Osteomalacia revealing celiac disease and primary biliary cirrhosis-related Fanconi syndrome in a patient with systemic sclerosis

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ABSTRACT
Systemic sclerosis (SSc) may affect the gastrointestinal tract and cause very rarely malabsorption syndrome related to bacterial overgrowth. Malabsorption syndrome may be responsible for weight loss, diarrhea, osteomalacia, and iron and vitamins deficiency. We report the case of a SSc patient who developed osteomalacia caused by the combination of two exceptional conditions in the setting of SSc: celiac disease (CD) and primary biliary cirrhosis (PBC)-related Fanconi syndrome. Oral prednisone with angiotensin-converting enzyme inhibitors, was initiated because of active lesions of tubuli, and led to the complete regression of bone pains, and by the improvement of renal function and regression of the features of proximal tubulopathy. Thus, in the presence of vitamin deficiencies in a patient with SSc, together with a search for malabsorption syndrome secondary to bacterial overgrowth, CD and/or PBC-associated Fanconi syndrome should be investigated.

Introduction
Osteomalacia is characterized by impairment of mineralization leading to accumulation of unmineralized matrix or osteoid in the skeleton (1). Major causes are vitamin D deficiency (1), and/or renal phosphate wasting disorders (2). Systemic sclerosis (SSc) is characterized by vascular hyper-reactivity and collagen deposition (3). Bowel involvement occurs in approximately 20% of SSc patients and may cause malabsorption syndrome usually related to bacterial overgrowth (4). We report the case of a SSc patient who developed osteomalacia caused by the combination of celiac disease (CD) and primary biliary cirrhosis (PBC)-related Fanconi syndrome.

Case report
A 42-year-old woman was referred in June 2006 for the evaluation of diffuse non-inflammatory bone pains. SSc was diagnosed in April 2006. She had digital ulcers and diffuse skin sclerosis (Rodnan score 13/51) without evidence of diarrhea. Joint mobility was normal. Biological tests revealed: normal hemo-

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vitamin D3 supplementation was initiated in August 2006, with a good efficacy on bone pains. Upon follow-up, serum zinc, ferritin and 25(OH)-vitamin D3 levels normalized; while serum creatinin increased to 160 μmol/L (creatinine clearance 33mL/min) with features of proximal tubulopathy (Fanconi syndrome): hypokaliemia (3.2mmol/L), metabolic acidosis (serum bicarbonate 19mmol/L, serum chlorema 109mmol/L), hypophophatemia (0.74mmol/L), hyperphosphaturia (28.3mmol/L), increased urinary beta2-microglobulin (263 mg/L, normal <0.21), normoglycemic glycosuria (3.9mmol/L) and aminoaciduria. Urinalysis showed aseptic leucocyturia, no hematuria and proteinuria quantified at 0.9g/day. Finally, diffuse tubulointerstitial nephritis with active tubulitis was documented upon renal biopsy, without evidence for vascular and glomerular involvement (Fig. 2). Immunofluorescent study was normal.

Oral prednisone was initiated in January 2007 at the dose of 1 mg/kg/d for one month followed by progressive tapering of the dosage, together with low dose angiotensin-converting enzyme inhibitors (ACEi) (perindopril 1.25mg/d). Evolution after 3 months of treatment was marked by the complete regression of bone pains, and by the improvement of renal function (serum creatinin 101μmol/L, creatinine clearance 55mL/min) and regression of the features of proximal tubulopathy (normal kaliemia, serum bicarbonate, chlorema, phosphatemia, calcemia and phosphaturia; absence of glycosuria; proteinuria 0.4g/day).

Discussion
Osteomalacia was rarely described during SSc, and occurs almost exclusively in the setting of malabsorption syndrome caused by bacterial overgrowth. Our case is remarkable regarding the mechanisms responsible for osteomalacia: malabsorption syndrome with vitamin D deficiency caused by CD, and tubulointerstitial nephritis and Fanconi syndrome with renal phosphate wasting caused by PBC.

CD is a chronic inflammatory intestinal disorder due to an immune reaction towards gluten proteins. Its association with autoimmune diabetes and thyroiditis has been widely reported (5). However, the link with other autoimmune diseases is less clear. CD was exceptionally described in the setting of SSc (6) and more frequently in the setting of PBC (7). PBC is more frequently associated to SSc, defining Reynolds syndrome which is characterized by a limited cutaneous SSc and a slower progression of liver disease compared with matched patients with PBC alone. Renal involvement in patients with PBC is not rare since distal tubular acidosis, which is the main feature, is found in up to 33%, usually without any clinical consequence (8).
More exceptionally, tubulointerstitial nephritis and Fanconi syndrome have been reported (9-12). Type 2 antimitochondrial antibodies directed against 3 mitochondrial enzymes: pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched-chain keto-acid decarboxylase, seem to play a key role in its pathophysiology, since antimitochondrial antibodies decrease the activity of these enzymes (12-14). Thus, osteomalacia and other deficiencies in the present case were also related to tubulointerstitial nephritis and Fanconi syndrome responsible for renal phosphate wasting. The association of SSc, PBC, Fanconi syndrome and CD might led us to discuss overwhelming humoral autoimmunity secondary to polyclonal B cell activation and/or ischemia-reperfusion injury and production of reactive oxygen species responsible for structural alterations of autoantigens and generation of secondary autoimmune reactions.

Finally, high dose prednisone (1 mg/kg/d) was prescribed. Indications for corticosteroid therapy are scarce in SSc pertaining to the risk of induction of renal crisis. Corticosteroid treatment was associated with ACEi. The evolution was clinically and biologically favorable, although no control renal biopsy was performed. Thus, active tubulointerstitial nephritis may represent an additional indication for corticosteroid treatment in SSc patients with PBC. In conclusion, in the presence of vitamin and oligo-element deficiencies including osteomalacia in a patient with SSc, together with a search for malabsorption syndrome secondary to bacterial overgrowth, CD and/or PBC-associated Fanconi syndrome should be investigated.

References
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Fig. 2. Kidney biopsy. (A) Masson’s trichrome. Magnification x100. Acute tubulo-interstitial nephritis with inflammatory cells in interstitium. (B) PAS staining. Magnification x400. Inflammatory cells in interstitium and some infiltrating tubular sections (tubulitis indicated by arrows).


