We report a case of malignant pheochromocytoma recurred after debulking surgery. A 17-year-old male patient visited our hospital for right flank pain. He had not experienced palpitations, headache, sweating or weight loss. Level of urinary catecholamine and its metabolite increased above normal values and abdominal computed tomography showed a huge right adrenal mass. One month after debulking surgery, anterior mediastinal and multiple liver metastases were found. These tumors had no response to two conventional regimens of combination chemotherapy (cyclophosphamide, vincristine, dacarbazine and anthracycline; and etoposide and cisplatin). We treated the patient with sunitinib, a multiple tyrosine kinase inhibitor. The tumor showed very good metabolic response to the therapy. In patient with malignant pheochromocytoma, sunitinib might be one therapeutic strategy for malignant pheochromocytomas.

Key words: malignant pheochromocytoma – sunitinib – combination chemotherapy

INTRODUCTION

Pheochromocytomas are rare tumors arising from chromaffin tissue of the adrenal medulla. This tumor type is estimated to occur at an annual rate of 2–8 per 1 million persons. A common sign of a pheochromocytoma is paroxysmal or sustained hypertension and approximately 0.1% of hypertensive patients harbor this tumor (1). The clinical presentation is protean; for example, headache, sweating attacks, palpitations, panic attacks, abdominal pain, constipation, dilated cardiomyopathy and erythrocytosis. The diagnosis is based on the documentation of catecholamine excess by urinary or plasma tests and localization of the tumor by imaging modalities such as computed tomography (CT) and magnetic resonance imaging, or radionuclide imaging such as 131I-metaiodobenzylguanidine (MIBG) or 18F-dopa (or dopamine) positron emission tomography (PET). Approximately 5–10% of pheochromocytomas are malignant. Typical histological criteria of malignancy such as cellular atypia, presence of mitoses and invasion of vessels or adjacent tissues do not reliably identify the tumor’s capacity for metastasis. The diagnosis is established clinically in the presence of distant metastases mainly to the liver, lymph nodes, lung and/or bone (1,2).

Surgical resection is the treatment choice for resectable malignant pheochromocytomas. However, the prognosis is poor because of frequent local recurrence or metastases. For rapidly progressive metastatic disease or negative 131I-MIBG scan, chemotherapy should be considered as a first-line therapy (3). Among the various chemotherapeutic regimens, CVD (cyclophosphamide, vincristine and dacarbazine) with or without anthracycline or EP (etoposide and cisplatin) has been applied with varying success rates (4–6). However, the response has been generally brief and eventually the majority of the patients failed to respond to combination therapies.
cytotoxic chemotherapy. We report a case of malignant pheochromocytoma refractory to cytotoxic chemotherapy, which responded favorably to sunitinib.

CASE REPORT

In August 2007, a 17-year-old male visited our hospital with worsening right flank pain, upon deep inspiration, which had first appeared 1 week earlier. He had not experienced any palpitations, headaches, sweating or weight loss, and there was nothing significant in his past medical and familial history. On initial examination, his blood pressure was 131/78 mmHg, heart rate was 101 bpm and body temperature was 36.1°C. He was alert, his respiration was clear and there were no abnormal respiratory sounds. His heartbeat was regular and without murmur. Abdominal examinations showed no significant signs except for tenderness on the right costovertebral angle.

Electrocardiography showed sinus tachycardia. Peripheral complete blood count and electrolytes were: white blood cell count 7000/mm³, hemoglobin 11.8 g/dl, hematocrit 37.2%, platelets 442 000/mm³, sodium 137 mEq/l and potassium 4.5 mEq/l. Renal and liver function tests and urinalysis were all normal.

Chest radiography was normal. An abdominal CT scan revealed a right adrenal low-density mass (12 × 9 cm) that had infiltrated into the adjacent liver, right kidney and inferior vena cava (IVC) (Fig. 1). His 24 h urinary metanephrine (2.7 mg/day; normal range < 1.0 mg/day) and vanillylmandelic acid (VMA; 19.5 mg/day; normal range < 6.9 mg/day) excretion levels were above the normal upper limits. His 24 h urinary norepinephrine excretion was elevated (274.2 μg/day; normal range < 80 μg/day), but his epinephrine excretion was within normal limits (0.5 μg/day; normal range < 20 μg/day). There was no abnormal uptake of radioactivity on 131I-MIBG scintigraphy or bone scans. Based on the adrenal mass on CT scan and the urine biochemical tests, he was diagnosed with a pheochromocytoma.

Debulking surgery was performed in October 2007, after pretreatment with doxazocin (4 mg bid) and atenolol (25 mg qd). As the tumor had invaded the right hepatic lobe and IVC, right radical nephrectomy, right hepatic lobectomy and IVC thromboembolectomy were performed. Pathology findings of all removed tumors were consistent with pheochromocytoma. Following surgery, his 24 h urinary metanephrine (0.8 mg/day), VMA (5.2 mg/day) and norepinephrine (89.2 μg/day) excretion levels returned to normal.

In November 2007, he was found to have anterior mediastinal and multiple hepatic metastases and right pleural effusion, and was transferred to the oncology department for palliative chemotherapy. At that time, urinary catecholamine levels were within normal range. Following two cycles of the CVAD regimen (cyclophosphamide, 750 mg/m², Day #1; vincristine, 1.4 mg/m², Day #1; doxorubicin, 30 mg/m², Day #1; dacarbazine, 250 mg/m², Days #1–5) (5), the anterior mediastinal and multiple hepatic metastases had all increased in size. A second-line EP regimen (etoposide, 100 mg/m²; Days #1–3; cisplatin, 60 mg/m², Day #1) (6) was administered but the disease progressed (Fig. 2). Because the tumors were resistant to two combinations of conventional cytotoxic chemotherapies and there was no further cytotoxic chemo-regimen appropriate for this case, we recommended the patient and his caregiver to receive sunitinib 37.5 mg daily administration after thorough discussion and receiving the written informed consent. In April 2008, 7 weeks after the start of sunitinib therapy, treatment was halted because a large amount of right pleural effusion had developed and the patient complained of dyspnea. Although CT scans showed that the size of the anterior mediastinal and multiple hepatic masses had increased, the findings were consistent with necrotic change (Fig. 3). An 18FDG-PET scan showed that metabolic uptake of 18FDG by these metastatic tumors had decreased significantly compared with the values seen on scans performed in November 2007 (Fig. 4). These findings indicated that almost all of the masses seen on CT scans were necrotic and the pleural effusion was associated with

![Figure 1](https://academic.oup.com/jjco/article-abstract/39/5/327/885488/328) Abdominal CT shows huge right adrenal mass (A) with IVC thrombi (B, arrow). IVC, inferior vena cava; CT, computed tomography.
tumor necrosis. Pleural effusion improved after the cessation of sunitinib. At the time of this report, the patient is relatively well and on continuous treatment with 25 mg/day sunitinib. The additional CT scans which were taken 4 weeks after restart of sunitinib did not show significant interval change with the previous image (Fig. 4).

**DISCUSSION**

In this patient, 24 h urinary metanephrine and VMA excretion were increased and right adrenal mass was documented by abdominal CT scan. We diagnosed as malignant pheochromocytoma because anterior mediastinal and multiple liver masses were documented after debulking surgery. At that time, biochemical parameters, initially elevated, were not increased. The reasons for this finding were not clear.

Malignant pheochromocytomas have a poor prognosis and there is no established treatment. Although curative resection can seldom be performed, surgical resection should be considered even in patient with metastatic disease, particularly when there is an associated secretory tumor. Resection may ameliorate symptoms by reducing tumor bulk and may also increase the efficacy of other therapeutic modalities (6,7). After successful debulking, combination chemotherapy or $^{131}$I-MIBG therapy has been recommended. The latter was not performed in our patient, because there was no uptake on the initial diagnostic $^{131}$I-MIBG scan. The CVD regimen has been used for the treatment of malignant pheochromocytomas, with symptomatic and hormonal response rates of 50–100%, but with minimal tumoral responses (4,8). In a case report, a 50-year-old patient showed biochemical and tumoral responses after 12 cycles of an anthracycline plus CVD (ACVD) regimen (5). In addition, treatment with etoposide and a platinum-based drug has been recommended for patients with rapidly progressive disease (2,6). Although our patient received two cycles each of ACVD and EP, tumor progression was observed.
Novel principles for malignant pheochromocytomas have been tried. For example, a combination of temozolomide and thalidomide achieved a 40% biochemical and a 33% radiological response in patients with malignant chromaffin-cell tumors (9). Temozolomide is a cytotoxic alkylating agent and thalidomide has an anti-angiogenic effect. In contrast, the tyrosine kinase inhibitor, imatinib mesylate, was not effective in two patients with malignant pheochromocytoma (10).

As widely known, pheochromocytoma is a component of the von-Hippel Lindau syndrome, which is characterized by vascular tumors of the central nervous system and clear renal cell carcinomas caused by high expression of vascular endothelial growth factor (VEGF), mediated through loss-of-function mutations of the VHL gene. Although the patient did not have von-Hippel Lindau syndrome, pheochromocytomas are characterized by abundant vasculature and high levels of VEGF expression (11–14) and sunitinib is an inhibitor of multiple tyrosine kinases and has potent anti-angiogenic effects, we hypothesized that this targeted therapeutic agent might be effective in our patient.

We found that sunitinib was effective in the treatment of chemotherapy-refractory malignant pheochromocytoma. Although CT scans after sunitinib therapy showed progressive disease based on RECIST (Response Evaluation Criteria In Solid Tumors) criteria (15), metabolic uptake of $^{18}$FDG by these tumors decreased significantly, as shown in the $^{18}$FDG-PET scans and the patient’s condition improved. This finding also indicates that as with imatinib treatment of patients with gastrointestinal stromal tumors, radiological evaluation using RECIST criteria alone is not suitable for the assessment of treatment response (16).

To our knowledge, this is the first report of sunitinib treatment of patient with a malignant pheochromocytoma unresponsive to cytotoxic chemotherapy. These findings suggest that sunitinib might be a novel therapeutic agent for the treatment of patients with malignant pheochromocytomas.

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Conflict of interest statement

None declared.

References


