***Case Report* / Olgu Sunumu**

Atypical Celiac Disease and Concomitant Autoimmune Hepatitis

Atipik Çölyak Hastalığı ve Eşlik Eden Otoimmün Hepatit

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Celiac disease (CD) was diagnosed in a 10-year-old boy who was presented with refractory iron deficiency anemia (IDA), hypertransaminasemia and short stature. Anemia resolved within one month after the institution of gluten-free diet. We performed liver biopsy because of hypergamaglobulinemia and high titers of smooth muscle antibody. On the basis of histologic findings together with clinical and laboratory findings, type 1 autoimmune hepatitis (AIH) was diagnosed. We aimed to report a CD case displaying more than one type of atypical pictures. Concomitant AIH and unusual rapid response of hepatitis to conventional treatment are also emphasized.

Key words: Celiac disease; gluten-free diet; autoimmune hepatitis; children.

Burada tedaviye dirençli demir eksikliği, transaminaz yüksekliği ve boy kısalığı ile başvuran, çölyak serolojisi pozitif saptanan ve ince bağırsak biyopsisi ile çölyak hastalığı tanısı alan 10 yaşında olgu sunuldu. Anemi sadece glutensiz diyet ile bir ay içerisinde düzeldi. Başvuru anında hipergamaglobülinemi ve anti-düz kas antikor pozitifliği nedeniyle yapılan karaciğer biyopsisinde portal lenfoplazmositer infiltrasyon saptandı. Histolojik, klinik ve laboratuar bulgular ile otoimmün hepatit tanısı aldı ve immünsüpresif tedavi başlandı. Olgu, atipik prezentasyonun yanında eşlik eden otoimmün hepatitin glutensiz diyet altında immunsüpresif tedaviye alışılagelmişin dışında hızlı yanıt vermesi nedeniyle sunuma değer bulunmuştur.

Anahtar sözcükler: Çölyak hastalığı; glutensiz diyet; otoimmün hepatit; çocuklar.

During the past 25 years there has been a noticeable change in the age of onset of symptoms and the clinical presentation of celiac disease (CD). Mäki et al.[1] first reported an upward-shift of age at diagnosis in Finland to 5-6 years, with fewer than 50% of new cases presenting with typical gastrointestinal symptoms. Some other studies in children and adults, thereafter, have also shown that almost 50% of patients with newly diagnosed CD do not present with gastrointestinal symptoms and marked increase in atypical and late beginning forms were observed.[2,3]

Autoimmune hepatitis (AIH) has been shown to be a risk factor for CD development[4] and vice

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versa. Nonspecific liver involvement demonstrated as reactive hepatitis mostly precedes CD, although CD-specific antibodies also have been found in these patients by the time liver disease was diagnosed.[5]

Here, we report a CD case presenting with refractory iron deficiency anemia (IDA), hypertransaminasemia and short stature without classical gastrointestinal symptoms. Concomitant AIH and unusual rapid response of hepatitis to conventional treatment are also emphasized.

CASE REPORT

A 10-year-old boy presented to our outpatient clinic with IDA refractory to oral replacement therapy for one year. There was no complaint suggesting a gastrointestinal problem. He reported no history of recent blood loss, including any blood in the stool. Physical examination was unremarkable other than mild pallor. He had a prominent growth deficit with a weight of 23 kg (weight for age z score: –2.40) and a height of 122 cm (height for age z score: –2.71). Laboratory evaluation showed a hemoglobin of 8.3 g/dL, mean corpuscular volume (MCV) 62.6 fL, red cell distribution width (RDW) 29.6, reticulocytes 1.15%, ferritin 2.48 ng/dL, serum iron 13 μg/dL, and total iron binding capacity 416 μg/dL. Serum folate, vitamin B12, zinc and albumin levels were normal. Gamma-globulin levels were high in protein electrophoresis (30%). The stool guaiac test was negative on three separate occasions. Blood film showed severe microcytosis, anisocoria and hypochromia. Aminotransferase activities were elevated: aspartate aminotransferase (AST), 234 IU/L (normal, 20-45); alanine aminotransferase (ALT), 249 IU/L (normal, 8-35). Gamma glutamyl transpeptidase (GGT) was normal. There was no drug intake, and tests for hepatitis A and B, C, Epstein-Barr virus infection, cytomegalovirus, herpes simplex virus 6 and parvovirus B19 were negative. Metabolic and genetic disorders namely α1-antitrypsin deficiency, cystic fibrosis, and Wilson disease were excluded. Anti-gliadin, anti-endomysial antibodies were positive. Smooth muscle antibodies (SMA) were positive in titers of 1/640 whereas antinuclear antibodies, type 1 liver/kidney microsomal antibodies, type 1 liver cytosolic antibodies and autoantibodies to soluble liver antigen were all negative together with negative Coombs test. Ultrasound scanning of the liver did not show any abnormality. Histopathologic findings in biopsy of the small intestinal mucosa was consistent with celiac disease. Liver biopsy revealed portal lymphoplasmocytic infiltration (Fig. 1). The study of the HLA system, performed by a standard complement-dependent microlymphocytotoxicity assay, showed the following phenotype: A 02,03; B 08,51; DRB1 03,13. On the basis of clinical, laboratory, and histologic findings, type I AIH was diagnosed. According to the International AIH Group, AIH was defined as "probable" with the score of "15".[6]

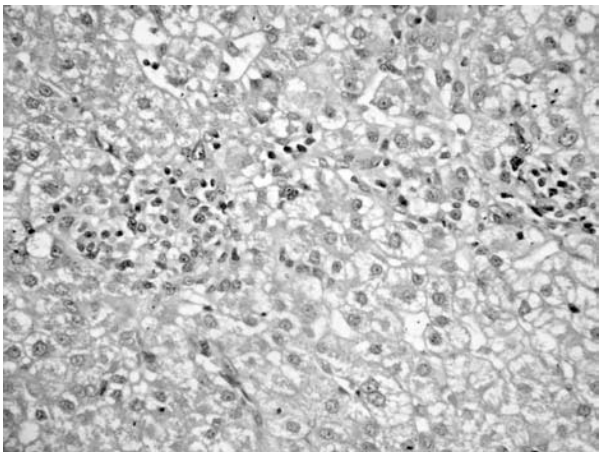

Fig. 1. *Inflammatory infiltration composed predominantly of plasma cells in the hepatic parenchyma (H-E x 200).*

The patient was put on gluten-free diet and immunosuppressive treatment with prednisolon (1 mg/kg/day) and azathioprine (1 mg/kg/day) was started. Transaminase activities were normalized at the end of first week of immunosuppressive treatment. Gamaglobulin levels normalized together with negativity in the SMA titers at the end of the second month. Hemoglobin raised to 12 gr/dl at 30th day after the institution of gluten-free diet together with iron supplementation.

DISCUSSION

Celiac disease may result in intestinal malabsorption of iron and occasionally occult GI bleeding.[7] So, it is not surprising that the inci-

dence of celiac disease in patients with refractory iron deficiency anemia was found to be 5% to 8.5%, much higher than the general population.[8] Iron deficiency anemia has also been determined as the sole manifestation of celiac disease.[9] Long-standing and refractory iron deficiency anemia in our patient was an important clue to consider the possibility of celiac disease. After celiac disease was confirmed by small intestinal biopsy, we put the patient on gluten-free diet together with multivitamin and iron supplementation. Anemia resolved at the 30th day of gluten-free diet.

Poor growth may be the only presenting symptom of celiac disease. Cacciari et al.[10] performed small intestinal biopsies on a group of 60 children who presented for evaluation of short stature, irrespective of the presence of gastrointestinal symptoms. They detected pathology consistent with celiac disease in five children (8.3%). Similar studies indicated a prevalence of celiac disease in patients with short stature equal to 5%[11] and 24%[12] respectively. Short stature together with iron deficiency anemia in the absence of gastrointestinal complaints were the findings of atypical CD in our patient.

Many authors have described a relation between CD and other autoimmune diseases.[13,14] Autoimmune hepatitis is one of the rare disorders occasionally reported in association with CD.[5] It has been shown to be a risk factor for CD development[4] and vice versa. Although transiently increased serum aminotransferase levels are more commonly observed in CD,[4] we performed liver biopsy in our patient because of hypergamaglobulinemia and high titers of smooth muscle antibody. On the basis of histologic findings together with clinical and laboratory findings, type 1 AIH was diagnosed. According to the International AIH Group, AIH was defined as "probable" with the score of "15". The impact of the gluten-free diet on the course of AIH is difficult to evaluate because patients with AIH and CD usually need immunosuppressive therapy together with a gluten-free diet. Although Ventura et al.[15] suggested that gluten-free diet might protect against the development of other autoimmune diseases, Iorio et al.[16] did not benefit from gluten-free diet in their patient with AIH. Arvola et al.[17] reported a boy with CD in whom thyrotoxicosis and AIH occurred one and two years after diagnosis, respectively, despite a strict gluten-free diet. So, we started immunosuppressive treatment together with gluten-free diet. Although an 80% decrease of initial transaminase level is obtained within six weeks in most patients receiving immunosuppressive therapy for AIH, complete normalization of the liver function may take several months (six months in children with type 1 AIH and nine months in children with type 2 AIH).[18] In the study by Gregorio et al.[19] the minimum time to achieve complete transaminase normalization was approximately 2½ months in 32 children with ANA/ASMA positive AIH. Complete normalization of transaminase activities were achieved at the end of the first week of treatment in our patient. This was an unusually rapid response. We do not know if gluten-free diet might have been an effect on this prompt response. It could be valuable to try gluten-free diet as sole therapy in our case with relatively low Alvarez score.[6]

In summary, it is important to diagnose atypical cases of CD early. Institution of gluten-free diet will prevent or treat various nutritional deficiencies, including iron deficiency anemia and its complications. Gluten-free diet, although needs confirmation by additional studies, might protect against the development of other autoimmune disease if started early on the course of the disease or possibly have a positive effect on treatment response of coexisting autoimmune disease.

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