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Case Report

Malignant transformation of neurofibromatosis-1 into low-grade malignant peripheral nerve sheath tumor: a case report

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Abstract: Malignant Peripheral Nerve Sheath Tumor (MPNST) is a malignant mesenchymal tumor. The majority of MPNSTs are found in patients with neurofibromatosis type 1 (NF-1) who have a high-grade sarcoma. At the moment, there are just a few instances of low-grade MPNST caused by NF-1. We present a case of malignant transformation of NF-1 into low-grade MPNST in a patient with a long history of the disease. Multiple protruding masses with ulceration on the right shoulder and chest wall were discovered during physical examination. Complete tumor excision was done, followed by hematoxylin-eosin and immunohistochemical staining. A portion of the tumor had higher cellularity, hyperchromatic cell nuclei, and mitoses were seen in only five out of ten high-power fields. S-100 and vimentin were positive, whereas cytokeratin, desmin, SMA, and CD34 were negative. Ki-67 (MIB1) labeling index hot-spotting was around 25%. This was thought to be NF-1 malignant transformation into low-grade MPNST. Overall, knowing the clinical and pathologic characteristics of the disease, plus growing knowledge or experience with the condition, may improve preoperative diagnostic accuracy and extending survival time.

Keywords: Malignant peripheral nerve sheath tumor, low grade, neurofibromatosis-1, malignant transformation

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a rare form of soft tissue sarcoma that develops from the cells that make up the nerve sheath. The majority of MPNSTs are seen in patients with neurofibromatosis type 1 (von Recklinghausen disease, NF-1). These patients usually satisfy the diagnostic criteria for a high-grade sarcoma with atypical nuclei, mitotic indices >10/10 HPFs, and predominant tumor necrosis. Those with lower mitotic indices (3-9 mitoses/10 HPFs) and no necrosis, on the other hand, are typically categorized as low-grade MPNST. They are frequently caused by a neurofibroma, but not by NF-1. As a result, a low-grade MPNST caused by NF-1 is typically thought to be an uncommon neoplasm, as the majority of MPNSTs are high-grade. We present a case of a low-grade MPNST caused by NF-1 malignant transformation.

Case report

A 70-year-old male presented to our outpatient clinic two months ago with the chief complaint of ulceration of a tumor on his right shoulder. He was diagnosed with neurofibromatosis type 1 (NF-1) after a history of numerous neurofibromas across his right shoulder and chest wall for several years, although there was no history of NF in the patient's family and no previous irradiation was found. A further physical examination found numerous protruding tumors in the right shoulder and chest wall area. There was no evidence of a compression symptom or neurologic dysfunction. The numerous masses were hypodense with an enhanced margin in the subcutis of the right chest wall and shoulder, according to computed tomography (CT) (**Figure 1B**). The results of standard laboratory tests were within normal limits. Because of the long history of NF-1, the clinician suspected that the ulceration of the core area of the tumor was caused by a long period of rubbing on the clothing. Except for an out-patient surgical dressing, no other medical measures were taken. There was still no healing after nearly two months of surgical dressing in the outpatient setting. Given the possibility of malignant transformation, a complete tumor excision was undertaken. The tumor had numerous nodules,

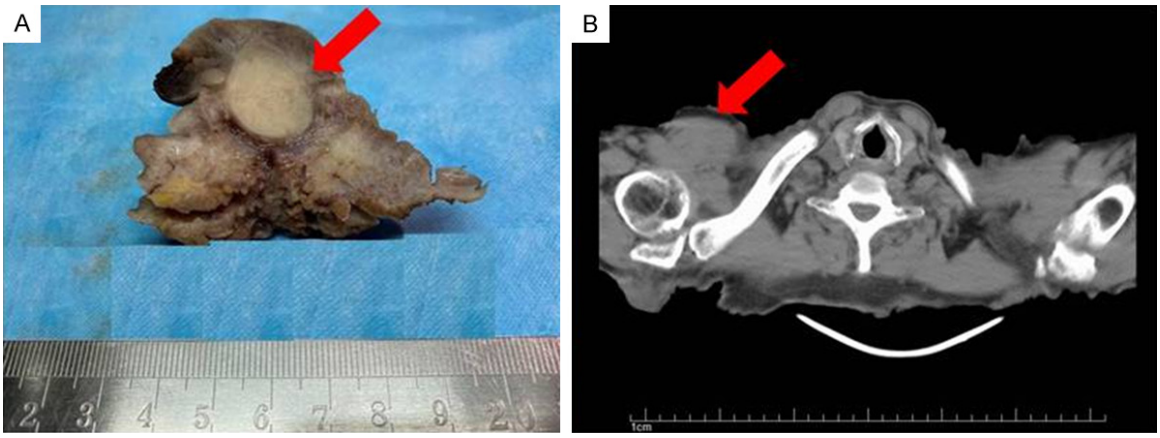

Figure 1. Radiologic and gross findings. A. Appearance of multiple nodules within the central tumor protruding toward the skin can be seen. B. The computed tomography indicating multiple masses as hypodense areas with an enhanced margin in the subcutaneous region.

extending towards the skin with variable-sizes of 0.5-1.3 cm in diameter, besides a central one with a volume of 4.5×4×3 cm on gross inspection of the surgical specimen (**Figure 1A**). The skin was grey-red in hue and had an incomplete surface with ulceration and infection. The cut surface of the tumor was pink with alternating yellowish patches on sections following fixation, well-circumscribed and unencapsulated. Histopathology indicated a diffuse proliferation of spindle-shaped cells organized in a fascicular pattern (**Figure 2A**). There was a steady shift from a low to a moderately greater cellular component. A large percentage of the nodules had typical neurofibroma-like characteristics. While the central one had more cellularity, hyperchromatic cell nuclei, and mitoses, there were only five mitotic figures per ten high-power fields (**Figure 2B**). Except for that, no hemorrhage or necrosis was found, which was traditionally thought to be a component of high-grade MPNST. Immunohistochemical staining was used to provide an accurate final diagnosis. S-100 and vimentin immunoreactivity were widespread in tumor cells (**Figure 2C**, **2D**). To rule out other spindle cell tumors, such as low-grade fibromyxoid sarcoma, low-grade myxofibrosarcoma, and fibrosarcoma, immunohistochemical staining for CK, desmin, SMA, and CD34 were conducted; all exhibited negative reactivity. Ki-67 (MIB1) labeling index hot-spotting was around 25%. The presence of hypercellular, mitotically active lesions 5/10 HPF with enlarged, hyperchromatic cell nuclei, no necrosis, and diffuse S-100 protein expression led to the pathologic diagnosis of malignant transformation of neurofibromatosis-1 into low-grade Malignant Peripheral Nerve Sheath Tumor. The post-operative assessment was fair, and no adjuvant chemoradiotherapy was accepted. The patient was clear of the illness after a nine-month follow-up, with no recurrence or metastases.

Discussion

Malignant Peripheral Nerve Sheath Tumor, which accounts for 2% of all malignant soft tissue tumors, is uncommon and has a poor prognosis [1]. The close relationship between MPNST and NF-1 has indicated that NF-1 is an independent poor prognosis factor in the development of MPNST [2]. According to certain research, the rates of recurrence and metastasis among MPNST with NF-1 are 45-78% and 39-84%, respectively, while the rates for patients with a solitary MPNST are only 38-58% and 16-52% [3, 4]. The majority of MPNSTs with NF-1 are high-grade with an aggressive course and poor survival due to frequent multifocal lesions, centrally distributed placement, and higher rates of recurrence and metastasis [5-7]. While low-grade MPNST has a minimal chance of recurrence and metastasis, it can also be caused by NF-1. Ducatman et al. performed research on a wide series of MPNST, which revealed that low-grade MPNST accounted for only 18% of patients with NF-1 [5]. As a result, malignant transformation of the NF-1 into a low-grade MPNST is a relatively rare occurrence.

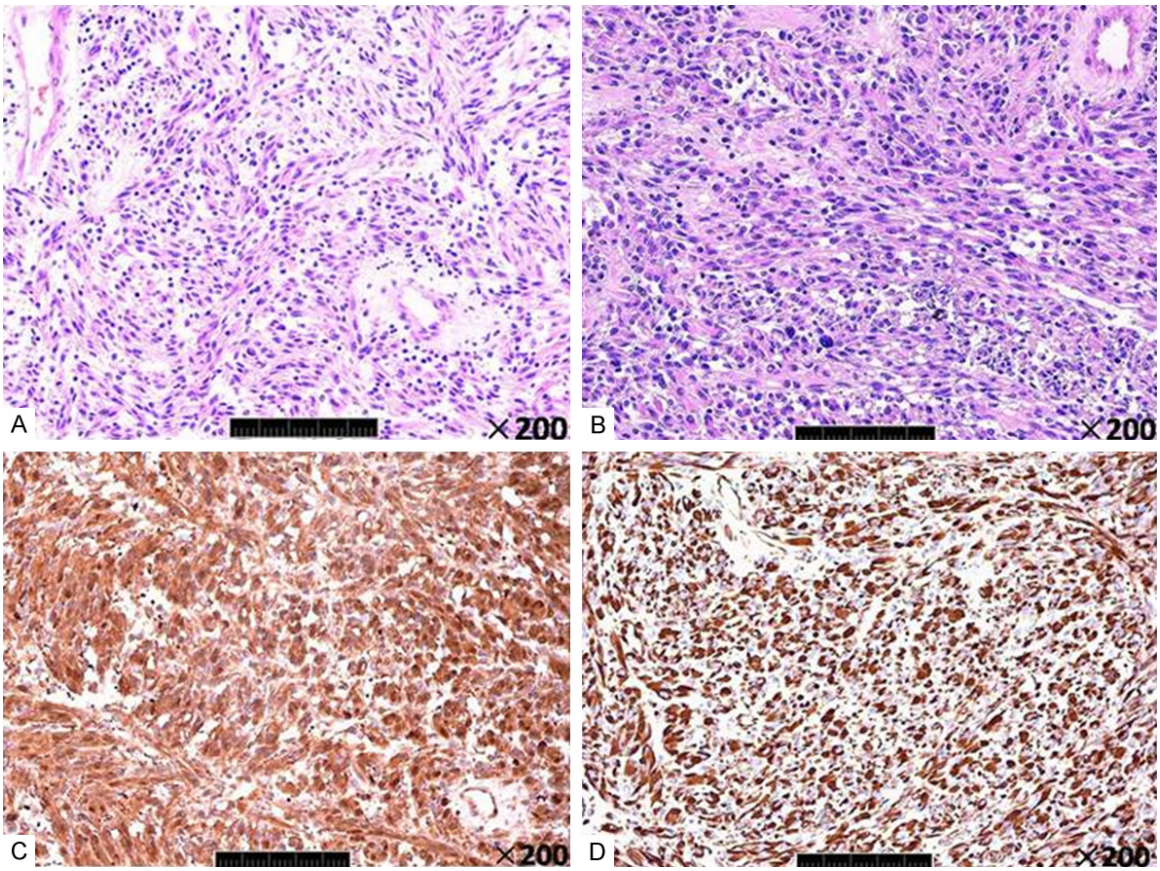

Figure 2. Histopathological findings. A. The diffuse proliferation of spindle-shaped cells is arranged in a fascicular pattern (×200). B. The tumor cells exhibited higher cellularity and hyperchromatic cell nuclei (×200). C. The tumor cells were diffusely positive for S-100 (×200). D. Vimentin stain was positive (×200).

The histogenesis of malignant transformation from NF-1 into a low-grade MPNST is still unknown, with most research focusing on high-grade lesions. Shogo Tajima's research found that loss of p16 expression and homozygous deletion of the CDKN2A/p16 gene were found in low-grade MPNST and that these alterations may be linked with malignant progression to high-grade MPNST [8].

Due to the rarity of this condition, there are few clinical investigations focused on a single institution's experience with low-grade MPNST caused by the malignant transformation of NF-1. According to the literature, the uncommon entity is often seen on the proximal limbs and trunk, in addition to the head, neck, and mediastinum, which is almost the same location as the high-grade lesion [9]. Even some researchers have determined that NF1-associated MPNST patients are typically younger, with a primary impacted age range of 20 to 50 years. Our patient, who was diagnosed at the age of 70 years, seems to have undergone a several-year malignant change following a long-standing benign NF-1. Based on the foregoing, we may conclude that the beginning age of low-grade MPNST caused by malignant transformation of NF-1 is somewhat delayed since the patient has a long history of benign disease. The low grade MPNST resulting from NF-1 malignant transformation is typically characterized by progressive enlargement of the mass, as a probable lengthy nature course of malignant transformation. Although there is no discomfort in the early stages, as the mass grows bigger, compression symptoms may develop, leading to pain or neurological dysfunction due to nerve affection or compression of the surrounding tissue. Our patient had ulceration of the core section of the tumor, which might have been caused by prolonged rubbing with the clothing. There is no discernible gender difference.

Magnetic resonance imaging (MRI) and computed tomography (CT) might be particularly effective in determining the extent of the MPNST before surgery, as well as detecting metastases or recurrences during follow-up. On T1-weighted images, an MRI generally displays a mass with clear boundaries and a high-intensity signal. While our patient's CT scan revealed a multifocal lesion with low density in the right chest wall and shoulder, no malignant features of this lesion were discovered.

In clinical practice, the differential diagnosis of low-grade MPNST is difficult because of the comparable pathological presentations with many other lesions. Spindle cell sarcomas, such as low-grade fibromyxoid sarcoma, low-grade myxofibrosarcoma, and fibrosarcoma, are generally evaluated in the differential diagnosis of low-grade MPNST. Metastatic carcinoma and malignant melanoma must be differentiated from low-grade MPNST based on the pathological appearance of epithelioid morphology. H&E staining findings in our case revealed a fascicular pattern with nuclear pleomorphism and hypercellularity focally, but 5 mitoses/10 HPFs without the picture of necrosis. Furthermore, diffuse positivity for immunohistochemical staining with S-100, a particular marker for low-grade MPNST, aids in differentiating it from high-grade MPNST. Because the low-grade MPNST has a strong and diffuse pattern of S-100 expression, whereas the high-grade subtypes always have a weak and focal positivity for S-100 protein [10, 11]. Meanwhile, non-reactivity for some immune profiles, such as desmin, SMA, EMA, cytokeratin, and melanocytic markers, may aid in ruling out the likelihood of the other neoplasms described above. Furthermore, clinical and histopathologic characteristics may complement one another in distinguishing these lesions from low-grade MPNST. A long clinical history of NF-1, pathologic examination, and immunohistochemistry staining with S-100 can all be used to make a definitive diagnosis.

The incidence of low-grade MPNST caused by NF-1 malignant transformation was relatively low. Most clinicians may have a lack of awareness or experience. If NF-1 exhibits rapid growth, inexplicable discomfort, or neurologic dysfunction, it should be considered highly suspicious of malignant transformation to MPNST. To prevent missed or misdiagnosis, additional medical examinations such as biopsy or surgical resection should be undertaken. In addition, because the sign of low-grade MPNST caused by the malignant transformation of NF-1 is not evident or easily overlooked by radiological examination, a delayed diagnosis or misdiagnosis would have an impact on therapy and prognosis. As a result, if a larger nodule, uneven signal, unclear boundary, or elimination of "small target sign" is present, there is a potential of malignant transformation. To avoid misinterpretation, a differential diagnosis of low-grade MPNST caused by malignant transformation of NF-1 in peripheral nerve and soft tissue is required, which encompasses a range of tumors with overlapping morphology. The cornerstone of therapy and a significant prognostic factor is complete surgical resection [12, 13]. In this example, broad and radical excision with a free margin was effectively accomplished. Several studies [14-16] have found that adjuvant chemotherapy or radiation is effective for advanced MPNST. However, owing to the different histologic criteria or specific immune profiles, a great deal of assistance would be offered. Predicting malignant transformation is difficult from both a clinical and a pathologic standpoint. The proper diagnosis may be determined by a mix of factors rather than by a single criterion. A careful history-taking, extensive investigation of the clinical and pathologic characteristics, and improved clinician knowledge of the low grade of MPNST caused by NF-1, all of the aforementioned approaches may assist to minimize missed diagnosis or reduce misdiagnosis.

After 9 months of the first surgery, our patient had neither recurrence nor metastases.

Conclusions

An MPNST caused by NF-1 is typically linked with a poorer prognosis than a single lesion. However, because it is a subtype of MPNST, low-grade MPNST has a low risk of recurrence and metastasis. We report an instance of NF-1-related low-grade MPNST. In the future, we hope to increase greater awareness and understanding, as well as enhance the accuracy of diagnosis for low-grade MPNST caused by NF-1 malignant transformation.

Disclosure of conflict of interest

None.

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