Immunoprofiles in Malignant Peripheral Nerve Sheath Tumor: Three Case Reports and Literature Review

Shih-Wen Hu,[1,2] Wei-Chen Lin,[3] Hui-Jen Tsai,[4] Song-Hsiung Chien,[5] and Kun-Bow Tsai[2,6]
Departments of [1]Pathology and [3]Medical Imaging, [4]Division of Hemato-oncology, Department of Internal Medicine, and [5]Department of Orthopaedics, Kaohsiung Medical University Chung-Ho Memorial Hospital, [2]Department of Pathology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, and [6]Department of Pathology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan.

Because there are no standardized radiologic and histologic criteria, the differential diagnosis of malignant peripheral nerve sheath tumors (MPNSTs) from other spindle cell neoplasms poses great challenges for pathologists. Because early diagnosis of MPNSTs arising from benign peripheral nerve sheath tumors (BPNSTs) means a better prognosis, many immunohistochemical and molecular studies have recently emerged. Nevertheless, no gold standard diagnostic criterion is to be found in the literature. For example, S-100 protein is widely used in the diagnosis of MPNST. Other promising ancillary markers are p53 and Ki-67; however, the staining patterns and possible mechanisms of these markers are seldom mentioned in the literature. These evoke our interest. Only six cases diagnosed as MPNST were retrieved from the archives of the Department of Pathology, Kaohsiung Medical University Chung-Ho Memorial Hospital between 1988 and September 2005. Clinical files were available for three of them, and we found nuances in the immunohistochemistry from these previous reports. Here, we present these rare sarcomas and review the literature.

Key Words: malignant peripheral nerve sheath tumor, S-100, p53, Ki-67
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Despite an increasing number of reports, there is no consensus on the pathologic diagnostic criteria of MPNSTs [1]. MPNSTs have several synonyms, including neurofibrosarcoma and malignant schwannoma [2,3]. They may arise *de novo* or be associated with von Recklinghausen's disease (neurofibromatosis 1) (NF1) [3]. They compose 5–10% of all soft tissue sarcomas [2,4]. Many studies have appeared about immunohistochemical and molecular analysis, and have made dramatic progress in this field. High levels of p53 and Ki-67 exist in MPNSTs, and their use may aid in the detection of early malignant transformation [5]. More frequent accumulation of p53 in NF1-associated MPNSTs is also found and, hence, may account for the poor prognosis [6]. Low-grade MPNSTs display diffuse or focal S-100 reactivity, whereas most high-grade ones show decreased or negative S-100 reactivity [7]. Some investigators have tried to explain the different intensity and staining patterns in BPNSTs, and in low- and high-grade MPNSTs. It has been suggested that lack of S-100 reactivity in most cases probably reflects a low degree of differentiation [8]. However, one of our cases did not conform totally to our expectations in light of these patterns. Three cases of MPNSTs are described (Tables 1 and 2).

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Address correspondence and reprint requests to: Dr. Kun-Bow Tsai, Department of Pathology, Kaohsiung Municipal Hsiao-Kang Hospital, No. 482, Shan-Ming Road, Hsiao-Kang, Kaohsiung 812, Taiwan.
E-mail: kbtsai@cc.kmu.edu.tw

Table 1. Summary of the clinical files

	Patient 1	Patient 2	Patient 3
Gender	Female	Male	Male
Age (years)	59	82	49
Tumor site	Pelvic	Right axilla	S1 and S2
Metastasis	+	–	+
Local recurrence	–	+	+
Follow-up period	1 month	10 years, 9 months	1 year

Table 2. Comparison between histologic features and immunohistochemical results

	Patient 1	Patient 2	Patient 3
Cellularity*	3	2	1
Mitoses	33/10 HPF	6/10 HPF	4/10 HPF
Necrosis	+	+	+
S-100	+ (almost 100%)	+ (40%)	– (totally negative)
p53 (%)	36	28	0
Ki-67 (%)	55	10	2
NSE (%)	+ (50)	+ (50)	+ (10)
SMA (%)	+ (7.5)	< 1, weak	1, weak
Desmin	–	–	–

HPF = high power field; NSE = neuron-specific enolase; SMA = smooth muscle actin.
*Cellularity in order; 1 = the highest cellularity among the three.

Case Presentation

Case 1

Patient 1, a 59-year-old female with no family history of NF1, developed an acute onset of low back pain and myoclonic movement of the left limbs not associated with conscious change, tonic gazing, and trismus. She had had hypertension for years with regular control, an intracranial hemorrhage 18 years ago, left hemiparesis since that episode, and uterine myoma without pathologic proof for nearly 4 years. Magnetic resonance imaging (MRI) disclosed multiple metastatic lesions at both hepatic lobes and bone. Abdominal computed tomographic (CT) scans revealed a 10-cm mass in the uterus. The lesion on L2 spine was explored surgically, and excision biopsy was subsequently performed. She refused further treatment and was lost to follow-up. The excised surgical specimen consisted of five solid gray-tan fragments of tissue measuring as large as 2.5 × 2 × 0.8 cm in size. Microscopic examination revealed an alternately hypercellular and hypocellular tumor destroying bone and soft tissue. The tumor cells had plump oval, round, spindle, to wavy nuclei in a fascicular pattern. Pleomorphism, necrosis, focal hyalinization, and frequent mitoses (as many as 33 mitoses per ten high-power fields (HPF) were identified (Figure 1A). Immunohistochemical testing showed diffuse S-100 staining and focal positive neuron-specific enolase (NSE) (50%), neurofilament protein (NFP) (2.5%), smooth muscle actin (SMA) (7.5%), and cytokeratin 7 (CK7)(2.5%), whereas CD34, desmin, CD117, and epithelial membrane antigen (EMA) were all negative (Figure 1B). There was substantial Ki-67 and p53 overexpression (mean 55.28% and 36%, respectively) (Figures 1C and 1D).

Case 2

Patient 2, an 82-year-old male with a history of gastric cancer and subsequent surgery, developed a mild tender mass palpable in the right axilla. MRI demonstrated a huge ovoid lesion. It was inhomogeneous and had a high T1W signal (Figure 2), a high T2W rim, and a low T2W center. Surgery was performed in 2002. Surgery demonstrated a 10-cm elastic and movable mass with adhesion to nerve and vessels. The soft tissue around the lesion was swollen and rich in vascularity. Although the surgeon removed as much of the tumor as possible, the lesion soon recurred. He had five courses of radiotherapy and chemotherapy. We were unable to follow up the patient approximately 1 year ago.

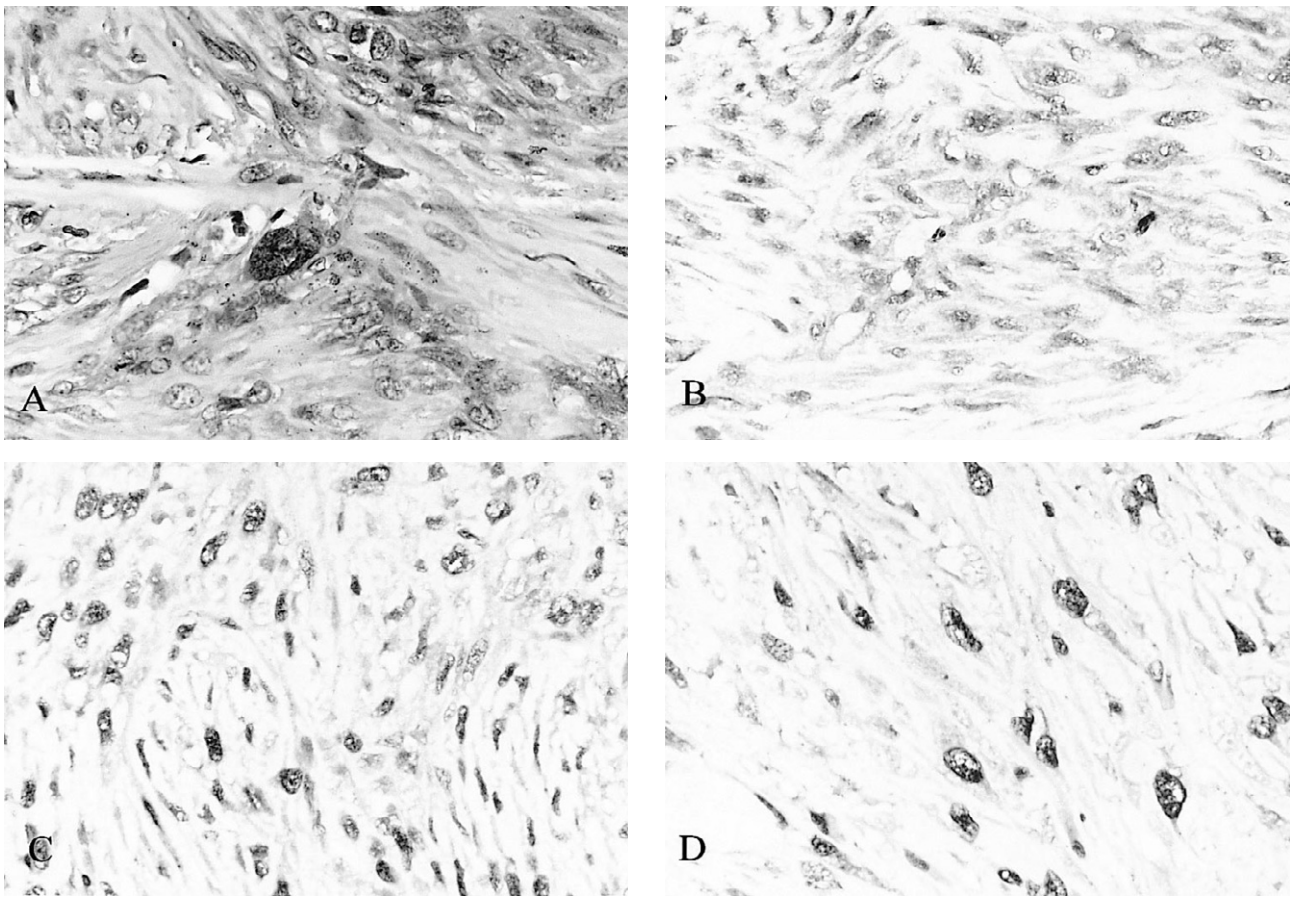

Figure 1. *Microscopic appearances. (A) The hypercellular tumor exhibited atypism and bizarre tumor giant cells (hematoxylin & eosin stain, original magnification × 400). (B) Diffuse S-100 immunopositivity (immunohistochemical stain, original magnification × 400). (C) Higher p53 overexpression (immunohistochemical stain, original magnification × 400). (D) Higher Ki-67 index (immunohistochemical stain, original magnification × 400).*

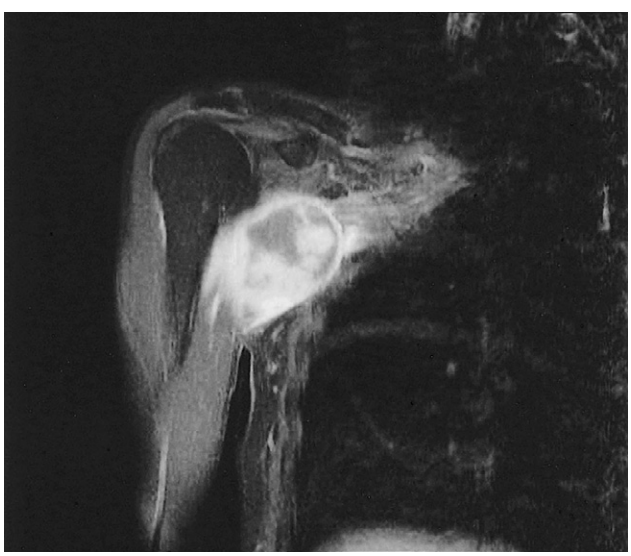

Figure 2. *The T1-weighted coronal section demonstrates an inhomogeneous but relatively well-circumscribed lesion with surrounding edematous soft tissue.*

The excised specimen for frozen section consisted of one gray-tan tissue fragment, measuring 2.2 × 1.5 × 0.6 cm. The specimen submitted later consisted of one well-circumscribed tissue fragment and measured 6 × 6 × 5 cm. The cut surface was tan-yellow with focal myxoid change and necrosis. Microscopic sections showed alternate hypercellular and hypocellular myxoid zones. It revealed patternless and interlacing fascicle with focal neurofibroma background. Tumor cells showed ovoid, wavy, or spindle nuclei with frequent bizarre cells, increased mitotic activity (6/10 HPF), and necrosis (Figure 3A). Immunohistochemical studies showed focal immunoreactivity of S-100 (40%) and NSE (50%) (Figure 3B). Staining for CD34, SMA, and desmin was negative. Interspersed collagen was demonstrated focally by Masson's trichrome stain. There was overexpression of p53 (mean 28%) and Ki-67 (mean 10%) (Figures 3C and 3D).

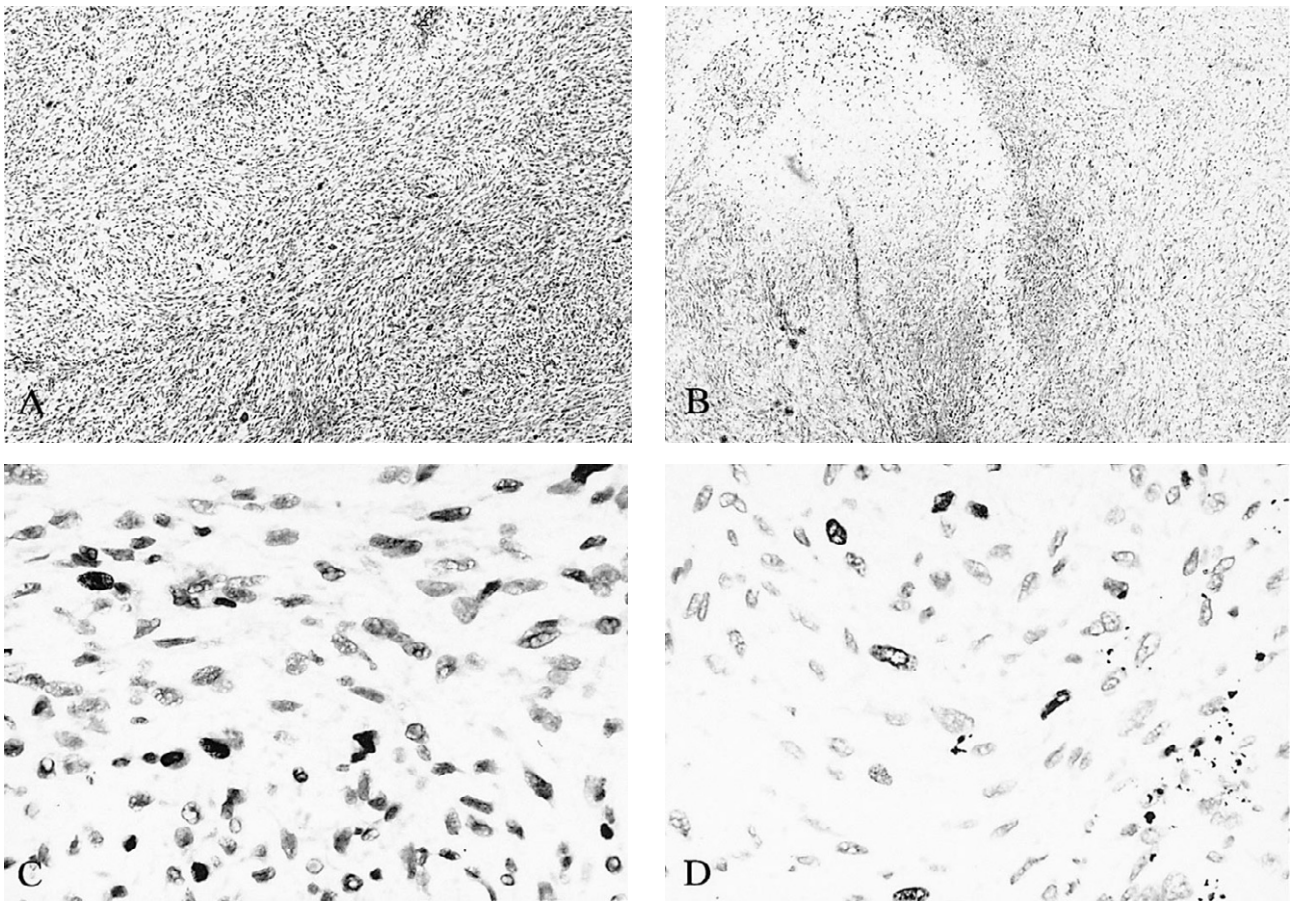

Figure 3. *Microscopic appearances. (A) Higher cellularity and more bizarre tumor cells than in patient 1 with short fascicular growth pattern. (hematoxylin & eosin stain, original magnification × 40). (B) S-100 reveals partially immunoreactive (immunohistochemical stain, original magnification × 100). (C) High p53 overexpression. (immunohistochemical stain, original magnification × 200). (D) High Ki-67 index (immunohistochemical stain, original magnification × 400).*

Case 3

Patient 3, a 49-year-old man without NF1, complained of right gluteal soreness with radiation to the lower leg since January 1997. He sought treatment in another hospital, and an invasive tumor mass in the sacrum was found. The pathologic specimen after surgery revealed a malignant schwannoma. He came to our hospital because of recurrence of sarcoma. He had six courses of radiotherapy and chemotherapy. We have been unable to follow up this patient in our clinic since April 1998. The surgical specimen of the recurrent tumor consisted of multiple gray-white fragments of tissue, measuring as large as 2 × 1.8 × 0.9 cm. The histopathologic appearance was of a highly hypercellular, mitotically active (4/10 HPF), spindle cell neoplasm with short interlacing fascicles. There were nuclear atypia with occasionally large bizarre cells and necrosis (Figure 4A). The immunohistochemical panel showed positive NSE (80%) and focal weak positive SMA (33%). The S-100, desmin, NFP, and p53 all stained negatively (Figures 4B and 4C). No collagen was found by Masson's trichrome stain. Low Ki-67 expression was seen (mean 2%) (Figure 4D).

Discussion

Most MPNSTs are well circumscribed but not truly encapsulated [9].The highly aggressive sarcomas are believed to be derived from components of the nerve sheath and may occur in any part of the body [10,11], although the retroperitoneum is a rare site [11]. Patient 1 had a huge pelvic mass. To the best of our knowledge, this is a rare case report. The standard diagnostic criterion is still enigmatic, as is reflected in the diverse histologic subtypes [10–12].

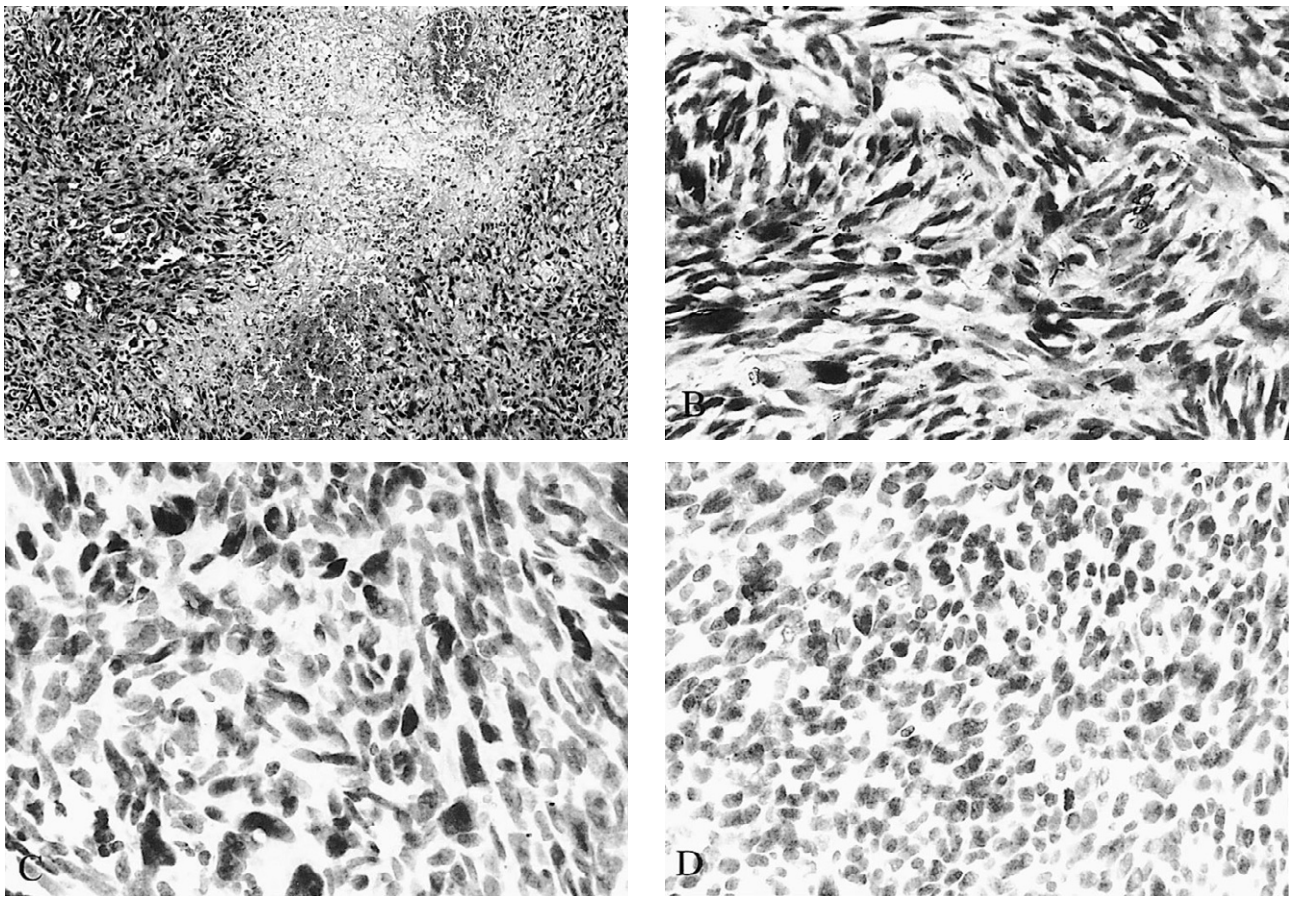

Figure 4. *(A) The highest cellularity and more bizarre tumor cells than in patients 1 and 2. It demonstrates typical palisading around necrosis. (hematoxylin & eosin stain, original magnification × 40). (B) Totally negative S-100 (immunohistochemical stain, original magnification × 400). (C) No p53 overexpression (immunohistochemical stain, original magnification × 200). (D) No Ki-67 expression in this field (immunohistochemical stain, original magnification × 400).*

Some authors have described low-grade and high-grade MPNSTs, whereas others have described well-differentiated and anaplastic MPNSTs [6,12]. These subcategories are not generally accepted. The diagnosis is facilitated by typical features such as palisading arrangement, nuclear atypia, bizarre giant cells, mitotic figures, and necrosis [13]. However, equivocal features may be encountered, and the differential diagnosis includes benign nerve sheath tumors and other spindle cell sarcomas [12]. The main differential diagnosis encompasses hemangiopericytoma, angiosarcoma, leiomyosarcoma, and malignant melanoma [12,14]. There have been several promising immunohistochemical markers [5,15]. Among these, S-100, p53, and Ki-67 attracted our attention. Although S-100 is widely used and valuable in the diagnosis of MPNSTs, there are no specific markers [14]. S-100 is highly characteristic of neural-derived neoplasms, but it is also expressed in a wide range of tissues [16,17]. S-100 is positive in 83% of BPNSTs and shows intensely positive with no relation to cell morphology [16]. Only 50–60% of MPNSTs express S-100 [18]. The most challenging of all is the method of diagnosing MPNST with a negative stain for S-100 as in our patient 3. We reviewed the literature and found that S-100 expression in MPNSTs is usually weak and focal, whereas BPNSTs demonstrate strong S-100 staining [10,19]. Our patient 1 showed strong and diffusely positive S-100 expression, which was not in accordance with the reports [10,19]. The staining pattern of S-100 varies greatly. What mechanism causes such great variation? Does S-100 play an important role in the ancillary studies? Some authors have proposed that S-100 negativity in most MPNSTs probably reflects their low degree of differentiation [8]. We decided to test the notion that, if S-100 is associated with the differentiation of MPNSTs, S-100 staining might predict

clinical behavior. We retrieved and analyzed the files of the Department of Pathology, Kaohsiung Medical University Chung-Ho Memorial Hospital between 1988 and September 2005. Only six patients diagnosed with MPNST were obtained, and three of these were lost to hospital records. We found that these three patients all had high-grade histologic results. According to the literature [10,19], S-100 staining should be focal and weakly positive; however, the specimen from patient 1 showed diffusely positive staining and that from patient 3 was totally negative. These findings were not in accordance with the concept that negative S-100 staining represents dedifferentiation of Schwann cells [20]. S-100 expression might be related to the predominantly neoplastic cells in MPNSTs, because they might have diverse differentiation [16]. This might reasonably explain the phenomenon we observed, although the study has the limitation of the limited number of patients. A large-scale study will be necessary to determine if the S-100 staining pattern could reflect the degree of differentiation or predict the clinical behavior.

p53 expression also plays an important role in the tumorigenesis of MPNSTs [21]. In addition to p53, Ki-67 expression also figures prominently in differentiating between the diagnoses of BPNST and MPNST [6,22,23]. Patients 1 and 2 had high Ki-67 and p53 expression as in the previous reports (Table 2) [6,22,23]. However, patient 3 had 2% immunoreactivity of Ki-67 and no p53 overexpression. Histopathologically speaking, patient 3 had the highest cellularity, more bizarre cells, and the presence of a more typical palisading pattern in the peripheral area of necrosis. Patient 2 had a higher histologic grade than patient 1.

However, the expression of p53 and Ki-67 was inversely related to the histologic grade, a most unexpected result. It seems that p53 and Ki-67 do not correspond with the histologic grade, although they may be relevant to the differentiation of BPNSTs from MPNSTs [6]. Moreover, we found that patients 1 and 3 had distal metastases, whereas patient 2 had local recurrence. It seems that Ki-67, p53, and histologic grade do not correlate with clinical behavior. Another problem lies in how to differentiate MPNSTs from BPNSTs if the ancillary studies of p53 and Ki-67 are not contributory. In such instances, other supplementary studies such as cytogenetic analysis are necessary [2].

Morphologic imaging techniques provide better visualization of the anatomic extent, and MRI is the first choice [24,25]. The MRI findings in our patients are heterogeneous because of necrosis; this is compatible with the nonhomogeneous lesions in the documented cases [26,27]. However, MRI is not a reliable tool for distinguishing benign and malignant nerve sheath tumors [27].

MPNSTs have a poor prognosis [28]. They can locally recur or metastasize to distant sites [29,30]. Sufficiently wide local excision is necessary, but this is restricted mostly by tumor location [29–31]. Furthermore, radiotherapy and chemotherapy are also used [31,32], but they have not, as yet, been proven to be totally effective [29–33]. With the advent of imaging techniques and immunohistochemistry, pathologists have come to rely on them. They seem to eclipse the traditional pathologic examination. With the nuance of the immunohistochemical staining pattern in our cases, we still believe that traditional histologic assessment is the mainstay of pathologic diagnosis. The combination application of Ki-67 and p53 are best regarded as an ancillary technique and should not supersede the traditional pathologic examination [34]. Because of short clinical follow-up and inadequate samples, a meaningful relationship between immunohistochemistry, histopathologic grade, and clinical behavior is not possible. Probably as a result of the rarity of MPNSTs, there have been few reports with longer clinical follow-up and more patient samples. A large-scale study is required to explain these findings.

References

1. Perrin RG, Guha A. Malignant peripheral nerve sheath tumors. *Neurosurg Clin N Am* 2004;15:203–16.
2. McComb EN, McComb RD, DeBoer JM, et al. Cytogenetic analysis of a malignant triton tumor and a malignant peripheral nerve sheath tumor and a review of the literature. *Cancer Genet Cytogenet* 1996;91:8–12.
3. Colville RJ, Camilleri IG, McLean NR, et al. Malignant peripheral nerve sheath tumour metastasising to the parotid gland. *Br J Plast Surg* 2003;56:418–20.
4. Bagan JV, Sanchis JM, Jimenez Y, et al. Malignant peripheral nerve sheath tumor of the maxilla. *Oral Oncol Extra* 2005;41: 70–3.
5. Kindblom LG, Ahlden M, Meis-Kindblom JM, et al. Immunohistochemical and molecular analysis of p53, MDM2, proliferating cell nuclear antigen and Ki67 in benign and malignant peripheral nerve sheath tumours. *Virchows Arch* 1995;427:19–26.
6. Liapis H, Marley EF, Lin Y, et al. p53 and Ki-67 proliferating cell nuclear antigen in benign and malignant peripheral nerve sheath tumors in children. Pediatr Dev Pathol 1999;2:377–84.
7. Zhou H, Coffin CM, Perkins SL, et al. Malignant peripheral nerve sheath tumor: a comparison of grade, immunophenotype, and cell cycle/growth activation marker expression in sporadic and neurofibromatosis 1-related lesions. *Am J Surg Pathol* 2003; 27:1337–45.

8. Koizumi Y, Utsunomiya T, Yamamoto H. Cellular schwannoma in the oral mucosa. *Acta Otolaryngol* 2002;122: 458–62.
9. Aydin MD, Yildirim U, Gundogdu C, et al. Malignant peripheral nerve sheath tumor of the orbit: cases report and literature review. *Skull Base* 2004;14:109–13.
10. Garg A, Gupta V, Gaikwad SB, et al. Scalp malignant peripheral nerve sheath tumor (MPNST) with bony involvement and new bone formation: case report. *Clin Neurol Neurosurg* 2004; 106:340–4.
11. Oğuzkurt P, Kayaşelcuk F, Arda IS, et al. Anterior abdominal wall malignant peripheral nerve sheath tumor in an infant. *J Pediatr Surg* 2001;36:1866–8.
12. Klijanienko J, Caillaud JM, Lagacé R, et al. Cytohistologic correlations of 24 malignant peripheral nerve sheath tumors (MPNST) in 17 patients: the Institut Curie experience. *Diagn Cytopathol* 2002;27:103–8.
13. Legbo JN, Shehu BB, Malami SA. Malignant peripheral nerve sheath tumour associated with von Recklinghausen's disease: case report. *East Afr Med J* 2005;82:47–9.
14. Nkere UU, Walter NM. Malignant peripheral nerve sheath tumour: a rare tumor and an unusual intrapericardial presentation. *Eur J Cardiothorac Surg* 1997;12:144–6.
15. Matsuda Y, Saoo K, Hosokawa K, et al. Epithelioid malignant peripheral nerve sheath tumor. Report of a case with inflammatory infiltration. *Pathol Res Pract* 2005;201:355–60.
16. Chijiwa K, Uchida K, Tateyama S. Immunohistochemical evaluation of canine peripheral nerve sheath tumors and other soft tissue sarcomas. *Vet Pathol* 2004;41:307–18.
17. Weiss SW, Langloss JM, Enzinger FM. Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. *Lab Invest* 1983; 49:299–308.
18. Smith TA, Machen SK, Fisher C, et al. Usefulness of cytokeratin subsets for distinguishing monophasic synovial sarcoma from malignant peripheral nerve sheath tumor. *Am J Clin Pathol* 1999;112:641–8.
19. Molina CP, Putegnat BB, Logroño R. Fine-needle aspiration cytology and core biopsy of malignant peripheral nerve sheath tumor of the uterus: a case report. *Diagn Cytopathol* 2001;24: 347–51.
20. Gonzalez-Martinez T, Perez-Piñera P, Díaz-Esnal B, et al. S-100 proteins in the human peripheral nervous system. *Microsc Res Tech* 2003;60:633–8.
21. Mawrin C, Kirches E, Boltze C, et al. Immunohistochemical and molecular analysis of p53, RB, and PTEN in malignant peripheral nerve sheath tumors. *Virchows Arch* 2002;440: 610–5.
22. Halling KC, Scheithauer BW, Halling AC, et al. p53 expression in neurofibroma and malignant peripheral nerve sheath tumor. An immunohistochemical study of sporadic and NF1-associated tumors. *Am J Clin Pathol* 1996;106:282–8.
23. Antinheimo J, Haapasalo H, Seppala M, et al. Proliferative potential of sporadic and neurofibromatosis 2-associated schwannomas as studied by MIB-1(ki-67) and PCNA labeling. *J Neuropathol Exp Neurol* 1995;54:776–82.
24. Otsuka H, Graham MM, Kubo A, et al. PDG-PET/CT findings of sarcomatous transformation in neurofibromatosis: a case report. *Ann Nucl Med* 2005;19:55–8.
25. Huang JH, Zhang J, Zager EL. Diagnosis and treatment options for nerve sheath tumors. *Expert Rev Neurother* 2005;5: 515–23.
26. Friedrich RE, Kluwe L, Funsterer C, et al. Malignant peripheral nerve sheath tumors (MPNST) in neurofibromatosis type 1 (NF1): diagnostic findings on magnetic resonance images and mutation analysis of the NF1 gene. *Anticancer Res* 2005;25: 1699–702.
27. Mautner VF, Friedrich RE, von Deimling A, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis type 1: MRI supports the diagnosis of malignant plexiform neurofibroma. *Neuroradiology* 2003;45:618–25.
28. Tucker T, Wolkenstein P, Revuz J, et al. Association between benign and malignant peripheral nerve sheath tumors in NF1. *Neurology* 2005;65:205–11.
29. Baehring JM, Betensky RA, Batchelor TT. Malignant peripheral nerve sheath tumor: the clinical spectrum and outcome of treatment. *Neurology* 2003;61:696–8.
30. Doorn PF, Molenaar WM, Buter J, et al. Malignant peripheral nerve sheath tumors in patients with and without neurofibromatosis. *Eur J Surg Oncol* 1995;21:78–82.
31. Mrugala MM, Batchelor TT, Plotkin SR. Peripheral and cranial nerve sheath tumors. *Curr Opin Neurol* 2005;18:604–10.
32. Wanebo JE, Malik JM, VandenBerg SR, et al. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. *Cancer* 1993;71:1247–53.
33. Satoh M, Komori K, Shin M, et al. Retroperitoneal malignant peripheral nerve sheath tumor (MPNST) complicated with von Recklinghausen's disease: a case report. *Hinyokika Kiyo* 2004;50:417–20.
34. Pfeifer JD, Hill DA, O'Sullivan MJ, et al. Diagnostic gold standard for soft tissue tumours: morphology or molecular genetics? *Histopathology* 2000;37:485–500.

惡性周圍神經鞘腫瘤的 S-100 蛋白和其他免疫組織化學染色的表現：三個病例報告和文獻回顧

胡士文[1,2]　林威辰[3]　蔡慧珍[4]　簡松雄[5]　蔡坤寶[1,2]

高雄醫學大學附設中和紀念醫院 [1]病理科 [3]醫學診斷部 [4]血液腫瘤內科 [5]骨科

[2]高雄醫學大學 醫學院醫學系病理學科

因為缺乏特殊的影像學和病理診斷標準，對於病理醫師來說，要區分惡性周圍神經鞘腫瘤和其他的腫瘤，往往是一項大挑戰。早期發現良性周圍神經鞘腫瘤的惡性轉變，能有較好的預後，所以很多的免疫組織化學和分子學的研究宛如雨後春筍般的出現。然而，文獻上還是沒有統一的診斷標準。S-100 一直是廣泛的用在惡性周圍神經鞘腫瘤的診斷上，而 p53 和 Ki-67 也是最有前景的輔助工具，不過，文獻上少有它們的染色類型分布和機轉的探討，於是這引發我們的興趣，我們搜尋高雄醫學大學附設醫院病理科的報告資料庫，從 1988 年到 2005 年九月間，只找到六位診斷為惡性周圍神經鞘腫瘤的病患，其中三位有病例記載。我們發現與以往文獻上些許不同的免疫組織化學染色差異，在此我們提出這罕見的腫瘤，並回顧一下文獻紀錄。

關鍵詞：惡性周圍神經鞘腫瘤，S-100，p53，Ki-67

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通訊作者：蔡坤寶醫師

高雄醫學大學附設中和紀念醫院病理科

台灣高雄市三民區自由一路 100 號