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Rarely seen autoimmune polyglandular syndrome; Type 3B complicated with celiac disease

Çölyak hastalığı ile komplike nadir görülen otoimmün poliglandüler sendrom; tip3B

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ÖZ

Otoimmün poliglandüler sendrom (OPS) farklı otoimmün hastalıkların kombinasyonudur. Klinik kriterler baz alınarak OPS'nin dört ana tipi tariflenmiştir.Tip 3 formu; Addison hastalığı olmadan, otoimmün tiroid hastalıklarından birine Tip 1 diabetes mellitus (Tip 3A) veya kronik atrofik gastrit, pernisiyöz anemi, çölyak hastalığı, otoimmün hepatit (Tip 3B), vitiligo,alopesi,myastenia graves (Tip 3C), kollajen hastalıklar, vaskülit (Tip 3D) gibi otoimmün hastalıkların eşlik ettiği sendromdur. Çölyak hastalığı (CD), güçlü bir genetik etkiye sahip immün aracılı bir hastalıktır. Tip 1 diabetes mellitus (T1DM) ve OTH, insanların bu hastalıklardan etkilendiği ve Çölyak hastalığı gelişimi için yüksek risk taşıyan iyi tanımlanmış iki hastalıktır. Burada T1DM ve OTH tanıları ile beraber Çölyak hastalığı ile komplike olmuş 32 yaşında kadın bir hastayı yani OPS Tip 3B sendromunu sunmaktayız.

Anahtar kelimeler: Otoimmün poliglandüler sendrom, Çölyak hastalığı, Tip 1 diabetes mellitus, Otoimmün tiroid hastalığı

ABSTRACT

Autoimmune polyglandular syndrome (APS) is a combination of different autoimmune diseases. APS type 3 is defined by the presence of autoimmune thyroid disease (ATD) without Addison's disease and at least one autoimmune disease such as type 1 diabetes mellitus (type 3A), chronic atrophic gastritis, pernicious anemia,autoimmune hepatitis or celiac disease (type 3B), vitiligo, alopecia, myasthenia gravis (type 3C), autoimmune rheumatic disorders, vasculitis (type 3D). Celiac disease (CD) is an immune-mediated disease with a strong genetic influence. Type 1 diabetes mellitus (T1DM) and ATD are well established and people suffering from these two diseases are considered at high risk of developing CD. Here we present a rarely seen case of a 32-year-old woman with T1 DM and ATD complicated with CD, which is defined APS type 3B.

Keywords: Autoimmune polyglandular syndrome, Celiac disease, Type 1 diabetes mellitus, Autoimmune thyroid disease

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Introductıon

Autoimmune polyglandular syndrome (APS) is a combination of different autoimmune diseases (1,2). Based on clinical criteria, four main types of APS have been described (Table-1) (1,3,4). Type 1 which is also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) presents in childhood with at least two of the following manifestations: chronic mucocutaneous candidiasis, hypoparathyroidism, or Addison's disease. Type 2, which is known as Schmidt syndrome, usually presents in young adults aged 20-40 years, usually women (female: male ratio is 3:1) (5). The following conditions occur in type 2 APS: Addison's disease and autoimmune thyroid disease (ATD) and/or type 1 diabetes mellitus (T1DM). Type 1 and type 2 APS both are well-defined entities with an important genetic background and with Addison's disease as the main observed affection. Type 3 is defined by the presence of ATD without Addison's disease and at least one autoimmune disease such as T1DM (type 3A), chronic atrophic gastritis, pernicious anemia,autoimmune hepatitis or celiac disease (type 3B), vitiligo, alopecia, myasthenia gravis (type 3C), autoimmune rheumatic disorders, vasculitis (type 3D) and type 4 represents a miscellaneous type encompassing pathologies which are not included in the other types. Here we present a rarely seen case of a 32-year-old woman with T1DM and ATD complicated with CD, which is defined APS type 3B.

Case Presentatıon

A 32-year-old woman presented with chronic fatigue, abdominal distention, weight loss, polyuria, and polydipsia. In her story, she was a teacher, married and had two children. She was diagnosed with Hashimoto's thyroiditis (HT) at the age of 18 and after using medicine for five years regularly, she got recovered clinically and in terms of lab results. The treatment of medicine was ended and she was followed. In the family story, her mother had type 2 diabetes, sister had HT. In physical examination, her skin was dry, hair was lank, conjunctiva was pale. Other system examinations were normal. The lab examinations are shown at table-2.

Table 1. Classification of autoimmune polyglandular syndrome (APS) (1,3,4)

APS-1 or APECED (autoimmune-poly-endocrine-candidiasis-ectodermal-dystrophy)	Chronic mucocutaneous candidiasis Chronic hypoparathyroidism Addison's disease (at least two out of three)
APS-2 or Schmidt's syndrome	Addison's disease + autoimmune thyroid disease and/or type 1 diabetes mellitus
APS-3 (excluding Addison's disease)	Thyroid autoimmune disease + -Type 1 diabetes mellitus: Type 3A -Gastrointestinal tract and liver involvement: Type 3B -Skin, muscles, nervous and haemotologic system involvement: Type 3C -Autoimmune rheumatic disorders, vasculitis: Type 3D
APS-4	Any other possible association of autoimmune diseases

In the lab examinations of the patient with chronic fatigue, dry skin, hair loss, polyuria and polydipsia; Anti-thyroid peroxidase and anti-thyroglobulin antibodies were positive, TSH was high, fT4 was low and also many millimetric hypo-anechoic nodular areas were observed with both lobes with the thyroid ultrasonography of the patient, gland vascularisation increased and it was compatible with HT. HbA1c and plasma fasting glucose were high, insulin and C-peptid levels were low, anti-glutamic acid decarboxylase antibody was positive. She was diagnosed with type 1 diabetes mellitus (T1DM).

Our patient with abdominal distention (especially after meals with wheat), weight loss, anemia of chronic disease and low level of vitamin D was evaluated in terms of celiac disease (CD). Tissue transglutaminase IgA and anti-endomysial antibodies were positive. Abdominal ultrasonography was

normal. In the evaluation of upper gastrointestinal tract endoscopy that made to ensure CD diagnosis. Esophagus and stomach were normal. The mucosa of bulbus and second part of the duodenum were in nodular appearance. Biopsies were taken. In pathology examination, the increase of intraepithelial lymphocytes and villous atrophy were observed as compatible to CD. Type 3b was determined according to MARSH classification.

Gluten-free diet for CD was recommended to the patient. Levothyroxine and insulin treatment was started for HT and T1DM. After three months later at controls, the levels of HbA1c, plasma fasting glucose, TSH, fT4, and hemoglobin were started to get better. After the gluten-free diet treatment that was regulated for vitamin D absence, the level of PTH and tissue transglutaminase Ig A became normal.

Table-2 Results of the patient

Plasma fasting glucose (75-110 mg/dL)	319	Haemoglobin (12,2-18,1 g/dL)	11,9
HbA1c (4-6%)	14,6	MCV (80-97 fL)	86,8
C-peptid (0,9-7,1 ng/mL)	0,3	Iron- Fe (47-169 ug/dL)	81
Insulin (3-25 uIU/mL)	1,5	Total iron-binding capacity (TIBC) (155-300 ug/dL)	276
Free T4 (0,6-1,4 ng/dL)	0,4	Ferritin (11-306,8 ng/mL)	7,8
Thyroid stimulating hormone (TSH) (0,3-5,6 uIU/mL)	33,8	Calcium (8,4-10,8 mg/dL)	8,6
Anti-Thyroid peroxidase antibody (0-5,6 IU/mL)	>1077	25-OH vitamin D (10-80 ng/mL)	8,6
Anti-Thyroglobulin (0-4,1 IU/mL)	31,4	Vitamin B12 (189-833 pg/mL)	210
Parathyroid hormone (PTH) (15-68 pg/mL)	68,9	Folate (2,5-20 pg/mL)	9,3
Cortisol (3,7-19,4 mcg/dL)	9,6	Tissue transglutaminase Ig A (<20: negative, >20: positive RU/mL)	>200
Adrenocorticotropic hormone(ACTH) (0-46 pg/mL)	34,6	Anti-endomycial antibody (<15: negative, >15: positive U/mL)	190,1
Anti-glutamic acid decarboxylase (<0,02 nmol/L)	POSITIVE		

Dıscussıon

Autoimmune polyglandular syndrome (APS) is a combination of different autoimmune diseases and four main types have been described. (Table-1) (1,3,4).

The diagnoses of type 1 diabetes mellitus (T1DM), Hashimoto's thyroiditis (HT) and celiac disease (CD) of our patient exist and they assort to APS type 3B. Our patient consulted with just abdominal distention as gastrointestinal symptoms. She had no complaints about diarrhea. It has been reported that the typical findings of CD, of which the clinical appearance is heterogeneous, such as diarrhea and abdominal distention, are seen rarely in the patients of T1DM (6). Also, it has been shown that CD may be seen asymptomatic or silently without gastrointestinal symptoms and it can be determined with serological indicators (7). Our patient who has T1DM and HT diagnoses was evaluated in terms of CD. After her tissue transglutaminase, IgA and anti-endomysial antibodies were positive, the evaluation of upper gastrointestinal system tract endoscopy was made, mucosa of bulbus and second part of the duodenum were in nodular appearance and biopsies were taken. The result of pathology confirmed the diagnoses of CD. After seeing that the cortisol and ACTH hormone levels of the patient, who doesn't have chronic mucocutaneous candidiasis and hypoparathyroidism, are normal, the Addison's disease was excluded and she was removed from APS type 1 and APS type 2 diagnoses. After the addition of CD, it has been determined that she assorts to APS type 3B.

APS Type 1 which is also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) presents in childhood, APS Type 2, which is known as Schmidt syndrome, usually presents in young adults aged 20-40 years, usually women (female: male ratio is 3:1) (5). The prevalence of APS type 1 in Finland has been estimated to be 1 per 25000 (8). In other ethnic groups include 1 per 14400 in Sardinians and 1 per 9000 in Iranian Jews (9,10). Approximately 14-20 people per million population are affected by APS type 2 in the United States.[11] The prevalence of APS type 3 isn't known certainly. The ethnical or racial difference hasn't been reported. T1DM and autoimmune thyroid disease (ATD) are well established and people suffering from these two diseases are considered at high risk of developing CD (12). It has been stated in the studies made that 5% of

patients with CD have ATD, conversely up to 2 to 4% of patients with ATD are affected by CD and 4 to 9% of T1DM subjects present with CD (13,14). In patients with ATD without other clinical autoimmune manifestations, Betterle et al. suggest not to perform a universal autoantibodies screening, but to limit the number of exams depending on the family history of the single patient and on the most common associations; obviously, the clinical suspect is fundamental. In the case of negativity, patients should be re-evaluated every 2 or 3 years. This approach permits to identify the eventual ongoing new autoimmune diseases and, if needed, to precociously treat the patient (4).

A strict gluten-free diet is the only accepted treatment for CD, which is effective to improve patients' health, to reduce the occurrence of complications. Further, a good adherence to a gluten-free diet has been shown to prevent the development of other autoimmune diseases (15).

In conclusion, keeping that CD may accompany to T1DM and ATD in mind will be beneficial to prevent possible complications that may emerge as a result of the fact that autoantibodies screening in these illnesses gives an opportunity to the treatment and early diagnosis of CD which may emerge later.

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