Case Report

Medical Principles and Practice

Med Princ Pract 2008;17:425–428
DOI: 10.1159/000141511

Received: April 15, 2007
Revised: August 7, 2007

Osteomalacic Myopathy Associated with Coexisting Coeliac Disease and Primary Biliary Cirrhosis

Mehmet D. Demirag[a] Berna Goker[a] Seminur Haznedaroglu[a]
Mehmet A. Ozturk[a] Tarkan Karakan[b] Reha Kuruoglu[c]

Section of [a]Rheumatology and [b]Gastroenterology, Department of Internal Medicine, and [c]Department of Neurology, School of Medicine, Gazi University, Ankara, Turkey

Key Words
Coeliac disease · Myopathy · Osteomalacia · Primary biliary cirrhosis · Vitamin D

Abstract
Objective: To report a patient with coeliac disease (CD) associated with primary biliary cirrhosis (PBC) who presented with myopathy without classical symptoms of CD. ***Clinical Presentation and Intervention:*** A 42-year-old woman presented with inability to walk and marked loss of motor function. She had elevated liver enzymes with a cholestatic pattern. Antimitochondrial antibody M2 band, anti-endomysial antibody, antigliadin IgA and IgM were positive. Histopathologic findings of the liver revealed PBC and duodenal biopsy was consistent with CD. She was also found to have osteomalacia. She showed slow response to gluten-free diet, but accelerated full recovery with vitamin D replacement. ***Conclusion:*** In PBC patients with subclinical CD and myopathy, vitamin D status can provide a basis for treatment.

Copyright © 2008 S. Karger AG, Basel

Introduction

Coeliac disease (CD) is characterized by small intestinal mucosal inflammation associated with mucosal injury [1]. It is seen in genetically susceptible individuals following enteric encounter with proline- and glutamine-rich protein in wheat, rye, and barley and is often accompanied by malabsorption of nutrients [1].

CD has a wide spectrum of clinical presentations. Classic CD is associated with symptoms of malabsorption, such as diarrhoea and/or weight loss. In contrast, subclinical CD is characterized by the absence of symptoms of malabsorption, but iron deficiency is very common [1]. Osteomalacia is a frequent complication of CD [1]. However, osteomalacic myopathy without classical symptoms of CD such as diarrhoea, steatorrhoea and abdominal discomfort is very uncommon and limited to a few case reports [2–4].

Primary biliary cirrhosis (PBC), histopathologically characterized by portal inflammation and immune-mediated destruction of the intrahepatic bile ducts, is a slowly progressive autoimmune disease of the liver that primarily affects women [5]. The association between PBC and CD is well known [6]. Screening for PBC in patients with CD using antimitochondrial antibody testing and in

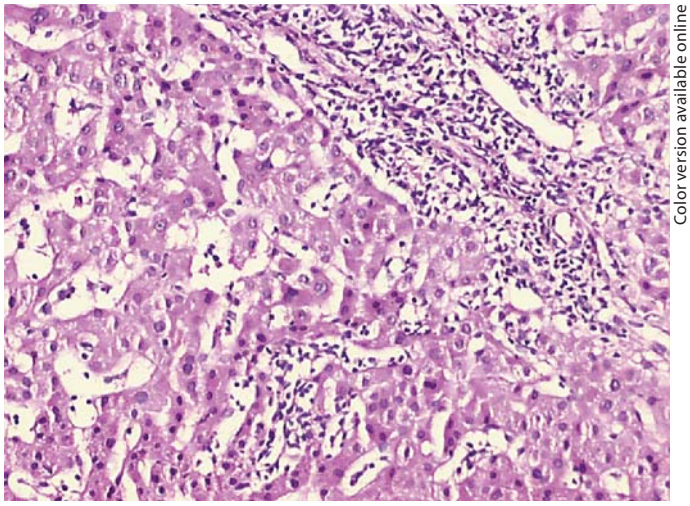
KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2008 S. Karger AG, Basel
1011–7571/08/0175–0425$24.50/0

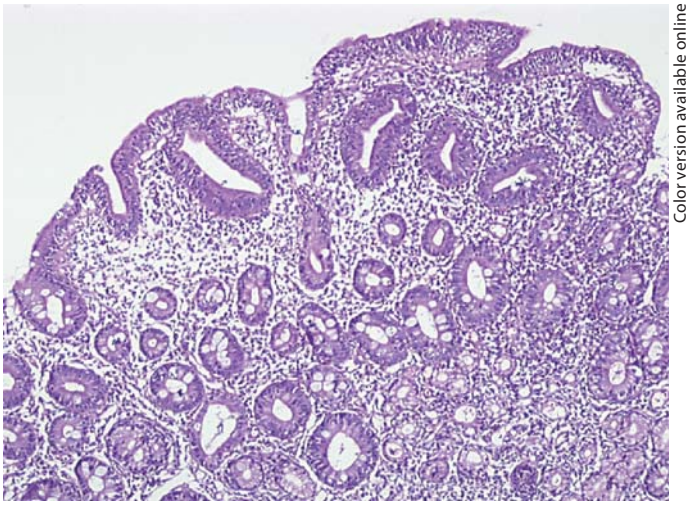
Accessible online at:
www.karger.com/mpp

Mehmet Derya Demirag
Demetgül Mah. 6. sokak No:13/13
TR–06200 Yenimahalle/Ankara (Turkey)
Tel. +90 312 202 5848, Fax +90 312 223 0528
E-Mail mehmetderyademirag@yahoo.com



Color version available online

Fig. 1. Liver biopsy demonstrating changes consistent with PBC, i.e. mixed type inflammation and loss of bile ducts. HE staining, original magnification ×400.



Color version available online

Fig. 2. Duodenal biopsy revealed diffuse villous atrophy accompanied by mononuclear infiltrates, compatible with CD. HE staining, original magnification ×10.

the same manner, screening for CD in patients with PBC using antigliadin antibody testing or duodenal biopsy are recommended [6]. The best tests for CD are IgA anti-human tissue transglutaminase and IgA endomysial antibody immunofluorescence [1]. Here, we describe a patient with CD associated with PBC who presented with myopathy without classical symptoms of CD. She showed slow response to gluten-free diet, but accelerated full recovery with vitamin D replacement.

Case Report

A 42-year-old premenopausal woman presented with inability to walk due to weakness in her legs. Her weakness had progressed gradually over the last 3 years and she had been unable to walk for the last 3 months. Her past medical history was significant only for diabetes mellitus for 5 years, for which she was on insulin. On physical examination, she had pale conjunctiva and marked loss of motor function in the shoulder and hip girdle muscles. Neck flexion strength was 4 on the Medical Research Council (MRC) scale. She had grade 3 weakness in both deltoid and biceps muscles. Right and left wrist dorsiflexion was 4 on the MRC scale. Iliopsoas and quadriceps muscle strengths were 2 and 3 on the MRC scale, respectively, but ankle dorsiflexion was 5 on the MRC scale on both sides. Deep tendon reflexes were normal, except for the hypoactive Achilles reflexes. The rest of the physical examination was unremarkable. Her weight was 46 kg and her height was 153 cm.

Laboratory investigation revealed a hypochromic microcytic anaemia (haemoglobin: 8.7 g/dl and mean corpuscular volume: 72 fl), elevated liver enzymes (aspartate aminotransferase: 101 U/l, alanine aminotransferase: 11 U/l, alkaline phosphatase: 10,680 U/l and γ-glutamyl transpeptidase: 537 U/l), hyperglobulinaemia (globulin: 6.1 g/dl), hypoalbuminaemia (2.7 g/dl), mild hypocalcaemia (7.8 mg/dl) and hypophosphataemia (1.8 mg/dl). She also had laboratory evidence of iron deficiency (iron: 30 μg/dl, iron-binding capacity: 440 μg/dl, ferritin: 15.1 ng/ml). Creatinine kinase and thyroid-stimulating hormone levels were found to be within normal range (75 U/l and 2 μIU/ml, respectively). Serum protein electrophoresis disclosed polyclonal gammopathy and total IgA and IgG levels were elevated (834 and 2,550 mg/dl, respectively). Antimitochondrial antibody M2 band was strongly positive. Antigliadin IgA and IgG and anti-endomysial antibodies were also positive. Other autoimmune antibodies were negative (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsome antibody and anti-soluble liver antigen/liver-pancreas antibody). Vitamin E level was not available.

Abdominal ultrasound examination was unremarkable. She underwent a liver biopsy. Histopathological findings were consistent with PBC (fig. 1). On endoscopic examination, the duodenal bulb showed a nodular mucosal pattern and the biopsy revealed a diffuse villous atrophy accompanied by mononuclear infiltrates, consistent with CD (fig. 2). Nerve conduction study revealed a moderate right-sided carpal tunnel syndrome. A diffuse sensorimotor peripheral neuropathy was not noted. Needle electromyography revealed positive sharp waves on the right vastus lateralis muscle. Short, small and polyphasic motor unit action potentials were detected on the right brachial biceps and iliopsoas muscles. Biopsy obtained from the right vastus lateralis muscle demonstrated muscle fiber atrophy, but no myopathic changes. Magnetic resonance imaging of the proximal muscles of the lower extremities was normal.

The patient was diagnosed with PBC associated with CD, along with myopathy. Ursodeoxycholic acid (750 mg/day) was

started in combination with a gluten-free diet. On day 30 of the therapy, right and left brachial biceps strength was 4 and iliopsoas muscle strength was 3 on the MRC scale, while she was able to ambulate with the help of a walker. Dual-energy X-ray absorptiometry scan was performed. Bone mineral density revealed markedly low density at both the lumbar vertebra and femoral neck (T scores/Z scores were –5.3/–5.3 and –5.1/–4.5 for L_1–L_4 and femoral neck, respectively). Work-up disclosed low vitamin D (9.8 ng/l) and high parathormone (343 pg/ml) levels; 24-hour urinary calcium was low (91.7 mg/day). A diagnosis of osteomalacia was made. She received 300,000 U of vitamin D intramuscularly, along with calcium supplementation. Within 1 month, she showed marked recovery of the motor functions and she was able to ambulate independently without the help of the walker.

At 10-month follow-up, she had no symptoms of weakness. Physical examination showed that she did not loose motor function except of the right iliopsoas muscle, which was 4 on the MRC scale. Needle electromyography examination showed no spontaneous activity of the studied muscles. The right iliopsoas muscle demonstrated short, small motor unit action potentials, however other investigated upper and lower extremity muscles were normal. The endoscopic findings were consistent with recovery and revealed resolution of the mucosal nodular pattern. However, the endoscopic biopsy was unchanged and showed persistence of the diffuse villous atrophy accompanied by mononuclear infiltrates.

After 2 years of oral high-dose vitamin D_3 therapy (alphacalcidiol 1 μg/day), the vitamin D level reached a normal range (28.1 ng/ml); however, it was not high enough to suppress parathormone to a normal level. Hence, her parathormone level was still slightly higher than the upper limit of the normal range (80.4 pg/ml). The bone density scores were within normal range, except for the femoral neck T score, which revealed mild osteopenia (–1.65).

Discussion

Our patient had PBC and CD confirmed by the laboratory and histologic studies described above. Association of CD with osteomalacic myopathy has previously been reported [2–4]. However, to the best of our knowledge, this is the first case of an association of PBC and subclinical CD, leading to osteomalacic myopathy. Hypocalcaemia in CD is caused by reduced intestinal calcium absorption as a result of vitamin D deficiency and reduced absorptive area secondary to villous atrophy, as well as calcium loss in the stool secondary to binding unabsorbed dietary fatty acids to form insoluble calcium soaps [3]. It has been suggested that myopathy in CD is due to hypocalcaemia secondary to vitamin D deficiency and few cases reported previously have responded well to vitamin D therapy [2–4]. Histopathological changes in the muscle fibres of these patients have varied from mild to diffuse atrophy of muscle fibres with no myopathic changes [7]. Our patient similarly had atrophy but no myopathic changes or sign of inflammation in the muscle biopsy.

Myopathy as a complication of osteomalacia has previously been reported [8]. Muscular involvement has also rarely been reported in patients with PBC and these cases were generally polymyositis [9]. A few cases with myopathy but no evidence of inflammation have been reported, however, unlike the present case, these cases had severe progressive myopathy with cardiac involvement and grave prognosis [10]. Anti-mitochondrial antibodies directed against specific mitochondrial proteins in the muscular tissue have been speculated to play a role in the pathogenesis of this condition [10]. It is unlikely to be the mechanism in our case because of the excellent response to vitamin D therapy and full recovery. Noteworthy, osteoporosis is a common complication of PBC. However, the pathogenesis of osteoporosis in PBC remains unclear. Shiomi et al. [11] found that calcitriol inhibited the usual decrease in bone mineral density in patients with PBC and was effective in the treatment of osteoporosis. In addition, Verma et al. [12] suggested that treatment of PBC with ursodeoxycholic acid for 8 weeks enhanced intestinal calcium transport. All of these data suggest that PBC might lead to vitamin D and calcium deficiency. Therefore, we consider that PBC might have contributed to osteomalacic myopathy in our patient. Vitamin E level prior to the initiation of the diet therapy for CD was unavailable. However, it is very unlikely that her myopathy was related to vitamin E deficiency since she had a marked rapid recovery with vitamin D replacement.

Our case is very unlikely to have had muscle involvement primarily associated with PBC for two reasons. First, the biopsy did not suggest polymyositis. Second, full recovery was achieved in a short period of time with the treatment of CD, especially when vitamin D was replaced. Adding vitamin D to the therapy resulted in an accelerated recovery of the weakness and confirmed that the myopathy was due to osteomalacia secondary to CD and PBC. Moreover, muscular recovery much earlier than the resolution of the mucosal pathology supports the role of vitamin D deficiency, rather than CD itself, in the pathogenesis of the weakness. In conclusion, CD may be subclinical and muscle weakness may be the only presenting feature. Moreover, when PBC accompanies CD, it might contribute to vitamin D deficiency and increase the risk of myopathy. Therefore, CD should be considered in the differential diagnosis of patients presenting with unexplained muscle weakness and screening for PBC using anti-mitochondrial antibody testing is recommend-

ed, especially when the liver function tests suggest cholestatic disease. Once diagnosed, therapy of the myopathy associated with osteomalacia is simple and the results are satisfactory.

Conclusion

CD, when accompanied by PBC, can contribute to vitamin D deficiency and increase the risk of myopathy. Therefore, CD should be considered in the differential diagnosis of patients presenting with unexplained muscle weakness. Checking for vitamin D deficiency should be a part of their management.

References

1 National Institutes of Health Concensus Development Conference Statement on Celiac Disease, June 28–30, 2004. Gastroenterology 2005;128:1–9.
2 Byrne MF, Razak AR, Leader MB, Sheehan KM, Patchett SE: Disabling osteomalacic myopathy as the only presenting feature of coeliac disease. Eur J Gastroenterol Hepatol 2002;14:1271–1274.
3 Wong M, Scally J, Watson K, Best J: Proximal myopathy and bone pain as the presenting features of coeliac disease. Ann Rheum Dis 2002;61:87–88.
4 Kozanoglu E, Basaran S, Goncu MK: Proximal myopathy as an unusual presenting feature of celiac disease. Clin Rheumatol 2005; 24:76–78.
5 Kaplan MM, Gershwin ME: Primary biliary cirrhosis. N Engl J Med 2005;353:1261–1273.
6 Freeman HJ: Hepatobiliary and pancreatic disorders in celiac disease. World J Gastroenterol 2006;12:1053–1058.
7 Dastur DK, Gagrat BM, Wadia NH, Desai M, Bharucha EP: Nature of muscular change in osteomalacia: light and electron microscope observation. J Pathol 1975;117:211–228.
8 Smith R, Stern G: Myopathy, osteomalacia and hyperparathyroidism. Brain 1967;90: 593–602.
9 Boki KA, Dourakis SP: Polymyositis associated with primary biliary cirrhosis. Clin Rheumatol 1995;14:375–378.
10 Varga J, Heiman-Patterson T, Munoz S, Love LA: Myopathy with mitochondrial alterations in patients with primary biliary cirrhosis and antimitochondrial antibodies. Arthritis Rheum 1993;36:1468–1475.
11 Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, Ochi H: Calcitriol for bone loss in patients with primary biliary cirrhosis. J Gastroenterol 1999;34:241–245.
12 Verma A, Maxwell JD, Ang L, Davis T, Hodges S, Northfield TC, Zaidi M, Pazianas M: Ursodeoxycholic acid enhances fractional calcium absorption in primary biliary cirrhosis. Osteoporos Int 2002;13:677–682.