



Case report

A healthy patient with positive mantoux test but negative quantiferon Gold assay and no evidence of risk factors – to treat or not to treat?

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ABSTRACT

A 56-year-old woman who vaccinated as a child with the Bacillus Calmette-Guerin (BCG), now tests positive to the tuberculin skin test (TST) but test negative to the Quantiferon Gold assay. She has no history of tuberculosis contact and is asymptomatic. This dilemma now is, should be treated for tuberculosis or not, based only on the TST results? To prevent these falsepositive results with TST and avoid treatment with isoniazid (INH) it may be helpful to use interferon-gamma release assay (IGRA) instead, which unlike the TB skin test is not affected by prior BCG vaccination.

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Introduction

Currently, the primary screening method for latent tuberculosis is the Tuberculin Skin Test (TST). An induration of 15 mm or more is considered evidence that the patient has been in contact with *Mycobacterium tuberculosis* (MBT). However, this test is sensitive but non-specific, which means that it is highly probable that a patient with a positive TST has latent tuberculosis (LTB). Although, at this stage, the patient does not transmit the disease as the MBT remains inactive. If the patient's immune system weakens, the MBT may become active, and tuberculosis (TB) disease may develop. Quantiferon Gold, also called interferon-gamma release assay (IGRA), another tool to diagnose LTB, has reportedly greater specificity, that is, the probability that a patient without the disease will have a negative test result.

To our knowledge at present, only one test is enough to make the diagnosis but how accurate this may be? A classic example is that of individuals with previous vaccination with the Bacillus Calmette-Guerin (BCG) vaccine, which has been linked to a false positive TST of 15 mm induration. This problem can commonly see in people born outside of the United States who have been given the BCG vaccine at birth. This false-positive TST leads to a question as the patient is advised to receive treatment with isoniazid (INH),

a drug is known to cause severe hepatotoxicity leading to fulminant liver disease and possible death.

A significant number of subjects caught in this dilemma are health care professionals, including medical doctors, nurses, among others. The majority refuses treatment because they argue that the positive TST is due to the presence of antigens in the BCG vaccine, causing a cross-reactivity. Most clinics that are aware of this cross-reactivity, follow a procedure that includes a Chest X-ray to identify possible pulmonary findings. If the X-ray is excellent, the patient will not be subjected to a 9-month treatment with INH.

Indeed, subjects with previous BCG vaccination and positive TST of 15 mm of induration have tested negative to IGRA. One wonders, how many patients may have tested positive to LTB with TST but negative with IGRA if the later had been offered. How many received treatment with INH without knowing if the test was negative? How many may have had to deal with the adverse effects of INH without need? How many develop severe hepatotoxicity or even death? This case reports a woman previously vaccinated as a child with the BCG who now is positive TST but negative to the Quantiferon Gold assay. This dilemma then pops the question of whether "to treat or not to treat" based on the TST result.

To resolve the problem, we insist that, an IGRA such as Quantiferon Gold, which has higher specificity and uses antigens not present in BCG, hence fewer chances of cross-reactivity, may be used instead of the TST in determining whether to treat or not to treat.

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Case presentation

The patient is a 56-year-old female who visited the primary care clinic to request a Mantoux or tuberculin skin test (TST), a test that required to update her nursing school file. She is in perfect health condition, with no symptoms or complaints of any sort.

She was born in Cuba, where she was vaccinated with the Bacillus Calmette-Guerin (BCG) at birth. She migrated to the United States three years ago. The patient denied having any history of or being in close contacts with anyone with tuberculosis disease or a chronic cough. She does not have a cough, night-time fever, fatigue or chills, working or residing in facilities or institutions with people who are at high risk for TB such as hospitals that care for TB patients, homeless shelters, correctional facilities, nursing homes, or residential facilities for patients with HIV infection/AIDS. She also denied having any previous or current diagnosis of silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunioileal bypass, solid organ transplant, or head cancer. The urine drug test was negative (Center for Disease Control and Prevention USA).

Her past medical history is unremarkable except for a history of papillary thyroid cancer. Her thyroid was removed via 131 radioactive iodides (thyroid ablation) 35 years ago. Since then she has been taking thyroxin replacements (Thyroxin-T4; 100 µg) once/day. She also suffers from gastroesophageal reflux and is on Omeprazole 1 capsule/day for over seven years now. In 2017 she had a gastroscopy, and a colonoscopy performed that revealed standard results. She had a hysterectomy 16 years ago due to massive intramural fibroids. She does not drink or smoke. She has no history of any allergies and is not known to be on any habit-forming medications. She is a very highly educated lady who lives with family members. Her father died 31 years ago from liver cancer and her mother two years ago from a thrombotic stroke. She is the last of four living siblings, all in good health conditions.

Her current physical examination was satisfactory. She is in no form of distress. She has normal vital signs with a bodyweight of 162 pounds. Her laboratory results such as full blood count, urea, electrolytes, and liver function tests are unremarkable. Her chest X-Ray reveals standard cardiac size and configuration. The lungs are clear and expanded. She has no active disease and no radiographic evidence of active or prior primary tuberculosis. Quantiferon Gold test was negative three years ago, and this year was still negative. The tuberculin skin test (TST) done this year was positive. The diameter of the skin induration was 15 mm (Fig. 1).

Discussion

The MBT causes tuberculosis. The most common route of transmission of MTB is exposure to air droplets from a person with active TB in the lungs or throat when someone coughs, speaks, sings or even sneezes. The MTB may infect any organ in the body, including the brain, the kidneys and the spine [1]. The Mantoux tuberculin skin test using purified protein derivative (PPD), is the primary screening method for tuberculosis (TB) infection either active or latent. The TST test is sensitive but non-specific in the diagnosis of active TB [2]. Another test used in screening for TB is the interferon-gamma release assay, Quantiferon Gold test, and this has a more significant specificity [3].

There is a recommendation for patients with a positive tuberculin skin test to receive a course of therapy for latent TB (LTB), because although at this stage a patient does not transmit the disease, the MBT may remain inactive. If the patient's immune system weakens, the MBT may become active in developing into active and infectious TB. However, there is a puzzle or enigma if the patient has been previously exposed to the Bacillus Calmette-Guerin (BCG) vaccine [4,5]. The BCG vaccine has been given to



Fig. 1. A positive tuberculin skin test, which shows an induration of 15 mm, is consistent with the presumptive diagnosis of latent tuberculosis (LTB).

many people who are born outside of the United States, and it may cause a false positive reaction to a TST. Indeed, the Center for Disease Control and Prevention has acknowledged that it may complicate decisions about prescribing and commencing treatment [6].

That is the situation of this patient in this case study, a Cuban national who attended the Nurse Practitioner Clinic just to get a TST done to update her nursing file and only to realize she developed a 15 mm granuloma reaction to the TST. This result prompted the nurse practitioner to refer the patient to the TB clinic for an interview. The patient disclosed no contact with a TB infected individual. An X-ray and then an IGRA revealed a negative result as well as the one performed in 2015 when she entered the United States of America. The fact that this method uses antigens not present in Bacillus Calmette-Guerin (BCG) can attribute this concordance of IGRA results, which avoid the cross-reactivity.

A positive TST after a BCG vaccination implies that the cell-mediated immunity of an individual is intact. In immunological terms, this means that a significant effector mechanism of cell-mediated immunity in TB is the activation of MTB-infected macrophages by the gamma interferon (IFN- γ). NK cells and different T-cell subsets produce IFN- γ , and its synthesis is regulated by TNF- α , IL-1 β , IL-12, IL-18, and possibly IL-15, all released from activated macrophages and dendritic cells [7]. When a patient is vaccinated and develops a negative TST, it suggests that such patient is experiencing an impaired cell-mediated immunity, which is the most critical risk factor for the development of TB.

A meta-analysis conducted by Abubakar and collaborators (2013) reviewed clinical trials and observational studies concerning the effectiveness of BCG vaccines. Although most of the studies revealed protection for up to 10–15 years, results were not conclusive as many studies did not follow-up participants for a more extended period [8]. However, many health care professionals seem to be unaware of this fact and may argue that these individuals require being treated for LTB with INH even if the chest X-ray is clear. This approach may be dangerous because INH, although very efficient, it is also a potentially hazardous drug [9].

Isoniazid (INH) was introduced into clinical practice in 1954 for the treatment of pulmonary TB. Currently, it is considered the drug of choice to treat LTB (as monotherapy), although may also be regarded as part of combination therapy. The reason for this choice is based on its high efficacy. Also, it is known as a bactericidal agent

and needs to be activated by bacterial catalase before acting against rapidly-dividing mycobacteria such as *M. tuberculosis*. It does so by inhibiting the synthesis of mycolic acids, which are essential components of the mycobacterial cell wall. The bactericidal action disrupts both, actively growing intracellular as well as extracellular MTB [10].

Unfortunately, INH is not void of undesirable effects with hepatotoxicity being its significant side effect. INH-induced hepatotoxicity ranges in severity from an asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation [6]. Indeed, the FDA has issued a boxed warning stressing the possible development, and severe risks of this toxicity. The notice states that "INH treatment can lead to severe and sometimes fatal hepatitis. It also states that this toxicity usually occurs within the first three months of therapy, although it can develop even after several months of therapy. Although rare in children, INH hepatotoxicity may still occur and may be fatal. Reports reveal that patients 50 years and older, have the greatest risk (2.3%; 8%) respectively, as well as patients of African descent. The most current report from the Drug-Induced Liver Injury Network (DILI) indicates that the actual incidence of INH-induced liver injury is under-reported mainly in the United States, and it is ranked second among drugs that cause liver injury despite under-reporting [11].

To prevent such toxicity, before starting treatment with INH patients need to be monitored at monthly intervals and then periodically. Monitoring includes hepatic enzyme levels (AST, ALT) evaluation as well as the development of symptoms of liver damage. If ALT levels are five times above the upper limit of normal (ULN) or three times above ULN in the presence of symptoms, INH must immediately be discontinued [12]. Likewise, patients are requested to directly report to the healthcare provider if they develop jaundice, anorexia, nausea, dark urine, pale stool, or bloody or tar-colored stool, persistent itchiness and rash of the hands and feet, chronic fatigue, and weakness. They must also report fever of more than three days duration, as well as upper right quadrant discomfort. Nevertheless, even with monitoring, INH-induced hepatotoxicity remains a significant cause of acute liver failure and death as well as emergency liver transplantation. This toxicity is believed to be a result of an idiosyncratic response [13].

We want to stress that the diameter (mm) of induration after BCG vaccination tends to wane over time, but in some individuals, a Type-IV hypersensitivity reaction in the skin can occur leading to a greater induration (>15 mm) that can be confounded or be interpreted as TB. Besides, we underscore that the degree of

induration, in this case, was 15 mm, but this is not usually seen in the population after the administration of BCG, especially after years.

Conclusion

For more accurate results we propose the development of extensive studies in countries, where the BCG vaccine is administered at birth to determine if the antigens present in the BCG vaccine interfere with the TST results in some individuals. That is essential to avoid missing or making a wrong diagnosis and to provide precise treatment strategies instead of unnecessary treatment with INH. The influence of the BCG vaccine on the development of TST false-positive reactions needs further studies. The question as mentioned earlier to treat or not to treat a positive Mantoux test is still not answered. A positive IGRA test, as well as a strong history of TB exposure, is the author's opinion about it.

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