Case Report

Co-Occurrence of Neurofibromatosis-1 with Urticaria Pigmentosa: A Coincidental Association?

Abstract

Neurofibromatosis-1 (NF-1) is a neuroectodermal abnormality characterized by multiple neurofibromas, café-au-lait macules, axillary freckling, and Lisch nodules. Urticaria pigmentosa (UP) is a maculopapular cutaneous mastocytosis due to mast cell hyperplasia. We report a case of NF-1 associated with UP. A 19-year-old male presented with multiple neurofibromas, café-au-lait macules, axillary freckling, and Lisch nodules. He also had UP lesions with positive Darier's sign. A clinical diagnosis of NF-1 with UP was made and confirmed histopathologically. Mastocytosis exhibits mast cell hyperplasia due to C-kit gene mutation. Mast cell mediators directly contribute to neurofibroma growth. C-kit receptor abnormality is implicated in the formation of neurofibromas as well as in UP. With possible interconnected underlying pathology of mast cell hyperplasia and increased mast cell mediators in both UP and NF-1, a possible association of NF and UP beyond simple coincidence should be considered.

Keywords: *C-kit, mast cell, neurofibromatosis-1, urticaria pigmentosa*

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Introduction

Neurofibromatosis-1 (NF-1) or von Recklinghausen disease is the most common type of NF encountered. It is an autosomal dominant, inherited neuroectodermal abnormality characterized by multiple neurofibromas along peripheral nerves, six or more café-au-lait macules, axillary freckling, and Lisch nodules in the iris. Neurofibromas also show an increased number of mast cells which have been postulated to enhance growth of the tumor by the release of growth factors such as histamine and tumor necrosis factor-α.

Urticaria pigmentosa (UP) is the most common pattern of maculopapular cutaneous mastocytosis in both children and adults characterized by symmetrically distributed reddish-brown maculopapules mostly concentrated over the trunk. The lesions show urtication after gentle rubbing known as Darier's sign. It occurs due to the mutation of KIT gene causing its activation and increased mast cell mediator release.

With studies postulating underlying common pathophysiology probably related to increased mast cell infiltrate and its mediators, we would like to report, in this communication, a case of a patient having rare co-occurrence of NF-1 with UP.

Case Report

A 19-year-old male patient presented to the skin outpatient department with chief complaints of asymptomatic skin lesions over the trunk and extremities since childhood.

Cutaneous examination revealed multiple skin-colored ill-defined, oval, sessile, dome-shaped nodules of sizes varying from 5 to 20 mm over the trunk and extremities, which gave a feeling of invagination on digital pressure (buttonholing sign positive) [Figure 1]. Few light brown homogeneous sharply demarcated macules and patches of sizes varying from 5 to 30 mm suggestive of café-au-lait macules were observed [Figure 2]. Axillary freckling was present [Figure 3].

Multiple generalized monomorphic gray-brown, symmetrical, ill-defined, macules and papules present diffusely over the neck, extremities, and trunk [Figure 4]. Darier's sign was positive.

Large hyperpigmented patch with hypertrichosis measuring 15 cm × 8 cm over the right forearm clinically suggestive

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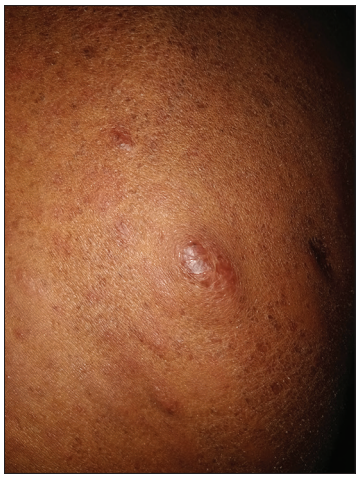

Figure 1: Skin-colored, ill-defined, oval, sessile, dome-shaped neurofibroma lesion

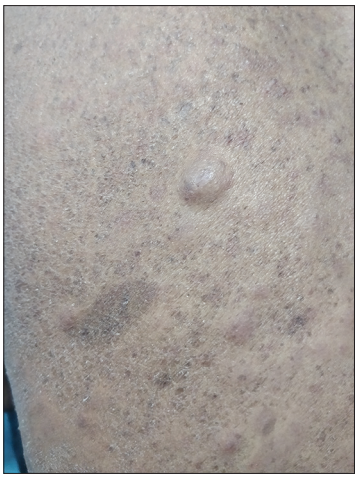

Figure 2: Light-brown homogeneous sharply demarcated café-au-lait macule

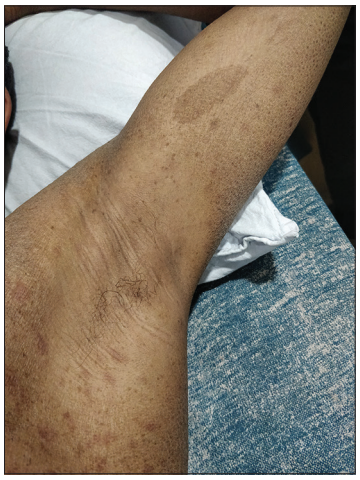

Figure 3: Light-brown freckles over the axilla

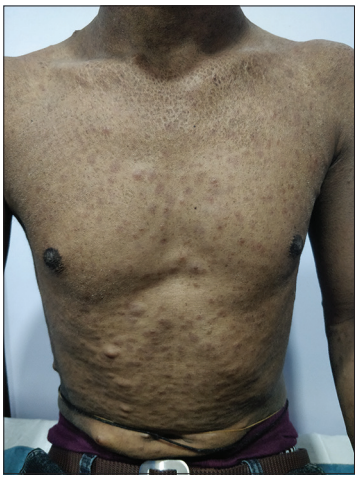

Figure 4: Multiple generalized monomorphic gray-brown, symmetrical ill-defined macules and papules

of plexiform neurofibroma or Becker's nevus was also noted [Figure 5a and b].

The patient did not give a history of seizures, delay in developmental milestones, or any other symptoms suggestive of neurological or cranial involvement.

A clinical diagnosis of NF-1 with UP was made. Ophthalmological examination with slit lamp revealed multiple Lisch nodules in both the irises. Water's view X-ray showed normal sphenoid sinus and bone.

Skin biopsy was taken from lesion suggestive of neurofibroma (sample A) as well as lesion suggestive of UP (sample B). On hematoxylin and eosin staining (H and E), sample A showed diffuse proliferation of spindle-shaped cells with wavy, buckled nuclei having a moderate amount of cytoplasm set in a loose myxoid stroma, which were features consistent with neurofibroma [Figure 6a and b]. Sample B was sent in normal saline for H and E as well as Toluidine blue special staining for mast cells. It showed increased pigmentation of the basal layer of the epidermis and perivascular and periadnexal lymphocytic infiltrate along with few mast cells in the dermis. Toluidine blue stain for mast cells was positive. These features were consistent with UP [Figure 7a and b].

The patient was unwilling for histopathological examination of the forearm lesion suggestive of plexiform neurofibroma or Becker's nevus. Therefore, a definitive diagnosis of that patch could not be established.

Discussion

Even though NF and cutaneous mastocytosis display different mutations, different morphology, clinical features, and histopathology, a rare association of these two conditions has been reported in the literature in the past.[1]

Mast cells arise from pluripotent bone marrow progenitor cells expressing CD34 antigen and undergoing proliferation and maturation in specific tissues.[2] Mastocytosis is a collection of clinical diseases that exhibit mast cell hyperplasia on histopathological examination. The reason

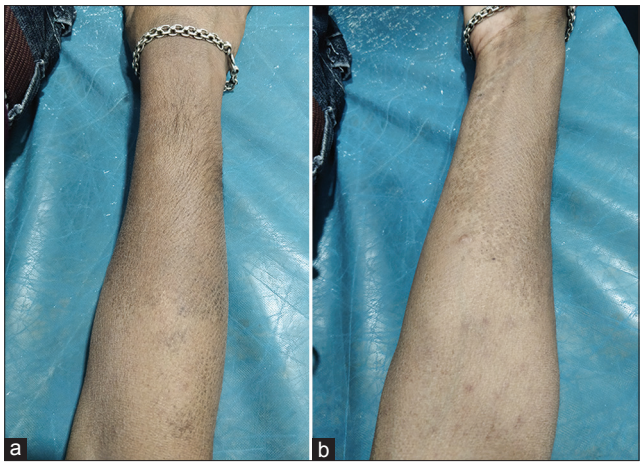

Figure 5: (a and b) Lesion suggestive of plexiform neurofibroma or Becker's nevus over the right forearm

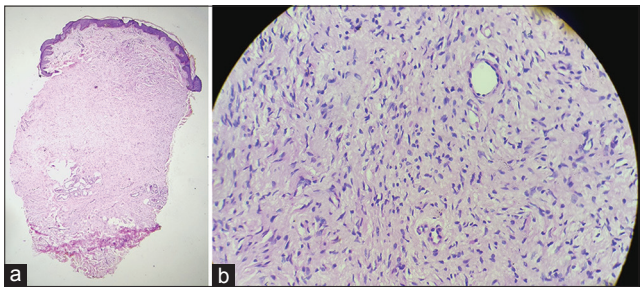

Figure 6: (a) Nonencapsulated tumor with pale matrix (H and E, ×100). (b) Diffuse proliferation of spindle-shaped cells with wavy, buckled nuclei and loose myxoid stroma (H and E, ×400)

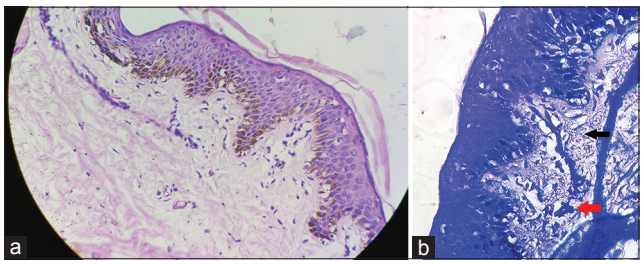

Figure 7: (a) Increased epidermal basal layer pigmentation and perivascular and periadnexal lymphocytic infiltrate with few mast cells in the dermis (H and E, ×400). (b) Toluidine blue staining showing increased number of mast cells (red arrow) and metachromatic granules (black arrow) in the dermis (H and E, ×400)

for proliferation and accumulation of mast cells in mastocytosis is only partially understood.

Longley *et al.* demonstrated increased concentrations of the soluble form of mast cell growth factor in cutaneous mastocytosis lesions.[3] Furthermore, c-kit receptors that are expressed on mast cells, which interact with the mast cell growth factor in the development of mast cells, may show mutations or other abnormalities resulting in a defective mast cell proliferation.[4,5]

Mast cells may result in the release of various mediators, synthesis of membrane-derived lipid metabolites, and inflammatory cytokines which have a proliferative action on many cells.[5]

Historically, UP was described with extracutaneous involvement of organs.[6] With respect to the index case, systemic mastocytosis was ruled out due to the absence of hepatosplenomegaly, normal complete blood counts, liver function test, and serum tryptase levels. Hence, further investigations, such as bone marrow biopsy, were not performed.

Greggio described increased number of mast cells in neurofibromas.[7] Binnazi and Landi were probably the first to hypothesize the involvement of mast cell secretions in the pathogenesis of neurofibroma growth.[8] Histamine and heparin released from mast cells have been characterized as potent mitogens and angiogenetic factors that may directly contribute to neurofibroma growth by Norrby K. and Azizkhan *et al.*[9,10]

Mérot *et al.* reported the case of a 62-year-old Swiss woman suffering from asymptomatic systemic mastocytosis with bone marrow involvement, neurofibromas, and café-au-lait spots.[11]

Viskochil reported a potential implication of c-kit receptor and its ligands in the formation of neurofibromas by secreting five times the normal levels of Kit ligand; the same Kit gene is found abnormally mutated in patients of UP.[12]

According to a hypothesis developed by Riccardi, secretions of mast cells, in particular, may influence the phenotype and proliferation of local neural crest-derived cells (including neurofibroma, Schwann cells, and perineural cells) or augment the effect of membrane components leading to the formation of neoplasms.[12-14]

NF is a relatively common autosomal dominant trait with a frequency of about 1 in 3000.[13,15] The chance of a coincidental co-occurrence of NF and cutaneous mastocytosis can be estimated at 1 in 3000,000–24,000,000 paving the way for a possible association of neurofibroma lesions and UP beyond simple coincidence.[1]

The presence of lesion suggestive of Becker's nevus was probably coincidental as it had no association with NF-1 or UP.

Conclusion

Mast cells definitely have a causative role in the development of neurofibroma lesions. To establish its certain association with respect to cutaneous mastocytosis, one should be vigilant during a clinical examination for better detection of cases and confirmation of the same with histopathological examination. Moreover, further genetic and molecular studies should be undertaken, keeping in mind a possible interconnected underlying pathology.

Declaration of patient consent

The informed consent was obtained for participation in the study and publication of data and images for research and educational purposes.

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Conflicts of interest

There are no conflicts of interest.

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