Unusual association between pure red cell aplasia and primary Sjögren's syndrome: a case report

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Abbreviations:
PRCA: pure red cell aplasia
SS: Sjögren's syndrome
SLE: systemic lupus erythematosus
NSAIDs: non steroid anti-inflammatory drugs
EPO: erythropoietin
JA: Jaccoud arthropathy
PIP: proximal interphalangeal
MCP: metacarpophalangeal

ABSTRACT

Pure red cell aplasia (PRCA) is an acute anemia due to selective suppression of erythropoiesis. We report a case of PRCA diagnosed before the onset of primary Sjögren's *syndrome (SS). A young woman, with autoimmune thyroiditis, developed polyarthritis with ANA and Rheumatoid factor positivity, diagnosed as Rheumatoid arthritis. During the time she developed anti-Ro and anti-La antibodies and deformities at proximal interphalangeal joints. After 4 years, she developed severe acute anemia, without reticolocytes: a bone marrow biopsy indicated a PRCA and she started transfusions, steroids, cyclosporin. A steroid-dependent anemia persisted. After 2 years she developed sicca, parotid swelling, fatigue, mild leukopenia, elevated serum creatinine, hypokalemia, hyposthenuria and tubular proteinuria. Lip biopsy and dacriologic tests confirmed a diagnosis of SS, while X-ray revealed a deforming nonerosive arthropathy (Jaccoud type). In present case, PRCA could be considered an autoimmune bone marrow disease within SS, whose extra-glandular manifestations onset before the sicca symptoms.*

Introduction

Pure red cell aplasia (PRCA) is an acute normochromic anemia characterised by autoantibody-mediated or T cell mediated erythroblastic suppression (1). In particular, autoantibodies directed to erythroblasts (2), erythroid colony forming units, erythropoietin (3) or erythropoietin receptor (4) were described. Different authors reported an association between PRCA and Systemic Lupus Erythematosus (SLE), with clinical and laboratory features similar to other SLE patients (4-6). PRCA has been also reported as manifestation of lymphocytic lymphoma in one patient with primary Sjögren's Syndrome (SS) (7). We report here the case of a patient with PRCA diagnosed before the onset of an overt primary SS.

Case report

A young woman, born in 1974, was admitted to hospital, on 1996, due to remitting fever, polyarthralgias, cervical, axillary and inguinal lymphoadenopathy. Laboratory tests showed severe hypergammaglobulinemia, neutrophilic leukocytosis, elevation of ESR and C-reactive protein: all infectious tests were negative, except for urinary E. Coli. Rheumatoid factor and anti-nuclear antibody tests were positive, while anti-dsDNA, anti-ENA and ANCA were negative. TSH elevation with anti-thyreoglobin and anti-thyreoperoxidase antibodies were detected. A complete CT scan and a lymphonodal biopsy were performed, showing a necrotizing histiocytc lymphadenitis, without any sign of lymphoproliferative disorder. A diagnosis of Kikuchi disease and autoimmune thyroiditis was made. During the following months arthritis in small and large joints persisted, leading a diagnosis of rheumatoid arthritis (RA), treated with oral prednisone (10 mg/day), NSAIDs and low dose cyclosporin A. During follow-up, she developed anti-Ro and anti-La antibodies, continuing to show arthritis with remitting-flaring trend and initial deformities swan-neck-like at proximal interphalangeal joints. In November 1999, she developed an acute severe normochromic and normocytic anemia (Hb: 4 g/dl), without reticolocytes' production. A bone marrow biopsy showed selective erythroid aplasia, signs of erythrophagocytosis with normal myeloid and platelet precursors. Pure red cell aplasia (PRCA) was diagnosed, treated with units of packed red cells, high dose of oral steroids, cyclosporin A (3-5 mg/Kg) and erythropoietin (EPO) with partial and steroid-dependent response. In November 2002, she was readmitted to haematological Unit due to uncontrolled anemia and fatigue. She showed swan-neck and ulnar reducible deviations at the hands, parotid glands' enlargement, subjective xerophtalmia and xerostomia. Laboratory tests showed low neutrophilic count, ESR elevation, polyclonal hypergammaglobulinemia, ANA positivity with anti-Ro and anti-La antibodies, normal complement, elevation of serum creatinine (2.3 mg/dl), partially improved after cyclosporin A withdrawal, hypokalemia, hyposthenuria and selective tubular proteinuria (600 mg/day).

Renal biopsy was not performed. Lip biopsy revealed a dense lymphocytic periductular infiltration with elevated focus score. Dacriologic tests showed reduced tears production with corneal damage. Hands and feet x-ray failed to demonstrate any structural bone erosions. A diagnosis of SS, according to Vitali criteria (8), with distal tubular acidosis and deforming arthropathy (Jaccoud type) (JA) was made. The patient was treated with bicarbonate, folate and potassium supplements, high dose of oral steroids and EPO (for recurrent anemia), maintaining thyroid hormone replacement given for hypothyroidism. Unfortunately she did not tolerate azathioprine, nor 6-mercaptopurine due to severe pancytopenia. At the present time no signs of active arthritis were evident, but she persisted to show distal tubular acidosis with hypokalemia, sicca and scarcely controlled PRCA, characterised by frequent falls of hemoglobin, followed by elevation of the daily dosage of prednisone, as shown in Figure 1, and an increasing weekly dose of EPO. Subsequently, a significant elevation of hepatic and cholestatic enzymes was periodically observed: a liver biopsy, performed on 2004, showed an initial steatosis with parenchimal siderosis. In addition, a new bone marrow biopsy, performed on 2005, confirmed the selective red cell aplasia with iron deposits in interstitial matrix. Genetic tests for hemochromatosis were normal; so the histologic picture of siderosis at liver and bone marrow could be justified by repeated episodes of acute onset of anemia.

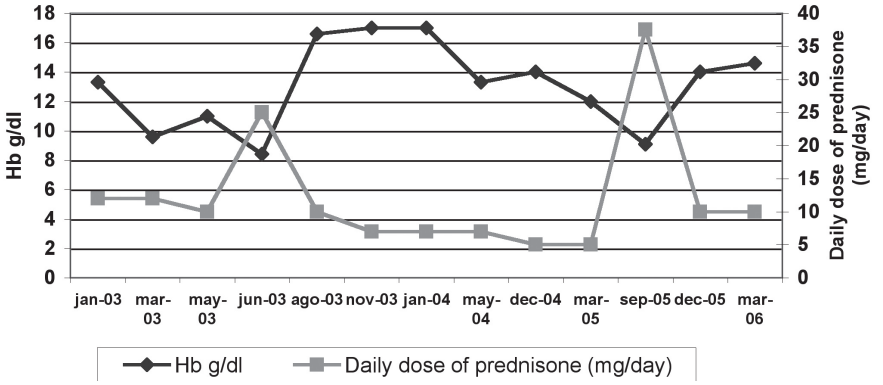

Fig.1. Hemoglobin and steroid dosage trend in patient affected by PRCA and primary SS.

Discussion

We described a case of a primary SS, characterised by glandular involvement, anti-nuclear antibodies with anti-Ro and anti-La specificities (8), and wide extra-glandular features. In particular, she showed a severe activation of immunological system since 8 years before the diagnosis of SS with Kikuchi syndrome and autoimmune thyroiditis, leading to hypothyroidism. Subsequently, she added articular and renal involvement, come out 7 and 2 years, respectively, before SS. The persistent seropositive polyarthritis was initially diagnosed as RA, though associated to anti-Ro and anti-La antibodies and mild neutropenia. Although these antinuclear specificities were detected in RA with rich extra-articular features (9), the radiological absence of erosions and the complete reducibility of deformities suggested a diagnosis of JA. This deforming and non-erosive arthropathy has been frequently considered an articular feature of SLE (10). Actually, some authors considered JA one of the clinical features more associated to anti-Ro specificity than to a specific disease such as SLE (11, 12). Furthermore, the progressive decline of renal function, initially ascribed to cyclosporin toxicity, associated to hyposthenuric urine and tubular proteinuria represented the most common clinical manifestations of distal tubular acidosis (13). The occurrence of extra-glandular features before the overt manifestation of primary SS is not uncommon especially in young patients that did not feel subjective dryness of eyes and mouth (13). Autoimmune tyroiditis, distal tubular acidosis, Jaccoud arthropathy are well described in primary SS, either before or after the diagnosis of SS (14). However, it is unexpected the onset of PRCA within this rich clinical picture. In fact, PRCA has been described in association with SLE, either as initial manifestation (3) or during the course of the disease (5, 6). Only one case of PRCA in a patient affected by long-standing primary SS was reported (7), as secondary to bone marrow infiltration of a lymphocytic lymphoma. In our case, although the patient showed polyclonal hypergammaglobulinemia and high titer RF, considered risk factors for the development for lymphoma (15), we did not find any sign of lymphoproliferation also in the second bone marrow biopsy, performed 5 years after the first one. Although the association between PRCA and SS could be accidental, this patient seems to show a systemic autoimmune disease, characterised by specific organ involvement (autoimmune thyroiditis and red cell aplasia), extra-glandular manifestations (Jaccoud arthropathy, distal tubular acidosis) and glandular features (sicca symptoms and parotid swelling).

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