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Chronic Polyarthritis and Graft-Versus-Host Disease

Sir—In previous studies, the presence of arthralgias and transitory arthritis in graft-versus-host disease (GVHD) has been reported, but not chronic arthritis. We will consider a case of non-erosive polyarthritis after a bone marrow transplantation in the context of chronic GVHD.

A 32-yr-old male was diagnosed at the age of 27 as having acute myeloblastic leukemia. One year after the diagnosis, he received an allogenic bone marrow transplant and prophylaxis against GVHD with cyclosporin A.

Seven months after the transplant, the patient was admitted for cough and greenish expectoration, with radiological pulmonary infiltration, diagnosed as interstitial bilateral pneumonitis. During the time he was in hospital, acute renal insufficiency developed, brought on by nephrotoxic drugs. The cyclosporin A was then stopped. An increased level of bilirubin and alkaline phosphatase was detected, with negative markers of hepatitis B and C, and the hepatic biopsy showed changes compatible with GVHD and moderate siderosis. A generalized pruritus began without evidence of skin lesions. The patient reported slight xerophthalmia. Schirmer’s test indicated a lacrimal secretion of 9 and 12 mm. Chronic GVHD was diagnosed with hepatic, pulmonary and ocular involvement, and treatment with prednisone 30 mg and thalidomide 300 mg was prescribed, with good response.

Seven months later, generalized oedema began, with nephrotic type proteinuria becoming evident with conservative renal function.ANA and anti-DNA antibodies were negative. The renal biopsy showed membranous glomerulonephritis, leading to treatment with prednisone 60 mg, by which nephrotic syndrome was resolved.

Two years after the transplant, through treatment with prednisone 20 mg, pain in the right elbow and left ankle began, at first subacute. General examination was normal; no skin lesions were observed. Synovitis was detected in the right elbow. Laboratory studies revealed a haemoglobin of 149 g/l, white blood count 7700/mm³, platelet count 210 000/mm³, ESR 60 mm/h, alkaline phosphatase 1201 IU/l, GGT 670 IU/l, ALT 71 IU/l, total bilirubin 11 μmol/l, creatinine 69 μmol/l and a proteinuria of 0.15 mg/dl. Rheumatoid factor, smooth muscle and antimitochondrial antibodies were negative. The serology and antigenaemia for cytomegalovirus (CMV) were negative. The synovial fluid of the elbow revealed 30 000 leucocytes/mm³ and a neutrophil tendency. The crystals study, cytology and the synovial fluid cultures in habitual media and in Lowenstein-Jensen medium, and for CMV, were negative. In the simple X-rays, signs of avascular necrosis of the right external humeral epicondyle were observed and minimal compact periostic reaction in tibial metaphysis. X-ray images of the thorax, lumbar spine and pelvis were normal. The bone scan with technetium-99m showed increased uptake in the elbows and ankles. The synovial biopsy on the right elbow showed up as unspecific, with degenerative signs, slight chronic inflammation, and centres of haemosiderosis and microcalcifications. The presence of granulomas or amyloid was ruled out, and the culture of biopsy material in Lowenstein-Jensen medium was negative.

Seven months after the initial elbow pain, polyarthritis was observed affecting the wrists, MCPs, PIPs, knees and ankles with prolonged morning stiffness; a similar picture to that of rheumatoid arthritis. There was no family history of relevance to the development of the arthritis. The synovial fluid had inflammatory characteristics and absence of crystals. In the X-rays, there were signs of avascular necrosis of the external condyle of the right knee. X-rays of the hands were normal. The patient was treated with indomethacin and small doses of deflazacort with partial improvement. Two years from the start, the polyarthritis showed a chronic course involving the elbows, wrists, PIPs and right knee. A bone marrow study showed complete remission of the leukaemia.

GVHD is the most common non-infectious complication in transplant patients [1]. It can be acute (<100 days post-bone marrow transplant) or chronic. The acute form occurs in between 42 and 75% of the cases. It is characterized by the presence of dermatitis, diarrhoea and hepatitis, and the skin is affected in almost 100%. The skin involvement brings to mind that which occurs in scleroderma. In the joints, articular contractures, arthralgias and arthritis occur [2–4]. In one study, arthralgias of the large joints were observed in eight of 20 patients and transitory arthritis in four of 18 [2]. Other frequent findings are hepatic [3] and oesophageal involvement, diarrhoea, malabsorption, sicca syndrome and interstitial pneumonitis. The
risk of suffering chronic GVHD increases in patients more than 30 yr old and with a history of previous acute GVHD. Distinct therapeutic remedies have been suggested, among them corticoids, thalidomide and cyclosporin A [5].

We believe that this is an interesting case because it is the first with non-erosive chronic polyarthritis associated with GVHD with hepatic, pulmonary and ocular affliction. Through 2 yr of follow-up, the patient continued with non-erosive polyarthritis that partially responded to treatment with non-steroidal anti-inflammatory drugs and deflazacort.

The case is noteworthy for the absence of skin affliction, found in 18 of the 20 patients studied by Shulmann et al. [2]. The presence of avascular necrosis in this case is presumably related to the glucocorticoid treatment. Two rare manifestations of GVHD present themselves: membranous glomerulonephritis and chronic polyarthritis. Although no changes in the renal functions are described, the necropsy studies have shown interstitial inflammatory infiltrations and mesangial proliferation [2, 3].

The differential diagnosis of polyarthritis includes: diffuse connective tissue diseases, viral polyarthritis, leukaemic infiltration and GVHD. The duration of the polyarthritis rules out viral arthritis, although a case of polyarthritis by CMV has been described in a 39-yr-old patient after a bone marrow transplant a month before, which was resolved with ganciclovir [6]. Although the patient fulfils four criteria of the American Rheumatism Association for rheumatoid arthritis [7], the absence of rheumatoid factor and erosions in the hands goes against this. The arthritis associated with acute leukaemia in adults appears in up to 16% of the cases, the polyarticular forms which respond rapidly to basic treatment of the disease being most frequent [8].

The bone marrow study has led us repeatedly to rule out a relapse of post-transplant leukaemia in this patient.

In conclusion, non-erosive chronic polyarthritis may be considered as a rare manifestation of GVHD, although we should wait for new descriptions of this entity.

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Pancreatic Function in Systemic Sclerosis

Sir—Malabsorption is well recognized in systemic sclerosis (SSc) and usually reflects small bowel bacterial overgrowth secondary to stasis [1]. However, exocrine pancreatic insufficiency may contribute in a proportion of patients [2]. Exocrine pancreatic dysfunction may manifest as an attack of acute pancreatitis, painless pancreatic failure, or as steady deterioration in pancreatic secretory capacity punctuated by painful attacks. A propensity to oxidative stress occurs in both chronic pancreatitis and SSc [3]. A package of three non-invasive tests can be used to assess exocrine pancreatic dysfunction [4]: measurement of pancreatic isoamylase in serum, the tubeless BT-PABA/[14C]PABA test (benzoyl-tyrosyl-p-aminobenzoic acid/[14C]-aminobenzoic acid) and ultrasound scanning. Measurement of serum total amylase activity, whilst more readily available, does not offer the specificity of isoamylase analysis.

The PABA test employs a standard test solution containing a synthetic probe for chymotrypsin activity (NBT-PABA), a radiolabelled marker to allow for individual variations in hepatorenal handling, [14C]PABA and casein as a competitive substrate. Six hour urinary PABA and [14C]PABA recoveries are then measured, enabling a PABA excretion index (PEI) to be calculated. We report a preliminary study of these tests in patients with SSc.

Eleven unselected patients [six limited cutaneous (LCSSc) and five diffuse (DSSc) disease], all fulfilling the American Rheumatism Association criteria for SSC [5], were investigated. All but one had gastrointestinal complaints on specific questioning (Table I). Two had malabsorption/abnormal glycocholate breath tests; one had been admitted with a second attack of acute pancreatitis 4 yr previously and two had primary biliary cirrhosis (PBC). One other patient had Sjögren’s syndrome.

The concentration of isoamylase in serum was normal in all patients. Exocrine secretory impairment was shown in three patients by subnormal urinary PABA/[14C]PABA excretion index (<3 SD. below the control mean). These were the three patients with a history of small bowel bacterial overgrowth, PBC or both. Ultrasound scanning confirmed an atrophic pancreas in the patient with the lowest PABA/[14C]PABA value. The pancreas was not visualized in the patient with the second lowest PABA/[14C]PABA value.