Malignant Peripheral Nerve Sheath Tumor with Neurofibromatosis Type 1: A 2-Case Report and Review of the Literature †

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Abstract

Malignant peripheral nerve sheath tumor is a very rare soft tissue tumor in the general population but there is an increased incidence in patients with neurofibromatosis type 1. Two cases of malignant peripheral nerve sheath tumor associated with neurofibromatosis type 1 whom we were able to follow-up long term are presented. Although wide excision was performed successfully in these patients, they suffered from local recurrence of the tumors shortly after surgery and died with distant metastases. The literature concerning the natural history and the management of this specific condition was reviewed.

Key word : Malignant Peripheral Nerve Sheath Tumor, Neurofibromatosis Type 1

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Malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma arising from a nerve or neurofibroma. It has a wide spectrum of histological features with the major component being the schwann cell. MPNST has many synonymous terms such as malignant schwannoma, neurofibrosarcoma, malignant neurilemoma and neurogenicsarcoma, however, the term MPNST is usually preferred[1,2]. When this tumor is associated with neurofibromatosis (NF), an inherited condition with potential for malignant change, which is also named von Recklinghausen's

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disease, first described in 1882, it has a worse prognosis than a sporadic case[1]. Although a wide margin excision without lymph node dissection is recommended for the treatment of this particular tumor, local recurrence and distant metastasis often occur shortly following surgery[1,3,4]. There is no significant benefit in outcome from adjuvant chemotherapy and radiotherapy[2,5,6]. The purpose of this study was to present the long-term clinical and radiographic characteristics, treatment response and oncologic outcome of two NF type 1 patients with MPNST. We also reviewed the literature concerning the natural history, investigation and management of this specific condition.

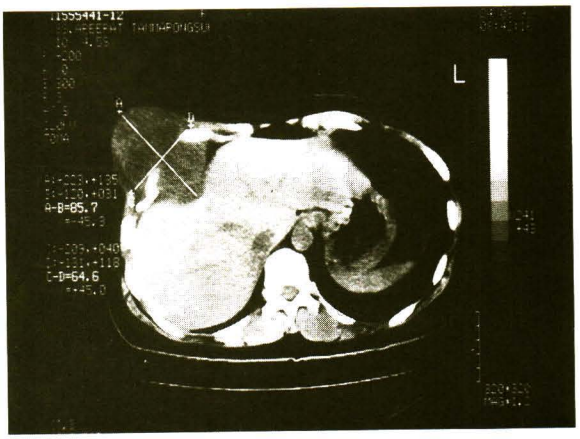

Fig. 1. Computed tomography of upper abdomen showing a well-circumscribed hypo-dense mass in the right chest wall with intra-abdominal extension.

MATERIAL AND METHOD

The authors reviewed the medical records and radiographs of two patients diagnosed with MPNST associated with NF type 1 who were treated at the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital between July 1998 and December 1999. The clinical diagnosis of these two patients was confirmed by the pathologist. The diagnosis of NF type 1 was made according to the criteria of National Institutes of Health (NIH) Consensus Development Conference[7]. Further follow-up information was obtained from the medical records or by phone from the patients and family members.

CASE REPORTS

Case 1: A 32-year-old female was diagnosed with NF type 1 with characteristics of café au lait macules and axillary freckling. She was referred to our hospital with a slow growing mass on her right chest wall which had been present for 2 years. This mass was progressively enlarging and was painful. A plain chest radiograph did not demonstrate any mass at first. However computerized tomography scan (CT scan) yielded a positive result on examination of the chest (Fig. 1). An incisional biopsy was performed for definitive diagnosis. Histological examination and special immunohistochemistry staining showed the features of MPNST (Fig. 2A-B).

She developed a right pleural effusion one month later and a wide excision was performed. The tumor mass was found to have invaded through the diaphragm and had a pressure effect on the upper surface of the liver. It had also invaded the pleura and adhered to the inferior surface of the middle lobe of the right lung parenchyma. The tumor was removed including part of the 10^{th}-12^{th} ribs, a segment of the middle lobe of the right lung parenchyma and the dome of the diaphram. The tumor measured 16x15x8.5 cm. Following tumor resection, reconstruction of the defect at the chest wall was performed with a Prolene mesh (Johnson & Johnson, Inc, Brussels, Belgium). She did well postoperatively without any complication. She received no adjuvant chemotherapy or radiotherapy. The final pathological examination revealed a MPNST with involvement of the lung parenchyma, pleura and diaphragm. Tumor necrosis was estimated about 20 per cent. All resected margins were free of tumor.

One month postoperatively, multiple local recurrent masses were found along the surgical scar and the right chest wall. Three months after surgery, the tumor masses progressively enlarged and were painful. Hepatomegaly was found without any sign of jaundice or ascites. Thoracoabdominal magnetic resonance imaging (MRI) demonstrated multiple local recurrences associated with lung, liver and pericardial metastases (Fig. 3A-B). A palliative dose (300 cGy AP/PA chest x 7 times) of radiotherapy was administered to relieve pain and reduce tumor growth. However,

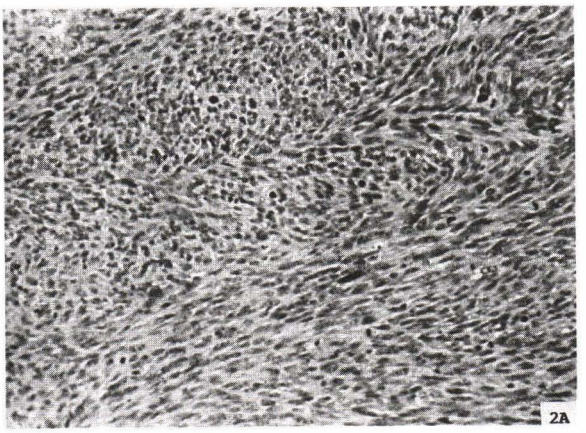

Fig. 2A. Section from resection specimen showing highly cellular spindle-shaped tumor arranged in herringbone-pattern. Individual tumor cells showing plump-spindle to polygonal-shaped and elongated hyperchromatic nuclei with high mitotic rate (over 10/10 HPF). (H&E, 100X)

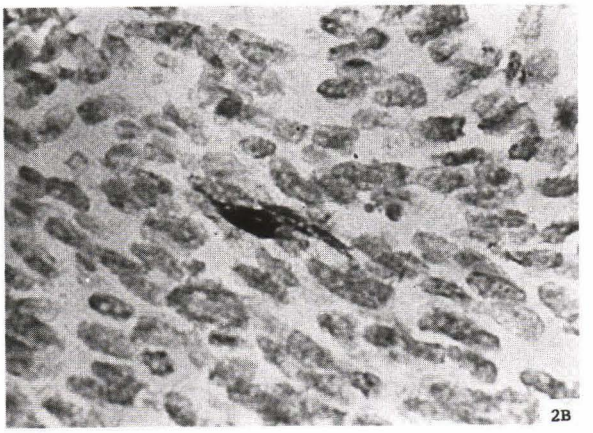

Fig. 2B. Immunohistochemistry study for S-100 protein demonstrating focal positivity in tumor cell. (400X)

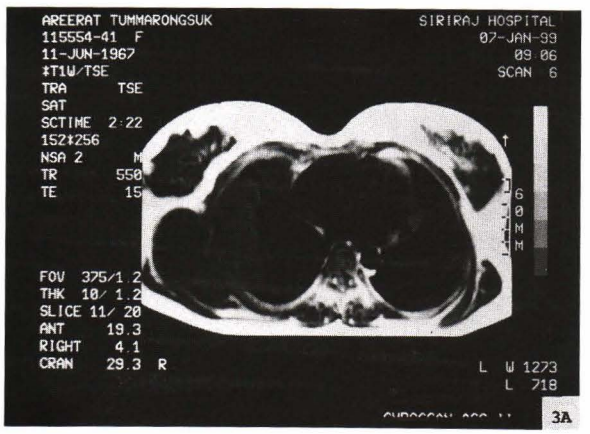

Fig. 3A. Axial T1WSE of thorax revealing a large right chest wall hypo-intense mass which involved both extra and intra-thoracic compartments.

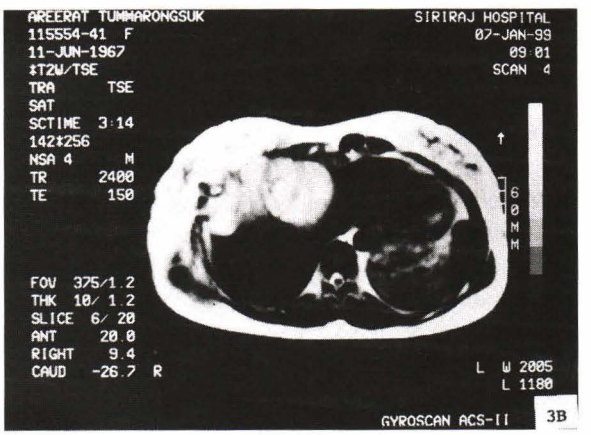

Fig. 3B. Axial T2WSE of upper abdomen demonstrating the right chest wall change signal intensity to high signal in T2WSE.

the masses continued to increase in both size and number. Finally, she developed restrictive pulmonary function and jaundice. She died 8 months after the initial surgery.

Case 2: A 35-year-old female with NF type 1 (Fig. 4) presented with an enlarged mass on the sacral area with right hip pain and sciatica down to the right lower extremity. She had had

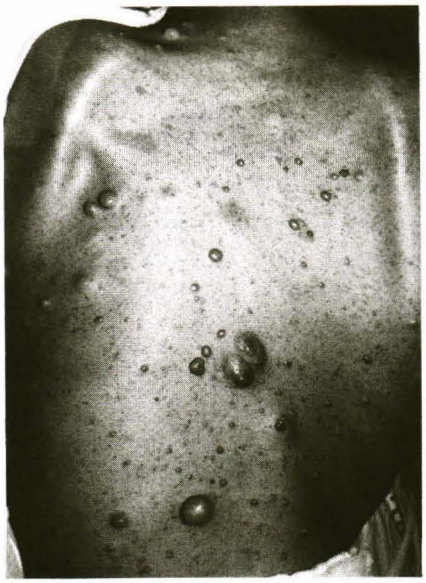

Fig. 4. Photography showing cutaneous neurofibromas and *café au lait* spots on the trunk of the patient (case 2).

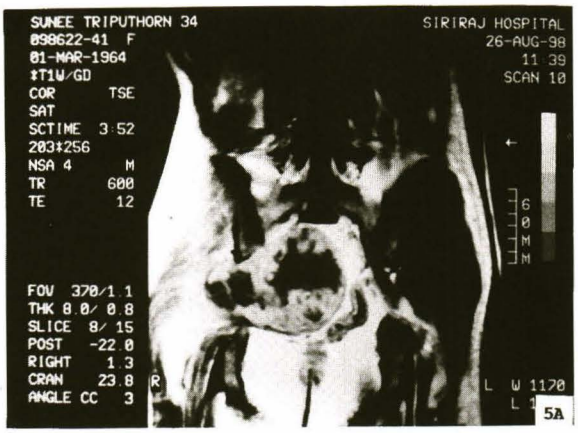

Fig. 5A. Coronal T1WSE with GD of pelvis showing the malignant schwannoma mass in right pelvis has central non-enhancing portion (hypo-intense) and peripheral irregular enhancing portion (hyper-intense) which extends into right buttock.

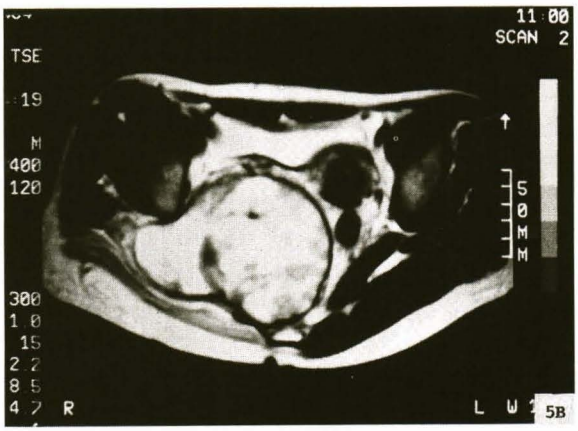

Fig. 5B. Axial T2WSE of pelvis demonstrating high signal in the central necrotic (cystic) portion and intermediate signal in peripheral irregular solid portion. The margin of the mass is well-delineated and the extension *via* greater sciatic notch is well demonstrated.

difficulty in walking for 4 months. Weakness of the right extensor hallucis longus, tibialis anterior, flexor hallucis longus and decreased sensation on the medial aspect of the dorsum of the right foot and peri-anal area were found on physical examination. Plain radiographs of the lumbosacral spine in AP and lateral views yielded nothing remarkable. MRI showed an ill-defined homogeneous intra-pelvic mass (Fig. 5A-B). One month later, her neurological deficit was progressively worse and she developed right foot drop. An ultrasonography-guided biopsy was done and histological examination showed a MPNST. Wide excision of the tumor which sacrificed the sciatic nerve was performed *via* partial iliac resection. Final histological examination confirmed the diagnosis with 60 per cent tumor necrosis (Fig. 6A-B).

She developed a deep wound infection caused by *Escherichia coli* and *Enterococcus* on day 2 postoperatively. The infection was eradicated twice by debridement and appropriate antibiotics. She was able to walk with a walker at the time of discharge wearing a foot-ankle-orthosis. Tumor recurrence was found 3 months after initial surgery (Fig. 7). Palliative treatment was considered at this time. However, the tumor

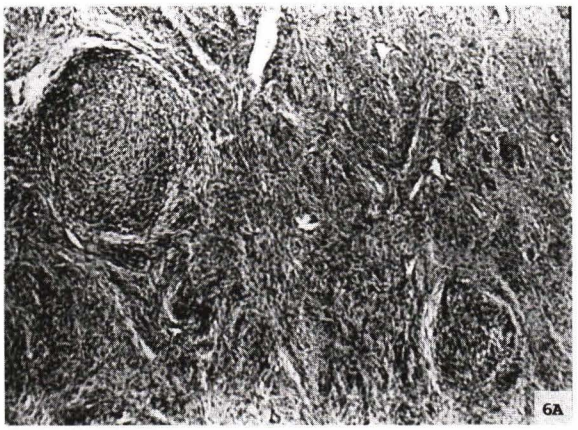

Fig. 6A. Section showing a spindle cell sarcoma with hyperchromic nuclei and high mitotic rate (over 10/10 HPF). The whorled features are obvious in this case. (H&E, 40X)

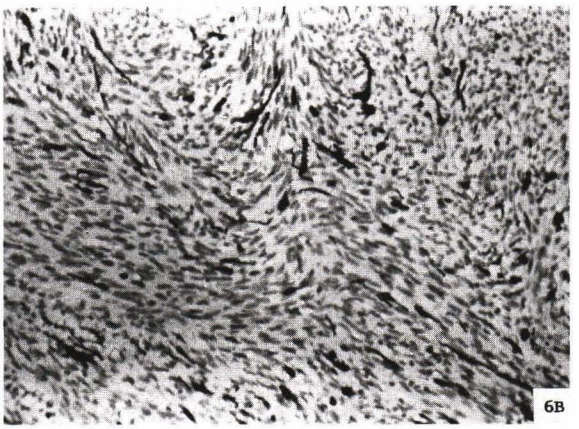

Fig. 6B. Immunohistochemistry showing tumor cells marked with S-100 protein. (200X)

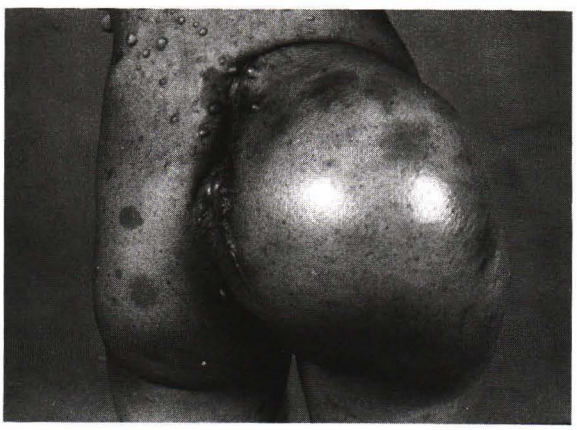

Fig. 7. Photography showing the huge-size tumor recurrence which occurred 3 months after initial surgery.

enlarged rapidly and her general condition deteriorated. She developed pulmonary metastasis and died 15 months after definitive diagnosis.

DISCUSSION

MPNST is a spindle cell sarcoma arising from a peripheral nerve, neurofibroma or showing nerve sheath differentiation[1,4]. It accounts for approximately 5-10 per cent of all soft tissue sarcomas[1,7]. Forty to 60 per cent of these tumors are associated with NF type 1, one of the most common single gene disorders which is inherited as an autosomal dominant[1,2,4-8]. However, half of these patients represent new mutations[1,8,9]. Both patients in this series had NF type 1 without a family history, so it was assumed that they had a new mutation. Although most of the literature suggests that there is no significant relationship between a malignant and benign schwannoma, a MPNST may also develop in a pre-existing neurofibroma [1,4,6,10]. The tumor tends to grow along the epineurium and/or perineurium of the involved nerves and produces satellite lesions around the primary one[5,10]. Patients with NF type 1 have a significant risk of developing malignant transformation, especially those who have had the disease for a long time. This condition is, therefore, quite rare in children[1,11]. Ducatman et al reported that malignant transformation was found in 81 per cent with NF type 1 and only 41 per cent was found in the other group[2].

Neither the primary defect nor the mechanism involved in malignant transformation and tumor progression in NF type 1 is fully understood. It may involve a multi-step process of tumorigenesis[1,4,19]. Some reports have docu-

mented various abnormalities on chromosome 17[19-21]. Menon et al reported a deletion on chromosome 17p outside the region of the NF1 gene[20]. Reynolds et al demonstrated a 17q 11.2 translocation[21]. Other authors reported the disease might involve the p53 gene[9,12,20,21]. About 10 per cent of MPNST occurs as a result of therapeutic or occupational irradiation after a latent period of 12 years[1,2,6,7,13]. Therefore, we should be aware that we should follow-up patients with NF type 1 who have a history of radiotherapy.

The true incidence of MPNST associated with NF type 1 is 4.6 per cent which is much higher than in the general population (0.001%)[2]. Therefore, patients with NF type 1 should be closely monitored for MPNST. The mean age of NF type 1 patients with MPNST ranges from 26.4 to 42 years old which is younger than patients with MPNST without NF type 1 (39.7-48 years)[2,4,5,7,12-15]. There is no significant difference in gender for patients with MPNST. The most common sites are usually located at the major nerve trunks such as the sciatic nerve, brachial plexus and sacral plexus and the proximal part of the extremities and trunk are the most common anatomical sites[1,4,5,15-17]. One patient in this report had a MPNST which developed in the right buttock and was thought to have originated from the sciatic nerve. The other had a tumor on the right chest wall which may have derived from an intercostal nerve.

Most patients present with an expanding mass with or without pain The pain is often worse in patients with NF type 1[1-5,7,9-11,18]. Patients may have paresthesia and motor weakness[4,7, 15]. One patient in this series presented with an expanding mass associated with pain but the other had no pain However, the symptoms of sciatica and weakness of the affected limb indicated that the tumor site was located at the sciatic nerve. The duration of symptoms before the tumor is recognized is very difficult to ascertain in most cases. Hruban et al reported symptom duration lasting from between 2 to 18 years before recognition of the MPNST[4]. Our patients had symptoms for 2 years and 4 months respectively before a definite diagnosis was made.

Both CT scan and MRI help to determine the extent of the tumor and its relationship to adjacent structures. The characteristics of imaging such as inhomogeneitiies or an infiltrative tumor border suggest malignancy. However, MRI is often preferable to CT scan because of the advantage of good soft tissue delination which assists the surgeon in determining the margin of resection[22,24].

The pathohistological diagnosis of MPNST is not always easy because of the wide spectrum of histological features and the lack of standardized diagnostic criteria[4]. Most MPNSTs appear as a large circumscribed fusiform or eccentric mass within a major nerve without a true capsule. Stout and D'Agostino et al found that MPNST originated in a nerve and noted the presence of a contiguous neurofibroma[1,2,7,14, 15,17,23]. The tumor spreads along the epineurium and perineurium by thickening of the nerve proximally and distally to the main mass. Most MPNSTs in NF type1 are deeply situated and are usually large with an average diameter of more than 5 cm[1,2,7,23]. The cut surface of the tumor commonly shows a mass of firm consistency which may be white, tan, yellow, or a combination of two or more of these colors. Some tumors demonstrate obvious whorling or interlacing fascicles and may be marked by areas of hemorrhage, necrosis or a degenerative cystic component[4,7,15,17,23].

On histological examination it may look like a fibrosarcoma, synovial sarcoma, leiomyosarcoma, malignant fibrous histiocytoma or other spindle cell sarcomas[1-4,14,15,18,24]. It classically recapitulates the normal schwann cell which is a spindle cell with markedly irregular contours [1,11,15,25]. The hyperchromic nuclei can have many characteristics appearing as wavy, buckled, or comma shaped. The indistinct lightly stained cytoplasm is free of coarse longitudinal fibrils and there is no discernable cell membrane[1,4,7, 16-18,23-25]. The specific pattern of tumor organization is very useful in diagnosis. It is usually arranged in fascicles that may show interlacing, whorled, herring-bone and storiform patterns[1,2, 4,7,11,14-16,18,23-25]. Nuclear palisading may be observed and demonstrated more frequently in NF1 patients[1,2,6,15,23,24]. Other appearances of MPNST may be present such as proliferation of tumor in the subendothelial zone of vessels, hyaline bands and nodules with cross sections which resemble giant rosettes[1,14,18]. Twelve to 27 per cent of MPNST have heterogeneous

elements indicating divergent differentiation. Cartilage and bone are the most common differentiated tissue. Other elements such as muscle or mucin secreting gland are rare[1,2,4,7,14,18]. MPNST sometimes resembles a neurofibroma but it has a greater degree of cellularity, pleomorphism and mitotic activity. Thus, it has been named malignant neurofibroma. Rare cases of divergent differentiation such as angiosarcoma, epithelioid or malignant Triton tumor have been reported[1,4,7,14,16-18,23,25,26,28]. The histological findings in our patients revealed the typical feature of MPNST. The first case showed epithelioid differentiation and all our patients were considered to have high grade MPNST similar to most of the patients in Ducatman et al's report[2].

Immunohistochemical study is very useful to identify tumors with nerve sheath differentiation. Although none of these markers is specific for neural differentiation, it has been widely used to differentiate this tumor from other similar spindle cell tumors[1,2,4,23,25,27]. Since none of the markers is highly specific for MPNST, the diagnosis is based on several markers of immunohistochemistry stains such as S-100 protein, Leu-7, Vimentin and NSE (neuron specific enolase). Many authors have used electron microscopic study to help reach the diagnosis[1,2,17,19,24,29].

Nowadays, complete resection with an adequate margin is the recommended treatment [4,10,13]. Kunisada et al suggested that all MPNST should be excised with at least 3 cm from tumor margin to get a large enough margin and to avoid local recurrence[5]. To prevent local recurrence of the tumor, some authors have used a frozen section of the nerve margin at the time of surgery to demonstrate intraneural tumor propagation and ensure an adequate margin of resection[1,16]. Hruban et al found that patients who were treated by amputation had better results in tumor control especially for tumors that enclosed nerve or vascular structures[4]. The incidence of local recurrence of the tumor is related to NF type 1, MPNST with NF type 1 had a rate of 45 per cent while 53 per cent were found in MPNST without NF type 1[2,4-7]. Chemotherapy and radiation therapy in most studies did not show a significant improvement in patient survival, but some studies showed some beneficial effects, especially in those with MPNST with NF type1 or those who had undergone previous radiation treatment[1,2,4-6,14]. Less than 10 per cent of patients have lymph node metastases, so prophylatic regional node dissection does not play an important role in the management of these tumors unless lymphatic metastasis was found clinically [1,4].

Overall, distant metastasis is present in 55 per cent in MPNST[4]. The common sites of distant metastasis are lung, bone, pleura, retroperitoneum, soft tissue, liver, intraabdominal cavity etc[1,2,4-7,13,14]. In our first patient, distant metastases were found at the time of local recurrence in the pleura, lung, and liver. The other patient was found to have pulmonary metastasis 14 months after initial surgery. A previous study demonstrated the mean time of distant metastasis 20.6 months after surgery[13].

MPNST associated with NF type1 has a worse prognosis when compared with a sporadic case[1,10]. Significant prognostic factors differ in each study. Kourea et al found a tumor size less than 5 cm, the presence of a low-grade component and complete tumor resection were good prognostic factors[7]. Wanebo et al indicated that patient survival was influenced by patient age ($\leq$ 30 years old), tumor location (thoracic or retroperitoneal area) and tumor size ($\geq$ 10 cm) [14].

Patient survival varies in different studies. Three-year survival was 42 per cent in patients with NF type 1 and 70 per cent in the other group. Five-year survival was 32 per cent and 49 per cent respectively[4,6,13]. Survival of a patient with MPNST after pulmonary metastasis is very poor both with and without NF type 1. Only 4 per cent of these patients survived more than 2 years[6]. Both of our patients were followed-up until they died from pulmonary metastasis. The one who had a right chest wall mass died 9 months after the first diagnosis of lung and liver metastasis. The other patient with a right buttock mass died from lung metastases and bleeding from a local recurrence of tumor at 15 months postoperatively.

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มะเร็งของปลอกหุ้มเส้นประสาท กับ โรคท้าวแสนปม : รายงานผู้ป่วย 2 รายและทบทวนวรรณกรรม

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มะเร็งของปลอกหุ้มเส้นประสาท เป็นโรคที่พบน้อยในประชากรทั่วไป แต่พบว่ามีอุบัติการณ์เพิ่มมากขึ้นในผู้ป่วยโรคท้าวแสนปม ผู้รายงานได้นำเสนอผู้ป่วยโรคมะเร็งของปลอกหุ้มเส้นประสาท 2 ราย ซึ่งได้รับการติดตามการรักษาเป็นเวลานาน ผู้ป่วยได้รับการรักษาโดยการผ่าตัดก้อนออกหมด ต่อมาทั้งคู่มีมะเร็งเกิดขึ้นใหม่บริเวณที่ได้รับการผ่าตัดและเสียชีวิตจากภาวะมะเร็งลุกลามในเวลาต่อมา คณะผู้รายงานได้ทบทวนวรรณกรรมที่เกี่ยวข้องกับมะเร็งของปลอกหุ้มเส้นประสาทในผู้ป่วยโรคท้าวแสนปมในหลายๆด้าน

คำสำคัญ : มะเร็งของปลอกหุ้มเส้นประสาท, โรคท้าวแสนปม

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