A patient with malignant cardiac pheochromocytoma with bone metastasis of the iliac bone is described. The primary tumor was located between the pulmonary trunk and the left atrium, while metastatic lesions were found in the iliac bones. Treatments with antihypertensive agents, \( \alpha \)-methylparatyrosine, and combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine partially improved the patient's symptoms, catecholamine levels, and the metastatic lesion of the iliac bones. However, the primary tumor in the heart progressively increased in size and the patient died of disseminated intravascular coagulation and other various complications about 4 years after the diagnosis of the disease.

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Introduction

Approximately 10% of pheochromocytomas originate from extraadrenal tissues. Although most come from paraaortic ganglia and are localized in the retroperitoneum and posterior mediastium, pheochromocytoma rarely originates from the juxtacardiac tissues. Since the earliest reports by Besterman et al (1) and Wilson et al (2) in 1974, at least 45 cases have been documented (3). Only two cases, however, have been reported to be definitely malignant with bone metastasis (4, 5). While the outcome of the surgical intervention for the benign cardiac tumor has been quite satisfactory despite the difficult anatomical localization (6), the prognosis of cases with malignant pheochromocytoma is poor (7).

Recently, we treated a patient with cardiac pheochromocytoma with bone metastasis of the iliac bone, in which treatments with an antihypertensive agent, \( \alpha \)-methylparatyrosine (\( \alpha \)-MPT), and intense chemotherapy with a combination of cyclophosphamide, vincristine, and dacarbazine (8) were partially effective in improving the symptoms and the metastatic lesion of the iliac bone in addition to reducing catecholamine levels. However, the primary tumor of the heart showed a progressive enlargement and the patient died of disseminated intravascular coagulation 4 years later.

Case Report

A 59-year-old woman with cardiac pheochromocytoma was admitted to the Tokyo Women's Medical College Hospital in 1991. The patient was previously described as a case report by Iwama et al (9). Briefly, the patient began to experience palpitation and effort-dependent dyspnea since 1986. The patient was admitted to the Tokyo Metropolitan Bokutou Hospital in 1988 because of loss of body weight and lumbago. She had episodes of sweating and a sudden increase in blood pressure to 210/140 mmHg with tachycardia. Chest X-ray examination showed prominence of the upper left heart border. Plasma and urinary catecholamine levels were significantly elevated: plasma norepinephrine, 32.6 ng/ml; urinary norepinephrine excretion, 4,033.3 \( \mu \)g/day; urinary normetanephrine excretion, 20,370 ng/mg creatinine; urinary metanephrine excretion, 1,664.4 ng/mg creatinine. Computed tomographic (CT) scan of the chest visualized a soft tissue mass behind the root of the aorta just below the pulmonary trunk. Iodine-labeled metaiodobenzylguanidine (\( ^{131}\)I-MIBG) scintigraphy demonstrated a moderate accumulation in the heart and a more intense accumulation in both sides of the iliac bone (Fig. 1), findings compatible with the diagnosis of malignant cardiac pheochromocytoma. Pathological diagnosis of paraganglioma was confirmed by biopsy of the left iliac bone.

After medication with a-blocker, prazosin (4 mg/day), paroxysmal hypertension disappeared. From the Department of Medicine, ""Department of Surgery, Institute of Clinical Endocrinology, **the Department of Radiology, Tokyo Women's Medical University, Tokyo and *the Department of Medicine, Tokyo Metropolitan Bokutou Hospital, Tokyo Received for publication November 6, 1997; Accepted for publication August 5, 1998
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therapy using dacarbazine and α-MPT (500 mg/day), urinary metanephrine (527 ng/mg creatinine) and normetanephrine (3,549.8 ng/mg creatinine) concentrations showed a significant decrease. The patient was in a generally good condition for about 2 years. At the end of 1990, the patient began to suffer from chest pain, palpitation, general fatigue, and vertigo. Since there was no significant change in the urinary concentrations of catecholamine metabolites and possible adverse effects of α-MPT and/or dacarbazine were not completely excluded, those medications were withdrawn, which however was followed by a significant increase in urinary catecholamine levels and worsening of symptoms (Fig. 2).

The patient was referred to the Tokyo Women’s Medical College for a further evaluation and management in August 1991. She was 150 cm tall and 44 kg in weight. Her blood pressure was 118/74 mmHg and heart rate was 112 bpm with normal sinus rhythm. Physical examinations disclosed apical systolic murmur and tumor on the left iliac crest. Urinalysis was normal. By complete blood cell count, slight anemia (hematocrit (Ht): 31.6%; hemoglobin (Hb): 10.3 g/dl), leucocytosis (10,400/mm³), and thrombocytosis (49.7x10⁴/mm³) were found. Serum potassium level was slightly decreased (3.3 mEq/l) and serum alkaline phosphatase was significantly elevated (364 IU). Other major findings including electrolytes, renal function, and liver function were all within normal limits.

Endocrine examination showed an extremely elevated plasma norepinephrine (13.0 ng/ml), urinary metanephrine (603.7 ng/mg creatinine) and normetanephrine (12,354 ng/mg creatinine) levels. Electrocardiogram showed left ventricular hypertrophy. Chest X-ray examination showed slight prominence of the left heart border. CT-scan of the chest showed a 6-cm mass with a central low density area between the aorta and pulmonary trunk (Fig. 3A), which was confirmed by magnetic resonance images (data not shown). CT-scan of the pelvis showed an osteolytic lesion with a surrounding soft tissue mass of the left iliac bone (Fig. 4A), and osteosclerotic change of the right iliac bone (Fig. 5A).

After re-administration of α-blocker (doxazosin 4–6 mg/day), and α-MPT (750–1,000 mg/day), the symptoms of the patient became improved and the urinary normetanephrine showed a significant decrease (Fig. 2). Subsequently, chemotherapy with a combination of cyclophosphamide (750 mg/m² BSA on day 1), vincristine (1.4 mg/m² BSA, on day 1), and dacarbazine (600 mg/m² BSA on days 1 and 2) were repeated every 3 to 4 weeks in addition to antihypertensive therapy with propranolol (20–30 mg/day), diltiazem (90 mg/day), and prazocin (4–1 mg/day). The patient became free of the symptoms including palpitation and chest pain and urinary norepinephrine and its metabolites showed a significant decrease after March 1992 (Fig. 2). In addition, in contrast to the primary tumor of the heart, which showed a progressive enlargement (Fig. 3B), the metastatic osteolytic lesion of the left iliac bone with surrounding tumor mass (Fig. 4B) and the osteosclerotic change of the right iliac bone (Fig. 5B) showed a partial improvement. There was no specific adverse effect of the chemotherapy except for nausea on the first day of the chemotherapy.

The patient began to suffer from appetite loss and vomiting at the end of September 1992. Subsequently, hypovolemic shock, hypotension, disseminated intravascular coagulation, aspiration pneumonia, and sepsis developed. All efforts to control blood pressure, sepsis, and bleeding tendency were not
Figure 2. Clinical course of a patient with malignant cardiac pheochromocytoma. U-NM: urinary normetanephrine, U-M: urinary metanephrine, U-NE: urinary norepinephrine, U-E: urinary epinephrine, D: Dacarbazine, α-MPT: α-methyl paratyrosine, CVD: combined chemotherapy with 700 mg cyclophosphamide and 1.3 mg vincristine on day 1 and 570 mg dacarbazine on days 1 and 2, Arrow: admission to the Tokyo Women’s Medical College Hospital.

successful. The patient died 2 weeks after the admission.

Discussion

Although approximately 45 cases of cardiac pheochromocytoma have been reported (3), most of the cases were reported to be cured or showed improvement after resection of the tumor. In contrast, the prognosis of the two cases with malignant cardiac pheochromocytoma have been reported to be poor (4, 5). In the present case reported as the third case of malignant pheochromocytoma originating from heart, surgical treatment was not indicated due to multiple bone metastases.

Much controversy exists regarding the treatment of malignant pheochromocytoma (10). Surgical treatment has almost no role in the management of metastatic tumor, except when one or two isolated metastases are found in lung, liver, or brain (10). Although external beam teleradiotherapy has been reported to provide good initial palliation for bone pain in skeletal metastases, the effectiveness is limited in a minority of cases and temporary, requiring repeated courses of the irradiation (10). Shapiro et al (10, 11) reported the effectiveness of 131I-MIBG therapy in 18 patients out of 28 patients: 8 patients with improvement in the tumor size and catecholamine levels and 10 patients with suppression of the tumor growth. However, a more recent study (7) did not necessarily support the usefulness of the therapy. In addition, the effect depends on the intense uptake and prolonged retention of 131I-MIBG. Although the present case was positive in the 131I-MIBG scintigraphy, the uptake ratio was ascertained not to be sufficient to treat with large doses of the agent.

Averbuch et al (8) reported the usefulness of the combined chemotherapy of three regimens: cyclophosphamide, vincristine, and dacarbazine, showing reduction of tumor size in about 60% and a decrease in catecholamine levels in about 80% in a study of 14 patients with malignant pheochromocytoma. We therefore introduced the combined chemotherapy in addition to α-MPT (12). After several course of the combined chemotherapy, improvement of the metastatic tumor of the bone in addition to the decrease of the urinary catecholamine excretions were noted. However, whether these effects could simply be
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Figure 3. CT scan of the chest of a patient with malignant cardiac pheochromocytoma. Arrows represent the mass lesion with a central low density area between the aorta and pulmonary trunk before (A. August 1991) and after (B. June 1992) the combined chemotherapy. The size of the primary cardiac tumor increased progressively.

Figure 4. CT scan of the pelvis of a patient with malignant cardiac pheochromocytoma. Arrows represent the osteolytic lesion of the left iliac bone before (A. August, 1991) and after (B. June, 1992) the combined chemotherapy. The iliac bone metastatic lesion was significantly decreased after the combined chemotherapy.

Figure 5. CT scan of the pelvis of a patient with malignant cardiac pheochromocytoma. Arrows represent the osteosclerotic lesion of the right iliac bone before (A. August, 1991) and after (B. June, 1992) the combined chemotherapy. The metastatic lesion in the iliac bone was significantly decreased after the combined chemotherapy.

attributed to the combined chemotherapy remains unclear. Since α-MPT has been shown to reduce tumor size in some of the cases treated (13), the possibility that the decrease in the tumor size and urinary catecholamine levels were due to α-MPT can not be completely excluded.

It should be noted that the urinary catecholamine level was decreased despite the significant enlargement of the primary tumor of the heart. One possibility is that the improvement of the metastatic lesion of the iliac bones, where 131I-MIBG was more prominently uptaken than the primary tumor of the heart and therefore assumed to be the major site of catecholamine production, was closely related to the decrease in the urinary catecholamine levels. Another possibility is that the primary tumor of the heart began to produce a lesser amount of catecholamine through changes of the phenotype during the growth and

Figure 4. CT scan of the pelvis of a patient with malignant cardiac pheochromocytoma. Arrows represent the osteolytic lesion of the left iliac bone before (A. August, 1991) and after (B. June, 1992) the combined chemotherapy. The iliac bone metastatic lesion was significantly decreased after the combined chemotherapy.
aggraviation of the tumor cells.

The chemotherapy was partially effective in the metastatic lesion but not in the primary tumor in the heart. Similar phenomenon has been described in the chemotherapy of other types of malignant tumors (14–16). Heterogeneity of the cell component in the cancer tissue as well as the difference in the tissue distribution of the agents between the primary tumor and the metastatic lesion have been implied to be closely involved in the phenomenon (17–19). Since cancer tissue consists of highly heterogeneous type of cells, the sensitivity to the chemotherapy of the metastatic lesion could be different from the primary tumor if cells which are sensitive to chemotherapy develop metastatic lesions (20).

The effect of various treatments including chemotherapy on bone metastasis has not been completely satisfactory (21–24). In the present case of cardiac malignant pheochromocytoma, although the combination of chemotherapy, α-MPT, and various antihypertensive agents resulted in a partial remission of the symptoms, (urinary catecholamine levels, and bone metastasis). The primary tumor of the heart showed a progressive aggravation and the patient died of various complications, indicating that the cure of malignant pheochromocytoma awaits further development of new treatment.

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References