Malignant peripheral nerve sheath tumor (MPNST), an aggressive spindle cell sarcoma is found predominantly in adults. The tumor is closely associated with neurofibromas, neurofibromatosis type 1 (NF-1) and from the sites previously irradiated. Individuals with NF-1 account for 50-60% of all of the patients with MPNSTs [1]. Herein, we describes a fatal case of MPNST in NF-1 with atypical age of onset and multicentric tumors at different sites occurred over a short period of time after the initial surgery. The lesion was studied with ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). The most characteristic findings in our case was heterogeneously low density masses without any apparent organ-based primary site within the mesentery and retroperitoneum. The diagnosis was established by histologic picture, combined with clinical manifestation and imaging findings. The characteristic clinical, radiologic and histopathologic features of this process are reviewed along with the diagnostic and therapeutic options.

Key words: Computed tomography; Malignant peripheral nerve sheath tumor; Neurofibroma; Neurofibromatosis

MPNST is a distinct clinicopathologic entity that accounts for approximately 10% of all soft tissue sarcomas and half of that occurs in NF-1. These tumors can be solitary or multicentric. MPNST associated with NF-1 has worse prognosis when compared with the sporadic case. The overall 5-years survival rate of MPNST ranges from 16 to 30% which is influenced by tumor size, location, resection margin and presence of the NF-1 [1,2]. Based on the image study, preoperative diagnosis for MPNST is difficult because similar clinical and radiological findings sometimes occur in benign nerve neoplasm and other malignant mesenchymal tumor which gives a diagnostic challenge. Histopathological and immunohistochemical technique is the only reliable way to establish a definite diagnosis. Five cases of Type-1 NF with involvement of the mesentery had been reported but there is no report of malignant mesenteric tumor in the published English literature [3]. We report a NF-1 patient with mesenteric and retroperitoneal MPNSTs in order to increase the awareness of this rare malignancy and alert the radiologists to include this disease in differential diagnosis.

CASE REPORT

A 56-year-old man with neurofibromatosis-1 diagnosed in childhood went to our clinic with one year history of abdominal pain and progressive left leg numbness. His past medical history was remarkable except only for NF-1. The family history showed that 3 of his 4 children had both multiple cutaneous nodules but never sought medical attention. On physical examination, he had multiple cutaneous nodules, the cafe-au-lait spots and lisch nodules of iris which were consistent with a diagnosis of NF-1. Routine laboratory examination, including hematologic data, serum biochemical data and the urine analysis were within normal limits. An abdominal sonogram disclosed a
huge hypoechoic mass at left lower abdomen. Intravenous urography (IVU) showed bulging mass at left paraspinal region of L3 to L5 with lateral displacement of the psoas muscle and the left ureter, but no hydronephrosis was noted. In addition, osteolytic lesion at the left pedicle of L5 was found. CT showed a low density mass with poor contrast enhancement at left retroperitoneum, involving L5 prevertebral space with L5 vertebral body destruction. Spinal MRI by using 0.5 T scanner in various scanning planes were obtained. The MRI findings showed a large heterogeneous mass at the L5 prevertebral region with L5 destruction and neural foramen invasion (Fig. 1). The mass had slightly higher signal intensity than the muscle on T1-weighted images and had a high signal intensity on T2-weighted images. There was enhancement in the mass following administration of gadolinium DTPA. In view of the clinical diagnosis of NF-1, the preoperative radiologic impression is retroperitoneal neurogenic tumor secondary to NF-1 and malignant potential could not be excluded. Exploration of the abdomen revealed a 15 × 10 × 17 cm retroperitoneal mass infiltrating at the L3-5 level with left ureter, colon, left iliac vessels, aorta, IVC compression, and with further extension into the left neural foramen of L5. The bulk of the tumor was excised with residual lesion in L5. Histology showed spindle cell sarcoma (Fig. 2) and immunohistochemical stain was negative for S-100 protein, Desmin and Vimentin. The final pathological examination confirmed the diagnosis of MPNST. Residual tumor was irradiated with dosage of totally 6540 cGy/36Fr for pain relief and reducing tumor size. After a period of 8 months since the first operation, he suffered from progressive bowel habit change and right leg numbness. Abdominal CT disclosed heterogeneous enhanced mass at mesentery and another soft tissue lesion at right paraspinal area of L5. Operation was suggested but the patient refused. At the 5th month of the follow-up from recent previous CT scan, both lesions had doubled in size (Fig. 3). At laparotomy, two firm nodular masses measuring 3 cm × 2 cm × 1 cm and 15 cm × 11 cm × 9 cm were seen in the ileal mesentery and transverse mesocolon. The margin of the tumors was well demarcated, but the larger one extended to the mesenteric base with local invasion to transverse colon. Both tumors were completely excised. Pathological evaluation showed that the resection margin was free. Histology revealed spindle cell tumor with hypercellular, hyperchromatic, fascic-
ulated, and actively mitotic cells. Immunohistochemical studies demonstrated reactivity to Vimentin and the focal patch was positive with S100 protein while negative to Desmin and Keratin. The final diagnosis was malignant peripheral nerve sheath tumor. Four months after the second operation, his neurological deficit became worse and right foot-drop occurred. CT revealed infiltrative right paraspinal mass at the level of L5 with L4-5 bony destruction and with intraspinal and neural foramen extension. Partial removal of L4-5 extradural mass with transpedicle screw fixation was done for symptom relief. The histology confirmed MPNST. The patient's condition deteriorated rapidly with paraplegia 7 months after the second operation when the masses continued to grow and increased both in size and numbers (Fig. 4a), especially the mesenteric lesions (Fig. 4b). Further surgery was not attempted and he died of the disease 24 months later.

**DISCUSSION**

Neurofibromatosis (NF), also known as von Recklinghausen's disease, is a cancer-prone disease that affects all three germ cell layers and can involve any organ system. The classic syndrome consists of cafe-au-lait spots associated with mesodermal tumors of the viscera and central nervous system [4]. Although NF-1 shows autosomal dominant inheritance, there is no positive family history in approximately one half of newly diagnosed cases, which results from new mutation [5]. Our patient's children in this report had multiple cutaneous nodules but his parents, older sister and older relatives were all in excellent health. It is presumable that neurofibromatosis in the patient reported here is the result of a new mutation.

One of the hallmark of NF-1 is an increased propensity for developing both benign and malignant tumors. The most common benign tumor is plexiform neurofibroma and, less commonly, schwannoma. Malignant peripheral nerve sheath tumor is the most serious complication of NF-1 which is often fatal, and may develop in peripheral nerves, pre-existing plexiform neurofibroma, or following radiation therapy [1,6]. The risk of developing a MPNST in NF-1 has been estimated at 2-5% and 0.001% in the general population [1,3,6,7]. On the other hand, nearly half of these malignancies arise in individuals affected with NF-1. Thus, the risk for development of MPNST appears to be 4600 times greater in patients with NF-1 than in the general population.

Most cases of MPNSTs occur in patients who are 20-50 years old but MPNSTs in NF-1 are diagnosed earlier with the peak prevalence in the 3rd decade of life [1-3]. In this reported case, the age at the time of diagnosis was much older than that reported in the literature. Both genders were equally affected or slight female predominance (F:M = 1.3:1) [1-3]. Clinically, MPNST may be present as long as several years before the patient seeks medical attention. The presenting symptoms are related to tumor size, associated loss of function, or pain. The duration of symptoms before the tumor recognized is very difficult to
ascertain [2]. The one-year history of our patient corresponds to other case reports in which the interval ranging from 6 months to 4 years from onset of symptoms to diagnosis [2,3]. Patients with sporadic MPNST tend to locate in extremities but MPNST in NF-1 tends to locate deeply and centrally. Previous studies noted that the patients with central or paraspinal located MPNSTs had worse outcome and frequently with pain than those with limb lesions [1-3, 6-8]. In our case, like those reported in the literature, all tumors were centrally deeply located and clinically associated with pain. Radiologically, the characteristics of the presented lesions suggested an active rapid growing tumor of retroperitoneal and mesenteric origin. Malignant and benign lesions cannot be reliably distinguished by imaging criteria because the radiologic appearance of this tumor is noncharacteristic on CT and MRI. However, as stated in the previous literature, aggressive centrally, deeply located mass with inhomogeneities, infiltrative margins, or irregular bony destruction in the setting of neurofibromatosis should bring the diagnosis of MPNST to radiologist [9,10]. Higher rate of cystic change in retroperitoneal neurogenic tumor is also a recognized feature of MPNST [9], which may be an important preoperative diagnostic feature because the other retroperitoneal tumors rarely share the same finding. In this case, all image findings corresponds to those have been mentioned in the literature.

The frequency of gastrointestinal involvement in NF-1 is uncommon and has been reported in nearly 10%. The abnormalities include hyperplasia of the gastrointestinal nerve plexus, mucosal ganglioneuromatosis, gastrointestinal stromal tumors with varying degrees of neural differentiation [3,11-13]. The most common findings is stromal tumors such as neurofibroma and leiomyoma. They are frequently multiple. As the late manifestation of the NF-1 and the risk of malignant degeneration is estimated to be less than 5%. The most common site of involvement is the jejunum, stomach and ileum while any portion of the gastrointestinal tract may be involved [3,12]. Type 1 neurofibromatosis with isolated involvement of the mesentery has been reported in 5 case in published English-language literature but no case of MPNST had been reported. Patient with mesenteric neurofibromatosis may remain asymptomatic or present with variable symptoms including abdominal pain, diarrhea, nausea and vomiting. Complications such as hemorrhage, obstruction, intussusception and perforation may cause the presenting symptoms. The origin of mesenteric neurofibromatosis would be the autonomic nerve fibers. Our patient initially presented with progressive bowel habit change which may correspond to mesenteric MPNSTs involvement of the mesenteric plexus and subsequent bacterial overgrowth syndrome with diarrhea. Although the appearance of mesenteric neurofibromatosis on barium study is often non-specific, eccentric polypoid defects on the mesenteric side of small bowel, mass effect on adjacent barium-filled loop with obvious separation of the involved bowel segments have been reported as the typical findings. Characteristic CT findings include cluster of small, mass-like areas of soft tissue attenuation extending from the root of the mesentery to small bowel wall separately by intervening surrounding fat plane. On contrast enhanced CT scans, these masses demonstrate inhomogeneously low attenuation in comparison to muscle, that is attributable to a combination of factors including lipid rich cells, cystic degeneration and myxoid stroma. Tumors of muscle density are usually composed of compact fibroblasts and dense collagen. The low density in our case is most likely corresponding to both myxoid stroma and dense collagen [3,10,12,14].

Multifocal occurrence of MPNST is rare, which may imply metastatic growth from one possible site or independent growth of neural crest-derived cells of each site. In this case, MPNST developed at multiple sites (four of which are histologically proven) over a short period of time. We feel that tumor seeding or local recurrence along operation tract with metastasis is the most likely explanation for the multiplicity. A previous study demonstrated the patients with NF-1 did have a high risk for developing a second MPNST [1,3]. Our patient is in agreement with published literature as the interval between diagnosis and recurrence was 8 months. The interval of diagnosis of a sarcoma was long with the averaging time reported to be 16.9 years. In our case, postirradiation-induced MPNST can be excluded due to short radiation period.

The typical treatment include a combination of the complete resection of the tumor with adequate free margin, adjuvant radiotherapy and chemotherapy. The clinical course includes local tumor recurrence, perineural spread, and pulmonary metastasis. The incidence of local recurrence of the tumor and prognosis are related to the preexisting NF-1. According to the previous study, metastasis occurred in 39% of patients with NF-1 whereas only 16% in those without NF-1. The five-year survival rate was 16% in the group with NF-1 and 53% in the sporadic group. The most important prognostic factors are the large tumor size (> 5 cm), the practicability of total resection and the presence of the NF-1 [1,2,6,15]. Correspondingly, the patient presented here had a
deeply-seated tumor exceeded 5 cm in diameter, incomplete tumor resection margin and positive NF-1 history, all of which indicating worse prognostic factors.

In summary, MPNST in NF-1 appear to be a distinct entity. Because diagnostic delay was more common, we suggest careful investigation for such case to identify rapid growing deep-seated tumors and radiologists should be aware of this potentially life threatening entity which must be included in the differential diagnosis.

REFERENCES

腸系膜與後腹腔的惡性周圍神經鞘瘤合併第一型多發性神經纖維瘤症

吳金珠¹  彭惠玲¹  蘇誠道¹  盧大年¹  李進成²  陳良光¹
財團法人新光吳火獅紀念醫院  放射診斷科¹  病理檢驗科²

惡性周圍神經鞘瘤是一種罕見的高度惡性且預後極差的梭狀細胞性軟組織肉瘤。一般相信它是由“以前存在的”周圍神經鞘瘤演化形成或經由放射治療後而產生。它可發生在身體任何部位。將近有50-60%的病人會合併第一型多發性神經纖維瘤症。本文報告一多發性病例，病灶主要位於後腹腔及腸糸膜的惡性周圍神經鞘瘤。病人為56歲男性，臨床上沒有特殊的症狀。影像上也沒有較特殊的表徵。雖然最後的診斷需依賴病理切片，但臨床及影像學表現仍扮演著重要角色。此病患除了接受手術切除外，並接受了放射線及化學治療。但因病情惡化及多處轉移而於術後24個月死亡。此文的目的，是想藉以此病例的臨床、影像及組織學表現與治療，來提升放射科醫師對此少見腫瘤之經驗；並針對此做了回溯性探討。

關鍵詞：電腦斷層攝影，惡性周圍神經鞘瘤，第一型多發性神經纖維瘤症，周圍神經鞘腫瘤