Malignant Peripheral Nerve Sheath Tumour Manifested as a Perineal Mass: A Case Study and Review Of the Literature

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Abstract: *Background*: Malignant mesenchymal tumours originating from peripheral nerves or nerve sheath cells are classified as malignant peripheral nerve sheath tumours (MPNSTs), previously referred to as neurofibrosarcoma. Most cases of these lesions occur in patients diagnosed with neurofibromatosis type 1, while some instances may be linked to previous radiation exposure, and others arise sporadically.

Case report: This report presents a 53-year-old male patient who experienced swelling in the scrotal area over the past 18 months. Clinical assessment and histopathological examination revealed a diagnosis of a perineal MPNST.

Conclusion: Perineal MPNST is infrequent, presenting distinct diagnostic challenges and should therefore be considered in the differential diagnosis of perineal masses. The diagnosis was based solely on histological examination, lacking confirmation through immunohistochemical methods, which constitutes a limitation. Surgical resection yielded positive outcomes, as there were no signs of recurrence observed three months post-surgery with a longer follow-up period deemed necessary.

Keywords: Tumour of malignant peripheral nerve sheath, solitary, sporadic, perineum, resection

INTRODUCTION

Malignant peripheral nerve sheath tumours (MPNST) are defined as neoplasms that originate from the peripheral nerves or the cells of the nerve sheath, while specifically excluding those that involve the epineurium of the surrounding vascular structures [1,2]. This malignancy was formerly called neurofibrosarcoma (NFS) [3]. The prevalence of MPNST is 1 in 100,000 affecting both genders equally [1,2]. This rare malignant mesenchymal tumour accounts for 5-10% of soft tissue sarcomas (STS) [2,4]. Fifty to 60% of MPNST patients are associated with neurofibromatosis type 1 (NF1), while a history of radiation exposure is found in 10% of patients and the others were mostly sporadic [1,4,5]. Swelling, pain, and numbness are the major clinical features; however, these symptoms are not specific, as some patients may be painless, making it difficult to distinguish from other nerve lesions [6]. With the advancement in MRI technology, the sensitivity and specificity in the diagnosis of MPNSTs have improved [7]. The main therapy for MPNST is complete resection surgery with negative margins, while radiation and chemotherapy are widely used for advanced lesions [1,4]. The response in sporadic MPNST is better than in NF1-associated lesions. Poor survival has been associated with large tumour size, inadequate margins, high tumour grade, and distant metastasis [4]. The 5-year overall survival rate is reported to be 15-60% [4]. Presented is a 53-year-old man with a large painless perineal mass that was confirmed by histology to be MPNST, a rare tumour found in the perineum, also a rare site with a favourable outcome 3 months after surgery.The novelty and clinical relevance of the presented case stem from its unusual primary anatomical location in the perineum, a site rarely documented in existing literature compared to more frequently occurrence in limbs or general trunk. This case report aims to highlight the diagnostic consideration, management strategies and clinical associations with a perineal MPNST, offering valuable insights into the optimal management of this rare entity and contributing to the limited body of knowledge on tumour in this specific location.

CASE REPORT

A 53-year-old male presented with a swelling located beneath the scrotum that had developed over the prior 18 months. Initially manifesting as a boil, the mass gradually enlarged to a size comparable to that of an orange. The patient's medical history did not indicate any signs suggestive of Neurofibromatosis type 1 (NF1), either in himself or within his family. Furthermore, there was no reported history of exposure to petrochemicals or radiation, nor any history of trauma or previous interventions in the perineal region. The patient expressed discomfort while walking due to the swelling situated between his thighs. He had

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previously experienced a left ankle dislocation, which was resolved successfully 16 years prior, and underwent a right inguinal herniorrhaphy approximately two decades ago.

Upon examination, the patient appeared to be a middle-aged male in no apparent distress, afebrile, with no pallor or peripheral lymphadenopathy. A solitary, nontender mass was palpated in the perineum, predominantly on the right side, measuring approximately 10 cm at its greatest dimension. The mass exhibited a firm consistency and was not adherent to the overlying skin or the underlying structures. There was an absence of inguinal lymphadenopathy, as illustrated in Figure **1**. Examinations of the head, neck, chest, and abdomen yielded no remarkable findings. Consequently, a clinical diagnosis of a perineal soft tissue tumour was established.

The laboratory workup included a complete blood count (CBC), which showed a packed cell volume (PCV) of 43% and a white blood cell (WBC) count totalling 4.3 (reference range: 4.0-12.0) x 10^3/µl. The differential count indicated lymphocytes at 52 (reference range: 25-50), monocytes at 0 (reference range: 2-10), neutrophils at 48 (reference range: 50-80), eosinophils at 0 (reference range: 2-10), and basophils at 0 (reference range: 0-2). Serological tests I and II were nonreactive, and urinalysis results were within normal limits. An ultrasound scan (USS) identified a substantial heterogeneous mass measuring 6.2 x 4.0 cm, characterized by regular margins and primarily affecting the right subcutaneous tissue of the infra-scrotal region. The mass exhibited multiple punctate calcifications and demonstrated increased blood flow upon Doppler evaluation. Notably, the adjacent muscular plane remained intact, suggesting a diagnosis of soft tissue sarcoma, specifically a solitary fibrous tumour. He was unable to undergo an MRI examination due to financial constraints.

The patient underwent a wide excision biopsy under spinal anaesthesia while positioned in the lithotomy position, with a drain left in place. During the procedure, a perineal mass measuring 10 cm was observed, primarily composed of subcutaneous tissue, with some extension into the adjacent scrotum. The estimated blood loss during the operation was approximately 350 ml. The excised specimen was then sent for histological analysis, as shown in Figure **2a**. The postoperative course was stable until the second day when the patient developed penoscrotal oedema, which resolved spontaneously. Sutures were removed on the seventh postoperative day, and the patient was referred to the surgical outpatient department for follow-up. Subsequent evaluations in the outpatient setting indicated satisfactory wound healing. The histology report presented gross findings of a biopsy nodule measuring 8.5 x 8 x 4.5 cm, with the external surface displaying hyperpigmented wrinkled skin as depicted in Figure **2a**. The cut surface exhibited greyish-white regions alongside extensive haemorrhagic areas, shown in Figure **2b**. Microscopic examination revealed a malignant tumour within the dermis, characterized by spindle cells organized in a fascicular growth pattern. Notably, there were alternating hypercellular regions interspersed with areas of myxoid stroma. The spindle cells demonstrated hyperchromatic, wavy nuclei with varying degrees of pleomorphism, while the mitotic activity was quantified at less than 3 per 10 high power fields (HPF). The resection margins were reported as normal, classifying the tumour as a malignant peripheral nerve sheath tumour, illustrated in Figures **3a** and **3b**. The

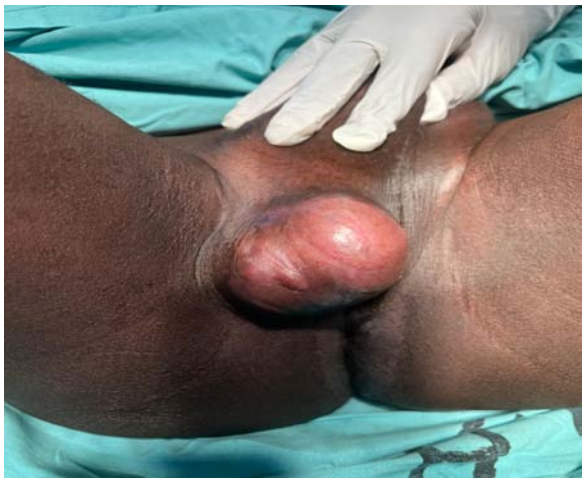


Figure 1: Clinical photograph of the perineal tumor.

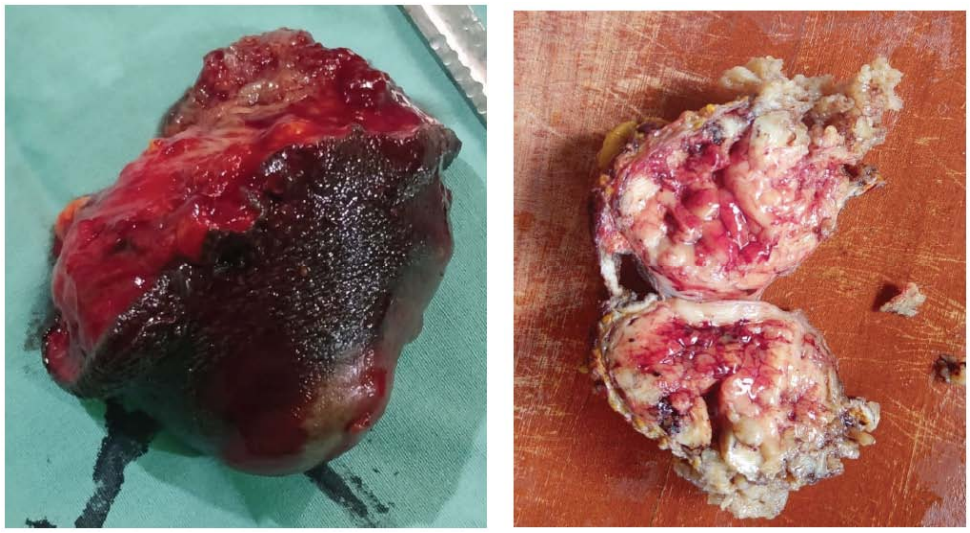
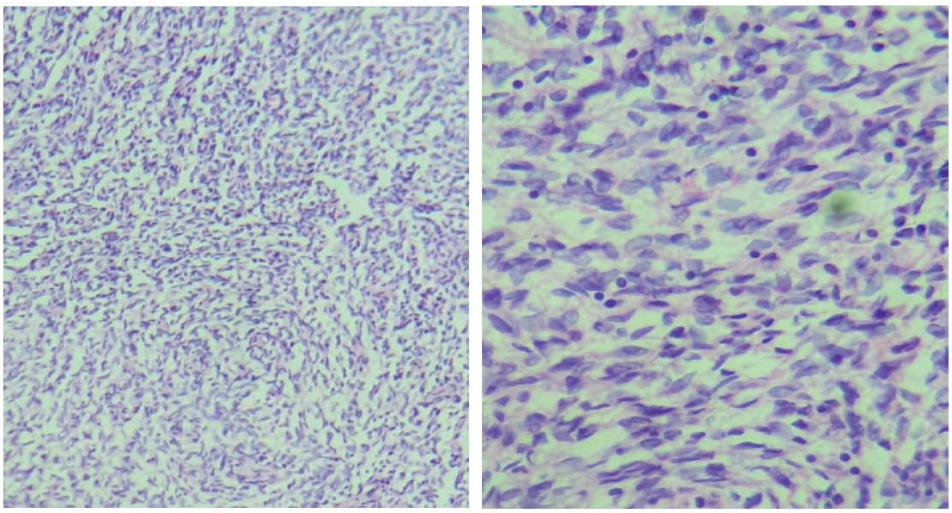


Figure 2: a) Excised tumor **b**) Cut surface of the tumor.

a- Showed excised tumor that showed a rim of hyperpigmented skin, part of the superficial and deep resection margins. **b**- Cut surface revealed greyish white areas with extensive areas of hemorrhage.



Figures 3: Histology, **a**- Haematoxylin&Eosinx 40, **b**- Haematoxylin&Eosinx 100, sections showed a malignant tumor in the dermis composed of spindle cells with fascicular growth pattern. There were alternating hypercellular zones with areas of myxoid stroma. The spindle cell showed hyperchromatic wavy nuclei with minimal to marked pleomorphism. The mitotic activity was <3/10 HPF- malignant peripheral nerve sheath tumour.

patient was counselled regarding the necessity for extended follow-up. Notably, there has been no evidence of recurrence observed three months post-surgery.

DISCUSSION

MPNST, previously referred to as malignant schwannoma or neurofibrosarcoma, represents a rare mesenchymal neoplasm that develops from the nerve sheath of both major and minor peripheral nerves, encompassing somatic soft tissues [8]. This tumour constitutes approximately 5-10% of soft tissue sarcomas (STSs). In the general populace, the incidence of MPNST is approximately 0.001%, although it can escalate to between 5-42% in individuals with neurofibromatosis type 1 (NF1) [8]. The condition predominantly affects individuals aged 20 to 50 years, although cases have been documented in children, and there appears to be no significant gender disparity in its occurrence. Although relatively uncommon, epidemiological data from the United States indicates a higher prevalence among Black individuals compared to Caucasians. The most frequent sites of origin for MPNST include the extremities, trunk, and head and neck regions, particularly involving the sciatic nerve, as well as the branchial and sacral plexuses [9-11]. Tumours located

in other areas of the body are exceedingly rare [8], a finding consistent with our report from Calabar, Nigeria, which identified a perineal MPNST—marking the first case recorded in this context. Previous studies have documented occurrences of MPNST in the pelvis by Ono *et al*. in Japan [9], in the urinary bladder by Ajani *et al*. in Ibadan, Nigeria [8], and in the ischiorectal fossa by Eberspacher *et al*. in Rome [2]. Furthermore, MPNST has been noted to affect multiple sites as reported by Etiuma *et al*. in Nigeria [12]. In a study by Ntumbaand Juma, MPNST was observed in four patients—one with an upper limb lesion and three with lower limb involvement in Kenya [2].

The World Health Organization (WHO) in 2013 classified MPNST as a subtype of STS, which includes epithelioid, malignant triton tumours, and glandular variants [13]. Identified risk factors for MPNST encompass NF1, post-radiation sarcomas, plexiform neurofibromas (PN), and atypical neurofibromatous neoplasms of uncertain biological behaviour (ANNUBP), which are usually benign but are considered precursors to malignancy, with an estimated progression rate to MPNST of 10-15% [1]. Approximately 50% of MPNST cases are classified as sporadic, typically arising around the age of 50, reflecting the age of our patient. Additionally, 50% of individuals with MPNST have been diagnosed with NF1, with an average age of onset between 30 and 50 years, occurring approximately a decade earlier than in non-NF1 associated cases [1,8,9].

It is estimated that approximately 70% of cases present as painless swellings, with clinical symptoms gradually developing as the tumour expands [2,9]. In sub-Saharan Africa, it is not uncommon for patients to present late with advanced lesions [5]. Some individuals may also present with pain accompanied by motor or sensory deficits; however, these symptoms can also occur in benign lesions. Instances of complications due to pathological fractures have been reported [5]. Magnetic Resonance Imaging (MRI) is the preferred diagnostic modality for soft tissue sarcoma (STS). Imaging studies of malignant peripheral nerve sheath tumours (MPNST) reveal low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Characteristics such as invasion into fat planes, heterogeneity, oedema, and poorly defined borders are associated with MPNST. As noted by Broski *et al*., features such as perilesional oedema, cystic degeneration or necrosis, and irregular margins can reach 100% specificity [14]. Yun *et al*. developed a scoring system that combines clinical presentation with imaging characteristics to achieve 100% sensitivity and specificity [15]. The integration of positron emission tomography/computed tomography (PET/CT) and MRI has proven to be complementary, though further research is warranted [16]. The absence of MRI evaluation in our patient is a notable limitation in this study. Differentiating between benign and malignant peripheral nerve sheath tumours remains complex due to the similarities in clinical presentations and imaging features [17]. Diagnosis is primarily established through surgical excision followed by histological assessment [1]. Recent advancements in diagnostic methods include gene mutation analysis and molecular detection in the context of MPNST pathogenesis. The expectation is that new molecular targets will enhance the accuracy of diagnosis and grading for MPNST. Additionally, it has been observed that biopsy may exhibit lower sensitivity compared to immediate surgical resection [18]. Another noted limitation in our report was the absence of immunohistochemistry (IHC) testing. The positivity rate for S-100 in MPNST is between 50-60%, while a negative S-100 result may suggest dedifferentiation of Schwann cells, potentially indicating a greater likelihood of malignancy [1,8]. Nestin has emerged as a sensitive marker for MPNST and may provide diagnostic value when used alongside other markers [19]. Furthermore, H3K27me3 has been identified as a novel marker for MPNST, with recent findings revealing PRC2 mutations as critical in the transition from atypical neurofibroma to MPNST. The complete loss of H3K27me3 detected via IHC occurs with a frequency of 30-90%, being more prevalent in sporadic and radiation-related MPNST than in those associated with neurofibromatosis type 1 (NF1) [1].

The optimal treatment strategy for managing this condition is comprehensive surgical resection aimed at achieving negative margins [9]. In cases where tumours exceed 5 cm in size, neoadjuvant radiotherapy is utilized to reduce tumour volume and minimize the risk of local recurrence [8]. In the case of our patient, resection was pursued based on the tumour's location, irrespective of its size, particularly as it was classified as low grade. The estimated recurrence rate for such tumours ranges from 40-65%, along with a notable risk of hematogenous spread [8,9]. For patients with unresectable or metastatic malignant peripheral nerve sheath tumours (MPNSTs), chemotherapy regimens incorporating adriamycin and ifosfamide represent alternative treatment options. However, the efficacy of adjuvant chemotherapy in improving survival rates and reducing recurrence has yet to be established. For high-grade lesions larger than 5 cm, radiotherapy is

advised, yielding favourable outcomes for local control; nevertheless, adjuvant radiotherapy has not demonstrated benefits for MPNSTs [1]. The future direction for unresectable or metastatic cases points towards targeted therapies, facilitated by enhanced insights into the molecular pathogenesis of MPNST. Preliminary studies combining heat shock protein 90 (Hsp90) inhibitors, such as Ganetespib, with mammalian target of rapamycin (mTOR) inhibitors like everolimus, have shown encouraging results. Additionally, the MEK inhibitor selumetinib has demonstrated clinical efficacy against MPNSTs, with ongoing research exploring its combination with the mTOR inhibitor sirolimus [20].

Malignant peripheral nerve sheath tumours are associated with a grim prognosis, with overall five-year survival rates averaging between 50-60% [21]. Another study specifically observing MPNSTs associated with neurofibromatosis type 1 (NF1) reported a five-year survival rate of merely 16-30%, coupled with median recurrence intervals of 6-9 months and distant metastases occurring within 8-9 months [9]. The French Federation of Cancer Centres Sarcoma Group (FNCLCC) grading system is advised for use, as it employs a three-tiered approach assessing tumour cell differentiation, mitotic activity, and necrosis extent. Recent investigations have indicated a strong correlation between elevated FNCLCC grades and survival outcomes. FNCLCC grading was unavailable but would have enhanced prognostic stratification [22].

CONCLUSION

This case of a spontaneous MPNST in the perineum is notable for its rare location and favourable outcome following surgical resection. However, longer follow-up is essential to confirm disease-free status. Complete surgical removal with clear margins in this instance led to no evidence of recurrence. The outcome highlights the central role of surgery as the most important factor for long-term survival in these rare tumours. This case reinforces the importance of prompt surgical intervention and achieving negative (clear) margin for the chance of long-term local control and best survival.

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