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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 7 6% 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 sub pleural scarring without any signs of pulmonary embolism (Fig. 1). An echocardiogram (ECHO) was performed which revealed moderate to severe tricuspid regurgitation, with a tricuspid regurgitant jet velocity (V_{TR} 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 (PAP_s) was 89 mm.

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Table 1
Clinical features, demographics and outcome of PAH in NF1 cases reported.

First author	Sex	Age (years)	CT scan	Outcome
Porterfield [10]	Female	56	Interstitial markings in lower lobes, bullae in apex	
Samuels [11]	Male	51	Bilateral perfusion defects	Improvement after endarterectomy
Aoki [12]	Female	16	Normal	Aggravation and then treatment with IV prostanoids. Death 2 years after the diagnosis.
	Female	70	Normal	Aggravation and then treatment with IV prostanoids.
Garcia Hernandez [27]	Male	44	Normal	Improvement and then death some years after diagnosis.
Engel [14]	Female	60	Lung cysts and T-7 schwannoma	Clinical improvement
	Female	69	Normal	Clinical improvement
Stewart [9]	Female	72	Mosaic perfusion	Death from respiratory failure
	Female	56	Mild ground glass attenuation in the upper lobes and lung cysts	Death 2 years after diagnosis from respiratory failure
	Male	68	Lung cysts	Death 6 years after diagnosis from RH failure
	Female	33	Mosaic perfusion	Death 1 year after starting treatment with ERA and PDE5 inhibitor
Simeoni [1]	Female	51	Nodular lesions and schwannoma in the upper mediastinum	Stable after 2 years of treatment
Montani [17]	Female	59	Normal	Death after 6 months
	Female	63	Moderate pulmonary fibrosis with large bullae	Death after 42 months
	Female	53	Lung cysts and interstitial infiltrate	Death after 46 months
	Female	69	Normal	Alive at 36 months, but more severe
	Male	66	Mosaic perfusion and mild emphysema	Alive at 8 months
	Female	63	Lung cysts	Alive at 18 months. On waiting list for lung transplant
	Female	53	Lung cysts	Alive at 3 months
	Female	61	Lung cysts and interstitial infiltrates	Alive at 8 months after diagnosis and 1 month after lung transplantation
Gumbiene [21]	Female	30	Mosaic perfusion	Death after 3 months
Malviya [28]	Male	34	Mosaic perfusion	Alive 8 months after diagnosis
	Male	33	Mosaic perfusion and localized fibrotic lesion	Alive after 15 months and improved
Tamura [29]	Female	30	NA	Alive 6 years after the diagnosis
Martignac [30]	Female	64	Lung cysts, ground-glass opacities and suspect mass	Death after 4 months
Kamdar [31]	Female	69	NA	Improvement and alive after 12 months
Giannakoulas [32]	Female	57	Normal	Improvement and alive after 24 months
Chaddha [33]	Female	63	Lung cysts, ground-glass opacities and interlobular septal thickening	Pulmonary edema under vasodilator. Death after three months
Kucuk [34]	Female	46	Mosaic perfusion pattern	Improvement
Poble [19]	Female	55	Lung cysts	Improvement and alive after 9 months
Palot [35]	Female	55	Intrathoracic meningocele and scoliosis	Improvement after 1 month

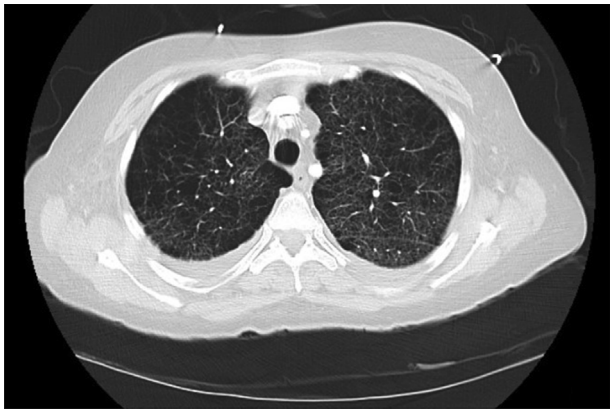

Fig. 1. CT chest depicting scattered bullous changes and posterior bilateral lower lobe basal sub-pleural atelectasis and/or scarring.

Hg (n = 18–25 mm Hg) [estimated $PAP_s = 4(V_{TR})$ 2 + estimated right atrial pressure; right atrial pressure was estimated at 20 mm Hg since the inferior vena cava was dilated]. The estimated mean pulmonary artery pressure (PAP_m) was 55.65 mm Hg (n = 12–16 mm Hg) [$PAP_m = 0.61xPAP_s + 2$]. 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, kyphoscholiosis, 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 hypoventilation, 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/cm [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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