who did develop TB, the clinical presentation varied between characteristic respiratory manifestations reported in more than 50% of documented cases, extrapulmonary manifestations reported in 25% of cases with complaints of abdominal discomfort, diarrhea and ascites and the disseminated manifestation accounting for one fifth of the cases [3]. Hence, all patients receiving anti-TNF treatments should be monitored for non-respiratory symptoms along with the typical symptoms of fever, night chills, weight loss and hemoptysis, as they can be alarming symptoms for tuberculosis, similar to our patient findings.

Nevertheless, rigorous screening for TB is pivotal before anti-TNF treatment administration to eliminate the risk of reactivation of latent disease secondary to immunosuppression triggered by anti-TNF therapy. The common baseline screening for latent TB is comprised of chest X-ray combined with tuberculin skin test [4]. However, this screening modality is inefficient and has limited validity as more than 70% of patients that develop TB post anti-TNF treatment had negative screening for latent TB [3]. For instance, TST has both low sensitivity and specificity because of its antigenic cross-reaction between BCG (Bacille Calmette-Guérin) vaccine and non-tuberculous mycobacteria. Furthermore, TST needs trained personnel, requires a two-step process and is associated with subjective interpretation of results. That being said, it cannot be identified whether our patient had a reactivation of a latent TB infection or he had a primary TB infection. As a result, the British society of Gastroenterology modified the screening guidelines to personalize the screening methodology depending on the patient risk factors and area of residence [4]. Such that, patients living in low prevalence areas should undergo a risk assessment questionnaire with clinical risk stratification considering demographic factors (gender, age), exposure to TB at work environment like prisons, shelters or hospital, a previously positive TB screening or chest X-ray [5]. If the assessment reveals high risk status, it is recommended to screen with a combination of chest x-ray and interferon-gamma release assays (IGRAs) [5]. Similarly, patients who reside in areas with high latent TB prevalence (> 12%) or have high tuberculin skin test false-positive rates (> 20%), the British society guidelines recommend screening with chest X-ray and interferon-gamma release assays (IGRAs) [4]. IGRA is a screening modality that targets interferon gamma, which is an inflammatory mediator secreted by T-cells when stimulated by M. tuberculosis antigens. IGRA has high sensitivity and specificity because its antigens do not cross react with BCG vaccine and non-tuberculous mycobacteria. Also, IGRA modality has a standardized results interpretation and requires a one-time visit. An important consideration prior to screening is the effect of the immune status on the results of tuberculin skin test and IGRA. Both tests depend on the patient's immune system for a precise result, and patients on immunosuppressant drugs like anti-TNF have an impaired response, resulting in elevated false-negative screening and an 80% decrease in positive tuberculin skin test [6]. Consequently, physicians must ensure that patients discontinue any immunosuppressant medications, when possible, prior to screening for TB [6]. Once a negative status of latent TB has been established, an annual tuberculin skin test and/or IGRA after the initiation of treatment with anti-TNF is recommended by some countries like the American and Canadian guidelines, however it is not a universal practice. This annual screening benefits patients

with treatment regimen of 3 years, as they possess the highest risk of tuberculin skin test positive conversion [7]. In patients with shorter treatment regimen close monitoring of clinical symptoms is sufficient.

Despite advancement in screening protocols patients may still develop TB infections, either de novo or reactivation of false-negative latent TB, in such circumstances it is a common practice to stop anti-TNF treatment and begin anti-TB therapy. However, the British Thoracic society recommends the continuation of anti-TNF treatment in patients complaining of severe inflammatory symptoms and complications secondary to Crohn's disease to prevent exacerbation of the underlying disease while treating TB [8].

There is a lack of data on the best timing to restart anti-TNF treatment, nonetheless the available data ensures the safety of suspending anti-TNF treatment till after the full TB treatment regimen ends. Exceptionally, it is favored to resume anti- TNF therapy after two months of anti-TB medication in patients with mild TB symptoms and vital need to resume anti-TNF therapy, given that they respond well to the anti-TB regimen and have proven sensitivity to the pharmacological agent used. Patients that satisfy all these criteria benefit from an early reinitiation of the anti-TNF therapy, with no complications in the TB symptoms and no relapse of TB in the future [7]. On the other hand, high-risk patients are required to start on isoniazid chemoprophylaxis at least 30 days prior to initiation of anti-TNF therapy and it is advised to be maintained for a total of 6 months while on anti-TNF therapy [7]. Hence, it can be inferred from this case report that a combination of IGRA test and CXR has a more diagnostic accuracy and is favored over TST as a screening modality for a latent TB infection prior to initiating anti-TNF therapy.

Conclusion

The development of TB in patients on anti-TNF is a common finding, however its incidence can be halted by applying rigorous screening protocols of higher sensitivities and tailored to the patient's risk factors. We reported a case of extrapulmonary miliary TB with minimal pulmonary manifestation in a patient screened with only tuberculin skin test. The absence of risk factor stratification calculation and IGRA usage possibly explain the false-negative tuberculin skin test and development of TB. Thus, physicians ought to employ IGRA prior to anti-TNF institution and be prudent about a potential TB infection while patients are taking anti-TNF, especially adalimumab.

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