

# A Case of Intrathoracic Giant Malignant Peripheral Nerve Sheath Tumor in Neurofibromatosis Type I (von Recklinghausen's Disease)

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The patient was a 32-year-old woman with neurofibromatosis I (von Recklinghausen's disease), with chief complaints of shortness of breath and back pain. CT and MRI revealed a giant mass occupying the right thoracic cavity almost completely. The mass compressed the mediastinal structure to the left and the liver downwards. She underwent surgery to alleviate respiratory and circulatory disorders caused by compression of the right lung and inferior vena cava due to the giant tumor. Intraoperatively, the tumor was found to have originated from the 5th intercostal nerve. The resected tumor was 20×17×15 cm in size and 2,300 g in weight. It was histologically diagnosed as a malignant peripheral nerve sheath tumor. Her postoperative course was uneventful. All indicators of respiratory function improved, and edema of the lower half of the body disappeared, accompanied by disappearance of shortness of breath. She was discharged 21 days after surgery. Seven months after surgery, however, a recurrent tumor was found in the right thoracic cavity. She died of rapid growth of recurrent tumor 3 months thereafter. This tumor often complicates neurofibromatosis I and has a high frequency of local recurrence and distant metastasis, resulting in poor prognosis. Neither an optimal extent of resection needed for complete resection of this tumor nor an optimal regimen of chemotherapy, radiotherapy, or other therapy for the tumor has yet been established. It is desirable to establish them in the near future. (*Ann Thorac Cardiovasc Surg* 2008; 14: 42–47)

**Key words:** malignant peripheral nerve sheath tumor, neurofibromatosis I, intrathoracic giant tumor

## Introduction

Malignant peripheral nerve sheath tumor (MPNST) accounts for 5–10% of all malignant soft tissue tumors. Of all cases of this tumor, 30–50% are accompanied by neurofibromatosis I (NF-1) (von Recklinghausen's disease).

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Received January 15, 2007; accepted for publication March 20, 2007

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On the other hand, the incidence of complication by MPNST is relatively low (2–13%) among patients with NF-1, and MPNST often affects the extremities in these cases and it rarely develops in the thoracic cavity.<sup>1)</sup> We recently encountered a case of giant MPNST of the right thoracic cavity which complicated NF-1, who was treated surgically. This paper will present this case, with reference to the literature.

## Case Report

The patient was a 32-year-old woman with NF-1. In December 2005, she began to complain of shortness of breath and back pain. A detailed examination at a nearby clinic allowed a diagnosis of massive hydrothorax on the right

side. She underwent thoracic drainage but adequate elimination of the thoracic fluid was not achieved. For this reason, she was referred and admitted to our department to receive a detailed examination and treatment.

The largest subcutaneous mass (3 cm in diameter) was found in the left axillary area, accompanied by many soft subcutaneous masses (below 1 cm in diameter) in the extremities and countless café au lait spots on systemic skin. Marked edema was noted in the lower half of her body. In auscultation, the right respiratory sound was weak and intense shortness of breath was noted, allowing a rating of degree V according to the Hugh-Jones classification.

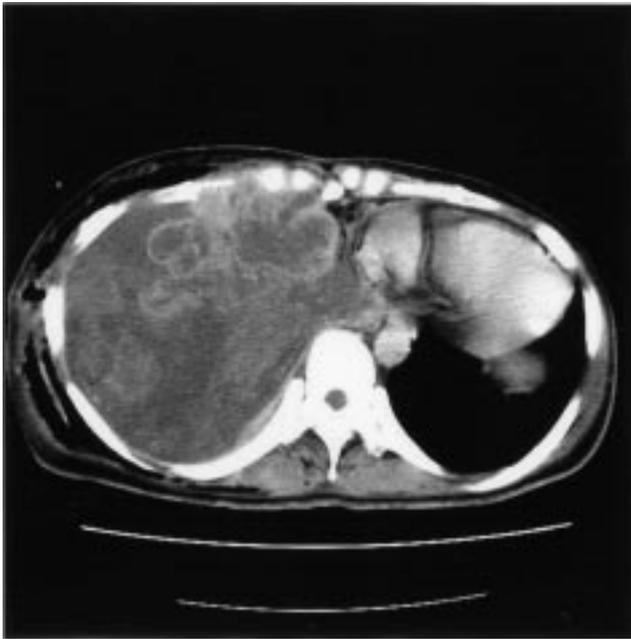
On admission, C reactive protein (CRP) was as high as 15.46 mg/dL, and elevation of leukocyte count (11,300/ $\mu$ L) was also noted. Of the tumor markers tested, only neuron-specific enolase (NSE) was elevated (64 ng/mL). Arterial blood gas analysis following oxygen inhalation at a rate of 3 L/min yielded the following results: pH 7.461, arterial pressure of carbon dioxide ( $PCO_2$ ) 37.6 mmHg, arterial pressure of oxygen ( $PO_2$ ) 77.6 mmHg,  $O_2$  saturation 95.8% and base excess (BE) 3.1 mmol/L (Table. 1). Chest X-ray (Fig. 1) revealed no air in the right thoracic cavity and the mediastinal deviation to the left, while visualizing the thoracic drain inserted at a nearby clinic. Chest computed tomography (CT) scans disclosed a giant mass occupying the right thoracic cavity almost completely. The area inside the mass showed an unhomogeneous contrast enhancement on contrast-enhanced CT (Fig. 2). The mass intensely compressed the mediastinal structure (involving the heart, large vessels, trachea, esophagus, etc.) to the left, and the right lung was free of air. Chest magnetic resonance imaging (MRI) revealed a large mass (19 $\times$ 17 $\times$ 14 cm) in the right thoracic cavity. A homogeneously high density was seen within the mass already in the early phase of the dynamic study. The mass intensely compressed the mediastinal structure to the left and the liver downwards, but the mass was well-demarcated, suggesting the absence of tumor invasion of the mediastinum or liver (Fig. 3). The feeding artery for this tumor seemed to be an intercostals artery, internal thoracic artery, inferior phrenic artery or something of the sort. However, because the CT and MRI findings suggested that the tumor in this case was not very invasive, we concluded that it would be relatively easy to deal with the feeding artery. This is why we did not make further efforts to identify the feeding artery preoperatively. On the basis of these findings, she was strongly suspected of having an intrathoracic giant malignant neurogenic tumor which had complicated NF-1. In view of the possi-



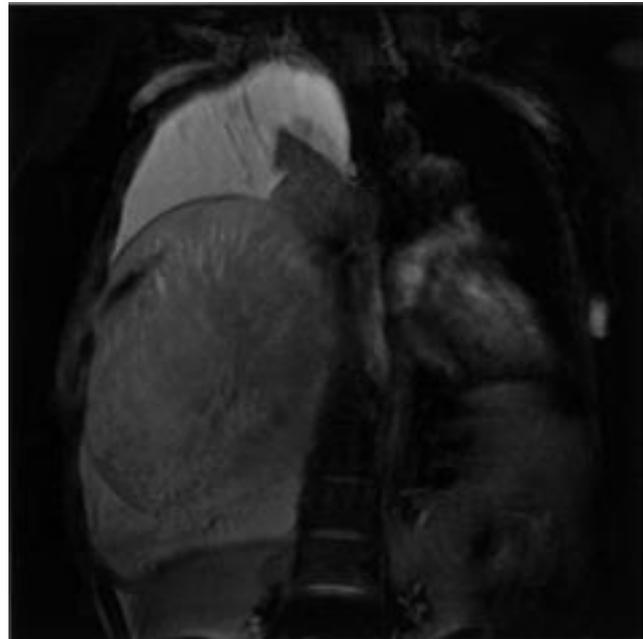
**Fig. 1.** Chest X-ray revealed no air in the right thoracic cavity and the mediastinal deviation to the left.

bility of subcutaneous metastasis of the intrathoracic giant tumor, we first carried out biopsy of the subcutaneous tumor of the left axillary area (about 3 cm in size). The tumor was pathologically rated as benign neurofibroma without mitosis. Thus, a definite diagnosis of intrathoracic giant tumor was not possible preoperatively. However, the intrathoracic tumor seemed to be malignant in nature, judging from its clinical course and size. She underwent surgery on January 30, 2006, to alleviate respiratory and circulatory disorders caused by compression of the right lung and inferior vena cava (IVC) due to the giant tumor. The ideal surgical procedure for cases like this would be to resect only the tumor, while leaving the lung as intact as possible. However, when beginning surgery for this case, we made ourselves ready to perform pleuropneumectomy, against the possibility that, during surgery, we might find extensive tumor invasion of the lung.

The chest was opened at the level of the 6th intercostals space by means of a long S-shaped skin incision (extending the standard posterolateral incision forwards and then below the costal arch), as shown in Fig. 4. When we conduct surgery on a giant intrathoracic tumor like the one seen in the present case, we usually adopt a posterolateral subcostal approach, which involves a larger incision than the ordinary posterolateral approach. Our practice is



**Fig. 2.** Chest CT scan disclosed a giant mass occupying the right thoracic cavity almost completely. The area inside the mass showed an unhomogeneous contrast enhancement on contrast-enhanced CT.



**Fig. 3.** Chest MRI revealed a large mass (19×17×14 cm) in the right thoracic cavity. A homogeneously high density was seen within the mass already in the early phase of the dynamic study. The mass intensely compressed the mediastinal structure to the left and the liver downwards.

based on the view that an approach allowing safer and more reliable surgical manipulations in a sufficiently wide visual field is essential for dealing with this kind of tumor. We adopted this approach for the present case because the tumor was very large, making it difficult to induce dislocation of the lesion and lung and thus elevating the risk of major bleeding from a site that was not directly visible. The tumor occupied the right thoracic cavity, while compressing the entire right lung upwards and the mediastinum to the left. The tumor had been covered with a capsule but had not invaded the diaphragm or the pericardium. Because dislocation of the tumor was not possible, we were unable to determine whether or not tumor invasion of the IVC was present. However, tumor invasion of the middle and lower lobes of the right lung was noted. For this reason, partial resection of these lobes was additionally performed. The border of the mass from the anterior aspect of the chest wall was not clear, suggesting that the tumor had originated from this area (the 5th intercostal nerve). To allow an adequate surgical margin, the 5th costal cartilage, intercostal muscles, intercostal nerves, intercostal arteries and veins were additionally resected. Since the tumor was large (20 cm in diameter) and because the visual field on the mediastinal



**Fig. 4.** The chest was opened by means of a long S-shaped skin incision (extending the standard posterolateral incision forwards and then below the costal arch).

side was not broad enough, even using the posterolateral subcostal approach we had adopted (an approach involving a larger than ordinary incision), it was not possible to resect the tumor *en bloc*. It was resected completely after having being divided into two pieces. After tumor resection, expansion of the right lung was resumed, but its ex-

pansion was not large enough to completely fill the dead space created by tumor resection. Two thoracic drains were kept inserted and the operation was completed.

Her postoperative course was uneventful. All indicators of respiratory function improved (Table. 1), and edema of the lower half of the body disappeared, accompanied by disappearance of shortness of breath, allowing a rating of degree II according to the Hugh-Jones classification. She was discharged 21 days after surgery, requiring no assistance to walk. Seven months after surgery, however, a recurrent tumor was found in the right thoracic cavity. She died of tumor 3 months thereafter.

The resected specimen consisted of a huge mass, 20×17×15 cm in size, 2,300 g in weight (Fig. 5). It had a fleshy appearance with elastic firm and partially mucinous consistency. Cut surface was yellow-white to greenish-yellow with foci of hemorrhage and necrosis. Histologically, the tumor had a spindle-celled fascicular appearance with alternating cellular and less cellular fibromyxoid areas. Many of the tumor cells had pale, poorly defined cytoplasm and hyperchromatic nuclei with a narrow, tapering outline, often with a wavy configuration (Fig. 6). In some cellular areas pleomorphic cells with clear or eosinophilic cytoplasm, and prominent nucleoli proliferated intersectingly. Mitoses including atypical ones were easily found. Perivascular accentuation and infiltration of vessel walls were frequently seen. The tumor infiltrated focally into the lung parenchyma which was resected together with the primary lesion. Immunohistochemically, many tumor cells expressed CD56, and focally expressed neuron specific enolase (NSE). The tumor did not express S100 protein, glial fibrillary acid protein (GFAP),  $\alpha$ -smooth muscle actin (SMA), desmin, myogenin, CD34, and cytokeratin. Based on these morphological, immunohistochemical, and clinical findings, the tumor was diagnosed as MPNST associated with NF-1.

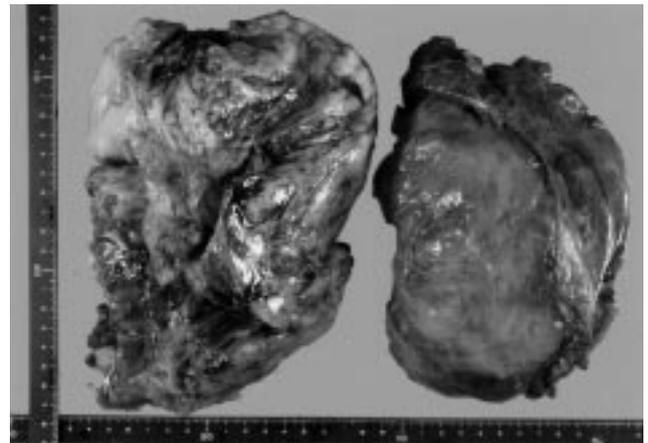
## Discussion

NF-1 was classically called “von Recklinghausen’s disease.” It is a genetic disease transmitted via the autosomal dominant trait and involves neurofibroma of skin, brain, spinal cord and nervous systems, café au lait spots, bone lesions, and so on. This disease was named in 1882 by von Recklinghausen. It has been reported that malignant nerve sheath tumor, which can determine the prognosis, complicates von Recklinghausen’s disease in about 10% of all cases. Complication of this disease by non-

**Table 1. Changes of pulmonary function tests**

	Pre	Post
Spirometry		
VC(L)	0.84	1.61
%VC	28.7	54.9
FEV <sub>1.0</sub> (L)	0.87	1.70
FEV <sub>1.0</sub> (%)	100	100
Blood gas analysis		
pH	7.461	7.427
PaCO <sub>2</sub> (mmHg)	37.6	38.9
PaO <sub>2</sub> (mmHg)	77.3	84.4
SaO <sub>2</sub> (%)	95.8	96.4
BE (mmol/L)	3.1	1.4
Hugh-Jones	V°	II°

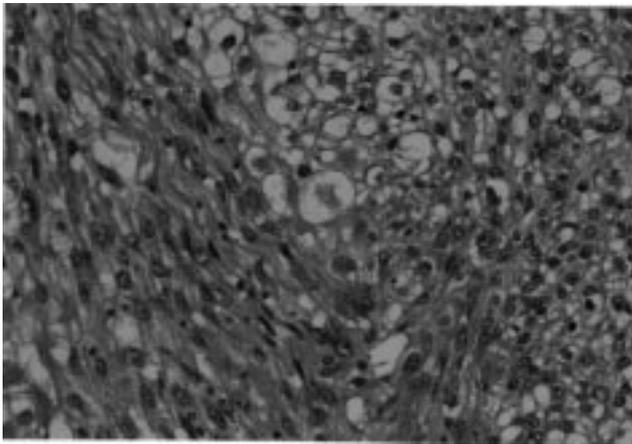
Pre, values before surgery under oxygen inhalation at a rate of 3 L/min; Post, values 3 weeks after surgery under room air; VC, vital capacity; FEV<sub>1.0</sub>, forced expiratory volume in 1.0 s; PaCO<sub>2</sub>, arterial pressure of carbon dioxide; PaO<sub>2</sub>, arterial pressure of oxygen; SaO<sub>2</sub>, degree of arterial oxygen saturation; BE, base excess.



**Fig. 5.** The resected specimen consisted of a huge mass, 20×17×15 cm in size, 2,300 g in weight. It had a fleshy appearance with elastic firm and partially mucinous consistency.

neurogenic malignant tumor has also been reported, although in a small number of cases. To put it concretely, Reports have been published concerning cases of NF-1 complicated by non-neurogenic malignant tumors such as gastric cancer, leiomyosarcoma, lung cancer and gastroenteric cancer.<sup>2)</sup>

Neurogenic malignant tumors are composed of cells which constitute the peripheral nerve sheath (schwann cells, perineural cells, etc.) and account for 5–10% of all malignant soft tissue tumors. In a majority of cases, this type of tumor is accompanied by NF-1. In the past, neu-



**Fig. 6.** Histologically, the tumor showed a spindle-shaped fascicular and intersecting appearance with pale or eosinophilic cytoplasm. The nuclei were hyperchromatic with a tapering outline and a wavy configuration. Large atypical cells with prominent nucleoli were frequently seen (HE stain, original magnification,  $\times 400$ ).

rogenic malignant tumors were classified into malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma and so on. However, the third edition of the General Rules for Surgical and Pathological Studies on Malignant Soft Tissue Tumors, prepared in July 2002,<sup>3)</sup> combined these tumors into a single disease entity “malignant peripheral nerve sheath tumor (MPNST).” MPNST is defined as tumors satisfying at least one of the following four requirements: (i) malignant tumors arising from peripheral nerves or continuous to nerves, (ii) benign neurogenic tumors (e.g., neurofibroma) having been converted into malignant tumors; (iii) malignant tumors developing in NF-1 cases, and (iv) tumors having histological features similar to those of the above-mentioned three types, accompanied by evident immunohistological or electron-microscopic signs of differentiation into the nerve sheath.

MPNST primarily affects extremities, but it can develop in other various sites including the trunk, head/neck region and so on. However, its onset in the thoracic cavity, as seen in the present case, is very rare.<sup>4-6)</sup> A typical clinical sign of MPNST having developed on the body surface is a rapidly growing hard red mass palpable on the skin surface. However, if MPNST originates from the nerves of deep tissue, like in the present case, direct observation of the tumor is not possible, and early diagnosis is difficult. Because of difficulty in early diagnosis, MPNST is often detected as a tumor with large diameter, showing invasion along the nerves. For this reason, surgical resection tends to be incomplete.

The only means of radical treatment for this tumor is complete surgical resection and the prognosis of patients with MPNST is significantly determined by whether or not complete resection has been achieved.<sup>7,8)</sup> We cannot rule out that the separated resection served as one of the factors responsible for the post-surgical recurrence. However, we chose the separated resection out of consideration that major bleeding due to injury of the IVC could develop if the operation were performed without adequate determination of orientation. Resection of about half of the giant tumor made it possible for us to induce dislocation of the tumor. This is probably the reason that we succeeded in safely resecting the tumor while viewing the IVC directly, without causing bleeding. Regarding the operative procedure we selected, we now reflect that we should have adopted pleuropneumectomy, accompanied by resection of the diaphragm and pericardium, to achieve a safety margin. However, regarding post-surgical recurrence of MPNST, we think that its recurrence is primarily associated with the biological malignancy level of MPNST.

On the other hand, the extent of resection needed for complete resection of this tumor has not been established, and quite high postoperative recurrence rates have been reported, i.e., 45.0% (28/62) by Ducatman et al.,<sup>9)</sup> 43.1% (85/197) by Taniguchi et al.<sup>7)</sup> and 46.4% (13/28) by Wanebo et al.<sup>10)</sup> As a means of reducing the local recurrence rate of this tumor, Kunisada et al.<sup>11)</sup> recommended resection with an at least a 3 cm safety margin, and Angelov et al.<sup>12)</sup> reported better prognosis following resection with a 5 cm or more margin. In the present case, it was difficult to take a 5 cm or more safety margin because the tumor was located close to the lung, IVC, esophagus, diaphragm and liver.

According to many reports, chemotherapy and radiotherapy are often ineffective against this tumor. However, cases responding well to high-dose chemotherapy with ifosfamide, vincristine, doxorubicin or cyclophosphamide<sup>13)</sup> and cases making remarkable responses to postoperative high-dose radiation<sup>14)</sup> have recently been reported. An appropriate next step would seem to be to evaluate the efficacy of these methods of treatment.

Regarding distant metastasis of MPNST, the incidence of distant metastasis (primarily to the lungs) has been reported to be 39.0% by Ducatman et al.<sup>9)</sup> and 17.9% by Wanebo et al.<sup>10)</sup> Distant metastasis of this tumor assumes the form of blood-borne metastasis in most cases, and metastasis to lymph nodes is rare.<sup>9,10)</sup>

The 5-year survival rate of patients with this tumor

has been reported to be 12.8% by Taniguchi et al.<sup>7)</sup> and 16.0% by Ducatman et al.<sup>9)</sup> Thus, the prognosis of patients with this tumor is poor. Factors possibly responsible for the poor prognosis are: (i) tumor onset at a relatively low age, (ii) difficulty in early diagnosis if located in deep tissue, and (iii) high incidence of death from distant metastasis due to likelihood for repeated local recurrence following surgical resection because the extent of resection needed for complete tumor resection has not been established. In the present case, local recurrence was seen 7 months after surgery, resulting in rapid growth of the recurrent tumor and death from tumor.

## Conclusion

A case of MPNST, having developed in the thoracic cavity, was presented. This tumor often complicates NF-1 and has a high frequency of local recurrence and distant metastasis, resulting in poor prognosis. Neither an optimal extent of resection needed for complete resection of this tumor nor an optimal regimen of chemotherapy, radiotherapy or other therapy for the tumor has yet been established. It is desirable to establish them in the near future.

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