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Case Report

Primary Hyperparathyroidism in Biopsy-Defined Adult Celiac Disease

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Abstract

Osteoporosis and secondary hyperparathyroidism commonly occur in celiac disease thought to be mainly due to impaired intestinal calcium and vitamin absorption. A 41-yr-old female diagnosed with celiac disease and osteoporosis in 1979 was on a life-long gluten-free diet. In 1997, she developed abdominal pain. Blood and abdominal imaging studies (ultrasound, CT and barium studies) were normal, except for a slightly elevated serum calcium level. Endoscopic studies showed rare gastric and duodenal bulbar erosions that responded initially to courses of ranitidine, and later, omeprazole. Serum gastrins were normal. Duodenal biopsies were normal with healed celiac disease. Later, serum calcium progressively increased with a rising parathyroid hormone (PTH) levels.

Primary hyperparathyroidism was suspected and, in 2001, neck dissection showed a parathyroid gland adenoma that was resected. This completely resolved her prior persistent hypercalcemia and abdominal pain. Primary hyperparathyroidism due to a parathyroid adenoma is rare in celiac disease but may cause osteopenic bone disease, recurrent bouts of abdominal pain and mucosal erosions responsive to anti-secretory agents.

Keywords: Primary Hyperparathyroidism; Biopsy; Adult Celiac Disease

Introduction

Celiac disease is an immune-based small intestinal mucosal disorder that occurs in genetically-predisposed individuals [1,2]. The disorder is often associated with extra-intestinal endocrine manifestations [3], also attributed to immune-based mechanisms, including autoimmune thyroiditis, usually with hypothyroidism [4], and type 1 diabetes, particularly in children [5]. In addition, adrenal, pituitary and ovarian failure may occur in celiac disease [6,7] and these are also thought, in some patients, to have an autoimmune basis.

Osteopenic bone disease frequently complicates the clinical course of celiac disease, attributed at least, in part, to impaired intestinal absorption of calcium and fat soluble vitamin D along with chronic inflammatory changes that may impact bone metabolism [8]. In celiac disease, elevated levels of parathyroid hormone (PTH) may develop, usually caused by secondary hyperparathyroidism [8]. These changes improve with a gluten-free diet [8].

However, an elevated PTH determination in celiac disease combined with the finding of hypercalcemia, as in the case here, is rare.

Case Review

A 41-yr-old female graduate nurse was initially evaluated for persistent epigastric abdominal pain and pale loose stools in 1979. There was no weight loss. Studies at that time, including upper endoscopic evaluation and biopsies, led to a diagnosis of biopsy-defined celiac disease. She was treated with a gluten-free diet and her symptoms resolved. Over the next 2 decades, however, she suffered from occasional episodes of abdominal pain.

She had remained on a strict gluten-free diet but did note a single episode of self-limited diarrhea during a visit to the United Kingdom. At the time, after negative fecal cultures, she was clinically diagnosed with a transient "viral" gastroenteritis. Recurrent abdominal pain symptoms led to blood studies, including a normal serum amylase, normal renal function and negative serological

studies for *Helicobacter pylori*. Barium studies of her upper gastrointestinal tract were normal. However, a serum calcium level was very slightly elevated, 2.62 mmol per L (normal, 2.10-2.60) and, later, a serum parathyroid hormone assay (PTH) was increased, 7.2 pmol per L (normal, 1.3-5.4), the latter consistent with hyperparathyroidism. In February 1997, she was treated with ranitidine that resolved her abdominal pain, but, off medication, in September 1997, pain recurred leading her to seek care in a rural hospital emergency center. Blood studies, including serum amylase, were normal and symptoms resolved with narcotic administration. Later barium radiographic studies, including the small intestine, were normal. Fecal occult blood and cultures were negative. Abdominal and pelvic ultrasound and CT studies were normal. Endoscopic evaluation was done and showed a few shallow erosions in the duodenal bulb, however, mucosal biopsies were normal.

Because of recurrent abdominal pain, repeated blood studies in 1998 revealed a normal hemogram, sedimentation rate, thyroxine, quantitative immunoglobulins, amylase and liver chemistry tests. Serum calcium was now increased to 2.67 mmol per L (normal, 2.00-2.60), PTH, 8.1 pmol per L (normal, 1.3-5.4), and gastrin, 48 ng per L (normal, 0-130). Endoscopic exam showed some shallow gastric antral erosions and a normal duodenum.

Biopsies were normal. A course of omeprazole 20 mg daily for a month resolved her abdominal findings suggesting that both her abdominal pain and endoscopically-defined mucosal erosions were related to hypercalcemia [9,10]. Endocrine re-assessment, however, revealed a further increase in serum calcium to 2.8 mmol per L as well as a decline in bone density. She was referred for surgical neck exploration of the parathyroid glands. This showed a single 1 cm right inferior parathyroid adenoma that was resected. Frozen sections of 3 other normal right and left parathyroid glands revealed no abnormality. Post-operatively, because of her osteopenia, she was prescribed daily calcium carbonate.

From 2001 to 2005, she was followed on a semi-annual basis. She had no further bouts of abdominal pain. Later blood studies were normal including her serum calcium 2.36 mmol/L (normal, 2.10-2.60), parathormone 6.9 pmol per L (normal, 1.0-8.2) and serum 25-hydroxy-vitamin D, 59 mol per L (normal, 25-100). Endoscopic exam in 2005 was normal with normal gastric and duodenal biopsies.

Discussion

This patient had well established celiac disease on a gluten-free diet and osteoporosis, initially presumed to be a result of impaired absorption of calcium with concomitant secondary hyperparathyroidism [11]. Bone loss in this setting is most often attributed to celiac disease, especially in females, particularly in the appendicular skeleton [11]. Aging may be another relevant factor in the pathogenesis of osteoporosis. However, her clinical course was also complicated by development of progressively increasing serum calcium levels associated with bouts of epigastric abdominal pain. Hypercalcemia in this setting is distinctly unusual and led to definition of a solitary functioning parathyroid adenoma. This was further emphasized in follow-up by her complete response to surgical treatment. Despite her clinical presentation, resection of the adenoma resulted in complete clinical and laboratory resolution.

In 75 to 80% of cases of primary hyperparathyroidism, prior studies have shown that one or more adenomas account for excessive hormone production with about 20% secondary to hyperplasia of all glands [12]. Up to 2006, there had been only a single report of hyperparathyroidism in a patient with celiac disease and Grave's disease that required a near-total thyroidectomy with detection of an incidental parathyroid adenoma [13]. At that time, Maida., *et al.* [12]. added 7 additional patients, primarily female, from a clinical practice cohort of 310 patients in the United Kingdom suggesting a 2.3% prevalence rate. Finally, a population-based cohort study from Sweden suggested that celiac patients were at increased risk for primary hyperparathyroidism [14].

It is well recognized that different gastrointestinal symptoms may occur in patients with primary hyperparathyroidism associated with a functioning parathyroid gland adenoma, regardless of the concomitant diagnosis of celiac disease. It has been estimated that 5 to 15 per cent may have some form of peptic ulcer disease [10]. Here, her symptoms and endoscopic findings appeared related to hypercalcemia and resolved with anti-secretory medications, including either ranitidine or omeprazole.

Moreover, after removal of the parathyroid gland adenoma, her abdominal pain resolved completely along with her hypercalcemia. Indeed, the osteoporosis with celiac disease was effectively managed with a gluten- free diet and later calcium supplements alone.

Conclusion

To summarize, celiac disease is often associated with evidence of vitamin D deficiency and malabsorption of calcium, both causing secondary hyperparathyroidism. This would suggest that the elevated PTH levels may be expected in celiac disease, however, the association of celiac disease with hypercalcemia is rare. Moreover, detection of hypercalcemia may not occur until a diagnosis of celiac disease is established and treated, potentially causing a delay in the appearance or "unmasking" of primary hyperparathyroidism. Clinicians should be aware of the potential underlying primary hyperparathyroidism as this may occur more often than currently appreciated.

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