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Neurofibromatosis And The Lung : An Interesting Case

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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 characterizedby a neuroectodermal abnormality and by clinical manifestations of systemic and progressive involvementwhich mainly affect the skin, nervous system, bones, eyes and possibly other organs. The disease maymanifest in several ways and it can vary from individual to individual. However till date the repisratorymenifestations of this disease have been extremely rare and seldom reported. Most cases are diagnosed bypaediatricians, especially in patients with multipleskin lesions. In some patients, however, the diseaseis diagnosed in adult life or remains undetected which is due to its clinical heterogeneity andsymptom 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),

alongwithhyperpigmented 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, alongwith

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multiple café au lait spots, the largest being more than 2 cms in dimension.

Figures :

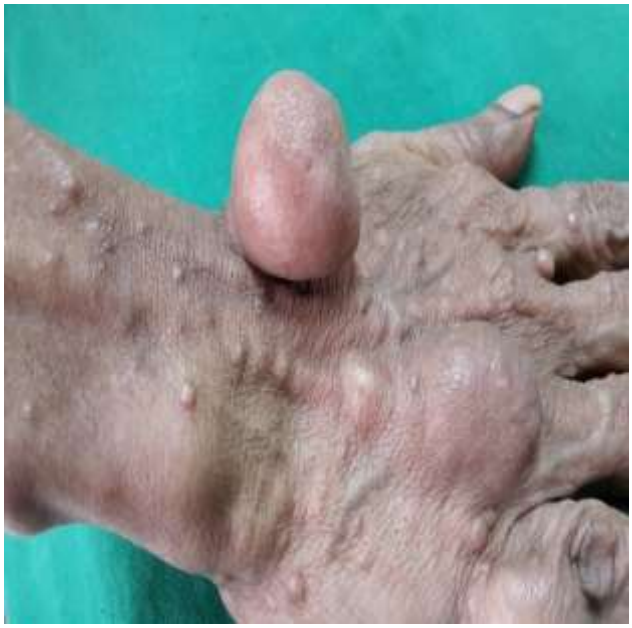

Figure 1 : Cutaneous neurofibromas.

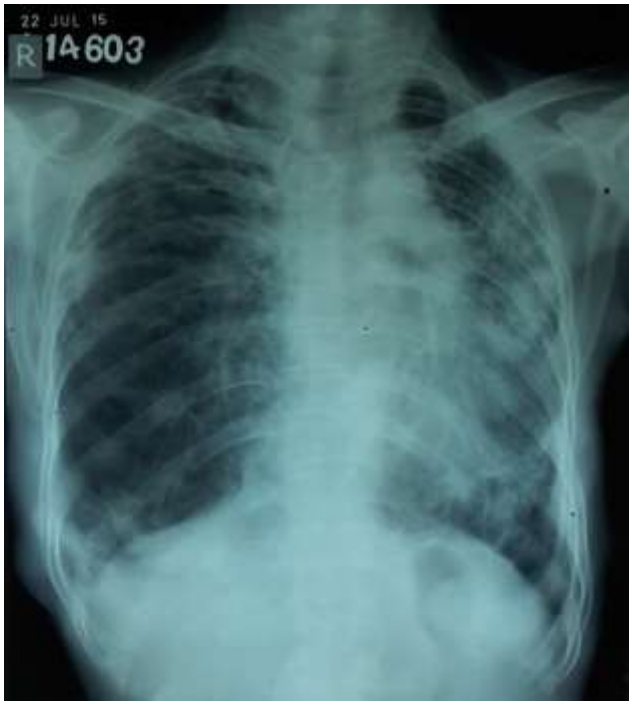

Figure 2 : Chest x ray showing bilateral fibrocystic changes, left more than right.

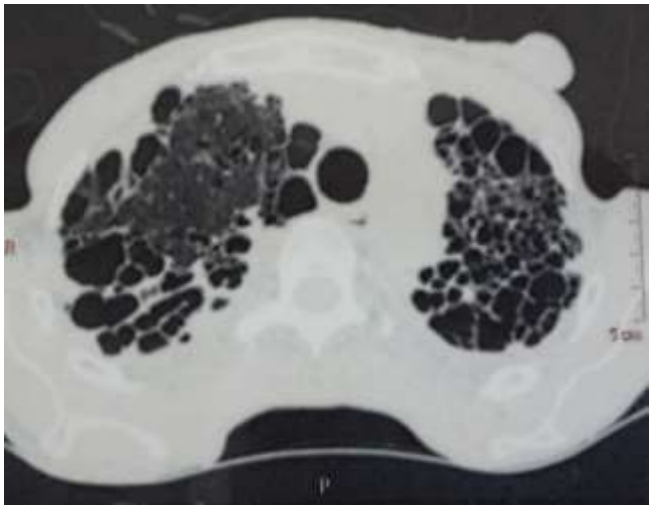

Figure 3 : High resolution computed tomography of thorax shows bilateral diffuse cystic changesalongwith a cutaneous tag.

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.[3,4] 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 perinerve and endonerve. 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 NF1, 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 NF1 gene leads to a permanent stimulation of a cascade of signals

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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 plexiformneurofibromas – they form an extensive network in the subcutaneous tissue,
4) diffuse plexiformneurofibromas – 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 morethan six spots greater than 0.5 cm in diameter beforepuberty or greater than 1.5 cm in diameter afterpuberty is suggestive of Neurofibromatosis type 1. Their presence in theaxillary region, constituting the so-called ephelides oraxillary freckling, is considered pathognomonic ofthis 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 periosteum 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 neurofibromatosiswere classified by Huson (1994) in “major”,“minor” and associated complications.[19] The “major”manifestations are specific to NF, affect most patientsand are the basis of the diagnostic criteria of theNational Institute of Health (1988).[2] They are constitutedby café au lait spots, axillary freckling, peripheralneurofibromas and Lisch nodules. The “minor” manifestationsare specific to NF and also appear at a highfrequency in those affected, but they are not used asdiagnostic criteria. Macrocephaly and short statureare 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 pulmonaryparenchymal disease in Neurofibromatosis is attributed to a mesenchymaldefect, resulting in primary deposition of collagen in the lung parenchyma.[25]Fabricant and Todaro found increased nerve growth factor in theserum of patients with Neurofibromatosis, which is responsible for direct activation of fibroblasts, stimulating differentiation into more pro-fibrogenicmyofibroblasts, a process which may contribute to thepathogenesis 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 neurofibromatosistype 1 (NF) is an autosomaldominant dysplasia of ectoderm andmesoderm with a variable clinical expressioncharacterised by collections of neurofibromas,cafe´-au-lait spots and pigmented hamartomas inthe iris (Lish nodules). The respiratory manifestations of this disease are extremely rare. However the authors are of the firm belief that a cross-sectionalcohort study is needed in which patients with neurofibromatosisundergo high-resolution computed tomography and havecareful medical histories taken. It is hoped that a betterunderstanding of neurofibromatosis with diffuse lung disease,together with an increased understanding of the pathobiologyof neurofibromatosis, will

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lead to future therapies for this rarebut highly morbid condition.

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