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Case Report

Congenital Beckers nevus overlying plexiform neurofibroma in neurofibromatosis type-1: more than a rare association

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ABSTRACT

Plexiform neurofibroma (PFN) is the hallmark of Neurofibromatosis type 1 (NF-1), an autosomal dominant disorder caused by mutations in the neurofibromin gene.1 Becker's nevus (BN) is an acquired pigmentary disorder characterized by hyperpigmentation and hypertrichosis, presenting in adolescence.2 Here we present a 28-year-old male with a congenital hyperpigmented pigmented patch over his back which later on increased in size and developed excessive hair growth and subsequently swelling. The patient had no other swellings of neurofibroma but satisfied all the criteria of Type-1 Neurofibromatosis. Clinical, dermoscopic and histopathologic features confirmed the diagnosis of PFN with BN in NF-1. Two special stains including S-100 and Fontana Mason stain ruled out other possibilities and further confirmed the diagnosis of Congenital Becker's Nevus with Plexiform Neurofibroma in NF-1. The report emphasizes that in NF-1, Becker's nevus can masquerade an ominous presence of plexiform neurofibroma. The case has been reported for the rarity of association of Congenital Beckers Nevus with Plexiform Neurofibroma in NF-1

Keywords: Plexiform neurofibroma, Congenital Becker's nevus, Neurofibromatosis-1, Congenital pigmented plaque, Congenital hairy plaque, Co-occurrence

INTRODUCTION

Neurofibromatosis-1 (NF-1) is an autosomal dominant genetic disorder characterized by the development of multiple neurofibromas of the peripheral nerves. It occurs due to a mutation in the neurofibromin gene located on chromosome 17.

Plexiform neurofibroma (PFN) are pathognomonic of NF-1. Becker's nevus (BN) is an acquired pigmentary hamartoma that presents at puberty and exhibits localized hypertrichosis and hyperpigmentation.[2] Occurrence of congenital Becker's nevus is rare and the association of plexiform neurofibroma with congenital Becker's nevus is even more rarely reported.

CASE REPORT

A 28-year-old male, born of consanguineous marriage, presented with swelling on the back since, 2 years. At birth, the patient had a dark brown patch at the same site. The patch started gradually increasing in size when the patient was around 13 years and developed hair eventually. Two years back he noticed a swelling at the centre of the patch.

The patient sought medical advice since the swelling was progressively enlarging and was associated with pulling sensation. The patient also complained of saggy left eyelid with gradual diminution of vision in left eye over past 2 years. There were no swellings elsewhere in body.

Patient had history of similar brown patches and multiple swellings in maternal uncle.

Cutaneous examination revealed multiple cafe-au-lait macules (CALM), ranging from 1cm to 4 cm on the trunk. Multiple axillary, inguinal and palmar freckles were also noted.

On the left side of the mid-back, there was a large geographic shaped brown patch with maximum width of 20 cm with irregular margin and coarse terminal hair (Figure 1). The middle of the patch revealed a well-defined pinkish-brown elevated swelling with a mamillated surface and relatively sparse hair. It was soft to touch with a "bag of worm" feel. There was no scoliosis or neurologic deficit in the lower limbs.

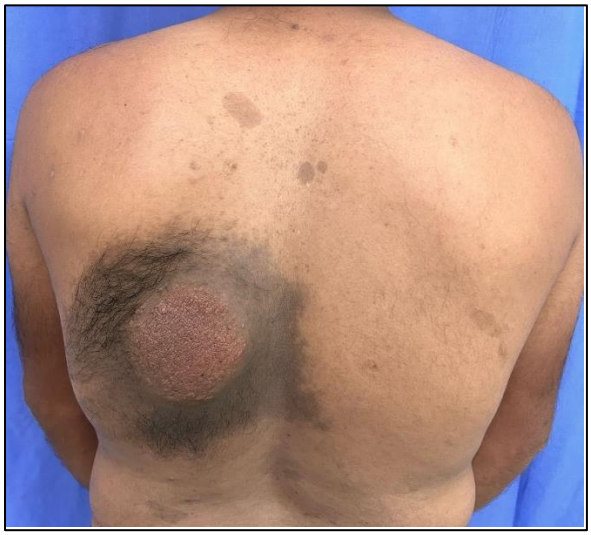

Figure 1: Giant patch of becker's nevus with central swelling of plexiform neurofibroma.

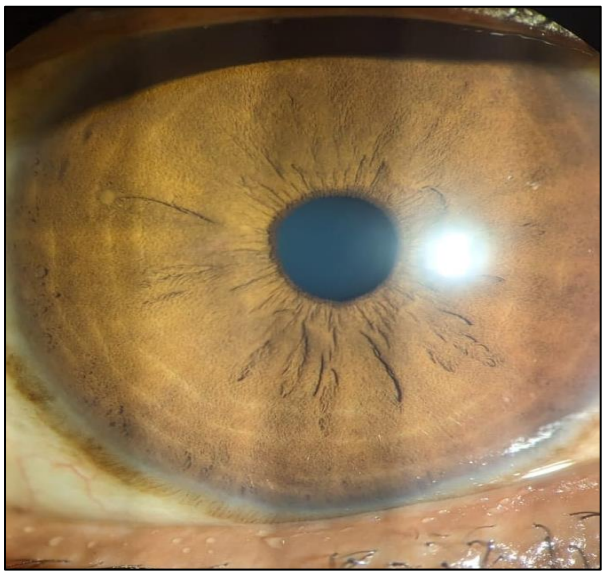

Figure 2: Lisch nodules on slit lamp examination (indicated by black arrow).

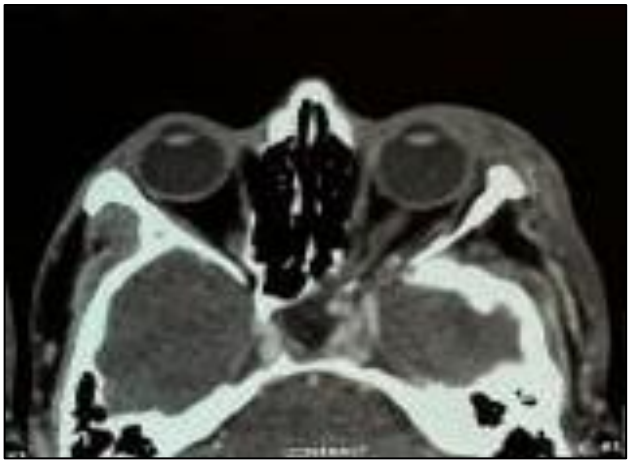

Figure 3: CT scan of skull showing sphenoid dysplasia.

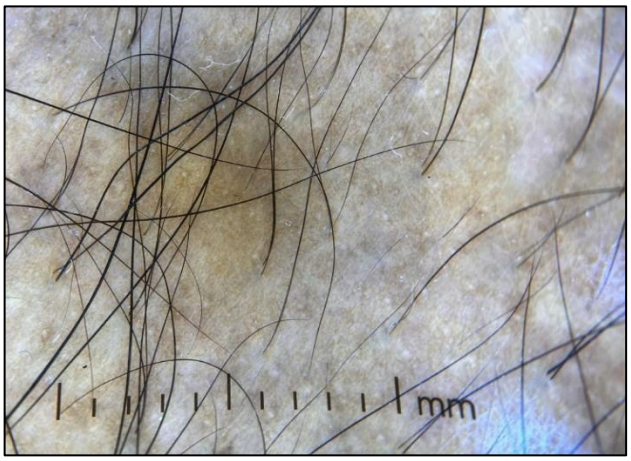

Figure 4: Dermoscopy of Becker's nevus showing exaggerated pigment network (indicated by black arrow) with perifollicular hypopigmentation (indicated by white arrow).

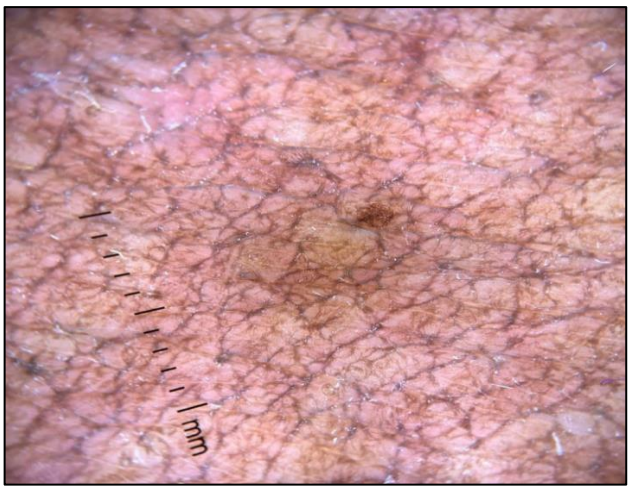

Figure 5: Dermoscopy of swelling showing chicken-wire pattern of pigment network (indicated by black arrow).

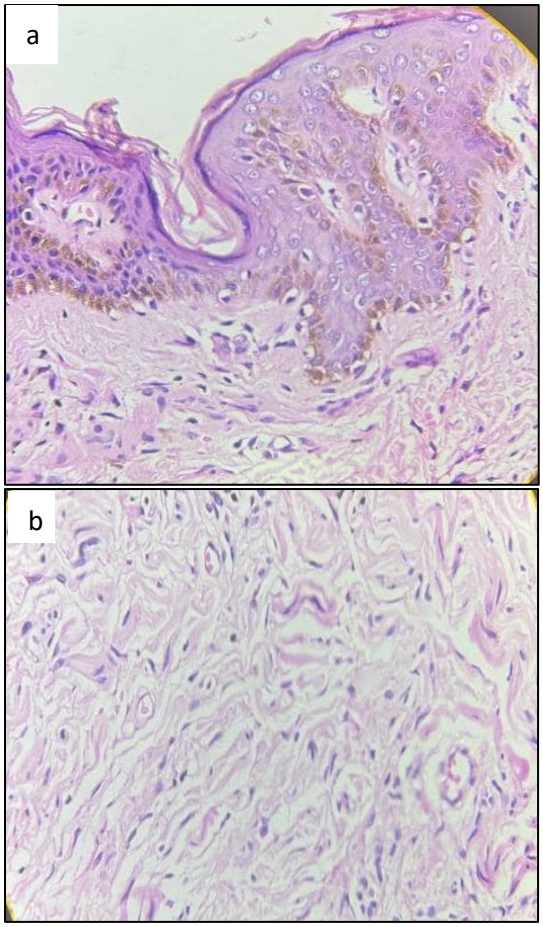

Figure 6: (a and b) Biopsy from the hyperpigmented patch showing elongated, squared out retepegs, (indicated by blue arrow) increased basal melanisation, mid-dermis with proliferation of spindle cells with tapering nuceli (indicated by black arrow).

Figure 7: Biopsy from pigmented patch with swelling showing spindle cells in mid and deep dermis staining positive for S-100 stain.

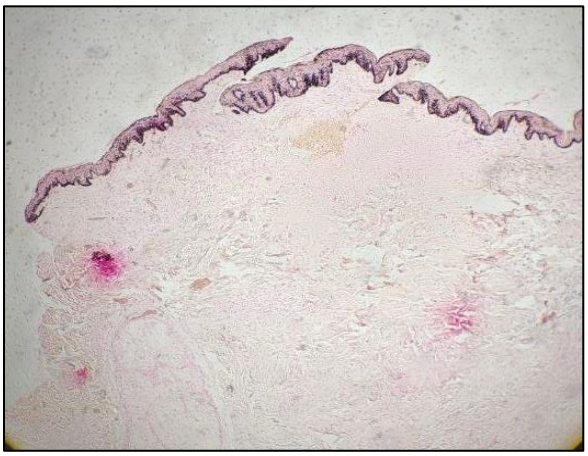

Figure 8: Biopsy from pigmented patch with swelling showing positive staining of Fontana Mason in basal layer of epidermis and negative staining in dermis.

There were no swellings elsewhere other than the redundant left upper eyelid. The patient was referred to ophthalmology in view of the above findings where slit lamp examination showed Lisch nodules in both eyes (Figure 2). With the above finding of a congenital hyperpigmented hypertrichotic patch overlying a bag of worm like swelling, we considered differential diagnosis of congenital melanocytic nevus (CMN) with plexiform neurofibroma, congenital Becker's nevus with plexiform neurofibroma, giant cafe-au-lait macule with plexiform neurofibroma, pigmented plexiform neurofibroma and congenital smooth muscle hamartoma.

Nonpolarized contact dermoscopy with dermlite DL4 on the hairy patch showed thickened reticular pigmentation with perifollicular hypopigmentation and increased terminal hair (Figure 4). Dermoscopy of the skin over the central swelling revealed accentuated pigment network giving a mesh like appearance (Figure 5).

A wedge biopsy from edge of swelling (included part of hyper pigmented patch) revealed increased acanthosis with basal cell melanisation, elongated squared rete pegs and follicular plugging consistent with Becker's nevus. (Figure 6a). Superficial and deep dermis showed non-encapsulated interlacing elongated spindle cells with wavy nuclei with expanded nerve bundles (Figure 6b).

Immunohistochemical staining with S-100 revealed strong positivity in mid and deep dermis confirming the PFN (Figure 7). Since S-100 stains both melanocytes and Schwann cells, stain which can differentiate melanocytes from Schwann cells was essential.

Melan-A or HMB-45 was not available in our setup, hence we performed fontana masson which stained positive at the basal epidermis and negative in dermis (Figure 8). CT scan of orbit revealed left optic nerve glioma and sphenoid wing dysplasia (Figure 3). The patient satisfied all the criteria of NF-1. Thus, the final

and definitive diagnosis was congenital becker's nevus with plexiform neurofibroma with neurofibromatosis-1. The patient was informed about the risk of malignancy associated with plexiform neurofibroma and the potential for blindness due to optic glioma. He was referred to neurosurgery for excision.

Table 1: Clinical, dermoscopic and histopathological differences of the congenital hyperpigmented patch with underlying swelling.

Differential diagnosis	Cafe-au-lait macule with PFN	Congenital melanocytic nevus with PFN	Congenital smooth muscle hamartoma	Pigmented Plexiform neurofibroma	Beckers nevus with PFN
Time of onset	birth	birth or within few weeks of life	birth	early in life	puberty
Site	Trunk, buttocks and extremities	Trunk or extremities	Lumbosacral, trunk, extremities	Scalp, neck, buttock and limbs	Chest, shoulders or upper back
Colour	Well-defined uniform light or dark coffee coloured	Well-defined brown black elevated plaque	Skin coloured to minimally hyperpigmented	Ill-defined grey to brown patch	Well-defined brown black
Borders	Smooth borders in NF-1	smooth borders and nodular surface	Ill-defined irregular borders Transient elevation on rubbing (pseudo-Darier's sign)	Irregular borders and rubbery consistency	Geographical borders, splashed margins
Hair, specific features	Hypertrichosis rare	Coarse terminal hair	Vellus hair	Hypertrichosis rare	Acne, hypertrichosis
Evolution	Persists for life	Persists for life	Hyperpigmentation and hypertrichosis reduce in puberty	Persists for life	Persists for life
Dermoscopy	Homogenous brown pigmentation. Peri follicular halo and reticular brown pigmentation.[13]	Globular, reticular or mixed pigmentation, Perifollicular hypopigmentation Milia like cysts dotted and comma vessels.[13]	Pseudo pigmentary network, milia like cyst and brown structureless areas.[14]	Lack of studies Accentuated pigment network sparing around hair follicles resembling "Chicken-wire-mesh" [15]	Exaggerated reticular network Focal, skin furrow and perifollicular hypopigmentatio[13]
Histopathology	Melanocytes increased at dermo-epidermal junction Giant melanosomes in NF-1.[16]	Round pigmented nevus cells arranged in nests in lower dermis, subcutis, around nerves, blood vessels and appendages.[16]	Thick long straight well-defined smooth muscles fibers scattered throughout dermis.[16]	Melanocytes and melanisation increased at dermo-epidermal junction. Oval to rounded. Bulky pigmented melanocytes individually and in nests in papillary dermis[17]	Acanthosis Melanocytes and melanisation increased at dermo-epidermal junction. Elongated rete pegs. Increased terminal hair. Melanophages in papillary dermis.[16]
Special stain	FM, Melan A - + epidermis S-100- + epidermis &dermis	FM - + epidermis and dermis S-100- + epidermis &dermis (nevoid cells in dermis on HPE)	FM & S-100-negative. Actin - + in dermis	FM - + epidermis & dermis S-100- + epidermis &dermis. (Bulky ovoid melanocytes in dermis	FM - + epidermis S-100- + epidermis &dermis.

DISCUSSION

Neurofibromatosis-1 is an autosomal dominant tumour predisposition syndrome that affects skin, bones and nervous system. This genodermatosis is caused by mutation of Neurofibromin gene which is a crucial negative regulator of Ras, a proto-oncogene that is essential for cell proliferation and differentiation.[3] Plexiform neurofibroma are the most characteristic manifestation of NF-1 and is seen in 30 to 60% of NF-1.[1] PFN is a non-encapsulated tumour arising from the nerve sheath of peripheral or cranial nerves that grows rapidly, involving to form soft, painless protuberant masses of skin and subcutaneous tissue. PFN are congenital but are

clinically visible in early years of life. They are infiltrative and impinge on vital structures in surroundings. PFN carry 2-16 % risk of transformation to malignant peripheral nerve sheath tumour and thus account for major cause of mortality in NF-1.[3]

Our patient presented with hyperpigmented patch with splashed margins, rapid increase in size and development of hair during puberty, had consistent dermoscopy, histopathology and Fontana Mason staining for BN. The absence of nevoid cells and macromelanosomes on histopathology rule out congenital melanocytic nevus (CMN) and café-au-lait macules, respectively. Negative staining of Fontana mason in dermis with positive staining for S-100 rules out the possibilities of pigmented plexiform neurofibroma and congenital smooth muscle hamartoma and proves beyond doubt the definitive diagnosis of BN with PFN. The distinguishing features of the differential diagnosis considered are tabulated (Table 1).

It is intriguing to note that multiple pigmentary anomalies including CALM, intertriginous freckles, Lisch nodules, Nevus Spilus, Becker's nevus, CMN and malignant melanoma are associated with NF-1.[4-7] Mutations of NF-1 gene cause an activation of proto-oncogene Ras that results in unregulated proliferation and differentiation of many cells including melanocytes.[8] Mutation of NF-1 gene also result in long dendrites which orchestrate the unequal migration of melanocyte resulting in hyper pigmented patch.[8,9] This explains the frequent pigmentary anomalies associated with NF-1.

The association of PFN with overlying congenital BN is rarely described. Singh et al, reported a case of a 22-year-old male with giant congenital Becker's nevus overlying a plexiform neurofibroma without any other features suggestive of NF-I.[7] Choudhary et al. has reported a giant café-au-lait macule overlying PFN in 35-year female patient of NF-1.[10] Vathulya et al, reported series of five cases of blaschkoid pigmentation overlying PFN.[11]

Several theories are proposed supporting the co-localization of pigmentary anomaly with PFN and neurofibromas. Mast cells in neurofibromas produce pro-opiomelanocortin which stimulates the synthesis of interleukin-8, tumour necrosis factor-α, and melanocyte-stimulating hormone. These cytokines induce pigmentation and hamartomatous alterations.

Second, it has been proposed that the fibroblasts in the dermis of neurofibromas secrete nerve growth factor, hepatocyte growth factor, and stem cell factor which stimulate melanocytes and hair growth.[7,12] Though this hypothesis purports the PFN in dermis induces the pigmentary alterations in epidermis resulting in co-localization of the two, in our patient BN presented earlier than PFN. This is probably because pigmentary alterations are easily clinically recognized and the presence of deep congenital PFN cannot be made out at birth.

CONCLUSION

To the best of our knowledge, this is the second case report of the association of congenital Beckers nevus with plexiform neurofibroma with no other swellings of neurofibroma. The report emphasizes that Becker's nevus can masquerade an ominous presence of PFN in type-1 Neurofibromatosis. Presence of giant patch of pigmentation, localized hypertrichosis in neurofibromatosis could be an important clinical clue for underlying plexiform neurofibroma. Deep biopsy is diagnostic and hence is an essential tool in management.

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Ethical approval: Not required

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