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CASE REPORT

Neurofibromatosis type 1: a case highlighting pulmonary and other rare clinical manifestations

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SUMMARY

Neurofibromatosis type 1 (NF1)-related lung disease is a rare but increasingly recognised, high morbidity associated feature of the condition. We present a 48-year-old male patient with NF1, who was initially admitted for a subarachnoid haemorrhage requiring aneurysmal coil embolisation. During his recovery, he developed a left-sided pneumothorax requiring chest tube placement followed by concerns for re-expansion pulmonary oedema requiring intubation. Subsequently, the patient also developed a right-sided pneumothorax requiring additional chest tube placement but did not develop right-sided pulmonary oedema. During his hospitalisation, the patient also exemplified other important NF1-related pathophysiology including pheochromocytoma, cerebrovascular abnormalities and cardiovascular manifestations. Due to his multiple comorbidities and poor prognosis, we held a goals of care discussion with the patient's mother, and with her agreement, the patient underwent compassionate withdrawal of artificial life support.

BACKGROUND

Neurofibromatosis type 1 (NF1), formerly known as von Recklinghausen's disease, is an autosomal dominant condition caused by mutations in the *NF1* gene. The prevalence of NF1 is approximately 1:3000 to 1:4000. NF1 affects males and females equally and affects individuals of all racial and ethnic backgrounds.[1] The criteria for diagnosis of NF1 were developed by the National Institutes of Health Consensus Development Conference in 1987 and require an individual to have two or more of the following major clinical features:

- six or more café-au-lait macules >5 mm in greatest diameter in prepubertal patients and >15 mm in postpubertal patients;.
- two or more neurofibromas or one plexiform neurofibroma;
- skinfold (axillary or inguinal) freckling;
- optic pathway tumour;
- two or more iris hamartomas;
- characteristic bony lesion;
- first-degree relative with NF1.

Thoracic manifestations of NF1 are well described and include cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis and ribbon deformity of the ribs.[2 3] In contrast, pulmonary manifestations are less frequently reported. NF1-related lung disease is a rare but increasingly recognised, high morbidity associated feature of the condition. As a result, we present a case report of a patient with an interesting pulmonary manifestation of NF1 as well as other NF1-associated pathology.

CASE PRESENTATION

The patient is a 48-year-old male with NF1, diagnosed in childhood by his paediatrician, and a 33 pack-year smoking history who developed a severe headache while watching television that lasted for 4 days with progression to double vision. The patient had not seen a doctor for several years prior to presentation. The patient presented to the emergency room and was found to have a left anterior communicating artery aneurysmal subarachnoid haemorrhage. He subsequently underwent aneurysmal coil embolisation. The patient developed postprocedural embolic strokes in the left hemisphere confirmed on brain MRI resulting in right-sided hemiplegia. Physical examination during hospitalisation also showed multiple café-au-lait macules, bilateral inguinal freckling and diffuse cutaneous neurofibromas, diagnostic for NF1.

The patient was recovering appropriately in a rehabilitation unit for poststroke care for approximately 2 weeks when he developed sudden onset chest pain. Cardiac workup revealed negative troponin with ECG showing sinus tachycardia. Two days later, while in bed, the patient reported sudden onset, pressure-like left-sided chest pain lasting about 2 hours. A chest X-ray showed a left-sided tension pneumothorax and a left chest tube was placed with subsequent lung expansion. Echocardiogram showed left ventricular hypertrophy with impaired diastolic function that persisted even when the tamponade physiology resolved.

The next evening, the patient developed worsening hypoxia requiring emergent intubation and placed on assist control volume control mechanical ventilation. Repeat chest X-ray showed prominent pulmonary vasculature with worsening left lung opacities thought to be due to re-expansion pulmonary oedema. Intravenous furosemide and nitroglycerin drip was started as supportive therapy. The following morning, he developed a right pneumothorax with mediastinal shift requiring chest tube placement. A follow-up chest X-ray, seen in figure 1, showed patchy consolidation of the left lung and re-expansion of the right lung. Further characterisation on CT scan can be seen in figure 2.

During the remainder of the hospital course, the patient had transient episodes of hypertension with blood pressure values reaching as high as

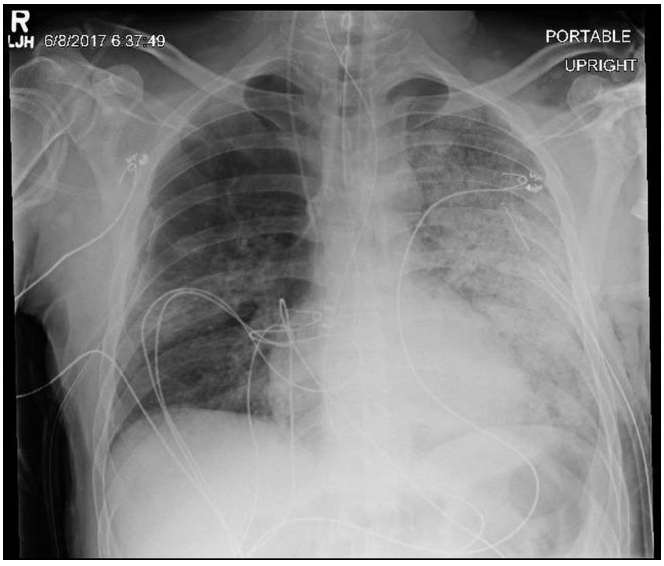

Figure 1 Portable anteroposterior chest X-ray showing asymmetric pulmonary oedema with bilateral chest tube placements.

236/123 mm Hg. His CT scans demonstrated new bilateral anterior cerebral artery infarctions with concerns for haemorrhagic conversation seen in figure 3 and an incidental adrenal mass seen in figure 4. Plasma metanephrine was elevated at 1.97 nmol/L (0.00–0.49 nmol/L), consistent with pheochromocytoma.

OUTCOME AND FOLLOW-UP

A goals of care discussion was held with the patient's mother with the assistance of the palliative care team, and the patient underwent compassionate withdrawal of artificial life support. Prior to extubation, the patient was started on a morphine and versed drip for comfort measures. The patient died 20 min after the removal of the endotracheal tube with his mother at the bedside.

DISCUSSION

We present a case report in which we believe NF1-related pulmonary pathology has led to a patient's morbidity and mortality. Scant literature exists regarding the prevalence, clinical characteristics and pathophysiology of NF1-related pulmonary disease. Pulmonary findings have included both interstitial fibrosis that is usually bilateral with basal predominance and emphysematous bullae formation with upper lobe predominance harbouring mycetomas.[3] High-resolution chest CT of patients with NF1 may show bullae, cysts, emphysema, bibasilar reticular opacities and/or ground glass opacities. Lung biopsy may show interstitial fibrosis. The relationship between smoking and NF1-related lung disease is also unclear; smoking may increase the risk for lung disease in patients with NF1 and conversely, NF1 may increase the risk of smoking-related lung disease.[4] Further research is warranted to address this association. Chest CT for our patient demonstrated severe paraseptal and centrilobular emphysema, which may have contributed

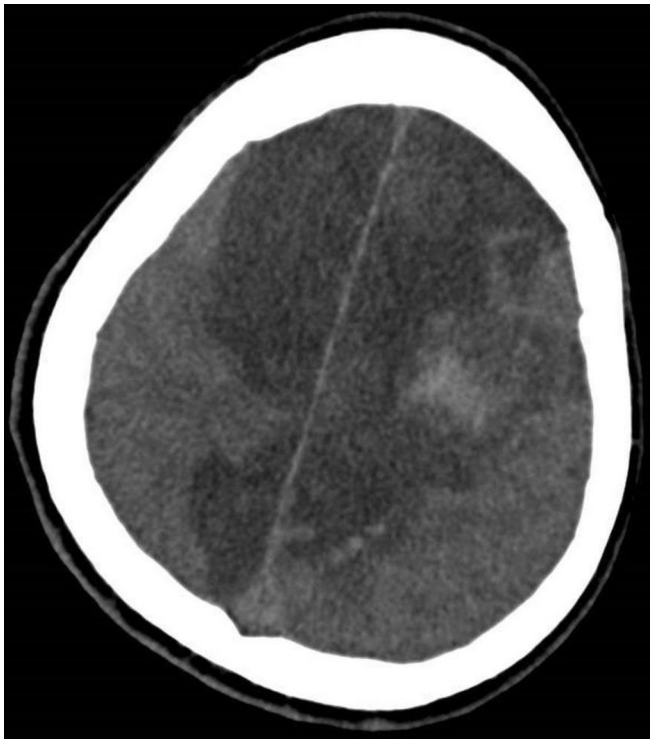

Figure 3 Head CT showing bifrontal foci of decreased attenuation with haemorrhage more prominent on the left.

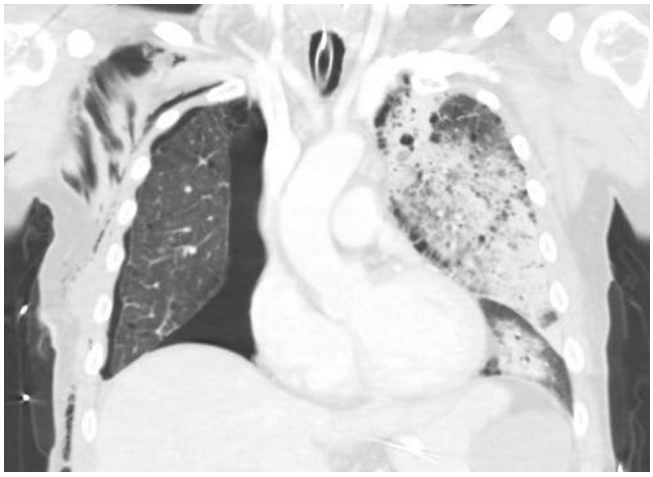

Figure 2 Chest CT showing moderate right pneumothorax and ground glass opacities in left upper lobe. Several pneumatoceles and severe paraseptal emphysema are noted.

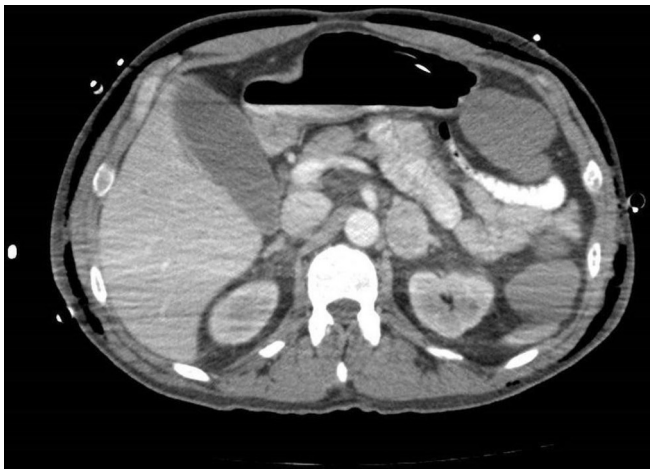

Figure 4 A left adrenal nodule on CT measuring 2.8×3.3 cm, 125 Hounsfield units.

to his increased risk for development of pneumothoraces and clinical decompensation. Given these findings, we suspect that both his extensive smoking history and underlying NF1-related lung pathology contributed to the development of his pneumothoraces.

In addition, the patient developed what we believe was re-expansion pulmonary oedema (RPE) of the left lung given the timing of the inciting event of chest tube placement. The pathogenesis of RPE is multifactorial defined primarily by the alteration of capillary permeability and the increase of hydrostatic pressure. One of the major contributing factors in the development of RPE is the chronicity of the collapse, usually more than 3 days.[5] Prolonged collapse causes local hypoxaemia and decreased surfactant production. Ultimately, there is release of inflammatory mediators including interleukin-8, monocyte chemoattractant protein-1 and free radicals that alters the capillary permeability. Pulmonary re-expansion on chest tube placement then not only further induces abrupt alveolar distension but also increase blood flow to the lung capillary pressure followed by an increase of hydrostatic pressure. This leads to increase of fluid and protein overflow into the interstitial and alveoli spaces.[6] Treatment measures for RPE primarily consist of supportive measures including oxygen supplementation, ventilator support, inotropic agents and diuretics.

Briefly, we will cover the remaining interesting manifestations of NF1 in our patient. Our patient had several episodes of paroxysmal hypertension late in his hospital course and an incidental adrenal mass noted on abdominal CT. The plasma metanephrine collected showed a significant increase in comparison to normal, consistent with pheochromocytoma; but unfortunately, we were unable to obtain a 24-hour urine fractionated metanephrines and catecholamines sample prior to the patient's death. Pheochromocytoma is generally a rare feature of NF1, present in 0.1%–5.7% of patients; however, in the setting of hypertension this risk increases to 20%.[7] NF1 is also associated with an increased risk for cerebral vascular abnormalities including anatomically variant cerebral arteries, ectatic vessels and intracranial aneurysms.[8 9] Our patient's finding of intracranial aneurysms may or may not have been related to his underlying diagnosis of NF1; however, the concomitant pheochromocytoma likely increased his risk for intracranial aneurysmal rupture and cardiomyopathy due to paroxysmal hypertension. Other cardiovascular manifestations associated with NF1 include pulmonary stenosis, aortic coarctation and catecholamine-induced cardiomyopathy in patients with pheochromocytoma.[10 11]

Our justification for withdrawing artificial life support was in line with the wishes of the patient's mother, his medical decision-maker. Given the patient's brain infarctions and haemorrhages, his return to baseline function is impossible. Although his lung dysfunction might improve, he would require long-term tracheostomy and percutaneous endoscopy gastrostomy support. His mother understood these options and declined them for she feels he is unnecessarily suffering; therefore, she opted for compassionate withdrawal of artificial life support.

CONCLUSION

Our case report demonstrates several rare but serious manifestations of NF1. Our case highlights the contribution of NF1-related lung disease to patient morbidity and mortality. The relationship between smoking and NF1-related lung disease is unclear; however, advising patients to avoid or stop smoking would be prudent. New-onset headache or hypertension in individuals with NF1 is a medical emergency and may indicate a life-threatening complication of the disorder. Finally, patients with NF1 require lifelong care with genetics, neurology or other specialist familiar with the disorder in order to guide appropriate anticipatory management and surveillance of NF1-related complications.

Patient's perspective

Patient's mother:
Prior to the aneurysm and stroke on 19 May, my son was hardly ever sick. After being in the intensive care unit (ICU) for 10 days and the stroke ward for 5 days, he was moved to rehab on 1 June where he was doing well. So I was surprised and frustrated when on 6 June he was moved back to ICU because his left lung had collapsed and pushed his heart into the right cavity. His right lung filled with fluid/he was intubated and put on a ventilator. He was also heavily sedated so I could not communicate with him. On 13 June, he had another brain bleed. I was told he would not walk again and would probably lose use of his arms and not speak again. I made the sad and difficult decision to take him off the ventilator on 16 June. He passed way 20 min later while I held him and cried.

Learning points

- Pulmonary manifestations of neurofibromatosis type 1 (NF1) may include both interstitial fibrosis and emphysematous bullae formation with an unclear relationship to smoking.
- The cause of re-expansion pulmonary oedema is primarily due to the alteration of capillary permeability and the increase of hydrostatic pressure with chronicity of lung collapse as a significant risk factor.
- Pheochromocytoma is a rare manifestation of NF1 but must be taken into consideration in the setting of transient episodic hypertension and may confound other possible cerebrovascular and cardiovascular abnormalities associated with NF1.
- Lifelong anticipatory care from specialists in the field of genetics, neurology, and other specialists with knowledge of the disorder is critical to the management of patients with NF1.

Contributors KAN was involved in drafting the case report. ME, NMG and MT was involved in the clinical expertise in revising for important intellectual content. All authors contributed to the conception, acquisition of data and interpretation of data. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

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