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Case Report

Malignant Peripheral Nerve Sheath Tumor of the Neck: Transformation From a Recurrent Neurofibroma in a Patient Without Neurofibromatosis

Han-Ju Chen[1], Huan-Sen Chen[1], Yen-Liang Chang[1,2], Yi-Yiing Wu[3]*

[1]*Department of Otolaryngology–Head and Neck Surgery, Cathay General Hospital, Taipei, Taiwan*
[2]*College of Medicine, Fu Jen Catholic University, Taipei, Taiwan*
[3]*Department of Pathology, Cathay General Hospital, Taipei, Taiwan*

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Abstract

Malignant peripheral nerve sheath tumor (MPNST) is a rare tumor that is one of the most aggressive malignant lesions in the head and neck area. The majority of MPNSTs arise *de novo* or from malignant transformation of pre-existing neurofibromas, particularly in individuals with neurofibromatosis type 1 (NF1). However, solitary neurofibromas without an association with NF1 seldom recur after excision and rarely develop malignant changes. We present a 70-year-old man with a recurrent neurofibroma of the right side of the neck which transformed to low-grade MPNST after multiple excisions. The patient had no cutaneous features or family history consistent with NF1. Progression from a recurrent sporadic neurofibroma to malignancy is an extremely rare event and we found only two case reports in the literature. Any recurrent mass at the site of an excised neurofibroma or a rapidly enlarging, painful swelling of antecedent lesions should prompt consideration of MPNST. (*Tzu Chi Med J* 2010;22(4):195–199)

*Corresponding author. Department of Otolaryngology–Head and Neck Surgery, Cathay General Hospital, 280, Section 4, Jen-Ai Road, Taipei, Taiwan.
E-mail address: ylchang@cgh.org.tw

1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon and highly aggressive soft tissue sarcomas with high rates of local recurrence and distant metastasis. MPNSTs can arise *de novo* as isolated malignancies, whereas approximately half of these tumors develop through malignant transformation of pre-existing neurofibromas in patients with neurofibromatosis type 1 (NF1), also known as von Recklinghausen's neurofibromatosis (1). Solitary neurofibromas without an association with NF1 have a low recurrence rate after excision and very rarely become malignant (2). Our patient had multiple recurrences of a neck mass which was treated with surgical excision. The pathologic diagnosis in each recurrence was neurofibroma, but malignant transformation to MPNST was noted in the last pathological exam. The clinical presentation of malignant alteration in a recurrent neurofibroma without association with NF1 is extremely rare. We found only two similar case reports in the English literature (Table 1) (3,4).

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Table 1 — Literature review of MPNSTs arising from recurrent sporadic neurofibromas

Reference	Age (yr)/ sex	Histology of neurofibroma (type)	Re-excision of neurofibroma (times)	Time to malignant transformation (yr)	Presentation of MPNST	Immunohistochemistry	Treatment	Survival* (mo)	Recurrence* (mo)
Molenaar et al (3)	67/F	Diffuse	2	5	Right foot: 9×18 cm	S-100: positive	Limb amputation	48	N
Cheng et al (4)	52/F	Not stated	7	5	Right orbit	S-100, Ki 67: positive	Resection, radiotherapy	60	N
Present case	70/M	Diffuse	4	12	Right neck: 5.5×5 cm	S-100: positive	Resection, radiotherapy	20	18

*At the time of publication.

2. Case report

A 70-year-old man was admitted to our department with a 1-month history of a progressively enlarging, painful swelling on the upper right side of his neck. In 1995, he had undergone surgical resection of a neurofibroma in the right cervical region. The tumor recurred at the previous operation site. Consequently, four more neck surgeries were done over the next 9 years. All pathologic diagnoses were diffuse neurofibroma (Fig. 1). When the patient presented to our department, a recurrent, solid, and ill-defined mass tightly encased by skin was palpated on examination. Computed tomography disclosed a 5.5×5×2 cm soft tissue mass posterior to the sternomastoid muscle (Fig. 2).

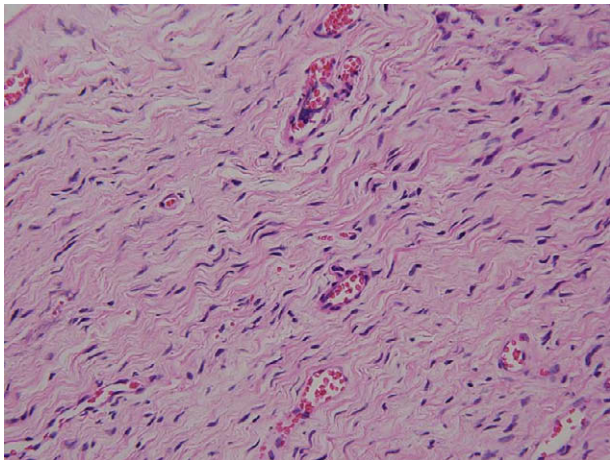

Fig. 1 — The tumor is composed of proliferated slender spindle cells with wavy nuclei, growing in fascicles in a fibrotic stroma. Low cellularity and only mild nuclear atypia are noted.

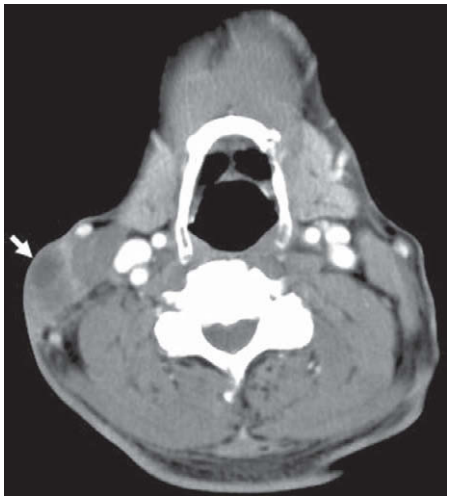

Fig. 2 — Axial computed tomography of the head and neck shows an inhomogeneous mass (arrow) with ill-defined margins involving the right upper cervical area.

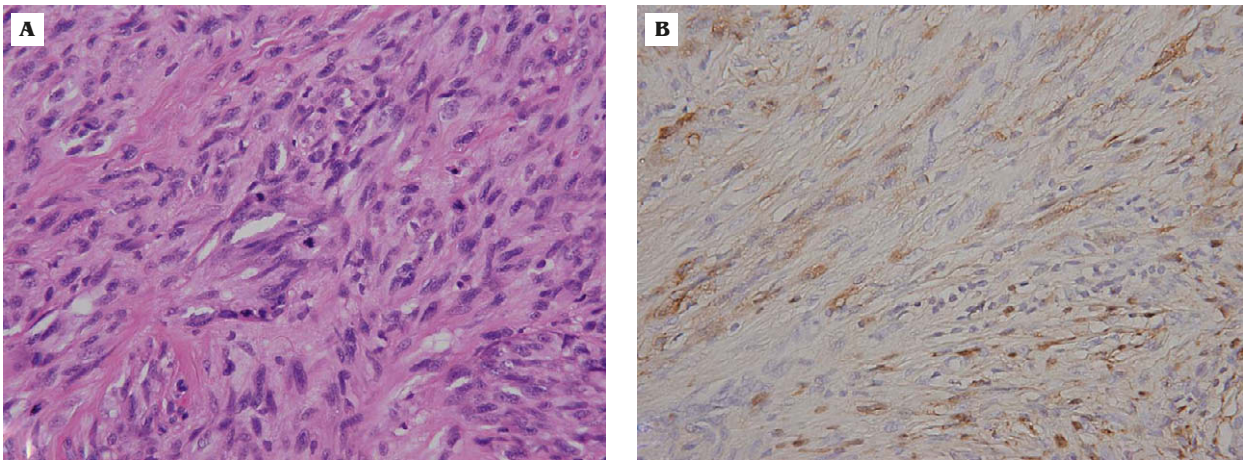

Fig. 3 — (A) Area of spindle cells with increased cellularity, moderate to marked cellular pleomorphism, common mitotic activity, and hyperchromatic nuclei. (B) Focal S-100 immunoreactivity in the MPNST.

The tumor was completely excised and microscopic examination revealed a low-grade MPNST arising within a neurofibroma, with areas of the lesion showing the typical features of a neurofibroma but also focal areas of increased cellularity with moderately to markedly pleomorphic cells, common mitotic activity and atypical mitotic figures. Immunohistochemically, the tumor cells were positive for S-100 protein (polyclonal rabbit; Dako Denmark A/S, Glostrup, Denmark) (Fig. 3), but negative for cytokeratin (AE1/AE3; Leica Biosystems, Newcastle Upon Tyne, UK), desmin (monoclonal mouse, D33; Dako Denmark A/S), epithelial membrane antigen (monoclonal mouse, E29; Dako Denmark A/S), smooth muscle actin (monoclonal mouse, 1A4; BioGenex Laboratories Inc., San Ramon, CA, USA), and CD34 (QBEnd/10; Leica Biosystems). The patient had no history of radiotherapy of the head and neck region or physical features of NF.

Postoperatively, the patient received 7020 cGy of adjuvant radiotherapy. Eighteen months following diagnosis and surgery, the patient began to complain of submental swelling and progressive right-sided facial palsy. Magnetic resonance imaging demonstrated extensive tumor progression with invasion of the submental, right parotid and carotid space (Fig. 4). The patient underwent a right selective neck dissection with in continuity total parotidectomy, and histological examination confirmed the recurrence. The patient was lost to follow-up 2 months after the operation.

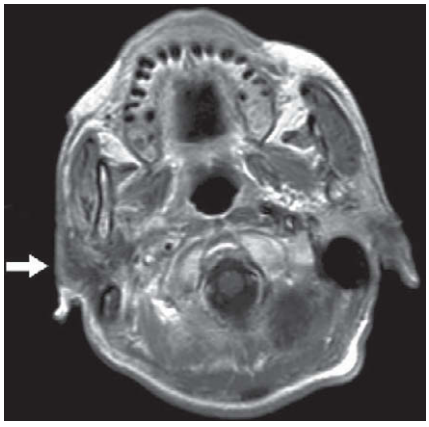

Fig. 4 — Axial magnetic resonance imaging shows infiltrative lesions (arrow) involving the right parotid and carotid spaces.

3. Discussion

MPNSTs have been reported to originate throughout the body, but the lower extremities and trunk are the most frequently involved areas. Although approximately 25% of all neurofibromas are found in the head and neck region, fewer than 10% of MPNSTs affect this anatomic area. In this region, the neck is most frequently (40–60%) involved [2,5].

MPNSTs have a variety of origins. A majority (25–50%) originate in patients with NF1, presumably from an antecedent neurofibroma. The remaining cases are tumors arising *de novo* or within neurofibromas in patients without the stigmata of NF1 [6]. It is estimated that 8–13% of NF1-associated neurofibromas eventually become malignant, usually after a latency of 10–20 years. Irradiation and long-standing plexiform types have been recognized as risk factors [7,8]. Pain, a change in texture, increase in size and neurological deficits should increase suspicion of malignancy [9]. However, the majority of neurofibromas in the head and neck region appear as isolated lesions without association with NF1. The clinical behavior of isolated neurofibromas is characterized by a benign course with a low frequency of recurrence after

surgical excision. Malignant change is rare and difficult to detect; hence, the incidence is unknown [2]. A search of the literature revealed two well-documented case reports [3,4] of MPNST that transformed from a recurrent solitary neurofibroma in patients without NF1; our case is the third (Table 1). Clinical and histological caution should be exercised in the presence of multiple recurrences of isolated neurofibromas which may signify malignant change.

On computed tomography and magnetic resonance imaging, a large tumor (>5 cm), heterogeneity, ill-defined margins, invasion of fat planes, and evidence of aggressiveness should raise suspicions of MPNST. However, differentiation of benign tumors from MPNSTs is often difficult with these tools [1,10].

Histologically, the distinction between neurofibromas and low-grade MPNSTs is difficult because there is a continuum between these two lesions. Generalized nuclear atypia, increased cellularity and usually low levels of mitotic activity may help to establish the diagnosis of low-grade MPNSTs arising within a neurofibroma [11]. The immunoreactivity of S-100 protein in MPNSTs tends to be focal and patchy, not strong and diffuse as seen in neurofibromas and schwannomas. These patterns of immunopositivity may be useful in distinguishing benign nerve sheath tumors from MPNSTs [12]. However, the expression of S-100 protein is reduced or absent in some low-grade MPNSTs and in more than two-thirds of high-grade MPNSTs. A recent study reported that CD10 expression helps in distinguishing solitary, localized neurofibromas from NF1 cases and from atypical, plexiform and malignant cases, but further investigation is necessary [13]. The diagnosis of MPNST requires a combination of clinical information and histomorphological features with supportive immunostains.

Curative treatment of MPNSTs is difficult. Every effort should be made to perform *en bloc* resection with tumor-free margins [14,15]. A prophylactic neck dissection is not warranted because lymphatic spread is rare. Adjuvant radiotherapy is recommended whether tumor-free margins can be obtained or not. The role of systemic chemotherapy remains controversial [1,14].

The prognosis of MPNSTs of the head and neck is relatively poorer than that of the extremities and trunk, with documented 5-year survival rates from 15% to 35% [14,15]. This difference is related mainly to a difference in local tumor control. Because of the great density of vital structures and unresectable areas in the head and neck, such as the skull base, internal carotid artery and cervical vertebrae, failure to perform adequate wide excision is common and generally associated with an unacceptably high local recurrence rate [14,16]. Even with negative surgical margins, up to 50% of MPNSTs recur locally, often on multiple occasions [15]. This marked tendency for local recurrence has been attributed to the ability of this tumor to infiltrate surrounding tissues and invade perineural areas. One year following adjuvant radiotherapy, our patient had local recurrence with extension to the carotid space that made complete resection impossible.

In conclusion, MPNSTs tend to be under-recognized and initial diagnosis is hampered by the clinical, radiological and histological similarity of MPNSTs to benign tumors. Our reported case and those in the literature show that close monitoring of patients with recurrent neurofibroma is merited as this feature may signify malignant transformation. The tendency to local recurrence contributes to the poor prognosis of the neoplasm, especially in the head and neck region. The outcome is principally a function of local control by means of surgical resection.

References

1. Grobmyer SR, Reith JD, Shahlaee A, et al. Malignant peripheral nerve sheath tumor: molecular pathogenesis and current management considerations. *J Surg Oncol* 2008;97:340–9.
2. Marocchio LS, Oliveira DT, Pereira MC, et al. Sporadic and multiple neurofibromas in the head and neck region: a retrospective study of 33 years. *Clin Oral Invest* 2007;11:165–9.
3. Molenaar WM, Dijkhuizen T, van Echten J, et al. Cytogenetic support for early malignant change in a diffuse neurofibroma not associated with neurofibromatosis. *Cancer Genet Cytogenet* 1997;97:70–2.
4. Cheng SF, Chen YI, Chang CY, et al. Malignant peripheral nerve sheath tumor of the orbit: malignant transformation from neurofibroma without neurofibromatosis. *Ophthal Plast Reconstr Surg* 2008;24:413–5.
5. Hoffmann DF, Everts EC, Smith JD, et al. Malignant nerve sheath tumors of head and neck. *Otolaryngol Head Neck Surg* 1999;99:309–19.
6. Anghileri M, Miceli R, Fiore M, et al. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution. *Cancer* 2006;107:1065–74.
7. Ducatman BS, Scheithauer BW, Piepgras DG, et al. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer* 1986;57:2006–21.
8. Sorensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. *N Engl J Med* 1986;314:1010–5.
9. Valeyrie-Allanore L, Ismaïli N, Bastuji-Garin S, et al. Symptoms associated with malignancy of peripheral nerve sheath tumours: a retrospective study of 69 patients with neurofibromatosis 1. *Br J Dermatol* 2005;153:79–82.
10. Li CS, Huang GS, Wu HD, et al. Differentiation of soft tissue benign and malignant peripheral nerve sheath tumors with magnetic resonance imaging. *Clin Imaging* 2008;32:121–7.
11. Weiss SW, Goldblum JR. *Enzinger and Weiss's Soft Tissue Tumors*, 5th edition. New York: Mosby Inc., 2008:849–52.
12. McGee RS Jr, Ward WG, Kilpatrick SE. Malignant peripheral nerve sheath tumor: a fine-needle aspiration biopsy study. *Diagn Cytopathol* 1997;17:298–305.

13. Cabibi D, Zerilli M, Caradonna G, et al. Diagnostic and prognostic value of CD10 in peripheral nerve sheath tumors. *Anticancer Res* 2009;29:3149–55.
14. Minovi A, Basten O, Hunter B, et al. Malignant peripheral nerve sheath tumors of the head and neck: management of 10 cases and literature review. *Head Neck* 2007;29: 439–45.
15. Bailet JW, Abemayor E, Andrews JC, et al. Malignant nerve sheath tumours of the head and neck: a combined experience from two university hospitals. *Laryngoscope* 1991; 101:1044–9.
16. Imamura S, Suzuki H, Koda E, et al. Malignant peripheral nerve sheath tumor of the parotid gland. *Ann Otol Rhinol Laryngol* 2003;112:637–43.