Giant Tuberculin Reaction Associated With the Homeopathic Drug Tuberculinum: A Case Report

Ekaterini Syrigou,[1] Ioannis Gkiozos,[2] Ioannis Dannos,[2] Dimitra Grapsa,[2] Sotirios Tsimpoukis,[2] and Konstantinos Syrigos[2]

[1]Allergy Department and [2]Oncology Unit GPP, "Sotiria" General Hospital, Athens School of Medicine, Athens, Greece

Giant reactions to the tuberculin skin test are extremely rare and have been previously reported almost exclusively in patients with lepromatous leprosy. We herein report a giant tuberculin reaction associated with the homeopathic drug Tuberculinum in a patient with no evidence of active tuberculosis or leprosy.

Keywords. BCG vaccination; giant reaction; tuberculosis; tuberculin skin test.

The tuberculin skin test (TST) is the most widely used screening tool for the detection of latent tuberculosis. Skin reaction to intradermal injection of tuberculin, a purified protein derivative (PPD) of tubercle bacilli, is based on the induction of a delayed-type hypersensitivity response in subjects presensitized to mycobacterial antigens [1]. According to the latest guidelines and recommendations by the American Thoracic Society and the Centers for Disease Control and Prevention, a cutoff point of 15 mm should be used for separating positive from negative skin reactions to tuberculin in low-risk groups (patients from low-incidence regions, with no history of tuberculosis contact, immunosuppression, or other known risk factor for tuberculosis) [1].

Giant reactions to tuberculin, defined as accelerated and exaggerated responses typically exceeding 40 mm in diameter, are extremely rare and have been previously reported almost exclusively in individuals with lepromatous leprosy [2, 3] and only occasionally in patients with active tuberculosis [2, 4]. To the best of our knowledge, large tuberculin reactions in the absence of active mycobacterial infection have been previously reported only as a result of inadvertent injection of vaccine instead of a PPD product [5]. We report a tuberculin reaction of 100 mm in diameter, associated with administration of Tuberculinum, a homeopathic drug prepared from tuberculous tissue, in a patient with no evidence of active mycobacterial infection. A propos of this case, the need for improved safety and quality control of homeopathic medicines prepared from potentially hazardous biological materials is also briefly discussed.

CASE REPORT

A 43-year-old man presented to the Allergy Department at "Sotiria" General Hospital, Athens, Greece, with a 10-week history of intermittent cough, wheezing, and dyspnea following a viral upper respiratory infection. The patient had been diagnosed with bronchial asthma 3 years earlier, which was well controlled under a combination of maintenance and symptomatic treatment as needed (montelukast/formoterol) until about 1 year prior to presentation. At that time, the patient discontinued conventional therapy in favor of alternative treatment options (homeopathy) for his asthma symptoms. At presentation, physical examination was unremarkable, except for mild bilateral wheezing on forced expiration. Chest radiographic and complete blood count results were within normal limits. The erythrocyte sedimentation rate and C-reactive protein level were normal (9 mm/hour and 2 mg/L, respectively). The patient had a documented history of Bacille Calmette-Guerin (BCG) vaccination received 23 years ago, as evidenced by immunization records and a visible BCG scar. He had no demographic, occupational, or other known risk factors for tuberculosis (eg, immunosuppression, positive human immunodeficiency virus status, recent tuberculosis contact, or recent travel to an endemic country). Screening for latent tuberculosis was nonetheless recommended prior to treatment initiation, due to recent studies suggesting that the risk of developing active tuberculosis among patients with respiratory diseases may be exacerbated by use of inhaled corticosteroids [6]. After obtaining the patient's consent, a TST was administered by intradermal injection of 0.05 mL (5 tuberculin units [TU]) of PPD (PPD RT-23, 10 TU/0.1 mL, Statens Serum Institut, Copenhagen, Denmark) into the volar forearm, using the Mantoux method. The skin test result was read 48 hours later as a very strong positive reaction with a redness of approximately 117 mm and an induration

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Correspondence: Dimitra Grapsa, MD, PhD, Oncology Unit GPP, "Sotiria" General Hospital, Mesogion 152, 115 27 Athens, Greece (dimgrap@yahoo.gr).

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of approximately 100 mm, using the ballpoint-pen method. No ulceration was noted, and the tuberculin reaction gradually decreased following 5 days of treatment with a topical corticosteroid (mometasone furoate cream). Upon a more detailed review of his homeopathic regimen, it was further revealed that he was taking the homeopathic drug Tuberculinum of 1M potency (1 tablet daily) for the last 3 months. A QuantiFERON-TB Gold test (QFT) was performed in the Greek National Reference Laboratory for Myobacteria ("Sotiria" General Hospital) with negative results, thereby strongly arguing against the possibility of tuberculosis infection. The final working diagnosis was asthma exacerbation due to upper respiratory infection. The patient was advised to discontinue use of Tuberculinum and resume regular preventive treatment (montelukast) for adequate asthma control with the addition of symptomatic relievers (salbutamol/fluticasone) in acute attacks.

At 4 months' follow-up, the patient reported no recurrence of cough, dyspnea, or wheezing and no emergence of new symptoms (including fever, weight loss, fatigue, or night sweats). He also reported that he had discontinued use of Tuberculinum since his last visit. Clinical examination was unremarkable. Repeat QFT testing was performed with negative results (nil, 0.09 IU/mL; tuberculosis antigen, 0.12 IU/mL; mitogen, 13.21 IU/mL; tuberculosis antigen-nil, 0.03 IU/mL; mitogen-nil, 13.09 IU/mL). The patient was again advised to return to our department every 6 months for regular follow-up evaluations.

DISCUSSION

Previous exposure to *Mycobacterium tuberculosis* or nontuberculous mycobacteria as well as prior vaccination with BCG may all cause a positive TST result, and the interpretation of positive tuberculin reactions in previously vaccinated patients remains a problematic and rather controversial issue [7, 8]. In contrast to the prevailing belief that larger reactions to the TST indicate an increased probability of current or future active tuberculosis, there is also the view that the size of a positive TST response may not reliably discriminate between BCG-induced reactions and those caused by natural mycobacterial infections [7–9]. On the other hand, novel interferon-γ release assays (IGRAs), including the QFT test, have higher specificity than tuberculin skin testing in BCG-vaccinated populations and may be used either as an alternative to the TST or to confirm positive TST results before initiation of treatment for latent tuberculosis [10].

Tuberculin sensitivity caused by previous BCG may range from no response to an induration of 20 mm (with a mean reaction size of 10 mm), tends to decrease with time (although it can be "boosted" by subsequent TST), is typically more pronounced in younger adults, and is unlikely to persist for more than 10 years after vaccination [1, 7]. Interestingly, a correlation between the number of BCG scars and the size of tuberculin induration has also been reported in several studies [11, 12], suggesting that repeat BCG vaccination may significantly enhance the TST response, although not always enhancing protective immunity as well.

The giant tuberculin reaction observed in our reported case—one of the largest reported in the literature—was attributed to the homeopathic drug Tuberculinum for the following reasons: the patient had no known risk factors for tuberculosis and no symptoms or radiographic signs consistent with active tuberculosis or atypical mycobacterial infection; the initial and repeat QFT test results were negative; and BCG vaccination had been administered >20 years ago. It is, therefore, conceivable that repeat administration of Tuberculinum, a homeopathic vaccine (nosode) originating from the causative agent of tuberculosis, may have "boosted" the TST response in our patient, producing an impressive tuberculin reaction through a yet unknown mechanism. Notably, although a negative IGRA cannot rule out completely the possibility of latent tuberculosis, development of active tuberculosis—which is the only gold standard for the presence of latent tuberculosis—in immunocompetent low-risk individuals with negative IGRAs is very unlikely [13, 14]. Nonetheless, long-term follow-up of asymptomatic patients with discordant TST and IGRA results (such as the present case) is still warranted to monitor for potential development of active tuberculosis in the future.

Evidence-based information on the quality and safety of homeopathic preparations is surprisingly limited, despite their widespread use. According to a recent World Health Organization report, "although homeopathic medicines are in general considered to be safe when administered appropriately, toxicological aspects should not be neglected especially when using lower dilutions of unsafe starting material" [15]. Clinicians of all specialties should be aware that alternative treatments, and especially those of biological origin, may not necessarily be pharmacologically inactive and may occasionally interact with conventional medications and procedures, as in our reported case.

In conclusion, we herein report a giant tuberculin reaction associated with the homeopathic drug Tuberculinum in a patient with no evidence of active tuberculosis or leprosy. Undoubtedly, thorough review of all available epidemiologic, laboratory, and clinical data, including a complete medication history, is a prerequisite for accurate interpretation of a positive TST. Longitudinal follow-up in such patients is also required to safely exclude the presence of latent tuberculosis, even among low-risk individuals.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med **2000**; 161:1376–95.
2. Waters MF, Stanford JL. Giant reactions to tuberculin in lepromatous leprosy patients. Int J Lepr Other Mycobac Dist **1985**; 53:546–53.
3. Murthy V, Horowitz HW, Pham VP, et al. Giant PPD reaction with positive QuantiFERON-TB Gold in a patient with lepromatous leprosy. J Drugs Dermatol **2012**; 11:1151–52.
4. Avasthi R, Chaudhary SC, Mohanty D. Giant Mantoux reaction. Indian J Med Microbiol **2009**; 27:78–79.
5. Chang S, Pool V, O'Connell K, et al. Preventable mix-ups of tuberculin and vaccines: reports to the US Vaccine and Drug Safety Reporting Systems. Drug Saf **2008**; 31:1027–33.
6. Ernst P, Suissa S. Systemic effects of inhaled corticosteroids. Curr Opin Pulm Med **2012**; 18:85–9.
7. Tissot F, Zanetti G, Francioli P, et al. Influence of bacille Calmette-Guerin vaccination on size of tuberculin skin test reaction: to what size? Clin Infect Dis **2005**; 40:211–17.
8. Al Zahrani K, Al Jahdali H, Menzies D. Does size matter? Utility of size of tuberculin reactions for the diagnosis of mycobacterial disease. Am J Respir Crit Care Med **2000**; 162:1419–22.
9. Wang L, Turner MO, Elwood RK, et al. A meta-analysis of the effect of bacilli Calmette-Guerin vaccination on tuberculin skin measurements. Thorax **2002**; 57:804–9.
10. Diel R, Loddenkemper R, Meywald-Walter K, et al. Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold in Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. Chest **2009**; 135:1010–18.
11. Gundogdu Z, Aydogan M, Arisoy ES, et al. Effect of number of BCG vaccination on tuberculin induration size. J Paediatr Child Health **2007**; 43:476–79.
12. Saito M, Bautista CT, Gilman RH, et al. The value of counting BCG scars for interpretation of tuberculin skin tests in a tuberculosis hyperendemic shanty-town, Peru. Int J Tuberc Lung Dis **2004**; 8:842–47.
13. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm, Sweden: ECDC, **2011**.
14. Diel R, Loddenkemper R, Meywald-Walter K, et al. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. Am J Respir Crit Care Med **2008**; 15:1164–70.
15. World Health Organization. Safety issues in the preparation of homeopathic medicines. Geneva, Switzerland: WHO, **2009**.