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THE NERVE THAT NEVER RESTED: PLEXIFORM NEUROFIBROMA PRESENTING AS MASSIVE SOFT TISSUE SWELLING IN AN 82-YEAR-OLD: A LINICOPATHOLOGICAL STUDY

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ABSTRACT

Background: Plexiform neurofibroma is a rare benign peripheral nerve sheath tumour that is strongly associated with Neurofibromatosis Type 1 (NF1). Although most lesions present during childhood or early adulthood, giant plexiform neurofibromas occurring in elderly individuals without an established diagnosis of NF1 are exceptionally uncommon and frequently mimic malignant soft tissue tumours, posing significant diagnostic and therapeutic challenges.

Case Presentation: An 82-year-old female presented with progressively enlarging swellings over the right thigh and right leg for five years, associated with rapid enlargement and pain during the preceding few months. Magnetic resonance imaging demonstrated a well-defined multilobulated exophytic subcutaneous lesion measuring 140 × 130 × 110 mm in the medial aspect of the right thigh and a large ill-defined intramuscular lesion measuring 245 × 122 × 85 mm involving the anterior compartment of the right leg with trans-fascial extension. Multiple cutaneous and subcutaneous nodules were identified throughout the thigh, raising suspicion of a plexiform neurofibroma with malignant peripheral nerve sheath tumour as an important differential diagnosis. Histopathological examination of the biopsy and excised specimens demonstrated spindle-shaped cells with elongated wavy nuclei embedded within abundant myxoid and collagenous stroma without significant atypia, increased mitotic activity, or tumour necrosis. Complete surgical excision was performed, and the final diagnosis was diffuse (plexiform) neurofibroma with tumour-free surgical margins. Immunohistochemistry was recommended for definitive confirmation.

Conclusion: This case highlights the rare presentation of a giant diffuse plexiform neurofibroma in an elderly patient without documented NF1. Despite its enormous size and aggressive radiological appearance, histopathological evaluation confirmed a benign lesion. Accurate diagnosis requires careful correlation of clinical findings, imaging, histopathology, and ancillary investigations. Complete surgical excision remains the treatment of choice for resectable lesions, while long-term clinical and radiological surveillance is essential because of the recognised risk of recurrence and malignant transformation.

KEYWORDS: Plexiform neurofibroma; diffuse neurofibroma; peripheral nerve sheath tumour; Neurofibromatosis type 1; malignant peripheral nerve sheath tumour; magnetic resonance imaging; histopathology; giant soft tissue tumour; elderly; case report.

INTRODUCTION

Peripheral nerve sheath tumors (PNSTs) comprise a diverse group of neoplasms arising from the supporting elements of peripheral nerves, including Schwann cells, perineurial cells, fibroblasts, and associated connective tissue. According to the World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours (5th Edition), these tumors are broadly classified into benign, intermediate, and malignant lesions, with neurofibromas representing one of the most common benign peripheral nerve sheath tumors. Among the various subtypes, plexiform neurofibroma (PN) is a distinctive lesion characterized by diffuse expansion of multiple nerve fascicles, producing the classical "bag of worms" appearance. Unlike localized neurofibromas, plexiform neurofibromas exhibit an infiltrative growth pattern, often extending into adjacent soft tissues, muscles, and neurovascular structures, making complete surgical excision technically challenging and predisposing to local recurrence. Importantly, these lesions possess a recognized risk of transformation into malignant peripheral nerve sheath tumor (MPNST), particularly in patients with **Neurofibromatosis Type 1 (NF1).**[1]

Plexiform neurofibromas are composed of a heterogeneous proliferation of Schwann cells, fibroblasts, perineurial-like cells, mast cells, and entrapped axons embedded within abundant myxoid and collagenous stroma. Histologically, they demonstrate hypocellular spindle-shaped cells with elongated, wavy nuclei arranged in a loose myxoid background, with minimal cytological atypia, absent or infrequent mitotic figures, and no tumor necrosis in benign lesions. These

characteristic microscopic features help distinguish plexiform neurofibroma from malignant peripheral nerve sheath tumors, although overlapping morphological findings may occasionally necessitate immunohistochemical evaluation. The pathogenesis is primarily linked to mutations involving the NF1 tumor suppressor gene located on chromosome 17q11.2, resulting in dysregulation of the RAS/MAPK signaling pathway and uncontrolled proliferation of neural crest-derived cells.[2]

Clinically, plexiform neurofibromas usually develop during childhood or early adulthood and frequently involve the head and neck, brachial plexus, pelvis, or extremities. Their clinical presentation varies according to the anatomical location and extent of involvement. Small lesions may remain asymptomatic for years, whereas larger tumors can produce progressive swelling, pain, cosmetic disfigurement, neurological deficits, vascular compression, functional impairment, and reduced quality of life. Rapid increase in tumor size, persistent pain, neurological deterioration, increasing firmness, or development of heterogeneous imaging characteristics should raise suspicion for malignant transformation. Although the estimated lifetime risk of MPNST development in patients with NF1-associated plexiform neurofibroma is approximately 8–13%, giant lesions occurring in elderly patients without a previously established diagnosis of NF1 are distinctly uncommon and present considerable diagnostic and therapeutic challenges.[3]

Magnetic resonance imaging (MRI) remains the imaging modality of choice for evaluating peripheral nerve sheath tumors because of its superior soft tissue resolution and ability to delineate tumor extent, relationship to adjacent neurovascular structures, and internal characteristics. Typical MRI findings include multilobulated masses with high T2-weighted signal intensity, the characteristic "target sign," and extensive involvement along the course of peripheral nerves. Nevertheless, imaging findings alone cannot reliably differentiate benign plexiform neurofibroma from malignant peripheral nerve sheath tumor, particularly in large, rapidly enlarging, or deeply infiltrative lesions. Consequently, histopathological examination remains the diagnostic gold standard, with immunohistochemical markers such as S-100, SOX10, Ki-67, and H3K27me3 providing valuable adjunctive information in diagnostically challenging cases. Current management emphasizes a multidisciplinary approach involving surgeons, radiologists, pathologists, oncologists, and rehabilitation specialists. Complete surgical excision remains the preferred treatment whenever feasible, while advances in targeted therapies, particularly MEK inhibitors, have expanded treatment options for selected patients with unresectable or progressive plexiform neurofibromas.[4]

The present report describes an 82-year-old woman presenting with a massive plexiform neurofibroma involving the right thigh and leg, manifesting as progressively enlarging soft tissue swellings over several years with recent rapid enlargement and pain. The patient's advanced age, extraordinary tumor size, extensive soft tissue involvement, and radiological suspicion of malignancy make this an exceptionally rare clinical presentation. This case highlights the importance of integrating clinical findings, radiological evaluation, histopathological examination, and appropriate ancillary investigations to accurately distinguish benign plexiform neurofibroma from malignant peripheral nerve sheath tumor, thereby facilitating optimal management and long-term surveillance.

MATERIALS AND METHODS

This report is based on a single patient managed at an outpatient surgical clinic with referral to a tertiary diagnostic center. The following data were collected and analyzed:

- Clinical history, presenting complaints, and physical examination findings
- MRI findings from two sequential imaging studies (right thigh on 28-03-2026 and right leg on 27-03-2026) performed at Indian Scan, Tambaram
- Histopathological examination of biopsy cores from thigh lesion (Specimen A) and leg lesion (Specimen B), processed at Anderson Diagnostic Services Pvt. Ltd., Chennai
- Microscopic morphology assessed for cellularity, cell type, stromal composition, mitotic activity, and necrosis

Tissue sections were stained with Hematoxylin and Eosin (H&E). The specimen was grossed and submitted totally for histopathological analysis. Tumor grade and malignant potential were assessed based on WHO Classification of Soft Tissue Tumours (5th Edition, 2020).

CASE PRESENTATION

An 82-year-old female presented to the surgical outpatient department with progressively enlarging swellings over the medial aspect of the right thigh and the anterior aspect of the right leg for five years. The swellings were initially small, painless, and soft in consistency, gradually increasing in size over time. During the preceding few months, both lesions exhibited rapid enlargement associated with pain, prompting medical evaluation. There was no history of trauma, fever, constitutional symptoms, or weight loss. The patient had no previous history of similar lesions, surgical intervention, or biopsy. There was no known family history of neurofibromatosis or other hereditary tumor syndromes.

Clinical Examination

The patient was conscious, alert, and haemodynamically stable. General physical examination was unremarkable, with no pallor, icterus, cyanosis, clubbing, generalized lymphadenopathy, or pedal edema. A detailed local examination revealed two dominant soft tissue masses involving the right lower limb. The thigh lesion was located along the medial aspect of the mid-thigh, while the second lesion occupied the anterior compartment of the right leg. Multiple smaller cutaneous and subcutaneous nodules were also present over the thigh.

The thigh mass measured approximately 140 × 130 × 110 mm, whereas the leg lesion measured 245 × 122 × 85 mm. Both swellings were multilobulated with a bosselated surface and soft-to-firm consistency. The overlying skin was intact without ulceration, erythema, or local warmth. Mild tenderness was present on palpation, particularly over the larger

lesions. The leg lesion appeared fixed to the underlying structures, whereas the thigh lesion remained predominantly subcutaneous. Distal neurovascular examination was normal.

Laboratory Investigations

Routine hematological and biochemical investigations, including complete blood count, renal and liver function tests, coagulation profile, and blood glucose levels, were within normal limits.

Radiological Evaluation

Magnetic resonance imaging (MRI) of the right thigh demonstrated a well-defined multilobulated exophytic subcutaneous lesion measuring 140 × 130 × 110 mm along the medial aspect of the mid-thigh. The lesion abutted the underlying muscle plane without evidence of osseous involvement. Associated inflammatory changes were present within the surrounding subcutaneous fat. Correlative computed tomography revealed a small calcific focus with interlobular fatty areas, while ultrasonography demonstrated a few cystic areas containing thin septations. Numerous T2-weighted hyperintense cutaneous and subcutaneous nodules were identified throughout the thigh. The femur, surrounding musculature, and femoral vessels were preserved. The radiological differential diagnosis included plexiform neurofibroma and a myxomatous lesion.

MRI of the right leg demonstrated a large ill-defined multilobulated intramuscular lesion measuring 245 × 122 × 85 mm involving the anterior compartment with extension into the subcutaneous tissue. The lesion displaced the tibialis anterior muscle anteriorly and the remaining muscles posteriorly, with trans-fascial extension through the interosseous membrane into the posterior compartment. Mild inflammatory changes were present within the adjacent subcutaneous fat. The tibia and fibula showed preserved marrow signal without cortical destruction. Based on these findings, the radiological differential diagnosis included plexiform neurofibroma, myxomatous lesion, and malignant peripheral nerve sheath tumour (MPNST).

Histopathological Examination

Core needle biopsies obtained from both lesions demonstrated spindle cell proliferations arranged in sheets within a loose myxoid and collagenous stroma. The tumour cells exhibited elongated wavy nuclei with eosinophilic cytoplasm. Scattered foamy histiocytes and inflammatory cells were present. No significant cytological atypia, increased mitotic activity, or tumour necrosis was identified. The initial pathological impression was a spindle cell neoplasm of neural origin, favouring neurofibroma, and immunohistochemistry was recommended for confirmation.

Subsequently, complete excision of both lesions was performed. Gross examination revealed encapsulated soft tissue masses measuring 19 × 11 × 6 cm (thigh) and 23 × 12 × 6 cm (leg). Histopathological examination demonstrated spindle-shaped cells with characteristic wavy nuclei embedded in abundant myxoid and collagenous stroma. Focal infiltration into adjacent skeletal muscle fibres was identified in the leg lesion; however, there was no evidence of increased mitotic activity, tumour necrosis, or significant nuclear atypia. All circumferential surgical resection margins were free of tumour. The overall histomorphological features were consistent with diffuse-type neurofibroma, and immunohistochemistry was advised for definitive confirmation.

Final Diagnosis

Based on the clinical findings, radiological characteristics, and histopathological examination, a diagnosis of giant diffuse (plexiform) neurofibroma involving the right thigh and right leg was established. Complete surgical excision with histologically negative margins was achieved, and the patient was advised regular postoperative surveillance because of the lesion's infiltrative nature and the potential risk of malignant transformation.

DISCUSSION

Plexiform neurofibroma is a rare benign peripheral nerve sheath tumour characterised by diffuse proliferation of Schwann cells, fibroblasts, perineurial cells and axons involving multiple nerve fascicles. It is regarded as a hallmark lesion of Neurofibromatosis Type 1 (NF1) and demonstrates infiltrative growth with a recognised risk of malignant transformation into malignant peripheral nerve sheath tumour (MPNST). The WHO Classification of Soft Tissue and Bone Tumours (5th Edition) recognises plexiform neurofibroma as a benign tumour with locally aggressive behaviour, particularly when complete surgical excision is not feasible because of extensive anatomical involvement [1]. The present case is unusual because the patient presented at 82 years of age with giant lesions involving both the thigh and leg, whereas most plexiform neurofibromas are diagnosed during childhood or early adulthood.

The histopathological findings in the present case closely resembled the classical microscopic features described in Robbins and Cotran Pathologic Basis of Disease. Histology demonstrated spindle-shaped cells with elongated wavy nuclei embedded within abundant myxoid and collagenous stroma without significant nuclear atypia, mitotic activity or tumour necrosis [2]. These findings supported a benign neural tumour despite the unusually large tumour size. Similarly, Rosai and Ackerman's Surgical Pathology describes diffuse neurofibromas as infiltrative spindle cell neoplasms composed of Schwann cells with characteristic wavy nuclei in a loose collagenous and myxoid background. The absence of hypercellularity, pleomorphism and necrosis effectively distinguishes diffuse neurofibroma from MPNST, which was consistent with the findings observed in the present patient [3].

Radiological evaluation demonstrated a multilobulated exophytic subcutaneous lesion in the thigh and a large intramuscular lesion involving the anterior compartment of the leg with trans-fascial extension through the interosseous membrane. Although these findings raised suspicion for malignant transformation because of the lesion size and deep extension, histopathological examination confirmed benign diffuse neurofibroma. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, rapidly enlarging peripheral nerve sheath tumours should undergo detailed MRI evaluation followed by tissue diagnosis before definitive treatment, particularly when

malignancy is suspected [4]. The present case followed this recommended diagnostic pathway, enabling appropriate surgical planning.

Recent advances in targeted therapy have significantly changed the management of unresectable plexiform neurofibromas. Gross et al. evaluated selumetinib in children with inoperable plexiform neurofibromas and reported a confirmed partial response in approximately 68% of patients, together with sustained reduction in tumour volume, improvement in pain and better functional outcomes [5]. Unlike that study, the present patient had a giant but surgically resectable lesion; therefore, complete surgical excision remained the preferred treatment option rather than medical therapy.

Similar observations have recently been reported in adults. Yuen et al. evaluated selumetinib in adults with NF1-associated plexiform neurofibromas and demonstrated clinically meaningful tumour reduction with improvement in pain, physical function and quality of life while maintaining an acceptable safety profile [6]. However, the current patient had no definite evidence of NF1 and achieved complete tumour excision with histologically negative margins. Consequently, systemic targeted therapy was not indicated, although it may represent a valuable alternative should recurrence or unresectable disease develop during follow-up.

The long-term management of patients with giant neurofibromas extends beyond surgery. Miller et al. emphasised that survivorship care should include structured follow-up, rehabilitation and early recognition of recurrence or secondary malignancy to optimise functional recovery and long-term quality of life [7]. In the present case, postoperative physiotherapy together with regular clinical and radiological surveillance was advised because of the extensive soft tissue involvement and the known risk of recurrence associated with diffuse neurofibromas.

The biological mechanisms responsible for malignant transformation continue to be investigated. Muniz et al. demonstrated that multiple genomic alterations involving tumour suppressor pathways contribute to the aggressive behaviour of MPNST-like tumours, highlighting the importance of molecular evaluation in diagnostically challenging lesions [8]. Likewise, Cimino and Gutmann described the central role of NF1 gene inactivation and dysregulation of the RAS-MAPK signalling pathway in neurofibroma development and progression [9]. Although no clinical features strongly suggested NF1 in the present patient, the unusually extensive disease burden warranted continued surveillance because malignant transformation cannot be predicted solely by histopathological findings.

With regard to treatment, Hwang et al. concluded that complete surgical excision remains the treatment of choice whenever technically feasible, whereas MEK inhibitors should be considered for unresectable, progressive or recurrent plexiform neurofibromas [10]. Our management closely paralleled these recommendations, as both lesions were completely excised and histopathological examination confirmed tumour-free surgical margins. Similarly, the European Society for Medical Oncology (ESMO) recommends multidisciplinary decision-making involving surgeons, radiologists, pathologists and oncologists for complex peripheral nerve sheath tumours to optimise diagnosis and treatment planning [11]. This multidisciplinary approach was adopted throughout the present case.

Recent molecular evidence has further improved understanding of malignant progression. Yu et al. reported that transformation from benign neurofibroma to MPNST results from sequential accumulation of genetic and epigenetic alterations involving multiple signalling pathways rather than a single molecular event [12]. Their findings reinforce the importance of recognising clinical warning signs such as rapid enlargement, persistent pain and neurological deficits. In the present case, despite rapid enlargement and exceptionally large tumour size, histopathological examination demonstrated no evidence of increased mitotic activity or necrosis, confirming the benign nature of the lesion.

Overall, this case represents a rare presentation of giant diffuse plexiform neurofibroma in an elderly patient without a documented history of NF1. The exceptionally large tumour size, trans-fascial extension and rapid recent enlargement initially raised concern for malignant peripheral nerve sheath tumour. However, careful correlation of clinical findings, MRI features and histopathological examination established the diagnosis of benign diffuse neurofibroma. This case underscores the importance of a multidisciplinary approach, meticulous pathological evaluation and long-term postoperative surveillance in the management of giant peripheral nerve sheath tumours.

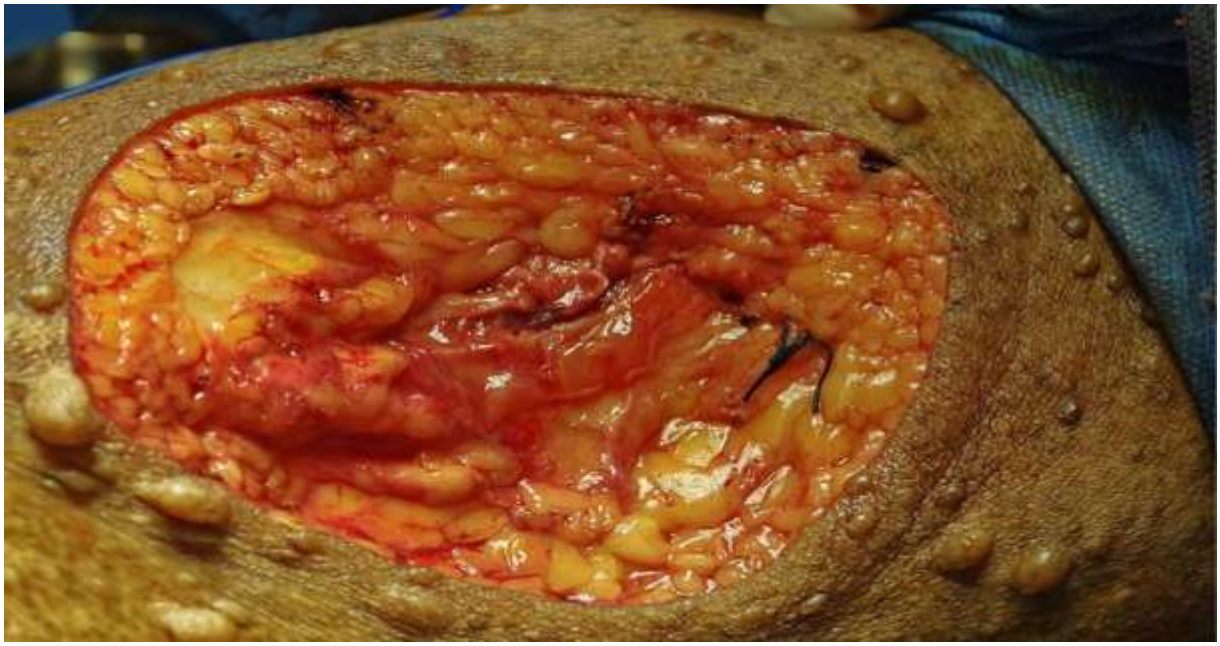

Figure 1. Gross photograph showing the excised right thigh specimen with a lobulated soft tissue mass.

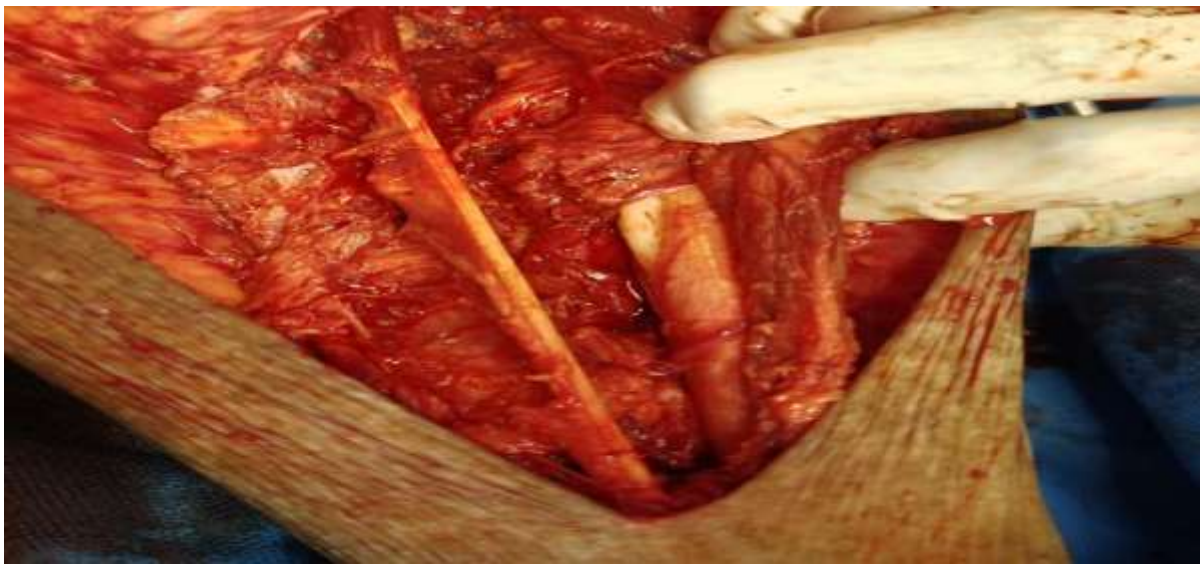

Figure 2. Gross photograph showing the excised right leg specimen with a large lobulated soft tissue mass.

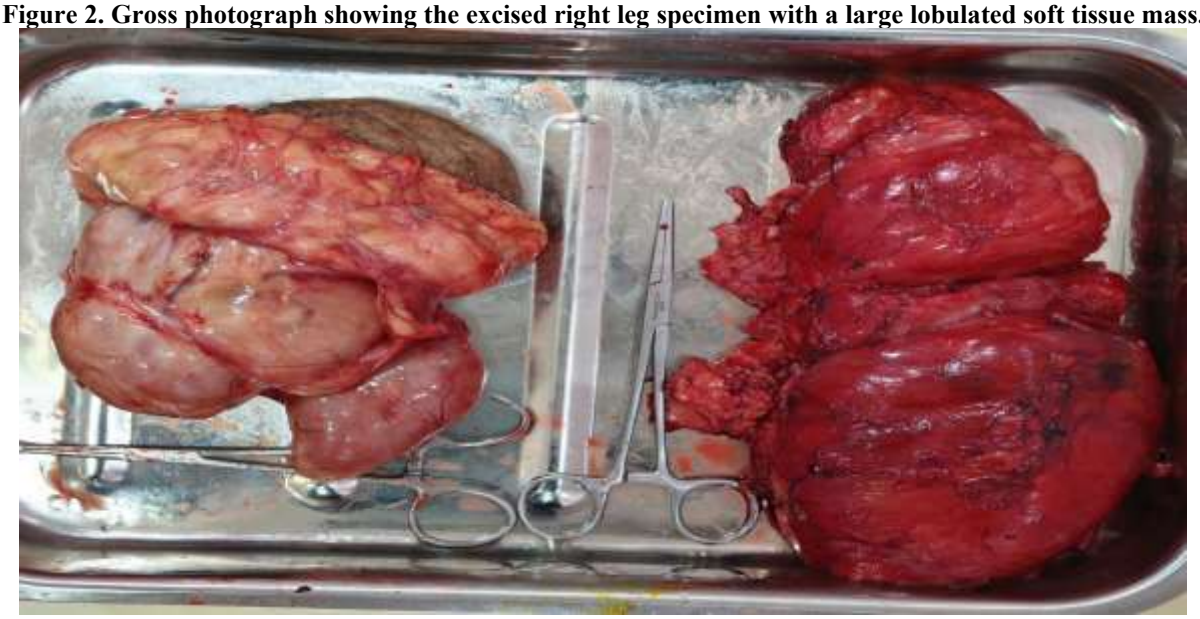

Figure 3. Post-excision gross photograph showing the right thigh and right leg surgical sites following complete tumour excision.

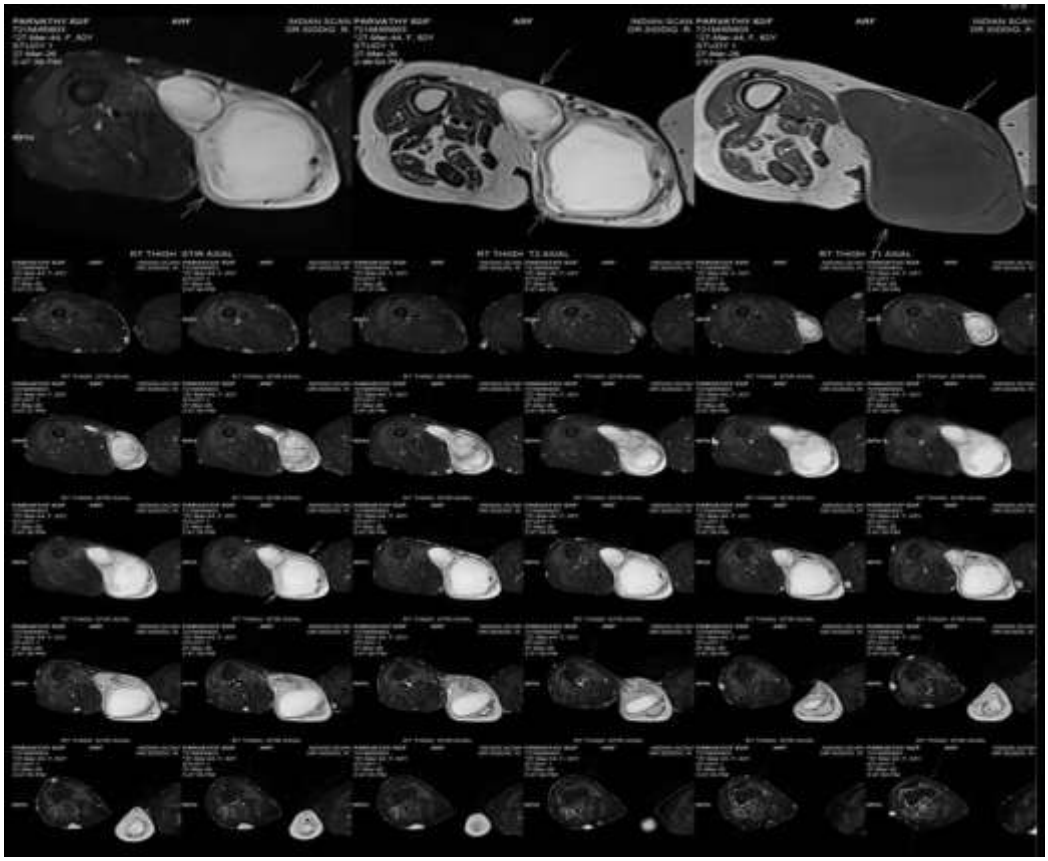

Figure 4. Magnetic resonance imaging (MRI) of the right thigh demonstrating a well-defined, lobulated/multilobulated exophytic subcutaneous lesion in the medial aspect of the mid-thigh, suggestive of plexiform neurofibroma or a myxomatous lesion.

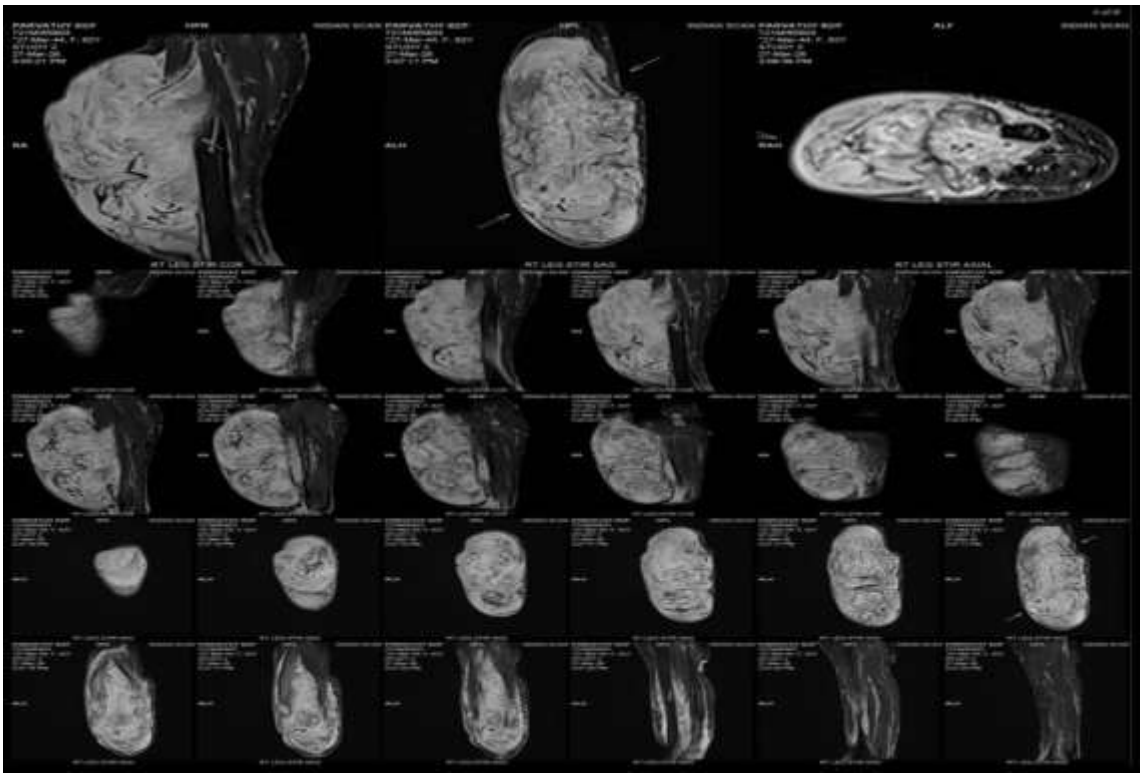

Figure 5. Magnetic resonance imaging (MRI) of the right leg demonstrating an ill-defined lobulated intramuscular lesion with subcutaneous extension in the anterior compartment, suggestive of plexiform neurofibroma, myxomatous lesion, or sarcomatous lesion.

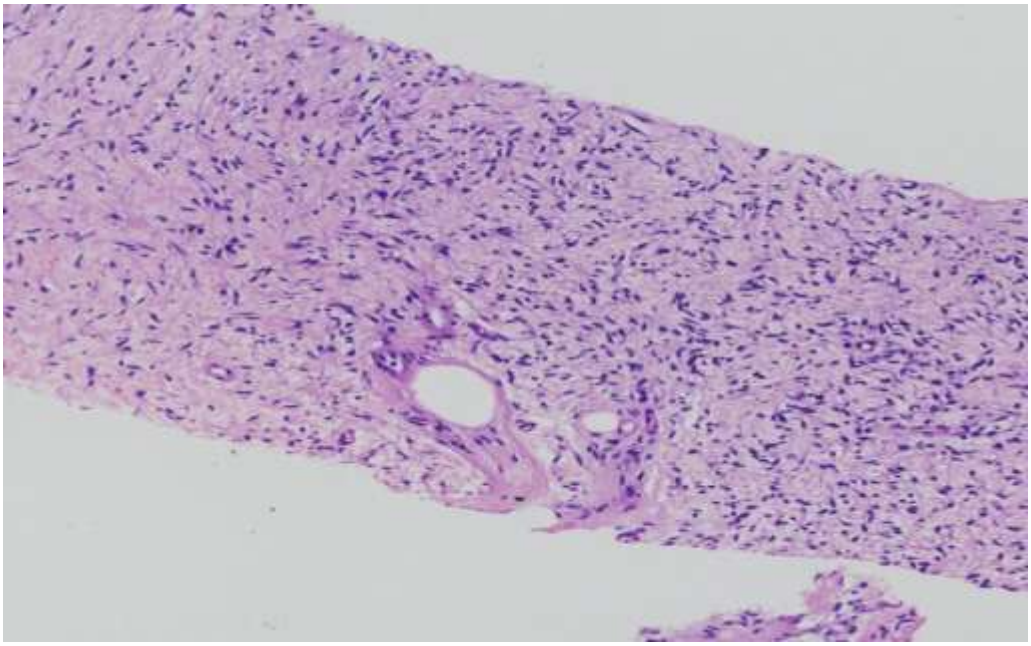

Figure 6. Histopathological photomicrograph showing a spindle cell neoplasm consistent with diffuse-type neurofibroma, composed of spindle cells with elongated wavy nuclei embedded in a myxoid and collagenous stroma (H&E stain, ×100).

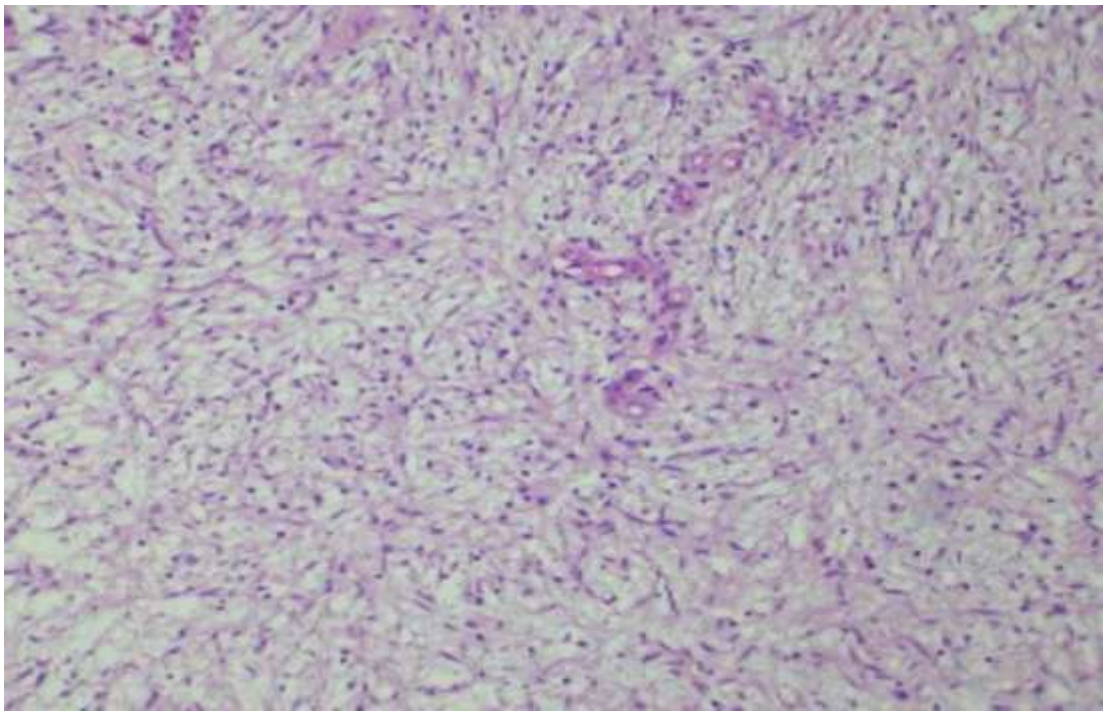

Figure 7. Histopathological photomicrograph showing the characteristic features of diffuse-type neurofibroma, with bland spindle cells lacking significant atypia, mitotic activity, or tumour necrosis (H&E stain, ×400).

MANAGEMENT AND OUTCOME

Following comprehensive clinical evaluation, radiological assessment, and histopathological confirmation, the patient underwent complete surgical excision of both the right thigh and right leg masses. Intraoperatively, the lesions were found to be extensive but amenable to complete resection while preserving adjacent neurovascular structures as far as possible. Histopathological examination of the excised specimens demonstrated diffuse-type neurofibroma with tumour-free circumferential surgical margins and no evidence of malignant transformation. Immunohistochemistry was advised for further confirmation of neural differentiation and to exclude malignant peripheral nerve sheath tumour.

The postoperative period was uneventful. The patient received adequate analgesia, wound care, and early physiotherapy to restore limb function and mobility. She was discharged in stable condition with advice for regular outpatient follow-up. Considering the infiltrative nature of diffuse plexiform neurofibroma and its recognised potential for recurrence and malignant transformation, periodic clinical examination and serial magnetic resonance imaging were recommended. At

the most recent follow-up, there was satisfactory wound healing, improvement in pain, and no clinical evidence of local recurrence.

CONCLUSION

Giant diffuse plexiform neurofibroma presenting in an elderly patient without an established diagnosis of Neurofibromatosis Type 1 is an exceptionally uncommon clinical entity. The present case highlights the diagnostic challenges posed by rapidly enlarging giant peripheral nerve sheath tumours, particularly when radiological features mimic malignant soft tissue neoplasms. Careful integration of clinical findings, advanced imaging, histopathological examination, and immunohistochemistry is essential for establishing an accurate diagnosis and differentiating benign diffuse neurofibroma from malignant peripheral nerve sheath tumour.

Despite the unusually large tumour size and trans-fascial extension, complete surgical excision with tumour-free margins resulted in a favourable outcome in the present patient. This case further emphasises that tumour size alone should not be considered indicative of malignancy and reinforces the pivotal role of histopathological evaluation in guiding management. Long-term clinical and radiological surveillance remains essential because of the infiltrative behaviour of diffuse neurofibromas and the recognised risk of recurrence and malignant transformation.

LEARNING POINTS

- Giant diffuse plexiform neurofibroma may rarely present in elderly patients without a previously established diagnosis of Neurofibromatosis Type 1.
- Rapid enlargement and extensive soft tissue involvement do not necessarily indicate malignant peripheral nerve sheath tumour and should always be confirmed by histopathological examination.
- Magnetic resonance imaging is invaluable for determining tumour extent and surgical planning but cannot reliably distinguish benign from malignant peripheral nerve sheath tumours.
- Complete surgical excision remains the treatment of choice whenever feasible, while immunohistochemistry serves as an important adjunct in diagnostically challenging cases.
- Long-term multidisciplinary follow-up with periodic clinical examination and imaging is essential because of the potential risk of recurrence and malignant transformation.

ETHICAL CONSIDERATIONS

Written informed consent was obtained from the patient for publication of the clinical details, radiological findings, operative photographs, and histopathological images. Every effort has been made to maintain patient confidentiality by removing all personal identifiers. Institutional ethical approval was not required as this manuscript reports a single case in accordance with institutional policy. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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