Bullous lung disease in association with an isolated giant plexiform neuroma: A case report and brief review of pulmonary involvement in neurofibromatosis type 1

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Neurofibromatosis is common. It can be accompanied by abnormalities related to the thorax. These vary in severity and can be life-threatening. We present a case of plexiform neuroma with associated extensive bullous lung disease.
Keywords. isolated plexiform neuroma; bullous lung disease.

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Case

A 41-year-old male patient with a large plexiform neuroma involving the right arm was referred to our respiratory clinic with a long-standing dry cough and progressively worsening and severe shortness of breath. The symptoms had been ongoing for approximately 9 years, and he was now breathless at rest. He had no associated orthopneoa, paroxysmal nocturnal dyspnoea or ankle swelling. There was no previous history of cardiac disease. He is a life-time non-smoker and has no history of substance abuse. He had no environmental or occupational exposures of note. There was family history of emphysema.

Clinically, he was breathless at rest and centrally cyanotic. He was in overt right heart failure. There was no digital clubbing or lymphadenopathy. His chest was hyperinflated and there was clinical pulmonary hypertension. The plexiform neuroma involving his right arm was evident. Café au lait macules were conspicuously absent and there were no other nodules on the body.

Pulmonary function tests were not performed as the patient was seen amid the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic. His alpha-1 antitrypsin level was normal, and he was non-reactive for the retroviral disease. His arterial blood gas showed severe hypoxaemia with carbon dioxide retention (partial pressure of O_2 (PaO_2) = 5.44 kPa; $PaCO_2$ = 7.17 kPa; pH = 7.357; and bicarbonate ion = 30.1 mmol/L).

A computed tomography (CT) scan of the chest showed scattered bullous changes and prominent pulmonary arteries (Figs 1 and 2). He was treated for right heart failure and arranged for long-term oxygen therapy.

Discussion

Neurofibromatosis type 1 (NF1) affects ~1 in 2 000 - 3 000 live births.[1] Approximately half of the cases are sporadic, and the other half are familial with autosomal dominant inheritance. Penetrance is complete but the clinical manifestations and disease severity are variable, even within the same family.[2]

Plexiform neuromas are among the most common and debilitating complications of NF1. They occur in about 30% of patients with NF1, and they have been described to occur in isolation.[3,4] They are benign, diffuse tumours, originating from nerve cell sheaths and can involve multiple fascicles. They are subject to malignant transformation.

The first description of pulmonary involvement in patients with NF1 was over half a century ago.[5] Since then, there have been several case series and case reports worldwide. We are aware of only one case report in South Africa that was described >30 years ago, and it is believed that there are likely to be more.[6]

Thoracic involvement can be severe and life threatening.[7,8] Virtually all components of the thorax can be involved. The abnormalities have

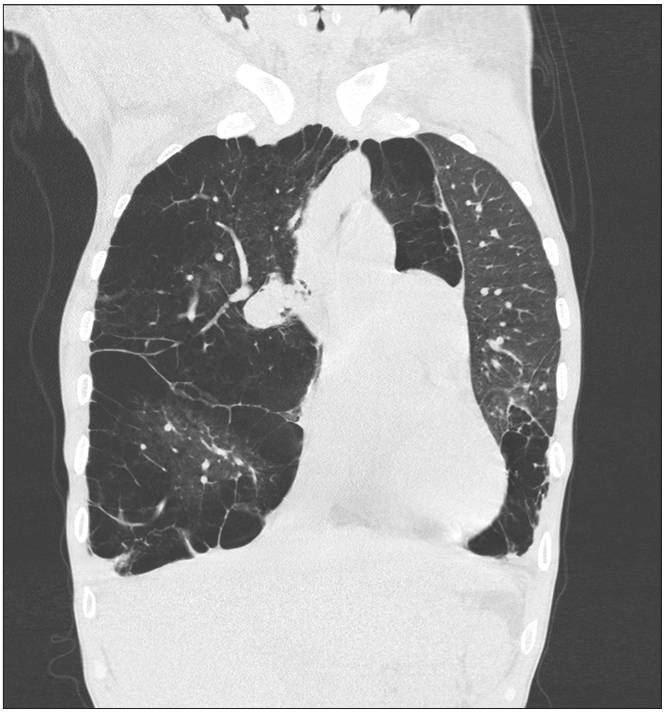

Fig. 1. Coronal cut showing extensive bullous changes.

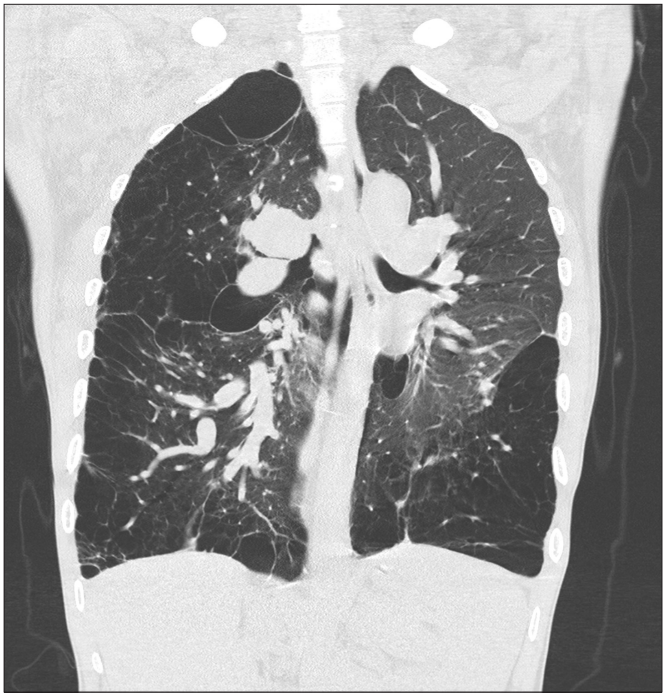

Fig. 2. Coronal chest computed tomography cut showing marked dilatation of pulmonary arteries.

been clearly demonstrated on high-resolution chest CAT scans, and in some cases, surgical lung biopsy.[9,10]

Neurofibromas can be found in the skin and subcutaneous tissue of the chest wall.[9] Defects in the development of the thoracic skeleton lead to varying degrees of kypho-scoliosis, vertebral abnormalities, and characteristic rib deformities.[11]

Neurofibromata arising from the pleuro-parenchymal nerves, as well as endobronchial neurofibromata have been described, although these are rare.[12] An association between NF1 and lung cancer has been proposed following reports of a few scattered cases of NF1 and lung cancer.[13,14] Additional studies with larger cohorts are necessary to firmly establish NF1 as a risk factor for lung cancer

Diffuse parenchymal lung disease occurs in ~10 - 20% of individuals.[13] Pathologically, interstitial fibrosis with lympho-plasmocytic inflammation consistent with nonspecific interstitial pneumonitis has been described.[10,13] The interstitial reticulations predominate at the lung bases. The pathogenesis of the fibrotic process is thought to be secondary to the mesenchymal defect that leads to primary deposition of collagen.[10] Elevated serum levels of nerve growth factor have also been described. This factor is known to directly stimulate fibroblasts differentiation into more pro-fibrogenic myofibroblasts.[15] Other interstitial/parenchymal findings have included micro-nodules, ground-glass opacities, cysts, emphysematous bullae, and honeycombing.[10] The cysts have tended to predominate in the upper lung fields in the central and subpleural locations.

Mediastinal lesions in the form of neurofibromata, malignant peripheral nerve tumours and lateral meningocoeles have been observed.[10]

Pulmonary arterial hypertension is a rare but serious complication of NF1 and carries a poor prognosis.[8] Its pathogenesis is not clearly understood and likely multifactorial. While it may be secondary to the architectural distortion and hypoxia resulting from the underlying lung disease, pulmonary vasculopathy associated with NF1 has also been postulated.[16] NF1 has a well-known association with systemic vasculopathy, affecting multiple vessels. In addition, neurofibrin, an *NF1*-encoded protein, is expressed in endothelial and smooth-muscle cells. It regulates cell growth and proliferation, and its deficiency is expected to interfere with the response of these vessels to growth suppressor signals.[16]

The general care of adult patients with NF1 is summed up in guideline documents.[17] Targeted treatment of the specific thoracic complication is largely the same as pathologically similar pulmonary problems in the general population. Patient education is important in relation to the use of tobacco products and timely report of respiratory symptoms. Routine radiological screening for the chest manifestations is not recommended by most NF1 guidelines.[17] However, it remains advisable for patients to be offered regular clinic visits so complications can be detected early and appropriate treatment, where available, initiated timeously.

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