Neurofibromatosis And The Lung : An Interesting Case

Dr KapilIyer , Dr Mahesh Jansari ,Dr SwapnilKulkarni
Department of Pulmonary Medicine,
ESI Hospital, LBS Road, Mulund West, Mumbai – 400080, Maharashtra, India.

iyerkapil@gmail.com
xangpongmak@gmail.com
drswapnilkulkarni@gmail.com

Corresponding author :Dr KapilIyer
501 Spring Leaf, Military Road, Marol, Andheri East, Mumbai – 400059, Maharashtra, India.

Abstract :
Neurofibromatosis is an inherited disease, having a predilection for tumour formation.(1) These diseases were previously referred to as “phakomatoses” or neurocutaneous syndromes. The clinical spectrum of these diseases usually involves the nervous, locomotor and cutaneous systems. However the involvement of the nervous system is very dangerous, and is often the leading cause of mortality in this condition. It disturbs cell growth in the nervous system which leads to the formation of tumours, either malignant or benign, on nerve tissue. The involvement of the respiratory system in these patients is very rare. We present an interesting case of a patient with neurofibromatosis induced diffuse parenchymal lung disease.

Keywords : neurofibromatosis, diffuse parenchymal lung disease, café au lait spots.

Introduction :
Neurofibromatosis, which was first described in 1882 by Von Recklinghausen, is a genetic disease characterized by a neuroectodermal abnormality and by clinical manifestations of systemic and progressive involvement which mainly affect the skin, nervous system, bones, eyes and possibly other organs. The disease may manifest in several ways and it can vary from individual to individual. However till date the respiratory manifestations of this disease have been extremely rare and seldom reported. Most cases are diagnosed by paediatricians, especially in patients with multiple skin lesions. In some patients, however, the disease is diagnosed in adult life or remains undetected which is due to its clinical heterogeneity and symptom variability. The following case of neurofibromatosis type 1 induced diffuse parenchymal lung disease was diagnosed in a patient attending our out patient department.

Case report :
A 51 year old woman, housewife, non smoker, was referred to our out patient department in view of chest x ray changes. She had complaints of cough, predominantly dry, associated with progressive breathlessness on exertion since the past 5 years. She did not give any history of acute increase in respiratory complaints.

On examination, she was conscious and well oriented in time, place and person. Her oxygen saturation was 96% at room air, and her blood pressure was 110/80 mm Hg. She did not exhibit cyanosis, clubbing, lymphadenopathy or pedal edema. She had multiple cutaneous outpouchings especially on her face and extremities (Figure 1), along with hyperpigmented macules all over her back. On auscultation she had bilateral basilar crackles. Her chest x ray revealed bilateral fibrocystic changes, with loss of volume on left side (Figure 2). Her past history was unremarkable for any other disease. She denied a past history of tuberculosis, which was reverified by separate questioning of first degree relatives.

The patient was hospitalised for further evaluation. Her haematological and biochemical parameters were within normal limits. Her arterial blood gas was also normal. Her sputum was negative for acid fast bacillus. A high resolution computed tomography of thorax revealed bilateral diffuse cystic changes accompanied by septal thickening at the bases (Figure 3). Spirometry showed severe restrictive ventilatory defect, with a Forced vital capacity (FVC) of 0.42 litres or 19%, a forced expiratory volume in first second (FEV1) of 0.39 litres or 21%, and a FEV1/FVC ratio of 93. There was poor bronchodilator reversibility Her connective tissue disease profile was negative. A dermatological reference confirmed that her cutaneous findings were typical of neurofibromatosis.

She was thus diagnosed as a case of neurofibromatosis (type 1), (based on the diagnostic criteria)[2] induced diffuse parenchymal lung disease. She had multiple superficial cutaneous as well as subcutaneous neurofibromas, along with...
multiple café au lait spots, the largest being more than 2 cms in dimension.

Figures:

Figure 1: Cutaneous neurofibromas.

Figure 2: Chest x-ray showing bilateral fibrocystic changes, left more than right.

Figure 3: High resolution computed tomography of thorax shows bilateral diffuse cystic changes along with a cutaneous tag.

Discussion:

Neurofibromatosis type I (von Recklinghausen disease) is a genetically determined disease with complex symptomatology concerning multiple organs of neuroectodermal origin. This group of diseases is also commonly called phakomatoses, from the Greek phakos meaning “stigmatized at birth”. The main symptoms concern skin, nervous system, bones and eyes. However it very rarely affects the lungs. Neurofibromatosis type 1 has autosomal dominant inheritance and has an incidence of 1:3,500 live births.

Descriptions of individuals, probably having neurofibromatosis have been discovered in manuscripts dating from 1000 AD.[5] In fact the oldest cases about the disease appear in the literature, described by Madigan, Schaw, and Masello on “Neurofibromatosis in the 13th Century and Report of NF-Like Case - Monstrorum History” – in Neurofibromatosis, vol.1 and 2, 1988.[6,7] In 1882 – Friederich Daniel Von Recklinghausen recognized NF as a nosological entity by describing two cases of multiple neurofibromatosis, and postulated that tumors along major peripheral nerves and also false skin neuromas originate from the connective tissue of nerve sheaths and nerve plexuses, particularly perineural and endoneural. In fact he was the first person to coin the term “neurofibroma”. [8,9]

The gene responsible for the development of neurofibromatosis type 1, is known as NFI, is located on the long arm of 17th chromosome, and encodes a protein known as neurofibromin. [10,11] This protein is predominantly expressed in neurons, Schwann cells and astrocytes. [12] Oncogenic mutations in Ras genes or inactivation of NFI gene leads to a permanent stimulation of a cascade of signals
and excessive cell division, leading to the formation of tumors.[13]

The main clinical manifestations can be subdivided as:

- **Cutaneous** – there are various cutaneous manifestations which chiefly include neurofibromas, café au lait spots and axillary freckling. There are four types of neurofibromas:
  1. Superficial cutaneous neurofibromas, soft and buttonous;
  2. Subcutaneous neurofibromas – deeper, in the dermis adjacent to subcutaneous nerves with direct involvement of the nerve roots and routes, and which are often accompanied by localized pain;
  3. Nodular plexiform neurofibromas – they form an extensive network in the subcutaneous tissue;
  4. Diffuse plexiform neurofibromas – they compromise all layers of the skin and can penetrate deep into the muscles, bones and also involve, depending on location, the viscera.[14]

Café au lait spots are harmless, brownish hyperpigmented macules which are usually present at birth, or may develop during adolescence. The presence of more than six spots greater than 0.5 cm in diameter before puberty or greater than 1.5 cm in diameter after puberty is suggestive of Neurofibromatosis type 1. Their presence in the axillary region, constituting the so-called ephelides or axillary freckling, is considered pathognomonic of this disease.[15,16]

- **Neurological** – these chiefly include neurofibromas (as already described), brain tumors, learning disabilities, macrocephaly, epilepsy and spinal abnormalities.

- **Ophthalmological** – the presence of Lisch nodules are highly characteristic for this disease. They are well-defined, dome-shaped hamartomatous lesions of a gelatinous aspect projecting from the surface of the iris, varying in color from clear yellow to brown.[17,18] Rarely these patients may also present with optic gliomas.

- **Musculoskeletal** - Changes in other bones occur in less than 10% of cases. These changes are erosion of the periosseum by neurofibromas or in adjacent soft tissues, solitary cystic lesions or within the bone, disorders such as growth stunting or gigantism, increased striatal density of tubular bones, thinning and springing of the ribs and long bones.

The clinical manifestations of neurofibromatosis were classified by Huson (1994) in “major”, “minor” and associated complications.[19] The “major” manifestations are specific to NF, affect most patients and are the basis of the diagnostic criteria of the National Institute of Health (1988).[20] They are constituted by café au lait spots, axillary freckling, peripheral neurofibromas and Lisch nodules. The “minor” manifestations are specific to NF and also appear at a high frequency in those affected, but they are not used as diagnostic criteria. Macrocephaly and short stature are considered “minor” characteristics.

Our patient was diagnosed as a case of Neurofibromatosis type 1 as she satisfied 2 out of the 7 major criteria, which were the presence of neurofibromas and café au lait spots.

The affection of the respiratory system in these patients is extremely rare. However sporadic case reports of pulmonary manifestations due to neurofibromatosis do exist. The first published article of neurofibromatosis induced pulmonary manifestations was in 1963, when Davies reported a case of neurofibromatosis and interstitial lung disease.[20] This opened the floodgates to many more such sporadic reports linking the respiratory system with neurofibromatosis.[21-24]

Several hypothesis exist which try to explain the pulmonary manifestations in this disease. Patchefsky et al. suggested that the pulmonary parenchymal disease in Neurofibromatosis is attributed to a mesenchymal defect, resulting in primary deposition of collagen in the lung parenchyma.[21] Fabricant and Todaro found increased nerve growth factor in the serum of patients with Neurofibromatosis, which is responsible for direct activation of fibroblasts, stimulating differentiation into more fibrogenic myofibroblasts, a process which may contribute to the pathogenesis of lung fibrosis in these patients.[26,27]

The exact extent of pulmonary manifestations of neurofibromatosis is very hard to gauge. Majority of the case reports till date, even though insufficient, describe a diffuse parenchymal lung involvement. Earlier there were proposals to include the lung involvement into the major diagnostic criteria. However this could not be substantiated due to insufficient cases. Hence the coexistence of neurofibromatosis and its pulmonary manifestations leaves a void which can only be filled by a complete and in depth evaluation of these patients.

**Conclusion:**

Von Recklinhausen’s disease or neurofibromatosis type 1 (NF) is an autosomal dominant dysplasia of ectoderm and mesoderm with a variable clinical expression characterised by collections of neurofibromas, café-au-lait spots and pigmented hamartomas in the iris (Lisch nodules). The respiratory manifestations of this disease are extremely rare. However the authors are of the firm belief that a cross-sectional cohort study is needed in which patients with neurofibromatosis undergo high-resolution computed tomography and have a careful medical history taken. It is hoped that a better understanding of neurofibromatosis with diffuse lung disease, together with an increased understanding of the pathobiology of neurofibromatosis, will

**Cite As:** Neurofibromatosis And The Lung : An Interesting Case; Vol. 2|Issue 10|Pg:1358-1361

**DOI:** 10.18535/ijmsci/v2i10.01
lead to future therapies for this rare but highly morbid condition.

References: