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Large para-testicular intra-scrotal malignant peripheral nerve sheath tumor managed with radical penectomy: A case report

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ABSTRACT

Neurofibromatosis 1 is a relatively rare genetic disease characterized by widespread neurofibromas originating from the peripheral nervous system. Most growths are benign, but some carry a risk of transformation to malignant peripheral nerve sheath tumors. Although these growths can be found anywhere in the body, they are rarely found in the male external genitalia. This report discusses a case of a 25-year-old male patient with neurofibromatosis 1 presenting with a scrotal mass found to have a very large para-testicular intra-scrotal malignant peripheral nerve sheath tumor that required testicle-sparing radical penectomy.

Introduction

Neurofibromatosis 1 (NF1) is genetic condition involving variable mutations in chromosome 17 which disrupt development of neural crest derivatives in 1 in 3000 live births.[1] Approximately 50% of cases are inherited and 50% are *de novo* mutations. Presentation classically involves skin changes, such as café-au-lait spots, axillary or inguinal freckling, dyspigmentation of the iris and optic gliomas, and benign tumors of the nerve sheath termed neurofibromas. These neurofibromas may arise from small cutaneous, spinal, or deep peripheral nerves (plexiform neurofibromas). Plexiform neurofibromas carry a risk of transformation into a malignant peripheral nerve sheath tumor (MPNST) in approximately 8–13% of cases.[2] Herein we present a case of a para-testicular plexiform neurofibroma which evolved into a malignant spindle cell sarcoma managed with primary wide surgical resection that included the penis.

Case presentation

A 25-year-old male with a history of NF1 and two benign plexiform neurofibromas resected from the left hemi-scrotum nine years prior presented to the emergency department with complaints of acute penile pain and life-long inability to maintain erection during intercourse. Examination revealed a large para-testicular mass present for an unknown length of time (Fig. 1). Initial scrotal ultrasound showed a para-testicular mass greater than 10 cm. A CT showed a heterogenous. Irregularly enhancing mass separate from the testicles, but suspicious for involvement of the scrotum and base of the penis. Subsequent MRI confirmed a solid and cystic mass located in the left upper scrotum, sparing the left testicle and inguinal canal without lymphadenopathy. A PET/CT displayed heterogenous intense uptake in the para-testicular mass with a small separate focal uptake inferior to the large lesion that were concerning for malignancy, along with low uptake lesions throughout the body suspicious for benign neurofibromas (Fig. 2). After a multidisciplinary team discussion, a transcrotal percutaneous biopsy was recommended to help guide surgical and/or chemotherapy options, which returned as high-grade spindle cell sarcoma. Surgery was recommended as primary management given the low response rates of chemotherapy or radiation and no metastatic disease. A *trans*-scrotal incision was made and revealed the left testicle was freely mobile and not involved. The mass, however, was found to be grossly invasive into the corporal bodies bilaterally with additional concern for invasion into the pubic bone (Fig. 3). Given need for wide excision and adequate margins for sarcoma surgery, radical penectomy with perineal urethrostomy was then completed. Orthopedics assisted with shaving off the pubis periosteum to help achieve a negative margin. His entire scrotum and bilateral testicles were spared. Several benign neurofibromas were found within his corpora cavernosum. Final pathology

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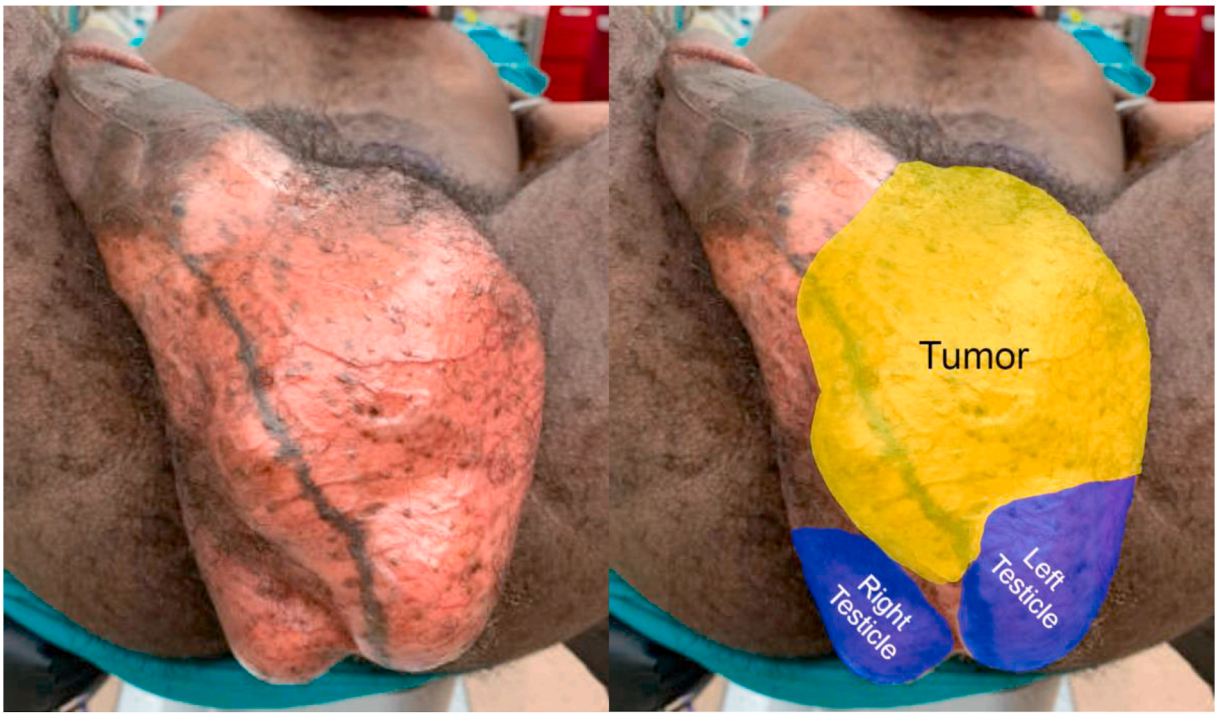

Fig. 1. A large para-testicular mass, shaded areas mark testicles and tumor.

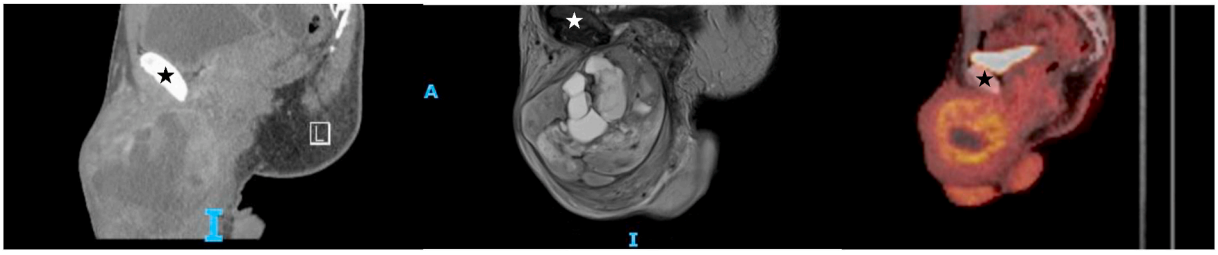

Fig. 2. Sagittal imaging of a large scrotal mass (left to right: CT, MRI, PET/CT; anterior is left of photo, inferior is bottom of photo; star marks pubic bone).

revealed a high grade MPNST with necrosis present, and negative margins. His post-operative course was unremarkable. Inpatient psychiatry consulted for genital loss counseling. At follow-up two weeks after surgery, the patient's wounds were healing appropriately without clinical signs of persistent disease.

Discussion

Over half of patients with NF1 will have internal plexiform neurofibromas. The natural history of these growths is one of indolence; however, they are susceptible to malignant transformation with acquisition of a second hit mutation in tumor suppressor genes such as *p53*, *PTEN*, or *Suz12*. In fact, NF1 confers a greater than one-thousand-fold increase in risk of malignant peripheral nerve sheath tumors.[2] Challengingly, the symptomatic presentation of MPNSTs is often indistinguishable from that of benign plexiform neurofibromas: localized symptoms such as pain or functional impairment in the area of the tumor. Symptoms suggesting MPNST transformation include rapid growth, a fixed mass, persistent or nocturnal pain, or neurological deficit. Workup can include ultrasound and/or MRI for characterization. PET for malignant uptake and occasionally biopsy if the diagnosis is still unclear.

Intratesticular MPNST are extraordinarily rare and often arise from prior neurofibromas. In a previously reported case, a MPNST arose 7 years after resection of an intrascrotal benign nerve sheath tumor.[3] The MPNST was managed with surgical resection and the patient was doing well at 6-month follow-up.

It is theorized that malignant transformation of neurofibromas is due to modulation of GTPase-activating proteins leading to hyperactivity of the RAS growth pathway.[1] Recently, selumetinib, a MAP kinase inhibitor targeting the RAS pathway, was approved for non-operable symptomatic plexiform neurofibromas.[4] Historically, resection and pain management were therapeutic mainstays of symptomatic neurofibromas. Resection with negative margins remains the only potentially curative treatment for MPNST, which confers an improved prognosis compared to positive margins in five-year overall survival (67% vs 22%) and local recurrence (6% vs 30%).[5] However, only 58% of pelvic resections achieve negative margins. The role of adjuvant chemotherapy is debated, but it has been suggested that radiotherapy may benefit those with larger tumors and difficult margins.

Unfortunately, literature regarding the natural history and management of MPNSTs is sparce. A systematic review of 50 patients with NF1-associated MPNST uncovered wide variation in characteristic reporting, overall survival, follow-up, and treatment regimens. For those receiving surgery alone, as in this case, 21 patients from 7 studies were identified. Overall survival, defined as survival at last follow-up, was 42% (9/21) over a range of follow-up ranging from 1 to 5.6 years. Recurrent patients measured 38% (8/21) in an average of 8.1 months (mo) (SD 3.9 mo), and patients developing distant metastasis measured 24% (5/21) in an average of 18.25 mo (SD 4.6 mo). However, only 62%

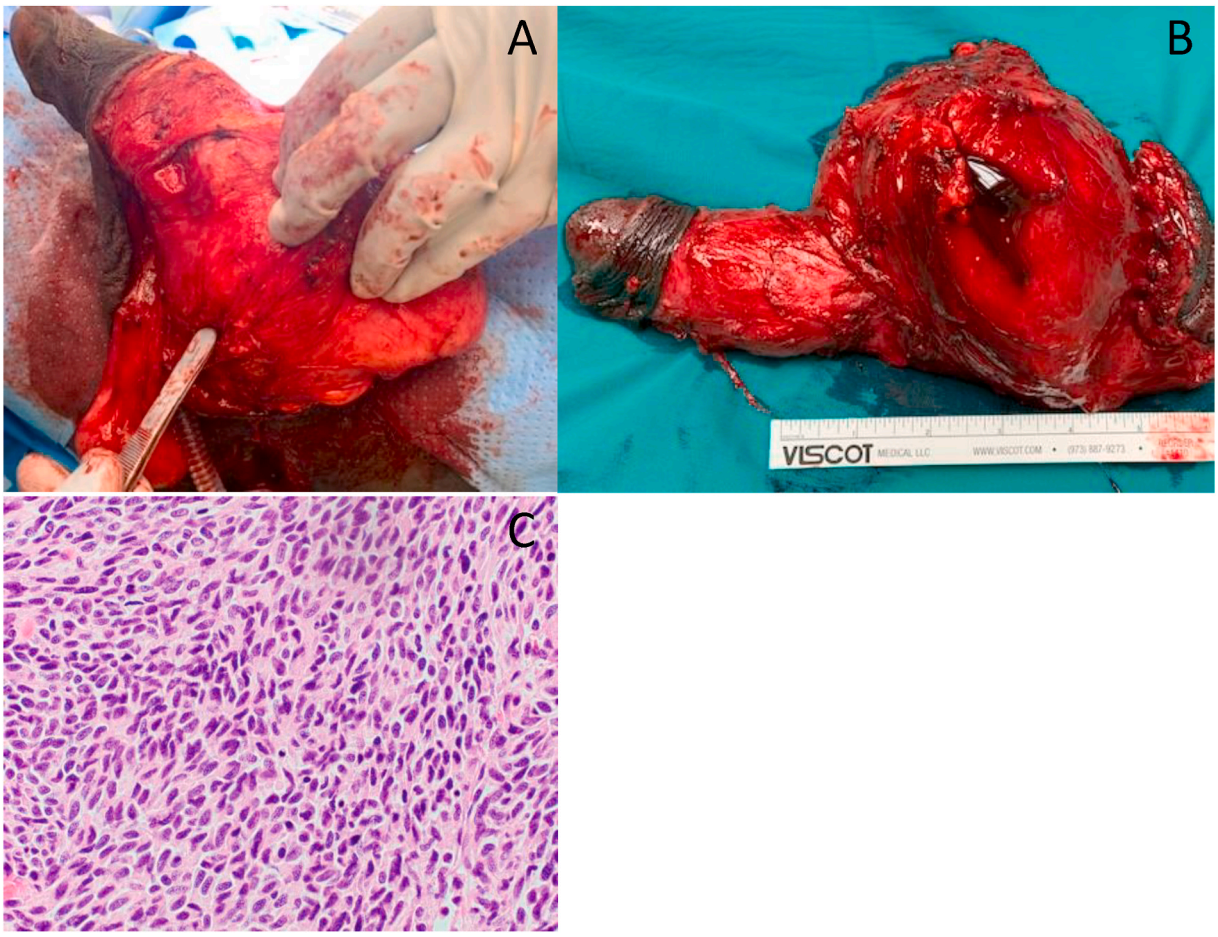

Fig. 3. A) Scrotal mass in situ (instrument marks gross invasion of corporal body). B) Radical penectomy removed en-bloc with paratesticular mass. C) Malignant peripheral nerve sheath tumor composed of pleomorphic spindle-shaped cells with hyperchromatic nuclei and scattered apoptotic bodies and mitotic figures.

(13/21) of surgical patients underwent complete tumor excision, defined as gross total resection or amputation, with the remaining 38% undergoing subtotal or marginal resection, limiting the application of these data to cases of complete resection.[2]

Conclusion

In conclusion, we are reporting a rare case of scrotal neurofibroma with malignant transformation to a large, aggressive MPNST managed with wide surgical excision requiring complete genital resection. While surgery offers the only opportunity for cure, these tumors have a penchant for recurrence or metastasis after 6 months and may recur years after surgery. Strong data is not available regarding expected natural history nor optimal follow-up. Physicians should consider long-term scheduled follow-up with imaging after surgical excision to assess for recurrence or progression given the aggressive nature and possible late recurrence associated with these tumors.

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Declaration of competing interest

There are no conflicts of interest in connection with this paper.

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Abbreviations

NF1: neurofibromatosis 1,
MPNST: malignant peripheral nerve sheath tumor