A Case Report: Cushing's Disease Presenting with Polycythemia and Venous Thromboembolism

Polisitemi ve Venöz Tromboemboli ile Başvuran Bir Cushing Hastalığı Vakası

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Abstract

We present the case of a woman with Cushing's disease who had originally received a diagnosis of primary polycythemia. Her major complaints were headache, weakness, and blushing of the face. She had been admitted to another hospital about 6 months previously for same symptoms, and she received a diagnosis of polycythemia vera. Before planned bone marrow aspiration and biopsy could be performed, the patient developed a popliteal vein thrombosis; heterozygotic mutation of factor V Leiden (1691 GA) had been identified. She was admitted to our hospital for bone marrow biopsy. Considering her physical examination and medical history which revealed facial plethora, moon-face, supraclavicular fullness, central obesity, purple striae at her abdomen, shoulder, and thighs, in addition to frontal balding, acne, hirsutism and infertility, she was evaluated for possible Cushing's disease. A diagnosis of Cushing's disease was made. Her haematological situation and clinical symptoms resolved after she underwent hypophysectomy for Cushing's disease. Cushing's disease is a possible cause of secondary erythrocytosis. Venous thrombosis can occur during the course of both Cushing's syndrome and primary polycythemias. It is important to exclude such secondary causes of polycythemia before making a final diagnosis. *Turk Jem 2012; 16: 43-5*

Key words: Cushing's disease, polycythemia, venous thromboembolism

Özet

Primer polisitemi tanısı ile izlenirken Cushing Hastalığı tanısı alan bir vaka sunulmaktadır. Başlıca yakınmaları başağrısı, güçsüzlük, yüzde kızarma olan hasta, 6 ay önce aynı şikayetlerle başka bir hastaneye başvurduğunda polisitemia vera tanısı almış. Kemik iliği biyopsisi planlandığı sırada popliteal ven trombozu gelişen hastada heterozigot faktör V Leiden (1691 GA) mutasyonu tespit edilmiş. Antitrombotik tedavi verilen hasta, yapılamayan kemik iliği biyopsisini yaptırmak üzere hastanemize başvurdu. Öyküsünde infertilite nedeniyle de takip edildiği öğrenilen hastanın, fizik muayenesinde fasiyal pletora, aydede yüzü, supraklaviküler dolgunluk, santral obezite, karın, omuzlar ve uyluklarda mor strialar, frontal saç dökülmesi, akne ve hirşutizm mevcuttu. Hastaya hipofizer Cushing Hastalığı tanısı kondu. Hematolojik ve klinik tablosunda hipofizektomi sonrası düzelme gözlendi. Cushing, muhtemel sekonder eritrositoz nedenlerindendir. Venöz tromboemboli, hem Cushing Sendromu hem de primer polisitemilere eşlik edebilir. Tanı koyulurken sekonder nedenleri dışlamak önemlidir. *Türk Jem 2012; 16: 43-5*

Anahtar kelimeler: Cushing Hastalığı, polisitemi, venöz tromboemboli

Introduction

The interaction between erythropoiesis and glucocorticoid receptor activity has been inferred by clinically and experimentally (1-6). Clinically, patients with Addison's disease-which results in a lack of glucocorticoid production-have been shown to have normocytic anaemia, whereas patients with Cushing's disease-involving redundant glucocorticoid production-show increased numbers of erythrocytes and elevated hematocrit concentration (1-4).

Erythrocytosis, or polycythemia, is an increase in the absolute mass of red blood cells (7). Primary polycythemia relates to defects in erythroid progenitor cells (EPCs), with polycythemia vera being

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the most common form (7,8). Secondary causes of polycythemia usually result either in an increase in erythropoietin levels or in enhanced sensitivity of EPCs to normal levels of erythropoietin (8). Glucocorticoids have been shown to enhance EPC proliferation in experimental models (5). Activation of glucocorticoid receptors with dexamethasone also has been shown to induce the proliferation and expansion of EPCs (6). We present the case of a woman with Cushing's disease who had originally received a diagnosis of primary polycythemia. Her haematological situation resolved after she underwent surgery for the Cushing's disease.

Case Report

The Department of Haematology referred a 30-year-old woman to our clinic with a likely diagnosis of Cushing's disease. Her major complaints were headache, weakness, and blushing of the face. She had been admitted to another hospital in Istanbul about 6 months previously for the same symptoms, and she received a diagnosis of polycythemia vera after her blood counts were analyzed. At that time, the levels of haemoglobin was 16.7 g/dL (normal range: 11.5-17 g/dL) and the hematocrit, 56.5% (normal range: 32-50%). Normal findings were noted for peripheral blood smear, oxygen saturation (95%), serum erythropoietin level (13.5 mU/mL; normal range: 4.5–33 mU/mL), and vitamin B12 level (385 pg/mL; normal range: 211–911 pg/mL). Abdominal ultrasonography revealed no splenomegaly. Fluorescence in situ hybridization (FISH) polymerase chain reaction (PCR) analyses were negative for the Janus kinase (JAK2) V617F mutation and Bcr-abl.

After a session of phlebotomy, bone marrow aspiration and biopsy was planned. Before planned bone marrow aspiration and biopsy could be performed, the patient developed swelling in her left leg that was identified as a popliteal vein thrombosis. Prothrombin 20210 and methylenetetrahydrofolate reductase (MTHFR) mutation analysis were negative, but heterozygotic mutation of factor V Leiden (1691 GA) had been identified. She began taking warfarin.

She was then referred to the outpatient haematology clinic at our hospital for performance of the bone marrow biopsy. After her initial examination, however, which revealed facial plethora, severe hirsutism, and infertility, she was referred to our clinic for evaluation for Cushing's disease. At admission to our hospital, her level of haemoglobin was 14.9 g/dL and hematocrit was 43%. We learned that she had had oligomenorrhea and infertility for 3 years. The physical examination revealed facial plethora, moon-face, supraclavicular fullness, central obesity, purple striae at her abdomen, shoulder, and thighs, in addition to frontal balding, acne, and hirsutism (Ferriman-Gallwey score >13).

Her laboratory findings were as follows: dehydroepiandrosterone sulphate (DHEA-S) level: 625.6 µg/dL (normal range: 98.8–340 µg/dL); testosterone level: 0.682 ng/mL (normal range: 0.28–11.1 ng/mL); follicle-stimulating hormone (FSH) level: 5.56 IU/L (normal range: 2.5-10.2 IU/L); luteinizing hormone (LH) level: 0.783 IU/L (normal range: 0.5-16.9 IU/L); and prolactin level: 16.2 ng/mL (normal range: 2.8-29.2 ng/mL). Her endogenous blood cortisol level was 10.5 µg/dL (normal range: <1.8 µg/dL) upon overnight dexamethasone suppression testing (DST) using 1 mg of drug. After low-dose DST (Liddle test), her cortisol level was found to be 14.3 µg/dL (normal range: <1.8 µg/dL), and her adrenocorticotropic hormone (ACTH) level was 21.7 pg/mL. After measuring her basal cortisol level (22.6 µg/dL), we performed high-dose DST using 8 mg of dexamethasone. Her cortisol level was 2 µg/dL after this testing, indicating suppression.

Given the likely diagnosis of Cushing's disease, we performed pituitary magnetic resonance imaging (MRI). No adenoma was revealed, but inferior petrosal sinus sampling showed a central origin. After stimulation with corticotropin-releasing hormone (CRH), the origin was narrowed to the left side (Table 1). During the trans-sphenoidal surgery, no adenoma could be visualized, thus, a left hemihypophysectomy was performed (Figure 1).

One month after surgery, and with no further intervention, the patient's haemoglobin level had decreased to 12.5 g/dL. Her plethora had disappeared, and the striae had faded.

Table 1. Adrenocorticotropic hormone (ACTH) levels in the inferior petrosal sinus before and after infusion of corticotropin-releasing hormone

	ACTH Level (pg/mL)		
	Periphery	**Right**	**Left**
Time before infusion			
5 minutes	42.7	46.2	56.4
2 minutes	42.3	47.4	51.4
Time after infusion			
2 minutes	47.8	80.9	225
5 minutes	120	275	1021
10 minutes	266	388	820

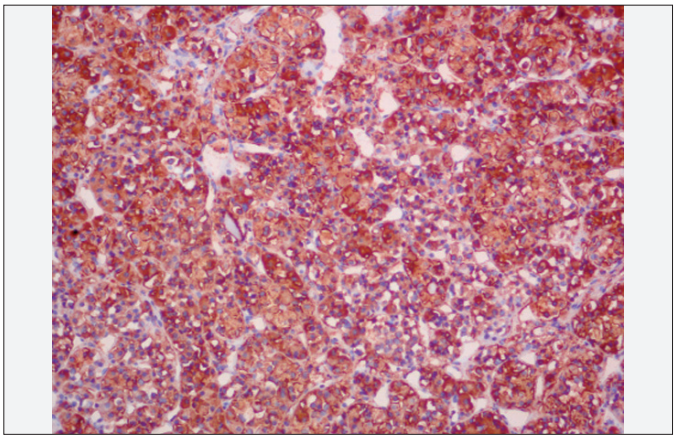

Figure 1. Adenomatous cells with positive immunohistochemistry for ACTH. (Magnification, 20x)

Discussion

Polycythemia vera is a chronic, myeloproliferative disease not related to Bcrl-abl genotype. After the discovery of JAK2, the World Health Organization revised the diagnostic criteria for polycythemia vera (8). In women, the major diagnostic criteria are

a haemoglobin level >16.5 g/dL and the presence of the JAK2 V617F gene mutation. The minor criteria include bone marrow trilineage myeloproliferation, low erythropoietin level, and growth of endogenous erythroid colony (8). The presence of two major criteria and one minor criterion, or the first major criterion and two minor criteria, is required for diagnosis (8).

More than 95% of patients with polycythemia vera carry the JAK2 V617F gene mutation (9). When findings are negative for this mutation, the patient should undergo analysis for the JAK2 exon 12 mutation, and the minor criteria should be evaluated by means of bone marrow biopsy (5). Following this strategy with our patient revealed a diagnosis of Cushing's disease, which in turn was causing secondary polycythemia vera. One month after undergoing trans-sphenoidal surgery for the Cushing's disease, our patient's haemoglobin level was reduced to 12.5 g/dL.

Bilgir and colleagues (10), hypothesised that as JAK2-STAT pathway is essential for the secretion of both CRH and pro-piomelanocortin via processing ACTH, there may be an increased prevalence of subclinical hypercorticolism among polycythemia vera patients. They found that baseline serum cortisol levels and the Liddle test showed a trend for higher serum cortisol levels in polycythemia vera patients than in control subjects (10).

Cushing's disease is a possible cause of secondary erythrocytosis (1,2). It is important to exclude secondary causes of polycythemia before making a final diagnosis. In our patient, although she had been admitted to the other hospital with non-specific complaints, obtaining a detailed history and physical examination gave us a record of oligomenorrhea, infertility, facial plethora, moon-face, supraclavicular fullness, central obesity, and purple striae on her abdomen, shoulder, and thighs, in addition to frontal balding and acne.

Because androgens can be used in the treatment of some refractory anaemias, increased androgen levels have been assumed to contribute to erythrocytosis, especially in women with Cushing's syndrome (4). Indeed, an in vitro study by Leberbauer and colleagues (11) has shown that androgen enhances proliferation of female, but not male, human erythroblasts. Our patient had a high level of DHEA-S.

Before she could undergo the original and planned bone marrow biopsy, our patient developed venous thrombosis in the left popliteal vein. Cushing's disease is known to carry risks for arterial and venous thrombosis, given the typical accompanying increases in procoagulant factors and reduced fibrinolytic activity (12). As a result, some have proposed that patients with active Cushing's disease receive routine thromboprophylaxis in conjunction with surgery (12). Our patient's thrombosis resolved after warfarin treatment. Endogenous hypercortisolism also has been associated with excess levels of homocysteine, which might contribute to the prothrombotic state in such patients and their future risks of cardiovascular disease and/or venous thrombosis (13). Although the factor V Leiden mutation does not appear to be more frequent in patients with Cushing's disease compared with general population, when it is present (as in our patient), it can promote the risk of thrombosis (13).

In conclusion, Cushing's disease can manifest as secondary polycythemia, and polycythemia can be the first sign of Cushing's disease. Venous thrombosis can occur during the course of both Cushing's syndrome and primary polycythemias. Physicians should consider the possibility of Cushing's disease in all patients with unexplained polycythemia.

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