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Untreated tuberculosis may be associated with lymphopoenia, not lymphocytosis

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Summary

Initial full blood counts were compared in 25 consecutive adult patients admitted with active tuberculosis and 25 matched, healthy controls and, if available, repeated at 6 and 12 months during treatment. Patients with tuberculosis had significant lymphopoenia associated with anaemia, neutrophil leucocytosis and monocytosis. None of these derangements correlated with radiological extent of lung disease or cutaneous tuberculin reactivity. Lymphocyte counts returned to normal within 2 weeks of initiating chemotherapy in all lymphopoenic patients and normal ranges for all blood counts were restored by 6 months in all the patients studied. In a smear-negative patient, a clinical diagnosis of tuberculosis would be supported by the finding of lymphopoenia, not lymphocytosis.

Résumé

Les numération-formule sanguines initiales de 25 patients adultes hospitalisés pour tuberculose active furent comparées à celles de 25 sujets témoins et répétées, chaque fois que cela fut possible, au 6ème et 12ème mois du traitement. Les patients atteints de tuberculose avaient une lymphopénie significative associée à une anémie, une neutrophilie et une monocytose. Aucune de ces anomalies ne put être corrélée à l'étendue des lésions pulmonaires radiologiques ou à l'intensité de l'intradermoréaction à la tuberculine. Chez tous les patients lymphopéniques, les numérations lymphocytaires sont revenues à la normale dans un délai de 2 semaines après la mise en route du traitement et chez tous les patients étudiés, les numération-formule sanguines ont retrouvé des valeurs normales dans un délai de 6 mois. Chez un patient dont l'examen bactériologique direct est négatif, le diagnostic clinique de tuberculose serait appuyé par la découverte d'une lymphopénie et non d'une lymphocytose.

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Introduction

There is a popular misconception among medical graduates that active tuberculosis causes lymphocytosis. For instance, 14 of 26 (54%) junior doctors questioned at Northwick Park Hospital, Harrow would consider the presence of lymphocytosis as evidence in favour of a diagnosis of tuberculosis in a patient in whom bacteriological proof was difficult to obtain. Furthermore, some standard haematology texts [1,2] inexplicitly list tuberculosis as a cause of lymphocytosis. The following study was undertaken to determine the full blood counts in a group of patients with newly diagnosed tuberculosis, and their possible correlations with two clinical parameters: radiological extent of lung disease and cutaneous reactivity to tuberculin-purified protein derivative (PPD).

Subjects and methods

Twenty-five consecutive patients aged 18–65 years, admitted into Northwick Park Hospital, Harrow with proven tuberculosis, and healthy controls matched for age, sex (18 male, 7 female) and ethnic group (19 Indian subcontinent, five Caucasian, one African) were studied on entry and, if available, at 6 and 12 months. Diagnosis was based on the demonstration of acid-fast bacilli in sputum, body fluids or

histology specimens and was eventually confirmed by positive cultures of *Mycobacterium tuberculosis*.

Twenty-one patients had lung disease, two had meningeal, one miliary and one glandular tuberculosis. Further clinical details of the patients are given elsewhere [3].

Full blood counts were measured by Coulter counter and differential white counts by visual counting (500 cells) on a blood smear stained with May–Grünwald Giemsa. The extent of lung disease was assessed from chest X-ray according to the MRC Hong Kong Study criteria [4]. Skin reactions were measured at 48 h to 1, and if negative 10, tuberculin units of PPD (Evans Medical Ltd, Greenford, UK) given intradermally.

Statistical evaluation was performed by Student's *t*-test. Neutrophil and monocyte counts required logarithmic transformation, and are therefore summarized as the mean and 95% confidence intervals. Chemotherapy consisted of rifampicin, isoniazid and ethambutol for 2 months, continuing with rifampicin plus isoniazid for 7 (pulmonary) or 16 (extrapulmonary) months.

Results

Compared with controls, tuberculosis patients had significant anaemia haemoglobin ((mean ± s.d.) 12.9 ± 2.1 g/dl versus 14.8 ± 1.2 g/dl; $P < 0.0001$), neutrophil leucocytosis (mean 5.6 (95% confidence intervals 4.9–6.3) × 10^9/l versus 3.3 (2.9–3.9) × 10^9/l; $P < 0.0001$), monocytosis (mean 405 (286–545)/μl versus 253 (185–331)/μl; $P = 0.03$) and lymphopoenia (mean 1.5 ± 0.8 × 10^9/l versus 2.2 ± 0.6 × 10^9/l; $P = 0.02$) (Fig. 1). Ten patients (40%), as against two controls (8%), had lymphocyte counts of less than 1.3 × 10^9/l ($P = 0.008$, Fischer's exact test), and four controls, but no patients, had lymphocyte counts above 3 × 10^9/l (Fig. 2). Normal ranges for all blood counts were restored within 6 months of initiating chemotherapy. In all 10 lymphopoenic patients studied daily, consistently normal lymphocyte counts, or high counts in two, were observed within 14 days of starting treatment. Blood counts did not correlate with duration, site or extent of lung disease, cavitation, sex, age, ethnic distribution or cutaneous tuberculin hypersensitivity.

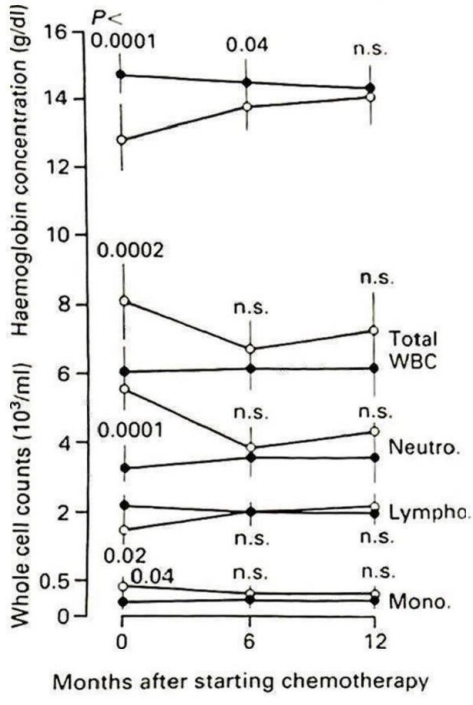

Fig. 1. Changes in mean haemoglobin and white cell counts of 25 tuberculosis patients (○) and matched healthy controls (●). 2 s.d. or 95% confidence intervals are indicated.

Discussion

These data confirm that untreated tuberculosis in this unselected group of patients was associated with anaemia, increased neutrophil and monocyte counts, but normal or decreased lymphocyte counts, although lymphocytosis occurred in two patients during treatment. Lymphopoenia in active tuberculosis results from a reduction predominantly in T-helper cells [5,6]. Rapid restoration of normal counts during treatment suggests that T-lymphopoenia may be caused by local recruitment [7], probably at sites of granuloma formation, rather than total body depletion as occurs in AIDS. The mechanism of lymphocyte trapping or its reversal by chemotherapy is not known. It is possible that the rapid killing of tubercle bacilli by potent modern drugs in some way permits the release and return into the circulation of such sequestered cells. In contrast, blood

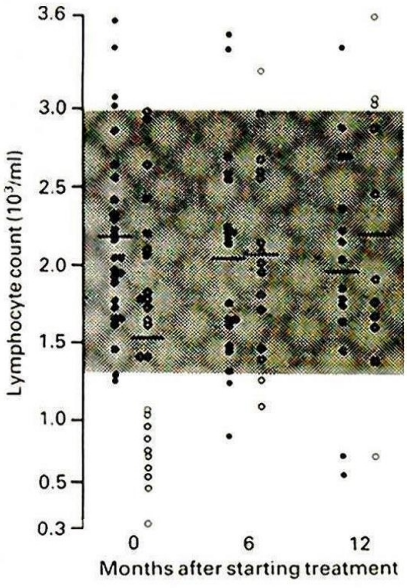

Fig. 2. Distribution of peripheral blood lymphocyte counts among tuberculosis patients (○) and matched healthy controls (●). Shaded area represents the normal laboratory range.

monocyte counts rise in parallel with the activity of tuberculous infection owing to hyperproliferation of monocytes consequent upon their increased consumption in granulomas [8]. Indeed, evidence from the older literature [9,10] suggests that the monocyte:lymphocyte ratio may be a useful index of activity in human tuberculous infection. Active tuberculosis is usually associated with peripheral blood lymphopoenia, not lymphocytosis, although the latter may occur during treatment or healing. However, lymphopoenia does not correlate with extent of lung tuberculosis or tuberculin hypersensitivity. Normal lymphocyte counts are restored within a few weeks of initiating standard chemotherapy.

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