

VON RECKLINGHAUSEN'S DISEASE WITH INTERSTITIAL LUNG DISEASE (ILD): A RARE ASSOCIATION

Neel Jayesh Thakkar¹, Ketaki Utpat², Unnati Desai³, Jyotsna M. Joshi⁴

¹Senior Resident, Department of Pulmonary Medicine, Topiwala National Medical College, Mumbai, India.

²Assistant Professor, Department of Pulmonary Medicine, Topiwala National Medical College, Mumbai, India.

³Associate Professor, Department of Pulmonary Medicine, Topiwala National Medical College, Mumbai, India.

⁴Professor and Head, Department of Pulmonary Medicine, Topiwala National Medical College, Mumbai, India.

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PRESENTATION OF THE CASE

Von Recklinghausen's Disease or Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder that is characterized by cutaneous, skeletal, nervous system tumours and pulmonary manifestations. Pulmonary manifestations include fibrosis, lung parenchymal nodules, bullous lung disease and rarely Interstitial Lung Disease. (ILD). NF1 related ILD has been reported previously in upto 60 cases with variable patterns radiologically but frequently confounded by smoking related changes and rarely proven on biopsy. Diagnosis is based on defined clinical criteria of NF-1 with characteristic radiology and confirmed on histopathology with a lung biopsy. We hereby report a noteworthy case of NF1-ILD with non-specific interstitial pneumonitis (NSIP) pattern in a non-smoker female with typical cutaneous and oculars features with a diagnosis attained by a multidisciplinary approach and an amalgamation of radiology and histopathology.

A 48-year-old housewife presented with progressive exertional dyspnea and dry cough since 8 years which had increased since 6 months. She had been on inhaler therapy since 7 years intermittently with little benefit. She had been diagnosed as NF1 at the age of 35, and later detected to have systemic hypertension since 1 year. She gave history of occupational exposure to fire extinguisher powder at work place. On examination, she had grade III clubbing, exertional desaturation (70% post exertion) with a six-minute walk distance (6MWD) of 360 m. She had characteristic skin lesions including multiple neurofibromas over face, neck, trunk, axilla, shoulders and back and a large plexiform neurofibroma over her right thigh (figure 1a). She had multiple Café-au-lait spots (>6) over her back, axilla and shoulder with axillary freckles on both the sides (figure 1b). Respiratory system examination showed diminished chest expansion with bilateral end inspiratory fine crepitations best heard in infrascapular regions.

On ophthalmic evaluation, her slit lamp examination showed presence of the classical Lisch nodules in the eye (figure 4).



Figure 1a. Image showing Multiple Neurofibromas on the Back



Figure 1b. Image showing Axillary Freckles



Figure 1c. Cafe Au Lait Spots

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Corresponding Author:

Dr. Neel Thakkar,

#602, Royal Accord Apartments,

Opp. Shivsena Bhavan,

Dadar West- 400028, Mumbai.

E-mail: neeljthakkar@gmail.com

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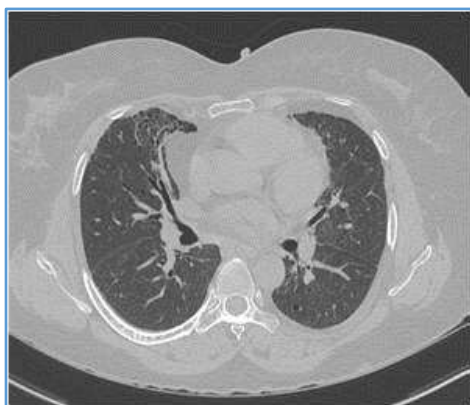


Figure 2. High Resolution Computed Tomography (HRCT) Thorax Showing Interstitial Septal Thickening, Ground Glass Attenuation in both the Lungs and Ill-Defined Bronchocentric Nodules with Sub-Pleural Sparing

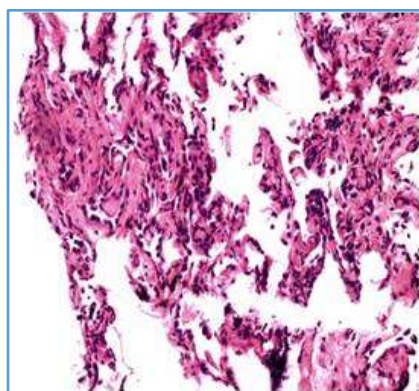


Figure 3. Trans-Bronchial Lung Biopsy (TBLB) Slide Photomicrograph showing Features Suggestive of Thickened Peribronchiolar Alveolar Septa with Patchy Fibrosis in Interstitium, Lymphocytes, Anthracotic Pigment Laden Macrophages and Plasma Cells Infiltration

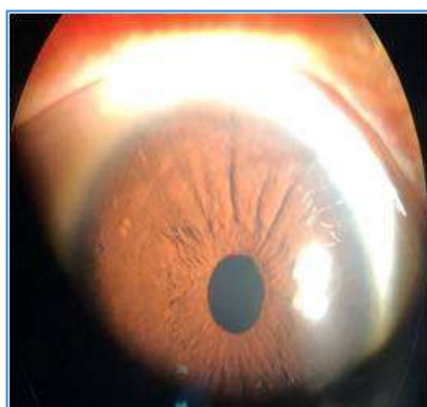


Figure 4. Lisch Nodules

PATHOLOGICAL DISCUSSION

Chest Radiograph (CXR) suggested bilateral reticulonodular opacities. It was followed by a High-resolution Computed Tomography (HRCT) of thorax (figure 2) which showed interstitial septal thickening, ground glass attenuation in both the lungs and ill-defined bronchocentric nodules with sub pleural sparing. Her spirometry showed a restrictive

deformity with forced expiratory volume in first second (FEV1) to forced vital capacity (FVC) ratio of 0.9, FVC of 1.48 liters (48% predicted) with FEV1 of 1.32 liters (50%). A fiber optic bronchoscopy (FOB) guided trans bronchial lung biopsy (TBLB) was performed, which showed a normal end bronchial tree with the biopsy histopathology (figure 3) suggestive of thickened per bronchiolar alveolar septa with patchy fibrosis in interstitium, lymphocytes, anthracotic pigment laden macrophages and plasma cells infiltration, suggestive of NF-1 related ILD. On cardiac evaluation her two-dimensional echocardiography (2D Echo) showed mild pulmonary artery hypertension with a tricuspid regurgitation (TR) jet estimated pulmonary artery systolic (PASP) pressure of 45 mm Hg. She was assessed with polysomnography (PSG) in view of her snoring. The PSG revealed oxygen desaturation index of 18 with lowest saturation 79% suggestive of nocturnal sleep related desaturation. Pulmonary rehabilitation was done, and nocturnal oxygen therapy was prescribed.

The neurofibromatosis (NFs) are among the most common neurogenetic disorders and represent a group of autosomal-dominant diseases that have widespread effects on neuroectodermal and mesodermal tissues. There are two main forms of NF which are recognized, NF type 1 (NF1) and NF type 2 (NF2) whose genes are localized on chromosome 17q11 and on chromosome 22q respectively. NF1 and NF2 genes appear to function as tumor-suppressor genes, and their respective gene products have been named neurofibromin and merlin (or schwannomin) respectively. Von Recklinghausen's disease or NF1 is a multisystem genetic disorder due a mutation in the gene on the long arm of chromosome 17 causing dysplasia of ectoderm and mesoderm with a variable clinical expression characterised by collections of neurofibromas, cafe'-au-lait spots and pigmented hamartomas in the iris (Lisch nodules).¹ Incidence of NF-1 is 1 in 2500–3000 and in 30–50% of cases there is no family history of the disease.² About half of the cases are familial with an autosomal dominant inheritance, the rest are due to spontaneous mutations. Although thoracic manifestations are diverse and quite common, the involvement of lung parenchyma in NF1 appears to be rare. In NF1, the thorax and lungs can be affected in several ways. Cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis, meningoceles, ribbon deformity of the ribs, intrathoracic neurogenic tumours and interstitial lung disease (ILD) are the various manifestations seen.³ Among these, approximately 60 NF1- related diffuse lung disease cases have been individually reported, but few have been proven on high resolution computed tomography (HRCT) and lung biopsy.⁴ Here we elicit one such case report with clinical evidence of NF1 with a paradigm of patterns on radiology and histopathology.

The biological rationale behind the causal association NF and ILD is ambiguous and lacks strong evidence. There have been various hypothesis postulated. The cause of pro fibro genic state in NF-ILD can be explained due to a mesenchymal defect resulting in primary deposition of collagen along with a fibrotic environment in some cases.

These are similar to the findings in our case where the pigment laden macrophages in the background of NSIP are likely due to exposure to fire extinguisher powder. The fire extinguisher powder has been associated with changes of ILD specifically diffuse interstitial pneumonia (DIP) especially in non-smokers.⁸ A similar association has been explored by Uddeen et al where a combination of NSIP and respiratory bronchiolitis associated ILD (RB-ILD) pattern was observed in an elderly female.⁹ In his report, radiology showed numerous sub pleural cystic foci with upper lobe predominance and patchy ground glass opacity throughout the lungs. The surgical lung biopsy demonstrated extensive sub pleural blebs/ bullae with background non-specific interstitial pneumonia (NSIP) pattern (fibrotic variant) of the right upper lobe and respiratory bronchiolitis of the right middle lobe.

This is similar to the NSIP pattern observed in our case which is not as common in smokers as desquamative interstitial pneumonia (DIP), RB-ILD or UIP patterns which more frequently associated with smoking as per Vasallo's classification. The PH encountered in NF and associated ILD is usually mild however cases reporting a severe PH and cor pulmonale have also been described suggesting that the disease can have a morbid course if not addressed early.¹⁰ The clinical, radiological and histopathological correlation in our case definitely suggests a relation between NF-1 and interstitial lung disease with an NSIP pattern even in presence of confounders like her exposure to fire extinguisher powder. A systematic approach, precise radiology and definitive histopathology are essential tools in identifying specific association between a rare disease and its rarer demeanour of pulmonary features.

Neurofibromatosis-associated interstitial lung disease (NF-ILD) was first described in 1963 by Davies, and over the following decades, other reports have described the association between NF and ILD. Some of these have been incidental case reports; however most of the patients were symptomatic with dry cough and progressive dyspnea on exertion. Our patient was diagnosed as neurofibromatosis based on the diagnostic criteria⁵ of NF1, with >6 café-au-lait spots more than 15mm in size, >2 axillary freckles, scattered neurofibromas over entire body, one plexiform neurofibroma as well as more than 2 Lisch nodules in both eyes. NF1 can affect the lungs and thorax in numerous ways including cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis, ribbon deformity of the ribs, thoracic neoplasms and ILD.³ Parenchymal lung involvement has been detected by chest radiography in 7 to 23% of adult patients with NF in its three largest surveys.⁶ There has been a debate on whether NF-DLD is a primary manifestation of NF. Also, there is paucity of literature pertaining to the exact biological association. Ryu et al argued that the association seen in previous reports may be due to confounders like smoking induced manifestations.⁷ However Zamora et al in his case series and elucidation postulated that NF associated ILD is a distinct entity and the association could be causal.⁴ In his case series the most common radiological findings were bullae predominantly upper lobe followed by basilar

reticulations, ground glass opacities and rarely honeycombing. In contrast our patient showed no such localization of lesions with intralobular interstitial thickening, ground glass opacities, nodules and thin walled cysts seen across both lungs. The borders of the cysts and bullae are thicker and more sharply defined in NF-ILD than is seen in smoking-related emphysema. The differentiation from smoking related changes from NF1-ILD can also be made using histopathology where NF1-ILD has been shown to be associated with alveolar septal lymphoplasmocytic inflammation and fibrosis consistent with nonspecific idiopathic pneumonia (NSIP) pattern compared to intra-alveolar accumulation of pigmented macrophages in smokers.⁶

DISCUSSION OF MANAGEMENT

The management of NF-ILD in our case included low dose maintenance steroids, measures for pulmonary rehabilitation including diet, nutrition, chest physiotherapy, vaccination and assessment for long term oxygen therapy. The patient was investigated for comorbidities associated with chronic respiratory disease and was found to have mild pulmonary artery hypertension, vitamin D deficiency and osteoporosis with a T score on DEXA scan < -2.5. She was given Vitamin D supplementation and subsequently bisphosphonates for the same. ABG showed a low PaO₂ with a raised A-a gradient, she underwent aa level III sleep study which showed an ODI of 7.8 with lowest saturation 79%, she was initiated on overnight LTOT. She was advised routine follow up to look for progression of pulmonary and extra pulmonary lesions, regular eye check-up to rule out optic nerve lesions as well as to screen for secondary causes of hypertension such as associated pheochromocytoma and renal artery stenosis which have been found to be associated with Neurofibromatosis.

The clinical, radiological and histopathological correlation in our case definitely suggests a relation between NF-1 and interstitial lung disease with an NSIP pattern even in presence of confounders like her exposure to fire extinguisher powder. A systematic approach, precise radiology and definitive histopathology are essential tools in identifying specific association between a rare disease and its rarer demeanour of pulmonary features.

FINAL DIAGNOSIS

NF1 related Intestinal lung disease (NSIP Pattern).

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