IMMEDIATE HYPERSENSITIVITY REACTION TO TUBERCULIN ON SKIN-PRICK TESTING IN TUBERCULOUS PATIENTS

YC Chee

SYNOPSIS

Forty seven patients with tuberculosis of various severity and duration on treatment were skin-prick tested once to tuberculin PPD RT 23 solution on an outpatient basis for the presence of immediate hypersensitivity reaction. Six patients were positive with small weals. Five of these six had severe tuberculosis (four out of eleven with far advanced culture-positive pulmonary disease and one with miliary tuberculosis) in contrast to one out of seventeen with minimal pulmonary tuberculosis. The other patients with negative results comprised one with tuberculous lymphadenitis, another with a solitary pulmonary tuberculoma, four with tuberculous pleural effusion and thirteen with moderately advanced pulmonary tuberculosis.

Tuberculin skin testing gives five distinct temporal responses. The significance of the immediate response is not known. It is suggested that patients with more severe disease are more likely to produce IgE antibodies to tuberculin.

INTRODUCTION

The tuberculin skin tests have been the traditional method of diagnosing infections with Mycobacterium tuberculosis. Purified protein derivative (PPD) injected intracutaneously (Mantoux Test) is used diagnostically to detect delayed hypersensitivity as tuberculosis is the classic example of a disease that is controlled almost entirely by cell-mediated immunity involving the macrophage as the effector cell and the lymphocyte (especially the T-cell) as the immunoresponsive cell (1). Humoral immunity is also present in tuberculous patients and antibodies to mycobacterial antigens of the IgG, IgM and IgA classes have been documented (2). Tuberculin has been shown to cause other distinct dermal reactions besides the typical type IV hypersensitivity. These include an immediate (type I), an early (type III) reaction and a Listeria-type response due to macrophage activation detectable at 24 hours (3).

This study sought to define if the presence of immediate type I hypersensitivity reaction of tuberculous patients to tuberculin indicated severity of the disease.

Department of Medicine III
Tan Hock Seng Hospital,
Moulmein Road
Singapore 1130

YC Chee
MBBS, MRCP, M Med (Int Med)
Senior Registrar

PATIENTS AND METHOD

Forty seven patients on treatment for tuberculosis at the outpatient clinic were skin-prick tested to three solutions, viz, negative control, positive control with histamine 1 mg/ml and PPD RT 23 solution. They were consecutive patients seen at the chest clinic on Thursday mornings by me over a month. Details of the methodology of skin-prick testing are given elsewhere (4).

The patients ranged from 16 to 75 years of age. Nineteen were females. One was a European, three Indians, eight Malays and the rest Chinese. All except one had post-primary tuberculosis. One patient had tuberculous lymphadenitis, one a tuberculoma in his right lung, four had only tuberculous pleural effusion and the rest pulmonary tuberculosis. Of the remaining 41 patients with pulmonary tuberculosis, 17 had minimal disease, 13 moderately advanced disease and 11 had far advanced disease (of which one had miliary tuberculosis and another tuberculous orchitis as well). Twenty one of these 41 patients were sputum culture-positive for niacin-positive mycobacteria. Three of the patients had relapsed pulmonary tuberculosis while another six had concomitant diabetes mellitus (all nine were sputum culture-positive patients).

Skin-prick testing was carried out once in each patient but at various stages during disease treatment ranging from the day treatment started to 2 years 5 months after the initiation of therapy i.e. 5 months after all therapy had ceased. All patients were on standard antituberculous therapy consisting of regimens using streptomycin, ethambutol, para-amino-salicylic acid, or isoniazid while relapsed patients had also rifampicin, kanamycin or pyrazinamide as well.

RESULTS

Six of these 47 patients reacted positively to the skin-prick test with a small weal after 15 to 20 minutes. None reacted to the negative control solution. These weals were better felt than seen because they were small. Three were males, two Malays, one Indian and three Chinese. None was diabetic. One had minimal apical, culture-negative tuberculosis (Mantoux reaction 10 mm), another miliary tuberculosis (Mantoux reaction 18 mm) and four had far-advanced culture-positive disease where the Mantoux test to PPD RT 23, 1 TU was not indicated. The skin-prick tests were done in these six patients at one, two, four, sixteen (two patients) and 29 months from the day therapy started.

DISCUSSION

Of the various dermal reactions to intracutaneous tuberculin, the Arthus reaction may account for the type III reaction seen at 6-8 hours as IgG, IgM and IgA antibodies have been reported although their correlation was not significant (2). The immediate reaction to intracutaneous tuberculin probably is IgE-mediated but of the three available methods for documenting type I reactions, the prick test is superior to the scratch test and the intracutaneous test, and with appropriate extracts, it serves to identify almost all the subjects with specific IgE antibody (5). Weal sizes correlate significantly with the amounts of the specific IgE antibodies (5).

In an early study of humoral antibodies to components derived from mycobacterium tuberculosis, Bardana, McClatchy, Farr and Minden (6) found the universal occurrence of antibodies to tubercle bacilli in sera from non-tuberculous and tuberculous individuals. More recently, Grange, Gibson, Batty and Kardjito (7) in assessing the specificity of the humoral response to soluble mycobacterial antigens in tuberculosis concluded that the availability of highly purified soluble antigens specific for mycobacterium tuberculosis would not permit more cases of tuberculosis to be diagnosed serologically although the most discriminating class of immunoglobulin was Ig G while the least was IgM (8). In all these reports, there was no mention of the IgE response. Dannenberg (9) stated that tuberculosis remains the classic example of a disease that is controlled almost entirely by cell-mediated immunity. Collins (10) in a review of the immunology of tuberculosis saw little or no role of specific immunoglobulins in anti-tuberculous immunity.

Despite the foregoing, tuberculin testing has been observed to give five distinct responses occurring immediately after injection, and after 30 minutes, 6-8 hours, 24 hours and 48 hours (11). The degree of reaction at 6-8 correlated significantly with the levels of specific antibodies in the IgG and IgA classes and the 48 hour response with specific antibodies in the IgG class. In the same study (11), 15 (16.7%) out of 90 patients showed an immediate response, a rate comparable to this study where 6 (12.8%) out of 47 patients were positive although the more sensitive prick test was used instead.

There is a suggestion from this study that those patients with more severe disease were more likely to produce IgE antibodies to tuberculin (one out of 17 with minimal versus four our of 11 with far advanced pulmonary tuberculosis and the sole patient with miliary tuberculosis). Kardjito and Grange (11) noted however that none of the skin-test peaks correlated with the extent of disease or with the presence of cavitation but they did not give the breakdown of disease severity in the 15 patients showing immediate response after skin testing. Immediate reactions to prick tests however, may be mediated by antibodies other than IgE (5) though this is rare, and immediate hypersensitivity to the constituents of the diluent used in PPD RT 23 is not unknown (1).

Lenzini, Rottoli and Rottoli (12) classified patients with tuberculosis into two polar groups, those reactive showing good cell-mediated immunity with little or no antibody formation and those unreactive with poor cellular responses but exuberant antibody production. As five out of the six patients with immediate hypersensitivity reaction to tuberculin had severe disease, this could fit into the unreactive group of the above classification where the IgE response would presumably represent part of the total exuberant antibody production.

REFERENCES

1. American Thoracic Society. The tuberculin skin test. Am Rev Resp Dis 1981; 124: 356-63.
2. Kardjito T, Handoyo I, Grange JM. Diagnosis of active tuberculosis by immunological methods. 1. The effect of tuberculin reactivity and previous BCG vaccination on the antibody levels determined by ELISA. Tubercle 1982; 63:269-74.
3. Kardjito, Grange JM. Diagnosis of active tuberculosis by immunological methods. 2. Qualitative differences in the dermal response to tuberculin in patients with active pulmonary disease and healthy tuberculin-positive individuals. Tubercle 1982; 63:275-8.
4. Chee YC. Skin-prick tests for atopy in asthmatic adults in Singapore. ASEAN J Clin Science 1982; 3:259-64.
5. Pepys J. Laboratory methods in clinical allergy. Proc roy

soc med 1972; 65:271-4.
6. Bardana EJ, McClatchy JK, Farr RS, Minden P. Universal occurrence of antibodies to tubercle bacilli in sera from non-tuberculous and tuberculous individuals. Clin Exp Immunology 1973; 13:65-77.
7. Grange JM, Gibson J, Batty A, Kardjito T. The specificity of the humoral immune response to soluble mycobacterial antigens in tuberculosis. Tubercle 1980; 61:153-6.
8. Grange JM, Gibson J, Nassau E, Kardjito T. Enzyme-linked immunosorbent assay(ELISA): A study of antibodies to Mycobacteriuim tuberculosis in the IgG, IgA and IgM classes in tuberculosis, sarcoidosis and Crohn's disease. Tubercle 1980; 61:145-52.
9. Dannenberg AM. Pathogenesis of pulmonary tuberculosis. Am Rev Resp Dis 1982; 125 (supp):25-9.
10. Collins FM. The immunology of tuberculosis. Am Rev Resp Dis 1982; 125 (supp):42-9.
11. Kardjito T, Grange JM. Immunological and clinical features of smear-positive pulmonary tuberculosis in East Java. Tubercle 1980; 61:231-8.
12. Lenzini L, Rottoli P, Rottoli L. The spectrum of human tuberculosis. Clin Exp Immunology 1977; 27:230-7.