Combination Chemotherapy for Malignant Paraganglioma

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Treatment with a combination chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and dacarbazine for malignant paraganglioma with hepatic metastasis is reported. A 51-year-old male presented with tumors in the retroperitoneal space and liver. The patient was diagnosed as having paraganglioma based on elevated levels of serum neuron-specific enolase, urinary catecholamine and vanillylmandelic acid, and on histological findings of the liver specimen. The patient was treated with this combination chemotherapy in repeated 21-day cycles. Temporary improvement in laboratory findings and a 20% reduction in the size of the hepatic masses were observed without severe adverse effects.

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Key words: retroperitoneal tumor, CVD regimen, hepatic metastasis

Introduction

Pheochromocytomas arising from outside the adrenal glands, are called paragangliomas (1) and constitute a rare disease. Most paragangliomas are malignant and their diagnosis is difficult; furthermore, adequate therapies have not been established.

Here, we present a case of malignant paraganglioma with hepatic metastasis treated with a combination chemotherapy. The regimen of this chemotherapy is based on published experience with the treatment of advanced stage neuroblastoma, since this tumor has several pathological and biochemical features in common with malignant pheochromocytoma (2, 3).

Case Report

A 51-year-old man visited our hospital in February 1993, with a six-month history of anorexia and 4 kg weight loss. Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen showed a retroperitoneal mass near the left kidney and multiple hepatic masses (Fig. 1). He was hospitalized with complaints of sweating, loss of appetite, and constipation. He had diabetes mellitus treated with sulfonyl urea, but this was not accompanied by hypertension. Both his parents also had diabetes mellitus.

On physical examination, his conjunctivas were anemic but

not icteric. The liver was palpable 12 cm below the right costal border. His blood pressure was 130/80 mmHg, and pulse rate was 72/min and regular. Blood examination on admission showed liver dysfunction and hyperglycemia. Serum neuron-specific enolase (NSE) and urinary catecholamines and vanillylmandelic acid (VMA) levels were elevated (Tables 1, 2). Gallium scintigraphy revealed abnormal accumulation only in the hepatic masses, while thyroid scintigraphy, adrenal scintigraphy, and bone scintigraphy showed no abnormal accumulation. Angiography of the celiac artery indicated no tumor stains. When an ultrasound guided needle biopsy of the retroperitoneal mass was performed, only necrotic tissues were obtained. First, exploratory laparotomy was performed, but the retroperitoneal mass could not be resected because of involvement of the vessels. However, tissues of the hepatic masses were obtained for microscopic examination. Histologically, the masses consisted of cells which had round or oval nuclei and eosinophilic cytoplasm and showed a positive stain for NSE (Fig. 2).

Based on the symptoms, as well as on laboratory data, and histological data, the masses were diagnosed as hepatic metastasis of malignant paraganglioma arising from the intra-abdominal ganglion tissues. As of June 1993, he was treated with a combination chemotherapy (CVD regimen; cyclophosphamide (CPA) 1,000 mg i.v. on day 1, vincristine (VCR) 2 mg i.v. on day 1, and decarbazine (DTIC) 900 mg i.v. on days 1 and 2

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in 21-day cycles). By the end of the second cycle, the patient had shown no signs of severe nausea or hematological toxicity. Therefore, he was discharged from the hospital in July and continued to be treated with this chemotherapy. After four and a half months of therapy, CT scan showed a 20% reduction in the size of the hepatic masses but no change in the retroperitoneal mass (Fig. 3). Serum NSE and urinary catecholamines and VMA levels had also decreased (Fig. 4).

However, during a follow-up examination nine months later at the out-patient department, the hepatic masses were observed to be gradually increasing and the serum NSE level was elevated again in spite of the continuing chemotherapy. Liver dysfunction recurred, while abdominal ascites and pleural effusion appeared. The patient suffered from liver failure in June 1994 and died in July 1994.

Figure 1. CT scans of the abdomen show a retroperitoneal mass near the left kidney and multiple hepatic masses.

Table 1. Laboratory Data on Admission

WBC	6,700/ μ l	GOT	49 IU//
RBC	421 $\times 10^4$ / μ l	GPT	34 IU//
Hemoglobin	11.3 g/dl	ALP	715 IU//
Hematocrit	35.0%	LDH	369 IU//
Platelet	44.0 $\times 10^4$ / μ l	LAP	123 IU//
PT	10.6 s	γ -GTP	246 IU//
PT	76%	Cholinesterase	0.71 Δ pH
APTT	29.6 s	Total Protein	7.2 g/dl
Fibrinogen	394 mg/dl	Albumin	3.5 g/dl
TT	44%	Total-Bilirubin	0.4 mg/dl
HPT	59%	Amylase	82 IU//
Blood Sugar	145 mg/dl	CPK	164 IU//
Urinalysis		BUN	11 mg/dl
occult blood	(-)	Creatinine	0.5 mg/dl
protein (-), sugar (-)		CRP	0.4 mg/dl
urobilinogen	(+)	Na	138 mEq//
Stool		K	4.4 mEq//
occult blood	(-)	CL	104 mEq//
		Ca	10.0 mg/dl
		HBs-Ag (-), HCV-Ab (-)	

Underlined data indicate abnormal findings. WBC: white blood cell, RBC: red blood cell, PT: prothrombin time, APTT: activated partial thromboplastin time, TT: thrombo test, HPT: hepaplastin test.

Autopsy showed a yellowish or reddish brown mass in the left retroperitoneal space, which weighed 1,200g (Fig. 5). The tumor was composed of two cellular types. One was a trabecular growth pattern of large and pleomorphic cells with eosinophilic cytoplasm and small nuclei, and the other was a ribbon-like growth pattern of small-sized basophilic-stained cells (Fig. 6). Both types of cells stained positively with NSE antibody, while the second type was also positive for S-100 protein. These findings showed that the tumor was a paraganglioma consisting of chief cells (type I) and sustentacular cells (type II). Numerous

Table 2. Laboratory Data Related to Endocrine Glands and Tumor Markers

Serum	adrenaline	60 pg/ml (100↓)
	noradrenaline	271 pg/ml (100–450)
	dopamine	39 pg/ml (20↓)
	aldosterone	51 pg/ml (35.7–240)
	cortisol	16.1 μ g/dl (5.0–15.0)
	renin	2.9 ng/ml/h (0.6–1.2)
Urine	adrenaline	38.3 μ g/day (3.0–15.0)
	noradrenaline	438.0 μ g/day (26.0–121.0)
	dopamine	3,129.6 μ g/day (190.0–740.0)
	VMA	5.8 mg/day (1.3–5.1)
	HVA	3.8 mg/day (1.5–6.6)
	metanephrine	0.09 mg/day (0.05–0.23)
	normetanephrine	0.24 mg/day (0.07–0.26)
Tumor Markers (serum)		
	AFP	2 ng/ml (10↓)
	CA19-9	10.0 U/ml (37.0↓)
	NSE	463.1 ng/ml (4.0–9.0)
	SCC	1.0 ng/ml↓ (2.0↓)

Underlined data indicate abnormal findings. VMA: Vanillylmandelic acid, HVA: Homovanillic acid, AFP: α -fetoprotein, NSE: Neuron-specific enolase, SCC: Squamous cell carcinoma-related antigen.

Figure 2. Histological findings of the hepatic metastasis. The tumor cells are positive for NSE (NSE stain, $\times 200$).

Figure 3. CT scans of the abdomen, (A) before chemotherapy on April 8, 1993 and (B) after 6 cycles of the chemotherapy on Oct. 21, 1993. Note the approximately 20% decrease in the size of the hepatic masses.

areas of metastasis were noted in the liver (weight 4,560g), the right adrenal gland, and para-aortic lymph nodes.

Discussion

Approximately 18% of pheochromocytomas are extra-adrenal, and are called paragangliomas. Their malignancy ratio is 30 to 40%, which is higher than that of adrenal pheochromocytomas (2 to 11%) (4, 5).

Pheochromocytomas with their typical features of hypertension, headache, hyperidrosis, hyperglycemia, hypermetabolism and adrenal tumors are not difficult to diagnose. However, the diagnosis of paragangliomas, which do not show such typical symptoms and signs such as the present case, is difficult.

The diagnosis of pheochromocytoma can be established biochemically on the basis of elevated levels of catecholamines

Figure 5. Cut surface of the retroperitoneal tumor showing yellowish masses, necrosis, and hemorrhage.

and VMA in the blood and urine; and radiologically by means of CT, MRI, ^{131}I -MIBG scintigraphy, and angiography. However, histological diagnosis of malignant pheochromocytoma remains difficult. For instance, one report described a case of pheochromocytoma, which was diagnosed initially as benign on the basis of the histological examination on adrenalectomy, but 20 years later it turned out to be malignant and was accompanied by hepatic metastasis (6). In contrast, a case diagnosed histologically as malignant pheochromocytoma turned out to be benign without metastasis or recurrence (7). Three studies have provided a new approach for an accurate diagnosis. First of all, malignant pheochromocytomas have been found to feature a decreased number of chief cells posi-

Figure 4. Effect of the chemotherapy of CVD regimen on serum NSE and transaminase.

tively stained by antibodies to NSE or chromogranin, and a decreased number of sustentacular cells positively stained by antibody to S-100 (8). In addition, these tumors include many nodules, necrosis, and cells without hyaline globules (9). Finally, Ogawa et al (7) have reported that DNA histogram is useful for the differentiation of benign and malignant cells.

Once the diagnosis of pheochromocytoma has been established, surgical removal of the tumor is the treatment of first

Figure 6. Note the sustentacular cells around the chief cells (HE stain, $\times 400$).

choice. If total removal is impossible because of invasion or metastasis, radiological intervention or combination chemotherapy is performed. Success with ^{131}I -MIBG therapy has been reported (10) but recently it is difficult to obtain the necessary material. Transcatheter arterial embolization (TAE) was found to be effective for tumors rich in vessels (6). When the tumor is poor in vessels, as in the case reported here, or the effect of TAE is transient, systemic administration of chemotherapy should be performed. Because of the rarity of malignant pheochromocytomas, information on chemotherapy for this neoplasm is minimal. Between 1949 and 1993, only 11 reports on the chemotherapy for a total of 21 patients with malignant retroperitoneal paragangliomas were published. Cyclophosphamide was the most frequently used drug; it was administered to 14 of the 21 patients with palliative results for eight. Vincristine was used for 12 patients, of whom six experienced palliation, and dacarbazine for 10 patients with seven showing palliative results. Finally, combination chemotherapy was used for 20 of the 21 patients (2, 11–20) (Table 3).

The CVD regimen reported by Keiser et al in 1985 (2), is a combination chemotherapy originally used for neuroblastoma. It consists of CPA, 750 mg/m^2 i.v., on day 1; VCR, 1.4 mg/m^2 i.v., on day 1; and DTIC, 600 mg/m^2 i.v., on days 1 and 2 in 21- to 28-day cycles. Doses of the drugs are adjusted depending on the hematological toxicity, neurotoxicity, and the patient's condition. Positive response prognosis is 50 to 80%, and there

Table 3. Chemotherapy of Malignant Retroperitoneal Paragangliomas

No.	Year	Authors	Metastasis	Drugs	Response
1.	1984	Bukowski	Lymph nodes, Epidural space	5FU, CTX, STZ	(–)
2.	1985	Keiser	Bone, Liver	CTX, VCR, DTIC	(+)
3.	1986	Mikhail	Bone	CTX, VCR, DOX, DTIC	(+)
4.	1987	Ubayama	Bone, Lung	ADM, CTX, VCR, CDDP	(±)
5.	1988	Murao	Bone, Liver	ADM, VCR	(–)
6.	1989	Koshihara	Lymph nodes	CTX, DOX, CDDP	(+)
7.	1990	Sclafani	Spine	CTX, VCR, DTIC	(–)
8.			Spine	DTIC, ADM, Novantrone	(±)
9.			Femur	VP16, ADM, DTIC, CDDP	(±)
10.			Bone, Abdomen	MTX	(±)
11.			Bone, Abdomen	VCR, CTX	(–)
12.			Paraortic nodes	CTX, VCR, ADM	(±)
13.			Liver	CTX, VCR, DTIC	(+)
14.			Liver	Leukeran, Actinomycin	(–)
15.			Liver	5FU, ADM, MTX, STZ	(–)
16.			Lung	CTX, VCR, ADM	(–)
17.			None	DTIC, ADM, VP16	(+)
18.	1991	Honma	Bone	CTX, VCR, DTIC	(+)
19.	1992	Massey	Liver, Lung	CTX, VCR, DOX	(–)
				CTX, DOX, DTIC	(–)
20.	1992	Kuvshinoff	Liver	CTX, DOX, CDDP, VP16	(±)
21.	1993	Yoshihara	Bone	CTX, VCR, DTIC	(–)

CTX: cyclophosphamide, VCR: vincristine, DTIC: dacarbazine, ADM: adriamycin, CDDP: cisplatin, 5FU: 5 fluorouracil, STZ: streptozotocin, DOX: doxorubicin, VP16: etoposide, MTX: methotrexate.

are few adverse effects.

In the present case, we performed combination chemotherapy because surgical removal was impossible due to direct invasion and hepatic metastasis; in addition, the tumor was poor in vessels. The therapy with the CVD regimen was temporarily effective, showing a 20% reduction of the hepatic masses without severe adverse effects except for depilation. On the other hand, the primary lesion in the retroperitoneal space remained unchanged. Past reports of combination chemotherapy for malignant paragangliomas included a case in which the primary lesion in the retroperitoneal space responded to the treatment but the patient later died of growth of the lung metastasis (13) and another case in which the primary lesion in the epicardial area did not respond to the treatment but bone metastasis did respond to it (21). In the latter case, Naruse et al stated that the chemotherapy used in this case was effective, on the grounds that the growth of the primary lesion was successfully inhibited (21). In the present case, the retroperitoneal tumor had almost become necrotized by the time chemotherapy was started. It is therefore unreasonable to assess the response in this case on the basis of the course of the size of the primary lesion. It is a histological fact that chief cells (type I) are found in most cases of paraganglioma. Chemotherapy was effective in cases of paraganglioma where the tumor cells had differentiated into sustentacular cells (type II), i.e., cases of S-100 protein-positive paraganglioma (15, 19), whereas S-100 protein-negative cases of paraganglioma tended to be resistant to chemotherapy (14). In the present case, some tumor cells were S-100 protein positive. However, it finally failed to inhibit the tumor growth. In conclusion, the results showed that further study is needed on the most adequate chemotherapy for malignant pheochromocytomas.

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