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Osteomalacia as an extraintestinal manifestation of Celiac disease in a patient treated for Gaucher disease

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ABSTRACT

Gaucher disease (GD) is the most prevalent lysosomal storage disorder. Bone marrow infiltration by Gaucher cells and the subsequent inflammatory events cause bone lesions, which frequently accompany anemia, thrombocytopenia, and hepatosplenomegaly. We present the case of a 22-year old woman with GD who was referred for bone assessment after 5 years on enzyme replacement therapy (ERT). Although the patient's hematological parameters improved with ERT showing good response to treatment, she had extensive bone marrow infiltration, and very low bone density. In addition, the patient reported severe bone pain, weakness, and difficulties walking up the stairs. Bone and mineral metabolism assessment showed hypocalcemia, hypophosphatemia, elevated bone alkaline phosphatase, secondary hyperparathyroidism and vitamin D deficiency. All these parameters were compatible with nutritional osteomalacia, and they improved with vitamin D and calcium supplementation. Worsening of her anemia and sustained vitamin D deficiency led to the diagnosis of celiac disease. We highlight the importance of detecting co-morbidities in patients with GD, especially in cases showing poor or inadequate response to specific GD treatment with enzyme replacement or substrate inhibition therapy.

Introduction

Gaucher disease (GD) is the most prevalent lysosomal storage disorder with a pan-ethnic distribution and an incidence of approximately 1/40,000 to 1/60,000 births, respectively, rising to 1/800 in Ashkenazi Jews (Stirnemann et al., 2017). Gaucher disease is an autosomal recessive, inherited disease caused by pathogenic variants in *GBA1* that leads to deficiency of glucocerebrosidase (GCase), the enzyme that catalyzes the hydrolysis of the glycolipid glucosylceramide (GlcCer) to ceramide and glucose (Stirnemann et al., 2017). Deficiency of GCase activity results in GlcCer accumulation in macrophages, mainly in the spleen, liver, bone marrow, and lungs (Stirnemann et al., 2017; Futerman et al., 2004).

Bone marrow infiltration by Gaucher cells and the subsequent inflammatory events cause bone lesions, which frequently accompany anemia, thrombocytopenia, and hepatosplenomegaly. Patients with GD may present with bone pain, osteoporosis, fragility fractures, bone infarcts, and avascular necrosis (Marcucci et al., 2014). Even hematologically asymptomatic patients may present with bone complications that affect their quality of life. The pathogenesis of such complications, nevertheless, remains to be elucidated (Mikosch and Hughes, 2010). Children and adolescents may present with growth retardation and delayed puberty.

Enzyme replacement therapy (ERT) rapidly improves hematological parameters, whereas bone lesions respond more slowly, and complete recovery remains uncertain (De Fost et al., 2008; Deegan et al., 2011). We report the case of an adult patient with GD on ERT who had bone manifestations that were initially attributed to GD but were found to be compounded by osteomalacia secondary to asymptomatic celiac disease (CD).

Case report

A 22-year old female with GD was referred for assessment of GD-related bone involvement after 5 years on Velaglucerase therapy. The patient reported severe bone pain, weakness, and difficulties walking up the stairs that led to functional decline. Her body weight, height and BMI were 41 kg, 146 cm, and 19.2 kg/m^2, respectively. At 17 years old, she was investigated for severe hepatosplenomegaly (spleen length = 18 cm, liver length = 17 cm), and pancytopenia (hematocrit: 15%, hemoglobin: 5.3 g%, white blood cell count: 1.750/mm^3, platelet count: 160,000/mm^3). Bone marrow evaluation showed diffuse

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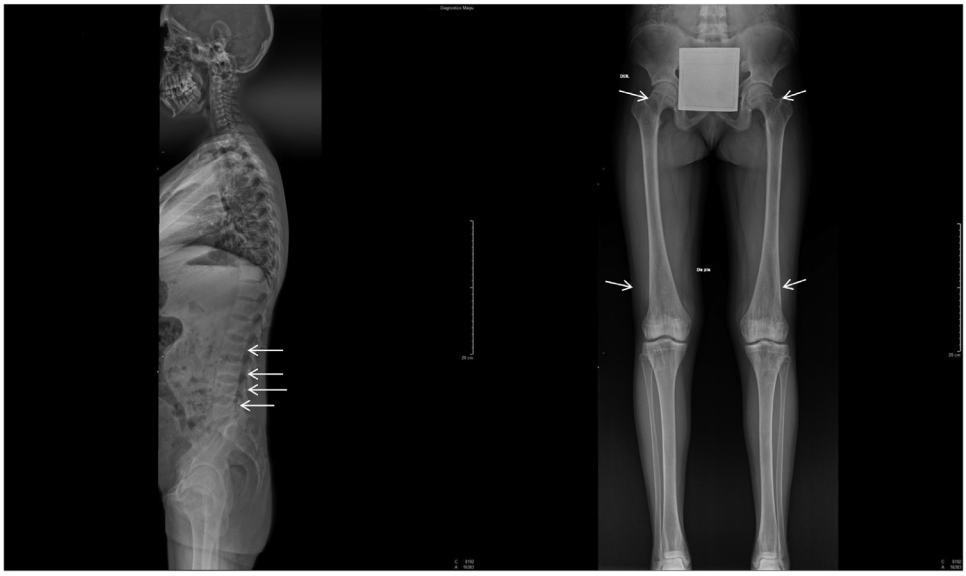

Fig. 1. Radiograph of the spine showing biconcave deformities in lumbar vertebrae (A) and radiograph of lower limb showing ill-defined radiolucent areas in both proximal femurs and Erlenmeyer flask deformity of the distal femurs (B).

infiltration of giant foamy cells with eccentric nuclei, compatible with Gaucher cells. Diagnosis of GD type 1 was confirmed by enzymatic activity assay (GCase activity = 1.3 nmoles/h/mg prot; reference value: 5.14–24.8) and *GBA1* genetic testing (c.1226A>G/c.1448T>C). Levels of chitotriosidase, a marker of GD activity, were high (2.488 μmol/l.h; reference range =7.77 a 110.50 μmol/l.h). The patient's eldest sister was confirmed to have asymptomatic GD.

Six months after diagnosis, treatment with 60 U/kg of intravenous Velaglucerase every two weeks was initiated. After two years of treatment, the patient showed very low spine bone mineral density values (0.767 g/cm^2; Z-score= −4.0). She was therefore started on intravenous infusions of 90 mg of pamidronate every 60 days for 6 months, and on calcium and vitamin D supplementation. The latter was prescribed even though her vitamin D levels had never been tested. The patient had her menarche at the age of 19 years with regular menses lasting approximately 7 days. Long menses were initially considered the cause of her persistent anemia, which was treated with iron infusions due to intolerance to oral iron supplements.

Her imaging assessments revealed several abnormalities. Spine X-rays showed biconcave deformities in the lumbar vertebrae, especially L3 and L4. Lower limb X-rays showed ill-defined radiolucent areas in both proximal femurs, and Erlenmeyer flask deformity of the distal femurs (Fig. 1A and B). Hand and wrist radiographs showed a bone age of 14.5 years (Greulich and Pyle standard (Greulich and Pyle, 1959)), whereas chronological age was 22 years. Magnetic resonance imaging showed bone marrow infiltration in the spine, femurs, iliac bones, tibiae, humerus, radius, ulnae, astragalus and calcaneus, and bone edema in the humerus, radius, and calcaneus. Moreover, there was enlargement of the liver and a moderate increase in spleen volume (1.3 and 7.3 times larger than the normal reference values, respectively).

Bone mineral density assessment revealed spine, total femur, and total skeleton Z-scores of −4.2, −3.0, and −3.2, respectively, indicating that the patient had very low BMD. Although there are no reference values for individuals aged less than 40 years to date, TBS was also determined. Absolute BMD (g/cm^2), Z-scores and TBS values are shown in Table 1.

Laboratory tests while on ERT showed low hemoglobin and hematocrit (11.4 g/dL 37 % respectively), normal platelet counts (199,000/mm^3), and an acceptable chitotriosidase level (177umol/hl). Assessment of bone and mineral metabolism showed hypocalcemia, hypophosphatemia, elevated bone-specific alkaline phosphatase, CTX, and PTH levels, and vitamin D deficiency (Table 2). Her GD was in metabolic control due to ERT (Drelichman et al., 2015). Therefore, her bone symptoms were attributed to osteomalacia secondary to vitamin D deficiency. Calcium supplementation and administration of high doses of vitamin D were prescribed.

At the 1-year follow-up visit, the patient was 23 years old. She showed no changes in body weight or stature, and reported a significant improvement in pain and mobility. She had received 100,000 IU of vitamin D_3 every 15 days for 3 months, and a non-specified daily oral dose of calcium. Chitotriosidase levels and platelet counts were within normal ranges, showing that GD remained stable and that the patient was responding well to Velaglucerase. In contrast, anemia had worsened, and the vitamin D deficiency persisted. Although calcemia, phosphatemia, BAP, and CTX values had improved, they still remained outside the normal range (Table 2). Despite the absence of gastrointestinal symptoms, a malabsorptive disease in addition to GD was suspected. Serological tests were positive for celiac disease (CD): antitransglutaminase IgA antibody levels were 166 U (reference value <10 U), and anti-deaminated gliadin peptide IgG antibody levels were 101 U (reference value < 20 U). Upper digestive endoscopy showed villous atrophy in the bulb and second part of the duodenum, and intestinal mucosa biopsy revealed the presence of lymphocytic enteritis type 3c according to Marsh's classification. Both findings were compatible with CD. No Gaucher cells were detected. The timeline of events is shown in Fig. 2. The patient was prescribed a gluten-free diet (GFD), and she was instructed to continue taking daily calcium supplementation and monthly supplementation with 100,000 IU of vitamin D_3.

At the 2-year follow-up visit, the patient reported she was not complying with the GFD and only partially complying with calcium and vitamin D supplementation due to socioeconomic and environmental limitations. Clinical course was nevertheless favorable.

Three years after the first bone assessment (3-year follow-up visit), the patient showed no significant changes in MRI, or in spine and femur X-rays. Bone age was 18 years (the highest value referenced in the Greulich and Pyle atlas). A substantial increase in spine, hip, and total skeleton BMD values was observed, and all three sites were within age-matched reference ranges. A significant increase in TBS was also observed (Table 1). All the biochemical parameters of bone and mineral metabolism had improved, and serum calcium, phosphorus and PTH values were within the normal range. Although a three -fold increase in 25OHD was observed as compared to initial values, levels remained

Table 1
Bone densitometry and TBS at baseline and throughout the 3-year follow-up.

Age (years)	Spine L1-L4 g/cm^2	Z-score[1]	TBS	Total Femur g/cm^2	Z-score	Total Skeleton g/cm^2	Z-score
22	0.589	−4.1	1120	0.556	−3.0	0.647	−3.2
23	0.820 + 23%*	−2.2		0.808 +25%*	−1.0	0.793 + 14.6 *	−1.8
24	1.119 + 30%*	−0.2	1374 +22.6%*	1.075 +27 %*	1.0	0.950 + 15.7 %*	−0.3
25	1.284 + 14.7%*	+1.6		1.214 +13 %*	+2.2	1.106 + 16. %*	+1.2

* Increase % vs. previous value
[1] Z-score is defined as the number of standard deviations from the mean BMD of a healthy population of the same age, race, and sex. According to the International Society for Clinical Densitometry guidelines, Z-scores are used in patients under the age of 50 years and a value below -2 indicates reduced BMD [Position Development Conference on bone densitometry. J Clin Densitom. 2013;16(4):455–66].

Table 2
Bone and mineral metabolism at baseline and throughout the 3-year follow-up.

		Age (years)			
Serum determinations	Reference range	22#	23*	24*	25*
Calcium	8.4–10.2 mg/dl	7.4	8.3	8.7**	8.9**
Phosphate	2.7–4.5 mg/dl	2.9	2.2	3.2**	3.3**
Bone Alkaline Phosphatase	31–95 U/l	1815	653	234	109
25-OH-D	≥20 ng/ml	6.7	8.1	15.8	19
Parathormone	15.0–65.0 pg/ml	431	227	84	56**
CrossLaps	Premenopause: 0.3–0.58 ng/ml	4.23	1.88	2.59	1.36

After 5 years on enzyme replacement therapy (ERT)
* Receiving ERT, and vitamin D and calcium supplementation
** Normalized values

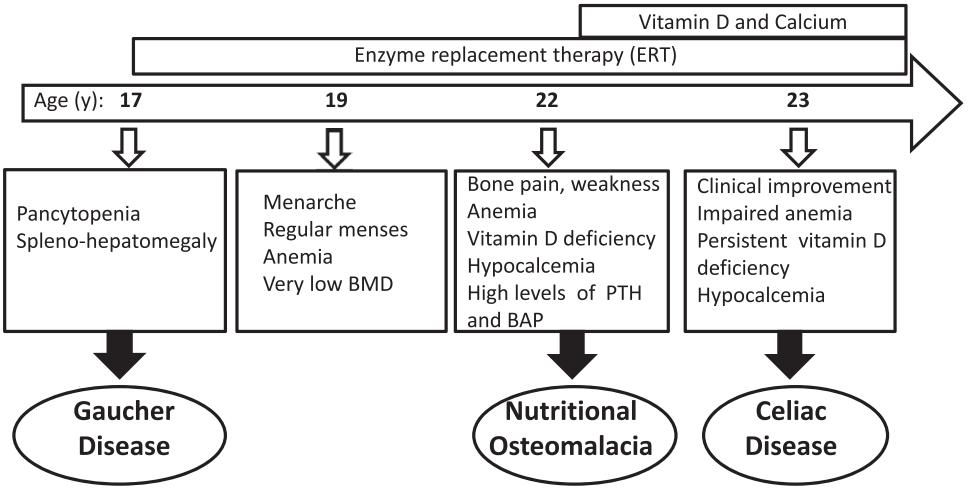

Fig. 2. Timeline of clinical events recorded from initial diagnosis of Gaucher disease to diagnosis of celiac disease.
The upper lines show age at initiation and duration of each treatment.
(y): years; BMD: bone mineral density; PTH: parathormone; BAP: bone alkaline phosphatase

in the deficiency range (Table 2). The patient informed us that she had never followed the GFD.

Discussion

Gaucher disease is in the constellation of rare diseases. It is characterized by marked phenotypic heterogeneity and a variable clinical course. The disease can present with varying degrees of severity at all stages of life.

The classic clinical triad is thrombocytopenia, anemia, and visceromegaly (mainly splenomegaly). Nevertheless, around 35% of patients initially have bone symptoms (pain, fractures, osteoporosis, avascular necrosis) as the only presenting symptom or together with hematological manifestations (Rossi et al., 2011, Ben- Chetrit et al., 2011).

GD patients can suffer bone complications that severely affect their quality of life. Bone assessment at the time of diagnosis is therefore important so as to determine the degree of bone involvement. Although ERT does not totally prevent the onset of bone lesions, it has been proven to effectively decrease bone pain and bone crises, and to decrease the frequency of new bone events. It has also been shown to improve bone mineral density and to decrease infiltration by Gaucher cells (Drelichman et al., 2016).

At the time of the first bone assessment performed by our team, the patient had been receiving Velaglucerase for almost 5 years. Therapeutic goals for anemia, thrombocytopenia, and hepatosplenomegaly, and almost normal levels of chitotriosidase were achieved, showing good hematological response to treatment (Drelichman et al., 2015). Although vitamin D deficiency has been reported in GD (Mikosch et al., 2008; Parisi et al., 2008), the deficit observed in our patient was severe, and her response to treatment with high doses of vitamin D was slow and insufficient. Further tests were therefore conducted in order to detect the cause of poor response to vitamin D supplementation, and diagnosis of malabsorption secondary to celiac disease was established.

Positive autoantibodies have been observed more frequently in GD type 1 than in the healthy population (52% vs. 26%), though the prevalence of clinically active autoimmune diseases is not higher in GD1 (Serratrice et al., 2018). The presence of autoantibodies has also been reported in other lysosomal storage disorders (Dimitriou et al., 2019). Celiac disease could therefore be considered a comorbidity

or a concurrent disease associated with GD, since it is a chronic immune-mediated disease of the small intestine that is precipitated in genetically predisposed subjects by ingestion of gluten (Ludvigsson et al., 2013). To our knowledge, however, no significant association between GD and CD has been reported to date.

Unlike GD, the prevalence of CD is high, affecting approximately 1% of the population worldwide (Dubé et al., 2005; Fasano et al., 2003). Celiac disease may also present with anemia, weakness, abdominal discomfort, growth retardation, developmental delay, osteopenia, osteoporosis, and increased fracture risk. The pathogenesis of bone complications involves two main mechanisms: intestinal malabsorption of calcium and vitamin D, and the presence of chronic inflammation (Bianchi and y Bardella, 2008). Although osteopenia and osteoporosis are frequent in symptomatic celiac patients, they may also occur without the typical gastrointestinal symptoms of diarrhea and abdominal distension (González et al., 1995; Mazure et al., 1994; Shaker et al., 1997).

The patient reported here presented with bone pain, weakness, low bone mass, and a history of growth retardation and delayed puberty. All these clinical signs are common to both GD and CD. Nevertheless, the observed visceromegaly and pancytopenia initially led to diagnosis of GD. Although the patient showed good hematological and visceral response to ERT, she was started on short-term bisphosphonate treatment due to her very low spine BMD. Given the lack of assessment of the patient's vitamin D status, administration of bisphosphonate treatment may have been inadequate due to its hypocalcemic effect.

The biochemical study of bone and mineral metabolism evidenced vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, and highly elevated BAP levels, all of which are biochemical features of an osteomalacic syndrome.

Osteomalacia is a metabolic bone disorder affecting skeletal mineralization. It is infrequent in symptomatic CD, and even more infrequent as an extra intestinal clinical form of presentation of CD (Gifre et al., 2011). Non pathognomonic clinical, radiographic, and biochemical features include crippling pain, muscle weakness mainly of the proximal muscles, and radiological finding of pseudofractures or Looser's zones.The latter were not detected on our patient's radiographs. Of note, performing bone scintigraphy might have allowed identifying focal areas of increased uptake due to the presence of Looser´s zones, since these sites can often be visualized on radionuclide images before they become radiographically apparent.

Diagnosis of osteomalacia may require bone biopsy demonstrating accumulation of non-mineralized or poorly mineralized osteoid tissue. However, complementary to clinical findings, the presence of hypocalcemia, hypophosphatemia, severe vitamin D deficiency, secondary hyperparathyroidism, and markedly elevated BAP levels allows establishing diagnosis of osteomalacia with no need for confirmation by invasive methods (Bingham and Fitzpatrick, 1993).

The patient presented here had very high bone formation and resorption marker levels (BAP and CTX). There is considerable variability in reported levels of bone remodeling markers in GD. Van Dussen found that most patients had low osteocalcin levels and CTX levels in the normal range. The authors therefore posited an imbalance in bone remodeling at the expense of a decrease in bone formation (van Dussen et al., 2011). Conversely, BAP is markedly increased in osteomalacia, in which mineralization is impaired (Harris et al., 1969).

The cause of osteomalacia secondary to vitamin D deficiency is multifactorial in the patient presented here, namely insufficient exposure to sunlight and malabsorption of vitamin D and calcium. The resulting hypocalcemia promoted a secondary increase in PTH. The secondary hyperparathyroidism, in turn, promoted conversion of 25OHD to the active metabolite $1,25(OH)_2D$, decreasing the half-life of 25OHD and exacerbating the Vitamin D deficiency (Mawer, 1997).

Normalization of biochemical parameters is expected with a GFD. Despite the patient not complying with the GFD, her blood calcium levels normalized and her PTH and BAP levels decreased, likely due to calcium and vitamin D supplementation. Although the patient's vitamin D levels remained in the deficiency range, the attained increase was sufficient to induce positive biochemical changes.

Even though the patient's estradiol levels were not assessed, spontaneous menarche and resumption of menses would seem to confirm that her estradiol levels were adequate. Nevertheless, neither the observed hormonal recovery nor the almost five years on Velaglucerase treatment improved bone mass. BMD may be decreased in untreated GD patients, and ERT improves and may even normalize BMD in children and adolescents. Lumbar spine DXA Z-scores have been reported to improve from −1.95 (95% CI −2.26 to −1.64) to −0.67 (95% CI −1.09 to −0.26) in young adults on ERT (Mistry et al., 2011).

In the case reported here, the very low BMD values observed prior to treatment indicate the replacement of mineralized by unmineralized osteoid, which is characteristic of osteomalacia. Supplementation with calcium and vitamin D reinitiated mineralization of the accumulated osteoid, resulting in a remarkable increase in BMD. Lumbar spine Z-score improved from − 4.0 to + 1.6, and absolute BMD increased 68 %, 65 %, and 46%, at the lumbar spine, total femur, and total skeleton respectively, reaching normal values at all three skeletal sites. Changes of such magnitude are consistent with reported findings on response to osteomalacia treatment and are in contrast to that observed in treated osteoporotic patients, even in those receiving osteoanabolic drugs such as teriparatide (Bhambri et al., 2006). The marked increase in BMD observed in our patient not only indicates adequate response to treatment but also confirms diagnosis of osteomalacia (Bhambri et al., 2006)

Trabecular bone score is an index of bone microarchitecture. It is obtained using special software that is installed in the same equipment used for DXA densitometry of the lumbar spine. Values below 1200 indicate degraded bone structure (Harvey et al., 2015). Our patient showed a remarkable change in TBS, which shifted from very low (1120) prior to calcium and vitamin D supplementation to normal values at two years follow up. There are reports of altered TBS values in GD patients (Baldini et al., 2018, Oliveri et al., 2019). To our knowledge, there are no data on longitudinal follow up of TBS during ERT or in osteomalacia.

Unlike response of CD-associated osteoporosis to a GFD, total recovery of bone quantity (normalization of BMD) and quality (normalization of TBS) was observed in the patient described here.

To sum up, we highlight the importance of detecting co-morbidities in patients with GD, especially in cases showing poor or inadequate response to enzyme replacement or substrate inhibition therapy. In the case of the patient reported here, who showed bone involvement secondary to GD, complete assessment of bone and mineral metabolism was key to finally identify an undiagnosed co-morbidity such as celiac disease.

Declaration of Competing Interest

DCG and BO have received honoraria for speaking from Shire/Takeda.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.endmts.2020.100052.

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