

## Malignant Paraganglioma Arising from the Posterior Mediastinum: A Case Report and Review of the Literature

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### ABSTRACT

An unusual case of paraganglioma of posterior mediastinum occurred in a young adult with local recurrence and multiple distant metastasis. Because of its rarity, the determinants of prognosis factor between benign and malignant paraganglioma are uncertain. In this case, we investigated abnormalities of the p53 gene and *ras* gene mutations in tissues of primary and metastatic lesions. Neither abnormalities of p53 gene nor *ras* gene mutations were detected. The molecular approach is recommended as a means of clarifying the trend towards the malignancy of paraganglioma.

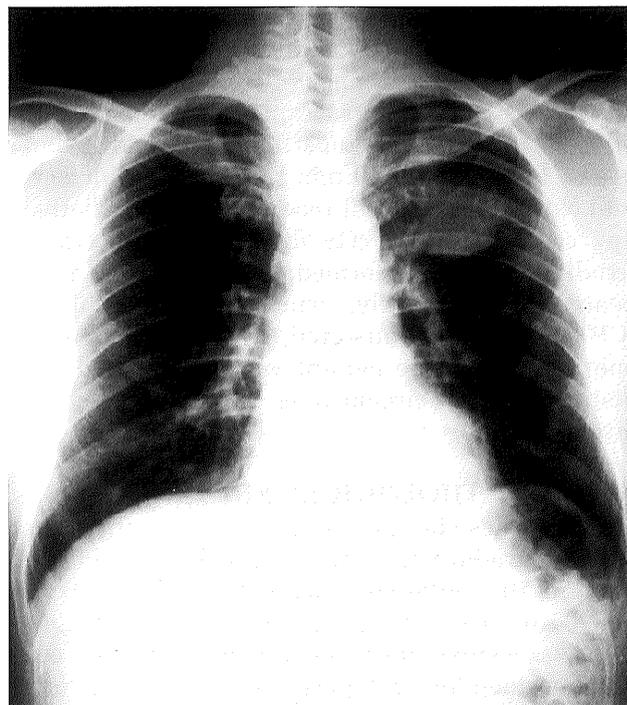
**Key words:** *Malignant paraganglioma, Posterior mediastinum, p53, ras*

Paragangliomas, especially mediastinal paragangliomas, are rare tumors arising from cells associated with the ganglia of the autonomic nerve system. Although posterior mediastinal paragangliomas are generally considered to be benign tumors from the histological and clinical aspects, some cases are documented to have exhibited metastases. In this report, a case of malignant paraganglioma originating in the posterior mediastinum is described and an update survey on paragangliomas is provided.

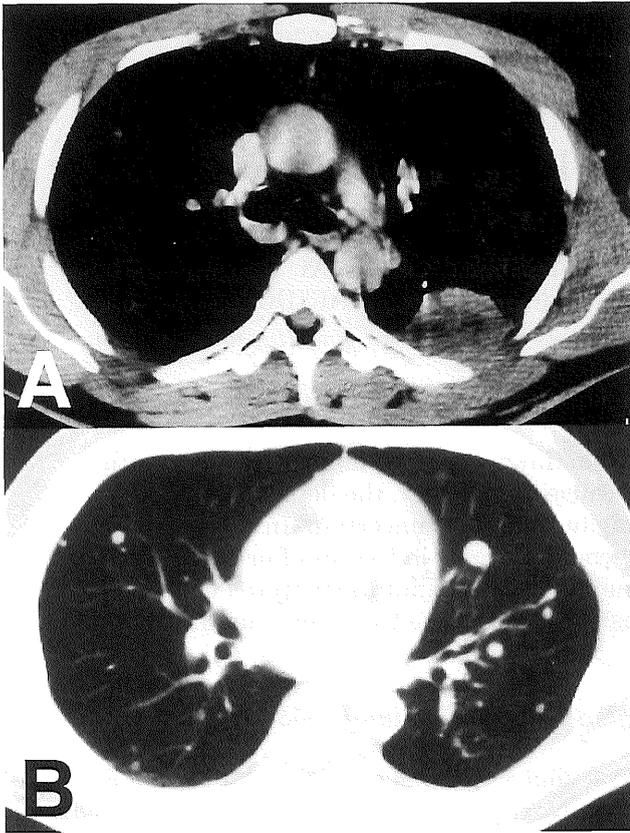
### CASE REPORT

A 40-year-old man, a smoker, presented with an abnormal chest roentgenogram. Six years previously, the patient was diagnosed with paraganglioma of the posterior mediastinum and a complete surgical resection was performed. Physical examination revealed no symptoms. Lymph nodes, liver, and spleen were not palpable. Blood and urine examinations were normal and urinary catecholamine were not elevated. A routine chest roentgenogram and computed tomography (CT) scan showed a sharply defined tumor located on the left chest wall and multiple small nodules of bilateral lung fields (Fig. 1, 2). Bone scintigrams showed an increased uptake in the 5th of thoracic vertebra. Needle aspiration cytology from the posterior chest wall mass showed consistency with paraganglioma. Chemotherapy (carboplatin + etoposide, carboplatin + mitomycin

C + vindesine) was carried out, but was not effective. Next year, the patient was re-admitted with weakness of the lower extremities. Magnetic resonance imaging (MRI) showed a metastatic tumor at the extradura of spinal cord in Th3 ~ Th6 and



**Fig. 1.** A routine chest roentgenogram showed a sharply defined tumor located on the left chest wall.

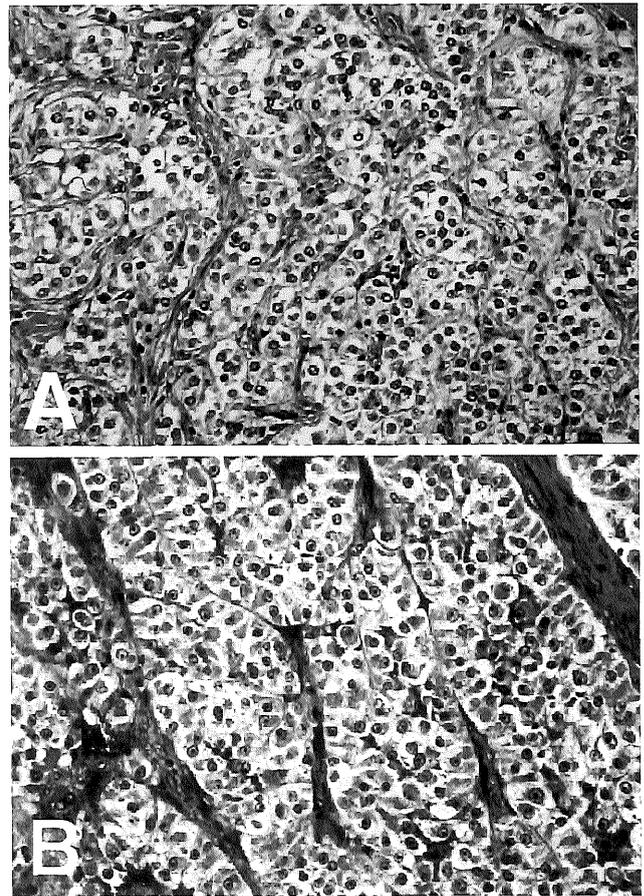


**Fig. 2.** Chest computed tomography showed multiple small nodules of bilateral lung fields.

surgical resection was performed. Two years later, the patient was re-admitted complaining of headache. CT scan and MRI showed multiple metastasis of the intracranial extradura, liver, bilateral kidney, retroperitoneum, and lymph nodes. For the 60 × 40 mm tumor of the intracranial extradura, surgical resection and a radiotherapy course of 5000 cGy directed to the cranial irradiation was performed; the headache disappeared. Subsequently, irinotecan hydrochloride (CPT-11) was administered, with no effect. After one more year, the patient was re-admitted with disturbance of consciousness and died three days later.

#### **PATHOLOGICAL FINDINGS**

The tissues obtained from the metastatic tumor at the extradura of spinal cord in Th3 ~ Th6 were fixed in 10% buffered formaldehyde. Hematoxylin and eosin staining showed that the nesting pattern was composed of monotonous neoplastic cells with eosinophilic cytoplasm with round to oval nuclei and that the cellular nests were separated by a fibrovascular area (Fig. 3B), similar to first resection of the posterior paraganglioma (Fig. 3A). Mitotic figures and vascular invasion were not identified. With an immunohistochemical technique, we studied chromogranin, neuron-specific enolase (NSE), and S-100 protein; all immunoreactivities were positive. Further, in order to investi-



**Fig. 3.** The tissues obtained by first resection of posterior paraganglioma (A) and obtained from metastatic tumor at extradura of spinal cord in Th3 ~ Th6 (B). Hematoxylin and eosin staining showed that the nesting pattern composed of monotonous neoplastic cells with eosinophilic cytoplasm with round to oval nuclei and the cellular nests were separated by fibrovascular area (A, B).

gate the relation between abnormality of the p53 gene or *ras* gene mutations with malignant paraganglioma, we examined the abnormalities of the p53 gene by polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE) analysis and *ras* gene mutations by PCR-restriction fragment length polymorphism (RFLP) analysis as described previously<sup>9)</sup>. However, neither abnormality of p53 gene nor *ras* gene mutations revealed primary and metastatic lesions. In order to evaluate proliferative activity, we studied the Ki-67 labelling index by immunohistochemical technique; both primary and metastatic lesions showed less than 1.0% labelling index.

#### **DISCUSSION**

Mediastinum paragangliomas are rare tumors originating from cells associated with the paraganglia of neuroendocrine cells. Its rarity was confirmed in a previous report<sup>9)</sup> in which only two paragangliomas out of 215 primary tumors of the mediastinum were found. As regards the classifi-

cation of extra-adrenal paragangliomas, Glenner and Grimley<sup>6</sup> proposed a classification from anatomical distribution, histochemical features, and innervation based on the extra-adrenal paraganglia. According to these criteria, mediastinum paragangliomas were classified into two anatomic locations: aorticopulmonary paragangliomas (associated with the branchiomic group of paraganglia anatomically related to the pulmonary artery and aortic arch) and aortico-sympathetic paragangliomas (associated with the sympathetic chain). Paragangliomas originating from the anterior component (aorticopulmonary paragangliomas) were more frequent than those from the posterior component (aortico-sympathetic paragangliomas)<sup>20</sup>. Occasionally, there were functional tumors in mediastinum paragangliomas, in which serum and urine catecholamines were elevated. Further, mediastinum paragangliomas also tend to be multicentric. Odze et al<sup>19</sup> reported that 41% (17 out of 41) reported benign cases of posterior mediastinal paraganglioma had functional manifestations. Herrera et al<sup>7</sup> also reported that 71% (10 out of 14) of mediastinum paragangliomas had functional manifestation and 43% (6 out of 14) were multicentric.

It is difficult to diagnose mediastinum paragangliomas because of the difficulty of obtaining histological samples before surgical resection. If a tumor is catecholamine-producing, the elevation of urinary catecholamine is useful for diagnosis. Thus, many imaging modalities, such as chest tomography, CT, MRI and angiography, have played major roles in detecting tumors and have assisted diagnosis. MRI is especially useful for determining the overall tumor extent by enabling various direction images. Moreover, MRI safely provides information on the vascularity of tumor as flow void, which represents very fast blood flow in its vessels<sup>24</sup>. Thus, the contrast of soft tissues and vessels is obtained with MRI. However, there are multicentric or malignant cases in paragangliomas<sup>7,19</sup>, and the above-mentioned technique may fail to detect a tumor at the site of the extra-adrenal or metastatic lesion. The mIBG scan can provide an additional method of detecting unusual or unexpected locations of paraganglioma<sup>14,23</sup>, even if they are not functional tumors<sup>11</sup>.

As histological features, paragangliomas are characterized by a nesting growth pattern of chief cells and sustentacular cells resting within a well vascularized stroma<sup>6</sup>. However, since carcinoid tumors display similar histologic features, it is important to distinguish especially, those from intrathoracic tumors. Moran et al<sup>16</sup> indicated that the presence of a positive immunohistochemical reaction for keratin would favor a feature of carcinoid tumors and might thus serve as a distinguishing feature from paragangliomas. The presence of melanin pigment in paragangliomas is

relatively uncommon, and important in separating those from malignant melanoma. This finding does not alter the behavior of the neoplasm<sup>15</sup>. The usefulness of immunohistochemical staining, such as chromogranin and S-100 protein is reported<sup>15</sup>.

Therapeutic options include surgery, chemotherapy, and radiotherapy. The first choice of treatment for mediastinal paragangliomas is, of course, surgical resection. However, malignant cases with locally advanced (macroscopic invasion and/or lymph node metastasis) or distant metastasis receive chemotherapy and/or radiotherapy. Chemotherapy had been reported to show poor response<sup>12,13</sup>, and in our case carboplatin based chemotherapy also revealed poor response as reported previously<sup>10</sup>. However, Patel et al<sup>21</sup> recently mentioned that combination chemotherapy of cyclophosphamide, doxorubicin and dacarbazine was effective in patients with paraganglioma and should be considered for patients with unresectable or metastatic disease. Definitive radiotherapy could succeed in showing the growth of tumor and has been described to be partially efficacious<sup>12,17,22</sup>. Verniers et al<sup>26</sup> demonstrated that radiotherapy was an effective treatment modality without mutilation or severe late morbidity compared with the results of surgery in head and neck lesion. Moreover, Massey et al<sup>13</sup> reported that radiotherapy would be effective for pain relief of bone metastasis. Our case also indicated that radiotherapy would be effective for pain relief of intracranial metastasis. In addition, <sup>131</sup>I-MIBG is reported to be successful therapeutic use in malignant paragangliomas of mediastinum<sup>4</sup>. Furthermore, a recent report has suggested that octreotid, a somatostatin analogue, could be useful in the treatment of malignant paraganglioma at a certain stage of the disease<sup>25</sup>.

Although an exact prognosis of mediastinum paraganglioma is uncertain because of its rarity, it is generally considered to be benign tumor from the histological and clinical aspect if complete surgical resection is performed<sup>12</sup>. Nevertheless, there are some cases which showed the presence of either local invasion or distant metastasis. In fact, locally advanced paraganglioma of posterior mediastinum destroyed the vertebrae with spinal cord compression<sup>18</sup>. In addition, there is a 26.6% incidence of metastasis in anterior and middle mediastinum paragangliomas<sup>12</sup> in comparison with 14.6% in the posterior<sup>19</sup>, and the metastatic lesion occurs more frequently in lung and bone<sup>19</sup>. Herrera et al<sup>7</sup> reported that 43% (6 out of 14) of mediastinal paragangliomas revealed a malignant course. However there are no reliable prognostic factors, and clinicopathologic features such as necrosis, hemorrhage, mitotic activity, and vascular invasion are not valid determinants of malignant behavior<sup>19</sup>. Some investigators suggest that local invasion<sup>7,16,19</sup>, DNA aneuploid pattern based

on flow cytometric analysis<sup>7)</sup>, proliferating cell nuclear antigen<sup>5)</sup> or the absence of S-100 positive sustentacular cells<sup>1)</sup> are important factors in aggressive behavior of paragangliomas. Sufficient follow-up is recommended even if complete surgical resection is performed.

In spite of attempts towards a molecular approach in familial paraganglioma<sup>2)</sup>, there have been few molecular examinations for extra-adrenal paraganglioma. In this case, we investigated abnormalities of p53 gene and *ras* gene mutations in both primary and all metastatic lesions, but neither abnormality of p53 gene nor *ras* gene mutations were detected (data not shown). Hirose et al<sup>8)</sup> examined aberrant p53 expression in olfactory neuroblastoma, most of which formed a morphologic spectrum intermediate between paraganglioma and neuroblastoma. Although, abnormalities of the p53 in 62% (16 out of 26) of tumors they were detected, there was no significant correlation between abnormalities of the p53 and survival rates. However, only immunohistochemical analysis was employed and statistical examination was performed in only intermediate cases. Yoshimoto et al<sup>27)</sup> reported a relatively high incidence of p53 gene mutations in multiple and malignant pheochromocytomas, but not in benign solitary cases. We think that molecular approach should be encouraged in order to make clear the trend toward malignancy of paraganglioma.

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