Dilemma in the Diagnosis of Celiac Disease: Case Report

Çölyak Tanısı Koymada İkilem

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ABSTRACT Celiac disease (CeD) can remain undiagnosed with nonspecific complaints. We reported a female patient with previously unrecognized celiac disease and multiple extra intestinal manifestations, presenting with gastrointestinal bleeding and severe anemia, and misdiagnosed as Behcet's disease because of her oral aphthous ulcers. The patient who admitted to hospital with dizziness and fatigue had severe anemia. Laboratory findings revealed hypocalcemia, hypokalemia, hypomagnesemia. Vitamin A, vitamin B12, folic acid and vitamin D levels were low. In the light of this malabsorptive state anti tissue transglutaminase and anti endomysial antibodies were positive. Esophagogastroduodenoscopic findings were compatible with CeD. When we evaluated her for the accompanying manifestations we found osteoporosis, epilepsy, hypothyroidism, partial empty sella syndrome, oral aphthous ulcers, short stature, hematological abnormalities such as coagulation disorders and anemia. All the complaints can easily resolve with a dietary intervention in CeD if practitioners make the diagnosis with a comprehensive history and physical examination.

Key Words: Celiac disease; anemia, iron-deficiency; malabsorption syndromes; epilepsy; osteoporosis; hypothyroidism

ÖZET Çölyak hastalığı (ÇH) tanısı nonspesifik yakınmalar nedeniyle gecikebilir. Bu yazıda gastrointestinal kanama ve derin anemi ile gelen ve multiple ekstraintestinal yakınmaları da olan, oral aftları nedeniyle yanlışlıkla Behçet tanısı almış bir kadın hastada çölyak tanısına ulaşmamızı sunduk. Baş dönmesi ve halsizlik yakınmaları ile hastaneye başvuran hastada derin anemi mevcuttu. Hipokalemi, hipokalsemi, hipomagnezemi bulgularının yanı sıra vitamin A, vitamin B12, folik asit ve vitamin D seviyeleri düşüktü. Bu malabsorptif zeminde anti doku transglutaminaz ve endomisyal antikorları pozitifti. Özofagogastroduodenoskopik görünümü ÇH için tipikti. Eşlik eden durumları araştırdığımızda osteoporoz, epilepsi, hipotiroidizm, parsiyel boş sella, oral aftlar, boy kısalığı ve koagülasyon bozuklukları ve anemi gibi hematolojik anormallikler saptadık. Sonuç olarak detaylı bir anamnez ve fizik muayene ile tanı konulabilen ÇH'de tüm patolojik bulgular glutensiz diyet ile kolayca düzelir.

Anahtar Kelimeler: Çölyak hastalığı; anemi, demir eksikliği; malabsorpsiyon sendromları; epilepsi; osteoporoz; hipotiroidizm

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Celiac disease (CeD) is an autoimmune disorder that occurs in genetically predisposed individuals as a result of an immune response to gluten. It is present in approximately 1% of the population. Diarrhea has become a less common mode of presentation (<50% of cases) than it once was. Other presentations include iron-deficiency anemia, osteoporosis, dermatitis herpetiformis, and neurologic disorders, mainly periph-

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eral neuropathy and ataxia. Overall, autoimmune diseases occur more frequently (three to ten times more) in those with celiac disease than in the general population. A gluten-free diet is the standard of treatment, although its effect on some of the extraintestinal manifestations remains to be determined.

CASE REPORT

A 46 year old woman was admitted to emergency service for severe fatigue and dizziness. The patient was transferred to internal medicine clinic for workup of severe anemia as the hemoglobin level was 3.42 mg/dL. On physical examination her conjunctivas were pale, tounge papillas were insignificant, rectal examination revealed black stool that was consistent with oral iron treatment. Blood pressure was 100/70 mmHg, heart rate was 130 beats/minute, temperature was 36.8°C, and body mass index was 20.4 kg/m^2. Electrocardiogram showed a sinus rythym with T wave inversion in V1, V2, V3 derivations. Her past medical history included a history of iron deficiency anemia, hypothyroidism, epilepsy and Behcet's disease. She was receiving colchicine, carbamezepine, L-thyroxin, oral iron, vitamin D and folic acid pills and calcitriol. 26 years ago when she admitted to a doctor complaining of oral aphtous ulcers, she was possibly misdiagnosed as Behcet's disease and given colchicine. She was advised to not to have a baby because of Behcet's disease and taking colchicum, so the couple has no children. This 46-year-old woman was in menopause since last year. She says that her aphtous ulcers did not recurred much; she did not lose weight but says her weight was stabile for years and she had diarrhea rarely. Her rectal examination revealed black stool without bright red blood, tarry looking or foul odor. Hemoccult test was positive. The patient underwent upper gastrointestinal system endoscopy that revealed the presence of hyperemia on the antral mucosa and edema on the duodenal mucosa. The mucosa was so fragile that easily bled while obtaining biopsies. Typical mosaic pattern of the mucosa was appearing as "cracked mud" appearance (Figures 1 and 2).

While the patient was in our internal medicine clinic, HLA-B5 was obtained and it was negative, eye consultation for uveitis was normal and there were no other stigmata of Behcet's disease, which has the highest prevalence in Turkey (80 to 370 cases per 100,000),[1] so we excluded it.

Laboratory findings are seen at the table (Table 1). Coagulation parameters were as high as that the machine could not measure. The other biochemical results were within normal limits and routine urine examination was normal. Thyroid function tests revealed isolated hypothyroxinemia (note that she was going on daily L-thyroxin treatment). Anti-tiroid peroksidaz (TPO) was positive and anti thyroglobulin was negative. To view the status of hypothalamic-pituitary-adrenal function synachten test was performed, which excluded the possibility of adrenal insufficiency. Cortisol level was 17.5 mg/dL (normal range 5.0-25 mg/dL). The serological tests for various infectious agents (HBsAg, anti HBC, anti HIV 1 and 2) and

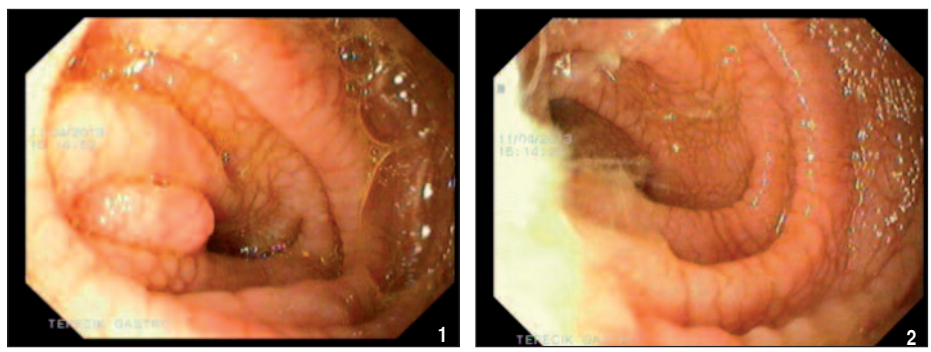

FIGURE 1, 2: Upper gastrointestinal endoscopic pictures at the time of the diagnose.
(See color figure at http://www.turkiyeklinikleri.com/journal/ic-hastaliklari-dergisi/500/tr-index.html)

TABLE 1: Laboratory findings of the patient.

Finding	Value	Range	Unit
Hemoglobin	3.42	11.5-14	g/dL
Hematocrit	10.2	37.7-47.9	%
Leucocytes	4.1	4.2-10.6	K/uL
Platelets	508	142-424	K/uL
Sedimentation	4	0-20	mm/h
Potassium	3.2	3.5-5.2	mmol/L
Calcium	6.8	8.8-10.2	mol/L
Magnesium	1.65	1.9-2.7	mg/dL
Protein	5.4	6.4-8.3	g/dL
Albumin	2.5	3.5-5.5	g/dL
Alkaline phosphatase	296	38-155	U/L
Gamma-glutamyl transpeptidase	127	7-32	U/L
Vitamin B12	357	193-982	pg/mL
Folic acid	3.46	3-17	ng/dL
Vitamin A	215	316-820	UG/L
Free T4	0.767	5-11.5	ng/dL
TSH	1.14	0.3-4.0	ng/dL
Parathormone	270	10-65	pg/mL
25 (OH) Vitamin D	9.97	10-40	ng/dL

the markers of autoimmune hepatitis and type-1 diabetes mellitus were all found to be negative. IgA and IgM levels were within normal ranges but IgG was low (690 mg/dL; normal range 751-1560 mg/dL). IgG subtypes revealed a low IgG4 level of 173 mg/L, normal range 230 to 1960 mg/L and normal levels of IgG1, IgG2 and IgG3. ANA was negative.

Because of the initial concern regarding celiac disease (CeD), the levels of anti-endomysium IgA and anti-gliadin IgG were both positive. The titers of antibodies were as follows: anti-gliadin IgG: 1/32 and IgA: 1/32; anti endomysium IgG: 1/32 and IgA: 1/100. Serologic studies revealed positive anti tissue transglutaminase (tTG) and anti endomysial antibody (EMA). Based on this evaluation, the patient was believed to have celiac disease. Insulin autoantibodies were all negative with fasting blood glucose level as 80 mg/dL and HbA1C was 5.7%. Gonadal hormones were compatible with menopause. We studied karyotype analysis to exclude Turner's syndrome and it was 46,XX.

Radiographs of pelvis revealed that there were remodelling changes at the right ramus of pubis which may be related to an old fracture sequelae.

Findings on echocardiogram, chest plain radiograph and abdominal ultrasonography were all normal. DEXA scan of the lumbar spine and right hip showed low bone mineral density (BMD) with a total T and Z score of <-2.5 and <-2.5, respectively. Thyroid gland was in heterogenous parenchyma with doppler ultrasound monitoring. In the upper endoscopy high specific findings of CeD were present; scalloping of the small bowel folds (Figures 1 and 2), paucity in the folds, mosaic pattern to the mucosa (described as a "cracked-mud" appearance), prominence of the submucosal blood vessels. Multiple biopsies were obtained from duodenum. The histology revealed chronic inflammation.

When our patient diagnosed as celiac disease we searched other accompanying diseases, a cranial magnetic resonance imaging revealed a partial empty sella.

Her hormonal analysis indicated a menopause state.

She was discharged home on the 7th day of her hospitalisation and followed as an outpatient where she did well without further diarrhea and other gastrointestinal symptoms with gluten free diet. Six months later in the visit she had gained 10 kilograms. Vitamin B12, folic acit, magnesium, calcium, vitamin D and calcium levels were all normal with replacement therapy. Through her control with upper gastrointestinal endoscopy, the mucosa was highly normalized (Figure 3). One year later her BMD evaluation was normal, too.

We obtained the informed and written consents of the patient and her family about publishing this case report.

DISCUSSION

Celiac disease is a food hypersensitivity disorder of the small intestine caused by an inflammatory response to wheat gluten and other barley and rye proteins. The condition can manifest with an un-

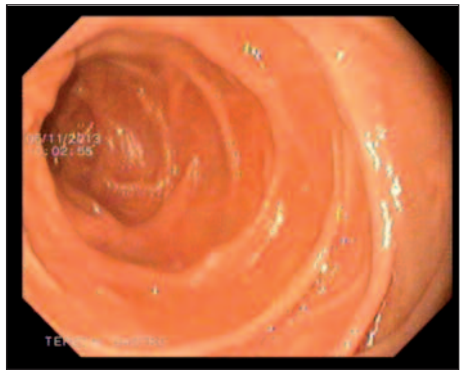

FIGURE 3: Upper gastrointestinal endoscopic picture 6 months later.
(See color figure at
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suspected range of clinical presentations, including malabsorption syndrome and symptoms potentially affecting any organ or body system. The disorder was previously called celiac sprue, that was used to describe a disease similar to tropical sprue which is presented by diarrhea, extreme weight loss and thinness due to a loss of subcutaneous fat and muscle, aphthous stomatitis and malabsorbtion.[2]

Celiac disease is considered as an 'iceberg disease' with a small number of individuals with classical symptoms and manifestations related to nutrient malabsorption and a varied natural history. A much larger number of individuals have manifestations that are not obviously related to intestinal malabsorption such as anemia, osteopenia, infertility, neurologic symptoms ("atypical celiac disease"); while an even larger group are essentially asymptomatic though with abnormal small intestinal histopathology and serologies ("silent celiac disease").

In this report, we described a female patient with unrecognized celiac disease who developed several clinical and/or subclinical diseases which were epilepsy, hypothyroidism (possibly due to Hashimoto thyroiditis), partial empty sella syndrome, osteoporosis, oral aphthous ulcers, shortness, hematological abnormalities such as coagulation disorders and anemia, that misdiagnosed as Behcet's disease because of her recurrent oral aphthous ulcers. She had malnutrition in terms of hypocalcemia, hypokalemia, hypomagnesemia and deficient of vitamin B12, folic acid and 25(OH)vitamin D. She also presented as occult gastrointestinal bleeding that we could not screen it with endoscopic evaluation. Bleeding occurred due to vitamin K deficiency that of international normalizing rate (INR) was so high. The patient was diagnosed as CeD based on clinical and serological findings and noticeable clinical improvement was observed on a gluten-free diet within several days.

Iron deficiency is frequent in patients with celiac sprue and may rarely cause severe anemia in such patients in the absence of diarrhea and steatorrhea. Malabsorption of dietary iron is presumed to be the major cause of this iron deficiency. On the other hand, chronic blood loss from gastrointestinal tract can be another cause of iron deficiency anemia.[3] In a prospective study the prevalence of patients presented with iron deficiency anemia in occult celiac disease was reported as 2.8%.[3]

Untreated CeD may induce malabsorption of many nutrients as vitamin K, which causes prolongation of the prothrombin time.[4] In a cross-sectional analysis of data that was collected on 390 adults with untreated CeD, the percentage of the prolongation of the prothrombin time (defined as INR ≥1.4) was reported as 18.5%.[4] Parenteral vitamin K therapy was required in 5.6% of those patients.[4] They revealed that patients with prolonged prothrombin time had significant lower values of haemoglobin, iron, proteins, cholesterol and serum aspartate transaminase, and significantly higher prevalence of diarrhea, weight loss, abdominal pain and low bone mineral density in comparison with patients with normal prothrombin time.[4] Forthwith parenteral vitamin K therapy should be given urgently. We treated our patient with parenteral vitamin K and also fresh frozen plasma.

Bone loss (principally osteopenia and less often osteoporosis) is common in CeD and majority of the bone loss is probably related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency.[5] Low BMD affects up to 75% of celiac patients, and can be found at any.[6] Lucenda et al. reported that the prevalence of CeD among osteo-

porotic patients was found to be significantly increased.[6] They tried to explain this origin of low BMD by two theories: Micronutrients malabsorption (including calcium and vitamin D) has been related to secondary hyperparathyroidism and incapacity to achieve the potential bone mass peak; chronic inflammation was also related with RANKL secretion, osteoclasts activation and increased bone resorption.[6] The biochemical laboratory studies of our case were consistent with the diagnosis of secondary hyperparathyroidism and she had significantly decreased BMD in the lumbar spine and femoral neck whose femur was once broken. Calcium and vitamin D supplements were used to reduce the risk of bone loss and fractures and to enhance the mineralization of bone. Additionally, once-weekly biphosphonate therapy was started after the diagnose of osteopenia. One year later her BMD was normal.

As patients with CeD get older, they tend to present with complaints not directly referable to the gastrointestinal tract and the diagnose likes to be atypical CeD.[7]

It is well known that CeD may be associated with various neurological manifestations. The most common neurological manifestations in newly diagnosed celiac patients were neuropathy, memory impairment and cerebellar ataxia.[8] In our case she did not have neuropathy but she was diagnosed as epilepsy. The increased prevalence of epilepsy in patients with CeD is well documented. In a study with 900 adult patients with epilepsy of unknown aetiology (n=199) the percentage of CeD was 22%.[9,10]

Among autoimmune disorders, increased prevalence of CeD has been found in patients with autoimmune thyroid disease, type 1 diabetes mellitus, autoimmune liver diseases and inflammatory bowel disease, and vice versa.[10] Prevalence of CeD was found to be 1% to 19% in patients with type 1 diabetes mellitus, 2% to 5% in autoimmune thyroid disorders and 3% to 7% in primary biliary cirrhosis in recent studies.[10] The pathogenesis of co-existent autoimmune thyroid disease and CeD is not known, but these conditions share similar HLA haplotypes and are associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4.[10]

Celiac disease may impair the reproductive life of affected women, eliciting delayed puberty, infertility, amenorrhea and precocious menopause.[11] In our case she had no children. As she was in menopause we couldn't search her fertility at the time of the diagnosis.

CONCLUSION

Celiac disease is an extremely common condition with potentially serious consequences to long-term health. Between 50% and 90% of people with celiac disease remain undiagnosed in the community with mild symptoms. Many patients with undiagnosed CeD spend years seeking help for complaints such as chronic tiredness or mild abdominal symptoms. The majority of people with CeD are symptom-free adults; the remainders are prone to a bewildering variety of signs and symptoms, ranging from infertility to Hashimoto's thyroiditis. Many other undefined associations may still be waiting for discovery.

This case illustrates several important points. The first is the frequent occurrence of unrecognized celiac disease in the adult population, some of them are misdiagnosed as some other disorders like Behcet's disease. In this patient with history, physical examination and laboratory results all supporting celiac disease, immediate dietary intervention resulted with a quick recovery.

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