Different Pathology of Peripheral Nerve Sheath Tumor in Neurofibromatosis Type 1: 3 Cases

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Neurofibromatosis type 1 (NF1) is an autosomal-dominant genetic disease that predisposes affected individuals to tumors. Neurofibroma and malignant peripheral nerve sheath tumor (MPNST) are examples of PNSTs that occur either sporadically or as part of hereditary neurocutaneous diseases such as NF1. We treated three patients with NF1 who presented with different PNSTs. All patients underwent surgical resection, and pathologic findings indicated neurofibroma, atypical neurofibroma, and MPNST, respectively. We managed each case based on its pathology. The patient with MPNST died after chemoradiotherapy; the other patients did not experience recurrence for several months.

Key Words: Nerve sheath neoplasms; Neurofibroma; Neurofibromatosis 1

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal-dominant hereditary disease with a prevalence of about 1 in 3000. The clinical characteristics of NF1 are café-au-lait spots, neurofibromas, freckling, optic gliomas, and Lisch nodules^{4,5}. Neurofibroma is a benign peripheral nerve sheath tumor (PNST) that can transform into atypical neurofibroma, a premalignant tumor, or malignant PNST (MPNST)^{1,9}. Because NF1 patients are at higher risk of malignancy, which is the most common cause of death, surgical resection and pathologic confirmation are very important to the treatment of symptomatic or growing tumors in NF1 patients^{3,4,11}. We present three cases of different PNSTs in NF1 patients.

CASE REPORT

Case 1

A 23-year-old man with NF1 diagnosed 6 years prior presented with left hip pain. Two round-shaped tumors were found on abdominal computed tomography (CT) and magnetic resonance imaging (MRI). Tumor sizes were 4.2 × 3.3 cm and 7.0 × 4.9 cm respectively. To reduce left hip pain, we decided to remove these tumors. The patient underwent two separate excisional operations. One originated from the left femoral nerve and the other originated from the left sciatic nerve. Pathologic diagnosis was neurofibroma (Fig. 1). After surgery, hip pain resolved and there were no neurologic complications and no evidence of recurrence on 1-year follow-up CT.

Case 2

A 25-year-old woman with NF1 diagnosed 7 years prior presented with abdominal pain. On abdominal CT and MRI, a 6.8 × 4.5-cm-sized and oval-shaped mass was found in the right retroperitoneal space with multiple nodular lesions. The size of this mass and the numerous nodular lesions were suspicious for malignancy. For relief of abdominal pain and pathologic confirmation, we performed surgical resection of the mass. The pathologic findings were moderate

Fig. 1. Case 1. Benign neurofibroma. (A) Computed tomography image of a 7.0 × 4.9-cm-sized tumor (arrow). (B) Gross image of excision. (C) Hematoxylin and eosin stain (H&E), ×400 magnification image of a wavy nuclei spindle cells and loose collagenous stroma.

Fig. 2. Case 2. Atypical neurofibroma. (A) Computed tomography of a 6.8×4.5 -cm-sized tumor (arrow). (B) Fat-saturated T2-weighted magnetic resonance image of a tumor (arrow) without perilesional soft tissue edema. Multiple nodular lesions (arrowhead). (C) Hematoxylin and eosin stain (H&E), $\times 400$ magnification image of a neurofibroma with focal nuclear atypia and increased cellularity without mitotic activity.

Fig. 3. Case 3. Malignant peripheral nerve sheath tumor. (A) Computed tomography image of a 12.8×9.2 -cm-sized (arrow) and 5.1×4.1 -cm-sized (arrowhead) tumor, (B) T2-weighted (left) and enhanced T1-weighted (right) magnetic resonance image of a tumor with perilesional soft tissue edema, peripheral enhancement pattern and intratumoral cystic lesion. (C) Gross image of excision. (D) Hematoxylin and eosin stain (H&E), $\times 400$ magnification image of a proliferation of spindle cells with numerous mitoses.

cellularity with nuclear atypia, leading to a diagnosis of atypical neurofibroma (Fig. 2). Abdominal pain was relieved postoperative without complications. On 1-year follow-up CT and MRI, there was no evidence of tumor recurrence or malignant changes.

Case 3

A 22-year-old man with NF1 diagnosed 6 years prior presented with left flank pain. We found 5.1×4.1 -cm-sized and 12.8×9.2 -cm-sized tumors on abdominal CT and MRI. Radiologic findings were

large-sized tumors with perilesional edematous changes and peripheral enhancement that are suggestive of malignancy. He underwent two separate excisional operations. These tumors originated from the left intercostal nerve and right lumbar plexus and were pathologically diagnosed as MPNST with cellular atypia and numerous mitoses (Fig. 3). The patient received adjuvant radiotherapy, but follow-up CT revealed tumor recurrence. The patient underwent reoperation 2 months after the first operation (Fig. 4). Postoperatively, he received chemotherapy, but 3 months later the patient died from tumor progression and complications.

Fig. 4. Case 3. Recurrence of tumor. (A) Postoperative day 30 and 42 computed tomography image of tumor recurrence. (B) Gross image of excised tumor.

DISCUSSION

MPNST is a rare disease that is very concerning due to its poor prognosis. The incidence of MPNST is approximately 0.001% in the general population. The recurrence rate is approximately 40% to 65%, and metastasis is found in 16% to 39% of patients. The 5-year survival rate is approximately 25% to 42%.^{2,3,7} Factors related to prognosis include tumor size, the extent of resection in surgery, and rate of mitosis. Total resection or wide tumor excision is considered appropriate because chemotherapy and radiotherapy tend to be ineffective.^{2,7} In case 3, we performed surgical resection, radiotherapy, and chemotherapy, but the patient experienced extremely rapid progression of malignant tumor. Despite potential perioperative complications including neurologic deficits, pathologic confirmation and surgical treatment of MPNST is important.

NF1 patients are at high risk of neoplastic disease; the overall risk of cancer in NF1 patients is 2.7 times higher and the risk of malignancy in 50-year-olds is approximately 20%.¹¹ Also, approximately 50% of MPNSTs are related to NF1. In NF1 patients, MPNST is less rare than in the general population. The incidence is around 4.6% and the lifetime risk is 8% to 13%. Furthermore, the prognosis of MPNST with NF1 is poorer.^{2,3} Therefore, appropriate surveillance is required for NF1 patients. A particularly close follow-up examination is necessary in cases of growing neurofibroma.

We observed nuclear atypia without mitotic activity on histology in case 2. One-year follow-up CT and MRI revealed no recurrence. However, atypical cells can be found in gray zones between benign

and malignant lesions, and transform into malignant tumors in specific genetic characteristics such as deletion of CDKN2A/B. Therefore, atypical neurofibroma is considered a premalignant tumor.^{1,9} Because of the possibility of malignant change, detection and treatment of atypical neurofibroma are important in NF1 patients. Serial MRI and 18F-fluorodeoxyglucose-positron emission tomography can be used for detection of atypical neurofibroma.¹⁰

Before pathologic confirmation, imaging findings are used for the differentiation of benign and malignant lesions. Differentiation using image findings is helpful for treatment planning. Previous studies described MRI findings indicative of malignancy, including large size, a peripheral enhancement pattern, perilesional soft-tissue edema, and intratumoral cystic lesions.^{8,12} In case 3, these features were observed on MRI before surgery, leading to suspicion of MPNST. Additional radiotherapy was planned. In case 2, there was no peripheral enhancement pattern, perilesional soft-tissue edema, or intratumoral cystic lesions. However, the large tumor size and distinct multiple nodular lesions on MRI suggested a malignant or atypical lesion.⁶ Our experience suggests that MRI findings are important and useful for the differentiation of three types of PNSTs.

CONCLUSION

When dealing with PNSTs in NF1 patients, neurosurgeons should consider the possibility of malignant changes. Further study and specific management plans are needed for PNSTs in NF1.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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