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Accepted 29 January 2002

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CD5+ B cells and uveitis

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Ann Rheum Dis 2002;**61**:854–855

High levels of circulating B1a lymphocytes expressing CD5 have been reported in some patients with non-organ-specific autoimmune diseases, such as systemic lupus erythematosus, primary Sjögren's syndrome, and rheumatoid arthritis, although CD5+ B cells do not seem to be only agents of autoantibody production.[1] Thus, B cells display a variety of characteristics other than antibody production—for example, in lymphoid architecture development, regulation of T cell subsets and antigen presenting cell function through cytokine production, and in activation of T cells.[2 3] In addition, CD5+ B cells have a role in several organ-specific autoimmune diseases, such as chronic urticaria,[4] insulin dependent diabetes mellitus,[5] myasthenia gravis,[6] and immune thrombocytopenic purpura, where the increased proportion of CD5+ B cells in spleen and peripheral blood, and their ability to produce antiplatelet antibodies, indicates that they are directly involved in the pathogenesis.[7] Furthermore, Liversidge *et al* isolated CD5+ B lymphocytes and TCR γ-δ T lymphocytes from the vitreous humor of a patient with acute sympathetic ophthalmitis[8]; Sampalo *et al* found a correlation between CD5+ B cells and HIV disease progression[9]; and Printz *et al* discovered that a subset of patients with schizophrenia had raised levels of CD5+ B cells, which provides evidence suggestive of autoimmune manifestations in schizophrenia.[10]

Uveitis is a general term denoting any type of intraocular inflammatory disease, which may be of unknown origin or associated with many general diseases.[11–14] Although immunological disturbances play a part in the pathogenesis of uveitis, it is still difficult to understand the mechanism by which tissue damage is mediated; further research is needed.[15] Since 1989 the uveitis unit of our hospital has comprised an interdisciplinary team of internists and ophthalmologists studying the cause of uveitis in patients with uveitis of unknown origin. By 2000 we had prospectively studied 315 patients with uveitis, none of whom had been previously diagnosed with systemic diseases which might have been caused by uveitis. We aimed at evaluating the average level of CD5+ B cells in peripheral blood from 27 patients with idiopathic uveitis (20 with anterior uveitis, seven, with posterior uveitis) and 21 healthy subjects matched for age and sex who served as control group. Patients were consecutively enrolled between May 1999 and November 2000, and the control group was recruited from the hospital staff. Double labelling with CD5 and CD19 monoclonal antibodies (BD Oncomark CD5 FITC/CD10 PE/CD19 perCP-Cy5.5; Becton Dickinson, California, USA) was used for lymphocyte staining. The flow cytometry analysis was carried out with a FACScan cytometer. Statistical analysis was performed with a *t* test for independent continuous variables and Fisher's exact test for categorical variables.

The mean (SD) level of CD5+ B cells in peripheral blood was found to be significantly higher in the 27 patients with uveitis (91 (76) cells×10^6/l; percentage 28 (20)) than in the control group (58 (34) cells×10^6/l; percentage 18 (5)); $p<0.05$). Moreover, we also found increased levels of CD5+ B cells in various subgroups of uveitis—namely, anterior uveitis (94 (79) cells×10^6/l; percentage 29 (19)) and clinically severe cases of uveitis (108 (93) cells×10^6/l; percentage 34 (21)), which were significantly different from those in control subjects ($p<0.05$). However, no significant differences were found between anterior and posterior uveitis subgroups, or between unilateral and bilateral disease, or between single and repeated episodes of inflammation.

Thus, CD5 + B cells may lead to uveitis by acting as antigen presenting cells, stimulating CD4+ T cells with an unknown antigen. Patients with non-organ-specific and organ-specific autoimmune diseases, such as uveitis, may have increased levels for CD5+ B cells, which indicates an immunoregulatory role of CD5+ B cells in autoimmunity, and suggests that effective ways of testing and controlling the immune response in patients with uveitis might be devised.

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Accepted 25 February 2002

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Absence of human parvovirus B19 DNA in myoepithelial sialadenitis of primary Sjögren's syndrome

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Ann Rheum Dis 2002;**61**:855–856

Sjögren's syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and presents as persistent dryness of the mouth and eyes owing to functional impairment of the salivary and lachrymal glands. The histological hallmark is local infiltration of lymphocytes, which play a major role in tissue damage. Although B cells represent a minority of the lymphoid infiltrates in SS tissue, they may undergo polyclonal activation and oligoclonal/monoclonal expansion, which may, in turn, predispose them to a still unidentified B cell neoplastic transformation. The process of B cell activation and expansion is presumably a consequence of a chronic, although at present unidentified, antigenic stimulus that activates specific subsets of B lymphocytes.[1 2] This process resembles a germinal centre reaction, in which B cells that express the antigen receptor with the highest affinity for the stimulatory antigen are selected, giving rise to the oligoclonal/monoclonal population seen in the advanced phases of the disease.[1 2]

We recently analysed seven monoclonal lymphoproliferations from six patients with primary SS[1] according to the European Criteria of 1993[3]; (one patient with SS showed a different monoclonal B cell population in two subsequent parotid specimens). DNA was extracted from frozen parotid biopsy specimens, and a B cell monoclonal expansion was verified by the VDJ protocol of amplification.[1] The immunoglobulin antigen receptor (IgR) variable region genes and third complementarity determining region segments (CDR3), which mainly contribute to the antigenic specificity of the IgR, were sequenced.[1]

Comparison of the deduced amino acid sequences of the CDR3 region with antibodies of known specificity reported in a database, showed in six cases a high similarity between VH CDR3 and rheumatoid factor (RF) antibodies, presumably autoantibodies produced against an infectious agent(s), and in one case an antibody putatively reactive with parvovirus B19 (table 1).[1] This suggests that RF producing cells have a role in SS pathogenetic events, as recently confirmed by Martin *et al*.[4]

Because human parvovirus B19 is a common DNA virus, present in 30–60% of the population positive to B19 antibodies,[5] which infects not only erythrocytes and erythroblasts but also megakaryocytes, endothelial and epithelial cells[6] and is possibly involved in several autoimmune diseases,[7–9] we searched for B19 genomes in tissues affected by the SS associated lymphoproliferative processes. This was in agreement with the proposed models for the pathogenesis of MALT lymphoma.[10]

A polymerase chain reaction (PCR) amplification using the Ampliquality B19 kit (Ab ANALITICA srl, Padova, Italy) was performed, in accordance with the manufacturer's instructions, to search for the presence of B19 DNA directly in the parotid specimens affected by SS. The PCR products were analysed on 2% agarose gel stained with ethidium bromide. Positive cases must show a fragment of 218 bp, which derives from amplification of the 1390 to 1608 region of the viral genome.

The region encoding for the β-globin gene was also amplified by PCR to confirm the quality of DNA (data not shown).

Despite the high sensitivity of the PCR approach, B19 DNA was not detected in patient 5, who showed a high homology of