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Case Series

Pathology Section

Unusual Presentations of Plexiform Neurofibroma: A Series of Three Cases

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ABSTRACT

Neurofibroma is a benign peripheral nerve sheath tumour, and Plexiform Neurofibroma (PN) is pathognomonic of Neurofibromatosis Type 1 (NF1). It occurs equally in males and females and presents at birth or a very early age. The incidence is 1 in 2500 births per year, with an estimated genital association of 1.8%, where clitoral involvement is very rare in the Indian population. In the present case series, three patients were diagnosed with PN through surgical histopathology and Immunohistochemical (IHC) stains like S-100 and Cluster Differentiation 34 (CD34) at a tertiary care hospital. All three patients were children who had painless, gradually increasing swellings that underwent surgical treatment. Among them, a five-year-old girl presented with painless clitoromegaly, multiple café-au-lait spots, and underwent plastic surgery. She was later clinically diagnosed with NF1 after histopathological and IHC correlation. A two-year-old boy with a firm swelling over his left leg showed hyperintensity and multilobulation on magnetic resonance imaging. A 10-year-old boy with a similar swelling in his right upper arm showed multiple hypoechoic masses on ultrasonography. Both of them were later diagnosed with PN using the same methodology. Although it is benign, there is a risk of malignant transformation in diffuse PNs, and they should be managed by wide excision with a safety margin to prevent recurrence.

Keywords: Café-au-lait, Clitoromegaly, Hypoechoic

INTRODUCTION

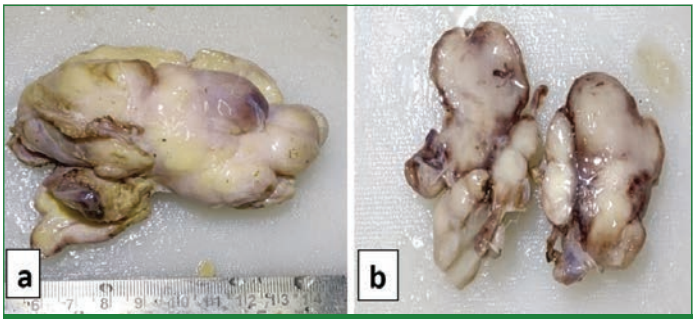
Neurofibroma is a benign nerve sheath neoplasm. Before the word neurofibroma was introduced, cutaneous fibromas were used for skin tumours and neuromas for deep nerve tumours in patients with neurofibromatosis [1]. Neurofibroma is a benign peripheral nerve sheath tumour consisting of differentiated Schwann cells, perineural or perineural-like cells, fibroblasts, and mast cells embedded in a myxoid and collagenous extracellular matrix [2]. PN which are pathognomonic of NF1, can be found in deep or superficial locations in association with nerve roots or large nerves [3]. The incidence of PN is estimated to be 1 in 2500 births per year [4]. The incidence of genital involvement in both sexes has been estimated at 1.8% [5]. A retrospective analysis was conducted in the Department of Pathology at IPGME and R-SSKM Hospital, Kolkata, West Bengal, India. In this case series, three children with PN have been reported, among whom one patient presented with clitoral involvement, while the other two presented with swelling in the leg and arm, respectively.

CASE SERIES

Case 1

A five-year-old girl reported to the Gynaecology Outpatient Department (OPD) with a complaint of a backward stream of urination for three years. Clitoromegaly was noticed from birth, initially small and painless, but progressively increasing in size. She was referred to the Endocrinology OPD for hormonal assessment and adrenal function. Her grandfather had multiple swellings over his body. On physical examination, multiple café-au-lait spots were found, with the largest one measuring 4×5 cm, and multiple nodular swellings were seen in the distal upper and lower limbs and face. There were no signs of virilisation. Examination of the genitalia revealed an enlarged phallus-like structure measuring 5×2×1 cm without any palpable gonads. Laboratory investigations revealed that the serum 17-OH-progesterone level was 0.31 ng/mL, which is normal for her age. Ultrasound revealed an obvious swelling noted in the clitoris, and the uterus bilateral and ovaries were within normal limits. After being referred to the Plastic Surgery OPD, a reduction clitoroplasty was performed. The patient is now in follow-up, with no recurrence occurring in the same site, but she has been diagnosed with NF1.

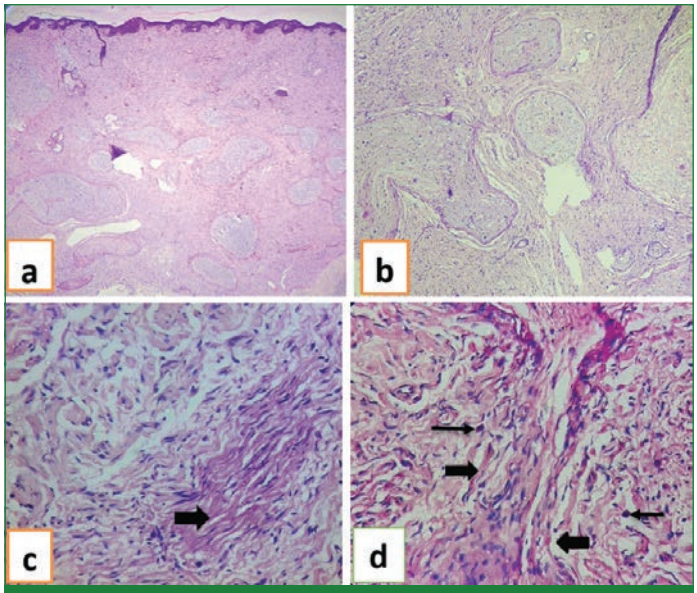
On gross examination, the specimen consisted of a multinodular greyish-white firm mass measuring 5×3×1 cm in size, with overlying skin. On cut-section, it appears as a glistening tan-white plexiform growth [Table/Fig-1a,b]. In the microscopic examination, the lesion shows a nodular or plexiform growth pattern and is composed of spindle-shaped cells arranged in a haphazard manner in a myxoid background. The cells are spindle-shaped with elongated wavy nuclei and indistinct cytoplasmic processes. Fascicles of collagen, nerve bundles and mast cells are seen in the background [Table/Fig-2a-d]. IHC shows that the CD34 stain is diffusely positive throughout the lesion, taking on a curvilinear configuration resembling a fingerprint pattern and S-100 stain showed positivity [Table/Fig-3a-c].



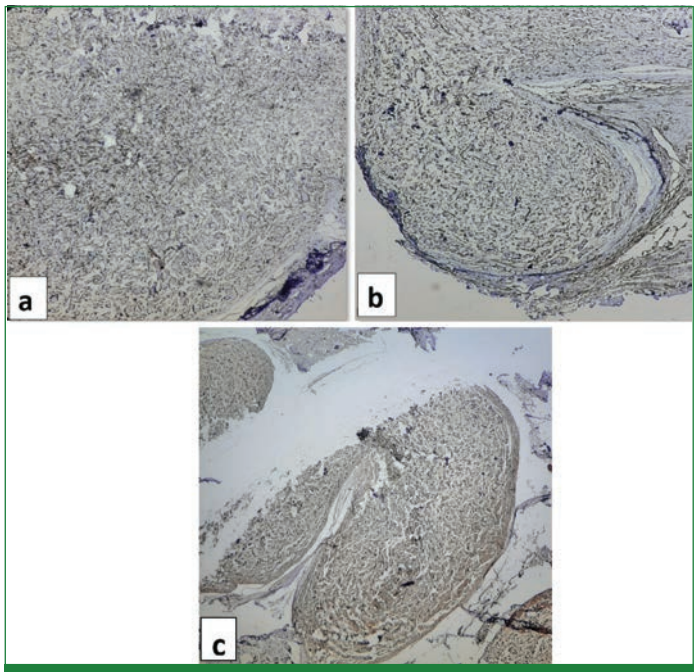
[Table/Fig-1]: Gross picture of PNF: (a) Irregular greyish white multilobulated or multinodular mass measuring 8×4×3 cm; (b) Cut-section was glistening white.

Case 2

A two-year-old boy presented with a painless swelling over his left lower limb for the last year to the Surgery OPD. The swelling was gradually increasing in size and causing difficulty in walking. There was no history of trauma. Upon examination, the swelling was mobile, measuring 5×3×2 cm. During a general physical examination, a few similar nodules were found on his anterior chest wall. There was no family history of a similar lesion. Magnetic Resonance Imaging (MRI) showed a lobulated, serpiginous morphology with central hypointensity surrounded by a rim of hyperintensity signal

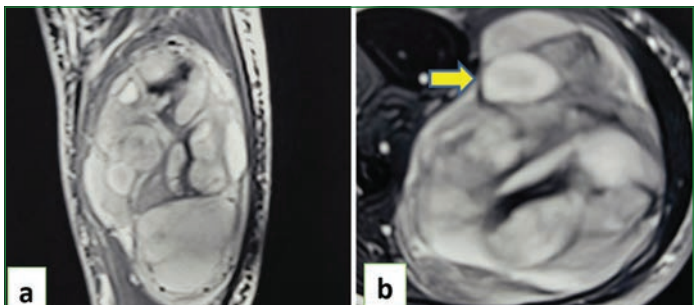


[Table/Fig-2]: Plexiform neurofibroma in H&E stain. (a) (4x); (b) (10x) Images showing nodular or plexiform growth pattern in subcutaneous tissue; (c) (40x)Image showing nodules composed of spindle shaped cells arrange in haphazard manner in a myxoid background with nerve (marked with arrow). The cells are spindle shaped having elongated wavy nuclei and indistinct cytoplasmic process; (d) (40x) Image showing fascicles of collagen (marked with thick arrow) and mast cells (marked with thin arrow) in background.

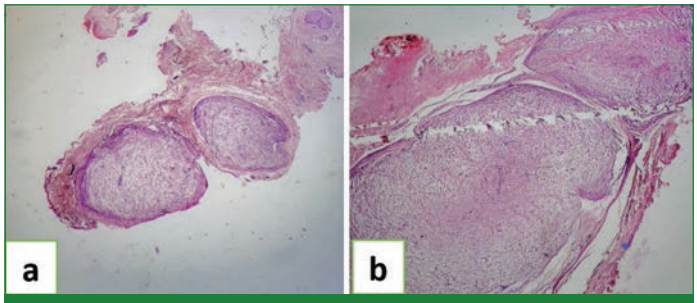


[Table/Fig-3]: Plexiform neurofibroma IHC. (a) (4x); (b) (10x) Images showing CD34 stain is diffusely positive throughout the lesion and takes a curvilinear configuration with an appearance of a fingerprint pattern; (c) (4x) Image showing S-100 stain positivity.

on T2 Weighted (T2W), known as the target sign, with each target depicting an involved nerve fascicle [Table/Fig-4a,b]. Surgical excision of the growth was performed, and his follow-up period has been uneventful, so far. On gross examination, a greyish lobulated mass measuring 5×3×2 cm was observed, and on cut-section, it displayed a glistening white and plexiform appearance. On histopathology examination, the lesion exhibited a nodular growth pattern with spindle-shaped cells arranged in a haphazard manner in a myxoid background, along with fascicles of collagen, nerve bundles and mast cells [Table/Fig-5a,b]. Immunohistochemistry revealed a curvilinear pattern of positivity for the CD34 and stain positivity for the S-100 stain.



[Table/Fig-4]: In the two-year-old boy MRI of left leg. (a,b) Lobulated, serpiginous morphology with central hypointensity surrounded by hyperintensity signal T2W- 'Target sign' with each target depicting involved nerve fascicle 'Target sign' (marked with arrow) with each target depicting involved nerve fascicle.



[Table/Fig-5]: Plexiform neurofibroma of left leg in 2 year old boy H&E stain. (a) (4x) Images showing nodular or plexiform growth pattern; (b) (10x) Image showing nodules composed of spindle shaped cells arrange in haphazard manner in a myxoid background.

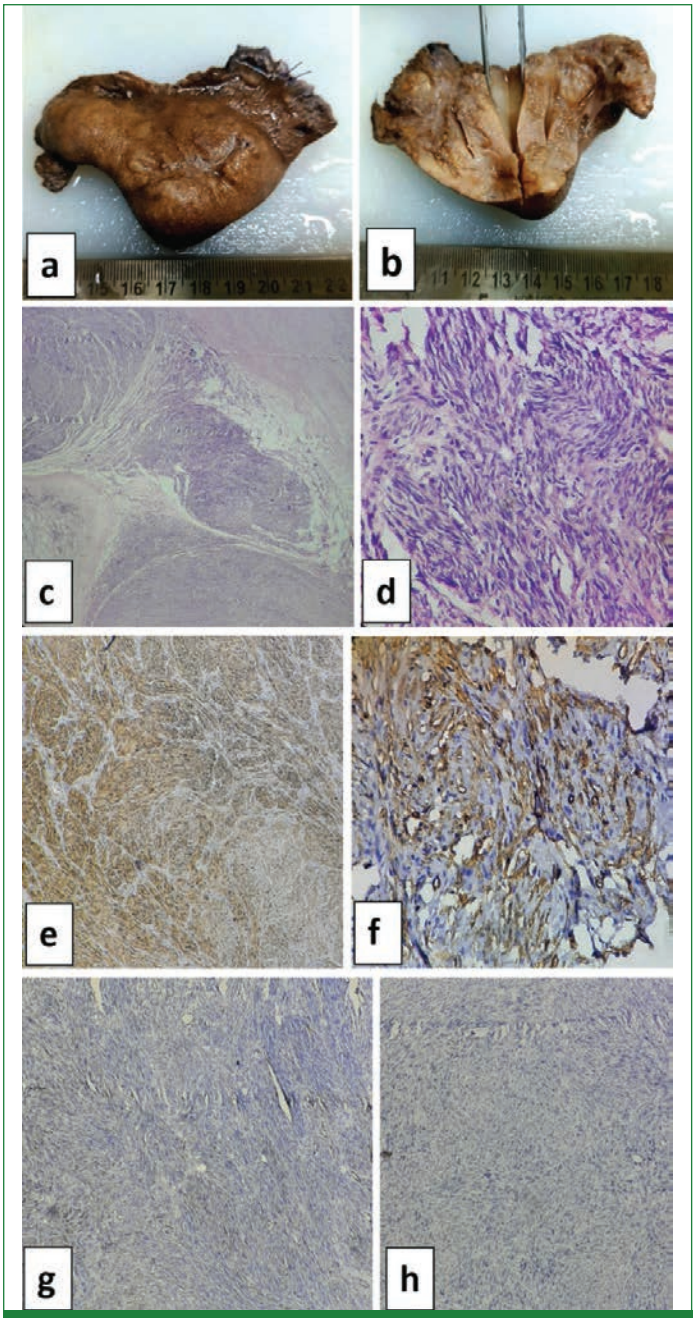
Case 3

A 10-year-old male reported to the Surgical OPD with a history of a swelling in his arm for the last eight years. The swelling was painless and gradually progressive in size. It first appeared when he was one year old as a small nodule, but as it grew larger, it began to restrict the movement of his arm. There was no history of trauma or family history. Upon general physical examination, the swelling was firm, mobile and measured 6×3×3 cm. Additionally, two nodules were found on his back. On Ultrasonography (USG), multiple well-defined hypoechoic masses were observed along the peripheral nerve, measuring 6×3×3 cm, but the image was not available, as it was lost by the patient's party. Surgical excision was performed, and there was no recurrence in the same location after a long follow-up. On gross examination, a greyish lobulated mass measuring 6×3×3 cm with overlying skin was observed, and the cut-section displayed a glistening white and nodular appearance. In histopathology, the lesion exhibited a plexiform growth pattern with spindle-shaped cells arranged in a haphazard manner, along with lymphocytes and mast cells in the background. IHC showed positive staining for S-100 and CD34, while vimentin and desmin staining showed negative results [Table/Fig-6a-h]. All three cases have been summarised in [Table/Fig-7].

DISCUSSION

Neurofibromatosis is a neuroectodermal heterogeneous disease originating from neural crest cells and is classified into two types, NF1 and NF2. NF1 is an autosomal dominant disorder in which Schwann cells exhibit a complete loss of the NF1 gene product, neurofibromin, a tumour suppressor that inhibits Rat Sarcoma (RAS) activity by stimulating Guanosine Triphosphatases (GTPases) and leading to uncontrolled cell proliferation [2]. Neurofibromas are soft tumours mainly located in the trunk and extremities. NF has four variants: discrete, cutaneous in the epidermis and dermis, subcutaneous located deep in the dermis along the course of peripheral nerves, localised nodular PNF, and diffuse PNF. PNFs are an uncommon variant of NF-1 but have one of the worst prognoses [6]. Diffuse PN is a multinodular subtype involving multiple nerve fascicles, each surrounded by perineurium, which most often involves large nerves or plexus.

The diagnostic criteria for NF1 were established by the National Institutes of Health (NIH) in 1987 based on consensus among experts in the field [2]. To diagnose NF1, the presence of two or more of the following criteria is required:



[Table/Fig-6]: Plexiform neurifibroma: Gross, H&E and IHC stain (a-h) in 10 years boy with arm swelling. (a) Gross image showing nodular growth pattern. (b) On cut-section it is grayish white nodular growth; (c) (10x) image showing nodular or plexiform growth pattern; (d) (40x) image showing spindle shaped cells arrange in haphazard manner with lymphocytes and mast cells in background; (e) (10x) image showing S-100 stain positivity; (f) (40x) image showing CD34 stain positivity; (g) (10x) image showing Vimentin stain negative result; (h) (10x) image showing Desmin stain negative result.

- Lisch nodules on the iris of the eye.
- Optic glioma.
- Specific skeletal abnormalities.

A family history of NF1 in a parent, sibling, or offspring.

In the present study, the five-year-old girl met three of the above criteria and was later diagnosed with NF1, while the other cases met only one criterion.

This is also a rare phenomenon that two of the present cases do not meet the criteria for NF1. There is literature supporting the present study findings. Singh P et al., and Atkins NK et al., presented cases of PN without meeting all the other criteria for the diagnosis of NF1 [7,8]. In another study, Lin V et al., examined fifty-one patients with PNs, five of whom had a single solitary PN with no other lesions appearing on follow-up [9]. Similarly, Koko AM and Lasseini A, in a retrospective analysis, reported that only three out of five cases met the criteria for the diagnosis of NF1, with two presenting only with plexiform neurofibromatosis [10]. From the literature review above, it is evident that there is controversy regarding the NIH criteria, but in the present study, the authors will follow-up for a long time to see if any of them develop any other features of NF1.

Clitoral neurofibroma was first reported by Haddad HM and Jones HW Jr [11]. Pascual-Castroviejo I et al., reported three girls and one boy with PNF involving the external genitalia [12]. Two girls had clitoral hypertrophy, one girl had a labial lesion, and the boy had asymmetric penile hypertrophy. Amer MI and Alloob A described a vulval PNF of the diffuse type in a child without clitoral involvement, which is extremely rare, and Almesned R et al., presented a similar type but a huge clitoral PN [6,13]. In all the mentioned cases, there was progressive, painless clitoral involvement with café-au-lait spots, similar to the current study. Collins-Sawaragi YC et al., reported that limb involvement in PNF is 18%, with the most common site being the craniofacial region at 35% [14]. They studied 127 patients with PN, aged between 8 months and 17 years, with 57% presenting disfigurement, 28% experiencing pain and 23% having impairment of function. Fifty-four percent of patients were managed conservatively, 28% underwent surgical treatment, but in the present study, all the patients had painless swelling and were treated surgically due to the risk of malignant transformation. According to Amer MI and Alloob A, four years later the patient presented with a recurrence of vulval swelling, but in our cases, no recurrence occurred [6].

According to the World Health Organisation (WHO), PNF is a multinodular greyish-white firm mass that forms a bag of worms appearance. On cut-section, it appears glistening tan-white with a plexiform growth pattern. Microscopically, it exhibits a nodular or plexiform growth pattern and is composed of spindle-shaped cells arranged in a haphazard manner in a myxoid background.

Case no.	Age	Sex	Chief complaint, family history and clinical details	Physical examination	HPE and IHC	Management	Follow-up
Case 1	5 years	Female	Clitoromegaly. Family history present.	Multiple nodular swellings and café-au-lait spots.	Plexiform Neurofibroma (PN) S-100 (+) CD34 (+)	Reduction clitoroplasty	No growth occurs in same site but she is diagnosed as NF1.
Case 2	2 years	Male	Swelling over left lower limb. Family history absent.	Nodules on anterior chest wall.	Plexiform Neurofibroma (PN) S-100 (+) CD34 (+)	Surgical excision	No growth developed during follow-up.
Case 3	10 years	Male	Swelling in arm. Family history absent.	Two nodules on back.	Plexiform Neurofibroma (PN) S-100 (+) CD34 (+) Vimentin (-) Desmin (-)	Surgical excision	No growth developed during follow-up.

[Table/Fig-7]: Family history, clinical features, Histopathological Examination (HPE), immunohistochemical details, management and follow-up of the three cases have been described in the table below.

- Six or more café-au-lait spots measuring atleast 5 mm in size before puberty and 15 mm in size after puberty.
- Freckles in the axilla or groin.
- Two or more neurofibromas or one PNF.

The cells are spindle-shaped with elongated wavy nuclei and indistinct cytoplasmic processes. Fascicles of collagen and mast cells are also noted [2]. The diagnostic IHC features include CD34 diffuse positivity throughout the lesion, which takes on a curvilinear

configuration with an appearance of a fingerprint pattern and S-100 positivity [15]. The cases in the present study also exhibit similar macroscopic, microscopic and IHC features. There is a risk of malignant transformation and generally, PNFs can transform into Malignant Peripheral Nerve Sheath Tumours (MPNST). The risk of MPNST in NF1 patients is 9-13% [2]. Therefore, surgical excision is the primary treatment option for most lesions in NF1.

CONCLUSION(S)

Authors hereby report three cases of PN presenting with clitoromegaly, arm and leg swelling. Patients with NF-1 present in an extremely variable manner, as it can affect many organs and sites, so proper imaging studies are mandatory. Simultaneously, as it has malignant potential, complete surgical excision and long-term follow-up are necessary to prevent complications.

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