

Neurofibromatosis type I with malignant peripheral nerve sheath tumors in the upper arm

A case report

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Abstract

Rationale: Malignant peripheral nerve sheath tumor occurring in the context of neurofibromatosis type I (NF1) is relatively rare. Herein, we report a case of NF1 with malignant peripheral nerve sheath tumor in the upper arm.

Patient concerns: A 24-year-old man presented with a mass in the medial part of the left upper arm that had been present for more than 20 years. In the previous 1 year prior to admission, the mass had grown significantly. Physical examination showed cafe-au-lait spots of variable sizes throughout the body and multiple masses in the medial part of the left upper arm. Three months later after the resection of the masses, the patient was readmitted to our department due to tumor recurrence. Two months after the extended resection, in situ recurrence of the tumor was noted again. Four months after the operation and the administration of radiotherapy, a mass was found in the outside of the left upper arm.

Diagnosis: Immunohistochemical staining showed the masses were positivity for vimentin, CD34, and S100; the tumor cells were negative for PGP9.5, CD57, EMA, and SMA. The Ki-67 labeling index was approximately 40%. A diagnosis of malignant peripheral nerve sheath tumor was made.

Interventions: Surgical resection was performed for both the primary tumors and the 2 subsequent recurrence tumors. The patient underwent radiotherapy with 60 Gy in 30 fractions after the third operation. Four months after the administration of radiotherapy, the patient underwent tumorectomy of a mass in the outside of the left upper arm.

Outcomes: During the 4-month follow-up after the fourth operation, the patient's condition was stable.

Lessons: Malignant peripheral nerve sheath tumor in NF1 is an exceedingly rare entity that poses a great diagnostic challenge. High-frequency ultrasound can support the diagnosis.

Abbreviations: MRI = magnetic resonance imaging, NF1 = neurofibromatosis type I.

Keywords: case report, malignant peripheral nerve sheath tumor, neurofibromatosis type I

1. Introduction

Neurofibromatosis type I (NF1) is an autosomal dominant disease that is caused by mutations of the neurofibrin 1 gene located on chromosome 17q11.2.^[1] Malignant peripheral nerve

sheath tumor is a highly malignant tumor originating from the connective tissue surrounding nerves.^[2] The average incidence of malignant peripheral nerve sheath tumor in the general population is approximately 0.017 per 1 million persons per year,^[3] whereas that in patients with NF1 is about 1/3500.^[4] The estimated lifetime risk for a malignant schwannoma in patients with NF1 ranges from 8% to 13%.^[5]

Here, we report a case of NF1 with malignant peripheral nerve sheath tumor in the upper arm.

2. Case presentation

2.1. Ethical approval

The study was approved by the Institutional Review Board and Ethics Committee of The First Hospital of Jilin University. Written informed consent was obtained from the individual participant included in the study.

2.2. Case report

A 24-year-old man presented to our department with a mass in the medial part of the left upper arm that had been present for more than 20 years. In the last 1 year prior to admission, the mass had grown in size significantly. Physical examination showed cafe-au-lait spots of variable sizes throughout the body and multiple masses in the medial part of the left upper arm. The

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The study was approved by the local Ethics Committee of the First Bethune Hospital of Jilin University. Written consent was obtained from the patient.

Written informed consent for publication of this Case Report was obtained from the participant. A copy of each written consent form is available for review to the Editor of this journal.

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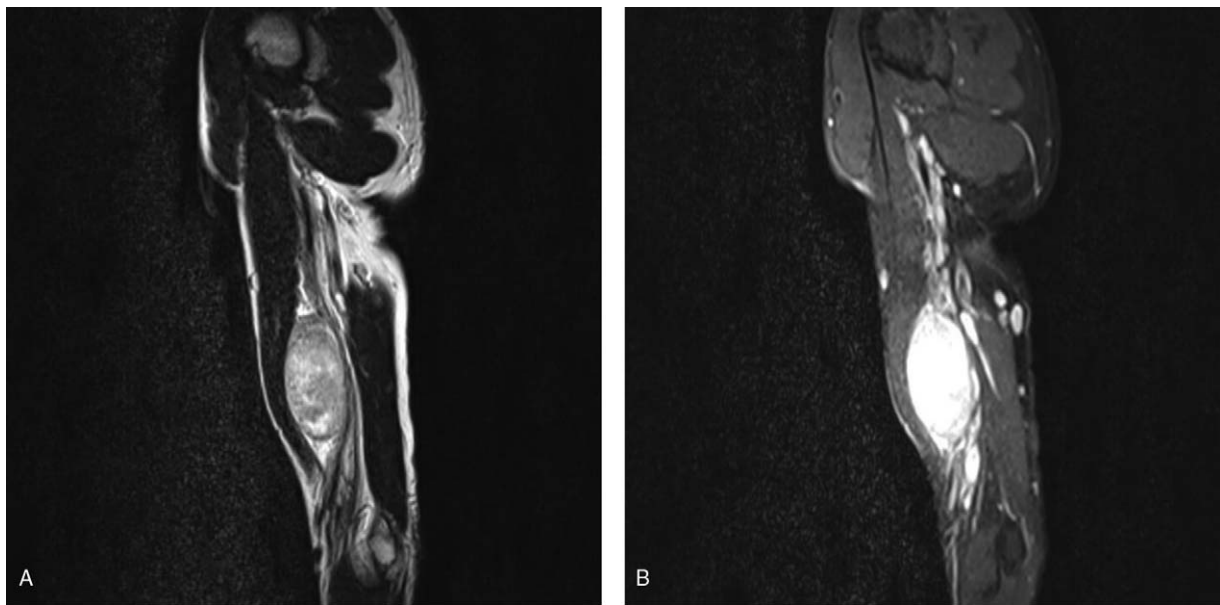


Figure 1. Magnetic resonance imaging of the left upper arm. Magnetic resonance imaging of the left upper arm revealed an 8 cm × 5 cm mass in the soft tissue anterior to the left humerus, which was hyperintense on T2-weighted imaging (A) and fat-suppression imaging (B).

masses were soft in nature and movable with local tenderness; the largest one was 8 cm × 5 cm. Neurological examination showed a positive Tinel sign and numbness in the lateral portion of left upper arm and forearm. Magnetic resonance imaging (MRI) of the left upper arm revealed multiple masses in the soft tissue anterior to the left humerus (Fig. 1). A diagnosis of neurofibromatosis was suspected. Surgical resection of the masses in the left upper arm was performed under general anesthesia. Intraoperative findings showed the masses originating from the musculocutaneous nerve were enveloped and well demarcated. The masses and the affected musculocutaneous nerve were removed. Histopathological examination showed dense cellular fascicles composed of spindle cells with nuclear pleomorphism, necrosis, myxoid changes, and mitotic activity. Immunohistochemical staining showed positivity for vimentin, CD34, and S100; the tumor cells were negative for PGP9.5, CD57, EMA, and SMA. The Ki-67 labeling index was approximately 40% (Fig. 2). A

diagnosis of malignant peripheral nerve sheath tumor was made. Postoperatively, adjuvant radiotherapy was recommended, but the patient refused. Three months later, the patient was readmitted to our department due to tumor recurrence. Ultrasonography of the left upper arm showed 2 solid hypoechoic masses, and the larger one was 5.3 cm × 2.9 cm. Color Doppler ultrasound showed abundant blood flow signals, and pulsed-wave Doppler ultrasound showed an arterial blood flow spectrum with a resistance index of 0.73 (Fig. 3). Ultrasonographical examination also revealed diffuse thickening and tortuosity of the left median nerve with spindle-shaped nodular enlargements as well as multiple oval solid hypoechoic masses in the muscularis and adipose layer. Color Doppler ultrasound showed abundant blood flow signals in the masses of adipose layer (Fig. 4). A diagnosis of neurofibromatosis with recurrent malignant peripheral nerve sheath tumor was made. An extended resection of the malignant peripheral nerve sheath tumor in the

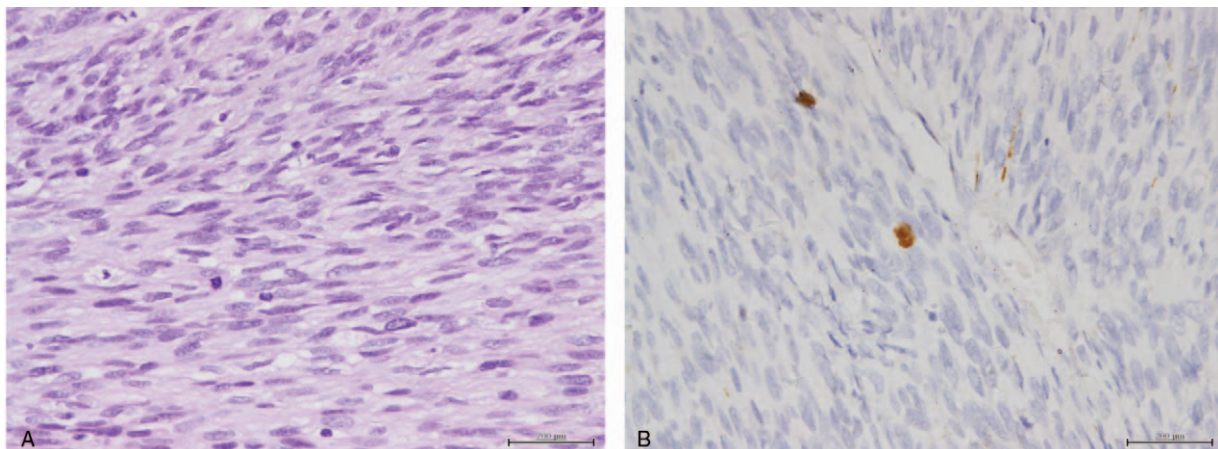


Figure 2. Histopathological examination. High-power microscopy showed nuclear hyperchromatism with pleomorphism (original magnification 400×). Immunohistochemical staining showed positivity for S100 (original magnification 400×).

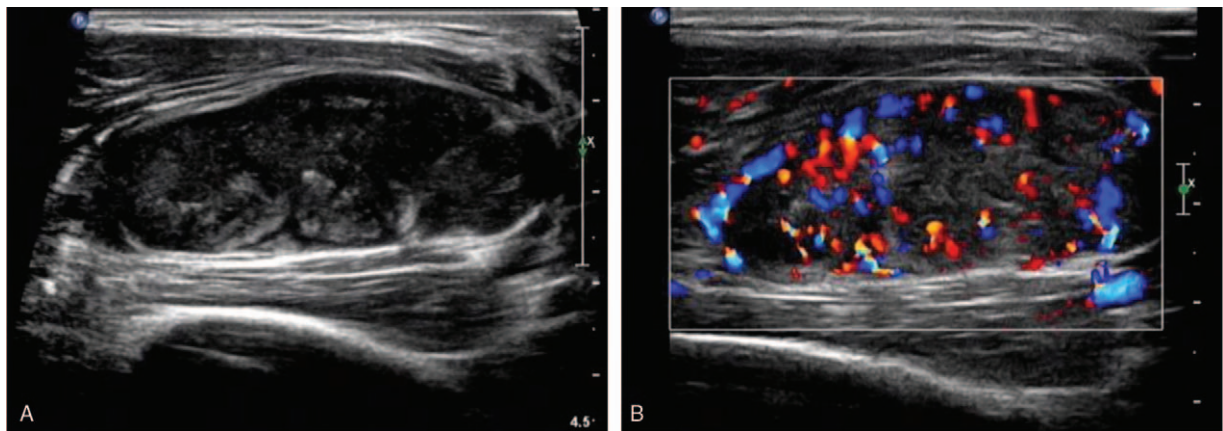


Figure 3. Ultrasonography of inner muscularis in the left upper arm. (A) Ultrasonography revealed a well-defined tumor with intratumoral heterogeneous echoes and scattered calcifications. (B) Color Doppler ultrasound showed abundant blood flow signals.

left upper arm was performed under general anesthesia. Intraoperatively, we noted an irregular mass between the bicipital muscle and brachialis that was distributed along the musculocutaneous nerve with infiltration into the bicipital muscle. The tumor, bicipital muscle, and involved cutaneous nerves were completely resected with the surgical margin of more than 3 cm from the tumor. Histopathological examination was consistent with a recurrent malignant peripheral nerve sheath tumor. The Ki-67 labeling index reached up to 80%. Two months after the second operation, *in situ* recurrence of the tumor was noted again, and the tumor was again surgically resected. Three weeks later, the patient began radiotherapy with 60 Gy in 30 fractions. Four months after the administration of radiotherapy, another tumor was noted in the lateral border of the left upper arm. It was removed via an *en-bloc* resection, and the pathological diagnosis was malignant peripheral nerve sheath tumor. During a 4-month follow-up after the last operation, the patient's condition remained stable.

3. Discussion

NF1 is a common autosomal dominant disease with no significant gender or racial propensities.^[6] The *NF1* gene is a tumor-suppressor gene encoding neurofibromin 1 that functions as a negative regulator of the rat sarcoma viral oncogene

homolog (RAS) signal transduction pathway. According to the diagnostic criteria for NF1 established by the National Institutes of Health (NIH), NF1 can be diagnosed if a patient has any 2 of the following clinical manifestations:

1. cafe-au-lait spots;
2. intertriginous freckling;
3. Lisch nodules;
4. multiple neurofibromas;
5. optic pathway gliomas;
6. distinctive bony lesions; and
7. a first-degree family relative with neurofibromatosis.

Malignant peripheral nerve sheath tumor are malignant soft-tissue neoplasms in the nervous system. These entities account for 5% to 10% of all soft-tissue sarcomas.^[7] According to the previous literature, in patients with NF1, the occurrence of malignant peripheral nerve sheath tumors may be associated with the dysfunction of the *CDKN2A* and *TP53* genes.^[8] The histogenesis of malignant peripheral nerve sheath tumor has three subtypes: sporadic type, malignant transformation from NF1, and malignant transformation from other tumors such as schwannomas and gangliocytomas.^[9] We speculated that the malignant peripheral nerve sheath tumor in the current case represented a malignant transformation from NF1. Malignant

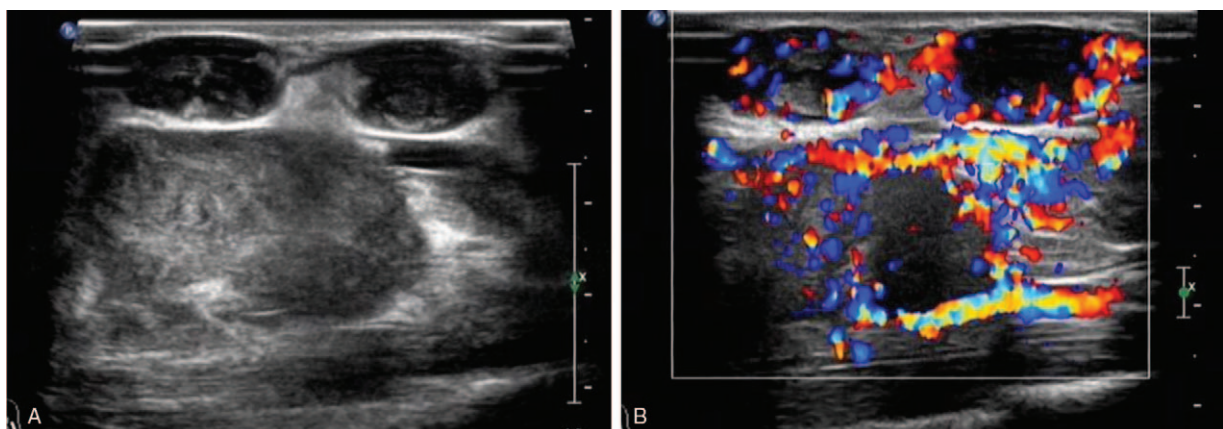


Figure 4. Ultrasonography of inner adipose layer in the left upper arm. (A) Ultrasonography revealed well-defined tumors with intratumoral heterogeneous echoes. (B) Color Doppler ultrasound showed abundant blood flow signals.

peripheral nerve sheath tumors are highly aggressive and most commonly arise from main nerve trunks. The most frequent locations are the head and neck regions followed by the trunk and extremities, while malignant peripheral nerve sheath tumor in the paravertebral regions,^[10] intraosseous areas,^[11] and enteric canal^[12] have also been reported. In the present case, the primary tumor originated from the musculocutaneous nerve, and the recurrent tumor involved the superficial small nerves. As reported, about 40% to 65% of malignant peripheral nerve sheath tumors lead to local recurrence after operation, and approximately 30% to 60% of malignant peripheral nerve sheath tumors develop distant metastasis, with pulmonary metastasis being the most common.^[13] In our case, no distant metastasis was noted during the follow-up period.

The optimal neuroimaging modality for the diagnosis of malignant peripheral nerve sheath tumor remains inconclusive. Computed tomography can show the location and size of tumors but has little benefit for differentiating malignancies from benign lesions.^[14] MRI is the mainstream method for radiological examination, and scholars have proposed that some characteristics can suggest the diagnosis of malignant peripheral nerve sheath tumor: a diameter >5 cm, poorly-defined demarcation, peritumoral edema, intratumoral heterogeneous intensities, central necrosis, and calcification.^[15] Because the radiological features of malignant peripheral nerve sheath tumor are nonspecific, the preoperative diagnosis is challenging. Additionally, MRI has limited value for identifying intratumoral arteries and veins.^[16] Ultrasonography is a convenient and economical modality that can help reveal the intratumoral vessels and provide clues of malignancy.^[16] In the current case, the radiological characteristics could not yield a definitive diagnosis of malignant peripheral nerve sheath tumor; however, the large size and irregular shape of the tumor, involvement of a large nerve trunk, abundant intratumoral feeding arteries, and intratumoral calcifications supported the diagnosis.

Currently, the standard treatment regimen for malignant peripheral nerve sheath tumor is extensive surgical resection.^[15] Moreover, postoperative adjuvant radiotherapy can help control local recurrence and improve the 5-year survival rate.^[17,18] For unresectable malignant peripheral nerve sheath tumors or those with extensive metastasis, chemotherapy with doxorubicin or ifosfamide may be effective.^[17] In our case, repeated recurrences were noted, and a much longer observation is necessary.

4. Conclusion

Malignant peripheral nerve sheath tumor in NF1 is an extremely rare entity that is challenging to diagnose. High-frequency ultrasound can facilitate the identification of intratumoral vessels and suggest the diagnosis of malignant peripheral nerve sheath tumor. Considering the malignant nature of these tumors, a much longer follow-up is still needed for the present case.

Author contributions

Lili Zhang and Lirong Zhao designed the study, conducted all searches, appraised all potential studies and wrote and revised the

draft manuscript and subsequent manuscripts. Fangfang Sun and Hongyu Li revised the draft manuscript and subsequent manuscripts. Jie Du assisted with the presentation of findings and assisted with drafting and revising the manuscript. All authors read and approved the final manuscript.

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Data curation: Lili Zhang, Jie Du, Lirong Zhao.

Writing – Original Draft: Lili Zhang, Hongyu Li, Jie Du, Lirong Zhao.

Writing – Review & Editing: Lili Zhang, Fangfang Sun, Lirong Zhao.

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