CARDIOLOGIE TUNISIENNE

CASE REPORT

Severe Pulmonary Hypertension with RV Dysfunction: A Fatal Complication of Neurofibromatosis Type 1

Hypertension pulmonaire sévère avec dysfonction du ventricule droit : une complication fatale de la Neurofibromatose type 1

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Summary

Introduction: Neurofibromatosis type 1 (NF1) complicated by pulmonary hypertension (PH) is a rare condition, which typically presents with advanced-phase symptoms and death.

Case summary: 60-year-old male patient without significant past medical history presented with progressively deteriorating exertional dyspnea (NYHA class III) and oedema of both lower limbs. Clinical examination found signs of right-sided heart failure like elevated jugular venous pressure, hepatomegaly, and peripheral oedema. Dermatological examination revealed multiple café-au-lait macules and numerous cutaneous neurofibromas, consistent with neurofibromatosis type 1 (NF1, von Recklinghausen disease).

Echocardiography showed marked dilation of the right atrium and right ventricle, severe right ventricular systolic dysfunction, and an estimated systolic pulmonary artery pressure of 100 mmHg, while left ventricular function remained normal.

The overall presentation was consistent with severe pulmonary hypertension most likely associated with NF1.

Management included initiation of diuretics, supplemental oxygen, and referral for specialized pulmonary hypertension therapy.

Conclusion: This case reports a rare association between NF1 and severe pulmonary hypertension, calling attention to the importance of thorough cardiovascular assessment in patients with NF1 who have unexplained dyspnea.

Keywords

Pulmonary hypertension, Neurofibromatosis type 1, Right ventricular dysfunction, Dyspnea.

Résumé

Introduction :

La neurofibromatose de type 1 (NF1) compliquée d'hypertension pulmonaire (PH) est une affection rarissime. Le diagnostic est généralement fait au stade des symptômes avancés et des complications. Néanmoins une prise en charge précoce permet d'alléger les symptômes et retarder l'évolution de la maladie

Résumé du cas : Patient de sexe masculin âgé de 60 ans sans antécédents médicaux significatifs présente une dyspnée d'effort (NYHA classe III) avec des œdèmes des membres inférieurs avec aggravation progressive. L'examen clinique a révélé des signes d'insuffisance cardiaque droite type : turgescence des veines jugulaires, hépatomégalie et des œdèmes périphériques. Par ailleurs, on a constaté à l'examen dermatologique la présence des taches café-au-lait et des neurofibromes cutanés, caractéristiques de la NF1 (maladie de von Recklinghausen).

Ainsi, l'échocardiographie a montré une dilatation de l'oreillette droite et du ventricule droit, une dysfonction ventriculaire droite sévère, et une pression artérielle pulmonaire systolique estimée à 100 mmHg avec une fonction systolique ventriculaire gauche normale.

Le patient a été diagnostiqué avec une hypertension pulmonaire sévère probablement secondaire à la NF1. Le traitement comprenait des diurétiques, l'oxygénothérapie, avec une prise en charge spécifique de l'hypertension pulmonaire.

Conclusion : ce cas illustre une association rare entre la NF1 et l'hypertension pulmonaire, soulignant l'importance d'une évaluation cardiovasculaire approfondie chez les patients atteints de NF1 présentant une dyspnée inexpliquée.

Mots-clés

Hypertension pulmonaire, Neurofibromatose de type 1, Dysfonction ventriculaire droite, Dyspnée

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INTRODUCTION

Pulmonary hypertension (PH) is a progressive and fatal disease characterized by elevated pulmonary arterial pressure leading to right ventricular failure. While its most common causes are left heart disease, chronic lung disease, and chronic thromboembolic pulmonary hypertension, less common etiologies such as genetic syndromes must also be taken into account.

Neurofibromatosis type 1 (NF1), or von Recklinghausen's disease, is an autosomal dominant disorder caused by mutation in the NF1 gene on chromosome 17(1). It is characterized primarily by dermatological and neurological manifestations of café-au-lait macules, cutaneous neurofibromas, and Lisch nodules. Cardiovascular manifestations are less frequent and can include vasculopathies, congenital heart defects, and very rarely pulmonary hypertension.

The underlying pathophysiologic mechanisms for the association of NF1 and PH remain to be determined, but hypothetical hypotheses are pulmonary vasculopathy as a result of endothelial dysfunction, overgrowth of smooth muscle, and remodeling of small vessels(2). Characterized cases illustrate NF1-associated PH is typically severe on presentation, with a poor prognosis and disappointing response to conventional therapies(3).

We report the case of a 60-year-old male patient with NF1 developing severe pulmonary hypertension and right ventricular failure, illustrating this rare cardio-dermatologic correlation and emphasizing the utility of cardiovascular evaluation in NF1 patients with unexplained dyspnea.

CASE PRESENTATION

A 60-year-old man with no prior medical history presented with progressive exertional dyspnea over several months, now classified as NYHA functional class III, associated with bilateral lower limb oedema. There was no history of chest pain, syncope, fever, or recent respiratory infection.

He had no family history of NF1, also there is no history of sleep apnoea, drug use, or toxin ingestion.

Upon presentation, the patient's blood pressure was 110/50 mmHg, heart rate 90 bpm, respiratory rate 30c/min, oxygen saturation: 95% on 3-L nasal cannula oxygen, without fever . Jugular venous distension and bilateral pitting oedema of the lower limbs. A fixed split second heart sound was heard. Hepatomegaly was also noted upon abdominal examination. On dermatological inspection unveiled multiple café-au-lait spots and cutaneous neurofibromas characteristic of neurofibromatosis type 1 (figure 1).In addition, eye exam had revealed Lisch nodules.

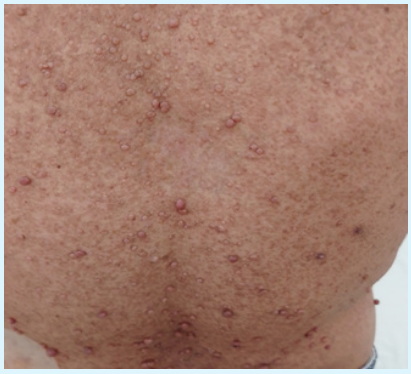

Figure 1. dermatological lesions

Laboratory results showed a normal blood count with chronic renal involvement and normal liver function tests. Studies for hypercoagulability were all within normal limits. Arterial blood gas (on room air) were as follows: pH 7.45, PCO2 36 mm Hg, PO2 58 mm Hg, SaO2 91% . We excluded antiphospholipid syndrome, collagen, thyroid, blood, and liver diseases via serology testing and ultrasound. Unfortunately, genetic testing for neurofibromatosis type 1 and pulmonary hypertension/ bone morphogenetic protein receptor 2 (BMPR2) and others were not available. Human immunodeficiency virus testing was negative.

A chest radiograph revealed mild cardiac enlargement, but no acute intrathoracic pathology was noted (figure 2).

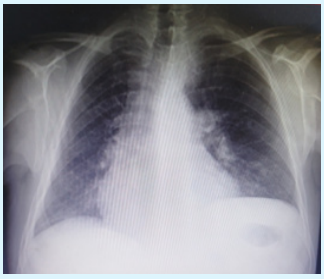

Figure 2. Chest radiography

Electrocardiogram revealed sinus rhythm with right ventricular hypertrophy. Transthoracic echocardiography revealed marked dilatation of the right ventricle and right atrium with severe systolic dysfunction of the right ventricle, severe tricuspid regurgitation and an

estimated pulmonary artery systolic pressure of 100 mmHg. However, Systolic function of the left ventricle was intact without left side valvopathies (figure 3).

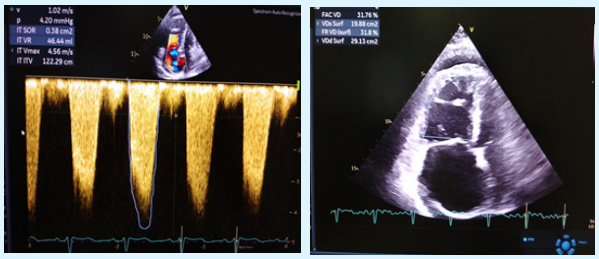

Figure 3. HTTE findings: estimated PASP (left), RV dilatation(right)

Initially, he was treated with loop diuretics with dramatic alleviation of oedema peripherally. His condition (no dyspnoea at rest) and functional capacity improved gradually (6-min-walk distance 300 m). he was discharged from the hospital and remain on 1-L nasal cannula oxygen.

Diagnosis of severe pulmonary hypertension with right heart failure, secondary to NF1, was made on the basis of echocardiographic data and cutaneous findings (he meet three diagnostic criteria of NF1: ≥ 6 café-au-lait macules > 15 mm in greatest diameter in post pubertal patients , ≥ 2 Lisch nodules identified by slit-lamp examination and freckling in the axillary and inguinal region).

DISCUSSION

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≥20 mmHg on right heart catheterization (4). Severe PH, as in this case (estimated systolic PAP ≈ 100 mmHg on echocardiography), is classically associated with massive right ventricular remodeling and dysfunction, culminating in progressive right heart failure. In the presented case, the most likely etiology was NF1-associated pulmonary vasculopathy, a known but uncommon complication of this hereditary syndrome.

NF1 is a rare genetic disease caused by mutations in the NF1 gene, which codes for tumor suppressor neurofibromin. NF1 is transmitted as an autosomal dominant and fully penetrant trait with no sex predominance (1). To the best of our knowledge, only 18 case reports describing 31 patients with NF1-associated PH have been published so far (3) .

Precapillary PH is a severe complication of NF1, initially described in patients with advanced parenchymal lung disease (1,2). Cardiovascular NF1 manifestations include systemic hypertension (often renovascular), and medium and small artery vasculopathies. Pulmonary vascular involvement is rare but has been reported in adults and children.

In contrast to heritable pulmonary arterial hypertension, the age of onset is very late, with median age being more than 60 (2). also, the median time from diagnosis of type 1 neurofibromatosis to diagnosis of pulmonary arterial hypertension is more than 30 years(2). This further suggests that arteriopathy of pulmonary vasculature is late phenomenon in natural history of type 1 neurofibromatosis and develops in the long-standing disease.

Most reported patients have presented with advanced disease before diagnosis and this may be due to lack of awareness of this association and consequent delay in the diagnosis. As previously discussed, the lung abnormalities are variable (2).

The pathogenic processes of PH in NF1 remain poorly understood. Several hypotheses have been raised like endothelial dysfunction and smooth muscle overgrowth have the potential to cause small pulmonary artery remodeling. However, Severe intimal fibrosis consistent with vascular involvement with neurofibromatosis was found on endarterectomy with no evidence of pulmonary thromboembolism (5) .There is also a Thromboembolic predisposition because patients with NF1 can be predisposed to in-situ thrombosis or recurrent pulmonary embolism.

Interstitial lung disease was also incriminated as a small minority of patients with NF1 develop fibrotic or cystic changes of the lung that can cause PH (6).

Furthermore, response to standard PAH therapy (endothelin receptor blockers, PDE5 inhibitors, prostacyclins) is unpredictable, with some reports indicating limited efficacy, perhaps because structural vascular changes in the advanced stage are not easily reversed (4,5).

For our patient, he was first treated with loop diuretics to reverse congestion with resulting dramatic improvement of edema. Oxygen therapy was initiated for hypoxemia. Because of the rarity of NF1-associated PAH, there are no recommended treatment guidelines. Rather, management is borrowed from idiopathic PAH treatment algorithms and targets early referral to a PH center.

Although specific pulmonary vasodilators including epoprostenol, bosentan and sildenafil are considered useful in the management, lung transplantation offers the ultimate cure.

This study emphasizes the importance of maintaining PH in the differential diagnosis in NF1 patients with unexplained dyspnea, even when lung disease is absent. Skin inspection can provide important diagnostic information. Screening by echocardiography in symptomatic NF1 patients early on can allow for earlier detection and treatment (7).

CONCLUSION

Pulmonary hypertension is a rare but serious cardiac presentation of type 1 neurofibromatosis. It may be insidious in onset with progressive dyspnea and signs of right heart failure, typically at an advanced stage. Our case reiterates the fact that this unusual association needs to be remembered and cardiovascular evaluation must be considered in NF1 patients presenting with unexplained effort intolerance. Early diagnosis could potentially improve management and survival, although the prognosis remains guarded.

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