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CASE REPORT

Metachronous Intramedullary Anaplastic Astrocytoma and Liposarcoma Complicated by Neurofibromatosis Type 1: A Family History Analysis

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Neurofibromatosis type 1 (NF1) is one of the most frequently encountered familial tumor syndromes. NF1 patients are highly prone to have multiple nervous system tumors, and are also at increased risk for various nonnervous mesenchymal or neuroendocrine tumor developments. This is an NF1 patient who developed two different unusual tumors: an intramedullary anaplastic astrocytoma of the thoracic spine and myxoid liposarcoma of the lower limb. The family members were carefully investigated as per the NF1 diagnostic criteria. A strong cutaneous NF1 penetrance was found in 6 of the 14 family members in four successive generations, two of whom had NF1 and developed breast cancer and bilateral optic gliomas. The NF1 tumor syndrome highlights a wide-ranging tumor spectrum, and clinicians should keep an eye on tumor surveillance and encourage medical counseling, and long-term NF1 family follow-up is warranted for prophylactic warning.

Key words: Neurofibromatosis 1, spinal cord neoplasm, astrocytoma, liposarcoma, family analysis

INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most frequent hereditary neurocutaneous disorders and an autosomal dominant familial tumor syndrome.[1,2] Many of these manifestations may not be found at birth and may be apparent when transitioning to adulthood. Clinical NF1 features have vast variability, which indicates that genotypic penetrance may be attributed to stochastic events, environmental factors, or modifier gene expression. These NF1 patients are highly prone to develop multiple nervous system tumors, and are also at increased risk for mesenchymal tumor development, such as sarcomas or leukemias.[1-3] Intramedullary spinal cord tumors and liposarcoma are two very rare tumor entities arising from NF1 patients.[4-7]

This is an NF1 patient who developed two different tumors: an intramedullary anaplastic astrocytoma of the thoracic spine and myxoid liposarcoma of the limb. These rare tumors highlight the mesenchymal sarcoma and intramedullary glioma spectrum in NF1 and also aim to learn this NF1 family's high tumor burden.

CASE REPORT

A 37-year-old female with NF1 developed generalized soft, cutaneous tumor, and multiple café-au-lait spots on her trunk and proximal low extremities since her teenage years [Figure 1a]. She first noticed a swelling tumor in her right leg, near the knee region, and was excised at an outside regional hospital in 2008. The tumor measured 6.5 cm × 5.5 cm × 3 cm and was histologically diagnosed as a myxoid liposarcoma. She was referred to our department for adjuvant radiotherapy owing to the close excision margin, and no obvious residuum on following magnetic resonance imaging postoperatively [Figure 1b and c]. A total dose of 66.6 Gy in 1.8 Gy daily fractions was prescribed and

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administered in the surgical bed. She was regularly seen in the oncology department without evidence of recurrence.

She complained of back pain, lower limb numbness, and clumsy gait symptoms lasting for several months in 2017, and then she called on her physical therapist for exercise and hands-on care to improve the ability to move and reduce pain. Progressive limb weakness alerted physicians to order a spinal magnetic resonance imaging, which revealed an expansive intramedullary lesion with ill-defined and enhancing tumor features at the 6th–10th thoracic spine level [Figure 2a and b]. She was referred to a neurosurgeon and underwent a T4–T8 laminectomy with subtotal spinal tumor excision in May 2017. Histological analysis revealed hypercellular tumor cells with distinct nuclear anaplasia, nuclear inclusions, multinucleation, and increased mitosis (up to 3 in 10 high-power field). The tumor cells were stained diffusely positive for glial fibrillar acidic protein by immunohistochemical study and expressed as low proliferation index (around only 5%) by Ki-67 staining. The pathologic features are compatible with WHO Grade III anaplastic astrocytoma [Figure 3]. She was referred to the oncology department for temozolomide-based chemoradiotherapy following tumor diagnosis. The radiation dose was delivered to the involved spinal target volume, with totaling dose up to 54 Gy in 27 daily fractions. The spinal tumor progressed and neurologic symptoms deteriorated rapidly, which led to complete hemiplegia about 8 months after radiation. She succumbed to respiratory failure in August 2018.

Careful case investigation of the family tree [Figure 4] revealed a characteristic cutaneous feature with six of the 14 family members diagnosed with NF1 in four successive generations. Her mother and grandfather had NF-like soft tissue tumors and her mother died from breast cancer in her early 50s. Her grandfather died in her early adulthood without a definite diagnosis due to remote recall. Two of her siblings (boys) developed dozens of neurofibromas and café-au-lait macules in early childhood. The older son had symptomatic exophthalmos and distortion in both eyes at 2 years of age. Imaging studies found bilateral retrobulbar tumors compatible with bilateral optic gliomas, but this site is unsuited for surgery to obtain a histological examination, so systemic chemotherapy and radiotherapy was done. He passed away at the age of 11 years following 9 years of battling the disease. Her younger son, aged 21 years, had no clinical abnormalities in the case report.

DISCUSSION

NF1 patients are diagnosed when two or more of the following seven criteria are present: Café-au-lait skin spots,

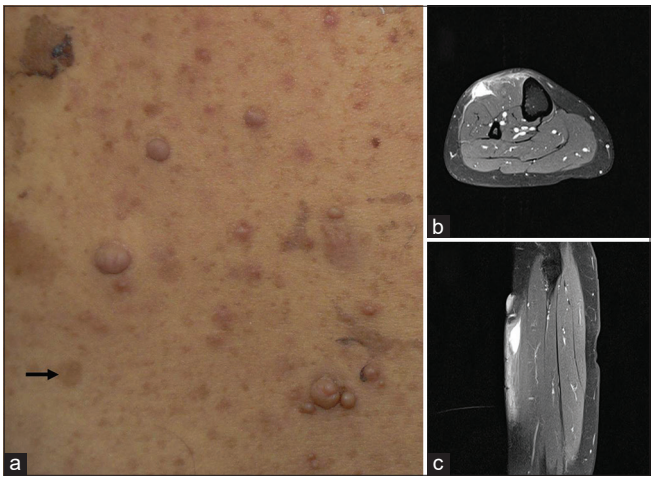

Figure 1: Cutaneous lesions of neurofibromatosis type 1 and lower limb magnetic resonance imaging. (a) Multiple cutaneous and subcutaneous neurofibromas and café-au-lait macules (arrow) on the trunk. (b and c) Axial and sagittal views of T1-weighted MRI gadolinium-enhanced with fat suppression showing no obvious residuum at tibialis anterior muscle of the right lower leg postoperatively. MRI = Magnetic resonance imaging

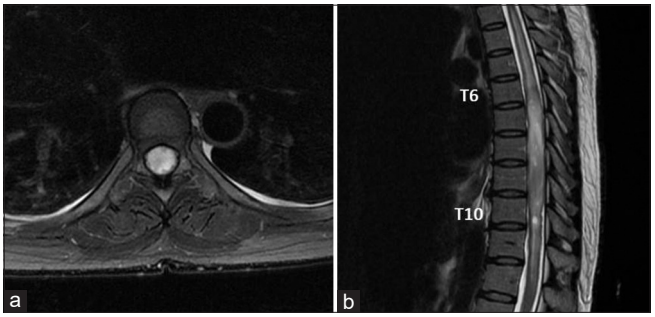

Figure 2: Spinal magnetic resonance imaging. (a) Axial T1-weighted gadolinium-enhanced with fat suppression images showing high intensity and swollen spinal cord lesion with loss of subarachnoid space. (b) Swollen spinal cord from the 6th to 10th thoracic spine levels

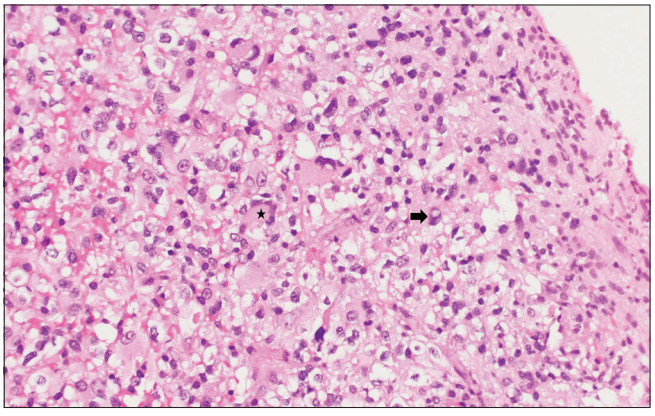

Figure 3: Histological appearance of the spinal anaplastic astrocytoma, WHO Grade III. Hypercellular tumor with distinct nuclear anaplasia, nuclear inclusion (arrow), and multinucleation (asterisk) (H and E, ×400). WHO = World Health Organization

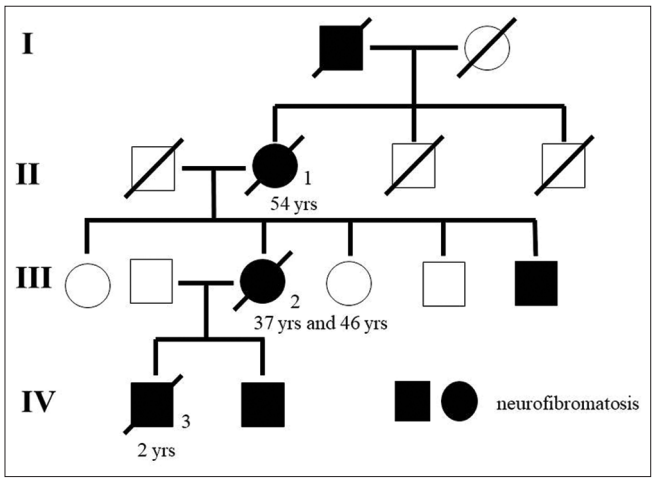

Figure 4: Analysis of family tree. The age denotes the occurrence of tumor

neurofibromas, intertriginous freckling, optic glioma, Lisch nodules, distinctive osseous lesions, and first-degree relative NF1.[1,2] Central nervous system tumor types, either nonneoplastic or neoplastic, occur in up to 15%–20% of NF1 patients. There is a trend that it is 4–6 times more common in NF1 patients than in the general population.[1-3] Sporadic intramedullary spinal cord tumors are relatively rare neoplasms accounting for 2%–4% of all central nervous system tumors and intramedullary high-grade glioma, either anaplastic astrocytomas (WHO Grade III) or glioblastomas (WHO Grade IV), only accounting for approximately 8%–13% of intramedullary astrocytic origin tumors.[8,9] We can postulate that an even rarer ratio holds true for these spinal tumors with NF1 because sporadic intramedullary spinal cord gliomas are rarer than sporadic intracranial gliomas. However, intramedullary gliomas have been reported in NF1 patients.[4,5,8,9] The recommended protocol for intramedullary malignant glioma is the same standard of regimen for cranial glioblastoma with safe spinal tumor resection followed by concurrent chemoradiotherapy.[8,9] Survival remains poor in NF1-associated intramedullary gliomas. Nonetheless, further research for novel therapeutic therapy should be targeted for possible resistance imposed by NF gene loss.[3,8]

Liposarcoma in NF1 is also a very unusual malignancy. Moreover, our reported case with the development of myxoid liposarcoma and metachronous intramedullary anaplastic astrocytoma might be extremely rare. The majority of liposarcomas arose from the deep soft tissue of the extremities or retroperitoneum, so clinician should be aware of the potential malignant change on numerous neurofibromas in NF1 patients.[6,7] Early intensive wide excision and adjuvant radiotherapy has an efficacy on local disease control concerning liposarcoma therapy.[6,7]

Chinese patients with NF1 are also susceptible to malignancies, which have similar frequency to Western countries.[2] Females with NF1 carried a higher breast cancer risk than in the general population.[1,10] Children with NF1 are affected, and approximately 20% of individuals with optic gliomas and children with early manifestations, similar to our case occurring at 2 years old, may encounter a worse outcome.[1,3,9]

CONCLUSION

In summary, we present an NF1 family with four different tumors: intramedullary anaplastic astrocytoma, myxoid liposarcoma, optic gliomas, and breast cancer. The rarity of these malignancies highlights the NF1 diverse tumor spectrum, so clinicians should be vigilant on tumor surveillance and medical counseling, which warrants NF1 families' long-term follow-up for prophylactic warning owing to wide-ranging of neoplasms occurrence in NF1 patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patients' consent forms. In the form, the patient and her family have given their consent for their images and other clinical information to be reported in the journal. The patient and her family understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Data avavilability statement

The data that support the findings of this study are available from the corresponding author, S-Y H, upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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