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EDITORIAL

Soluble immunological markers of disease activity in tuberculosis

C. Saltini*, V. Colizzi**

The obtention of a microbiologically confirmed diagnosis of tuberculosis (TB), assessment of the extent and intensity of disease activity, and follow-up of the patient response to treatment are all encumbered by our still limited ability to quantify the infectious load using the microbiological tools available in current practice. In this context, a number of attempts have been made to determine the role that soluble disease markers could play as diagnostic and prognostic indicators in pulmonary, pleural and extrapulmonary TB. As in other lung diseases, molecules which become overexpressed during immune cell activation have been measured in biological fluids such as serum, pleural fluid and the epithelial lining fluid (ELF) of the lower respiratory tract of TB patients, with the intent of gauging the activation of the immune system in response to the TB bacillus, to assess disease activity and predict the disease course.

A number of specific and nonspecific immune marker studies have thus appeared in the literature in the last twenty years. Among them *Mycobacterium tuberculosis*-specific serum antibodies, the T-lymphocyte enzyme adenosine deaminase, the macrophage activation product neopterin, the mononuclear cell surface protein β_2 microglobulin, soluble T-cell interleukin (IL)-2 receptors as well as soluble CD4 and CD8 receptors, macrophage and T-cell adhesion molecules and acute phase reactant proteins have all been proposed as indicators of disease activity in pulmonary and extrapulmonary TB [1–5] and as diagnostic and prognostic indicators in tuberculous pleural effusions [6]. More recently, the cytokines tumour necrosis factor (TNF-α), IL-1, IL-6, interferon gamma (IFN-γ) and IL-12 and the chemokines IL-8, monocyte chemotactic peptide-1 (MCP-1) and regulated on activation, normal T cell expressed and secreted (RANTES) have been found to be elevated in the bronchoalveolar lavage fluid or serum of patients with active disease and have been proposed as markers of disease activity [7–12]. However, none of these markers has shown itself as unarguably better than the measurement of haemoglobin concentration and of erythrocyte sedimentation rate, which are the most inexpensive and generally used inflammation markers.

By analogy with the other major disease caused by a mycobacterium, leprosy, in which a relationship between the type of immune reaction, the immunopathology and the clinical course has been characterized in the lepromatous and tuberculoid forms of leprosy [13], the identification of immunological markers of the "classic" pathological expressions of disease, *i.e.* the exudative and productive forms of TB, has been attempted, although not as successfully. Based upon the leprosy model, a spectrum of immunopathological reactions was identified in TB in 1977 [14], whereby the tuberculin reaction and the level of specific antibodies in serum were proposed as the markers of a spectrum of clinical presentations. In that study, the self-limiting course and the good response to chemotherapy of paucibaciliary productive or reactive TB was associated with a strong tuberculin reactivity. Conversely, the precipitous course and poor response to treatment of multibaciliary TB, a reactive disease with a low tuberculin responsiveness and a strong antibody reaction. Since then, understanding of the mechanisms of cell-mediated immunity has advanced apace, and the terms T helper cell (Th)-1 (indicating the type of reactions dominated by the release of IL-12, IL-2 and IFN-γ and associated with granulomatous diseases) and Th2 (the type of reactions dominated by IL4 and IL-5 and associated with allergy) [15] have become part of the pulmonologists allergologists jargon and several studies have been published showing that, as expected, the local immune response in pulmonary TB is dominated by a Th1 response [16], whereas the systemic blood T cells are characterized by a relative inability to produce the Th1 cytokine IFN-γ [17]. There is some evidence that although the immune response to the TB bacillus of those individuals with latent TB infection or with paucibaciliary TB is dominated by Th1, that of those affected by active disease is, at least in part, a Th2-type response, suggesting that a Th1/Th2 dichotomy may exist here, as in leprosy, and may correlate with the classic disease immunopathological presentations of exudative and productive TB.

Recently, a central role in the development of TB has been attributed to TNF-α, a cytokine capable of inducing fever and weight loss, *i.e.* the typical symptoms of the disease. It has been proposed that immunity and protection against the offending agent are provided by a protective reaction called cell-mediated immunity, which is characterized by macrophage production of IL-1 and IL-12 leading to IL-2 and IL-2 receptor expression and to CD4 T cell proliferation and polarization toward IFN-γ production, *i.e.* toward a Th1-type reaction. Ultimately, this reaction will elicit the activation of macrophages, resulting in a reduction in the proliferation and spread of the mycobacterium, thereby helping in the control of the progression of the infection. On the other hand, another type of reaction, the delayed-type hypersensitivity (DTH) reaction, may be initiated by the activated macrophages which generate large amounts of TNF-α, thereby amplifying the release of chemokines such as MCP-1 and RANTES at the site of infection, leading to an exaggerated influx of naive monocytes and lymphocytes from the blood and to tissue-damaging reactions such as caseation and liquefaction [18].

*Dept of Medical Sciences, Università di Modena, Modena, and **Dept of Biology, University Tor Vergata, Rome, Italy.

Correspondence: C. Saltini, Dept of Medical Sciences, Università di Modena, Modena, Italy. Fax: 390 59424231.

In this context, the cytokine study described TSAO *et al.* [19] in this issue of the Journal is important in that it confirms that TNF-α is released at a higher concentration at the site of disease activity in those patients with more extensive lung disease, constitutional symptoms of fever and weight loss. Although it fails to demonstrate a correlation between the levels of the cytokine and those of its soluble receptors, a finding that previously suggested the presence of a TNF-regulating loop whereby the elevation of the cytokine induced its own soluble inactivators, it lends further support to the idea that the cytokine TNF-α plays a central role in the progression of disease, probably through the elicitation of and exaggerated DTH reaction and the development of the typical immunopathology of severe TB: caseation and liquefaction.

This study may disappoint clinicians looking for the serum marker of disease activity since it indicates that in TB, as well as in other lung diseases such as sarcoidosis and berylliosis, the markers of disease activity need to be measured in the lung ELF. This notwithstanding, the study is important since it confirms that the levels of TNF-α in ELF can predict disease status, thereby suggesting that this marker might be of use in the clinical setting, gauging disease activity by measuring the DTH reaction induced by TB bacilli. Importantly, these findings are also consistent with the important clinical observation that thalidomide, a TNF-α inhibitor, alleviates the fever, weakness and, most importantly, the progressive weight loss that accompany the release of TNF-α in severe TB and in combined TB and human immunodeficiency virus infection [20, 21].

Over the years, a number of reports appeared which described the empirical use of prednisolone to reduce inflammation in tuberculosis and to improve its clinical course, alas without convincing proof of efficacy and clinical benefit [22]. In this context, the identification of reliable cytokine markers strongly associated with the immunopathology of the exaggerated delayed-type hypersensitivity reaction to tuberculosis infection and with disease progression may be of help in designing and carrying out studies aimed at rational immune interventions in tuberculosis, in conjunction with the newer and more powerful measurement of the mycobacterial load during the course of disease and during treatment [23].

References

1. Hosp M, Elliott AM, Raynes JG, *et al*. Neopterin, beta-2 microglobulin and acute phase proteins in HIV-1-seropositive and seronegative Zambian patients with tuberculosis. *Lung* 1997; 175: 265–275.
2. Ameglio F, Giannarelli D, Cordiali-Fei P, *et al*. Use of discriminant analysis to assess disease activity in pulmonary tuberculosis with a panel of specific and nonspecific serum markers. *Am J Clin Pathol* 1994; 101: 719–725.
3. Lai CK, Wong KC, Chan CH, *et al*. Circulating adhesion molecules in tuberculosis. *Clin Exp Immunol* 1993; 94: 522–526.
4. Chan CH, Lai KN, Leung JC, Lai CK. T-lymphocyte activation in patients with active tuberculosis. *Am Rev Respir Dis* 1991; 144: 458–460.
5. Bäumer I, Zissel G, Schlaak M, Müller Quernheim J. Soluble intercellular adhesion molecules (sICAM-1) in bronchoalveolar lavage (BAL), cell culture and in the circulation of patients with tuberculosis, hypersensitivity pneumonitis and sarcoidosis. *Eur J Med Res* 1998; 3: 288–294.
6. Valdes L, San Jose E, Alvarez D, Valle JM. Adenosine deaminase (ADA) isoenzyme analysis in pleural effusions: diagnostic role and relevance to the origin of increased ADA in tuberculous pleurisy. *Eur Respir J* 1996; 9: 747–751.
7. Chensue SW, Davey MP, Remick DG, Kunkel SL. Release of interleukin-1 by peripheral blood mononuclear cells in patients with tuberculosis and active inflammation. *Infect Immun* 1986; 52: 341–343.
8. Law K, Weiden M, Harkin T, Tchou-Wong K, Chi C, Rom WN. Increased release of interleukin-1 beta, interleukin-8 and tumor necrosis factor-alpha by bronchoalveolar cells lavaged from involved sites in pulmonary tuberculosis. *Am J Respir Crit Care Med* 1996; 153: 799–804.
9. Taha RA, Kotsimbos TC, Song YL, Menzies D, Hamid Q. IFN-gamma and IL-12 are increased in active compared to inactive tuberculosis. *Am J Respir Crit Care Med* 1997; 155: 1135–1139.
10. Verbon A, Juffermans N, Van Deventer SJ, Speelman P, Van Deutekom H, Van Der Poll T. Serum concentrations of cytokines in patients with active tuberculosis. *Clin Exp Immunol* 1999; 115: 110–113.
11. Bekker LG, Maartens G, Steyn L, Kaplan G. Selective increase in plasma tumor necrosis factor and concomitant clinical deterioration after initiating therapy in patients with severe tuberculosis. *J Infect Dis* 1998; 178: 580–584.
12. Juffermans NP, Verbon A, van Deventer SJ, van Deutekom H, Speelman P, van der Poll T. Tumor necrosis factor and interleukin-1 inhibitors as markers of disease activity of tuberculosis. *Am J Respir Crit Care Med* 1998; 157: 1328–1331.
13. Modlin RL, Melamcon-Kaplan J, Young SMM, *et al*. Learning from lesions: patterns of tissue inflammation in leprosy. *Proc Natl Acad Sci USA* 1988; 85: 1213–1217.
14. Lenzini L, Rottoli P, Rottoli L. The spectrum of human tuberculosis. *Clin Exp Immunol* 1977; 27: 230–237.
15. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; 7: 145–173.
16. Condos R, Rom WN, Liu YM, Schluger NW. Local immune responses correlate with presentation and outcome in tuberculosis. *Am J Respir Crit Care Med* 1998; 157: 729–735.
17. Zhang M, Lin Y, Iyer DV, Gong J, Abrams JS, Barnes PF. T-cell cytokine responses in human infection with *Mycobacterium tuberculosis*. *Infect Immun* 1995; 63: 3231–3234.
18. Orme JM, Cooper AM. Cytokine/chemokine cascades in immunity to tuberculosis. *Immunol Today* 1999; 20: 307–312.
19. Tsao TCY, Li L, Hsieh M, Liao S, Chang KSS. Soluble tumor necrosis factor-a form and interleukin-1 receptor antagonists are elevated in the bronchoalveolar fluid from patients with active pulmonary tuberculosis. *Eur Respir J* 1999; 14: 490–495.
20. Tramontana JM, Utaipat U, Molloy A, *et al*. Thalidomide treatment reduces tumor necrosis factor alpha production and enhances weight gain in patients with pulmonary tuberculosis. *Mol Med* 1995; 1: 384–397.
21. Klausner JD, Makonkawkeyoon S, Akarasewi P, *et al*. The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 11: 247–257.
22. Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis (Cochrane Review). *In*: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.
23. Desjardin LE, Perkins MD, Wolski K, *et al*. Measurement of sputum mybobacterium tuberculosis messenger RNA a surrogate for response to chemotherapy. *Am J Respir Crit Care Med* 1999; 160: 203–210.