LEADING ARTICLE

CIRCULATING IMMUNE COMPLEXES IN TUBERCULOSIS - WHAT IS ITS CLINICAL SIGNIFICANCE?

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Circulating immune complexes (CICs) are found in a wide variety of diseases, of infective or non-infective aetiology. Conditions which are associated with CICs include the autoimmune diseases, bacterial and viral infections, parasitic disorders, vasculitic conditions, and malignancy. Among diseases involving the lung, immune complexes have been reported in idiopathic pulmonary fibrosis, sarcoidosis, bronchiectasis, cystic fibrosis and extrinsic allergic alveolitis. The frequency of CICs in tuberculosis has been found to vary from 56 to 68%[1,2]. An article in this issue of the Journal reported a frequency of 96% in 75 patients with active tuberculosis[3].

Immune complexes (ICs) are made up of a specific antibody combined with an antigen. The antigen combines with antibody in various proportions. This may result in precipitation of ICs when both the antigen and antibody are at equivalence or the ICs may remain soluble and circulate in the blood when there is an excess of antigen.

Many assays have been developed to detect ICs. These can be divided into 2 groups: antigen specific, where the identity of the antigen is known and antigen non-specific, where the antigen is unknown. As the antigen in ICs is not known in most diseases, assays in the second group, based on the physical or biological characteristics of ICs are frequently used. The incidence of CICs depends on the method or combination of methods used to detect its presence. The PEG (polyethylene glycol) method was used by the present authors to precipitate circulating immune complexes. This method is simple to perform and inexpensive but one drawback is that it may precipitate monomeric immunoglobulins in addition to complexed immunoglobulin, leading to an overestimation of CICs. However, the PEG precipitates have been demonstrated to be ICs containing immunoglobulins, albumin, complement components and mycobacterial antigens[4].

The role of CICs in the pathogenesis of TB is not clear. The main response to infection by the tubercle bacilli is a cell mediated immune (CMI) reaction leading to activation of T lymphocytes, release of lymphokines and activation of macrophages. The development of CMI is indicated by a positive tuberculin reaction. However, ICs may also be involved in the formation of granuloma when they are formed at equivalence and precipitate in the lung[5]. The cell mediated immune response is suppressed by a mycobacterial arabinogalactan[6], which is present as immune complexes in some tuberculous sera. Indeed, an inverse relationship between cell mediated response and humoral activity has been noted.

Immune complexes can also activate the complement system which leads to its solubilisation and clearance[7]. This may explain why vasculitis, which is often associated with ICs in other diseases is uncommon in tuberculosis.

It has been suggested that the measurement of CICs levels may be useful in the diagnosis of bacillary negative tuberculosis; higher levels are seen in patients with active tuberculosis than healthy (control) subjects. The titre of CICs increases with the extent of disease[7] and this may limit its value as a diagnostic test for patients with minimal or smear negative disease. In addition, the levels of CICs may remain elevated in patients who had received a course of treatment[8]. However, in patients with confirmed tuberculosis, the measurement of CICs can be used to assess disease activity and monitor response to chemotherapy.

Various authors have postulated the existence of an immune spectrum in tuberculosis[9-11] corresponding to that in leprosy, which is represented by tuberculoid leprosy (the reactive form of the disease) at one end of the immune spectrum and lepromatous leprosy (the unreactive form) at the other end. In tuberculosis, the reactive form (RR) is characterised by patients who have localized disease, a positive tuberculin reaction, paucity of tubercle bacilli in tissues and low levels of antibody and immune complexes. The unreactive form (UU) of the disease is characterised by patients who have disseminated disease, tuberculin anergy, increased numbers of bacilli with absence of granuloma formation in tissues and high levels of antobody and immune complexes. There is an intermediate group (RI or UI) of patients falling in the middle of the immune spectrum who have features resembling one or the other polar groups. The titre of CICs increases from the reactive to the non reactive forms of the disease.

Further work remains to be done to improve the accuracy of the assays. There is a need to characterise the nature of the antigen or antigens in CICs. In addition to the detection of CICs, progress has also been made in the diagnosis of paucibacillary tuberculosis and extrapulmonary disease by serologic methods[12-14]. Methods using ELISA to detect antibodies to mycobacterial antigens have been encouraging, but they have not reached the stage where they can be used in routine clinical practice.

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