Retroperitoneal Nonchromaffin Paraganglioma

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1 Introduction

The paragangliomas, also known as chemodectoma or nonchromaffin paraganglioma tumor, belong to neuroendocrine tumors. They are generally named according to anatomical sites, such as the carotid body tumor and jugular body tumor (referring to paragangliomas located in the carotid body). Paraganglioma is common in adults aged 30–60 years, while patients with retroperitoneal paraganglioma are younger (mostly 30–40 years old) than those with head and neck paraganglioma. Malignant paraganglioma may occur at a younger age. Retroperitoneal paragangliomas are rare tumors, with the incidence equivalent between men and women. They are mostly solitary and sporadic and occasionally multiple. Patients often have a family history. Some cases are accompanied by paragangliomas in other parts of the body or complicated with gastrointestinal stromal tumor (GIST) and pulmonary chondroma as Carney's triad.

Approximately 20% of the retroperitoneal paragangliomas arise from extra-adrenal paraganglia, which are located in para-aortic region and closely related to sympathetic nerve chain. The body's largest group of paraganglia is chromaffin bodies, namely, the paired structure arranged para-abdominal aorta at the level of inferior mesenteric artery. Chromaffin bodies are highly developed in the early embryos, gradually degrade after the age of 12–18 years old, and finally leave minor residues. Although these residues have chemosensory functions in animals, their physiological functions in the human body is unclear. Most extra-adrenal paragangliomas originate from chromaffin bodies, and a small number of tumors arise from para-aorta (on other planes) and para-iliac vessel paraganglia.

2 Etiology and Pathology

Retroperitoneal paraganglioma is usually a brown clump, a few centimeters in diameter, and incompletely encapsulated. Intratumoral hemorrhage is common. Histologically, retroperitoneal paragangliomas have characteristics of branchial paragangliomas and/or pheochromocytoma, and the vast majority is very similar to pheochromocytoma.

The tumors are composed of small, polygonal, or spindle-shaped cells with eosinophilic cytoplasm and numerous deeply stained nuclei. Tumor cells are arranged into short and irregular sheet structures, with rich sinusoid in intercellular matrix, and accompanied by megakaryocytes and multinucleated giant cells. As tumor cells are always very fuzzy in appearance, the sheet

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structures are endowed with syncytial character. Eosinophilic bodies are present in the cytoplasm, varying in size (ranging from a few millimeters to the size of a nucleus). These structures appear to be the residue of dense-core granules, suggestive of benign tumors. Very few tumors are composed of the cells with melanoma-like cytoplasmic debris, and hemorrhage is common in the tumorous nests. Some retroperitoneal paragangliomas are similar to carotid body tumors, while a small number of round cells grow in small nests in retroperitoneal paragangliomas.

Pleomorphic tumor cells may be misdiagnosed as malignant cells, since they exhibit little mitotic activity that reflects the atypical changes. Ganglioma area can be rarely seen in paraganglioma. Not all of these tumors are functional; the chromaffin reaction is positive in about two-thirds of the retroperitoneal paragangliomas (Kafase and Branan). Lack et al. (1980) reported that chromaffin granules could be detected in all of the retroperitoneal paragangliomas.

The immunohistochemistry profile of retroperitoneal paraganglioma is similar to that of branchial paragangliomas, in that neuron-specific enolase (NSE), neurofilament protein, synaptophysin, and chromogranin can be identified in chief cells, which in turn are surrounded by a delicate sustentacular network outlined by the immunostaining for S-100 protein. Leu-enkephalin, an opiate-like pentapeptide comprised of β-endorphin molecules, can be identified in adrenal and extra-adrenal paragangliomas. This pentapeptide is produced by normal and hyperplastic adrenal medullary cells as well as tumor cells. Insulin-like growth factor II, a polypeptide of 67 amino acids that is homologous to the β-chain of proinsulin, has been identified in adrenal tissue, carotid body, and paraganglioma. This polypeptide can be localized in the chief cells of adrenal and extra-adrenal paragangliomas; however, its significance is unclear. To sum up, NSE, CgA, and S-100 are highly expressed in almost all of the retroperitoneal paragangliomas and can be used as reliable markers, and the sensitivity will be further improved if applied in combination with Syn.

3 Clinical Manifestation

Paragangliomas arising from sympathetic paraganglia of abdominal aorta are mainly located on both sides of the retroperitoneal spine, commonly seen in the bifurcation of abdominal aorta and connected to blood vessels. Retroperitoneal paraganglioma is asymptomatic in the early stage, while in the late stage, it is most commonly manifested by back pain and a palpable mass. Ten percent of patients firstly present metastatic tumors. About 20% of cases are incidentally identified at the autopsy. Approximately 25–60% of patients develop noradrenaline-related symptoms, such as chronic or periodic hypertension, headaches, and heart palpitations. In contrast, functional adrenal paraganglioma (chromaffin tumor) may be associated with elevated levels of epinephrine (adrenaline) and norepinephrine in the blood, and the development of definite syndromes depends on the relative levels of the two hormones. Hypertension is frequently seen in norepinephrine-secreting tumors. In contrast, hypotension, hypovolemia, heart palpitations, and rapid arrhythmia are characteristics of the adrenaline producing tumors. The difference in the secretion modes is considered to be associated with methyltransferase enzyme in adrenal pheochromocytomas. This enzyme converts norepinephrine into epinephrine and is absent in extra-adrenal paragangliomas. In very few cases of retroperitoneal paraganglioma, renal ischemia occurs due to compression of the renal vessels by the tumor, thus resulting in hypertension.

4 Examination and Diagnosis

4.1 Localization Diagnosis

Localization of the tumor prior to surgery is relatively easy. CT shows a well-circumscribed paraaortic hypervascular mass, accompanied by necrosis or calcification. MRI displays a well-defined tumor of low-intensity signal on T1-weighted image whereas significantly high intensity and enhanced signal on T2-weighted

image. With an increase in volume, the tumor is complicated by cystic degeneration and hemorrhage, resulting in heterogeneous signals. CT has been used as the primary method for localization diagnosis of functional tumors. However, I-MIBG scintigraphy can display complex tumors and detect small tumors that cannot be identified by CT. Selective arteriography is helpful in determining the location, size, and blood vessels of the tumor in order to facilitate preoperative embolization and intraoperative ligation.

4.2 Etiologic Diagnosis of Functional Paraganglioma

Retroperitoneal paraganglioma lacks pathological and cytological evidence before surgery. Few patients can be accurately diagnosed before operation. The preoperative etiological diagnosis is essential to prevent uncontrollable intraoperative bleeding as well as the risk of catecholamine-induced sudden-onset hypertension and heart failure. The catecholamines are released by paragangliomas in response to the induction of anesthesia and surgical operation. Prior to surgery, if patients with retroperitoneal tumors have complications such as hypertension and metabolic changes (an increase in basal metabolic rate or blood glucose) but do not present with hyperthyroidism or diabetes, they should be highly suspected of retroperitoneal functional chromaffin tumor or paraganglioma. Particularly, if the tumor is closely related to the adrenal gland, the diagnosis can be made based on the measurement of catecholamines and 3-methoxy-4-hydroxymandelic acid (VMA) in the blood and urine. Phentolamine inhibition test or histamine provocation test can be conducted if necessary. Paragangliomas are not necessarily located in the adrenal gland, and functional types don't always present with hypertension before surgery. In patients with preoperative hypertension, the levels of catecholamines in the blood and urine, as well as VMA in the urine, may be normal, which are possibly attributed to a stationary type and the absence of stimulation test. Using ^{131}I-labeled iodobenzoic acid (a structural analog of norepinephrine), adrenal and extra-adrenal paragangliomas can be localized. Through a similar mechanism to neurotransmitters, this agent is concentrated in adrenergic tissue and, at the minimal effective dose of 0.2 mg, enables the imaging of paragangliomas. Tiny tumors may also be localized with isotope-labeled octreotide similar to somatotropin release-inhibiting factors.

4.3 Diagnostic Criteria for Malignant Paraganglioma

Retroperitoneal paragangliomas can be divided into benign and malignant tumors. The nature of the tumor is not related to its functional status, and the degree of malignancy is not associated with its functional activity.

Based on the potential of distant metastasis and local infiltration, approximately 50% of adrenal and extra-adrenal tumors are malignant. The criteria for malignant paragangliomas have been controversial. Some studies propose that only the appearance of metastasis is the definitive evidence for malignancy. In a review of various characteristics of both benign and malignant tumors carried out by Linnoila et al. (1990), the extra-adrenal site, coarse tumor nodularity, widespread necrosis, and lack of intracellular hyaline globules were considered to be harbingers of malignant tumors. Seventy-one percent of such malignant tumors exhibited two to three of the above features, while 89% of benign tumors exhibit none or only one of the aforementioned features. They also suggested that low expression of neuropeptides in most cases is associated with malignancy and therefore can be used as adjunctive index to identify infiltrative behavior. More than five neuropeptides are found to be expressed in typically benign retroperitoneal paragangliomas, whereas only two are in malignant tumors. Clarke et al. (1998) proposed that extra-adrenal location, male gender, young age, high tumor weight, and high Ki-67 index were harbingers of malignant tumors. The correlation between the increasing rate of MIB-1 antibody and malignant

potential has also been identified in other studies. Relative values of flow cytometry have been used to assess the malignant nature of retroperitoneal paraganglioma. Although the chromosomes in a metastatic tumor are often aneuploidy or tetraploidy, it significantly overlaps with the benign tumors. Thus, ploidy cannot be used to distinguish benign from malignant tumors.

5 Treatment of Retroperitoneal Paraganglioma

Either benign or malignant retroperitoneal paraganglioma, once it is diagnosed, should be completely removed as soon as possible. The control of blood pressure, correction of arrhythmias, and improvement of potential cardiomyopathy before the surgery are essential to improve the treatment and outcome of patients who have been diagnosed with functional retroperitoneal paraganglioma preoperatively. The volume expansion and appropriate blockers can effectively prevent the risks of ultra-hypertension, heart failure, and bleeding. Usually α-receptor blocker phenoxybenzamine (20–40 mg/day) is administered preoperatively for 2 weeks to control the blood pressure. If patients who have received phenoxybenzamine present with heart rate greater than 90 bpm, additional β-blockers should be applied to control the heart rate. For a patient, whose blood pressure has not been well-controlled with α-blockers alone, the addition of calcium channel blockers or angiotensin-converting inhibitors can achieve good results.

Since retroperitoneal paragangliomas are located adjacent to blood vessels, it is challenging to perform a complete surgical resection. If necessary, a combined resection of blood vessels or organs that are adherent to or invaded by tumors, such as pancreatic body and tail, spleen, kidney, colon, or inferior vena cava, should be conducted. During the surgery, squeezing and pulling of the tumor should be avoided as possible. The separation is generally carried out outside the capsule to control blood supply to the tumor as early as possible. Modern radiotherapy techniques enable to accurately localize these tumors, so some patients may undergo laparoscopic surgery instead of laparotomy.

Whenever an unexplained dramatic increase in blood pressure with intensive fluctuations occurs during an operation under anesthesia, retroperitoneal paraganglioma or chromaffin tumor should be suspected. In this setting, the operation should be discontinued, and antihypertensive measures should be taken. The first step is to expand the blood volume and control the blood pressure with sodium nitroprusside. As an effective antihypertensive agent, sodium nitroprusside acts directly on vascular smooth muscle. As a quick-acting vasodilator, it dilates both arteries and veins, and the blood pressure can recover quickly upon discontinuation. It is considered as an ideal choice to control hypertension induced by functional paraganglioma intraoperatively. Surgeons should be aware that the tumor cannot be squeezed and the blood supply to tumors should be blocked as soon as possible. The purpose is to avoid a sudden increase in blood pressure caused by released adrenaline into the blood, as well as hypotension-induced shock after tumor resection. The close cooperation between surgeons and anesthesiologists in this setting will ensure the operation to proceed smoothly. An appropriate amount of blood transfusion can be performed at the beginning of the surgery, and the amount of fluid infusion should be increased within a short period of time before dissecting the major blood vessels. After the tumor resection, blood transfusion and fluid infusion should be administered at a constantly accelerated speed. Excessive rehydration is very effective in correcting hypotension after tumor resection. Ephedrine and norepinephrine are vasopressor agents commonly used following tumor resection. Adjuvant therapies for retroperitoneal paraganglioma include radiotherapy, chemotherapy, and iodobenzoic acids, all of which are considered palliative care.

6 Efficacy and Prognosis

Retroperitoneal paragangliomas can spread through lymphatics and blood, most often metastasizing to the regional lymph nodes, bone, liver, and lungs. In a study conducted by Clarke et al.

(1998), 10 of 66 cases of chromaffin tumor and retroperitoneal paraganglioma experienced metastasis, including four cases of extra-adrenal tumors.

Previous studies suggested that extra-adrenal paraganglioma was more invasive than adrenal paraganglioma. However, the studies conducted by MSKCC (Memorial Sloan Kettering Cancer Center, 1990) put forth opposite evidence that the 5-year survival rate was 77% in adrenal paraganglioma whereas 82% in extra-adrenal paraganglioma; and no significant differences in 5-year survival rate or tumor-free survival rate were observed between them.

The serum level of neuropeptide Y correlates with tumor relapse, which can be used as a reliable marker to detect recurrent retroperitoneal paraganglioma.

References

Clarke MR, Weyant RJ, Watson CG, et al. Prognostic markers in pheochromocytoma. Hum Pathol. 1998;29(5):522–6.

Lack EE, Cubilla AL, Woodruff JM, et al. Extra-adrenal paragangliomas of the retroperitoneum: a clinicopathologic study of 12 tumors. Am J Surg Pathol. 1980;4(2):109–20.

Linnoila RI, Keiser HR, Steinberg SM, et al. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol. 1990;21(11):1168–80.