DOI: 10.4274/tjem.2188

A Rare Presentation of Adrenal Insufficiency: Isolated Adrenocorticotropic Hormone Deficiency and Miyelofibrosis

Ender Görülen Bir Adrenal Yetersizlik Olgusu: İzole Adrenokortikotropik Hormon Eksikliği

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Abstract

Isolated adrenocorticotropic hormone (ACTH) deficiency is a rare cause of hypocortisolism, mostly associated with lymphocytic hypophisitis (LYH). Autoimmune miyelofibrosis is another rare autoimmune disease causing bone marrow fibrosis. Here, we report the case of a patient who presented with common symptoms (weakness, fatigue, weight loss, vague pain) and anemia and was diagnosed with both rare autoimmune disorders (lymphocytic hypophisitis and autoimmune myelofibrosis). A 34-year-old male presented with weakness, fatigue, weight loss, and diffuse musculoskeletal pain. He had mild normochromic normocytic anemia. Further investigations revealed bone marrow fibrosis. The World Health Organization criteria were not fulfilled for the diagnosis of primary myelofibrosis. Since his symptoms could not be explained by mild anemia, a thorough evaluation was performed which revealed hypocortisolism associated with undetectable ACTH. Insulin-induced hypoglycemia test yielded insufficient response of ACTH and cortisol. Sellar MRI demonstrated typical features of LYH. Resolution of all the symptoms and anemia was achieved with low-dose glucocorticoid replacement therapy. In conclusion, when evaluating a patient presenting with fatigue, weight loss, vague pain, backache, and mild anemia, hypocortisolism also should be kept in mind in the differential diagnosis. If the case is isolated ACTH deficiency, the most probable cause is LYH. In such a case, additional endocrinological or non-endocrinological autoimmune disorders are likely to be present. We report the first case of lymphocytic hypophysitis coexisting with autoimmune myelofibrosis. *Turk Jem 2014; 2: 47-51*

Key words: Fatigue, weight loss, ACTH deficiency, autoimmune myelofibrosis

Özet

İzole adrenokortikotropik hormon (ACTH) eksikliği, hipokortizoleminin nadir görülen ve sıklıkla lenfositik hipofizit ile ilişkili bir nedenidir. Otoimmün miyelofibrozis, diğer bir nadir otoimmün hastalık olup, kemik iliği fibrozisine yol açar. Burada, sık karşılaşılan şikayetlerle (halsizlik, yorgunluk, kilo kaybı ve müphem ağrılar) ve anemi bulgularıyla başvuran ve bu iki nadir otoimmün hastalıklarla (otoimmün hipofizit ve otoimmün miyelofibrozis) teşhis alan bir olguyu takdim ediyoruz. Otuz dört yaşında erkek hasta halsizlik, yorgunluk, kilo kaybı ve yaygın kas-iskelet ağrıları ile başvurdu. Laboratuvarda hafif normokrom normositer anemi saptandı. İleri tetkiklerde kemik iliği fibrozisi saptandı. Dünya Sağlık Örgütü Sınıflaması'na göre olgunun bulguları pimer miyelofibrozis tanısı koymak için yeterli koşulları sağlamıyordu. Hafif anemi ile hastanın tüm bulguları izah edilemediğinden, ayrıntılı incelemeler yapıldı ve ölçülemeyecek düzeyde düşük ACTH düzeyi ile hipokortizolemi saptandı. İnsülin-hipoglisemi testi yapıldığında ACTH ve kortizol yanıtının yetersiz olduğu gözlendi. Sella MR görüntülemede lenfositik hipofizitin tipik bulguları mevcuttu. Hastaya düşük-dozda glukokortikoid yerine koyma tedavisi başlandı. Bu tedaviyle hastanın bütün şikayetlerinde belirgin azalma oldu ve anemi düzeldi. Sonuç olarak, halsizlik, yorgunluk, kilo kaybı, sırt ağrıları, anemi gibi şikayet ve bulgularla başvuran bir hastada ayırıcı tanıda hipokortizolemi akılda tutulmalıdır. Olguda, izole ACTH eksikliği saptanırsa, en olası tanı lenfosittik hipofizittir. Böyle bir olguda, diğer endokrin ve endokrin-dışı otoimmün hastalık olasığı artmıştır. Burada, lenfositik hipofizit ve otoimmün miyelofibrozisin bir arada olduğu ilk olguyu sunmaktayız. *Turk Jem 2014; 2: 47-51*

Key words: Halsizlik, kilo kaybı, ACTH eksikliği, otoimmün miyelofibrozis

Introduction

Individuals with an autoimmune disease are at higher risk of a second autoimmune disorder (1). Indeed, although many autoimmune diseases are individually rare, collectively, they have been estimated to afflict 3% of the population (2). Therefore, clinical presentation of the autoimmune diseases may have a wide spectrum. For example, celiac disease is said to be a clinical chameleon that may be presented with osteoporosis, anemia, growth retardation, fatty liver, etc. (3). Similarly, the less prevalent lymphocytic hypophysitis (LYH) is probably underestimated rather than being a rare disease (4). It has to be suspected when other

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autoimmune endocrine or non-endocrine disorder present in a patient presenting with hyperprolactinemia, headache, visual field alterations and changes of one or more pituitary hormone secretions with secondary impairment of related peripheral target glands (4,5).

The most common autoimmune diseases are Hashimoto's thyroiditis, rheumatoid arthritis, Graves' disease, vitiligo, pernicious anemia, systemic lupus erythematosus, Addison's disease, and celiac disease (6). Hence, the concomitant presentation of autoimmune diseases usually include one of these more prevalent diseases. In fact, the most common association of LYH is with Hashimoto's thyroiditis or Graves' disease (7). This is followed by Type 1 diabetes mellitus, Addison's disease, hypoparathyroidism, chronic atrophic gastritis, pernicious anemia, systemic lupus erythematosus and primary biliary cirrhosis (8,9,10,11).

Here, we present the unusual case of a patient who presented with common symptoms (weakness, fatigue, weight loss, vague pain) and mild anemia, diagnosed with LYH associated with autoimmune myelofibrosis, an exceptionally rare autoimmune disorder (12).

Case Report

A 34-year-old Turkish male presented to our Endocrinology and Metabolic Diseases Clinic with weakness and fatigue in January 2009. His symptoms started 8 months earlier with nausea, subjective fever, and diffuse musculoskeletal pain. He was admitted to a local state-hospital where he had been prescribed omeprazol. With this medication, his nausea resolved. However, he lost 10 kg in weight within a month, had night sweats, proximal muscle weakness, and backache. Therefore, he was admitted to another facility (a university hospital) where he was found to have mild anemia (Hb 12.1 g/dL) associated with poikilocytosis and anisocytosis. The mean corpuscular volume was 86.1 fL and corrected reticulocyte count was 1.9%. Serum ferritin, iron, folic acid, and vitamin B12 levels were within normal range. Transferrin saturation was 49%, reticulocyte count was 2.45%. Haptoglobin and lactate dehydrogenase were within the normal ranges. Although the anemia was compatible with chronic disease anemia, hemoglobin electrophoresis was performed and, hemoglobinopathies were excluded. Serum and urine protein electrophoresis and markers of viral hepatitis were unremarkable. Abdominal ultrasonography demonstrated normal liver and spleen. Rheumatoid factor and C-reactive protein (CRP) were negative. Erythrocyte sedimentation rate (ESR) was 13 mm/hour.

Bone marrow aspiration biopsy was slightly hypocellular, demonstrated focal collagen accumulation and grade 3 fibrosis. Bone marrow biopsy demonstrated cellularity rate of 40%, focal grade 4 collagen, and grade 3 reticulin fibrosis. Immunohistochemistry revealed negative results for CD34, CD3, CD20 and TRAP. CD138 (+) cells were detected in 5%-10% of the cells. The patient was investigated for etiologies that may cause myeloid fibrosis: mycobacterial, fungal or viral infections and autoimmune rheumatologic diseases. PPD was 8 mm, ARB was thrice negative in both sputum and urine samples. Cultures yielded no growth. Bence-Jones protein and tumor markers, including AFP, PSA, CEA, CA19-9, CA72 were negative. JAK2 mutation, and bcr-abl were negative. All serologies were negative for anti-ds DNA, anti-nuclear antibody, herpes simplex virus, Ebstein-Barr virus, and Cytomegalovirus, toxoplasmosis, human immunodeficiency virus, rubella, anti SS-A, anti SS-B, anti-SCL 70, anti-Jo-1, anti-ribosomal P protein, anti-centromere, anti-nucleosome, anti-Sm, and anti-SM/RNP. Serum complement 3 and complement 4 levels were within normal ranges. The rheumatology department advised physical therapy for generalized musculoskeletal pain and proximal muscle weakness. The physical therapy and rehabilitation department asked for additional tests, including serum 25 (OH) D levels and thyroid function tests. The 25 (OH) D level was suggestive of moderate hypovitaminosis D [13.3 ng/ml (33,3 nmol/L)], whereas all TSH, free T3 and free T4 were normal. He was advised sunlight exposure and control at the end of 3-month duration.

He preferred to be admitted to the hematology department of our facility. His routine laboratory on December 2008 is given in (Table 1). He had anemia, pyuria, elevated levels of CRP, and ESR. These remarkable laboratory findings were attributed to cystitis, which resolved with a short-course antibiotic treatment. His plasma cortisol level and free urine cortisol were very low, while thyroid function tests were normal. He was referred to our endocrinology and metabolic diseases department. With those results, he was hospitalized in order to document the etiology of hypocortisolism, in January 2009.

He was still complaining of fatigue, generalized ache and proximal muscle weakness. His medical history was otherwise unremarkable. He never used medications containing glucocorticoids. Physical examination was unremarkable other than pale conjunctivas. His blood pressure was 100/60 mmHg, pulse 70/minute and rhythmic. No orthostatic hypotension was observed. During the whole hospitalization, neither hypotension nor hypoglycemia was documented. Serum electrolytes were within normal ranges. Serum ACTH was undetectable (<1 pg/mL), repeated serum cortisol level was 0.06 µg/dL. Serum IGF-I level was 110.4 ng/mL (between 5 and 50 percentile of the same age Turkish males). Serum FSH, LH, prolactin, as well as total and free testosterone levels were within reference ranges. Serum DHEA-S was low with a level of 32.8 µg/dL (reference: 106-464). Anti-thyroid peroxidase antibody was negative. Thyroid ultrasonography showed moderate heterogeneity suggesting thyroiditis.

With a preliminary diagnosis of secondary adrenocortical insufficiency, insulin-induced hypoglycemia test was performed (Table 2). The diagnosis was confirmed by insufficient both ACTH and cortisol secretion in response to severe hypoglycemia. Therefore, an ACTH stimulation test was performed (0.25 mg intramuscular) to evaluate adrenal gland response. There was insufficient response (cortisol levels at baseline: 0.02 µg/dL, at the sixth hour following ACTH administration: 2.45 µg/dL, at 8th hour 2.77 µg/dL). However, 24-hour urinary free cortisol increased to sufficient levels (156 µg/day).

In order to document the etiology of secondary adrenocortical insufficiency, some other tests were performed. For sarcoidosis,

serum angiotensinogen converting enzyme (ACE) and chest tomography were ordered. Although serum ACE level was slightly high, neither chest tomography nor clinical pictures of the patient suggested sarcoidosis (he had not cough or dyspnea, his lung function tests and ophthalmological examination were normal). Clinical picture and chest tomography suggested that the diagnosis of tuberculosis was unlikely. Other etiologies, such as pituitary involvement of some rare rheumatologic diseases (Wegener's granulomatosis, Churg-Strauss syndrome) or Langerhans cell histiocytosis, or eosinophilic granulomatosis were clinically unlikely. Serologies for C-ANCA, anticardiolipin IgG, anticardiolipin IgM, and antipituitary antibodies were all negative. Sellar magnetic resonance imaging showed prominent heterogeneity with minimal enlargement of the anterior pituitary gland and diffuse thickening of the stalk (Figure 1, 2). Surrenal gland tomography demonstrated bilateral normal glands. He was started on prednisolon (2.5 mg per day) treatment and discharged from the hospital. Four months later, in June 2009, he was again hospitalized in order to reperform dynamic tests. He felt better, although his symptoms did not resolve at all. He was told to cease prednisolon 3 weeks before hospitalization. At baseline, serum ACTH was undetectable, serum cortisol level was 0.08 µg/dL, serum renin activity was decreased by 0.42 ng/ml/hour (reference: 0.5-1.9), and serum aldosteron level was 1.2 ng/ml (reference 1-16), serum DHEA-S level was even lower than the level during the previous hospitalization (13.5 µg/dL). Serum FSH, LH, prolactin and total and free testosterone were normal. IGF-I level was within 5 to 50 percentile as compared to Turkish men in the same age group. There were insufficient response of cortisol to both insulin-induced hypoglycemia, and ACTH stimulation.

The last admission in June 2010, 18-months after the first diagnosis, he still has hypocortisolism, and he is on prednisolon (2.5 mg/day) and vitamin D replacement (2000 U/day) therapies. With these medications, he has no residual symptoms. Anterior pituitary hormone levels and thyroid and parathyroid hormone levels are within the normal ranges. He is being followed-up also for other probable subclinical autoimmune diseases. Anti-thyroid peroxidase, anti-thyroglobulin, and anti-glutamic acid decarboxylase antibodies all were negative.

Table 1. Laboratory values at presentation to Hematology Department of our facility

	December 25, 2008	December 29, 2008
Hemoglobin (g/dL, 12.9-16.6)	11.8	11.3
White blood cells (10^3/µL, 4.1-10.9)	6.7	5.1
Hematocrit (%, 38.6-48.0)	34.0	34.1
Platelets (10^3/µL, 184-370)	267	306
Mean corpuscular volume (fL, 81.2-95.1)	86.8	86.0
Reticulocyte (%, 0.52-3.53)	2.63	2.58
Monocyte (%, 2-10)		12.3
Neutrophil (%, 44-77)		39.2
Eosinophil (%, 1-6)		4.7
Lymphocyte (%, 20-47)		43.5
Fasting plasma glucose (mmol/L)	3.9	
Na (mmol/L, 136-145)	142	
K (mmol/L, 3.5-5.1)	4.1	
Ca (mmol/L, 2.1-2.5)	2.3	
P (mmol/L, 0.9-1.4)	1.4	
Alanine aminotransferase (UI/L, <41)	22	
Aspartate aminotransferase (UI/L, <37)	26	
Blood urea nytrogen (mg/dL, 6-20)	8	
Creatinine (mg/dL, 0.7-1.2)	0.7	
LDL-cholesterol (mmol/L)	2.62	
HDL-cholesterol (mmol/L)	0.70	
Tryglyceride (mmol/L)	1.38	
TSH (mIU/ml, 0.3-4.5)	3.92	
Free T4 (pmol/L, 10-22)	13.36	
Free T3 (pmol/L, 3-6.8)	5.77	
CRP (mg/L, 0-10)	61.6	
ESR (mm/hour, 0-20)	68	

Discussion

The present case is an example of rare presentation of adrenocortical insufficiency in at least two aspects. The first aspect is the presence of both uncommon conditions: isolated ACTH deficiency and autoimmune myelofibrosis. Indeed, it is the first report of such a rare association in the literature. The other aspect is the delayed diagnosis of adrenocortical insufficiency caused by a thorough hematological, rheumatologic, and

Table 2. Insulin hypoglycemia test in order to confirm secondary adrenocortical insufficiency and to investigate probable growth hormone deficiency

	At baseline	At 30 min. following insulin bolus	At 60 min. following insulin bolus	At 90 min. following insulin bolus	At 120 min. following insulin bolus
Plasma glucose level (mmol/L)	4.22	2.11	3.72	3.89	4.05
ACTH (pg/mL)	<1.0	<1.0	<1.0	<1.0	<1.0
Cortisol (µg/dL)	0.10	0.17	0.24	0.16	0.14
Growth hormone (µg/L)	0.06	0.17	8.7	3.1	

infectious but not endocrinological evaluation of anemia. Another distinguishing feature of the case is being a young male that is unusual presentation of LYH (13).

Isolated ACTH deficiency is a rare presentation of pituitary insufficiency which is mostly associated with LYH (4,14,15). In LYH, the pituitary gland is infiltrated by lymphocytes, plasma cells and macrophages. The disease mostly affects pregnant women and women with recent delivery. Females are 8 times more likely to be affected than males. The most frequent symptoms and signs are headache (60%), visual field impairment (40%), and hyperprolactinemia (30%). ACTH deficiency is the earliest and most frequent isolated pituitary deficiency. Pituitary autoantibodies are present in about 15%-20% of all LYH cases (4). The gold standard for the diagnosis of LYH is a histopathological study by pituitary biopsy showing the peculiar lymphoplasmacytic infiltration. However, in recent years, imaging techniques (nuclear magnetic resonance) and detection of antipituitary antibodies have improved the diagnostic procedures allowing LYH detection at a subclinical stage in patients with apparently idiopathic pituitary dysfunctions.

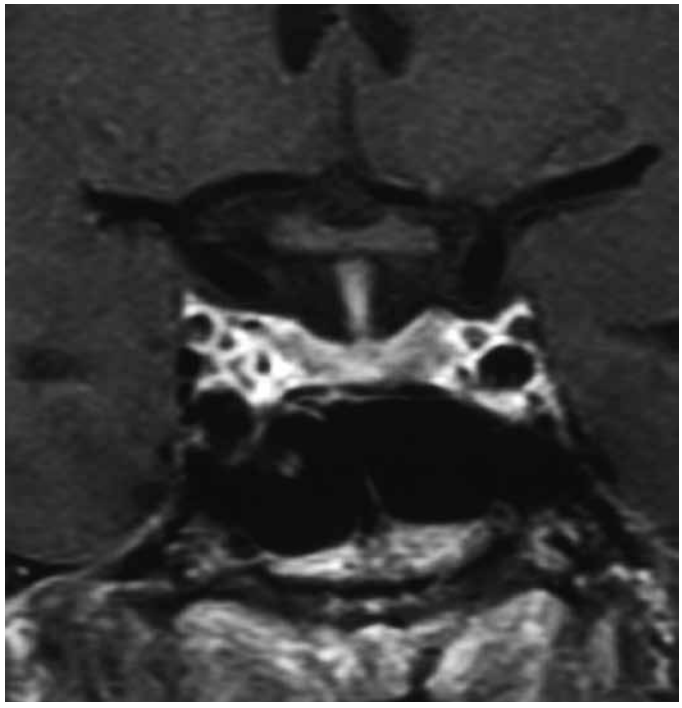

Figure 1. Coronal section of sellar MRI demonstrating heterogeneity in both part of pituitary, predominantly in the left part

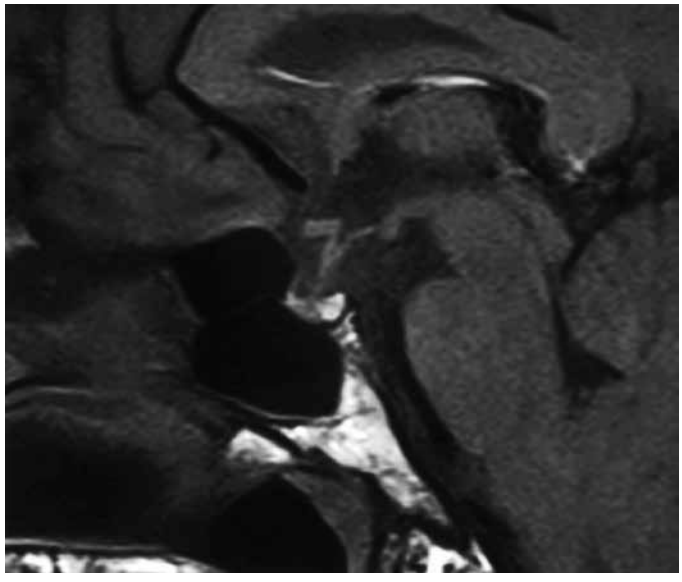

Figure 2. Sagittal section of sellar MRI through median part of pituitary and stalk demonstrating thickening of the stalk

Our patient presented with weakness and fatigue. The unique finding in his routine laboratory was a mild normochromic normocytic anemia, which his symptoms were attributed to. Anemia was further and thoroughly investigated, and the results yielded grade 3 fibrosis in bone marrow, which led to a diagnosis of myelofibrosis. However, since the diagnosis of primary myelofibrosis requires meeting all 3 major [a. Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased bone marrow cellularity, granulocytic proliferation and often decreased erytropoiesis, b. Not meeting WHO criteria for chronic myelogenous leukemia, polycythemia vera, myelodysplastic syndrome or other myeloid neoplasm, c. Demonstration of JAK2V617F or other clonal marker or no evidence of reactive bone marrow fibrosis] and 2 minor [a. Leukoerythroblastosis b. Increased serum LDH, c. Anemia, d. Palpable splenomegaly] criteria, the criteria for primary myelofibrosis were not fulfilled (16). In the course of his disease, secondary adrenocortical insufficiency was diagnosed by insulin-induced hypoglycemia test, and primary adrenocortical insufficiency was excluded by ACTH stimulation test. The classical ACTH stimulation test did not cause sufficient elevation in serum cortisol levels (17). On the other hand, 24-hour collection samples that may reflect prolonged effect of ACTH revealed sufficient elevation of free urine cortisol, and those results excluded primary adrenocortical insufficiency. Secondary causes of LYH were excluded and sellar MRI demonstrated typical features of LYH. We did not perform pituitary biopsy due to the associated high-morbidity risks, although it is the gold standard for the exact diagnosis,

Low-dose glucocorticoid replacement improved symptoms of the patient, resulted in resolution of the anemia. Although anemia in adrenocortical insufficiency is a common finding, usually, other disturbances in hematopoesis are also seen. For example, lymphocytosis and eosinophilia are frequent. In our patient, the anemia was predominant which was caused probably by autoimmune myelofibrosis (AIMF), a rare autoimmune disorder requiring low-dose glucocorticoid for the treatment. AIMF is a distinct clinicopathologic syndrome and should especially be differentiated from primary myelofibrosis, a neoplastic myeloproliferative disease, since AIMF appears to have an excellent prognosis, with a short course of corticosteroid therapy (12,18). The largest series (7 cases) of AIMF have been reported by Pullarkat et al. They have reported constitutional symptoms in 5 of 7 patients. Similarly, 5 of the patients had additional autoimmune disorders. Our case is consistent with that report.

The outcomes of LYH and AIMF are not well understood. This enigma is mostly associated with the rarity of the both pathologies. In our follow-up of about 18 months duration, his anemia resolved, his complete blood count and peripheral blood smear were normal suggesting remission of the marrow fibrosis. On the other hand, LYH was persisting on sellar MRI, and isolated ACTH deficiency is ongoing.

In conclusion, when evaluating a patient presenting with fatigue, weight loss, vague pain, backache, and mild anemia, hypocortisolism should also be kept in mind, in the differential diagnosis. If the cause is hypocortisolism associated with low ACTH, other pituitary insufficiencies should be suspected. If the case is isolated ACTH deficiency, the most probable cause is LYH. In this case, additional endocrinological or non-endocrinological autoimmune disorders are likely to be present.

Conflicts of Interest

There are no conflicts of interest.

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