A Case of Cardiac Malignant Paraganglioma

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ABSTRACT —— ***Background.*** Primary mediastinal paraganglioma is rare, accounting for only 2% of a large series of neural tumors of the thorax. ***Case.*** A 73-year-old Japanese man was hospitalized because of dyspnea, fever, general fatigue and cough. Chest X-ray and, CT and MRI of the chest revealed a tumor 14 cm in diameter which had invaded the pericardium, the inferior vena cava, the diaphragm, and the left atrium. The patient died of heart failure. At autopsy, the tumor was found to have originated from the outside of the posterior atrium and to have invaded the mid-mediastinum without distant metastasis. Histologically, tumor cells were large-polymorphous and showed nuclear pleomorphism. Immunohistochemical staining showed that tumor cells were positive for synaptophysin and NSE, and electron microscopic examination revealed neurosecretory granules of the epinephrine type in the cytoplasm. Therefore, this tumor was diagnosed as cardiac malignant paraganglioma. ***Conclusion.*** An autopsy case of cardiac malignant paraganglioma is reported. Immunohistochemical staining and electron microscopy can be helpful particularly when light microscopic findings are atypical. (*JJLC.* 2004;44:241-244)

KEY WORDS —— Paraganglioma, Heart, Immunohistochemistry, Electron microscopy, Neurosecretory granule

INTRODUCTION

Paraganglioma is a tumor resulting from neoplastic proliferation of paraganglionic cells. In the thorax, paraganglioma may present as chemodectoma or pheochromocytoma (functioning paraganglioma). Most primary mediastinal paraganglioma arise in the ascending or transverse portions of the aortic arch, adjacent to the heart, pericardium (aorticopulmonary paraganglioma) or the posterior mediastinum (aorticosympathetic paraganglioma).[1] Less than 2% of all pheochromocytoma occur in the thorax. Here, we report a case of primary cardiac malignant paraganglioma.

CASE REPORT

A 73-year-old Japanese man was referred to our hospital because of progressive dyspnea and fever lasting for 10 days, general fatigue and cough for two months with back pain. He suffered from dyspnea and occasionally

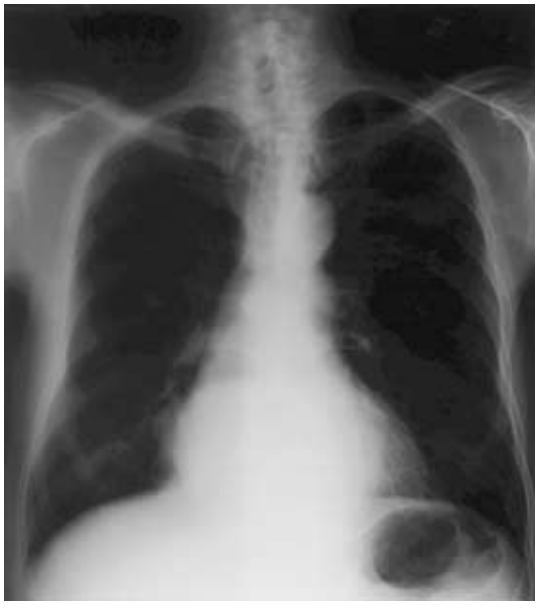

Figure 1. Chest X-ray showing a tumor behind the heart. Posteroanterior radiograph.

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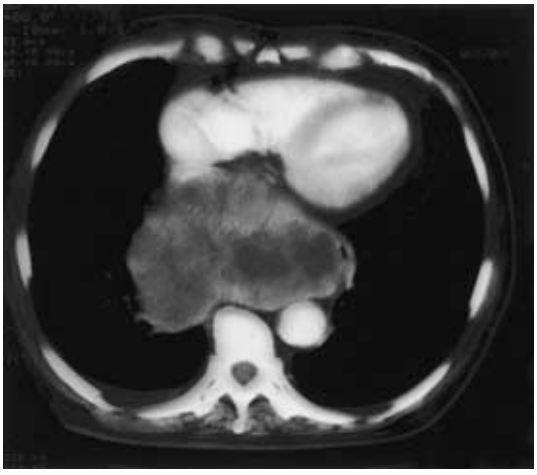

Figure 2. Contrast-enhanced CT showing obstruction of the inferior vena cava and the lateral displacement of the esophagus.

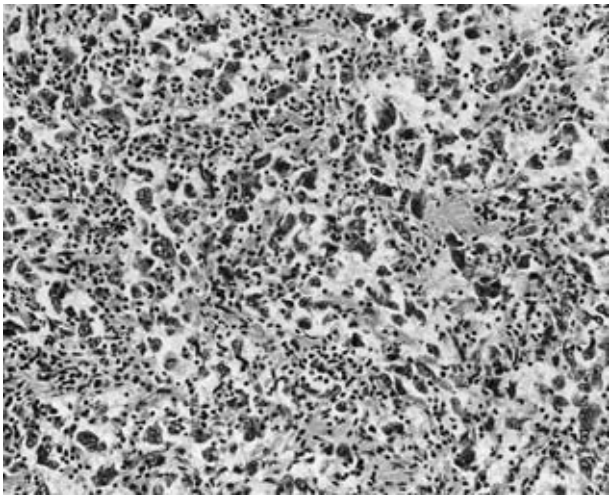

Figure 4. Tumor cells are large-polymorphous with a high nuclear-cytoplasmic ratio and prominent nucleoli. The nuclei of tumor cells showed polymorphism in nuclear size, shape, and chromaticity (H.E. stain, ×200).

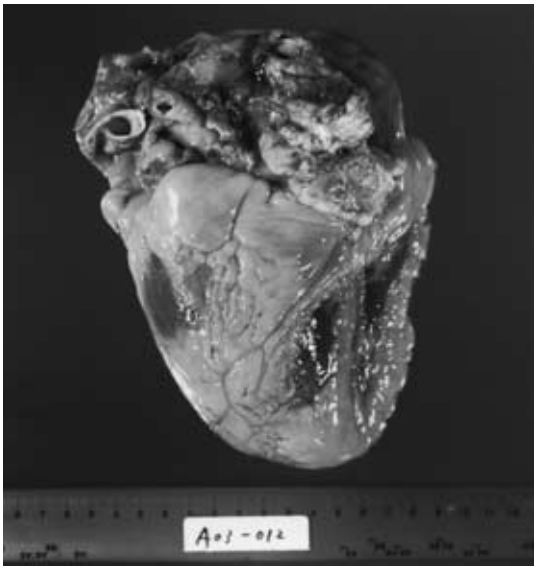

Figure 3. Macroscopic findings: tumor adherence to the atria and invasion of the pericardial sac.

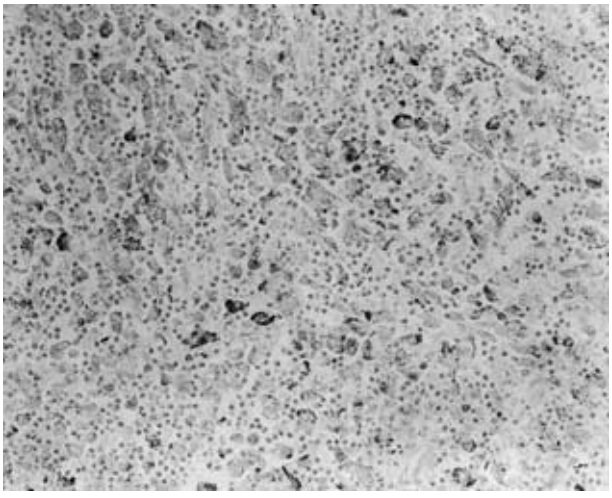

Figure 5. Immunohistochemical detection of synaptophysin (ABC method, ×200).

vomited undigested food. He had recently lost 5 kg in weight. He had a 30-year history of smoking and of hypertension as well as diabetes. He had no family history of hypertension or abnormal skin pigmentation. Blood pressure was 92/56 mmHg, temperature was 38℃. The patient had to remain in a sitting position or lie on his right side because he was unable to tolerate a supine position due to dyspnea. Both his lower legs and feet showed marked edema.

Laboratory values were as follows: hemoglobin, 7.5 g/dl; hematocrit, 24.3%; red blood cell count, 2,360,000/μl; white blood cell count, 9,100/μl (80% neutrophils, 11% lymphocytes, 8% monocytes, and 1% eosinophils); serum protein, 7.2 g/dl (albumin, 44.8%; α_1-globulin, 6.6%; α_2-globulin, 17.2%; β-globulin, 12.6%, γ-globulin, 18.8%), lactate dehydrogenase, 265 U/dl; carcinoembryonic antigen, 1.7 ng/ml; carbohydorate antigen 19-9, 21.4 U/ml; squamous cell carcinoma antigen, $<$0.5 ng/ml; neuron-specific enolase, 6.5 ng/ml. A specimen of arterial blood gas in room air showed that the PaO_2 was 67.7

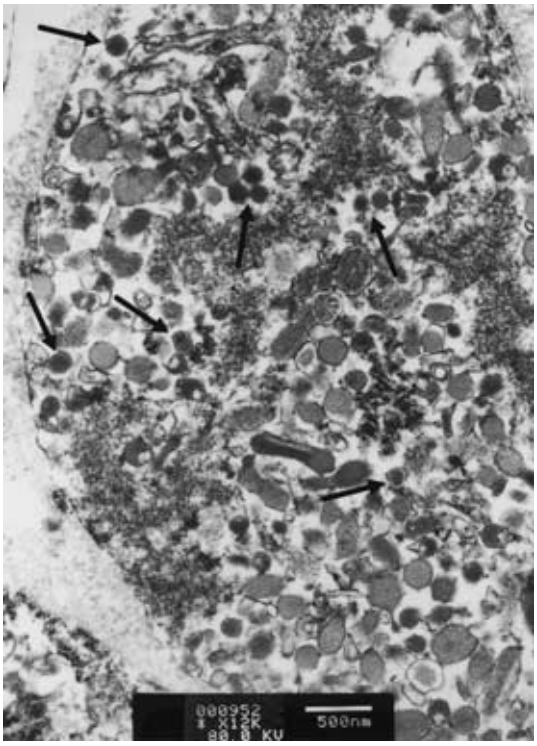

Figure 6. Electron micrograph of tumor cell showing dense-core granules of epinephrine type (arrows).

torr, $PaCO_2$ 40.4 torr, and the pH 7.45.

A chest X-ray revealed a mass behind the heart (Figure 1). Chest CT revealed a mediastinal tumor of 14 cm in diameter which invaded the pericardium, the inferior vena cava and the diaphragm and distorted the heart (Figure 2). The MRI scan of the heart and the echocardiogram showed that the tumor invaded the left atrium and the inflow route to the left ventricle.

The patient deteriorated rapidly and died of heart failure one month after admission.

Autopsy findings: The tumor arose from the outside of the wall of the atria and indented the atrium from the pericardial surface (Figure 3). It had invaded the mediastinal lymph nodes, right lung, both main bronchi, diaphragm, and inferior vena cava. There were no distant metastases and no other malignant tumors. The weight of the tumor was 680 grams, measuring 14×12×10 cm, and it was partially demarcated by a capsule. On cross sections, the tumor revealed yellowish-grayish tissue with numerous foci of necrosis. Histopathologically, the tumor cells were large and polymorphous and showed nuclear pleomorphism with epithelioid arrangement and inflammatory infiltrates (Figure 4).

Immunohistochemical staining for synaptophysin (Figure 5) and neuron-specific enolase (NSE) were positive, but CEA, cytokeratin 5/6, cytokeratin 19, vimentin, SMA, S-100 protein, LCA, CD56, CD68, and HHF35 were negative. The Ki-67 labeling index was 18.7%. Electronmicroscopically, tumor cells contained dense-core neurosecretory granules in the cytoplasm, ranging between 100 and 250 nm (Figure 6). Consequently, the pathologic diagnosis was primary cardiac malignant paraganglioma.

DISCUSSION

Mediastinal paraganglioma is a rare tumor. It accounted for only 2% of a large series of neural tumors of the thorax.[2] The aorticopulmonary paragangliomas are subdivided into cardiac and extra-cardiac paragangliomas. Cardiac paragangliomas are reported to arise from the posterior left atrium or the atrial septum. In this case, the tumor seemed to originate from the outside of the posterior left atrium and to invade the mid-mediastinum. The heart showed left ventricular hypertrophy which might be a result of excess catecholamine secretion along with diabetes and hypertension. Histologically, paragangliomas have a nesting pattern (Zellballen), composed of areas of fairly uniform cells separated by sclerotic, often vascular stromal trabeculae.[2] However, the pattern of the tumor may vary considerably, and tumors showing spindle cell features and granular cell morphology have been reported, although less frequently.[3] In other immunohistochemical studies, chromogranin was positive, approximately 50% of cells were neurofilament protein-positive, and keratin was negative. Immunohistochemical staining for S-100 protein was positive in the sustentacular cells, but was negative in the chromaffin cells.[3,4] In the present case, light microscopically, tumor cells did not have the appearance of typical paraganglioma. However, the results of immunohistochemical staining and the presence of ultrastructurally verified neuroendocrine granules indicated that this tumor was neuroendocrine in nature.

The incidence of metastasis of this type of tumor has been estimated at 13%.[5] Because of the absence of distant metastasis, differential diagnosis between benign and malignant paraganglioma is difficult. In some reports, cellular atypia, increased mitotic activity and vascular and capsular invasion are not reliable criteria for malignant paraganglioma,[6,7] but extensive local and vas-

cular invasion are accepted as a criterion for malignancy according to the Armed Forces Institute of Pathology (AFIP) classification. Malignant paragangliomas are larger and more necrotic, and have a higher mitotic index compared with those of benign paragangliomas. Malignant paragangliomas also have fewer neuropeptides.[8] In a recent report, Ki-67 and hTERT were shown to be useful for differentiation between malignant and benign pheochromocytomas and paragangliomas.[9] In the present case, the tumor was large and necrotic, invaded adjacent structures extensively, and showed cellular pleomorphism. Thus, the diagnosis of malignant paraganglioma was made.

In cell culture, PC12, derived from a rat pheochromocytoma, can be induced to neuronal differentiation by the K-ras oncogene,[10] but it is rare to find ras activation via point mutations in human adrenal neoplasms.

In previous reports, cardiac paraganglioma patients have signs or symptoms of excess catecholamine secretion, cardiomegaly, retrosternal pain, hemoptysis, palpitations, and murmur. Measuring the catecholamines or their metabolites is useful for diagnosis of pheochromocytomas and functioning paragangliomas. Radioiodine metaiodobenzylguanidine (MIBG) scintigraphy shows increased activity in paraganglioma,[11] and the combination of MIBG scintigraphy and CT is a good tool for identifying extra-adrenal paraganglioma and the planning of surgical treatment.[12] Alpha- and beta-adrenoreceptor blocking agents are administered to counteract the signs and symptoms of excess catecholamine secretion. Surgical treatment such as cardiopulmonary bypass, human cardiac explantation and autotransplantaion have been attempted following resection of tumor.[13,14] However, this type of tumor is often unresectable because of strong adherence and direct involvement of vital organs.[11] There have been some reports of systemic chemotherapy using cyclophosphamide, vincristin and dacarbazine (CVD) with response rates from 50-57%.[9] The effect of external irradiation remains uncertain, but in some cases, adjuvant radiation therapy may be beneficial.[15]

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