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# Diffuse Neurofibroma over Foot – A Rare Entity with Uncommon Presentation: A Case Report

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## Abstract

Diffuse neurofibroma is the distinct, rare, and infiltrative form of neurofibroma, which usually involves the skin and subcutaneous tissue of the head, neck and trunk. It is challenging to diagnose the lesion preoperatively because of the lack of distinctive clinical characteristics, especially when solitary. Moreover, if the characteristic morphological features are not known/found, it can be misdiagnosed as lipomatous neurofibroma, schwannoma, hamartoma or other lesions histologically. Due to its infiltrative nature, chance to recur and a rare chance to undergo malignant transformation, it is important to know and diagnose this entity so that a long term follow up of the patient is advised. Its association with neurofibromatosis warrants thorough clinical evaluation of the patient.

To the best of our knowledge, only seven cases have been reported in Indian literature. We report a rare case of diffuse neurofibroma in a 12 year-old-female child with unique involvement of the foot, which unveiled the associated manifestations of neurofibromatosis.

**Keywords**:Lipomatous neurofibroma, Neurofibromatosis, Schwannoma, Wagner-Meissner bodies

## Introduction

Neurofibroma is a benign peripheral nerve sheath tumor arising from a mixture of Schwann cells and perineural fibroblasts. Depending upon the growth pattern, it is categorised into three types: localised, diffuse, and plexiform. Diffuse neurofibroma is an unusual variant of neurofibroma, occurring primarily in children and young adults. It commonly involves the skin and subcutaneous tissue of the head, neck and trunk. It's a poorly defined lesion which spreads along connective tissue septa and between fat cells. It comprises less elongated Schwann cells embedded in matrix of fine fibrillary collagen, and is characterised by Wagner Meissner-like structures. The incidence of neurofibromatosis among patients with diffuse neurofibroma has been reported to be 10%.[1,2]

## Case Presentation

A 12 year-old-female child presented with gradually increasing swelling over right foot extending between medial and lateral malleolus for eight years. The swelling was neither mobile nor fixed to the underlying bone. It was firm with ill-defined borders, and was not associated with pain/tenderness/bleeding/discharge. There was no history of trauma/fever/ loss of appetite/weight. She

complained on and off pain in leg. On examination, there was no neurovascular deficit, and joints' movements were normal. On the clinical grounds, the tentative diagnosis of lipoma was made.

The mass was excised. Gross examination revealed an uncapsulated soft tissue mass measuring 7x5×3 cm. External surface was irregular with fatty projections. Cut surface was yellowish (fatty) intersected by whitish firm bands. No necrosis, hemorrhage, cystic changes seen. [Figure1] Microscopic examination revealed a spindle cell neoplasm comprising elongated bland oval spindle cells with wavy nuclei, entrapping lobules of mature adipose tissue.[Figure 2A and 2B] Many nerve bundles, Wagner Meissner-like bodies and a few Pacinian-like corpuscles, ectatic blood vessels, [Figure 2C] and a few mast cells [Figure 1 inset] were also present within the collagenous matrix. Approximately 50% of the tumor cells revealed nuclear and cytoplasmic positivity with S-100 protein. [Figure 2D]

After the histopathological diagnosis, detailed physical examination of the patient was done. Twenty eight café-au-lait spots were found over trunk, back and thighs varying in size from 0.5 to 3.5 cm. Skeletal abnormality in the form of pectus excavatum was observed. [Figure 3] Five Lisch nodules were seen on slit lamp examination; two in right and three in left eye. Positive family history suggesting neurofibromatosis type-I was obtained; her father, grandfather and uncle also had multiple café-au-lait spots and neurofibromas.

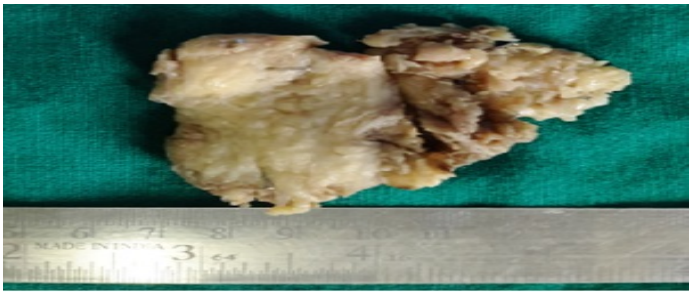

**Figure 1**. Cut Surface revealing yellow fatty soft areas intersected by white firm bands

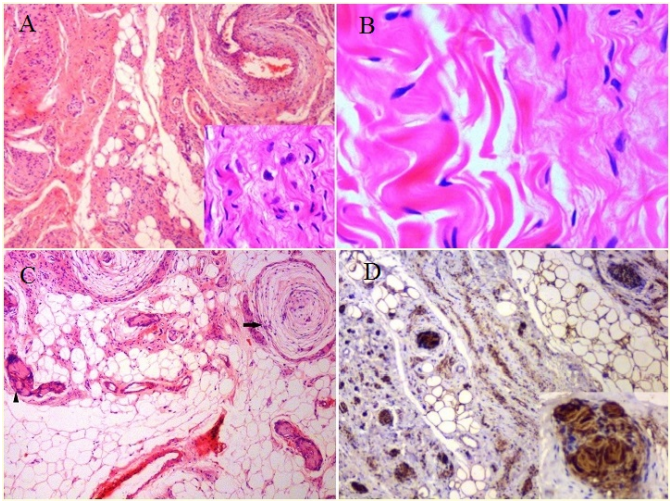


**Figure 2.**

A. Spindle cell neoplasm entrapping mature adipose tissue (H & E, 50x). Inset: Tumour with wavy nuclei, a spindle cell sprinkled with mast cells (H & E, 400x)
B. Microphotograph depicting spindle cells with wavy nuclei in the collagenous matrix (H & E, 400x)
C. Histopathological examination showed Wagner Meissner like bodies and Pacinian-like-corpuscles (arrow), (H & E stain, 50x)
D. Immunohistochemical staining for S-100 protein was positive (IHC, 50x). Inset: Positivity in Wagner Meissner like body (IHC, 100x)

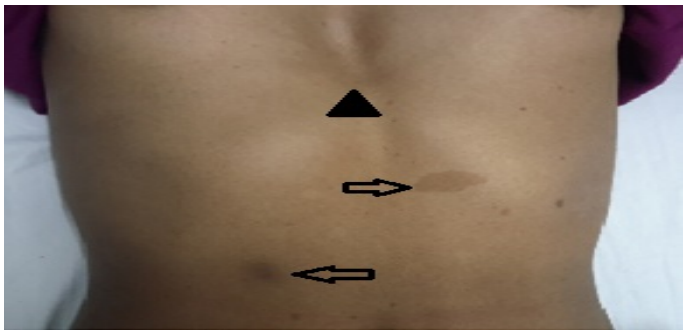

**Figure 3.** Café-au-lait spots on trunk (arrows) with pectus excavatum (arrow head)

**Discussion**

Neurofibromas are the most common benign peripheral nerve sheath tumor. They have a neuroectodermal origin, and consist of differentiated Schwann cells, perineurial-like cells, fibroblasts, mast cells and residual axons embedded in extracellular matrix.[3] Depending upon the

growth pattern, they may be categorized as localised, plexiform and diffuse types.[2] The localized form is seen most commonly as a superficial, solitary, skin-colored, dome-shaped or pedunculated papules with a 'buttonhole' sign. It can be sporadic or NF-associated. Plexiform neurofibroma diffusely involve single or multiple nerve branches, imparting a wormy sensation. It is pathognomonic of neurofibromatosis type 1.[4]

Diffuse neurofibroma is an uncommon but distinctive type of neurofibroma. To the best of our knowledge, only seven cases have been reported in Indian literature. [1,2,5-9] It presents as a plaque-like elevation of the skin. Many authors have reported predilection for head and neck, followed by trunk and then limbs [10], while others have concluded its predilection for trunk.[11] Only a few cases involving the extremities have been reported, but only a rare case involving the ankle has been found.[12] Clinically, it is known to simulate lipoma, hemangioma, schwannoma, pilomatrixoma, eccrine spiradenoma, and solitary localised neurfibroma. It is usually solitary and progressively enlarging and infiltrating, simulating malignant tumors.[2] Though rare, malignant transformation has also been reported.[7,13]

On histopathologic examination, the tumor is composed of spindle cells with elongated nuclei and fibrillar eosinophilic cytoplasm embedded within a loose matrix of fine fibrillary collagen. Wagner Meissner-like bodies are characteristic, but are not present in each case.[4,11] They are counterpart of perineurial-like cells; the constituent cells forming a spherical structure of circumscibed collection of S-100 positive stacked, lamellar processes. The site involved in the present case was uncommon, as well as few Pacinian-like corpuscles were found. Only Khan et al has reported presence of distorted organoid structures resembling Pacinian's corpuscles.[5] On immunohistochemistry, it shows distinctive immunoprofile with multiple cell populations. It shows positivity for S-100 protein, which is a sensitive, but non-specific marker [4], and labels around 40-50% cells. Scattered perineurial cells may show positivity for GLUT-1 and claudin-1. Other markers that might have labeled perineurial-like cells and stromal cells are EMA and CD-34, respectively. Residual axons may be demonstrated, on occasion, with neurofilament protein immunostains.[3]

Micoscopically, the differentials considered were schwannoma, hamartoma, dermatofibrosarcoma protuberans (DFSP) and lipomatous neurofibroma. The unencapsulation, infiltrative nature, less elongated spindle cells, presence of Meissner's bodies (initially confused with Verocay bodies), S-100 positivity in 50% cells only, and finally associated features and family history of NF-1 assisted to rule out the possibilities of schwannoma and hamartomas. The presence of Meissner bodies and S-100 positivity without storiform architecture ruled out DFSP. The lipomatous neurofibroma was ruled out due to diffuse nature, uneven distribution/entrapment of fat, absence of entrapment of normal structures such as skeletal muscles or dermal appendages, presence of Meissner bodies, supported by clinical details.

Diffuse Neurofibroma has a close association with neurofibromatosis type 1.[1] Neurofibromatosis I, also known as "von Recklinghausen disease," is the most common single gene disorder in humans which results from the defective protein neurofibromin-a tumor suppressor.[14] It may be associated with multiple neurofibromas. For the diagnosis of Neurofibromatosis type 1,the presence of two or more of the following signs is required [2]: Six or more café-au-lait macules (≥ 1.5 cm in post-pubertal individuals, ≥ 0.5 cm in pre-pubertal individuals); Two or more neurofibromas of any type or one or more plexiform neurofibromas; Freckling of armpits or groin; Pilocytic astrocytoma of optic pathway ("optic glioma"); Two or more Lisch nodules (iris hamartomas); Dysplasia/absence of the sphenoid bone or

dysplasia/thinning of long bone cortex ; and First-degree relative with NF1.

The present case had multiple café-au-lait spots over trunk, back and thighs, lisch nodules, as well as solitary diffuse neurofibroma and positive family history of NF-1.

The mainstay of treatment for diffuse neurofibroma is surgical resection. Regular follow ups are mandatory even after complete excision due to infiltrative growth pattern and chances of recurrences.[7] In neurofibromatoses, the large number of lesions might make surgical excision impossible. In such cases, surgery has traditionally been reserved for large/painful lesions and for the ones located in areas where continued expansion would compromise organ function, and those in which malignant change is suspected.[5]

**Conclusion**

1. Presence of diffuse neurofibroma raises the suspicion of neurofibromatosis, warranting thorough physical examination, opthalmological and radiodiagnostic investigations and counselling.
2. Extensive and infiltrating nature of lesion precludes complete surgical resection and follow ups.

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