Osteosarcoma in a Patient with Neurofibromatosis Type 1: A Case Report and Review of the Literature

Masahito Hatori, Masami Hosaka, Mika Watanabe, 1 Takuya Moriya, 1 Hironobu Sasano 1 and Shoichi Kokubun

Department of Orthopaedic Surgery, and ¹Department of Pathology, Tohoku University School of Medicine, Sendai, Japan

HATORI, M., HOSAKA, M., WATANABE, M., MORIYA, T., SASANO, H. and KOKUBUN, S. Osteosarcoma in a Patient with Neurofibromatosis Type 1: A Case Report and Review of the Literature. Tohoku J. Exp. Med., 2006, 208 (4), 343-348 — Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is a genetic disease generally characterized by café-au-lait spots and neurofibromas. Malignant tumors of the nervous system, such as malignant schwannomas, gliomas, or astrocytomas, have been well known to coexist with neurofibromatosis. However, occurrence of malignant tumors unrelated to the nervous system is rare. We report an unusual case of a 29-year-old NF1 female suffering from malignant peripheral nerve sheath tumor (MPNST) that eventually developed osteosarcoma in the proximal femur. Osteosarcoma is the most common high-grade malignant bone tumor in which the neoplastic cells produce osteoid. At 23 and 24 years old, she underwent excision of MPNST in the left posterior thigh. No osteosarcomatous portion was identified in these specimens. The patient underwent postoperative chemotherapy. At 29, left proximal thigh pain and swelling appeared. Computed tomography demonstrated cortical bone destruction in the left proximal femur where MPNST occurred. Magnetic resonance imaging revealed extraskeletal growth of the tumor. Bone scintigraphy demonstrated increased uptake in the left proximal femur. Hip disarticulation was performed. The removed tumor was composed of highly anaplastic cells. Lace-like irregular osteoid formation was observed among the tumor cells. MPNST component was totally absent. The tumor was diagnosed as osteoblastic type osteosarcoma. Two months after disarticulation the patient died of bilateral pulmonary metastasis. The correlation between the histogenesis of osteosarcoma and the genetic abnormality in NF1 patients has not been elucidated, but the finding of osteosarcomatous transformation in this case suggests the divergent cellular differentiation to mesenchymal malignant tumors of neuroectodermal tissue in NF1 - osteosarcoma; NF1; neurofibromatosis; malignant peripheral nerve patients. sheath tumor; femur

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Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is a genetic disease that affects approximately one in every 2,500 to 3,000 live births (Lowman and LiVolsi 1980). NF1 is an autosomal dominant inherited disorder with a high rate of penetrance. Café-au-lait spots and

Correspondence: Masahito Hatori, M.D., Department of Orthopaedic Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

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e-mail: mhato@mail.tains.tohoku.ac.jp

neurofibromas are the main symptoms (Enzinger and Weiss 1995). Patients with NF1 develop multiple neurofibromas that can transform into aggressive sarcomas known as malignant peripheral nerve sheath tumors (MPNSTs) (Carroll and Stonecypher 2005). It is well known that malignant tumors of the nervous system, such as malignant schwannomas, gliomas, or astrocytomas often coexist with neurofibromatosis (Mulvihill et al. 1990). However, malignant tumors unrelated to the nervous system rarely coexist with neurofibromatosis (Dohi et al. 2006). We report an unusual case of osteosarcoma, a high-grade malignant bone tumor, arising in the femur in a NF1 patient.

CASE REPORT

A 29-year-old woman had café-au-lait spots and neurofibromatosis of the skin on her whole body, with von Recklinghausen disease (NF1) diagnosed during infancy. Her familial history was unremarkable. At the age of 23 she underwent marginal excision of a 4×4 cm soft tissue mass in the left posterior thigh. Histological findings of the resected specimen were consistent with MPNST in which the spindle cells formed into tightly packed fascicles or nests and mitoses were detected (Figs. 1A and 1B). The cytoplasm was indistinct and eosinophilic. Multiple sarcomatous tissue types, especially osteosarcoma, chondrosarcoma and angiosarcoma were not detected at all in the specimen. At the age of 24, the tumor recurred and she underwent wide excision of the tumor attached to the femoral cortex followed by vascular reconstruction. The histological features of the removed tumor were similar to those of the primary surgery. Postoperative chemotherapy with "CYVADIC" (Cyclophosphamide, Vincristine, Doxorubicin, and Dacarbazine) followed by CYVADACT" (Cyclophosphamide, Vincristine, Adriamycin, dactinomycin) was performed. Radiation therapy was not done. At the age of 29, left proximal thigh pain and swelling appeared. Computed tomography (CT) demonstrated cortical bone destruction at the MPNST-attached site of the left proximal femur (Fig. 2). Magnetic resonance im-



Fig. 1. A: Microphotographs of malignant peripheral nerve sheath tumor in the left proximal thigh showing fascicular proliferation ([]) and mitosis (black arrow). B: Nuclear pleomorphism and hyperchromatism were prominent (white arrow). No osteosarcomatous portion was observed (Scale 100 μ). (A: × 20, B: × 40)

aging (MRI) revealed extraskeletal growth of the tumor (Fig. 3). Bone scintigraphy demonstrated increased uptake of the left proximal femur. Hip disarticulation was subsequently performed under the clinical diagnosis of recurrence of MPNST and the necessity of curability. Postoperative histological analysis showed that the removed tumor was composed of highly anaplastic osteoblastic cells. Mitoses were conspicuous. Lace-like irregular osteoid formation was detected among the bizarre looking tumor cells. The tumor of the proximal femur was subsequently diagnosed as osteoblastic type osteosarcoma (Fig. 4).



Fig. 2. Computed tomogram demonstrating bone destruction (arrow) of the left proximal femur.



Fig. 3. Magnetic resonance imaging demonstrating a tumor in the left proximal femur with extraskeletal growth (arrow). (T1 weighted image, gadolinium enhancement)

Immunohistochemical study was performed to characterize the primary MPNST at the age of 23 and the tumor removed at the age of 29. Immunohistochemically, the tumor cells expressed vimentin (× 500, DAKO, Carpinteria, CA, USA), S-100 (× 10, BioGenex Laboratories,



Fig. 4. Microphotographs of a tumor in the left proximal femur showing osteoblastic osteosarcoma; there were extensive proliferation of spindle-shaped or ovoid atypical cells with lace-like osteoid formation (\bigstar). Mitoses were present (arrow) (Scale 100 μ).



Fig. 5. Immunohistochemical examination of the primary tumor at the age of 23. The parts of tumor cells (\updownarrow) expressed S-100. The non timorous stromal cells (\bigstar) did not express S-100 (Scale 100 μ).

San Ramon, CA, USA) (Fig. 5) and neuron specific enolase (NSE: × 50, DAKO) and negative for HHF-35 (× 500, DAKO), α -smooth muscle actin (α -SMA: × 20, DAKO), desmin (× 50, Bioscience, San Jose, CA, USA), CD 34 (× 100, Nichirei, Tokyo), cytokeratin (AE1/AE3: × 300, DAKO), epithelial membrane antigen (EMA) (× 400, Novocastra Laboratories, Newcastle, UK). At the age of 29, the tumor cells were positive for HHF-35 and vimentin and negative for S100, neuron specific enolase (NSE), α -smooth muscle actin (α -SMA), desmin, CD34, AE1/AE3, and EMA. Two months after the disarticulation the patient died of bilateral pulmonary metastasis.

DISCUSSION

Neurofibromatosis and malignant peripheral nerve sheath tumor

NF1 is a syndrome with a predisposition for benign and malignant tumor development (Cinamon et al. 2002). It is known that patients with von Recklinghausen neurofibromatosis have an increased incidence of mesenchymal tumors and malignant neoplasms (Miyoshi et al. 1996; Dohi et al. 2006). Sorensen et al. (1986) reported 57 malignant tumors in 212 patients with NF. The subjects with NF1 have a 10% lifetime risk of developing a MPNST. MPNSTs are uncommon sarcomas of Schwann cell or fibroblastic derivation and often metastatic and are a frequent cause of death among people with NF1. Clinical evidence suggests that most MPNSTs in people with NF1 develop from preexisting plexiform neurofibromas (Tucker et al. 2005). MPNSTs are highly aggressive in NF1. Pain and enlarging mass were the first and predominant signs (Leroy et al. 2001). Investigations and deep biopsy of painful and enlarging nodular or plexiform neurofibromas should be considered in patients with NF 1 (Leroy et al. 2001).

Malignant mesenchymal tumors associated with malignant peripheral nerve sheath tumor

MPNST occasionally show histological evidence of focal divergent differentiation to rhabdomyosarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, epithelial elements, or a combination thereof (Ducatman and Scheithauer 1984). Rhabdomyoblastic differentiation of MPNST is termed "Triton tumor" (Woodruff et al. 1973). Hartley et al. (1988) reviewed 157 children with soft tissue sarcoma for reference to diagnostic features of NF and identified four children as having NF. All of them had rhabdomyosarcomas of

the bladder or prostate. Of the malignant neoplasms associated with NF, osteogenic sarcomas are rare (Cinamon et al. 2002). Sakaguchi et al. (1996) reported a 48-year-old man with NF1 presented with composite tumors consisting of pheochromocytoma and MPNST. The MPNST component showed a varied histological appearance, including hyalinized bands with polygonal cells, a cartilaginous and myxoid stroma, a hemangiopericytomatous architecture, and a fibrosarcomatous structure, which suggested the presence of osteosarcoma, chondrosarcoma, angiosarcoma, and fibrosarcoma, respectively. Miyoshi et al. (1996) reported a rare case of primary jejunal malignant mixed tumor arising in a 49-year-old Japanese male with NF1. The resected tumor was composed of adenocarcinoma admixed with various sarcomatous components, including rhabdomyosarcoma, osteosarcoma, and other sarcomas. Immunohistochemical analysis also supported this diagnosis. It is noteworthy that a report of NF1 showing malignant transformation into a single sarcoma is unusual. Extensive literature survey reveals only one case of osteosarcoma of a long bone in association with NF1 (Ferreira et al. 1994). The present case had MPNST arising from NF1 that was removed at the age of 23. Six years later osteosarcoma arose in the proximal femur at the MPNST occurrence site. By judging from the CT and MRI findings, it is most likely that osteosarcoma arose from the remaining MPNST cells in the medullary portion of the femur and extended extraskeletally. Composite type of MPNST was ruled out because of absence of any other sarcomatous character such as rhabdomyosarcoma, osteosarcoma, and chondrosarcoma by histological examination including immunohistochemical study.

Osteosarcoma and its etiology

Conventional osteosarcoma is the most common high-grade malignant bone tumor in which the neoplastic cells produce osteoid; estimated incidence of 4-5 per million population. It is largely disease of the young (Raymond et al. 2002). Rarely osteosarcoma begins in soft tissue (Oonuma et al. 2001). A number of variants of osteosarcoma exist, including conventional types and telangiectatic (Matsuno et al. 1976), multifocal (Hatori et al. 2001), parosteal (Wold et al. 1984), and periosteal types (Unni et al. 1976). Although the prognosis and quality of life of patients with osteosarcoma were improved significantly during the past decades, the pathogenesis and etiology of this disease remain obscure (Fuchs and Pritchard 2002). Marked dissimilarities in the epidemiology of osteosarcoma, Ewing's sarcoma and rhabdomyosarcoma indicate differences in their origins (Miller 1981). Ewing's sarcoma does not aggregate in families and is not part of any known syndrome. No environmental causes have been identified. The exact cause of osteosarcoma is unknown. However, a number of risk factors are apparent, as follows: exposure to radiation is known to an environmental risk factor. Radiation-induced osteosarcoma is a form of secondary osteosarcoma (Okada et al. 2004). Genetic predisposition is another risk factor. Osteosarcoma aggregated in families with the same tumor or with dissimilar tumors and in certain genetic disorders of bone (Miller 1981). In the present case, radiation induced osteosarcoma (Maghami et al. 2005) was ruled out because of the absence of irradiation treatment history. There have been some reports of osteosarcoma arising in the patients with NF1 with a parathyroid adenoma and hyperparathyroidism. There are studies that imply that the parathyroid hormone plays a role in the regulation and modulation of osteogenic sarcomas in vitro (Cinamon et al. 2002). Cinamon et al. (2002) reported a 50-year-old female suffering from NF1, with a 3-year documented history of untreated hyperparathyroidism and a parathyroid adenoma. The patient developed a mandibular osteogenic sarcoma. This is the first reported case of osteogenic sarcoma occurring in the mandible. The unusual tumor site for a patient with NF1, the conjugation with hyperparathyroidism and the rapid growth of an osteogenic sarcoma are intriguing. However the present patient did not have a parathyroid adenoma or hyerparathyroidism.

Genetic predisposition of malignant transformation

The composite character of MPNST suggests the divergent cellular differentiation of neural crest-derived cells to mesenchymal elements as well as neuroectodermal neoplasms (Miyoshi et al. 1996). The finding of these heterotopic elements in nerve sheath sarcomas is postulated to illustrate the differentiating capacity of neuroectodermal tissue (Ducatman and Scheithauer 1984). A number of genetic disorders are linked with excessive risk for developing these cancers, including neurofibromatosis (Hope and Mulvihill 1981). There appears to be a possible relationship between the histogenesis of MPNST and the genetic abnormality in NF patient (Miyoshi et al. 1996). The association of nervous system neoplasms and tumors of other sites may occur in patients with phacomatoses or particular genetic syndromes. In addition, certain nervous system neoplasms may be multicentric in origin. Retinoblastoma and osteosarcoma occur together in the same patient more often than expected by chance. These relationships are important in that they serve to identify the high risk patient, may provide etiologic clues, may point to the presence of genetic syndromes, and may highlight sites in which subsequent tumors are most likely to develop (Schoenberg 1977). NF1 is genetically related to an alteration of chromosome 17 (Barker et al. 1987). NF1 gene is thought to be a kind of tumor suppressor gene. Neurofibromin, a product of NF1 gene, has an important role in the activation of ras protein and in controlling the proliferation and differentiation of cells. The undetectable or reduced level of neurofibromin in the tumors obtained from NF1 patients suggests that this deficiency is closely related to their tumorigenesis (Takahashi et al. 1995; Izawa et al. 1996). Loss of expression of neurofibromin results in elevated levels of Ras-guanosine triphosphate. Subsequent molecular events result in sarcomatous transformation (Feldkamp et al. 1996). Further investigations are required for clarification.

In conclusion, occurrence of malignant tumors unrelated to the nervous system in NF1 is rare. An unusual case of osteosarcoma arising at the previously excised MPNST site is described. Osteosarcomatous transformation in this case suggests the divergent cellular differentiation of neuroectodermal tissue to mesenchymal malignant tumors. A high degree of suspicion is necessary with aggravation of pain and drastic radiological changes of NF1 patients.

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