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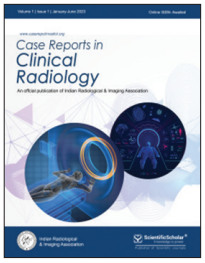

Case Report

An unusual manifestation of neurofibromatosis – A case report of a vulval mass

Shivraj Ingole[1], Ayantika Maity[1]

[1]Department of Radiology, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India.

***Corresponding author:**
Ayantika Maity,
Department of Radiology,
Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India.

ayantikam94@gmail.com

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ABSTRACT

Neurofibromatosis (NF) of the female genitalia is an uncommon manifestation. Selective involvement of the labium majus is quite rare. We describe a rare manifestation of a vulval plexiform neurofibroma without clitoral involvement in a post-pubertal girl. The patient had multiple café-au-lait spots over the neck, back, buttocks and thighs, a patch of pigmentation over the pelvis and inguinal region, axillary freckling, and a large hanging left vulval mass. On ultrasound, it showed hypoechoic nodules on a hyperechoic background with significant vascularity. Magnetic resonance imaging revealed T1-weighted (T1W) hypointense and T2-weighted (T2W) hyperintense, diffuse infiltrating lesion with few T2W hyperintense tubular and nodular areas, presence of "target sign," and intense post-contrast enhancement. A biopsy confirmed it to be neurofibroma. The patient was diagnosed with NF type 1 and underwent surgical resection.

Keywords: Rare vulval mass, Vulval neurofibromatosis, Plexiform neurofibroma, Neurofibromatosis type 1, Target sign

INTRODUCTION

Neurofibromatosis (NF) is a hamartomatous and neurocutaneous condition with multisystemic involvement.[1,2] It manifests as two types – NF type 1 (NF1) and NF type 2 (NF2). NF1 – also known as von Recklinghausen disease or peripheral NF, shows autosomal dominant inheritance and is one of the most common inherited central nervous system (CNS) disorders and tumor syndromes (incidence-1 in 3000 births).[1,2] NF1 occurs due to defective tumor suppression (gene locus: Chromosome 17), leading to multiple benign and malignant tumors, predominantly of the CNS, orbit, vascular, and cutaneous systems.[1,3]

Involvement of the female genital system by NF is uncommon.[2] Vulva is most frequently involved and clitoromegaly is the most common presentation. NF of vagina, cervix, endometrium, myometrium, ovaries, or the urinary tract is less frequent presentations. Clitoral neurofibromas in NF1 are rare, but even rarer are selective NF of the labium majus without clitoral involvement.[2,3] In this report, we present a post-pubertal girl with vulval plexiform neurofibroma (PNF) without clitoral or any pelvic organ involvement.

CASE REPORT

A 17-year-old girl presented with a swelling on the left side of her external genitalia for the past 3 years which was insidious in onset, gradually progressive with recent increase in size of swelling

since past 5 months and had occasional dull pain. No other similar swelling was present. She denied any history of fever, trauma, or any vaginal discharge.

On local examination, a large ill-defined soft tissue swelling was seen, measuring approximately: 10 × 8 cm, involving the skin and subcutaneous tissues of the left side of vulva and left labium majus. It was extending from the ipsilateral inguinal region till the perineum and gluteal region. The lesion was soft in consistency with few nodular components. Clitoris was spared. She had a hyperpigmented patch over the pelvis, bilateral inguinal regions, and perineum [Figure 1a]. A detailed systemic examination revealed few hypopigmented macules over her face. Café-au-lait macules were found over her neck, arms, back, buttocks, and thighs with axillary freckling [Figure 1a and b]. No evidence of shagreen patch, adenoma sebaceum or angiofibroma, or any positive ophthalmological findings was found. All these findings raised the suspicion of NF1. However, no positive family history was evident.

The patient then underwent an ultrasound examination of the local site, which showed a large ill-defined lesion involving the cutaneous and subcutaneous planes of the left inguinal region, labium majus, vulva, perineum, and extending posteriorly to the left gluteal region. The mass had a mixed echo-pattern, with few hypoechoic nodular areas on a hyperechoic background. On colour Doppler, it showed significant vascularity [Figure 1c and d].

Magnetic resonance imaging (MRI) of the pelvis revealed an ill-defined infiltrating lesion involving the cutaneous and subcutaneous tissues of the left inguinal region, vulva, labium majus, perineum, and the gluteal region. The lesion was hypointense on T1 weighted image (T1WI) and hyperintense on T2 weighted image (T2WI) with marked post-contrast enhancement, resembling a "bag of worm" appearance. Few T2W hyperintense nodular and tubular lesions were seen, some of them showing "target sign" (central hypointensity with peripheral hyperintense rim on T2WI). There was diffuse hypertrophy of the overlying subcutaneous fatty tissue and of the medial portion of the right gluteal region with intense post-contrast enhancement [Figure 2a and b]. Pelvic organs and adjacent bones were unremarkable.

Radiological and clinical findings raised the possibility of vulval PNF. Computed tomography (CT) brain and MRI brain screening revealed no abnormalities.

The patient underwent an ultrasound guided biopsy which clinched the diagnosis [Figure 3].

DISCUSSION

Derived from the neural crest cells, neurofibromas are essentially benign tumors having components of peripheral nerve such as Schwann cells and intraneural fibroblasts.[4] NF1 – the most common of the phakomatoses and a RASopathy, is inherited as an autosomal dominant disease in 50% of cases, while in the remaining 50%, *de novo* mutations lead to disease formation. The gene product encoded is neurofibromin which participates in Ras/MAPK pathway as a tumor suppressor, inactivation of which results in tumor formation.[1,3,5] NF2 (transmitted on chromosome 22) presents with bilateral acoustic schwannomas, meningiomas, and ependymomas.[5,6]

The diagnosis of NF1 is mainly clinical, relies on criteria established by National Institutes of Health Consensus Development Conference, as presence of two or more of the following: Café-au-lait macules, axillary or inguinal freckling, two or more neurofibroma or one PNF, optic nerve glioma, osseous lesions (sphenoid wing dysplasia or thinning of cortex of long bones with or without pseudoarthrosis), and two or more Lisch nodules, a primary relative with NF1.[1-3] Predominantly affecting the skin, peripheral nerves and bones, the female urogenital tract involvement in NF-1, however, is very rare.[1,2,7]

Neurofibromas are classically of three types – localized, diffuse, and plexiform.[8] PNF, a benign peripheral nerve sheath tumor, is an uncommon variant of neurofibroma, but it is typical of NF1.[3,8] PNFs mostly affect face, neck, and inguinal region.[8,9] Vulva is the most common affected part of the female genitalia, with rarely reported cases of vaginal, cervical, uterine, and ovarian NF.[5,7] Involvement of the clitoris with other areas of genitourinary system is the most common presentation, while affection of the labium majus alone is quite rare.[2,7]

PNFs rarely grow into large lesions; however, these can show progressive enlargement and typically increase in size in early childhood, puberty, and childbearing age.[9,10] Hence, clinically patients present with complaints of cosmetic disfigurement, pain, functional impairment, or history of sudden increase in size of the mass.[8-10] PNFs usually grow along a segment of nerve extending along its branches, thereby giving the typical "bag of worm" pattern on palpation and on imaging.[3,8] PNFs also have the potential for malignant transformation into highly malignant nerve sheath tumors and neurosarcoma.[2,7,8] Hence, such masses need to be evaluated meticulously and here comes the crucial role of imaging – in differentiating superficial from invasive lesions as well as benign from malignant lesions. In addition, for optimal planning of surgical resection, MR is the imaging modality of choice.[8,10]

Sonography is irreplaceable as the initial imaging modality as it rules out similar conditions and also being free of radiation hazard, can be safely used for the younger generation. Reuter *et al.* and Hong *et al.* were the earliest to report sonographic description of PNFs. Reuter *et al.* stated that these tumors comprised of hypoechoic nodules and merits differentiation

Table 1: Differential diagnoses of solid vulval masses.

Differential diagnosis	Definition	Clinical feature	Differentiating feature on imaging
Schwannoma	Type of benign peripheral nerve sheath tumour, arising from Schwann cells	Solitary, flesh colored, nodular lesion	Well-defined, Slight T2WI hyperintense, T1WI hypointense with heterogeneous enhancement
Leiomyoma	Benign, tumor arising from smooth muscle cells	Solitary, flesh colored nodule, typically painless	Well circumscribed, hypo-to-isoechoic on USG. MRI-hypointense on T2WI, intermediate on T1WI with variable enhancement, can show degeneration if large
Lipoma	Benign, slow growing tumor arising from adipose tissue	Soft, slow growing subcutaneous nodule	Well circumscribed Echogenic on USG Hyperintense on T1WI and T2WI with suppression on Fat saturated sequence
Myxoma/ angiomyxoma	Slow growing mesenchymal tumor	Extremely rare in the female genital tract	Well defined with low attenuation on CT. MRI-hyperintense on T2WI, hypointense on T1WI, swirling appearance, enhancement present.

T1WI: T1-weighted image, T2WI: T2-weighted image, MRI: Magnetic resonance imaging, CT: Computed tomography, USG: Ultrasound

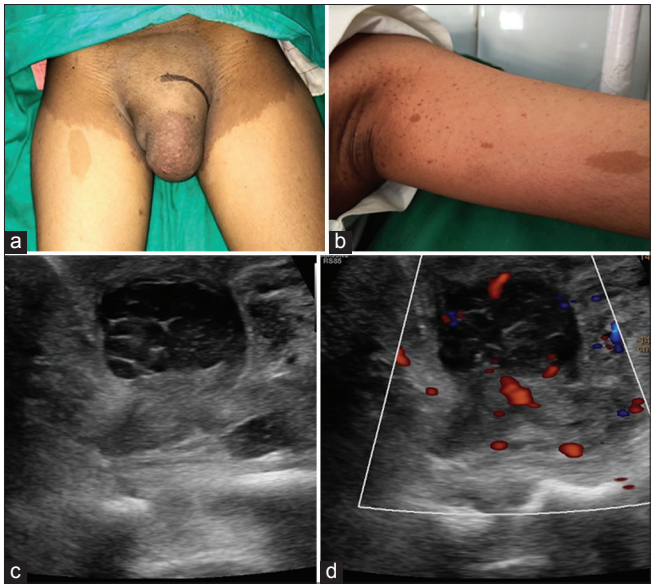

Figure 1: The patient presented with (a-b) a large ill defined hanging left vulval mass, extending from the left inguinal region to the perineum and upto the gluteal region. She had a patch of pigmentation over the bilateral inguinal regions, vulva, and perineum, multiple café-au-lait macules over her neck, arms, buttocks, and thighs, axillary freckling. (c-d) Ultrasound examination showed an ill defined mixed echogenicity mass, with hypoechoic nodular areas on a hyperechoic background with significant vascularity.

from abscess or vascular malformation. Hong *et al.*, elaborated these tumors to be poorly circumscribed masses showing hypoechoic nodules on a hyperechoic background with presence of considerable vascularity.[8] Our patient also had similar sonography findings.

On CT, PNFs appear to be low attenuating masses due to its myelin-lipid content and high water containing endoneurial

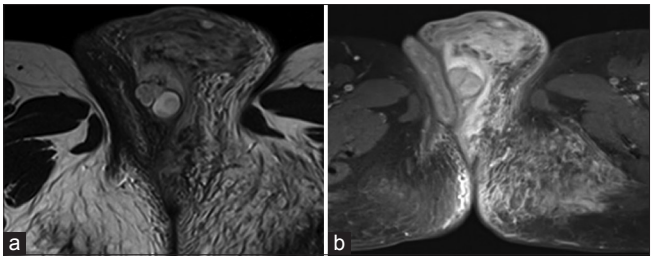

Figure 2: (a and b) Magnetic resonance imaging revealed an ill defined infiltrating lesion involving the cutaneous and subcutaneous tissues of the left labium majus, perineum, inguinal region, and gluteal region. The lesion was hypointense on T1WI and intermediate to hyperintense on T2WI with marked post-contrast enhancement showing a bag of worm appearance.

myxoid component. The primary role of CT is to look for any bone involvement or bony remodeling.[8,10]

MRI is the gold standard imaging modality for imaging of neural tissues, for delineation of extent of lesion and to look for nerve of origin. PNFs have characteristically been described on MRI as lobulated mass with T2 WI hyperintense signal and a diagnostic "target sign," which is representative of individual nerve fascicle showing central hypointensity (due to the fibrous component) with a peripheral rim of hyperintensity, imparted by the surrounding myxoid elements.[3,8] MRI findings in our patient were quite similar. A characteristic "reverse target sign" has also been defined on post-contrast imaging. Contrast scan is also needed for evaluation of suspected malignant transformation. Findings such as intratumoral cystic change, perilesional edema, and heterogeneous T1WI signal should raise suspicion of malignant transformation.[8,10]

The ideal treatment for PNFs is surgical resection.[8,10] However, surgical management can be challenging due to its

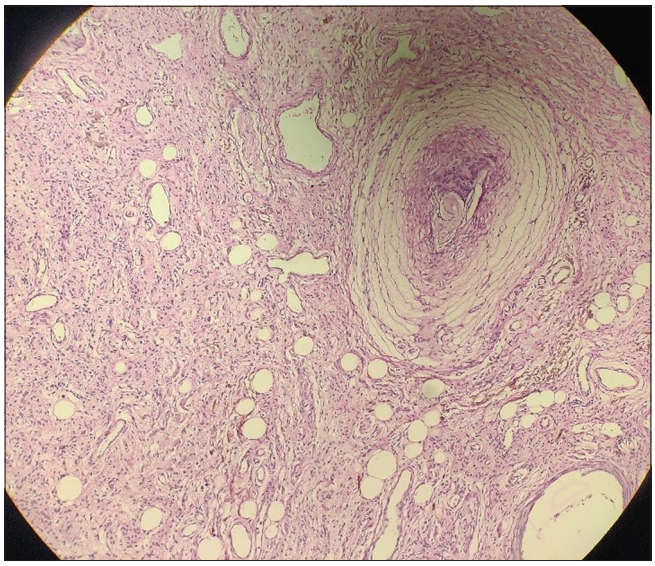

Figure 3: On histopathology, it was found that the mass was composed of spindle cells with thin wavy nuclei and delicate pale eosinophilic cytoplasm in a collagenous stroma admixed with mast cells. Focal areas show variable presence of melanin pigment. Tumor is infiltrative involving the subcutaneous tissue entrapping the adipocytes and showed the presence of Meissner bodies and Pacinian corpuscles – findings consistent with neurofibroma.

infiltrative nature, high vascularity, and tendency to recur.[4,7,9] Thus, plan of surgery should be individualized and for giant lesions a multidisciplinary approach is ideal.[10]

Counseling regarding the risk of recurrence, the nature of transmission of the disease, family screening, and the importance of follow-up forms crucial part of overall management.

DIFFERENTIAL DIAGNOSIS

1. Schwannoma
2. Myxoma/Angiomyxoma
3. Leiomyoma

NF should be an important differential in the evaluation of vulval masses [Table 1].

CONCLUSION

PNFs are benign tumors which are characteristically associated with NF1. Hence, local and systemic examination of the patient to look for stigmata of NF1 and relevant family history is of utmost importance. These tumors give characteristic "bag of worms" pattern on palpation and show diffuse infiltrative nature of growth involving the subcutaneous and cutaneous tissues along the neural components. Imaging appearances on ultrasound and MRI are characteristic and show fat and fluid contents with a typical "target sign." Surgical resection may be difficult but is the preferred treatment.

TEACHING POINTS

1. In a patient with stigmata of NF1, possibility of neurofibroma or a plexiform neurofibroma should be kept in mind, when dealing with a soft-tissue lesion at an unusual location.
2. Meticulous systemic examination and CT or MR screening (as applicable) to be done to rule out hypertension, ophthalmological, CNS or bone lesions in patients with NF1 along with appropriate counseling regarding disease transmission and family screening.

MCQs

1. Which of the following is not included in diagnostic criteria of NF1?
   a. Optic glioma
   b. Sphenoid wing dysplasia
   c. Lisch nodules
   d. Ependymoma

Answer Key: d

2. Which of the following is not true regarding plexiform neurofibroma?
   a. Typically associated with NF1
   b. Shows "bag of worm" appearance
   c. Commonly involves the Vulva
   d. Shows "target sign" on MRI

Answer Key: c

3. Which of the following is not a feature of malignant transformation of plexiform neurofibroma?
   a. Intratumoral cystic change
   b. Reverse target sign
   c. Perilesional edema
   d. Heterogeneous T1WI signal

Answer Key: b

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