Unusual presentation of more common disease/injury

Coeliac disease causing symptomatic hypocalcaemia, osteomalacia and coagulopathy

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Summary

A 36-year-old gentleman presented with 6 months of poor energy, tingling in fingers and weight loss with a change in bowel habit. He appeared cachectic and had clubbing, demineralisation of teeth, pectus carinatus, kyphosis, spinal tenderness, proximal muscle weakness and generalised muscle atrophy. Chvostek's and Trousseau's signs were positive. His haemoglobin (Hb) was 8.7 g/dl, MCV 64.7 fl with low iron. Calcium corrected was 1.30 nmol/l, parathyroid hormone 440.4 ng/l, vitamin D <12.5 nmol/l; INR was 2.7 with coagulation inhibitor studies negative. Radiographs of spine and pelvis commented on osteopenia with thoracic kyphosis and mild anterior wedging of thoracic vertebrae. Antitissue transglutaminase was 145 U/ml, and antiendomysial antibodies were positive. An oesophagogastroduodenoscopy was consistent with coeliac disease. A diagnosis of osteomalacia and coagulopathy secondary to coeliac disease was made. The hypocalcaemia was treated with calcium gluconate infusions with symptomatic relief. Coagulopathy was treated with vitamin K intravenously with normalisation of INR. Following treatment with coeliac diet, calcium slowly normalised.

BACKGROUND

This case was written up as it was an unusual and dramatic presentation of coeliac disease. The gentleman had minimal complaint of gastroenterological symptoms, with most symptoms being a manifestation of metabolic bone disease and hypocalcaemia. Coeliac disease was high on the initial differential, as there was evidence of malabsorption of other fat-soluble vitamins, including vitamin K.

CASE PRESENTATION

A 36-year-old gentleman presented with 6 months of poor energy, tingling in fingers, weight loss and joint pain involving mainly ankles, knees, lower back and shoulders. Paraesthesia had occurred on several occasions and was particularly troublesome while he was driving his car. He also noticed intermittent locking of his jaw and tongue. He denied perioral anaesthesia. He had normal physical and mental development. Past medical history was notable for bilateral tympanoplasty 10 years previously. His parents were alive, and his father had recently survived a hemorrhagic stroke. He had three siblings who were alive and well. He was self-medicating with aspirin for pain, but denied taking any other medications, including herbal preparations. He was an engineer, was separated and was living alone. He did not smoke and consumed alcohol only occasionally. He had not travelled in the previous year but in the last 5 years had been to Australia and Southeast Asia.

In the previous 6 months his exercise tolerance had decreased, and he found that he was not able to walk the distance he had been able for in the past. He had morning stiffness, difficulty standing up, as well as shortness of breath on moderate exertion.

He had noted a change in his bowel habit over the previous year. He related this to an outbreak of cryptosporidium

in the local water supply 1 year earlier. Since then he had urgency of bowel motions, frequent diarrhoea and flatus. Although this improved with eradication of cryptosporidium from the water supply, he continued to have irregular bowel schedule with stool that was difficult to flush away. He had lost about 5 kg in 6 months. He denied hematemesis, hematochezia, melaena, nausea, vomiting, regurgitation or abdominal pain.

He appeared cachectic and pale. He had grade III clubbing. There was no lymphadenopathy. He had pectus carinatus, kyphosis with thoracic spinal tenderness, proximal muscle weakness and generalised muscle atrophy. His gait was antalgic secondary to pain and stiffness. He had demineralisation of his teeth. Chvostek's and Trousseau's signs were positive. Examination of cardiovascular and respiratory systems was normal as was examination of the abdomen.

INVESTIGATIONS

Laboratory tests revealed a low Hb of 8.7 g/dl, and MCV 64.7 fl. This had been noted by his primary care physician prompting referral. Iron studies were low with iron at 3 µmol/dl, transferrin saturation 5%, total iron binding capacity 60 µmol/dl, ferritin 5.4 ng/ml, folate 1.2 ng/ml and B12 in the low normal range at 186 pg/ml. Blood film showed microcytic hypochromic anaemia with no evidence of hyposplenism. Calcium corrected was very low at 1.30 mmol/l, magnesium and albumin was normal at 0.74 mmol/l 36 g/l respectively. Parathyroid hormone (PTH) was elevated at 440.4 ng/l and vitamin D level was <12.5 nmol/l, 24 h urinary calcium was 0.5 mmol/h/24 h, both low. Coagulation studies showed an INR of 2.7. Coagulation inhibitor studies were negative. Liver function tests were abnormal; ALP 299 U/l, AST 62 U/l, ALT 54 U/l, GGT 29 U/l. Hepatitis serology and liver autoimmune panel were

Figure 1 Thoracic kyphosis.

Figures 2 CXR and spinal x-rays; osteopenia with thoracic kyphosis, mild anterior wedging of thoracic vertebral bodies.

negative. Inflammatory markers showed a CRP <1, ESR 32. Thyroid function tests were normal. Testosterone levels (20.9 nmol/l) and cortisol levels (220 nmol/l) were within normal range. LH (11.5 IU/l) was elevated, but FSH (6.5 IU/l) was normal.

Radiographs of thoracic, lumbar spine and pelvis commented on marked osteopenia with increased thoracic kyphosis and mild anterior wedging of the mid- and lower-thoracic vertebral bodies (figures 1, 2). x-Ray of the sacroiliac joint showed poor delineation of the cortex along the sacral margin of the sacroiliac joints bilaterally. Chest x-ray was normal. Ultrasound of abdomen showed normal liver, gallbladder, bile ducts, pancreatic head and neck. A DEXA

scan showed a T score of -5.3 at L-spine and -4.0 at femur and Z score of -5.5, which were all interpreted as indicative of low bone mass for his age.

Coeliac serology showed antitissue transglutaminase 145 U/ml and antiendomysial antibodies were positive. An oesophagogastroduodenoscopy showed mild atrophic gastritis, loss of granularity in the duodenal bulb, scalloping of mucosa with mosaic appearance, and no villi were seen. Histology revealed subtotal villous atrophy, crypt hyperplasia and diffuse increase in intraepithelial lymphocytes, increased inflammatory cells in the lamina propria, mild chronic gastritis, with no *Helicobacter* type organisms seen and no evidence of malignancy.

DIFFERENTIAL DIAGNOSIS

A 36-year-old gentleman presenting with marked weight loss, clubbing, hypocalcaemia and coagulopathy in the West of Ireland made malabsorption due to coeliac disease the likely diagnosis; however, other causes of malabsorption, including pancreatic insufficiency, HIV disease and tropical sprue, were also considered. On initial examination, marked cachexia with hypocalcaemia made malignancy a consideration with the hypocalcaemia being explained by sclerotic bone lesions absorbing calcium.

TREATMENT

Treatment of hypocalcaemia was with calcium gluconate infusions until a gluten-free diet and vitamin D replacement was instituted. Coagulopathy was treated with vitamin K intravenously with normalisation of INR. Iron was replaced orally. Vaccination for 23-valent pneumococcal, meningococcal C and haemophilus influenzae B was administered due to the possibility of functional hyposplenism.

OUTCOME AND FOLLOW-UP

On follow-up in clinic 2 months later, the patient showed marked clinical improvement, with no complaint of paraesthesia. Joint pain had resolved, and overall, the patient felt better. He had weight gain and gait and posture had improved. Calcium was still borderline low correcting to 2.00 nmol/l.

DISCUSSION

Coeliac disease is an immune-mediated inflammatory disorder of the small intestines induced by the prolamins of certain cereals causing loss of villous height, crypt hypertrophy leading to malabsorption. There is functional and histological reversal towards normalcy, with elimination and reappearance on luminal challenge to noxious prolamins. It is one of the most common lifelong disorders in Europe and the USA.^{1 2}

During the Second world war period, in Holland, with the elimination of bread from children's diet due to rationing, Paediatrician WK Dicke noted clinical improvement in children with previously diagnosed coeliac disease. Together with JH van Kamer and HA Weijers, using different dietary challenges and measuring faecal fat as an indicator of malabsorption, he went on to identify gliadin as the causative agent of coeliac disease.³

Coeliac disease is a condition more common in Caucasians. It is more frequent in those with HLA BQ- DR3-DQ2, with 90% of people with the condition having HLA-DQ2. There is a familial increase with 10% of first-degree relative being affected by the condition and a monozygotic concordance of 70%. Interplay between genes and environment lead to intestinal damage that is characteristic of the disease. Aberrancy in gut permeability induced by a protein involved in tight junction regulation is thought to allow gluten into the lamina propria where it is deaminated by tissue transglutaminase, recognised by antigen presenting cells bearing DQ2 or DQ8 leading to an autoimmune reaction that is characteristic of the early stages of coeliac disease.⁴

Malabsorption occurs from loss of absorptive area and the presence of a population of immature surface epithelial cells whose absorptive and secretory functions may be additionally impaired by cytokines and inflammatory

mediators. About 30 years ago, the use of intestinal biopsy was reserved for patients with symptoms of overt malabsorption, and, consequently, the prevalence of malabsorption among patients with coeliac disease was very high.⁵ Awareness of the disease and lowered threshold for its investigation, followed by the advent of serology, now means that the number of patients with minor symptoms is twice the number of people with overt malabsorption. This observation was accompanied by a significant rise in the rate of diagnosis and a progressive lowering of patients' age at diagnosis.⁶

In adults, presentation of coeliac disease varies from asymptomatic to severely symptomatic, depending on the severity and the extent of mucosal involvement. Gastrointestinal symptoms are more common and include other conditions such as diarrhoea, weight loss, malaise, lethargy and abdominal pain.⁷ Although less common, presentation with hypocalcaemia, osteomalacia, myopathy and coagulopathy as a first presentation of coeliac disease has been described and can occur without gastrointestinal symptoms.^{8–12} In a study of 47 patients with osteomalacia due to gastrointestinal causes, 26% of cases were due to coeliac disease.¹³

Studies have found significantly decreased bone-mineral density (BMD) in the lumbar spine and femoral neck in coeliac patients compared to controls.¹⁴ In adults, these changes may persist in the peripheral skeleton despite normalisation in the axial skeleton after patients are on a gluten-free diet. In a Swedish study looking at vitamin D and BMD in coeliac patients, a low vitamin D concentration was a typical biochemical abnormality (64% of men and 71% of women). Prevalence of osteopenia and osteoporosis was highest in newly diagnosed coeliac patients and in patients with disease not in remission.¹⁵

Osteomalacia refers to defective mineralisation of bone matrix due to deficiency or resistances to vitamin D. Severe vitamin D deficiency, with osteomalacia and hypocalcaemia, is rare unless vitamin D levels are below 12 nmol/l. Clinical features include bone pain, tenderness, skeletal deformity and proximal muscle weakness. Decreased physical activity secondary to pain with secondary hyperparathyroidism and hypocalcaemia also contribute to decreased BMD.¹⁶ An association between coeliac disease and osteomalacia was first reported in 1953.¹⁷ In coeliac disease, intestinal malabsorption of vitamin D contributes to plasma and urine calcium levels being lower than normal and defective absorption of phosphate consequently leads to hypophosphataemia. Hypocalcaemia stimulates PTH to correct for low calcium level. Secondary hyperparathyroidism occurs due to vitamin D and calcium malabsorption as well as increased bone turnover.

Hypocalcaemia in coeliac disease is thought to occur due to the following causes: There is a negative calcium balance, due to loss of villous surface area,¹⁸ with unabsorbed calcium binding to excess fatty acids in the intestinal lumen as a result of fat malabsorption.¹⁹ There is impairment of active intestinal calcium transport mechanisms because of depletion of calbindin from enterocytes.²⁰ Decreased vitamin D also contributes to decreased calcium absorption.

Hypocalcaemia as a feature of coeliac disease is well described.^{21 22} A screening study in the UK found serum calcium to be on average 0.02 mmol/l lower in asymptomatic

coeliac patients that the general population.²³ In an observational case series of 15 patients with coeliac disease, hypocalcaemia was present in 11 patients, with average corrected calcium of 1.800.30 mmol/L.²² In another case series of 42 patients with coeliac disease, symptoms of tetany was present in 10%.²⁴ Hypocalcaemia induced by medicines that are not commonly noted to do so should raise awareness for possible vitamin D deficiency and malabsorption. In one case, hypocalcaemia induced by bisphosphonates was the basis for the diagnosis of coeliac disease.²⁵ In another, symptomatic hypocalcaemia was induced by oral phosphosoda during the work-up of malabsorption in a patient subsequently diagnosed on histology as having coeliac disease.²⁶

In our patient, initial correction of calcium was with intravenous calcium gluconate. Replacement of calcium with intravenous calcium is recommended for patients who are symptomatic or have very low calcium levels. Replacement should be with cardiac monitoring, as intravenous calcium may cause a sinus bradycardia. Intravenous calcium is sclerosing to veins and should be administered through a central vein if possible. Once calcium is corrected to safer levels, oral calcium supplementation is sufficient. In the acute management of severe hypocalcaemia associated with coeliac disease, it is important to identify other possible factors, in addition to malabsorption, which might be contributing to the hypocalcaemia. Coeliac disease may cause hypomagnesaemic hypocalcaemia and hypokalaemia.²⁷ Severe magnesium deficiency can cause defective secretion and action of PTH, which leads to functional hypocalcaemia.²⁸ Initial replacement of calcium in these patients requires higher doses of oral calcium supplementation.

Activated vitamin D (alfacalcidol) was used along with intravenous calcium to treat our patient's hypocalcaemia initially. However, once vitamin D deficiency was confirmed biochemically and the diagnosis apparent, intramuscular cholecalciferol was administered to replace vitamin D stores in the body. Activated vitamin D was not continued as treatment for his vitamin D deficiency, as malabsorption was present and levels may not have responded adequately to oral replacement alone.

In our patient on discharge from hospital, the calcium level was still below normal range despite vitamin D and high-level calcium supplementation. This was likely due to decreased calcium absorption from ongoing damaged intestinal mucosa. At follow-up, however, calcium levels had normalised allowing a decrease in calcium supplementation.

During the initial recovery phase, it is important to follow patients closely to assess for improvement in calcium absorption as continued high-dose calcium and vitamin D supplementation may lead to hypercalcaemia.

Learning points

- Hypocalcaemia may be a manifestation of coeliac disease due to malabsorption of both or either vitamin D and calcium.
- Correction of low vitamin D alone may not be sufficient if absorption of calcium is also reduced due to malabsorption.
- Treating hypocalcaemia associated with coeliac disease requires close follow-up so that calcium supplementation can be adjusted as malabsorption improves.

Competing interests None.

Patient consent Obtained.

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