Normotensive renal failure in a patient with systemic sclerosis and p-antineutrophil cytoplasmic autoantibodies which developed into Paget’s disease of bone after immunosuppressive therapy

Sir, The association of antineutrophil cytoplasmic autoantibodies (ANCA) with systemic sclerosis (SSc) is very infrequent with only a few cases reported in the literature [1–3]. We report one patient with SSc and necrotizing glomerulonephritis in whom p-ANCA were detected. Moreover, the patient developed clinical Paget’s disease after the immunosuppressive therapy, which may have played a part in the development of the disease.

A 60-yr-old female with a 12-month history of Raynaud’s phenomenon, chronic coughing, sclerodactyly, antinuclear antibodies (ANA) and anti-Scl 70 antibodies, presented to our clinic. Radiological examination and bronchoalveolar lavage revealed interstitial pneumonitis as a complication of SSc and she was started on prednisone (1 mg/kg daily). Owing to the presence of hypertension, haematuria and proteinuria, a diagnosis of scleroderma renal crisis was reached and captopril (50 mg/day) was added to decreasing corticosteroid therapy, with control of blood pressure. One year later, while she was on deflazacort (6 mg daily), she had a rapid renal function impairment. Her physical examination revealed a blood pressure of 140/80 mmHg, microstomia, sclerodactyly, purpuric lesions over the lower extremities and crackling rales on pulmonary auscultation. Blood tests showed: haemoglobin: 11.1 g/dl (12–16), urea: 82 mg/dl (18–50), creatinine: 2.2 mg/dl (0.5–1.5), creatinine clearance: 28 ml/min (80–120), proteinuria: 4.3 g/day, alkaline phosphatase 234 U/l (90–280), ANA: 1/640, anti-Scl 70: positive, rheumatoid factor: 25.4 U/ml, p-ANCA [antimyeloperoxidase (anti-MPO)] by ELISA: 71%. Anti-SSA, anti-SSB, anti-RNP, anti-DNA and anti-Sm were negative.

Skin biopsy showed a leucocytoclastic vasculitis and renal biopsy revealed necrotizing glomerulonephritis with extracapillary proliferation compatible with vasculitis, and she was started on corticosteroids (1 mg/kg/daily) and cyclophosphamide (0.75 g/m² monthly for 6 months and then every 3 months for 1 yr). Renal function improved and ANCA became negative after the fifth cyclophosphamide pulse. Ten months after the immunosuppressive therapy interruption, while she was on deflazacort 12 mg daily, blood chemistries showed a progressive increase in serum alkaline phosphatase (highest reached value: 540 U/l). Pyridinoline and acid phosphatase were also elevated: 66.31 nmol/mmol Cr (16–45) and 6 U/l (0–5.5), respectively. Radiological examination showed a disorganized trabecular pattern in the right ischium, that she did not have in previous X-rays (Fig. 1). Radionuclide bone scan revealed an increased uptaking in the right ischium, pathognomonic for Paget’s disease. Because of Paget’s disease activity, although the patient was asymptomatic, a low dose of sodium etidronate adjusted for renal failure (3 mg/kg/daily) was added to corticosteroid therapy. Serum alkaline phosphatase and pyridinoline levels decreased after the etidronate therapy (246 U/l and 40 nmol/mmol Cr, respectively).

The association of p-ANCA with SSc is very infrequent with only a few cases being reported in the literature [1–3]. Its presence has been found to be highly specific for normotensive renal failure associated with SSc, and its titres were correlated with renal disease activity [1]. Several distinctions have been found between renal SSc associated with p-ANCA and scleroderma kidney [4, 5]. Scleroderma kidney is characterized by accelerated to malignant hypertension, progressive renal insufficiency, hyper-reninaemia and microangiopathic haemolysis [1, 5, 6]. Histopathological study reveals an intimal fibrosis with fibrinoid necrosis of the media, mainly in the interlobular and arcuate arteries. However, renal SSc associated with p-ANCA is characterized by rapidly progressive renal insufficiency without malignant hypertension and with normal plasma renin activity. Renal histology shows crescentic necrotizing lesions with minimal immune deposits, but no arterial or arteriolar

Fig. 1. Paget’s disease in the pelvis. Note the disorganized trabecular pattern in the ischium and the thickening of the innominate line.
lesions as in our patient. Moreover, the course of the disease in scleroderma kidney is shorter than that of renal failure associated with SSc and p-ANCA, which may be associated with thrombocytopenia and pulmonary haemorrhage [1].

Locke et al. [3] have recently confirmed the rarity of anti-MPO antibodies in SSc. They found only two patients out of 81 to be positive. Anti-MPO antibodies appeared in one patient, after β-penicillamine treatment was introduced. The clinical course and renal biopsy were typical of drug-induced vasculitis. The second patient died of unrelated disease before further investigations could be performed. Results of these studies suggest that anti-MPO antibodies must be investigated in patients with SSc and normotensive renal failure.

Our patient had the peculiarity of developing Paget’s disease 10 months after the cyclophosphamide therapy interruption and while she was on low steroid doses. Whether immunosuppressive therapy might play a part in activating quiescent Paget’s disease remains unclear.

Several observations suggest that Paget’s disease may be caused by a viral infection [7–9]. If this hypothesis is true, immunosuppression may cause an activation of a quiescent disease. Moreover, steroid therapy inhibits several proinflammatory cytokines such as interleukin (IL)-6 or IL-1 [10]. Recent studies suggest that cytokines, such as IL-6, could be responsible for bone remodelling disorders in Paget’s disease. It is possible that high daily steroids, which were administered to the patient at the beginning, originated a cytokine inhibition that could inhibit Paget’s disease reactivation.

Finally, bone fragility due to corticoid therapy in the affected pagetic bone could produce microfractures; this situation, and the lack of cytokine inhibition due to low steroid doses administrated after the immunosuppressive therapy was withdrawn, may have stimulated Paget’s disease activity.

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