Remarkable Regression of Malignant Paraganglioma in the Retroperitoneum and Neck after Chemotherapy: Report of a Case and a Review of the Literature

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The present communication describes a patient with paraganglioma found in the retroperitoneum and neck. She was treated with the combination chemotherapy employing cyclophosphamide, doxorubicin, and cisplatin (CAP therapy), and resulted in remarkable regression of the tumor in size. We reviewed the literature about the therapy of paraganglioma and the nature of retroperitoneal paraganglioma in relation with this case.

Key words: Paraganglioma, Chemotherapy, Tumor regression

Paraganglionic cells originate from the neural crest that arises in association with the segmental or collateral autonomic paraganglia throughout the body (1-5). Most paragangliomas are benign, but small percentage of them have proven to be malignant (1). Surgical procedure should be the treatment of the first choice, when the tumor is resectable. But in the cases with malignancy associated with metastases to other organs, the appropriate treatment has not been established.

We experienced a case with malignant paraganglioma which formed the tumors in both retroperitoneum and neck, and the CAP combination therapy gave rise to remarkable regression of the tumor in size. Since paraganglioma is rare and furthermore only a few cases were reported with tumor regression by the chemotherapy (6-12), this case is considered valuable to report with the review of the literature.

CASE REPORT

A 31-year-old woman had suffered from low back pain from March 1987 and had 5 kg weight loss for one month. She admitted to our hospital for low back colic in May. Physical examination revealed that the blood pressure was 112/60 mmHg, and pulse rate 76/min. Several left cervical lymph nodes were palpable (2×2 cm in size). Laboratory findings including CBC, blood chemistry, ECG, and chest X-ray were within normal limit. Abdominal CT scan (Fig. 1) and echogram (Fig. 2) revealed lobulated mass around the aorta and the inferior vena cava. We performed the detailed examinations of gastrointestinal tracts and other organs for the detection of malignancy, but did not find any significant abnormality. We suspect of malignant lymphoma, and the biopsy from the left cervical lymph node was done.

Microscopic findings of biopsy specimens showed that majority of cells had moderate amount of eosinophilic homogeneous cytoplasm and oval nuclei, surrounded by rich vascular stroma arrangement (Fig. 3). And classical “Zell ballen” organoid pattern was seen. Tumor cells were negative for the
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Fig. 1. Contrast enhanced CT scan at the level of the renal hilus.
(B) After CAP therapy. The tumor is much regressed.

staining of Fontana-Masson method but positive for Grimelius stain. In immuno-histochemistry, S-100 protein was weakly positive, and strongly positive for the staining of neuron specific enolase. Electron microscopic findings of the cytoplasm included rich mitochondrias, small dense core granules, and other organellae. The above mentioned evidences suggested the granules were compatible with catecholamine granules (Fig. 4) (1).

Urine specimens collected during 24 hours were normal for vanilmandelic acid, metanephrine (90 ug/day), normetanephrine (195 ug/day), noradrenaline (33.9 ug/day), adrenaline (6.75 ug/day), dopamine (316.5 ug/day), and 5-hydroxyindoleacetic acid. Regitine test was negative. The tumors did not uptake the isotope of $^{131}$I-MIBG, $^{99m}$Tc and $^{67}$Ga citrate. Thus the finally obtained diagnosis was malignant non-functional paraganglioma.

Because the tumor involved the retroperitoneum and the neck in this case, we concluded the case was inoperable and the chemotherapy was started. In July, the combination chemotherapy consisted of cyclophosphamide, dacarbazine, doxorubicin and vincristine given intravenously was carried out with no effect. In August, we tried $^{60}$Co irradiation to the abdomen and the neck. Tumor had transient regression in size, but soon enlarged again. In December, the combination chemotherapy consisted of cyclophosphamide (600mg/m$^2$, D1), doxorubicin (50 mg/m$^2$, D1), and cisplatin (75 mg/m$^2$, D2)

Fig. 2. Abdominal echograph (transverse section of the upper abdomen).
Top: Before CAP therapy (on May 1987). Lobulated mass is seen around the para-aortic area.
Bottom: After CAP therapy. The section corresponding to (A) echograph demonstrates marked tumor regression.
L: lesion, P: pancreas, S: splenic vein, A: aorta
Fig. 3. The tumor has an organoid pattern with "Zell ballen" arrangement or anastomosing pattern. Cuboidal tumor cells are separated by thin vascular septum. Section from left cervical lymph node biopsy. Hematoxylin and eosin, ×40.

Fig. 4. Electron micrograph of the tumor cells. Rich organellae are seen in the cytoplasm. And dense core granules with unit membrane are recognized. They are compatible with catecholamine granules, ×5000. Inset, dense core granules are covered with unit membrane, ×15000.

given intravenously every 4 weeks, was carried out. During the chemotherapy, transient nausea and vomiting, bone marrow suppression (nadir, WBC 600/mm³, platelet 2.1 × 10⁹/mm³), and alopecia were seen, but they were tolerable for the patient. After single course, the tumor regression was clearly seen. After the second course of the therapy, cervical lymph nodes were not palpable, and the cervical CT scan also confirmed it (Fig. 5). In abdominal CT scan (Fig. 1) and echography (Fig. 2), the tumor in the retroperitoneum showed marked regression in size. Over 11 months after four courses of CAP therapy, she was in excellent remission and could have a quality of life.

Fig. 5. Cervical CT scan.
(A) Before CAP therapy (on May 1987). The tumor invades the lymph nodes of left neck.
(B) After CAP therapy. The tumor is almost disappeared.
DISCUSSION

Paraganglioma is an unusual tumor of neural crest origin. According to Glenner and Grimley (13), extra-adrenal paragangliomas can be divided into three anatomic distributions: 1. Branchiometric paraganglioma (2), 2. Intravagal paraganglioma (3), and 3. Aortosympathetic paraganglioma (4, 5). The first group includes the jugulotympanic, intercarotid (carotid body), subclavian, laryngeal, coronary, aorticopulmonary, and orbital paraganglioma. The tumor cells are generally chromaffin-negative and grow in a "Zell ballen" arrangement surrounded by rich vascular stroma. The second group is histologically indistinguishable from the first one and located within the perineurium of the vagus nerve. The third group arises in association with the sympathetic nervous system. Chromaffinity, internal secretion and pathological findings vary from case to case.

In our patient tumors were found in the retroperitoneum and the neck simultaneously. Sporadic cases of multiple familial paragangliomas have been reported (14, 15), but in our patient, we believe that the primary tumor arose in the retroperitoneum and with metastases to the cervical lymph nodes via the thoracic duct. Our deductions are based upon the fact that the cervical tumor was found only in the subcutaneous space and its localization was shallower than normal cervical paraganglia. Furthermore, on echographic examination, the cervical lesion appeared to involve lymph nodes, and in addition the tumor in the retroperitoneum was much larger in size.

Paragangliomas generally occur in the head and neck, and retroperitoneal paragangliomas are rare. In 1985, Kryger-Baggesen et al (16) reviewed 38 cases described in the English literature between 1948 and 1983. Between 1984 and 1987, 15 further cases were added to the English literature. About 10% to 20% of retroperitoneal paragangliomas arise outside the adrenal gland in association with the sympathetic chain along the aortic axis. Most patients are aged from 30 to 45 years. Retroperitoneal paragangliomas occur at a relatively earlier age than in the head and neck. Signs and symptoms vary, but most present with back pain and/or a palpable abdominal mass. From 25% to 60% of patients suffer chronic or intermittent hypertension, headache, and palpitations as a result of the production of catecholamines (1).

The optimum treatment of paraganglioma has yet to be established. Most experts regard surgical resection as the best treatment for benign and even malignant paragangliomas. Although in cases of malignant paragangliomas with distant metastases, tumor resection is sometimes performed with 60Co irradiation added as adjunctive therapy, many malignant paragangliomas whose surgical treatment is impeded

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<th>Author(s)</th>
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<th>Response</th>
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<td>ACD, Cytoxan, VCR</td>
<td>neck and lung</td>
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<td>STZ</td>
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<td>CPM, DTIC, VCR</td>
<td>(case 1) retroperitoneum</td>
<td>60% regression</td>
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<td>(case 2) adrenal gland, lung, and liver</td>
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<td>(case 2) carotid body and bone</td>
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<tr>
<td>Mikhail et al (12)</td>
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because of difficult anatomic sites are treated with $^{60}$Co irradiation (17–20) alone. Spector et al (18) reported that 40–60Gy $^{60}$Co irradiation was effective in 65% of 20 patients with glomus jugulare tumors. Konefal et al (19) also had good results with $^{60}$Co irradiation of temporal bone chemodectomas. Nevertheless, with the exception of James' report (20) in 1972, most retroperitoneal paragangliomas have not been sensitive to $^{60}$Co irradiation. Recently, several reports have been published claiming reduction in tumor size using $^{131}$I-MIBG, a catecholamine analogue preferentially taken up by paragangliomas (21, 22).

Many attempts of chemotherapy of paragangliomas up to the present have been ineffective. Some reports have claimed efficacy, but in most cases, the effect of therapy was symptomatic relief. Tumor regression could be found only in isolated reports (Table 1). In 1986, Mikhail et al (12) reported that combination chemotherapy consisting of dacarbazine, cyclophosphamide, doxorubicin and vincristine, was highly effective. Similarly in 1976, Vogl et al (7) suggested that combination chemotherapy containing cisplatin was successful in paraganglioma. Schilcher et al (9) and Sridhar et al (11) reported successful cases with cisplatin. These reports encouraged us to use CAP combination chemotherapy in the present case with favourable results. We suggest that palliative chemotherapy with cisplatin is indicated in cases of inoperable paraganglioma.

REFERENCES