Malignant Paraganglioma of the Retroperitoneum with Lung Metastases: A 13-year Survivor After Radical Surgery

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We present a 23-year-old patient with extra-adrenal retroperitoneal paraganglioma with lung metastases who was successfully treated by complete removal of the tumour. Lung metastases were the first manifestation of the disease, and an abdominal computed tomography scan showed a large mass in the retroperitoneum with marked contrast enhancement. Angiography demonstrated a hypervascular mass with many feeding arteries, but vascular invasion was not apparent. The retroperitoneal tumour was resected completely followed by resection of lung metastases after 1 month of observation. The patient was disease free for 13 years after this radical surgery. The survival rate in patients with retroperitoneal paraganglioma with lung metastasis is low, and this case represents the longest surviving period reported in the literature. These tumours are usually large and located in the para-aortic region, and hence resection is sometimes challenging. We believe that a complete and meticulous surgical procedure is a prerequisite for long survival from this rare disease. [Asian J Surg 2007;30(1):75–9]

Key Words: extra-adrenal paraganglioma, retroperitoneal tumour, surgical treatment

Introduction

Paragangliomas (PGs) are rare tumours originally described as structural characteristic of neural crest origin. They are found in tissues such as the adrenal medulla, carotid bodies, organ of Zuckerkandl, and paraganglia of the sympathetic and parasympathetic neurons. PGs occur most commonly in head and neck lesions.4 Much less frequently, they are found in the retroperitoneum and it has been estimated that as much as 10% arise outside the adrenal gland.5 Distant metastasis to bones, lymph nodes and lungs has been reported as a unique feature of the metastatic spread of PGs.3 Although a recent long-term follow-up study showed a relatively indolent clinical course,3–6 the therapeutic modalities for patients with metastatic PGs, i.e. malignant PGs, are still controversial. Moreover, due to the rarity of retroperitoneal PGs,4,7 the clinical course and the treatment of choice are unclear. We present a patient with extra-adrenal retroperitoneal PG with lung metastases who was successfully treated by radical surgery including at the metastatic site. The patient has survived for 13 years without any sign of recurrence. Complete surgical removal of a tumour as well as metastases offers the only chance for cure, because no other therapeutic modality has been shown to provide long-term survival.

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Case report

A 23-year-old man was referred to The National Tokyo Medical Center (NTMC) because of abnormal shadows on chest X-rays. He had no remarkable symptoms. On admission, his blood pressure was 113/70 mmHg. Physical examination revealed a fixed and hard mass with slight tenderness in the left upper quadrant, protruding 4 cm below the costal margin. Laboratory data on admission were within normal ranges, including serum tumour markers (CEA, CA19-9) and catecholamines. Chest X-ray showed two round masses, 0.5 and 1.5 cm in diameter, in the middle lobe of the right lung (Figure 1). Computed tomography (CT) showed a low-density mass, 10 cm in diameter, with uneven contrast enhancement in the retroperitoneum dorsal to the pancreas and the spleen, and ventral to the left kidney and the abdominal aorta (Figure 2). No lymph node swelling and distant metastasis were detected except for the lesion in the right lung. On magnetic resonance imaging (MRI), the signal intensity of the primary tumour was higher than that of muscles on T1-weighted images (Figure 3), and remarkably higher on T2-weighted images; moreover, the tumour contained many flow voids. Selective angiography of the coeliac artery showed a hypervascular mass supplied by several feeding arteries originating from the splenic artery and the inferior phrenic artery (Figure 4A). In contrast, the right half of the mass was supplied mainly by the superior mesenteric artery (Figure 4B). A tumour stain appeared in the early arterial phase and lasted into the later phase as a dense capillary stain. Faint opacification of draining veins was also observed, and vascular involvement was not apparent. $[^{97}\text{Ga}]$ citrate and $[^{131}\text{I}]$ metaiodobenzylguanidine (MIBG) scans showed no abnormal accumulation.

Despite the metastases in the right lung, we chose surgical resection of the primary lesion for the initial treatment of this patient, which was performed in August 1992. The stomach, transverse colon, pancreas and spleen were found to be displaced ventromedially by a mass in the retroperitoneum. There was no significant adhesion to the ventral surface of the tumour, on which numerous tortuous vessels were observed. The hilum of the left kidney...
was tightly adherent to the left border of the tumour, and the left renal vein was buried in the ventral surface of the tumour. The tumour appeared to be separate from the left adrenal gland. It was difficult to identify the left renal artery even though we mobilized the left kidney from the retroperitoneum. Therefore, we decided to perform a combined resection of the left kidney. Resection of the tumour from the abdominal aorta was extremely difficult. We excised many fine feeding arteries originating from the abdominal aorta, sparing the coeliac artery and the superior mesenteric artery. We successfully removed the tumour without causing it to rupture.

The resected tumour (12.5 × 11.0 × 6.8 cm) was solid, with many tortuous vessels on its surface (Figure 5). The cut surface of the formalin-fixed tumour appeared brown-red, and vessels and fibrous septa were widespread. Macroscopically, tumour invasion into the kidney and the adrenal gland was not apparent, but renal vessels appeared to be involved in the tumour. Histologically, the tumour was an alveolar-like structure with many vascular septa (Figure 6). Tumour cells contained fine eosinophilic granules; cell mitosis and nuclear atypia were infrequent.

Immunohistochemical investigations were performed for α-smooth-muscle actin, S-100 protein and neuron-specific enolase, revealing only positive immunoreactivity to S-100 protein in the sustentacular cells. Electron microscopy demonstrated many mitochondria in the cytoplasm of the tumour cells, but no secretory granules were observed. These findings led to a histological diagnosis of nonchromaffin PG of the retroperitoneum.

The postoperative course was uneventful, and the patient was re-evaluated for the metastatic lesion. Lung metastases were unchanged and no other metastatic lesion was evident. The patient underwent a second operation for lung metastases 1 month after the first operation. A middle lobectomy of the right lung was successful, and

![Figure 4](image1.png) (A) Selective angiography of the coeliac artery shows a hypervascular mass supplied by several feeding arteries originating from the splenic artery and the inferior phrenic artery. (B) The right half of the mass is supplied mainly by the inferior mesenteric artery.

![Figure 5](image2.png) Combined resection of the left kidney was performed. The resected tumour (12.5 × 11.0 × 6.8 cm) is solid, with many tortuous vessels on its surface.

![Figure 6](image3.png) Tumour was an alveolar-like structure with many vascular septa. Mitotic structures and nuclear atypia are infrequent. Haematoxylin and eosin stain, reduced from 300×.
the patient was discharged 2 weeks later. The pathological diagnosis was metastatic PG. Thereafter, he received biannual follow-up evaluation at the NTMC. Thirteen years after the operation, the patient was alive without any sign of recurrence.

Discussion

Lung metastases were the first manifestation of the disease in the present case, and subsequent examination revealed a retroperitoneal tumour that was diagnosed histologically as PG. CT showed a large mass with marked contrast enhancement originating from the retroperitoneum and affecting the abdominal aorta. Usually, the tumours are closely related to the abdominal aorta, following the distribution of the aorticosympathetic chain. Retrospectively, MRI findings were rather typical for PGs: a mass with high signal intensity and containing many flow voids. Furthermore, angiography was very helpful in revealing the vascular supply as well as the extent of the invasion. Although an MIBG scan did not delineate the tumour in this case, in small tumours not seen on CT images, it may be helpful in determining whether the PGs are functional or nonfunctional. The preoperative diagnosis of retroperitoneal PGs is usually difficult if they are not functional. Histologically, the present case showed a typical alveolar appearance without any malignant cellular features, even though the patient had lung metastases. It is generally considered that malignant potential, local invasiveness and distant metastasis are not correlated with the histological appearance of the tumour. Immunohistochemically, the origin of the tumour was neurogenic, since sustentacular cells surrounding tumour cells were positive for S-100 protein. Electron microscopic examination failed to demonstrate any secretory granules in the cytoplasm of tumour cells. Instead, many mitochondria in the tumour cells were found, as also described by Oguma et al.

Retroperitoneal PGs are extremely rare, and few reports have described the natural history of the tumour. Sclafani et al reviewed 22 patients with extra-adrenal retroperitoneal PG. The male-to-female ratio was close to 1, and the median age was 42 years. Most patients complained of pain or the presence of a mass, and eight (36%) patients had functional tumours. They found that 11 of the 22 PGs (50%) metastasized to distant organs such as bone, liver, peritoneum, pelvis, ovaries, cervical lymph nodes and lungs. Two (18%) of the 11 patients had their first metastases more than 7 years after diagnosis, and hence a longer follow-up is needed in this disease. The malignancy rate of 50% reported by Sclafani et al is higher than that in all other previous studies (range, 22–44%). The malignancy rate of PG of the adrenal gland is about 10%, indicating that extra-adrenal retroperitoneal PGs tend to metastasize more frequently. Patients with retroperitoneal PGs have a long-term risk for recurrence; the disease-free 5- and 10-year survival rates are only 52% and 35%, respectively. The 5-year disease-free survival rate was 19% for unresected tumours and 75% for those that were completely resected. On the other hand, the 5-year survival rate of patients with metastatic disease dropped to 36%, with a median survival of 34 months. Mikhail et al reviewed 13 cases of malignant retroperitoneal PGs. The average age was 39 years (range, 12–68 years), predominantly male (69%). The most common sites of metastasis were bone, liver and lungs. The median survival of the patients with retroperitoneal PG with lung metastasis was 2 years (range, 7 months–11 years). The present case with lung metastases therefore represents the longest surviving period reported in the literature. Chemotherapy or radiotherapy may be used for palliation of symptoms related to recurrent or metastatic tumours, but their benefit in terms of prolongation of survival is yet to be elucidated.

The tumour resection required great care not to rupture the tumour and to ligate the substantial vascular supply. Resection is often challenging, as highly vascular tumours are large and located near vital blood vessels such as the aorta, vena cava, and renal and mesenteric vessels. A combined resection is inevitable when tumour invasion into the neighbouring organ is suspected. In the present case, we suspected tumour invasion into the kidney, ureter and the renal vessels. Fortunately, however, histological invasion into the neighbouring organs and lymph node metastasis were not apparent. It can be problematic deciding on a combined resection during operation. Since local lymph node involvement was reported in malignant retroperitoneal PG, en bloc resection is recommended. Because the tumour appeared indolent and a single metastatic site was operable, we performed a metastasectomy—resection of the middle lobe of the right lung after 1 month of observation—that
resulted in the complete removal of the tumour. We believe that complete and meticulous resection of the tumour was a prerequisite for the favourable outcome of this patient, although further follow-up will be needed to demonstrate a complete remission of the disease.

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**References**