CASE REPORT

Type 1 neurofibromatosis complicated by pulmonary arterial hypertension: A case report

Pulmoner hipertansiyon ile komplike olan tip 1 nörofibromatozis: Olgu sunumu

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Summary– Neurofibromatosis type I (NF1) is a rare genetic disease caused by mutations in the NF1 gene, which encodes the tumor suppressor neurofibromin. Precapillary pulmonary hypertension is a severe complication of NF1, initially described in patients with advanced parenchymal lung disease, which may complicate the course of NF1. Presently described is a case of neurofibromatosis complicated by pulmonary hypertension.

Özet– Nörofibromatozis tip 1 (NF1), tümör süpresor nörofibromini kodlayan NF1 geninde mutasyonların sonucu ortaya çıkan nadir bir genetik hastalıktır. Prekapiller pulmoner hipertansiyon, ileri parankimal akciğer hastalığı olan hastalarda tanımlanmış olup, hastalığın seyrini olumsuz etkileyebilir. Bu yazıda pulmoner hipertansiyon ile komplike olmuş bir nörofibromatosis hastası sunuldu.

Neurofibromatosis type I (NF1) or von Recklinghausen disease is a genetic disease with an incidence of approximately 1 per 3500 individuals that is transmitted as an autosomal dominant and fully penetrant trait.[1] NF1 is characterized by a number of distinct clinical features, including café au lait spots, neurofibromas, and axillary or groin freckling. According to published series, prevalence of vascular lesions varies between 0.4% and 6.4% overall. Pulmonary arterial hypertension (PAH) in patients with NF1 has been recognized and is hypothesized to be secondary to an underlying vasculopathy.[2] Vasculopathies are uncommon but well-recognized complications of NF1. Patients with NF1 and PAH typically receive diagnosis of idiopathic PAH. Described herein is a case of von Recklinghausen disease complicated by significant PAH.

CASE REPORT

A 46-year-old woman was referred to our clinic for evaluation of pulmonary hypertension. She had experienced exertional dyspnea for 6 months. The patient was in New York Heart Association (NYHA) functional class 2. She denied any history of chest pain, orthopnea, or paroxysmal nocturnal dyspnea. There was no history of deep vein thrombosis or recurrent thromboembolism, drug abuse, exposure to toxic inhalants, or cigarette smoking.

Abbreviations:

CT	*Computed tomography*
HRCT	*High resolution computed tomography*
MRI	*Magnetic resonance imaging*
NF1	*Neurofibromatosis type I*
NYHA	*New York Heart Association*
PAH	*Pulmonary arterial hypertension*
PAP	*Pulmonary arterial pressure*
Pro BNP	*Pro B-type natriuretic peptide*

Clinical examination revealed multiple café au lait spots, axillary freckling, and multiple neurofibromas on upper and lower limbs (Figure 1). Her pulse was 98/bpm regular and blood pressure was 170/100 mmHg. Cardiac examination revealed normal jugular venous pressure and prominent a waves. There was loud P2 with wide fixed splitting and right ventricular S3.

Laboratory results yielded normal blood count and normal renal and liver function tests. Plasma N-ter-

Received: October 28, 2016 *Accepted:* January 01, 2017
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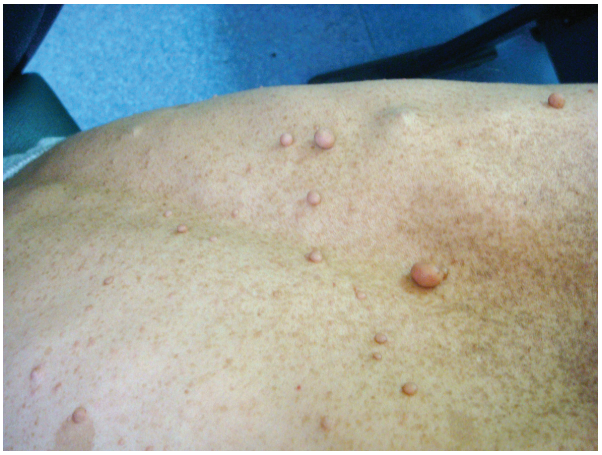

Figure 1. Multiple café au lait spots, axillary freckling, and multiple neurofibromas.

minal pro B-type natriuretic peptide (proBNP) level was 1339 pg/mL. Serological testing for HIV was negative. Electrocardiography indicated normal sinus rhythm with incomplete right bundle branch block. Chest radiograph revealed enlarged pulmonary arteries. Echocardiography showed dilated right atrium and pulmonary arteries, mild tricuspid regurgitation with velocity of 4.9 m/s and severe PAH with normal biventricular function. Tricuspid annular plane systolic excursion was 21 mm, tricuspid lateral annulus S' velocity was 12 cm/s and echocardiography revealed asymmetric septal hypertrophy of the interventricular septum (20 mm). Doppler study of lower limb was normal. There was no pericardial effusion. V/Q lung scan and high resolution computed tomography (HRCT) showed no evidence of pulmonary arterial thrombus. HRCT revealed enlarged central pulmonary arteries (truncus pulmonalis: 45 mm), and generalized geographic pattern was seen in parenchymal window. Computed tomography (CT) scan revealed no neurofibromas in lung, which could cause strictures in pulmonary arteries or their branches. Respiratory function tests showed forced expiratory volume in 1 second of 2.17 L (99.9% predicted), forced vital capacity of 2.36 L (90.6% predicted), and diffusion capacity of the lung for carbon monoxide of 17.6 mL/min/mmHg (93% predicted). Six-minute walk test was measured as 340 meters. Portal vein flow pattern was hepatopetal on Doppler examination, and there was no sign of liver failure.

Renal artery stricture and pheochromocytoma are both associated with hypertension etiology in neurofibromatosis patients. Renal magnetic resonance angiography and surrenal magnetic resonance imaging (MRI) were performed on our patient since she had diagnosis of hypertension. Twenty-four-hour urine vanillylmandelic acid, metanephrine, normetanephrine, and 5-hydroxyindoleacetic acid levels were measured. All test results were in normal ranges. While surrenal MRI result was normal, renal magnetic resonance angiography revealed stricture in proximal left renal artery. Conventional renal angiography was performed and nonsignificant lesion in the proximal left renal artery was observed. Medical follow-up was planned.

Right heart catheterization demonstrated pulmonary artery pressure (PAP) of 135/45 mmHg (mean: 85 mmHg), pulmonary capillary wedge pressure of 15 mmHg, total pulmonary resistance of 16 WU, right atrium pressure of 10 mmHg, and systemic arterial pressure of 205/110 mmHg. Cardiac output was 4.3 L/min and cardiac index was 2.9 L/min/m^2. Vasoreactivity testing was performed with adenosine, which showed that patient had negative vasodilator response (mean PAP decreased from 85 mmHg to 60 mmHg, but remained above 40 mmHg). There was no evidence of intracardiac shunt or coronary atherosclerosis. Diagnosis was idiopathic PAH complicated by von Recklinghausen disease.

Nifedipine (60 mg/day) was initiated for hypertension. Since endothelin receptor antagonists improve pulmonary hemodynamics and exercise capacity, use of dual edothelin receptor antagonist (bosentan) for pulmonary hypertension was planned according to clinical follow-up.

Patient's clinic symptoms improved significantly after 1 month. Her blood pressure was stabilized. Pro BNP level had regressed to 297.5 pg/mL. Control echocardiography indicated 50 mmHg systolic PAP. At time of writing, the patient was still in follow-up, in NYHA class 1 with systolic PAP of 40 mmHg. Six-minute walk test was measured 550 meters after 1 year.

DISCUSSION

Presently described is case of a patient with neurofibromatosis type 1 and PAH. Only 23 cases of PAH in von Recklinghausen disease have been reported so far (Table 1).[3]

Table 1. Summary of type 1 neurofibromatosis cases with pulmonary hypertension

Author	No.of patients	Age (years)/sex	PAP (mmHg)	CT scan	Biopsy
Porterfield	1	56/F	60/22	Interstitial fibrosis	NA
Samuels	1	59/M	90/-	Mosaic pattern	Arteriopathy
Aoki	2	19/F, 70/F	84/31/49;70/22/38	Dilated pulmonary artery, Not done	NA
Hernandez	1	44/M	62/30	Mosaic pattern	NA
Engel	2	60/F, 69/F	82/30;100/40	Cystic changes, Normal	NA
Montani	8	61 (mean),7F/1M	43.5 (mean)	Cystic changes (4) Normal (3) Mild fibrosis (1)	Arteriopathy
Stewart	4	58 (mean), 3F/1M	60 (mean)	Mosaic pattern	Arteriopathy
Simeoni	1	51/F	108/39/65	Mass lesion	Arteriopathy
Gumbiene	1	30/F	79/32/49	Mosaic pattern	NA
Malviya	2	34/M, 44/M	105/35/63;81/26/48	Mosaic pattern	NA

PAP: Pulmonary artery pressure; CT: Computed tomography; NA: Not available; F: Female; M: Male.

The prognosis is generally good in most patients with von Recklinghausen disease, but the course is occasionally complicated with systemic vasculopathy that results in renovascular hypertension, myocardial infarction, cerebral infarction, ischemic bowel disease, or rupture of an arterial aneurysm. Such vascular complications are major determinants of the morbidity and mortality in patients with von Recklinghausen disease.[4]

In our patient, all the conditions associated with PAH, such as connective tissue disease, chronic lung disease, HIV infection, drug and toxin exposure, hemoglobinopathies, and thromboembolism were excluded.

The present patient fulfilled the National Institutes of Health consensus criteria for diagnosis of NF1[5] because she had (1) more than 6 cafe au lait macules >15 mm in greatest diameter, (2) multiple cutaneous neurofibromas, and (3) axillary and inguinal freckling.

NF1 can also cause arterial vasculopathies, but frequency and pathogenesis of this serious complication of the disease remains unclear.[6] NF1 vasculopathy mainly involves the cerebral, renal, coronary, and peripheral vascular beds, and may cause stenosis, occlusion, aneurysm, rupture, or arteriovenous fistula formation.[7] In addition to malignant peripheral nerve sheath tumors, vasculopathies are the most relevant causes of early death in NF1 individuals. Neurofibromin, the NF1 gene-encoded protein, has a role in both tumor suppression and regulation of cell growth and proliferation. Since neurofibromin is expressed in endothelial and smooth muscle cells of blood vessels, it has been hypothesized that its deficient function could give rise to vasculopathy by impairing the response of these cells to growth suppressor signals.[8]

Pulmonary endothelial dysfunction is now believed to play a role in the pathophysiology of idiopathic PAH, and it leads to vasoconstriction and in situ thrombosis.[9,10] Vasoconstriction will lead to medial hypertrophy and/or plexiform lesions. In systemic vasculopathy of von Recklinghausen disease, intimal hypertrophy with smooth muscle cell proliferation, aneurysmal dilatation of small arteries, and plexiform lesions have been demonstrated. Therefore, vasculopathy of von Recklinghausen disease might underlie the pathophysiology of PAH in our patient, although we could not confirm it with histological evidence. Furthermore, neurofibromas could cause strictures in pulmonary arteries or their branches without affecting parenchyma or vascular structure in lung, but CT scan revealed no neurofibromas in lung in our case report.

Positive vasoreactivity test is defined as reduction in mean PAP >10 mmHg and absolute final mean PAP <40 mmHg without decrease in cardiac output.[11] In our patient, PAP decreased more than 10 mmHg, but as mean PAP did not decrease below 40 mmHg, test

was considered negative. Nifedipine treatment was initiated for its beneficial effects on hypertension, and it was observed that it also caused decrease in systolic PAP. This suggests that calcium channel blockers could be effective and useful in the treatment of these patients if 1 criterion of vasoreactivity test is positive.

In conclusion, pulmonary hypertension represents a rare but severe complication of NF1 that is characterized by late onset, female predominance, and severe functional and hemodynamic impairment. We think that PAH in our patient was a complication of NF1 and suggest that patients with NF1 need to be evaluated with transthoracic echocardiography for presence of PAH, even if it has low sensitivity for screening the early stages.

Funding

This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict-of-interest: None declared.

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Keywords: Neurofibromatosis; pulmonary arterial hypertension; vasoreactivity test.

Anahtar sözcükler: Nörofibromatozis; pulmoner arteryel hipertansiyon; vazoreaktivite testi.