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UNCOMMON THIGH MASS IN NEUROFIBROMATOSIS TYPE 1: UNVEILING AGGRESSIVE EPITHELIOID SARCOMA

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ABSTRACT

Background: Patients with neurofibromatosis type I (NF1) have an increased risk of developing soft-tissue sarcomas, particularly those related to the nervous system. Epithelioid sarcoma (ES) is an exceptionally rare subtype of soft-tissue sarcoma, with limited knowledge about its clinical presentation and optimal management in NF1. This report aims to provide insights into the characteristics and outcomes of ES in NF1 patients.

Case description: A 37-year-old man with a history of NF1 presented with a progressively worsening mass on his right inner thigh. An MRI scan revealed a well-defined tissue mass originating from the adductor magnus muscle, later confirmed as ES through histopathology and immunohistochemistry. Considering poor local and general prognosis, the multidisciplinary team recommended salvage hip disarticulation, however the patient refused and opted for palliative marginal resection to reduce the tumour size. The patient's condition declined rapidly, and he succumbed six days after the surgery.

Conclusion: This case highlights the rarity of ES in NF1 patients and underscores the potential for malignant tumour development in this population. Further research is needed to improve our understanding and management of sarcomas in the context of NF1.

KEYWORDS

Neurofibromatosis type 1, epithelioid sarcoma, soft-tissue tumour

LEARNING POINTS

- Patients with neurofibromatosis type 1 or von Recklinghausen's disease have a higher risk than those with other types of neurofibromatosis of developing benign or malignant soft-tissue tumours especially related to the nervous system.
- Epithelioid sarcoma is an extremely rare subtype of soft-tissue sarcoma and is exceptionally associated with neurofibromatosis type 1.
- A multidisciplinary approach remains essential in the diagnosis, management, and treatment of soft-tissue sarcomas in patients with neurofibromatosis type 1.

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INTRODUCTION

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a complex and multisystem autosomal dominant disease caused by mutations in the neurofibromin 1 gene[1]. It is associated with an increased risk of developing soft-tissue sarcomas, particularly those related to the nervous system, compared to other types of neurofibromatoses. However, the occurrence of epithelioid sarcoma (ES) in NF1 patients is exceptionally rare, with only one reported case to date[2]. ES is an uncommon variant of soft-tissue sarcoma, representing less than 1% of all cases in adults. It predominantly affects the limbs of young individuals and affects the dermis, subcutaneous tissue, or deeper soft tissues. The exact cause of ES is still unknown[3-5]. Due to the scarcity of reported cases, limited knowledge exists regarding the clinical presentation, imaging characteristics and optimal management strategies for ES in the context of NF1. In this paper, the authors report a case of ES in a patient with NF1, highlighting the clinical course, diagnostic challenges, and treatment outcomes. It emphasises the importance of understanding and managing this rare tumour subtype in NF1 patients to improve early detection, accurate diagnosis, and effective treatment, ultimately enhancing patient outcomes.

CASE DESCRIPTION

A 37-year-old male patient with a history of NF1, presented with a gradually worsening swelling on the inner aspect of his right thigh over the previous four months. He also experienced general malaise and had unquantified weight loss. Upon admission, the patient had no fever, and a thorough physical examination revealed a soft abdomen without any signs of visceromegaly. Furthermore, no palpable lymph nodes were detected. It is worth noting that the patient exhibited multiple cutaneous nodules resembling neurofibromas on the neck and abdomen *(Fig. 1)*. Additionally, café-au-lait patches were observed on the patient's back, *(Fig. 1B)*. The physical examination revealed a 15 cm painful swelling on the inner aspect of the right thigh. The swelling had a firm consistency and was non-mobile. No signs of local inflammation were observed, and there were some palpable inguinal lymph nodes. The femoral, pedal, and posterior tibial pulses were present and symmetrical, and no sensory or motor deficits were noted. The laboratory results showed a C-reactive protein (CRP) level of 92, an erythrocyte sedimentation rate (ESR) of 86, and a white blood cell count of 12,200. The magnetic resonance imaging (MRI) of the right thigh revealed a well-defined tissue mass originating from the adductor magnus muscle. The mass exhibited a heterogeneous solid-cystic signal, predominantly showing signs of haemorrhage, and demonstrated heterogeneous enhancement after gadolinium injection. It measured 10 × 11.5 cm in the axial plane and extended over a height of 14 cm in the sagittal plane, with no signs of extension into the surrounding muscular and bony structures *(Fig. 2)*. A surgical biopsy of the thigh mass was performed. Histologically,

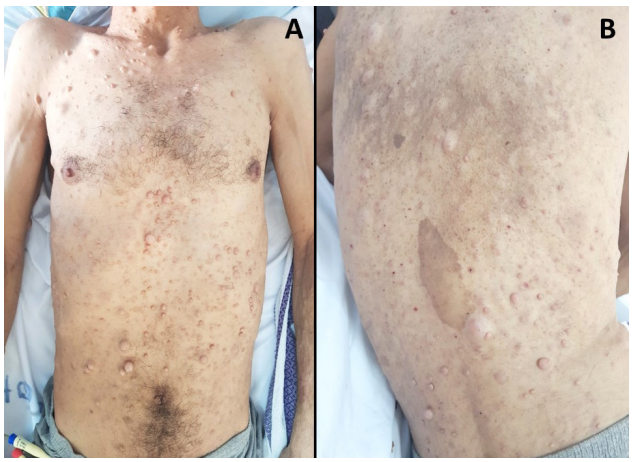

Figure 1. A) Presence of multiple cutaneous neurofibromas located on the neck, the thorax and abdomen of the patient; B) Presence of café-au-lait patches and multiple neurofibromas located on the back of the patient.

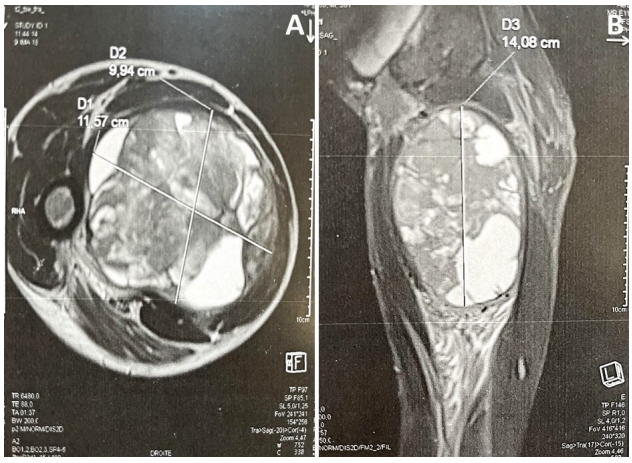

Figure 2. A) Axial and B) Sagittal MRI of the right thigh revealing a well-defined tissue mass originating from the adductor magnus muscle. The mass exhibited a heterogeneous solid-cystic signal, predominantly showing signs of haemorrhage, and demonstrated heterogeneous enhancement after gadolinium injection. It measured 10 × 11.5 cm in the axial plane and extended over a height of 14 cm in the sagittal plane, with no signs of extension into the surrounding muscular and bony structures.

the tumour exhibited an infiltrative growth pattern with ill-defined peripheral borders. The tumour cells displayed polygonal morphology and had abundant eosinophilic cytoplasm. The nuclei of the tumour cells were vesicular and showed prominent macronucleoli. Mitoses were observed at a rate of 18 per 2 mm^2, along with the presence of necrosis and haemorrhage within the tumour *(Fig. 3)*. Furthermore, the immunohistochemical study revealed positive immunostaining for vimentin and cytokeratin in the tumour cells, while S100 protein, CD34, desmin and caldesmon yielded negative results. Based on these findings, the final pathological diagnosis was proximal variant of ES. Fifteen days after the surgical biopsy, the affected area displayed evident local inflammatory symptoms such as redness, warmth, and pain, with no signs of pus or serous fluid discharge. Additionally, there was a significant increase

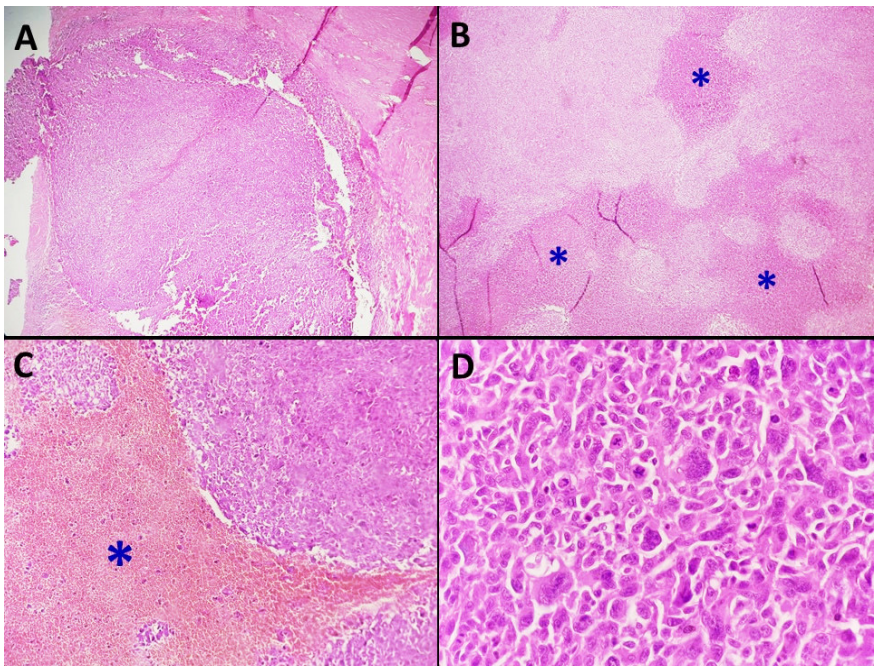

Figure 3. A) Nodular malignant tumour proliferation invading the adjacent tissues (H&E, × 40); B) Malignant tumour proliferation with extensive areas of necrosis (asterisk) (H&E, × 40); C) Tumour composed of sheets of large round or polygonal epithelioid cells with focal areas of haemorrhage (asterisk) (H&E, × 100); D) Tumour cells have abundant ill-defined eosinophilic cytoplasm, pleomorphic hyperchromatic irregularly shaped nuclei of varying sizes with open chromatin and prominent central nucleoli. Several mitotic figures were observed (H&E, × 400).

in the size of the mass *(Fig. 4)*. Throughout this period, the patient remained afebrile. However, there was a noticeable decline in the patient's overall condition. The white blood cell count was 18,260 (neutrophils: 15,980), the CRP level was 137 and the ESR level was 112. Bacterial culture showed negative results. The thoraco-abdominopelvic CT scan revealed a right mediastino-pulmonary peribronchovascular thickening, most likely of secondary origin. The decision of the multidisciplinary consultation meeting was to perform salvage hip disarticulation due to the active tumour flare, which makes achieving complete surgical tumour resection (R0) unfeasible at this stage and considering the very poor prognosis. The patient categorically refused the hip disarticulation. A marginal resection with palliative intent was performed to achieve tumour debulking. The patient passed away on postoperative day 6.

DISCUSSION

Neurofibromatosis type 1 is a complex genetic condition that primarily appears in childhood and adolescence, affecting approximately 1 in 3,000 live births worldwide[6,7]. It is characterised by diverse clinical manifestations and significantly increases the risk of developing malignancies. The diagnostic criteria for NF1 were established by the National Institutes of Health Consensus Conference in 1987 and confirmed in 1997[8,9]. These criteria include common features such as café-au-lait macules, freckling, neurofibromas and Lisch nodules, as well as specific complications such as optic pathway glioma, sphenoid dysplasia, cortical thinning of long bones with or without pseudarthrosis and having a first-degree relative with NF1. Neurofibromatosis type 1 is widely recognised as a cancer predisposition syndrome.

The link between NF1 and both benign and malignant tumours is well established in medical literature[9-11]. The risk of malignancies in individuals with NF1 is reported to be between 1.5 and 4 times higher than in the general population, although this estimate might be inflated due to the inclusion of hospitalised patients[9-11]. Similar to other syndromes associated with tumour predisposition, NF1-related malignancies often arise from neural crest and myeloid cell origins and tend to develop at an early age. It has been documented that multiple primary tumours can occur in NF1 patients. The most notable association between NF1 and paediatric cancers is the increased risk of central nervous system tumours, particularly optic gliomas[9-11]. Additionally, soft-tissue sarcomas, specifically malignant peripheral nerve sheath tumours, are more commonly observed in individuals with NF1[12]. Compared to the general population, NF1 patients also have a higher incidence of rhabdomyosarcoma[13]. Currently, there is no known direct association between neurofibromatosis and ES. To the best of our knowledge, our case is the second documented case of an ES developing in a patient with NF1.

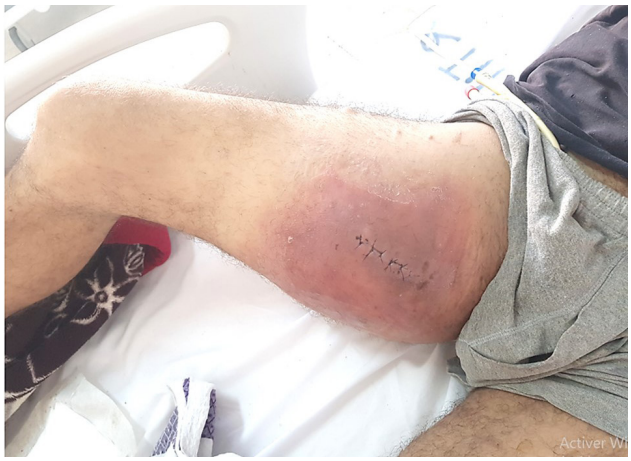

Figure 4. Image taken 15 days after surgical biopsy, demonstrating an increase in the size of the tumour located at the root of the thigh, accompanied by local inflammatory signs such as redness, warmth, and pain. No discharge of pus or serous fluid was observed.

The first reported case occurred in a 42-year-old man who presented with a growing mass on his posterior neck[2]. ES is an uncommon slow-growing tumour. It is frequently diagnosed in young individuals, with a median age of 26 years. However, it can also affect children[14]. This type of sarcoma can be classified into two distinct subtypes: classic ES and the proximal variant[14]. Classic ES often manifests as a mass beneath the skin or in the deep layers of the skin in the distal extremities of younger individuals. On the other hand, the proximal variant primarily affects the proximal regions of the limbs, limb girdles and the midline of the trunk[14]. Our case corresponds to the proximal variant of ES since it affects the proximal region of the right thigh. Given its rarity and histological similarities with other malignancies, inexperienced pathologists may overlook or misdiagnose ES. Histopathologically, the classic 'distal' form displays a nodular growth pattern, with tumour cells showing a mix of eosinophilic epithelioid and spindle cells. Mild nuclear atypia is observed, and the central area of the nodules exhibits necrosis while the peripheral cells remain intact, resembling a pseudogranulomatous appearance[14,15]. Mitotic activity with a few atypical mitotic figures is also noted. In contrast, the proximal-type ES demonstrates a multinodular growth pattern and consists of large epithelioid carcinoma-like cells with significant cytological atypia[14,15]. These cells have vesicular nuclei, prominent nucleoli and often exhibit rhabdoid features. Notably, there is an absence of a granuloma-like pattern in this subtype[14,15]. Both the classic and proximal types of ES consistently exhibit loss of INI1 (HSNF5/SMARCB1) expression, as confirmed by immunohistochemistry. These tumour cells also commonly express cytokeratin, vimentin, epithelial membrane antigen and endothelial markers, including CD34 and ERG, in around 50–60% of cases[14,15]. In our case, the immunohistochemical study revealed positive immunostaining of tumour cells for vimentin and cytokeratin, while S100 protein, CD34, desmin and caldesmon were negative. The histological differential diagnoses of ES include carcinoma, malignant melanoma, extrarenal rhabdoid tumour, epithelioid malignant peripheral nerve sheath tumour, myoepithelial carcinoma, and epithelioid carcinoma. The clinical course of ES can vary unpredictably. While some patients experience no recurrence of the disease, others face a slow but relentless progression characterised by frequent local recurrences and distant metastases[16]. Lung metastasis is common in ES, occurring in the majority of cases, while lymph node involvement is observed in around 30–45% of cases[14]. In our case, a CT scan revealed a right mediastino-pulmonary peribronchovascular thickening, most likely of secondary origin. Prognostic factors that significantly impact the outcome of ES include age, location within the body, tumour grade, TNM staging and the chosen treatment approach. Generally, younger patients and those with distal tumour locations tend to have more favourable outcomes, whereas individuals with proximal-type ES face a poorer prognosis[16]. Once the histopathological diagnosis of ES is confirmed, the standard treatment involves radical excision[1]. In cases where regional lymph node or systemic metastases are suspected, sentinel lymph node biopsy with therapeutic lymph node dissection is recommended. Radiation therapy may also be considered, and adjuvant chemotherapy is indicated when there is suspicion or confirmation of metastatic disease[1]. ES has shown limited response to chemotherapy, with available treatments demonstrating only modest effectiveness[14]. Investigating the specific biological mechanisms of carcinogenesis in ES is essential for the development of targeted therapies. By gaining a deeper understanding of these mechanisms, we can potentially improve treatment outcomes. Collaborative multinational initiatives offer great potential in advancing our knowledge of ES and ultimately enhancing patient outcomes[14].

CONCLUSION

This case report underscores the significance of early detection, precise diagnosis, and effective treatment of ES in NF1 patients. Further research efforts are warranted to unravel the underlying mechanisms and improve therapeutic options for this rare tumour subtype. By enhancing our understanding and management of ES in the context of NF1, we can strive to improve patient outcomes, enhance quality of life, and offer hope to individuals affected by this challenging condition.

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