Malignant Schwannoma of the Sciatic Nerve Originating in a Spinal Plexiform Neurofibroma Associated With Neurofibromatosis Type 1

—Case Report—

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Abstract

A 26-year-old man with neurofibromatosis type 1 (NF1) presented with a giant malignant schwannoma of the sciatic nerve. The differential diagnosis of malignant peripheral nerve sheath tumor (MPNST) was based on clinical, radiological, and histological evidence. The tumor apparently originated in a spinal plexiform neurofibroma. The lesion was resected totally without neural damage to the sciatic nerve. However, the tumor recurred within 2 months. The patient died of unknown factors probably associated with the spinal involvement. MPNST associated with NF1 has a poor prognosis due to recurrence or metastasis despite complete macroscopic removal.

Key words: neurilemmoma, neurofibroma, malignant peripheral nerve sheath tumor, malignant schwannoma, von Recklinghausen’s disease

Introduction

Neurofibromatosis (NF) is a disease of defective development of the neuroectodermal tissues and tends to involve multiple systems with an incidence of 0.25–0.05%. NF type 1 (NF1) is an autosomal dominant disease of the neurons and astrocytes whereas type 2 (NF2) is a disease of the sheathing of the central nervous system. Patients with NF1 tend to develop neurofibromas, whereas patients with NF2 harbor schwannomas. NF1 is also associated with pheochromocytoma, nephroblastoma, ganglioneuroma, brain tumors, and non-neural crest malignancies such as rhabdomyosarcoma and acute nonlymphoblastic leukemia. Sarcoma developing within a peripheral nerve or a previous neurofibroma is rare and is known as malignant schwannoma, malignant peripheral nerve sheath tumor (MPNST), neurofibrosarcoma, or neurogenic sarcoma. The true incidence is not known, although reported as 4.6%, but nerve sheath tumors account for 2–13% of soft tissue tumors. MPNST is often associated with NF1 at an incidence of 4–53%. The criteria for the diagnosis of MPNST are as follows: Tumor originating from a nerve; association with a contiguous neurofibroma; possible association with NF1; and epineural invasion from within, possibly containing heterologous mesenchymal and epithelial elements.

We report a case of giant MPNST associated with NF1 originating in a spinal plexiform neurofibroma.

Case Report

A 26-year-old man was admitted to our hospital on October 11, 1993 with a 25 × 30 cm mass on his posterior right thigh which had caused pain and slight weakness of the lower limb for 2 months and pruritus of the soles. Neurological examination found 4/5 motor strength in right plantar and dorsal flexion, but no other abnormalities. He had the stigmata of NF1, but was otherwise intellectually and neurologically intact. His family contained no history of NF1. The patient had café au lait spots and a few neurofibromas on the skin, but no Lisch nodules.
or posterior subcapsular cataracts \(^1,2,22\) or other diseases associated with NF1 \(^2,22,25,31\). He had no history of previous radiotherapy or surgery at the site of lesion.

Angiography of the lower limb demonstrated moderate neovascular reaction and posterior displacement of the femoral artery \(^20\) (Fig. 1). Cranial computed tomography found no abnormalities. Preoperative magnetic resonance imaging of the thoracic and lumbar area revealed spinal plexiform neurofibromas causing enlargement of the intervertebral foramina (Fig. 2).

He underwent surgery for the thigh mass on November 3, 1993. The tumor was found along the course of the nerve, infiltrating both proximally and distally into the sciatic nerve and the surrounding soft tissues. The mass was removed from the nerve trunk, and all functions were preserved (Fig. 3). Macroscopically, the cut surface was whitish, whorled, or homogeneous gray with areas of hemorrhage and necrosis. Histological examination revealed infiltration into the surrounding muscle tissue, high cellularity with spindle cells containing nuclear mitotic figures and pleomorphism, and pseudopalisading and necrosis (Fig. 4A). Staining with periodic acid-Schiff and mucicarmine, and immunostaining for myoglobin, F8-related antigen, Gomori’s reticulin, carcinoembryonic antigen, and keratin by the modified peroxidase-antiperoxidase method were all negative \(^10\) as well as staining for S-100 protein \(^14,33\) (Fig. 4B). The tumor was considered grade 4 based on cellularity, nuclear pleomorphism, mitotic rate, and necrosis and invasion \(^10,35\). Very few heterologous elements were noted. The diagnosis was malignant schwannoma.

Postoperatively, he did well, but the tumor recurred at the site of operation after 2 months (Fig. 5). Hindquarter amputation and radiotherapy was planned, but he died of an unknown cause during the hospital stay.

**Discussion**

Malignant transformation of neurofibroma to malignant schwannoma occurs in 2–29% of patients with NF1 \(^2,5,9,11\) but origin from a large nerve trunk is less common in patients with NF1 \(^5,34\). Some transformations occur after radiotherapy \(^10,11,31,32,36,37\) or previous surgery for a benign neurofibroma. The pleiotropic effect of the NF allele on chromosome 17 \(^4,22\) is responsible for increasing the risk for both neural crest and nonneural crest malignancies \(^1,3,5,7,16,18,22,25,32\). Development of malignant schwannoma from neurofibroma is associated with inactivation of the both NF1 (tumor suppressor gene) alleles, and by partial inactivation of the other tumor suppressor gene p53 located elsewhere on the centromere of chromosome 17 \(^4,17\). Neurofibromas increase in size under the control of the sex steroids in both sexes, directly or through mediation by nerve growth factor (NGF) \(^23\) whose receptor is located on the distal arm of chromosome 17 \(^28\). The onset of malignant schwannoma may be attributable to the abnormal and continuous stimulation of nerve cells sensitive to NGF \(^21,26\).

MPNST lesions tend to occur more centrally in patients with NF1 \(^11,13,31\) and peripherally \(^6,10,12,13\) or evenly distributed in patients without NF1 \(^31\). There is a male \(^8,36\) or female \(^10,31\) preponderance or even distribution \(^8,12\) in NF1. Patients with MPNST and NF1 are younger than patients without NF1 (28.7–36 years vs. 39.7–48 years) \(^10,31\) or no age/sex difference is noted \(^8,12\) and the mean age is 34 years \(^10,13,18\). The most common origin is the sciatic nerve followed by the brachial plexus \(^6,8,10,13\) spinal nerve roots, and the vagus, femoral, median, sacral plexus, popliteal, obturator, posterior tibial, and ulnar nerves \(^8,10,38\) and the vulva, posterior mediastinum, or retroperitoneal locations \(^5,9,10,12,13\). Association with intestinal \(^5,24\) spinal \(^5,16,22,24\) and segmental forms of NF

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**Fig. 1** Femoral angiogram of the lower limb showing moderate neovascularization in the field of the tumor (arrows) with the posterior displacement of femoral artery.
Malignant Schwannoma

Development of malignant schwannoma from a Schwann cell is extremely uncommon. A malignant spindle cell lesion containing sarcomatous cells in a whorled pattern in a nerve or a neurofibroma is called malignant schwannoma, and is characterized by high cellularity, with spindle-shaped or polygonal cells with ill-defined borders, nuclear pleomorphism, perivascular cell proliferation, high mitotic activity, and infiltration of adjacent tissue. High-grade sarcomas usually occur in NF1 (82% grade 3 or 4), and display cellular pleomorphism, brisk mitotic activity, prominent nucleoli, microvascular proliferation, necrosis, and palisading, as in our case. Fascicles of spindle cells may resemble fibrosarcoma or a storiform pattern of cell orientation without giant cells may resemble malignant fibrous histiocytoma. MPNST is composed of heterologous mesenchymal and epithelial elements. A wide range of metaplasia is attributed to the neurilemmal origin. Multipotential ectomesenchyme is responsible for the divergent differentiation.

Sarcomas arising from the nerves are less malignant and metastasize less frequently than other forms of sarcoma. However, MPNST generally causes local recurrence and metastases even after macroscopic total removal. Recurrence occurs at least once within 2–73 months in 45–78% of cases associated with NF1. Metastasis occurred in 39–65% of patients with NF1 and 16% without NF1. Hematogenous dissemination to the lungs, soft tissue, bone, liver, intra-abdominal cavity, adrenal glands, diaphragm, mediastinum, brain, ovaries, kidneys, and retroperitoneum and intraneural dissemination have been reported.

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MPNST has never metastasized to the regional lymph node.9,12) The presence of NF1, multiple or plexiform type neurofibromas, tumor size over 5 cm, and extent of resection and recurrence are poor prognostic factors.5,10,12,13,31) The 5-year survival is 10–47% and the 10-year survival is 30% and 39% in cases with NF1 and 47–75% in cases without NF1,2,10,12,26,31,35) respectively. Location and histological type (divergent differentiation/grade) are not major prognostic factors5,8,10,13,26,31) although patients with distal extremity lesions do better than those with head and neck lesions.10,31) Paravertebral malignant schwannomas had a worse outcome than in any other location.12) Prior local radiotherapy or surgery does not affect the prognosis.8,10) Patients with NF1 are younger, have malignant schwannomas centrally located, and a shorter 5-year survival than patients without NF1.31)

Radical tumor excision without damage to the nerve is possible because the tumor arises from only one fiber, displacing the rest to one side,30) but usually entails local recurrence. Muscle group excision and if necessary amputation5,9,10,12,31) combined with high-dose radiation therapy10,31) should be contemplated. However, radiotherapy is palliative and does not affect the survival.2,10) Chemotherapy is inconclusive for the treatment of malignant schwannoma.2,31) Treatment for spinal lesions is palliative, and the patients usually die of complications developing after involvement of the spinal cord.5)

Fig. 5 Photograph of the recurrent tumor at the operation site. Note the cutaneous neurofibromas on the opposite lower limb and the many café au lait spots on the buttocks.

References

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