CASE REPORT

Early-stage malignant peripheral nerve sheath tumour arising from a solitary neurofibroma

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ABSTRACT. We report a case of early-stage malignant peripheral nerve sheath tumour (MPNST) found in a solitary neurofibroma, and its CT and MRI findings. A 19-year-old male with no known history of a neurofibromatosis presented with a painless swelling in the left forearm. CT and MRI scans showed a well-circumscribed, intermuscular mass, which was 6.0 cm in diameter and contained a strongly enhanced 1.0 cm nodular structure with surrounding oedema. Peripheral nerve continuity with the mass was not seen. Histological evaluation proved the nodular structure was an MPNST component completely surrounded by neurofibroma. Following an excisional biopsy with wide margins, the patient was followed up for a year without treatment and no recurrence was observed.

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Malignant peripheral nerve sheath tumour (MPNST) is a rare soft tissue sarcoma [1], and the vast majority develop from pre-existing neurofibromas [2]. Half of MPNST cases occur in individuals with a history of von Recklinghausen's disease (neurofibromatosis 1[NF1]) [3, 4]. By contrast, 60–90% of neurofibromas are not associated with NF1 and sporadic neurofibroma occurs most commonly in the extremities [5].

It is difficult to predict whether a peripheral nerve sheath tumour will be benign or malignant and the slow growth of this tumour frequently results in a delayed diagnosis of MPNST [6, 7].

We describe the clinical, radiological and pathological findings in a patient with no known history of NF1, who was diagnosed with an early-stage MPNST arising from a solitary neurofibroma of the forearm.

Case report

A 19-year-old, right-hand dominant male presented with painless swelling in the left forearm, which the patient had noticed 4 months earlier. There was no familial history or constitutional symptoms. A physical examination revealed an elastic hard immobile mass in the flexor aspect of the left forearm, which was negative for Tinel's sign. There was no neurological deficit, paraesthesia or pain on palpation of the lesion. The patient had full flexion of the elbow and wrist. A radiograph showed a soft tissue

mass in the middle part of the left forearm. There was no definite bony lesion.

A CT scan revealed a fusiform-shaped homogeneous soft tissue mass measuring 5.5 × 6.0 × 2.5 cm (transverse, proximal distal and anteroposterior, respectively) in the flexor aspect of the left radius without cortical bone disruption (Figure 1). Biphasic contrast-enhanced CT revealed a 1-cm nodular, early enhancing lesion in the peripheral portion of the mass. Other parts of the mass showed a slight, gradual enhancement during the dynamic study.

MRI showed the lesion to be a well-circumscribed, intermuscular mass extending between the flexor carpi radialis muscle and the palmaris longus muscle without the peripheral nerve continuity (Figure 2). *T*₁ weighted MRI showed a hypo-intense mass without the adjacent bone change. *T*₂ weighted images showed an inhomogeneous hyperintense mass containing an iso-intense nodule with surrounding oedema. The contrast-enhanced *T*₁ weighted image using gadolinium chelate revealed two components: inhomogeneous enhancement of almost the entire mass and nodular enhancement corresponding to the enhanced CT image. Thallium-201 chloride (²⁰¹TlCl) scintigraphy showed no abnormal accumulation in the left forearm (not shown).

An excisional biopsy was performed under general anaesthesia 3 weeks after the patient first presented to our hospital. During surgery, the tumour was identified as an intermuscular mass between the flexor carpi radialis muscle and the palmaris longus muscle. The tumour surface was smooth and yellowish-white in colour with a slight haemorrhage. The peripheral nerves were not found to be in continuity with the tumour.

Histologically, most of the tumour was made up of spindle cells aligned in a loose collagenous matrix, which

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Figure 1. Transverse CT images on the same plane for the mass of the left forearm. (a) Plain CT image showing a well-circumscribed, homogeneous low-attenuating mass (arrows). The attenuation value of the nodular lesion was 33 HU. (b) Early phase of contrast-enhanced CT image revealing an enhancing nodule (arrowhead) in the peripheral portion of the mass. The attenuation value of the nodular lesion was 57 HU. (c) Delayed phase of contrast-enhanced CT image showing prolonged enhancement of the nodular lesion. The surrounding part of the nodule (asterisk) demonstrates slight enhancement. The attenuation value of the nodular lesion was 69 HU.

is consistent with neurofibroma (Figure 3). The tumour contained a nodular, well-circumscribed lesion measuring 7 mm that was enclosed in the mass. The nodular lesion showed definite cell crowding and general nuclear enlargement with a high mitotic index (5/10 high-power field [HPF]). Furthermore, the MIB-1 immunoreactivity had a significantly higher proliferative activity (the MIB-1 index; 8.9%) than the surrounding neurofibroma (<1%), which suggested a malignant potential. Immunohistochemical stain for S-100 showed scattered positive tumour cells in the neurofibroma component, which excluded the possibility of schwannoma or myxoma. There was no immunoreactivity for Factor XIIIa, CD34, epithelial membrane antigen or glial fibrillary acidic protein (GFAP). As a

result of these findings the tumour was diagnosed as MPNST arising in neurofibroma.

Because the excisional biopsy was curative for the MPNST component, the patient received no additional radiotherapy or chemotherapy. There was no nerve dysfunction after surgery and no signs of recurrence or metastasis during a year of clinical and MRI follow ups.

Discussion

MPNSTs are sarcomas arising either *de novo* or in transition from pre-existing neurofibroma [1–3, 7, 8]. The lifetime risk for the development of MPNST is very low

Figure 2. Sagittal MRI of the left forearm. (a) T_1 weighted image (610/10; 90° flip angle) showing a fusiform-shaped, low-signal-intensity mass (white asterisk). (b) T_2 weighted image (repetition time msec/echo time msec, 3500/95) showing an inhomogeneous hyperintense intermuscular mass containing an isointense nodule with surrounding oedema (arrowhead). (c) Post-contrast-enhanced sagittal T_1 weighted image with fat suppression (spectral presaturation with inversion recovery) (468/10; 90° flip angle) showing two components, with inhomogeneous enhancement of almost all of the mass (black asterisk) and nodular enhancement in the peripheral portion of the mass (arrowhead).

Figure 3. Microscopic findings (haematoxylin-eosin stain). (a) Low magnification aspect of the boundary of MPNST nodule (lower) and surrounding neurofibroma (upper) (x40). (b) Neurofibroma component consists of cells with bland and spindle-shaped curved nuclei in a background of stromal mucin and collagen (x100). 5-100 positive schwann cells are interspersed (inset). (c) The majority of MPNST are composed of spindle cells with nuclear enlargement and pleomorphism. MPNST nodule shows increased cellularity and mitosis. Three mitotic figures are seen (arrows) (x200). (d) Immunostaining for MIB-1 shows a significant proliferative activity in the MPNST lesion (x200). In contrast, MIB-1 was almost absent in the neurofibroma lesion (data not shown).

in cases without NF1 [3]. The peak incidence of MPNSTs is in the seventh decade of life in the general population and in the third or fourth decade in people with NF1 [3, 9].

Meanwhile, neurofibromas frequently affect patients aged 20–30 years [5]. MPNSTs are significantly more likely to be located on the limbs compared with benign nerve sheath tumours [3].

Histologically, the apparent transition of neurofibroma to MPNST suggests malignant transformation of the underlying neurofibroma [3]. Most MPNSTs (61%) have a coexisting neurofibromatous component, especially in patients with NF1 [3]. Previous reports have not sufficiently shown the proportion of the MPNST and the coexisting histological components (*e.g.* neurofibroma) in a single tumour. To the best of our knowledge, there is no published literature demonstrating MRI of malignant transformation of neurofibroma at such an early stage.

Distinguishing MPNST from neurofibroma often presents a diagnostic challenge to radiologists. Haemorrhagic

or necrotic heterogeneous enhancement on CT or MRI may suggest a malignancy, although these can also be seen in benign peripheral nerve sheath tumours [7]. Wasa *et al* [9] recently described the four significant features of MRI that are considered to be suggestive of MPNST: an increase in the largest dimension of the mass; the presence of peripheral enhanced pattern; the presence of perilesional oedema-like zone; and the presence of intratumoural cystic lesions. However, the previous investigations have mainly involved large MPNSTs (*e.g.* range of 6.5–9.9 cm) [9–11]. These features would not have been applicable to the present case because the MPNST component was too small relative to surrounding neurofibroma.

A differential diagnosis of the lesion in the present case could be myxoma, which is also hyperintense on T_2 weighted images with a gradual increase in enhancement and occasionally occurs in an intermuscular location (9%) [12]. The relatively decreased signal

intensity on the T_2 weighted image suggested a nerve sheath tumour rather than myxoma.

^{201}Tl scintigraphy has been reported to be sensitive in the detection of soft tissue sarcomas [13, 14]. However, this tumour was not seen on this imaging technique. The reason is indeterminate: it might be owing to the intrinsic limitation of planar ^{201}Tl to the low-grade malignancy of the tumour or to the small size of the malignant component. Recent articles have suggested the potential contribution of 18-fluorodeoxyglucose positron emission tomography to distinguish MPNST from neurofibroma, even within a single tumour [15, 16].

Thus, the radiological findings of the lesion suggested a benign tumour as a whole, except for the eccentrically located inner nodule with strong contrast enhancement on MRI. The tumour was resected because the distinct nodular enhancement suggested it was malignant, which was later confirmed with histological analysis.

The pre-operative diagnosis of neurogenic tumour was not obvious—the patient had negative Tinel's sign and no peripheral nerve continuity was seen on MRI. Also, there was no surgical or pathological confirmation of coexistence with a nerve obtained. The histological features of the tumour corresponded to a neurogenic tumour, so the tumour was considered to arise from an unidentifiable small nerve [17]. The fact that the excisional biopsy did not induce any neurological deficit might support this assumption [18].

The histological differential diagnosis of the 7 mm nodular component in the tumour was MPNST *vs* cellular schwannoma-like nodule in neurofibroma. Schwannoma-like nodules almost always demonstrate strong and uniform immunohistochemical reactivity for the S-100 protein. In the present case, immunohistochemistry revealed that the S-100 positive cells were scattered only in the neurofibroma component and not in the well-demarcated cellular nodule. This is consistent with the S-100 marker being absent in 10–50% of cases with MPNST owing to dedifferentiation [3, 7]. The high mitotic rate and MIB-1 labelling index (approximately 9%) convinced us that the hypercellular nodule should be diagnosed as MPNST. The apparent transition of neurofibroma to MPNST suggested malignant transformation of underlying neurofibroma [3]. An absence of necrosis may be attributed to its relatively small size.

Adverse prognostic factors of MPNST include larger tumours (>5 cm)—although more than 80% of MPNSTs are larger than 5 cm at diagnosis [2]—a history of NF1, non-extremity sites, a history of prior irradiation, a positive surgical margin, high-grade histology and an advanced stage of the disease [3, 10]. Besides genetic factors, one reason for the poor prognosis of patients with NF1 is thought to be delayed diagnosis: the tumours associated with neurofibromatosis are almost always benign and slow growing, which might impede the detection of malignant neoplasms [8]. Our patient is considered to have a favourable prognosis: the main reason is the small size of the MPNST completely surrounded by benign neurofibroma. The sporadic occurrence, the noticeable location of the tumour and the large size of the whole mass presented an opportunity for the early detection and subsequent radical removal of the MPNST inside the neurofibroma.

The current treatment for MPNST is complete surgical excision because it has the highest local recurrence rate

of any sarcoma [19]. Adjuvant radiotherapy has a role in treating MPNSTs larger than 5 cm, high-grade lesions and incompletely excised tumours [7, 20]. Our patient did not undergo radiotherapy because the surgical margin was considered sufficient, the MPNST was low grade and it was completely surrounded by neurofibroma. Local recurrence can occur several years after surgery [3]; therefore, further follow up is needed.

Conclusion

We report a surgically treated case of MPNST in which MRI visualised the early stage of malignant transformation of a pre-existing sporadic neurofibroma.

References

1. Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. *Am J Med Genet* 1999;89:23–30.
2. Hruban RH, Shiu MH, Senie RT, Woodruff JM. Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases. *Cancer* 1990;66:1253–65.
3. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer* 1986;57:2006–21.
4. Okada K, Hasegawa T, Tajino T, Hotta T, Yanagisawa M, Osanai T, et al. Clinical relevance of pathological grades of malignant peripheral nerve sheath tumor: a multi-institution TMTS study of 56 cases in Northern Japan. *Ann Surg Oncol* 2007;14:597–604.
5. Pilavaki M, Chourmouzi D, Kiziridou A, Skordalaki A, Zarampoukas T, Drevelengas A. Imaging of peripheral nerve sheath tumors with pathologic correlation: pictorial review. *Eur J Radiol* 2004;52:229–39.
6. Furniss D, Swan MC, Morritt DG, Lim J, Khanna T, Way BL, et al. A 10-year review of benign and malignant peripheral nerve sheath tumors in a single center: clinical and radiographic features can help to differentiate benign from malignant lesions. *Plast Reconstr Surg* 2008;121:529–33.
7. Gupta G, Maniker A. Malignant peripheral nerve sheath tumors. *Neurosurg Focus* 2007;22:E12.
8. Tucker T, Wolkenstein P, Revuz J, Zeller J, Friedman JM. Association between benign and malignant peripheral nerve sheath tumors in NF1. *Neurology* 2005;65:205–11.
9. Wasa J, Nishida Y, Tsukushi S, Shido Y, Sugiura H, Nakashima H, et al. MRI features in the differentiation of malignant peripheral nerve sheath tumors and neurofibromas. *AJR Am J Roentgenol* 2010;194:1568–74.
10. Wong WW, Hirose T, Scheithauer BW, Schild SE, Gunderson LL. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. *Int J Radiat Oncol Biol Phys* 1998;42:351–60.
11. Hirose T, Scheithauer BW, Sano T. Perineurial malignant peripheral nerve sheath tumor (MPNST): a clinicopathologic, immunohistochemical, and ultrastructural study of seven cases. *Am J Surg Pathol* 1998;22:1368–78.
12. Murphey MD, McRae GA, Fanburg-Smith JC, Temple HT, Levine AM, Aboulafia AJ. Imaging of soft-tissue myxoma with emphasis on CT and MR and comparison of radiologic and pathologic findings. *Radiology* 2002;225:215–24.
13. Sugawara Y, Kikuchi T, Kajihara M, Semba T, Ochi T, Fujii T, et al. Thallium-201 scintigraphy in bone and soft-tissue tumors: a comparison of dynamic, early and delayed scans. *Ann Nucl Med* 2005;19:461–8.
14. Terui S, Terauchi T, Abe H, Fukuma H, Beppu Y, Chuman K, et al. On clinical usefulness of Tl-201 scintigraphy for the

- management of malignant soft tissue tumors. *Ann Nucl Med* 1994;8:55–64.
15. Benz MR, Czernin J, Dry SM, Tap WD, Allen-Auerbach MS, Elashoff D, et al. Quantitative F18-fluorodeoxyglucose positron emission tomography accurately characterizes peripheral nerve sheath tumors as malignant or benign. *Cancer* 2010;116:451–8.
 16. Ferner RE, Lucas JD, O'Doherty MJ, Hughes RA, Smith MA, Cronin BF, et al. Evaluation of (18)fluorodeoxyglucose positron emission tomography ((18)FDG PET) in the detection of malignant peripheral nerve sheath tumours arising from within plexiform neurofibromas in neurofibromatosis 1. *J Neurol Neurosurg Psychiatry* 2000;68:353–7.
 17. Kehoe NJ, Reid RP, Semple JC. Solitary benign peripheral-nerve tumours. Review of 32 years' experience. *J Bone Joint Surg Br* 1995;77:497–500.
 18. Ogose A, Hotta T, Morita T, Yamamura S, Hosaka N, Kobayashi H, et al. Tumors of peripheral nerves: correlation of symptoms, clinical signs, imaging features, and histologic diagnosis. *Skeletal Radiol* 1999;28:183–8.
 19. Wanebo JE, Malik JM, VandenBerg SR, Wanebo HJ, Driesen N, Persing JA. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. *Cancer* 1993;71:1247–53.
 20. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. *Cancer Res* 2002;62:1573–7.