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CASE REPORT

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Paragangliomas: À Propos of Two Cases. Diagnostics and Treatment

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Summary

Background: Paraganglioma develops from cells of the parasympathetic and sympathetic system. It usually manifests as a slow-growing and painless mass. Peragangliomas may be hereditary, benign or malignant, unilateral or bilateral tumors. They are well vascularized. In most cases, paraganglioma is located around the common carotid artery, but may also be located within the middle ear or in the abdomen.

Case Report: A 49-year-old patient with bilateral paragangliomas around branches of carotid arteries. Diagnostic imaging was performed, including MRI and CT angiography. To reduce the size of the tumors, the patient was subjected to radiotherapy, with no result. Finally, the tumor on the right side was removed.

A 67-year-old patient with the third recurrence of retroperitoneal paraganglioma. Diagnostic imaging was performed. Vascular embolisation was not performed as the vessels were too narrow for microcatheter introduction.

Conclusions: Paragangliomas are rare tumors. Total resection is sometmies impossible because of the rich vascularity and difficult location. Radiotherapy is a good alternative, though not always effective. Proper diagnostic imaging is necessary.

MeSH Keywords: Angiography • Carotid Body • Embolization, Therapeutic • Magnetic Resonance Imaging • Paraganglioma • Tomography Scanners, X-Ray Computed

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Background

Paragangliomas are benign, solid, encapsulated slow-growing tumors characterized by potential for malignant progression in 10% of patients. They are also commonly referred to as glomus tumors. The goal of this article is to familiarize the readers with the subject of paragangliomas including the methods for their classification, diagnostics, imaging and treatment on the basis of two cases of tumors in typical locations.

Paragangliomas are sporadic tumors (0.2–1/100,000 individuals) that account for 0.03% of the overall number of tumors and 0.6% of head and neck tumors. The most common location of paraganglioma is the bifurcation of the common carotid artery (carotid body, glomus caroticum) in 60% of patients, followed by inner ear and/or jugular vein region (paraganglioma jugulotympanicum), and involvement of the vagus nerve (paraganglioma nervi vagi), larynx, organ of Zuckerkandl, aortic arch, femoral arteries, or parotid salivary gland. In 10% of patients, lesions are bilateral; in 40% of patients, they are associated with family predisposition. Carotid body tumor is more common in females (70%) than males while the opposite is true for other locations. Paragangliomas are detected most commonly between the ages of 20 and 60, with peak incidence

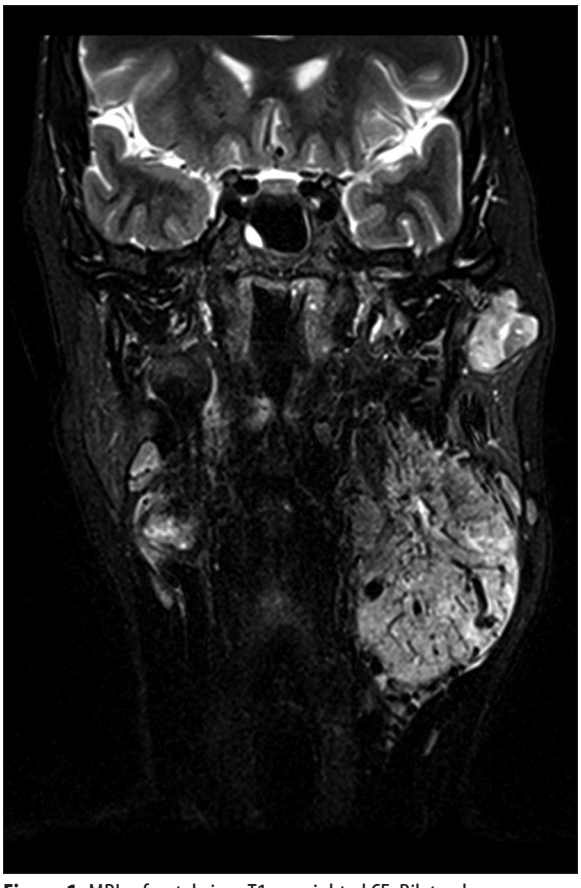

Figure 1. MRI – frontal view. T1 – weighted CE. Bilateral paragangliomas at the level of caroid bifurcation.

at about 50 years of age. In extremely rare cases they may occur in children. Only as much as 3% of these tumors are characterized by endocrine activity [1–6].

Case Report

Case 1

A 49-year-old female patient in good overall condition, with no comorbidities or positive family history presented at the hospital due to increased circumference of the neck and the onset of hoarseness. Chest CT scans were acquired with and without contrast administration as part of diagnostics for adenopathies, namely nodular sarcoidosis. No enlarged lymph nodes were detected within the mediastinum and hila while a tumor located on the left side of the neck, enhanced following the addition of CM, was partially visualized. The preliminary diagnosis of nodular sarcoidosis was ruled out.

As part of further diagnostics, MRI scans of the head and neck region (Figures 1, 2) were acquired in TSE, Vibe, and DWI/ADC sequences, in three planes, before and after contrast administration. Two pathological masses with rich vascularity were observed in bifurcations of common carotid arteries. The lesion on the left was 77×64×50 mm in size, remodeling and translocating submandibular salivary gland and the sternocleidomastoid muscle towards the front. The common

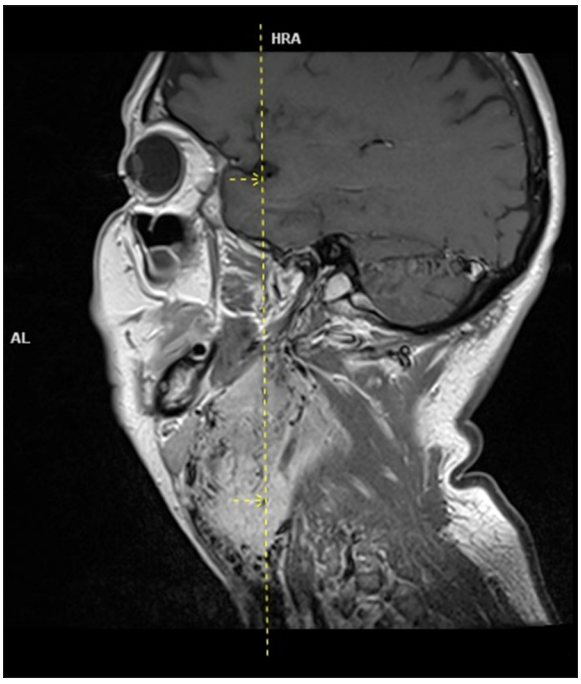

Figure 2. MRI – sagittal view. T1 – weighted CE. Paraganglioma at the level of caroid bifurcation –left side.

carotid artery was encircled by the tumor along the pre-bifurcation segment while the internal and external carotid arteries were pushed apart (Schamblin classification group II). The tumor was located 4 mm from the larynx. On the right, above the bifurcation of the common carotid artery, a focal lesion of similar morphology, 21×20×24 mm in size and respecting normal anatomical relationships, was detected. Cervical spine and maxillary sinuses were unremarkable. In addition, a well-circumscribed, homogeneous nodule without features of facial nerve infiltration. Left-sided paroidectomy was performed due to the lesion within the left parietal salivary gland (later shown to be a basal cell adenoma in a histopathological examination) while no specimen collection or resection of the right-sided tumor were attempted due to the size and macroscopic presentation of the lesion. Post-operative angio-CT scan (Figures 3–5) with contrast administration confirmed rich vascularity of bilateral cervical lesions located in the regions of common carotid artery bifurcations. Patency of cervical arteries was evaluated. No signs of bone destruction were identified. Bilateral paraganglioma was diagnosed on the basis of characteristic tumor location.

The patient was subjected to radiation therapy with good tolerance to the treatment. She was qualified for surgical removal of the right-sided lesion. Another MRI scan of the neck was performed. The examination showed a well-encapsulated tumor on the left, sized 84×65×50 mm – no regression observed following radiation therapy. A failed attempt at embolization of vessels of both tumors was performed during arteriography. A decision was made to remove the focal lesion on the right, with a successful outcome.

Histopathological examination revealed an encapsulated, partially fibrotic tumor without vascular involvement

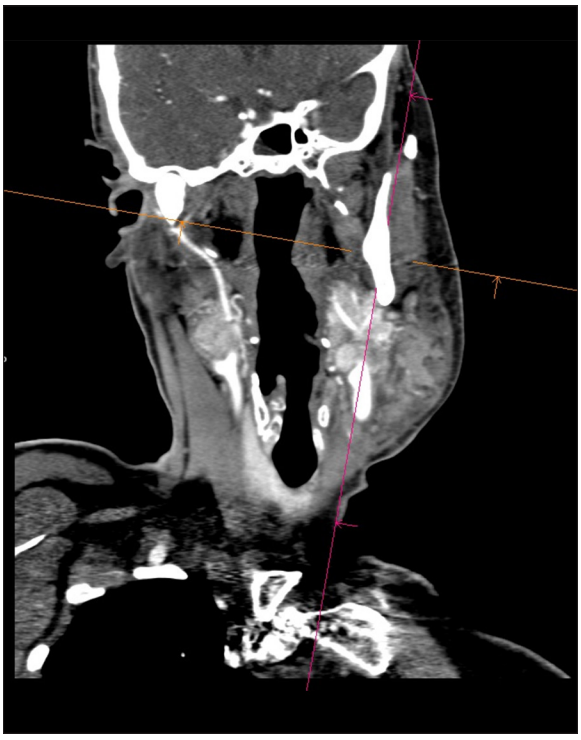

Figure 3. CE CT. Bilateral paragangliomas at the level of caroid bifurcation.

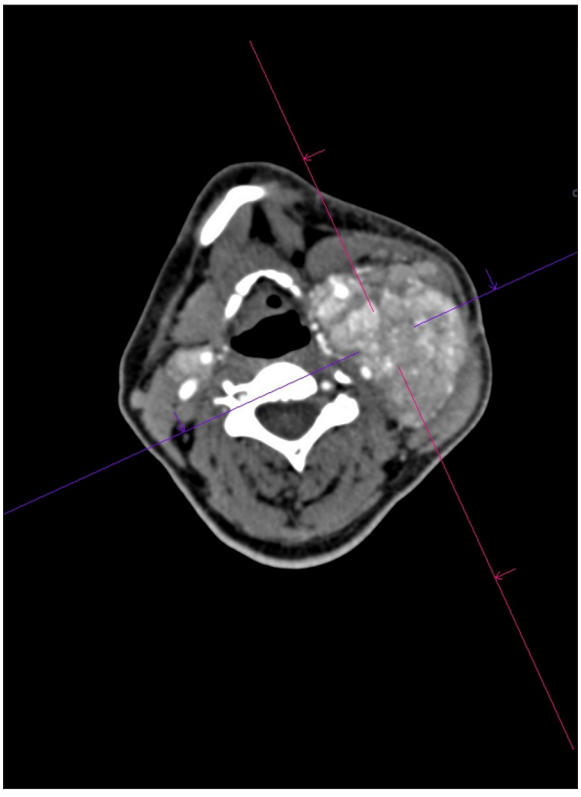

Figure 4. CE CT axial view. Bilateral paragangliomas at the level of caroid bifurcation.

(Schamblin I), characterized by high pleomorphism – paraganglioma. Presentation of level II jugular lymph nodes corresponded to reactive lymphoid hyperplasia.

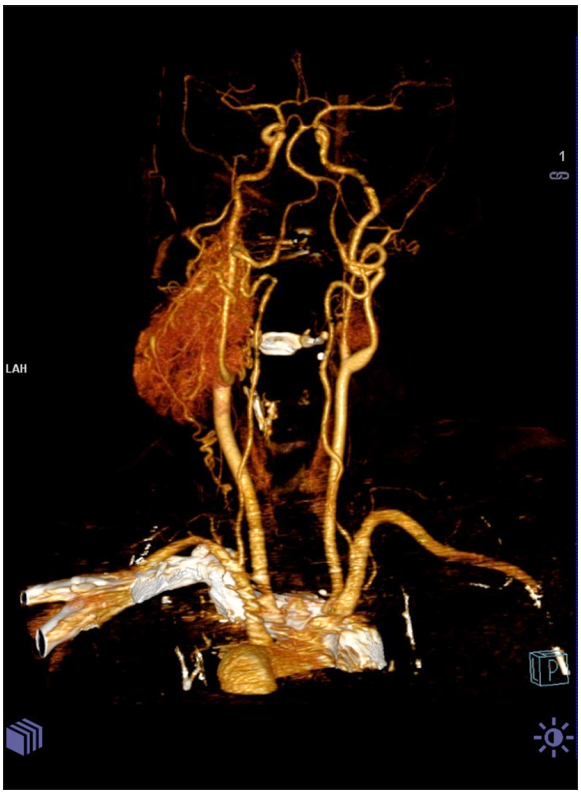

Figure 5. CT. Reconstruction 3D VR. Bilateral paragangliomas at the level of caroid bifurcation.

Case 2

A 67-year-old female patient was admitted to hospital for the treatment of an operable retroperitoneal tumor. This was the third recurrence of cancer disease. The patient had a history of numerous surgical procedures (correction of inguinal herniation in 1995, removal of leg varicose veins in 2002, thyroidectomy due to nodular goiter in 2007, excision of endometriosis in 2012), with no positive family history. The patient suffered from arterial hypertension and hypothyroidism.

For the first time, the patient had been operated on for retroperitoneal space tumor in 1989. An ultrasound scan was performed to reveal a well-circumscribed, round-shaped, hyperechogenic lesion adhering to the abdominal aorta and sized 75×60×48 mm. Histopathological examination revealed non-chromaffin paraganglioma. In 2012, the patient reported at the general practitioner due to pain within the mid-abdominal region. A decision was made to expand the diagnostic procedures by inclusion of imaging studies. A CT scan was performed to reveal a lesion sized 21×14 mm adjoining the anterolevolateral surface of the abdominal aorta and a smaller, lateral lesion with the diameter of 8 mm. A decision was made to resect the tumors. Pre-operative angio-CT scan (Figures 6, 7) (2014) revealed progression of the focal lesions. The size of the tumor located at the anterolevolateral surface of the abdominal aorta was 37×34×31 mm while the similar lateral lesion was 12 mm in diameter. Both lesions were removed in the surgical procedure. Retroperitoneal paraganglioma was diagnosed from histopathological

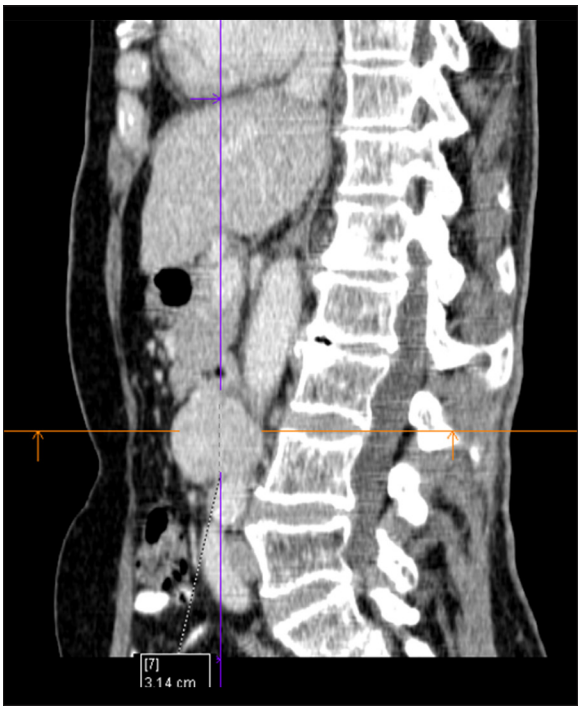

Figure 6. CE CT – sagittal view. Paraganglioma at the level of lumbal arteries.

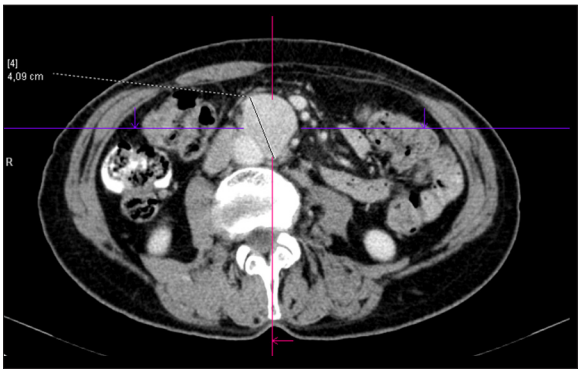

Figure 7. CE CT – axial view. Bilateral paragangliomas at the level of lumbal arteries.

examination of resected tumors; the tumor tissue extended to the resection line in both specimens.

Follow-up angio-CT scan (Figures 8, 9) performed 9 months after the procedure (2015) revealed a disease recurrence – focal lesion located at anterolevolateral abdominal aortic outline, 35×22 mm in size, another adjacent focal lesion 17 mm in diameter and a third lesion 8 mm in diameter. Next, abdominal arteriography was performed (Figure 10). The scan revealed a richly vascular lesion of paraganglioma type. The attempt of catheterization of arterial branches supplying blood to the tumor failed due to the vessel caliber being smaller than the size of microcatheter. A decision was made to abandon the procedure. The patient awaits surgery that would involve resection of tumors and the lesion-infiltrated segment of the abdominal aorta (to be replaced by a prosthesis).

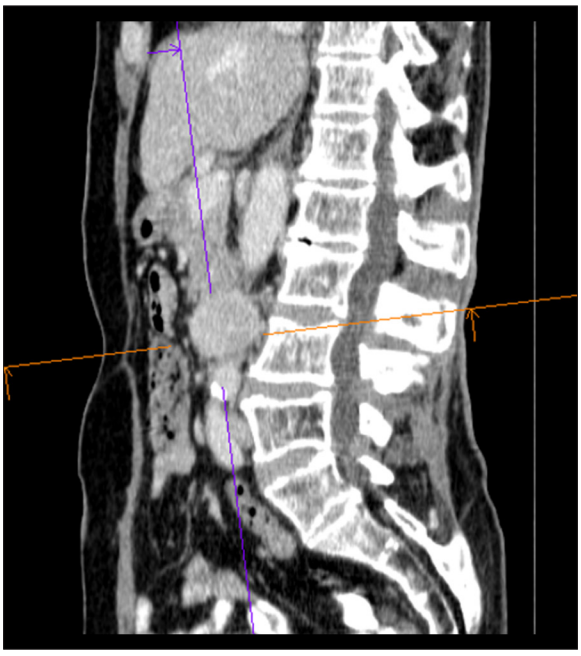

Figure 8. CE CT – sagittal view. Paraganglioma at the level of lumbal arteries – recurrence.

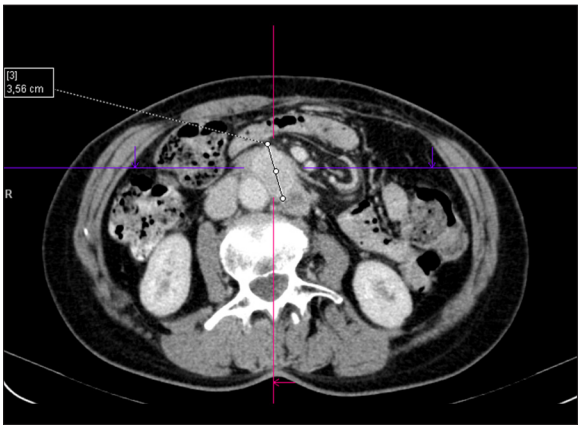

Figure 9. CE CT – axial view. Bilateral paragangliomas at the level of lumbal arteries – recurrence.

Discussion

Etiology

Family predisposition to paraganglioma was demonstrated in 10% of patients (or 30–50% due to underestimation, according to Szyfter). The trait is inherited in the autosomal dominant pattern with incomplete expression. Tumors do not occur in children of affected mothers (generation skipping) whereas children with genes inherited from the father (who may or may not experience clinical symptoms) are certain to develop the disease. About one third of hereditary head and neck paragangliomas (HNPGs) is due to gene mutations. Mutations within the succinate dehydrogenase genes were reported as causes of paraganglioma syndrome (PGL). Such mutations contribute to the occurrence of multiple locations of glomus tumors in 100% of cases. Tumors originating from paraganglial tissue may develop in various genetic diseases such as von

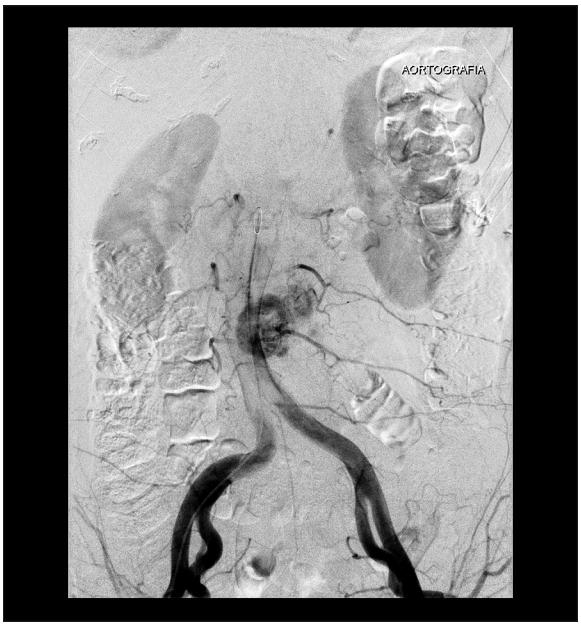

Figure 10. Retroperitoneal arteriography. Bilateral paragangliomas at the level of lumbal arteries.

Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (von Recklinghausen disease, NF1), multiple endocrine neoplasias of type 2 (MEN2 – mutation within the RET protooncogene), TMEM127, and MAX. It is recommended that patients with HNPGs might benefit from molecular diagnostic studies [3,7–10]. Risk factors may include chronic hypoxia; for instance, increased incidence was observed in individuals (particularly post-menopausal women) living at higher altitudes, as well as individuals with athletic body build, large lung capacity, or with history of chronic hypoxia [11,12].

Classifications

Paragangliomas derive from neuroendocrine paraganglia within the sympathetic nervous system (chromaffin paraganglia) and parasympathetic nervous system (non-chromaffin paraganglia). Parasympathetic paraganglia (chemodecta) play the role of a chemoreceptor responsible for monitoring and regulation of blood gas concentrations. Most common types of paragangliomas take origin in these bodies, including carotid body paraganglioma, jugulotympanic paraganglioma and nerve X paraganglioma. Malignant nature is often observed in paragangliomas originating from the vagus nerve compared to only 5% of patients with paraganglioma of carotid body. Glomus tumors of nerve X are most commonly responsible for distant metastases [3,13].

Chromaffin paraganglia are located along the sympathetic trunk. The spindle-shaped organ of Zuckerandl (para-aortic body) is the largest body of this type, located on both sides of the aorta at L3 level at the point of origin of the interior mesenteric artery from the abdominal aorta. The organ of Zuckerandl produces catecholamines; it deteriorates in a physiological manner by the age of 40. Due to its histological structure, adrenal medulla is often referred to as an example of paraganglial body. Neoplastic process within adrenal medulla may lead to the development of pheochromocytoma [3,13].

A number of classifications were developed to assess clinical stages of paragangliomas. One of them is the Glasscock and Jackson system. The system focuses on tumor location and differentiates jugular and tympanic paragangliomas. Four stages of lesion development are identified within both groups [6].

Another classification was proposed by Schamblin. According to that system, there are four tumor stages (I, II, IIIa, IIIb) associated with tumor location and vascular involvement (without remodeling of vessel walls, involvement of adventitia, involvement and stenosis of the vessel wall, involvement of hypoglossal nerve and superior laryngeal nerve [3,7].

Clinic signs

Tumor signs and symptoms depend on tumor location. Patients with carotid body tumors may observe a growing mass, moving upon palpation in horizontal direction while being immobile in vertical direction (Fontaine's sign). Carotid bruit is heard upon auscultation. The tumor gradually impinges the throat, leading to difficulties with swallowing, choking and body weight loss, and the larynx, causing respiratory problems. Symptoms of the hearing organ appear, including pain, disturbed perception of sounds, pulsatile tinnitus. The tumor mass is responsible for paresis and paralysis resulting from infiltration of the facial, glossopharyngeal, vagus, accessory and, in very rare cases, hypoglossal nerve. Depending of the affected region, different syndromes may develop including the Collet-Sicard's syndrome (nerves IX, X, XI, XII), Jackson's syndrome (nerves XI and XII before exiting the cranial cavity) or Tapia's syndrome (nerves XI and XII after crossing the jugular foramen), Vernet's syndrome (nerves IX, X, and XI), Schmidt's or Avellis' syndrome (nerves X and XI). In some cases, hoarseness (paralysis of the superior laryngeal nerve), sensory disturbances (including disturbed taste), muscle paresis, or Horner' syndrome are observed. Tachycardia, arrhythmia, hypertension, dizziness and fainting are observed in less than 5% of patients [7,11].

Diagnostics

The diagnosis is made on the basis of interview, physical examination, blood and urine tests, and imaging examinations. Blood and 24-hour urine levels of catecholamines (adrenaline, noradrenaline and dopamine) and their metabolites (metanephrine, VMA) are determined. In both cases no laboratory tests were performed to screen for catecholamines and VMA. Tumor biopsies are not indicated as the tumor is characterized by rich vascularity. Bilateral Doppler ultrasound scan is the first-line method. Contrast-enhanced CT, MRI, angio-CT (most accurate scan to confirm the diagnosis and determine the nature of the tumor) and PET scans are made in the first place. Paraganglioma should be differentiated from other tumors (medullary thyroid carcinoma, non-differentiated carcinoma and metastases of melanoma). The pathognomic symptom of paraganglioma is a very well-vascularized, circumscribed

homogeneous tumor as seen in early arterial phase CT scans together with the change in the angle of departure of the internal and external carotid arteries from the common carotid artery (in some cases, this angle may reach 180°). Paragangliomas in this region may infiltrate the jugular fossa. This is accompanied by asymmetry and deterioration of the septum between the fossa and the tympanic cavity. Cerebral location and infiltration is indicative of the invasive character of the tumor. Patients may present with symptoms due to increased intracranial pressure.

Vessels that deliver nutrients to the tumor are visualized in angio-CT scans. Embolization of some of these vessels may be performed (3–4 days before surgery) to inhibit the growth of the tumor and reduce intraoperative bleeding. Polyvinyl alcohol (PVA), 25–33% solution of PVA in absolute alcohol, or Avitene (gel foam soaked in thrombin) are used for that purpose. Complications of the embolization procedure may include facial nerve paralysis, stroke and difficulties in radical tumor resection; therefore, caution must be exercised when performing embolization [10,14–17]. Other techniques may include meta-iodobenzylguanidine (m-IBG) scintigraphy and positron emission tomography (PET). m-IBG scintigraphy is used in diagnostics of neuroendocrine tumors and neuroblastomas while positron emission tomography is used for the imaging of tumors of very high metabolic activity. PET scans are acquired with the use of ^{18}fluoro-2-deoxyglucose (^{18}F-FDG PET-CT) or ^{18}fluorodopamine (^{18}F-DOPA PET) [18,19].

Treatment

Surgical treatment is based on collaboration between a laryngologist and a vascular surgeon following radiological assessment of the tumor. The treatment of choice consists of a surgical procedure involving one or several branches of the common carotid artery. The surgery-related mortality rate is 5% while the risk of neurological complications is 10%. Radiation therapy is used in paraganglioma treatment following an incomplete surgical resection or before surgical resection of large lesions. Radiation therapy results in tissue fibrosis that may possibly hamper the surgery and elongate the healing process. Radiation is also used in palliative treatment of patients [10,11,16,20,21].

Prognosis of treatment outcomes is very good in case of radical resection (5-year survival rate of more than 90). Recurrent disease (10% of cases) and lesions infiltrating adjacent structures may form metastases and lead to death. Malignant tumors usually produce metastases to lymph nodes (90%), lungs, and bones (remaining 10%). In this group, long-term survival (of more than 10 years) was reported in less than 50% of patients [5,11,20].

Conclusions

Due to the locations of paraganglioma-type tumors, their efficient treatment is possible only upon early detection. Appropriate management should include the use of advanced diagnostic imaging techniques and surgical treatment, if possible.

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