Pulmonary hypertension and von Recklinghausen's disease: association and therapeutic difficulties

Hipertensiune pulmonara și boala von Recklinghausen: asociere și dificultăți terapeutice

Abstract

The neurofibromatosis type 1 (NF1) or Von Recklinghausen's disease is a genetic disorder. The café-au-lait spots and neurofibromas are the most common manifestations. Respiratory symptoms are rare in this disease, described as neurofibromas, infiltrative lesions, cysts, bubbles or emphysema. Pulmonary hypertension is rarely reported. It is due to the plexiform lesions in pulmonary arterioles or to parenchymal lung lesions reducing the vascular bed. We report a case of idiopathic precapillary pulmonary hypertension in a young patient with Von Recklinghausen's disease.
Keywords: *Neurofibromatosis type 1 (NF1), pulmonary arterial hypertension (PAH)*

Rezumat

Neurofibromatoza tip I sau boala Von Recklinghausen este o maladie genetică. Leziunile cutanate sub formă de pete "café-au-lait" și neurofibroamele sunt cele mai des întâlnite manifestări. Afectarea pulmonară este rară și cuprinde neurofibroame, leziuni infiltrative, chiste, bule de emfizem. Hipertensiune pulmonară este rar descrisă. Această manifestare este secundară leziunilor plexiforme de la nivelul arteriolelor pulmonare sau leziunilor parenhimatoase ce reduc patul de distribuție. Raportăm un caz de hipertensiune arterială pulmonară precapilară idiopatică la un tânăr pacient diagnosticat cu boală Von Recklinghausen.
Cuvinte cheie : Neurofibromatoza tip I, hipertensiune arterială pulmonară

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Introduction:

The neurofibromatosis type 1 (NF1) or Von Recklinghausen's disease is an autosomal dominant genetic disorder which is believed to affect 0.03% of the population[(1)]. The NF1 gene responsible for the disease is located on the long arm of chromosome 17 and encodes a protein named neurofibromin. Neurofibromin is a tumor suppressor gene. A mutation in this gene leads to the production of a defective protein and triggers the disease. The *café-au-lait* spots and neurofibromas are the most common manifestations. Respiratory complications are rare in the disease. Pulmonary hypertension (PH) has been reported in patients with Von Recklinghausen disease. Samuels et al. described one case complicated with pulmonary hypertension[(2)]. Aoki et al. reported two Japanese women with NF1 and PH secondary to vasculopathy[(3)]. Montani D et al present 8 patients with NF1 associted PH in whom the NF1 gene mutation was identified[(4)]. The mechanism of PH is unclear. In the PH clinical classification, NF1 is listed in Group 5 due to unclear and/or multifactorial mechanisms[(5)]. We report a new case of pulmonary arterial hypertension (PAH) during neurofibromatosis type I.

Case report:

A 19-year-old woman with neurofibromatosis type I since childhood, has noticed dyspnea, class II according to the New York Heart Association, discomfort and faintness with minimal effort the past three months.

The clinical examination revealed diffuse *café-au-lait* spots throughout the body with bilateral axillary freckling. There were no skin neurofibromas. Cardiovascular examination revealed pulmonary B2 sound. There were no signs of heart failure. The pleuropulmonary auscultation was normal. Ophthalmologic examination showed multiple Lisch nodules.

The chest X-ray showed a prominent left average arc without interstitial or cystic lesions (Figure 1). The electrocardiogram demonstrated signs of right ventricular hypertrophy and right axis deviation (Figure 2). Echocardiography showed a systolic pulmonary artery pressure to 108 mmHg (Figure 3) with right ventricular hypertrophy and a paradoxical septum (Figure 4). There was neither a left-to-right shunt nor a valve disease. The right heart catheterization showed an important precapillary pulmonary arterial hypertension: PAP of 122/55 mmHg (mean= 78 mmHg), RAP = 12 mmHg, PCWP= 13 mmHg, CI= 1.94 L/min/m2, PVRi= 22 Wood unit. After nitrite oxide (NO) (vasoreactivity testing), no acute vasodilator response was observed, PAP of 98/38 mmHg (mean 55 mmHg), PCWP = 7mmHg, PVRi= 5.1 Wood units and CI= 1.71L/min/m^2.

The contrast CT angiogram chest did not show any sign of embolism or parenchymal damage only central pulmonary artery dilatation (Figure 5).

Serological investigations were performed to search for immunological abnormalities including: anti-nuclear anti-

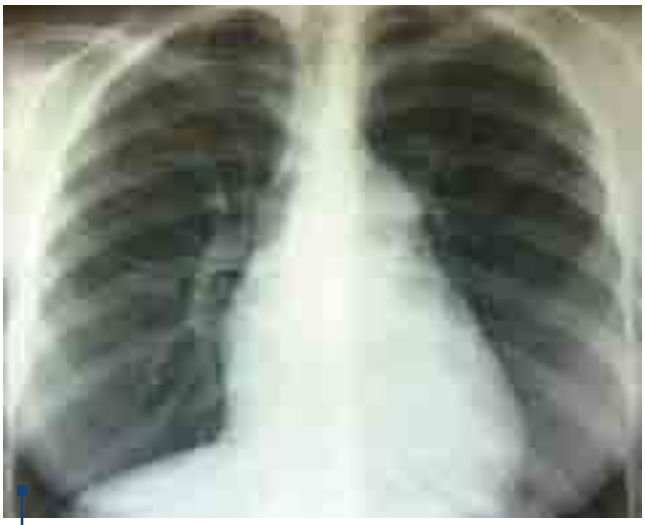

Figure 1. *Chest radiography demonstrates cardiomegaly and a prominent left average arc*

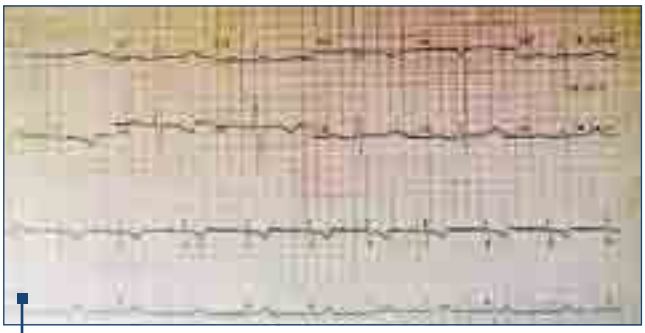

Figure 2. *Electrocardiogram demonstrating the right ventricular hypertrophy (long arrow) and the right axis deviation (short arrow)*

Figure 3. *Echocardiographic image showing dilated right cavities, VD= right ventricule (ventricule droit), VG =left ventricule (ventricule gauche), OD = right auriculum (oreillette droite), OG= left auriculum (oreillette gauche)*

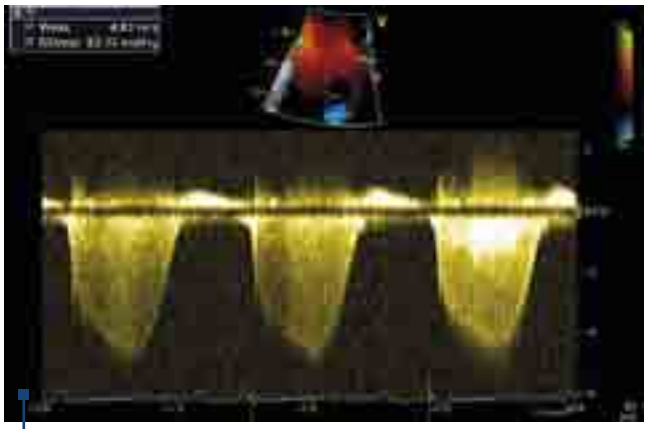

Figure 4. *Continuous Doppler curve showing tricuspid regurgitation, at Vmax = 4,8 m/s or a PAPs =108 mmHg*

body, anti-Scl-70, anticentromere, anticardiolipin IgG and IgM antibodies and Beta-2 Glycoprotein 1 IgG and IgM antibodies, the results were negative as was the HIV serology.

Liver function tests showed moderate cytolysis with AST level at 60 IU/L and ALT level at 53 IU/L. The viral serology B and C was negative as well as Immunological Testing in Liver. Doppler ultrasound of the hepatic veins and portal vein was normal and there were no changes in portal flow. Plasma N-terminal pro-B type natriuretic peptide (pro BNP) level was 3896 pg/ml. The 6MWT (6 minute walk test) was 350m. The patient was diagnosed with Idiopathic-like PAH and was treated with Phosphodiesterase 5 inhibitor and endothelin receptor antagonist combined with an anticoagulant (INR range 1.5-2.5).

After 6 months of treatment, her PAH became refractory, difficult to manage and the New York Heart Association functional class worsened from II to III. The 6MWD decrease to 200m. Repeat echocardiography revealed a pericardial effusion and right ventricular fraction ejection (TAPSE) decrease to 6 mmHg. Right heart catheterization showed mPAP= 61 mmHg, RAP= 19 mmHg, PCWP= 8mmHg,CI= 1.97 L/min/m2, PVRi = 16.6 Wood units and SvO_2=52.8%. A third specific PAH therapy, inhaled synthetic analog of prostacyclin, was added, but there was no clinical response with therapy.

Discussion

Respiratory complications of Von Recklinghausen's disease are rare between 5 and 20 %[6]. It can be airway impairment, mediastinal, parenchymal or vascular damage or other respiratory complications.

This respiratory disease may be related to neurofibromas compressing the mediastinum, upper or lower airways, or bullous or fibrotic lesions[7]. Pulmonary arterial damage was reported by several authors[8,9]. Pulmonary valvular stenosis has been reported in relation to genetic disorders in NF1: NOONAN, WATSON and LEOPARD syndromes whith which facial dysmorphia is often associated[10].

A pre-capillary pulmonary hypertension can be easily attached to a complication of parenchymal lesions at the stage of chronic respiratory failure reducing the vascular bed as well as chronic hypoxia related to vascular remodeling.

Cases of primary pulmonary hypertension have been reported. It would be due to vascular dysplasia or an invasion of arteries by neurofibromas[9]. The first case is the one described by Samuel et al.[2]. The patient was followed for NF1 and acute dyspnea occurred. Etiological evaluation suspected proximal embolism, but during the thromboendarterectomy a severe intimal thickening without thrombotic material was found and histological examination showed intimal fibrosis.

In our case, no tumoral process in the wall of pulmonary arteries was found and imaging tests did not show any paren-

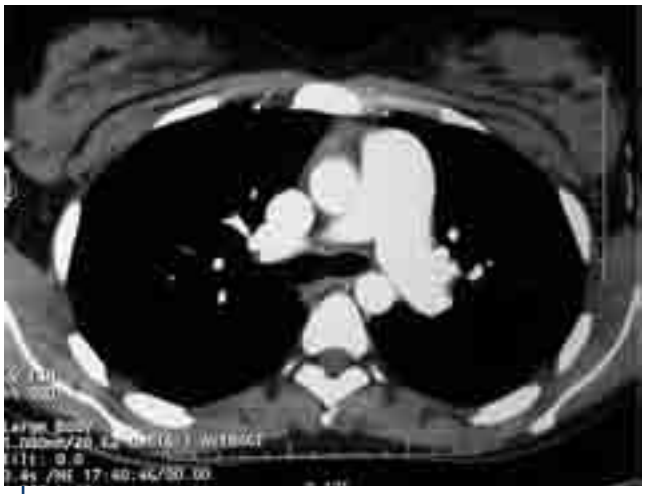

Figure 5: *contrast CT angiogram chest shows central pulmonary artery dilatation.*

chymal lesions. The pathogenic mechanism would be an intimal thickening because of Schwann cells invasion or smooth muscle cells invasion resulting in plexiform lesions similar to those observed in idiopathic PAH [11].

It has been reported in animal models[12] and in cultured human endothelial cells[13] in patients with neurofibromatosis type 1 a loss of expression of a protein that regulates cell growth called neurofibromin. This would be responsible for the proliferation of vascular smooth muscle cells, which could explain PAH in our patient. The therapeutic management of PAH is quite complex and involves molecules acting on different pathophysiological mechanisms. Conventional treatment is essential and consists in effort limitation, prohibiting hot baths, and avoiding altitude and pregnancy. Anticoagulant therapy with a target INR range between 1.5 and 2 is essential considering the risk of thrombosis. The etiopathogenic treatment targets both the mechanism leading to the pulmonary vascular proliferation and vasoconstriction. In our patient, despite the combination of Phosphodiesterase 5 inhibitor and endothelin receptor antagonist therapy the result remains not very satisfactory explaining the difficulty of treatment of patients with PAH during neurofibromatosis.

Calcium channel blockers cause vasodilatation which can improve PAH in some patients. The study conducted by Sitbon et al. identified responders in acute and long-term cases. Patients are called "acute responders" when the administration of inhaled nitric oxide (NO) decreases the mean pulmonary artery pressure by at least 10 mmHg to reach an absolute value of 40 mmHg or less without a decrease in cardiac output is currently. Diltiazem may be given at the dose of 360 to 720 mg per day or Nifedipine at the dose of 80 to 180 mg per day. It is therefore essential to study the vascular reactivity of patients before offering treatment with calcium channel blockers[14]. Acute vasodilator testing was negative in our patient.

Prostacyclin analogues can be administrated by continuous injection, orally, or subcutaneously, it remains an option for the most severe patients NYHA class III or IV not responding to NO.

Sorafenib, an oral inhibitor of multiple tyrosine kinase, is a promising drug for severe PAH. Tamura Y et al., hypothesized that Sorafenib would have novel therapeutic potential in NF1-associated PAH by suppressing MAPK (mitogen-activated protein kinase) cascade activities[15]. In patients who are refractory to medical therapy, lung transplantation is an important treatment option[16] however, in our patient with NF1 the complex plexiform lesions and vasculopathy could constitute a risk. One patient with NF1 and PAH was successfully transplanted in study of Montani et al.[4].

Conclusion

The prevalence of PAH during Von Recklinghausen neurofibromatosis is certainly underestimated, we can suppose it is greater than in the general population. This case is another argument for the idea that NF1 associated with PH may be observed in patients without parenchymal lung disease, reinforcing the hypothesis of an associated pulmonary vasculopathy. It should be detected at an early stage by echocardiogram, although the prognosis is not good in this particular field.

Abbreviations:

6MWT= 6 minute walk test, CI= cardiac index, HIV= human immunodeficiency virus, mPAP= mean pulmonary arterial pressure, NF1= neurofibromatosis type 1, NYHA= New York Heart Association, PAH= pulmonary arterial hypertension, PCWP= pulmonary capillary wedge pressure, PH= pulmonary hypertension, PVRi= indexed pulmonary vascular resistance, RAP= right atrial pressure. ■

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