Autoimmunity in chronic lymphocytic leukaemia

TJ Hamblin, DG Oscier, BJ Young

From the Department of Haematology, Royal Victoria Hospital, Bournemouth

Summary The prevalence of autoantibodies in B cell chronic lymphocytic leukaemia (B-CLL) was investigated. A lower prevalence of autoimmune haemolytic anaemia than that found in other series was found: large numbers of non-progressive stage A disease cases were included, in which the prevalence of autoimmune haemolytic anaemia is low. Non-haematological autoantibodies were no commoner than in age matched controls. Whatever explanation is offered for autoimmune phenomena in B-CLL it must take account of the fact that those phenomena are virtually confined to autoantibodies against the formed elements of the blood.

Although hypogammaglobulinaemia is the most prominent immunological abnormality in patients with B cell chronic lymphocytic leukaemia (B-CLL), paradoxically, the incidence of autoimmune disease is also high. Autoimmune haemolytic anaemia is believed to occur in between 10% and 20% of patients with B-CLL and autoimmune thrombocytopenia in about 2%. Autoimmune neutropenia is rarer, and pure red cell aplasia associated with autoantibodies to developing erythroblasts also occurs. Early workers noted the association of CLL with other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's disease, ulcerative colitis, and allergic vasculitis, and although such associations have not been prominently reported recently, reports of coexisting B-CLL and nephrotic syndrome and bullous pemphigoid have been published in the past six years.

The cause of autoimmune phenomena in B-CLL is unclear, although it is thought to be associated with disturbances in T cell subsets secondary to the B cell proliferation. Precise models for how autoimmune processes in B-CLL are initiated, however, would be easier to construct if it were known whether there is a generalised tendency to autoimmune disease or whether the autoimmune processes are largely confined to the bloodstream. In this study we looked at the prevalence of autoantibodies in a large unselected series of patients with B-CLL and compared this with the prevalence in age and sex matched controls.

Patients and methods

One hundred and ninety five patients with B-CLL who presented at this hospital from August 1972 to August 1985 were studied. We defined B-CLL as the chronic persistance of excess lymphocytes with characteristic morphology (small non-cleaved nuclei, condensed nuclear chromatin, and scanty cytoplasm) in the peripheral blood. Cell markers performed by the methods of Hamblin and Smith were used to define B cell monotypy. The following cell marker pattern was typical: weak positivity for surface immunoglobulin of one light chain class; positivity for mouse red cell rosettes, CD5, and CD20; negativity for sheep red cell rosettes and CD3.

All the patients came from the local population, which contains roughly 30% over the age of 65 years. Seventy two per cent of patients were diagnosed on an incidental blood count taken for an irrelevant reason. Patients were staged according to the system of Binet et al. Only those patients with anaemia or thrombocytopenia due to marrow failure were placed in group C. In addition, those in group A were designated as "progressive" or "non-progressive." To qualify as "progressive" entailed doubling of the lymphocyte count within 12 months, progressing to a more advanced stage, or transforming into a more malignant form of lymphoma.

There were 102 men and 93 women (this differs from the usual 2:1 men:women ratio because Bournemouth has an excess of elderly women), and the mean age at presentation was 71.8 years. The control population comprised 194 subjects, all of whom were part of an ongoing study of all patients in a group general practice who were in their seventh, eighth, and ninth decades. There were 103 men and 91 women, and
their mean age at testing was 75.4 years.

Patients were tested on either their first or second appearance at outpatient clinics and again later if there was a clinical indication. Sera from patients and controls were tested for the presence of autoantibodies by indirect immunofluorescence using cryostat sections of a multitissue block comprising mouse liver, rat kidney, stomach, and oesophagus, and human thyroid.\(^1\) Titres of greater than 1/40 for antinuclear antibodies and greater than 1/20 for other antibodies were reported as positive.

Direct antiglobulin tests were performed on blood samples from every patient but not on controls. Thrombocytopenia was judged to be immune mediated when it occurred in the absence of splenomegaly and marrow failure and in the presence of increased megakaryocytes in the marrow.

Results

Of the 195 patients tested, the direct antiglobulin test yielded positive results in 15 (7.7%). In one of these it was positive for complement only, and this patient had a high titre anti-I monoclonal antibody of IgMk specificity, the same class as the surface immunoglobulin of her tumour cells—and presumably produced by them. Of the other 14, 10 had evidence of haemolytic anaemia. Four patients (2.1%) had evidence of immune thrombocytopenia. In this series we also saw one patient with pure red cell aplasia and one with isolated neutropenia, both of whom were possibly immune mediated. Other autoantibodies were found in 42 patients (21.5%) and also in 42 of 194 age and sex matched controls. Table 1 shows the antibodies found.

Two of the patients had myxoedema, one thyrotoxicosis, and one pernicious anaemia. Other possibly autoimmune diseases found in association with CLL in this series and not associated with the autoantibodies detailed in Table 1 were two cases each of rheumatoid arthritis, cryogenic cirrhosis, and immune vasculitis, and one case each of interstitial fibrosis of the lungs, nephrotic syndrome, poly-myositis, and polymyalgia rheumatica.

Table 2 shows the relations between Binet stage and autoimmunity. A positive direct antiglobulin test was significantly less likely to occur in non-progressive stage A disease (\(p < 0.02\)).

Discussion

The prevalence of a positive direct antiglobulin test in B-CLL has been reported to be as high as 21%,\(^1\) 26%,\(^1\) or even 35%,\(^1\) although textbooks usually report a value of between 10% and 20%.\(^1\) Our finding of only 7.7% reflects the large numbers of very benign cases in our series. Although we did not look for positive direct antiglobulin tests in our controls, previous studies have shown a prevalence in the general population of 1–3 per 10,000.\(^1\) In non-progressive stage A disease a positive direct antiglobulin test is significantly less likely to occur (2.9%; \(p < 0.02\)) than in the other stages (13.3%). Most large series of B-CLL are reported from tertiary referral centres, which see the most severe cases. We therefore believe that our figure is closer to the true prevalence of autoimmune haemolyosis in B-CLL, while recognising that much stage A disease remains undiagnosed in the general population.

Our prevalence of immune thrombocytopenia of roughly 2% is the same as that of previously reported series.\(^2\) Reliable tests for platelet antibodies, however,
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were not available when we began this study, and we suspect that subclinical platelet antibody production is more common than we found. The cases of isolated neutropenia and pure red cell aplasia that we saw were not shown to have been caused by autoantibodies, although this remains a possibility.

Damasher reported sporadic cases of autoimmune disease in association with B-CLL, and Miller's personal series of 104 cases of B-CLL included patients with associated allergic vasculitis, chronic glomerulonephritis, ulcerative colitis, systemic lupus erythematosus, and rheumatoid arthritis. The association of pernicious anaemia and B-CLL has been reported at least nine times and that of nephrotic syndrome and B-CLL 11 times. Bullous pemphigoid, which is associated with antibodies to skin basement membrane, has also twice been described in association with B-CLL. Although we found 14 patients in our series with associated autoimmune disease, it is difficult to draw any conclusions from these associations. The two cases of allergic vasculitis and the one case of nephrotic syndrome improved on receiving specific treatment for B-CLL, but such treatment is in any case useful for the autoimmune condition. All three patients had detectable circulating immune complexes.

There was no difference in the prevalence of non-haematological autoantibodies between patients and age and sex matched controls, nor could an association with advanced rather than early stage B-CLL be shown for autoantibodies or non-haematological autoimmune disease. We think, therefore, that the association of autoimmune disease and B-CLL is largely confined to antibodies against blood components.

The precise pathogenesis of autoimmune haemolysis and thrombocytopenia in B-CLL is unknown. Disturbances of T cells have been reported by many authors, with reduced numbers of T helper cells and increased numbers of T suppressor cells and concomitant changes in helper and suppressor function. In pure red cell aplasia associated with B-CLL a direct effect of suppressor T cells is thought to operate, although in some idiopathic cases autoantibodies are implicated. The observation that autoimmune haemolysis may be initiated by treatment of B-CLL with cytotoxic drugs (a phenomenon that occurred once in our series, although three other patients had received previous treatment for their B-CLL) adds further weight to the idea that the autoimmune process is caused by an imbalance of T cell subset, but the precise mechanism is still unknown. Recent work on the aetiology of autoimmune disease has suggested that epithelial cells may be able to present their own surface molecules as autoantigens when they are induced, possibly by gamma interferon, to express aberrant mixed histocompatibility complex class II antigens. In B-CLL it could be that within the marrow infiltrating T cells secrete gamma interferon, which then induces the anomalous expression of HLA-DR on blood cell precursors, enabling them to present surface antigens to residual normal B cells. This hypothesis is currently being tested in our laboratory.

Whatever explanation for autoimmunity in B-CLL is given it should take account of the fact that the autoimmune processes are not generalised but largely confined to antibodies against the formed elements of the blood.

We are grateful to Professor GT Stevenson for helpful suggestions and to Mrs K Avery for typing the manuscript.

References

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Requests for reprints to: Dr TJ Hamblin, Department of Pathology, Royal Victoria Hospital, Shelley Road, Bournemouth BH1 4JG, England.