Rheumatology 2001;40:948–949

Autoimmune neutropenia, thrombocytopenia and Coombs positivity in a patient with primary Sjögren’s syndrome

Sir, Sicca symptoms are the sine qua non of diagnosis of primary Sjögren’s syndrome (pSS). However, extra-glandular involvement is common and often causes highly varied manifestations [1], which may precede or overshadow the sicca symptoms and cause significant diagnostic delay. We report a patient who presented with multiple cytopenias and three different autoantibodies directed against blood components due to pSS.

A healthy 40-yr-old woman presented with asymptomatic neutropenia, which was found in a routine blood count. Physical examination was normal. Laboratory tests showed erythrocyte sedimentation rate 9 mm/h, haemoglobin (Hb) 12.2 g/dl (normocytic), white blood cell count (WBC) $2.1 \times 10^3/\mu l$ and platelets $146 \times 10^3/\mu l$. Urinalysis, blood chemistry and serologies, chest X-ray and abdominal ultrasound were normal. Anti-nuclear antibodies (ANA) were positive (+1, speckled). Other autoantibodies were negative. Bone marrow examination was normal. Bone marrow grown in tissue culture media showed normal colony formation with granulocyte macrophage colony-stimulating factor as well as in the presence of autologous serum, autologous lymphocytes and normal serum. The patient was followed regularly without treatment. WBC fluctuated between $1.3 \times 10^3$ and $2.7 \times 10^3/\mu l$ (50% neutrophils). No infections occurred. At the age of 46 blood counts worsened, with Hb 11.1 g/dl (normocytic) and platelets 80–100 $\times 10^3/\mu l$. The direct Coombs test was positive (anti-IgG and anti-C3d). The indirect Coombs test was also positive and the antibodies were shown to be polyagglutinins. Reticulocytes, serum haptoglobin, bilirubin and lactate dehydrogenase were normal. Polyclonal hypergammaglobulinaemia appeared and ANA positivity was noted at a varying titre (+1 to +2 on a scale up to +4). Anti-DNA, anticardiolipin and other autoantibodies were again not detected. The bone marrow showed a slight increase in megakaryocytes and serum analysis revealed anti-platelet antibodies.

A repeated review of systems now revealed dry eyes and dry mouth. Work-up showed a positive Schirmer’s test (1–2 mm bilaterally), minor labial salivary gland biopsy with two clusters of $>50$ mononuclear cells/4 mm², and antibodies to SS-A (RO). Over the next 2 yr there were no additional complaints or physical findings and laboratory tests remained stable, showing pancytopenia, predominantly neutropenia. Autoantibodies to granulocytes, tested by a direct immunofluorescence method [2], were demonstrated repeatedly in the patient’s serum. The antibodies eluted from the patient’s erythrocytes reacted with autologous and control red blood cells (RBC) but did not show any reactivity with granulocytes and platelets.

This is the first report of a patient who presented with mild asymptomatic pancytopenia and three different
autoantibodies against blood components at the same time, due to pSS. Because frank haemolysis was never demonstrated despite positivity in the Coombs test, this patient’s anaemia was likely to have been due to chronic inflammation, possibly mediated by the effect of proinflammatory cytokines on the bone marrow [3]. However, there is no alternative explanation for the patient’s marked neutropenia and thrombocytopenia in the presence of an active bone marrow and normal spleen, other than the two distinct autoantibodies which we discovered. The sicca complaints were not volunteered by the patient until specifically questioned, and then a diagnosis of SS was readily established. She did not fulfill criteria for systemic lupus erythematosus or other rheumatic disorders, and she was therefore classified as having pSS.

Haematological abnormalities are common in patients with pSS [4]. Leucopenia is the most frequently encountered cytopenia, being present in 14–42% of pSS patients (median 20%) [1, 5]. Some patients develop a striking neutropenia or lymphopenia, possibly related to antineutrophil or anti-CD4 antibodies respectively [6, 7]. The prevalence of anaemia is about 11% and that of thrombocytopenia 5–15% (median 11%) [1, 4]. What is less well appreciated, but is clearly illustrated by our report, is that patients with undiagnosed pSS (asymptomatic patients or patients who fail to complain of sicca symptoms) [8] may present with isolated or combined cytopenia, which is usually asymptomatic. Such atypical presentations may be responsible in part for the long diagnostic delay, which averages 3.1 yr from the patient’s presentation [5]. Also, in contrast with the commonly held view that cytopenias in pSS are usually mediator-induced [1], our original observation of three different autoantibodies against blood components in a single patient re-emphasizes the importance of immune mechanisms in the pathogenesis of the cytopenias of pSS. In fact, other studies have documented that 22% of pSS patients have anti-RBC antibodies [4] and 45% may have antineutrophil antibodies [6]. This exceeds by about 2:1 the number of patients with overt cytopenia and exceeds by far the very few reports of patients with pSS who actually had symptomatic haemolytic anaemia, opportunistic infections or bleeding manifestations due to cytopenia [4]. The essentially asymptomatic course and fluctuating nature of the neutropenia and thrombocytopenia over many years appear to be characteristic of the autoimmune cytopenias of pSS [9].

Immune-mediated pancytopenia can occur as a result of a common antigen present in all three cell lineages, as in hypersensitivity to quinine [10]. In the cytopenias of pSS this is apparently not so. Our studies show that three distinct autoantibodies are involved, and to our knowledge this rare occurrence has never before been recorded.

pSS is one of the most common autoimmune disorders, affecting 3–4% of the adult population according to a recent European study [11]. The characteristic complaints may often be disregarded by the patient and not brought to the physician’s attention unless specific enquiries are made. It is therefore conceivable that a significant number of patients with varying degrees of single or combined cytopenia, which are not due to other identifiable causes, may in fact have immune-mediated cell destruction and occult pSS [9]. This important presentation should be well recognized because pSS is a treatable condition, and because it carries an increased risk of associated diseases, such as lymphoma, early diagnosis is necessary.

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Accepted 9 February 2001

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