Case report

Pulmonary arterial hypertension: A rare yet fatal complication of Neurofibromatosis Type 1

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ABSTRACT

Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 4,000 live births [1]. Pulmonary arterial hypertension (PAH) is a rare but extremely life-threatening complication associated with NF1. Timely recognition of this unusual and severe association between NF1 and PAH is imperative in prolonging the survival in this specific patient population. We present the clinical outcomes of a 47-year old female previously diagnosed with NF1, who presented with progressively worsening dyspnea.

1. Introduction

Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in NF1 tumor suppressor gene leading to the development of characteristic café-au-lait spots, optic gliomas, malignancies of peripheral and central nervous system as well as gastrointestinal and cardiovascular disorders [1–3]. Pulmonary arterial hypertension (PAH) is a rare, but extremely life-threatening clinical finding associated with NF1. Pulmonary artery hypertension in NF1 is thought to be due to an underlying vasculopathy [4,5]. The following case report is a significant addition to the limited available literature on this rare, but severe, condition. (see Table 1)

2. Case presentation

A 47-year-old Caucasian female, previously diagnosed with NF1, presented to the emergency department with the chief complaint of progressively worsening shortness of breath. On physical examination, the patient presented with specific clinical signs of NF1, such as axillary freckling, multiple neurofibromas in her upper and lower limbs as well as multiple café-au-lait spots on her trunk and back. She reported that, for the past 6 months, she could not walk a few steps without getting short of breath. She was previously diagnosed with severe chronic obstructive pulmonary disease (COPD). The patient was a nonsmoker and denied any evidence of tobacco exposure. Her COPD and worsening shortness of breath had been unresponsive to continuous home oxygen therapy as well as her home inhaler and nebulizer treatments. Additionally, she reported pleuritic chest and back pain associated with increased work of breathing, as well as a chronic productive cough of yellowish sputum, which had not increased in production or thickness. At initial presentation, the patient was afebrile, her blood pressure (BP) was 113/69 mm Hg, pulse was 102 b/min, and respiratory rate was 19 breaths per minute. She was saturating at 76% on 4 L (L) of oxygen therapy and her physical examination revealed decreased breath sounds and bilateral lower extremity edema. Laboratory tests at the time of admission were remarkable for an elevated hemoglobin and hematocrit of 17.2 g/dL (n = 12–16 g/dL) and 52.3% respectively. She also had mildly low potassium of 3.2 mEq/L (n = 3.5–5.0 mEq/L), elevated total bilirubin of 1.2 mg/dL (n = 0.1–1.2 mg/dL), and a brain natriuretic peptide (BNP) of 3059 pg/mL (n ≤ 125 pg/mL). Her arterial blood gas on admission revealed a PaO2 of 98.7 mm Hg, PaCO2 of 24.6 mm Hg, and a pH of 7.46. Antinuclear and antineutrophilic cytoplasmic antibodies were undetectable and rheumatoid factor screening was normal. Electrocardiogram (ECG) on admission revealed right axis deviation and right ventricular hypertrophy, while computed tomography (CT) scan of the chest showed scattered bullous changes, posterior bilateral lower lobe basal subpleural scarring without any signs of pulmonary embolism (Fig. 1). An echocardiogram (ECO) was performed which revealed moderate to severe tricuspid regurgitation, with a tricuspid regurgitant jet velocity (VTR) of 4.16 m/s along with the dilation of the right ventricle. Other significant findings demonstrated by the echocardiogram were a normal left ventricular size and systolic function, with an ejection fraction of 64%, no left ventricular wall abnormalities, a right ventricular systolic pressure (RVSP) of 104 mm Hg (n = 16–39 mm Hg) and signs of severe PAH. Estimated pulmonary artery systolic pressure (PAPs,) was 89 mm.
Pulmonary artery pressure (PAPm) was 55.65 mm Hg (n = 12 since the inferior vena cava was dilated]. The estimated mean pulmonary artery pressure; right atrial pressure was estimated at 20 mm Hg [PAPm = 0.61xPAPs+2]. Pulmonary function tests (PFT) were not performed due to the patient's severe dyspnea and desaturation while breathing room air.

A diagnosis of PAH was made secondary to NF1. A bubble study was done to rule out an intra-cardiac shunt. Unfortunately, invasive hemodynamic studies to confirm PAH were not carried out due to the patient's unstable status while in the hospital. A decision was made to consider emergent transfer to a tertiary care center for possible lung transplant. A lung biopsy was first required to be considered for transplant, therefore the patient was scheduled to undergo a bronchoscopy. On day seven of admission, she deteriorated with signs of severe hypoxemia even on 15 L of oxygen. Although the patient was critically considered for the lung transplantation, we planned to perform a bronchoscopy to assess the respiratory status of the patient further. Unfortunately, she developed acute on chronic hypoxic respiratory failure, her condition rapidly declined, and she died shortly after.

### 3. Discussion

**NF1** is an autosomal dominant condition with approximately 100% penetrance [3]. This disorder has variable expressivity regarding its clinical manifestations, with approximately 50% of NF1 cases being sporadic mutations [7,8]. Arterial vasculopathies can also arise in NF1, however the pathogenesis and frequency of this particular severe manifestation remain largely unknown [9]. To date, very few cases of PAH secondary to NF1 have been reported, and no large patient series exist. To the best of our knowledge, only 18 case reports describing 31 patients with NF1-associated PAH have been published so far [20].

NF1-associated PAH is often under-reported due to a difficulty in diagnosis and distinguishing it from other, more common pulmonary disorders. This challenge was evident in our patient, who had seen multiple doctors, and was diagnosed with severe COPD before her diagnosis of PAH was made. There has been evidence to suggest that non-smokers with NF1, in addition to possibly presenting with signs of pulmonary hypertension, can also demonstrate an emphysematous lung picture on presentation [25].

NF1-associated PAH is commonly reported in the female population, and oftentimes, presents later in the course of NF1, as was the case with...
our patient [19,20]. As this disorder is rare, and the exact mechanism of the pathophysiology behind it are still not well understood, NF1-associated PAH has been listed in group 5 of the pulmonary hypertension clinical classification [22]. The etiology of NF1-associated PAH is relatively unknown, but many studies have postulated that it could be the result of pulmonary vasculopathy [9,13,20]. This theory is strengthened by the fact that NF1 is well known to cause systemic vasculopathy affecting multiple systemic arteries of the body [4,20]. Other evidence to support the theory of pulmonary vasculopathy is that the NF1-encoded protein, neurofibrin, has a role in regulating cell growth and proliferation as well as tumor suppression [5]. Neurofibrin is expressed in endothelial and smooth muscle cells of blood vessels, and it is thought that a deficiency in this protein can lead to vasculopathy by interfering with the response of those cells to the growth suppressor signals [5].

Most reported patients with PAH, associated with NF1, present in the advanced stages of the disease, oftentimes reporting a chief complaint of progressively worsening dyspnea, as was seen in our patient. Patients will typically present with classic signs and symptoms of NF1, such as café-au-lait spots, axillary freckling cutaneous neurofibromas and optic gliomas [2,10].

There are multiple pulmonary manifestations related to NF1, which can affect both the thorax and lungs in various ways. These manifestations include cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis, thoracic neoplasms and interstitial lung disease [26]. Radiographic studies which have been performed on patients with pulmonary manifestations related to NF1 have shown large apical asymmetric thin-walled bullae, sometimes occupying a large portion of the hemithorax. These large bullae are oftentimes associated with areas of hypovascularity and bibasilar, subpleural reticular abnormalities. Another rare, but still reported, manifestation is honeycombing on radiographic studies, which can mimic idiopathic pulmonary fibrosis.

Diagnosing PAH in NF1 is difficult in many cases as it is not a common manifestation of NF1, and therefore not recognized early on. Ventilation-perfusion scans and high-resolution CT scans of the chest can demonstrate bilateral filling defects as well as a mosaic pattern of the lungs, which represents irregular perfusion [14]. This finding on CT scan also supports the theory of vascular involvement as a cause of PAH [14]. There has been much debate over diffuse lung disease in NF1, as many different patterns of lung involvement can present in these patients [23]. As previously mentioned, various respiratory manifestations in NF1 include chest wall deformities, upper airway obstruction, primary pulmonary hypertension, central hyperventilation, diffuse interstitial fibrosis and bullae, either in combination or solitary [24]. Our patient had evidence of both an obstructive lung disease pattern as well as a later diagnosis of PAH.

PAH in NF1 is characterized by pulmonary artery pressure > 25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance of 240 dyn/s/cm² [6,15,16]. Patients with PAH and pulmonary arteriopathy associated with NF1 usually have a relatively poor long-term prognosis [9]. In addition to malignant peripheral nerve sheath tumors, vasculopathy is one of the most important causes of early death in patients with NF1 [8].

In spite of the unfavorable outcome, there exist specific treatment options for PAH as well as supportive management to achieve some improvement in symptoms. Because of the complexity of the condition, patients should be managed at a tertiary care center or institution that specializes in PAH [15,18]. Although specific pulmonary vasodilators including epoprostenol, bosentan and sildenafil are considered useful in the management, lung transplantation offers the ultimate cure [18].

4. Conclusion

PAH represents a rare, and oftentimes, fatal complication of NF1. This manifestation of NF1 is characterized by functional and hemodynamic instability. Specific PAH therapies have been shown to have only a moderate effect in this particular set of patients. Clinicians should be able to recognize the possible diagnosis of PAH in a patient with NF1, who presents with progressively worsening dyspnea. In addition to PAH, NF1 is thought to possibly play a role in the formation of various other manifestations of lung involvement. The purpose of this report is to shed light on different manifestations of NF1: pulmonary hypertension, and the need for further research to develop more effective therapeutic strategies, and obstructive lung disease as an NF1-related entity, which requires further research into the relationship between the two. Early recognition and diagnosis of these life-threatening associations requires an early referral of eligible patients for lung transplantation.

Disclosure of conflict

All authors have nothing to disclose. There is no conflict of interest.

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