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CASE REPORT

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Severe osteomalacia due to undiagnosed cœliac disease: three case reports of Tunisian women

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Abstract We describe three cases of osteomalacia presenting in Tunisian women, all of whom had previously-undiagnosed cœliac disease (CD). Direct enquiry revealed an important weight loss and a history of diarrhoea in two patients, and a 15-year history of anaemia in one patient. Laboratory tests showed severe anaemia in the three cases. Reduced calcium was found in two cases, and corrected calcium was found in one case. Radiological examination showed fissure in two cases. The diagnosis of osteomalacia was made by clinical, biochemical and radiological features. Antigliadin, antireticulin, antiendomysial and anti-tissue transglutaminase antibodies were all positive in the three cases, and a small-bowel biopsy confirmed the diagnosis of CD. Treatment with gluten-free diet (GFD), supplemental calcium and vitamin D was initiated for the three patients, but only one patient complies strictly with the GFD; she showed a marked resolution of her symptoms.

Keywords Cœliac disease · Osteomalacia

Abbreviations AEA: Antiendomysial antibodies · AGA: Antigliadin antibodies · ARA: Antireticulin antibodies · AtTGA: Anti-tissue transglutaminase antibodies · BMD: Bone mineral density · CD: Cœliac disease · GFD: Gluten-free diet · IEL: Increased intraepithelial lymphocytes

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Introduction

Cœliac disease (CD) is an abnormal immuno-mediated response to the ingestion of gluten and other peptides from different cereals in genetically-susceptible subjects. Its treatment is the lifelong withdrawal of gluten from the diet. The clinical manifestations of CD, which are related to the extent and severity of the intestinal damage, may be different, and vary from the classical symptoms of malabsorption (diarrhoea, weight loss and complications caused by vitamin and oligoelement deficiency) to paucisymptomatic or monosymptomatic pictures, which may be intestinal or extra-intestinal. The detection of unusual cases of CD without diarrhoea is on the increase. The only observable symptoms of this pathology may be osteomalacia or persistent iron-deficiency anaemia despite oral iron therapy. We describe three cases of osteomalacia presenting in Tunisian women, all of whom had previously-undiagnosed CD.

Case reports

Case 1

A 20-year-old woman complained of bilateral thigh pain for 2 years, which followed a limitation of her walking ability. She denied any other symptom or a past medical history. Physical examination revealed a waddling gait without limitation of hips. Initial investigations showed anaemia (Hb 8.6 g/dl) secondary to iron deficiency, a raised alkaline phosphatase of 615 UI/l (normal range 100–290 UI/l) and a corrected calcium of 2.3 mmol/l.

Radiological examination showed a fissure in the left femoral diaphysis. An isotope bone scan showed increased uptake in the fifth costovertebral junction and in the left ankle. Further testing revealed low concentration of 25-hydroxy-vitamin D (7.9 μg/ml, normal range 14–75 μg/ml). The IgA and IgG antigliadin antibodies (IgA-AGA and IgG-AGA), IgA antireticulin antibodies (IgA-ARA), IgA antiendomysial antibodies (IgA-AEA) and IgA anti-tissue transglutaminase antibodies (IgA-AtTGA) were all strongly positive, and a small-bowel biopsy showed total villous atrophy with increased intraepithelial lymphocytes (IEL), confirming the diagnosis of CD. Treatment with gluten-free diet (GFD), supplemental calcium and vitamin D was initiated and led to a resolution of symptoms in our patient, who complies strictly with GFD. Laboratory tests, performed 1 month after the initiation of GFD, showed the correction of anaemia (Hb 13.8 g/dl). Six months later, a marked clinical improvement was found.

Case 2

A 32-year-old woman had been hospitalized in the rheumatology unit because of bone pain and rachialgia for the previous 3 months. Direct enquiry revealed an 18-month history of diarrhoea and weight loss. Her height was 167 cm and her weight was 51 kg. Laboratory tests revealed severe anaemia (Hb 7.7 g/dl) secondary to iron deficiency, an elevated alkaline phosphatase of 880 UI/ml and a hypocalcaemia. She had low concentration of 25-hydroxy-vitamin D (12.3 μg/ml). The diagnosis of biological osteomalacia was made. IgA-AGA, IgG-AGA, IgA-ARA, IgA-AEA and IgA-AtTGA were all positive. A small bowel biopsy showed total villous atrophy with increased IEL, which confirms the diagnosis of CD. Treatment with GFD, supplemental calcium and vitamin D was given. Within 3 months, there was a slight improvement of her symptoms and Hb was 10.6 g/dl.

Case 3

A 46-year-old woman presented to the rheumatology unit because of rib bone pain and rachialgia for 1 year. She was noted to be only 152 cm tall and weighed just 46 kg. Direct enquiry revealed a 15-year history of persistent iron-deficiency anaemia despite oral iron supplementation, a weight loss of 14 kg in 1 year, a diarrhoea episode 1 year earlier and another 3 years earlier. She also reported that she had had six spontaneous abortions. Laboratory tests showed anaemia (Hb 8.2 g/dl), an elevated alkaline phosphatase of 1800 UI/ml and reduced calcium of 2.2 mmol/l. A chest X-ray showed fissure at the seventh right rib (R7). An isotope bone scan showed increased uptake at R7 and R8 and in the right leg, and the pelvic X-ray demonstrated Looser's zones in the pubic rami.The IgA-AGA, IgG-AGA, IgA-ARA, IgA-AEA and IgA-AtTGA were all positive. The duodenal biopsy showed a subtotal villous atrophy with increased IEL, confirming the diagnosis of CD. Treatment with GFD, supplemental calcium and vitamin D led to a gradual resolution in her symptoms, within 1 year.

Discussion

Reduced calcium absorption due to intestinal villi atrophy, vitamin D deficiency and secondary hyperparathyroidism are all responsible for the development of osteomalacia. Secondary hyperparathyroidism as a frequent complication of calcium and vitamin D deficiency should be quantified by measuring PTH levels. At tissue levels, PTH causes an increasing osteoclastic activity and (fibro-)osteoclastic lesions. These findings, combined with the mineralization defect, are called mixed osteodystrophy.

Bone mineral density (BMD) has been reported to be lower in subjects with untreated CD [1] and subclinical CD [2] than in control group; and it was found to be even lower in silent as compared to symptomatic cœliac patients [3]. Patients whose disease was diagnosed in childhood, and who had resumed a normal diet during adolescence and remained free of intestinal symptoms, may develop bone complications in adult life [4]. Furthermore, osteomalacia may be the only presenting feature of CD [5–16]. It has been demonstrated that cœliac patients are at increased risk of fracture [17]. However, in another study, no increase in fracture risk could be demonstrated for CD [18].

We have described three cases of osteomalacia presenting as a major feature of CD in adults. These three patients had clinical, biochemical and radiological features of osteomalacia, which predated their diagnosis by a significant time period, and two patients have spontaneous fissure. Radiological evidence of osteomalacia-like Looser's zones has become more and more rare, and is a late feature of vitamin D deficiency. In most case reports of osteomalacia as the presenting symptom of CD, there were no gastrointestinal signs, but anaemia was present in most cases. A recent case study of CD showed that many patients in fact present with no gastrointestinal symptoms of which anaemia is the most common [19]. In another study, iron-deficiency anaemia was the most frequent extra-intestinal marker of subclinical CD [20]. Our three patients have anaemia, but two of them reported also a history of diarrhoea and weight loss. In fact, underdiagnosis and misdiagnosis of CD are common in general practice and often result in protracted and unnecessary morbidity. Dorst and Ringe [9] have reported a case of CD diagnosed at the age of 67 years; this woman had a 20-year history of recurrent abdominal pain, diarrhoea and diffuse bone pain. García-Porrúa et al. [12] described the case of a 57-year-old patient who had a 30-year history of anaemia. Furthermore, Hepburn and Kaye [14] have done the

diagnosis of CD complicated by osteomalacia and osteoporosis in an 80-year-old woman who had a history of anaemia, weight loss and intermittent diarrhoea.

In a prospective case-control study, Barera et al. [21] investigated 22 school-aged children with CD both at diagnosis and after 1 year of GFD, and 248 age-matched control participants. They confirmed that the mineral deficit observed by dual-energy X-ray absorptiometry at diagnosis is completely corrected after 1 year of treatment. These authors drew attention to the fact that these results are harder to achieve if CD is first diagnosed in adulthood. Kavak et al. [1] have also demonstrated that treatment of CD with GFD is associated with a significant increase in BMD.

It is essential that physicians bear in mind the possible link between CD and bone alterations: in particular, both gastroenterologists and rheumatologists should be fully aware of the problem, as low bone mass is one of the major long-term complications of untreated CD. Early diagnosis and effective treatment of CD are the most relevant measures to protect patients from the risk of fractures. Clinicians should have a high index of suspicion of CD in any patient with osteomalacia. The availability of sensitive and specific serological markers of CD, i.e., AGA, AEA and AtTGA [22, 23], to identify patients who could benefit from a diagnostic small-intestinal biopsy, has made the diagnosis of CD easy.

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