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CASE REPORT

Celiac disease manifested by polyneuropathy and swollen ankles

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Abstract

A 27-year-old male started to have his ankles swollen during his military service. He was examined at a military hospital where electromyoneurography showed the signs of distal sensory-motor polyneuropathy with axon demyelinization and weak myopathic changes, whereas histopathological examination of gastrocnemius muscle biopsy revealed some mild and nonspecific myopathy. Besides, he was found to have subcutaneous ankle tissue edemas and hypertransaminasemia. Due to these reasons, he was dismissed from the military service and examined at another hospital where bone osteodensitometry revealed low bone mineral density of the spine. However, his medical problems were not resolved and after the second discharge from hospital he was desperately seeing doctors from time to time. Finally, at our institution he was shown to have celiac disease (CD) by positive serology (antitissue transglutaminase and antiendomysial antibodies) and small bowel mucosal histopathological examination, which showed total small bowel villous atrophy. Three months after the initiation of gluten-free diet, his ankle edema disappeared, electromyoneurographic signs of polyneuropathy improved and liver aminotransferases normalized. Good knowledge of CD extraintestinal signs and serologic screening are essential for early CD recognition and therapy.

Key words: Celiac; Polyneuropathy; Swollen ankles

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INTRODUCTION

Celiac disease (CD) is a genetically determined autoimmune enteropathy induced by gluten ingestion. CD patients can have typical symptoms (chronic diarrhea and malabsorbtion), extraintestinal symptoms, or they can be symptom-free. Extraintestinal clinical signs and symptoms can be diverse. They are increasingly recognized as common CD clinical manifestations. Neurological manifestations are estimated to occur in 7%-10% of the affected patients[1,2]. Peripheral neuropathy is most commonly found among them[3].

CASE REPORT

A 27-year-old male started to have edematous and painful ankles during his military service. His history revealed that a week before, he had been treated with penicillin due to his sore throat and fever. He was allergic to a bee sting.

On admission to a local military hospital, he was noted to have gracile body and thoracical spine kyphoscoliosis. His ankles were edematous, pale and painful to touch. Peripheral pulses on both legs were weaker than normal. Neurological examination showed decreased sensibility to touch, pain and temperature on distal parts of both calfs. Vibration sense was preserved. Deep tendon reflexes were weaker than normal. His gait and heel-chin test were normal while Romberg sign was negative.

Laboratory tests showed normal erythrocyte sedimentation rate, c-reactive protein and complete blood count values. Biochemistry revealed normal creatine kinase while alanine aminotransferase (100, normal 5-35 U/L) and aspartate aminotransferase (118, normal 5-40 U/L) were elevated. All other liver function tests, including serum albumin, were normal. Antistreptolysin O antibodies titer, Waaler-Rose test and rheumatoid factor were negative. Urine analysis, urine proteins, and creatinine clirens were normal. Chlamydia trachomatis and mycoplasma were not detected by urethral swabs. Hepatitis Bs antigen, anti-hepatitis C viral antibodies and ELISA test on adenoviruses, cytomegalovirus, Ebstein-Barr virus and *Borrellia burgdorferi* were all negative. X-rays of both ankles were unremarkable. Ultrasound showed lymphoid retention in both ankles' subcutaneous tissue regions (more visible on right ankle) without signs of inflammation in joints. Both ankles' magnetic resonance imaging (MRI) showed diffuse edemas around the joints (more prominent on the right) without any signs of synovitis and tendonitis. Doppler ultrasound revealed normal blood flow in both legs. Electromyoneurography displayed signs

of distal sensory-motor polyneuropathy with mild axon demyelination and myopathic potentials in most of the examined muscles. Histopathological examination of gastrocnemius muscle biopsy showed slight and non-specific myopathic changes.

During hospitalization he was treated with non-steroidal anti-inflammatory drug and vitamin B complex. After four weeks, he was discharged from hospital with the diagnosis of sensory-motor polyneuropathy. Due to this condition, he was dismissed from military service. Later on, at another hospital he was thoroughly investigated rheumatologically. Slightly elevated alanine aminotransferase (67) and aspartate aminotransferase (99) were noted. Results of his ankles' ultrasound and MRI were the same as during the previous hospitalization. Osteodensitometry revealed low bone mineral density of his spine (T score was -2, normal > -1). Finally, he was discharged from hospital with the diagnosis of osteopenia without any inflammatory rheumatological disease. He was then referred to the clinical immunology of our hospital. On physical examination he had mild, pale edemas on both of his ankles. Apart from that, he also presented some depression signs. He was serologically tested on CD at our hospital, and both IgA antitissue transglutaminase [ELISA: 294 relative units (RU)/mL, normal < 20 RU/mL] and IgA antiendomysial antibodies (indirect immunoflorescence: 5, normal 0) were positive. To confirm CD, four endoscopic biopsies were taken from distal duodenum. Histopathological examination showed total villous atrophy (Marsh IIIc). The patient was put on a gluten-free diet, and three months later his ankles' edema completely disappeared. Control electromyoneurography showed substantial improvement in his neurological abnormalities. Moreover, his aminotransferases became normal and no signs of depression were found. Six months after the initiation of gluten-free diet, IgA antitissue transglutaminase and IgA antiendomysial antibodies became negative. He continued to visit his rheumatologist for osteopenia.

DISCUSSION

CD can be associated with various neurological diseases such as polyneuropathy, cerebellar ataxia, epilepsy, myelopathy and multifocal leucoencephalopathy[4-7]. Peripheral neuropathy is one of the most frequent neurological disturbances in CD. It is most commonly presented by symmetrical distal sensory deficiencies. Motor neuropathy and distal limb weakness have also been described in CD[8]. Moreover, associa-tion with CD, peripheral neuropathy and neuromuscular disorders has been documented[7]. The relationship between CD and different kinds of myopathies such as dermatomyositis, polymyositis and sporadic inclusion-body myositis, has also been reported[9-11].

The real cause of polyneuropathy as one of the extra-intestinal CD signs is not known. Some authors suppose that certain vitamin deficiency (especially in B_6, B_{12}, and E) can play a major etiological role[12-14]. Antiganglioside antibodies were found in 65% of adults with CD and polyneuropathy[15]. Patophysiological mechanisms in most of extraintestinal CD manifestations is not well understood. One of the reasonable explanations came from Karponay-Szabó *et al*[16] who proved that intestinal antitissue transglutaminase antibodies targeted against tissue transglutaminase can be found in different tissues outside small bowel mucosa. They speculated that this phenomenon could be responsible for extraintestinal CD manifestations. There are controversies on how peripheral neuropathy can be influenced by gluten-free diet. Some authors proved that CD patients benefited from gluten-free diet by symptoms regression and resolution of pathological electromyoneurographic findings[17,18]. However, others reported no benefits of gluten avoidance[19,20].

Low bone marrow density and osteoporosis are well known CD complications. Calcium malabsorption and proinflammatory cytokines production that lead to osteoclastic activation play a predominant patho-physiological role in bone derangement. It was estimated that 28% of newly diagnosed adult CD patients have osteoporosis[21]. In patients who were diagnosed as having CD in childhood, strict GFD alone is able to completely restore the bone marrow density. On the contrary, the bone mineralization of those CD patients who were diagnosed in adulthood, often does not improve on GFD.

Unexplained chronic hypertransaminasemia may be the only manifestation of CD. It can be caused by increased intestinal permeability to toxins and antigens due to chronic mucosal inflammation[22]. If CD is a underlying problem, aminotransferase levels are normalized on GFD in a six-month period[23].

In conclusion, CD may be initially manifested by protean manifestations outside the intestine, including peripheral polyneuropathy and swollen ankles. Further studies are needed to reveal the underlying mechanisms and assess the efficacy of gluten-free diet. Good knowledge of extraintestinal manifestations and practice of serological screening in CD can lead to not only early detection and therapy of this disease but also avoidance of unnecessary hospitalizations.

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