REVIEWS

Hypergammaglobulinaemia and autoimmune rheumatic diseases

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Hypergammaglobulinaemia is defined as an increase in immunoglobulins above the normal concentrations that occur in serum. IgG forms 80% (8–16 mg/ml) of the serum concentration of immunoglobulins in normal subjects but this percentage often increases in hypergammaglobulinaemia. IgG is further divided into four subclasses: IgG1–IgG4. IgG1 accounts for 50% of the IgG, IgG2 for 25%, IgG3 for about 20%, and IgG4 for 5%. A more modest increase in IgM (normal range 0.5–2 mg/ml) and IgA (normal range 14.4 mg/ml) often accompanies the increase in IgG. Increase in IgE concentrations is observed in atopic patients; increased IgD is rarely seen, but is associated with immune complex vasculitis.¹

In some autoimmune rheumatic diseases hypergammaglobulinaemia is a common feature, notably in systemic lupus erythematosus (SLE) and Sjögren's syndrome, whereas in others it occurs occasionally—for example, rheumatoid arthritis and polymyositis. Though it is usual for most of the classes of immunoglobulin to be increased to some extent, occasionally only one class or subclass is increased. Thus Sjögren's syndrome seems to be particularly associated with increased IgG1.² Interestingly, the highest concentration of IgG1 was found in patients with the shortest disease duration. Blanco *et al.* found that a high percentage of patients with Sjögren's syndrome had IgG1 antibodies to Ro but an equally high number had IgG4 antibodies to single stranded DNA.³ A decrease in the IgG concentration later in the course of the disease leading to an actual hypogammaglobulinaemia may herald the onset of a B cell lymphoma, which occasionally complicates the disease.

Lisak and Zweiman found increased concentrations of IgG, IgA, and IgM in nine, seven, and four of 11 patients with polymyositis/dermatomyositis.⁴ In our own experience the occurrence of hypergammaglobulinaemia in autoimmune myositis is approximately 30% (Ehrenstein M R, Isenberg D A, unpublished data).

Mild hypergammaglobulinaemia is found in up to 30% of patients with systemic sclerosis, especially those with overlap syndrome.⁵ In a classic study, Larsson and Leonhardt found that a proportion of unaffected relatives of patients with SLE had mild hypergammaglobulinaemia.⁶ This proportion decreased as the relationship moved from siblings (8/10) through nephews and nieces to first cousins (9/24) compared with controls (5/47).

In addition to determining the relative contribution of the various immunoglobulin classes in hypergammaglobulinaemia the specificities of the antibodies can also be assessed. A generalised increase in immunoglobulins can occur consisting of antibodies to a broad, unselected range of antigens, a true polyclonal response. Alternatively a more limited set of antibodies can be produced, an oligoclonal response, or at the extreme end of the spectrum the hypergammaglobulinaemia could consist of a monoclonal antibody, as is observed in myeloma. In autoimmune rheumatic diseases it is important to consider whether the antibodies, or a proportion of these, are directed against self or non-self. Our own, and other studies, have shown that approximately 25% of patients with myeloma have detectable serum autoantibody reactivity^{7 8} and may overexpress common DNA antibody idiotypes.^{9 10} These patients invariably lack the clinical features of autoimmune rheumatic diseases even in the presence of antibodies to double stranded DNA.⁷ Sestak *et al* examined serum samples from over 130 patients with myeloma and showed by enzyme linked immunosorbent assay (ELISA) that 13% had antibodies to Ro and 12% antibodies to La.¹¹ Detailed analysis of the myeloma proteins revealed, however, that in several instances it was a serum immunoglobulin other than the myeloma component which possessed the antibody reactivity. Similarly our own study of antineutrophil cytoplasmic antibodies in serum samples from patients with myeloma has confirmed that this autoantibody reactivity, although occasionally present, may be due to a concomitant antibody.¹²

Myeloma proteins may represent antibodies directed against self antigens reflecting a stochastic transformation of normal B cells producing natural autoantibodies. These natural autoantibodies are thought to play an important part in the defence of the host and in the development of the immune system.¹³ Hypergammaglobulinaemia occurring in autoimmune diseases is associated with specific loss of tolerance and the production of pathogenic autoantibodies in addition to a generalised, non-specific increase in immunoglobulins which include natural autoantibodies.

Carpenter *et al* found evidence of clonal restriction in some patients with rheumatoid arthritis but in most (>80%) there was polyclonal immunoglobulin synthesis.¹⁴ In patients with SLE there appears to be an increase in

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autoantibodies and antibodies against some common environmental antigens but also a specific increase in IgG antibodies to double stranded DNA, implying a specific antigen driven mechanism.¹⁵ Experiments in NZB/NZW mice (a model for lupus) give a similar result and show that the polyclonal B cell activation precedes by several weeks, and reliably predicts, an antibody response skewed towards DNA and the development of nephritis.¹⁶ These experiments suggest that B cell hyperactivity is an early phenomenon and that an antigen driven response occurs later in the disease.

Ishigatsubo *et al* examined the absolute numbers of splenic B cells from MRL/lpr mice and found that no bias towards autoantibodies was present.¹⁷ They did not separate IgM and IgG responses, however. In Sjögren's syndrome the hypergammaglobulinaemia consists mainly of autoantibodies directed against Ro/La and rheumatoid factor, unlike in SLE where the immunoglobulin specificity is less restricted.

The apparent existence of a polyclonal response and an antigen driven selective response has been supported by data from Suzuki *et al* who separated CD5+ and CD5- B cells in patients with SLE.¹⁸ Evidence exists for a particular role for CD5+ B cells in autoimmunity and, in particular, in murine models of lupus where CD5+ B cells have been shown to be the source of antibodies to DNA.¹⁹ Suzuki *et al* found that in human SLE two populations secreting antibodies to DNA exist with distinct induction mechanisms: one (CD5+) which independently secretes antibodies to DNA, and another (CD5-) which produces antibodies to DNA as an apparent consequence of polyclonal B cell activation.¹⁸ Similarly, in mice spleen cells producing Ig rheumatoid factor CD5+ B cells produced IgG rheumatoid factor independent of polyclonal B cell activation, whereas CD5- B cells produced IgM rheumatoid factor secondary to polyclonal stimulation.

The mechanisms and consequences of polyclonal B cell stimulation, the central driving force for hypergammaglobulinaemia, have been investigated by several workers. Cavallo and Granholm have shown that exposure to lipopolysaccharides from Gram negative bacteria causes polyclonal B cell activation in murine lupus and that this directly leads to the exacerbation of nephritis.²⁰ The lymphocyte response to *Staphylococcus aureus* (a known B cell mitogen) in patients with ankylosing spondylitis is increased compared with controls.²¹ Moreover, this hyperresponsiveness is associated with disease activity and the hypergammaglobulinaemia observed. The initial stimulus, however, remains obscure and could be due to a mitogen or virus.

The respective contribution of B and T cells to hypergammaglobulinaemia is the subject of much debate. Sobel *et al* have shown that in addition to the presence of double negative T cells in the lpr mice an intrinsic B cell defect is essential for the production of autoimmunity.²² A B cell abnormality in lpr mice has also been found by Nemazee *et al* who have postulated that faulty tolerance induction also lies at the

level of the B cell in this model of lupus.²³ Watanabe-Kukunaga *et al* have shown that mice carrying the lpr mutation have defects in the Fas antigen gene.²⁴ This protein, which is absent in the lpr strain of mice, is important in cell apoptosis. The authors conclude that auto-reactive T cells are not deleted in the thymus as a consequence, but this protein is also in B cells and, as discussed, these cells are crucial for the development of autoimmunity in these mice. Further support for a primary fault in the B cells comes from Strasser *et al* who have used a transgenic model in which a single dysregulated gene, BCL2, capable of enhancing the B cell life span, provokes hypergammaglobulinaemia and widespread systemic autoimmunity.²⁵ This implies that the rapid turnover of B cells in the normal mouse prevents the development of autoimmunity.

Several studies have considered the responsiveness of lupus B cells to cytokines. Several laboratories have reported that lupus B cells have a normal or decreased response to cytokines whereas others have found an increased response to cytokines. Alcarcon-Riquelme *et al* reported that interleukin 4 and interleukin 5 induced the production of IgM and IgG1 immunoglobulins from NZB/W mice.²⁶ A lesser effect could also be observed in normal mice when treated similarly. Pelton *et al* found that B cells from patients with lupus cultured in vitro spontaneously secreted high concentrations of immunoglobulin.²⁷ Interleukins 2, 4, and 6, either alone or in combination, did not augment this secretion. If they had already been stimulated in vivo by these cytokines, however, it would not be surprising that further stimulation had little effect.

Helper T cells play an important part in the pathogenesis of autoimmunity. Among the clinical conditions associated with polyclonal B cell activation, however, a number are noted for their lack of CD4+ cells—that is, patients with AIDS, patients treated with cyclosporine, and transplant recipients of T cell depleted bone marrow.^{28–30} Moreover, long term administration of antibodies to CD4 to DBA/2 and NZB/W mice leads to polyclonal B cell activation³¹ and the appearance of autoantibodies.

The appearance of hypergammaglobulinaemia in autoimmune rheumatic diseases is not helpful in the diagnosis but is central to the mechanisms producing autoimmunity. It is a common denominator in a variety of diseases and may give an understanding of the early events leading to autoimmune disease.

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