Two Cases of Malignant Schwannoma in Association with Neurofibromatosis

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We report two cases of malignant schwannoma of skin in association with non-familial neurofibromatosis. Case 1, a 47 year old man, had a large subcutaneous tumor on the sacral area and case 2, a 62 year old woman, a painful, ulcerating tumor on the posterior aspect of the left arm. Both cases were histopathologically confirmed as malignant schwannomas and immunohistochemical studies showed S-100 protein in the tumor cells.

After surgical excision of the tumors, case 1 was lost to follow up, while case 2 remained without evidence of disease for more than one and half years.

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Malignant schwannoma is a tumor of Schwann cells or nerve sheath cells. According to the literature, it accounts for approximately 10% of all soft tissue sarcomas; about one half occur with neurofibromatosis.1,2 It has been reported that three to thirteen percent of patients with neurofibromatosis will develop malignant schwannoma some time in their lives.3 However, D' Agostino et al4 noted that the incidence of malignant transformation of cutaneous neurofibroma is only 0.3%. In Korea, only two cases of cutaneous malignant schwannoma have been reported in association with neurofibromatosis.5

We report, herein, two patients with clinical and histopathologic features of malignant schwannoma arising in neurofibromatosis.

REPORT OF CASES

Case 1: A 47-year-old man presented to the Department of Dermatology at the Hanyang University, in October 1984, with an 1-year history of large, painful protruding mass on the sacral area.

Family and past medical history were unremarkable. On physical examination was noted to have several café au lait spots and multiple brown colored, sessile nodules over his entire body. In the sacral area, a 10×10cm sized soft protruding mass was was noted(Fig. 1). The rest of the physical examination was negative.

Neurologic examination was unremarkable.
Routine laboratory studies were all within normal limits. Chest radiography and computed tomography (CT) of the brain showed no abnormal findings. Total myelogram demonstrated a T1 compression fracture.

A skin biopsy of one of the left thigh nodules was consistent with pigmented neurofibroma. The epidermis overlying the tumor was remarkable for an increase in the amount of melanin in the basal layer which corresponded to the café au lait spot. The reticular dermis and the subcutis showed disorderly pattern of tumor cells with wavy, markedly elongated nuclei was in a somewrat myxoid stroma. Melanin pigment was scattered in the cytoplasm of the tumor cells.

Under the general anesthesia, en bloc excision of the tumor of the sacral area was performed at the Department of Neurosurgery. Grossly, the tumor mass was well circumscribed and globular in shape, measuring $19 \times 10 \times 6$ cm and weighed 450 gm. The cut surface was white-tan and firm in appearance with extensive areas of necrosis and secondary hemorrhage. Microscopically, compressed yellowish-white rubbery and somewhat myxoid tissue was present at the periphery of the tumor, consistent with neurofibroma.

The tumor showed varied histology with extensive areas of necrosis. Pleomorphic areas were composed of uni- or multinucleated large tumor cells having prominent nucleoli and abundant eosinophilic cytoplasm with many atypical mitotic figures (Fig. 2). In some areas, long sweeping fascicles similar to a fibrosarcoma were present. There were also areas of schwannian differentiation with a peculiar nodular, curlicue, or whorled arrangement of spindled cells with palisading nuclei (Fig. 3). In addition, thickened, hyalinized walled gaping blood vessels, perivascular arrangement of tumor cells (Fig. 4), and islands of metaplastic cartilage were also present (Fig. 5). The immunoperoxidase staining of S-100 protein

Fig. 1. Malignant schwannoma of buttock occurring in a patient with neurofibromatosis.

Fig. 2. Microscopic findings of malignant schwannoma, composed of highly cellular, pleomorphic spindle cells with many mitotic figures. (H & E stain, ×100).

Fig. 3. Schwannian differentiation showing nuclear palisading. (H & E, ×100).
showed focal positivity but the number of immunoreactive cells was small compared with neurofibroma.

After surgical removal of tumor, the patient was lost to follow up.

Case 2: A 67-year-old woman was admitted to our Department in June 1989, complaining of a painful tumor on the posterior aspect of the left arm. She had multiple sessile and pedunculated nodules over her entire body, which repeatedly developed over 40 years (Fig. 6). A painful tumor developed on the posterior aspect of the left arm one month previously (Fig. 7). The surface of tumor showed extensive ulceration with hemorrhagic necrosis. No café-au-lait spots and axillary freckles were present. The past medical and family history was unremarkable.

Neurologic examination was unremarkable. Laboratory studies were remarkable for: leukocyte count of 13,900/µm³ with normal differential count, a hemoglobin of 9.3 g/dl and erythrocyte sedimentation rate of 60mm/hr. Chest and skull radiographs were unremarkable.

Skin biopsies were taken from one of the multiple nodules on the back and the tumor on the left arm. The former showed the characteristic findings of neurofibroma. The epidermis showed an increase in the number of melanocytes with abundant melanin pigment. Beneath the epidermis, ill defined collections of wavy, sepenrine cells with pointed ends were
seen admixed with lipocytes. The tumor from the arm showed typical histologic features of malignant schwannoma, previously described.

For the malignant schwannoma it was treated by complete excision. The surgical specimens, consisted of two masses of cauliflower-like tumor measuring $4.5 \times 3 \times 2\text{cm}$ and $9 \times 8 \times 5\text{cm}$, covered by ulcerating skin. The cut surface was yellowish white, somewhat myxoid in appearance with a rubbery to firm consistency. Just beneath the ulcerated epidermis, highly cellular sweeping fascicles of spindle cells with many mitotic figures up to 20/10 HPF were present. The nuclei of the tumor cells were twisted, buckled, and irregular in shape (Fig. 8). Bi- or multinucleated tumor cells were also present. The cytoplasm of tumor cells was moderate in amount with indistinct borders. Thick, hyalinized blood vessels characteristic of neurogenic tumors, were frequently noted. A transitional zone from neurofibroma to malignant schwannoma was also observed at the periphery. Immunohistochemical stains with many immunoreactive cells for S-100 protein were markedly positive (Fig. 9).

After surgical excision of the tumor, she remains without evidence of disease for more than one and half years.

**DISCUSSION**

Von Recklinghausen's multiple neurofibromatosis, which is inherited as an autosomal dominant trait, is a classic example of a phakomatosis. One of the cardinal features of the phakomatosis is the presence of congenital tumors which sometimes undergo malignant changes. Malignant neoplasms that complicate multiple neurofibromatosis include gliomas of the optic nerve, astrocytomas of the cerebral and cerebellar hemispheres, intramedullary gliomas of the spinal cord, and sarcomas of peripheral nerves and somatic soft tissues. Malignant peripheral nerve tumors although generally rare, are one of the more common malignant tumors associated with neurofibromatosis. Therefore neurfibromatosis can be considered as predisposing factor to the development of malignant schwannoma. Three to thirteen percent of patients with von Recklinghausen's disease will develop a malignant schwannoma: usually after a long latent period of 10 to 20 years. Development of malignant schwannoma is particularly rare in cutaneous neurofibromas, reportedly occurring in only 2 of 678 patients. In Korea, two cases were reported by Lee et al.

Most patients with malignant schwannoma present with pain, an enlarging mass, and symptoms referable to nerve deficit or a combi-
nation thereof.\textsuperscript{2} In our cases, both patients presented with pain and an enlarging mass. Our patients, aged 47 and 67 years were considerably older than the reported mean age for malignant schwannoma\textsuperscript{(28)} years in association with von Recklinghausen's disease, 39 years in the solitary type.

Because of its difficult microscopic recognition, diagnostic errors are often made. Therefore, the diagnosis of malignant schwannoma for a soft tissue spindle cell lesion should be considered only in the following circumstances: (1) when the tumor develops in a patient with von Recklinghausen's disease, or (2) when the tumor is obviously arising within the anatomic compartment of a major nerve or in continuity with an unquestionable neurofibroma.\textsuperscript{3,8,9}

As with the normal Schwann cell, the tumor cells had elongated, wavy or buckled, hyperchromatic nuclei that had a sharply out-lined, or "punched-out" appearance and sparse cytoplasm with indistinct borders.\textsuperscript{3} Additional useful features in making the diagnosis include hyaline bands and nodules, extensive perineural and intraneural spread of tumor, the arrangement of a spindled tumor cells in a whorled pattern about thin walled gaping blood vessels, perivascular cellular proliferation, and the presence of prominent myxoid stroma containing abundant hyaluronidase-sensitive glycosaminoglycan (acid mucopolysaccharides).\textsuperscript{3,4,9} Heterotopic elements seem to be more common in malignant schwannoma than other sarcomas. Mature island of cartilage and bone are the most common elements.\textsuperscript{3} In our two cases, characteristic schwannian differentiation and transitional areas from the neurofibroma were present at periphery of the tumors. In some areas, heterotopic elements such as mature islands of cartilage were also seen in the case 1.

Malignant schwannoma should be differentiated from other spindle cell sarcomas such as a leiomyosarcoma, fibrosarcoma and synovial sarcoma. Leiomyosarcoma is characterized by more blunt-ended, centrally placed nuclei and more abundant and distinct eosinophilic cytoplasm containing longitudinal myofibrils that stained well with the Masson trichrome preparation.\textsuperscript{3,9} Both the fibrosarcoma and the synovial sarcoma have more uniform fascicular patterns and lack features of neural differentiation.\textsuperscript{3} S-100 protein is present in 50% to 90% of malignant schwannomas.\textsuperscript{10-14} Typically, the staining is rather focal and the number of immunoreactive cells is small compared with neurofibroma and neurilemmoma, reflecting either a loss of differentiation or a shift from a Schwann cell (S-100 protein positive) to a perineural cell (S-100 protein negative) population.\textsuperscript{1} S-100 protein basic protein also has been identified in about one half of malignant schwannomas.\textsuperscript{14}

Malignant schwannoma occurring in patients with neurofibromatosis frequently was a poor prognosis.\textsuperscript{3,4,9,15,16} Factors which portend a poor prognosis of the tumor in von Recklinghausen's disease include\textsuperscript{1} the occurrence of the tumor central axis of the body,\textsuperscript{2} a high mitotic rate (more than 6 mitotic figures/10 HPF), and\textsuperscript{3} large size (more than 7 cm in greatest dimension).\textsuperscript{4} Therefore, our cases seem to have poor prognosis due to presence of von Recklinghausen's disease, large tumor size, and high mitotic activity although case 1 was lost to follow up and case 2 showed good result without recurrence or metastasis for more than one and half years. The 5-year survival rate of patients with malignant neural neoplasms developing in multiple neurofibromatosis ranges from 15% to 30% compared with 53% to 75%\textsuperscript{2,3,15} in the solitary form.

Metastatic disease is reported to be more common in patients with von Recklinghausen's disease than in patients with the solitary form.\textsuperscript{2} The most common sites of metastasis are lung, followed in decreasing order of frequency by soft tissue, bone, liver, intra-abdominal cavity, adrenal glands, diaphragm, mediastinum, brain, ovaries, kidney, and retroperitoneum.\textsuperscript{2,3,17}
It should be noted that even tumors initially classified as histologically low-grade often eventually cause metastasis and death. Therefore, early treatment needs to be radical tumor resection with wide margins or amputation offers the best possibility for permanent cure in patients without distant metastases. When radical tumor removal is not possible, excision combined with high-dose radiation therapy appears to be the best alternative. The role of chemotherapy has not been settled, but its utility appears to be limited to the setting of disseminated rather than localized disease.

The development of pain, sudden enlargement of a preexisting mass, and the occurrence and rapid growth of new tumors should always suggest the onset of sarcoma. Therefore, close observation is most important for early detection of malignant transformation. Prompt, radical, ablative surgery appears to be the choice of treatment by which the sarcoma may be removed.

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Malignant Schwannoma with Neurofibromatosis

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