Journal of BUON **14:** 405-409, 2009

REVIEW ARTICLE

Laryngeal paragangliomas - controversies in diagnosis and management

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Summary

Paragangliomas of the larynx are rare neuroendocrine tumors with difficulties in diagnosis and management. A review of the literature was carried out, using Medline and other available databases. Electronic links and related books were also included. The most reliable diagnostic imaging procedures are MRI, CT scan, and octreotide scintigraphy. Complete surgical excision with the maximal possible preservation of the laryngeal function is the treatment of choice. Many different surgical techniques have been reported but open surgical procedures seem to provide better results with lower recurrence rates, although endoscopic approaches and laser surgery have also been used with variable results. The use of long-acting depot octreotide has been used for the relief of symptoms and stabilization of the disease, especially in inoperable lesions with positive initial octreotide scintigraphy imaging. Detailed preoperative assessment and treatment planning in individual basis are essential in the management of these tumors.

Key words: glomus, larynx, neuroendocrine, paraganglioma, tumor

Introduction

Paragangliomas are, in general, rare, solitary, and slow-growing neuroendocrine neoplasms of neural origin [1]. They arise from paraganglion cells as part of the diffuse neuroendocrine system, adjacent to sympathetic or parasympathetic nerves. They may produce a variety of neuroendocrine products. Paragangliomas are most frequently found in the head and neck, mainly associated with the vagus, jugulotympanic and superior - inferior laryngeal paraganglia. The commonest sites are the carotid bifurcation and the jugulotympanic area.

There are two-paired laryngeal paraganglia: the superior and the inferior. The superior paraganglia are situated in the false vocal fold along the course of the superior laryngeal artery and nerve [2]. The inferior paraganglia are found near the lateral margin of the cricoid cartilage in the cricotracheal membrane along the course of the recurrent laryngeal nerve [3]. Mostly the superior laryngeal artery, which is a branch of the superior thyroid artery, provides their blood supply. The majority of laryngeal paragangliomas are supraglottic. The sites of distribution are supraglottic (82%), subglottic (15%), and glottic (1%) [4].

Epidemiology - biologic behavior

Paragangliomas show a female preponderance (male: female ratio 1:3) and tend to occur during the 4th to 6th decade of life (range 14 to 83 years; median 44) [5]. They seem to be inherited in 10 - 50% of the cases [6,7]. In fact they occur in two forms: a sporadic form and a familial autosomal dominant pattern [8]. The gene for familial paragangliomas (PGL 1) has been identified at the 11q23 locus, but at least two other genetic loci have been also reported. Familial paragangliomas are frequently multiple and bilateral. Although a family history of paraganglioma does not necessarily predict the presence of hyperfunctioning tumors, it may be associated with mul-

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Received 24-07-2008; Accepted 21-10-2008

tiple tumors. The incidence of multicentricity for sporadic paragangliomas is reported to be about 10%, while familial paragangliomas are multiple in about 40% of the cases [9]. Although all paragangliomas contain cytoplasmic neurosecretory granules, only 1-3% of these tumors demonstrate clinical evidence of hyperfunctionality.

Symptoms

Laryngeal paragangliomas may appear as an asymptomatic, non-functional mass growing over a prolonged period of time. The common symptoms are hoarseness and dyspnoea, mainly caused by supraglottic lesions [10]. Dysphagia, dysphonia, stridor, sore throat, neck mass, cough, shortness of breath, foreign body sensation in the throat and ear pain have also been reported [11-14]. The vascular nature of these tumors may also result in episodes of haemoptysis. Laryngeal or pharyngeal pain or reflex otalgia have also been described, and, according to some authors, are suggestive of poor prognosis or malignant behavior [15,16].

Histology

Histologically these neoplasms are highly vascularised, composed of two cell types: chief cells and sustentacular cells [1,5,10]. Chief cells are polygonal with inconspicuous nuclei and eosinophilic cytoplasm and are packed in a characteristic alveolar or "Zellballen" pattern. Scattered spindled sustentacular cells with basophilic cytoplasm may be identified at the perimetry of the cell balls. The cells are argyrophil-positive and argentaffin-negative [5]. Immunohistochemically the chief cells express all neuroendocrine markers such as chromogranin and synaptophysin, but do not stain with epithelial markers (cytokeratin, carcinoembryonic antigen, epithelial membrane antigen) and this supports the diagnosis [17], as these antigens are identified in atypical carcinoid tumors. Sustentacular cells are stained by antibodies to S-100 protein and glial fibrillary acid protein. Chief cells are S-100 protein and glial fibrillary acid protein-negative. Electron microscopy reveals dense core neurosecretory granules in the cytoplasm of chief cells. Laryngeal paragangliomas, in most cases, are benign and the malignancy rate is less than 2% [5]. However, they tend to be locally invasive.

Diagnosis

The differential diagnosis of laryngeal paragangliomas includes haemorrhagic polyps, typical carcinoid, atypical carcinoid, small-cell neuroendocrine carcinoma, haemangiopericytoma, metastatic renal cell carcinoma, malignant melanoma, anaplastic and medullary carcinoma of the thyroid gland [10,18]. Basic otorhinolaryngologic examination may reveal a single mass growing over a long period of time. The diagnostic procedure may be continued with indirect and fiberoptic laryngoscopy, followed by diagnostic imaging of the tumor (CT or/and MRI) [4,19]. The typical appearance of laryngeal paragangliomas in fiberoptic endoscopy is that of a small, smooth, submucosal red-violet mass. There is a controversy regarding the necessity of preoperative biopsy because these patients usually bleed excessively when biopsied and may require some form of airway intervention, such as tracheostomy if bleeding is difficult to be controlled. However, some authors still recommend preoperative biopsies, although this requires at least two operations [20]. It is important to mention that these tumors are usually covered by intact mucosa; therefore a deep biopsy is necessary to avoid false-negative diagnosis. This may make the biopsy procedure even more hazardous [21-23].

Diagnostic imaging techniques

Myssiorek et al. suggest contrast CT scanning for any submucosal mass of the larynx [19]. Currently, the diagnostic imaging modality of choice for laryngeal paragangliomas is MRI with gadolinium enhancement [10]. However, CT scanning is also needed when information on cartilage destruction is needed. Although CT or MRI scans usually provide valuable information about tumor size and location, cranial nerve or vascular invasion and bony erosion, the radiologic data is not always conclusive regarding differential diagnosis, so other tumors such as meningiomas, schwannomas or metastatic lesions may be considered [24]. Additionally, CT and MRI focus on the anatomic region of the existing paraganglioma and it is impractical to use them for whole body scanning in order to reveal synchronous tumors.

Other imaging techniques such as octreotide scanning are also quite reliable in the detection of paragangliomas in general. Octreotide is a somatostatin analogue with high binding affinity for type 2 (S2) somatostatin receptors. Ninety-eight percent of all paragangliomas have S2 receptors and 2% bear somatostatin type 1 receptors [24]. Tagging the octreotide with radioactive tracer Indium (^{111}I) DTPA produces a scintigraphic image, which can demonstrate sites of somatostatin binding such as paragangliomas [25]. Paragangliomas appear to have

the greatest density of S2 receptors among all head and neck lesions, and demonstrate an intense uptake which is easily identified on both SPECT and planar imaging. Although several imaging techniques have been involved for the detection of the most common paragangliomas and statistical data is available, there are no studies with regard to laryngeal paragangliomas evaluating the various imaging techniques such as octreotide scintigraphy in these tumors [26]. However, according to Myssiorek et al. octreotide scanning appears to be a reliable test to detect laryngeal paragangliomas, quite helpful in patients' staging and preoperative planning, and when combined with MRI or CT, biopsies may be avoided. Unfortunately, lesions like carcinoid tumors, medullary thyroid cancer metastases and melanoma also pick up ^{111}I, so diagnostic problems may still appear.

Other imaging procedures such as I - Meta - iodobenzyl-guanine (MIBG) scintigraphy have also been used to detect paragangliomas. According to Krenning et al. MIBG scintigraphy does not appear to be equally accurate to octreotide scintigraphy in the detection of paragangliomas, probably because the normal uptake of MIBG in the salivary glands can be quite confusing [26]. Galium scanning has also been involved in the diagnosis of paragangliomas but the uptake is often nonspecific. This method is more suitable for large, rapidly growing tumors instead of the small and usually slow-growing paragangliomas [27].

Angiography - arteriogram

Preoperative angiography can provide valuable information about the size and extent of the lesion and its blood supply [10]. Angiography can identify whether any major feeding arteries are present and can be used for screening for synchronous lesions. It can be combined with superselective embolization to reduce the size of the tumor and the risk of massive intraoperative bleeding. As Sanders et al. suggest [20], an arteriogram can also determine the status of the circle of Willis and prepare the surgeon for the unlikely event of carotid resection.

Therapeutic approaches

Open surgical procedures

Surgery is the treatment of choice [10]. The goal of surgery is tumor eradication with respect to the surrounding normal tissues and the maximal possible preservation of the laryngeal function. Better results and lower rate of recurrences are usually obtained using open surgical procedures. The majority of the successfully treated patients had undergone local excisions with some form of supraglottic laryngectomy or a type of thyrotomy [5]. However, in some cases total laryngectomy was required. Lateral approaches for supraglottic lesions can be safely carried out without the need of tracheostomy. The endolarynx is left intact and the patient's hospitalization is minimal. Surgery for supraglottic lesions should preserve voice and swallowing function [10]. In subglottic paragangliomas the situation is usually much more demanding. Such lesions almost always require cartilage excision and some kind of reconstruction. However, functional postoperative results are usually satisfactory [10].

Endoscopic – laser microsurgical procedures

Some authors have employed endoscopic removal of small lesions, but such attempts frequently result in recurrences [21,28]. Microlaryngoscopy with laser excision (usually CO_2 laser) has also been used but the result is variable [29,30]. Such attempts frequently result in recurrences in the long-term [10]. These procedures have also certain disadvantages, mainly the significant risk of bleeding that may be very difficult to control due to the limitations of the surgical field [4,21,31]. In addition, the control of surgical margins may be also at risk, especially in subglottic lesions [29]. Partial epiglottectomy may be used to provide a better access to advanced supraglottic tumors before endoscopical laser excision is attempted [29].

Other therapeutic modalities

Elective neck dissection is not indicated, as laryngeal paragangliomas do not metastasize to cervical lymph nodes [32]. In fact, review of the laryngeal paraganglioma literature reveals that less than 2% metastasize, and recurrence is also rare when the lesion is completely removed [5]. Neck masses may indicate a carotid body paraganglioma or cervical lymph node metastases from an unrecognized atypical carcinoid [10]. Therefore, it is quite uncommon a neck mass to be associated with laryngeal paraganglioma. Radiotherapy and stereotactic radiosurgery have been used in other head and neck paragangliomas (especially in treating unresectable lesions or in altering growth rates in skull base neoplasms), but regarding laryngeal paragangliomas the experience is very limited [9, 33-35]. Chemotherapy has not been used widely in these laryngeal tumors [10].

Somatostatin receptor scintigraphy appears very

useful not only as a sensitive imaging technique for detecting paragangliomas but also as an additional method of management [36]. The use of long-acting depot octreotide may be used in the relief of symptoms and disease stabilization, especially in inoperable lesions with positive initial octreotide scintigraphy imaging [37]. The beneficial effects of such treatment can be evaluated by clinical and scintigraphic criteria [38] and may very well be attributed to direct inhibitory effect on hormone production and indirect effect on peripheral organs [39-42]. Although there is little or no effect on tumor growth (tumor shrinkage has been reported in 10-20% of the patients), stabilization of tumor growth can be achieved in about 50% of the patients [37,39]. Some authors have also used cryosurgery, but laryngofissure or radiotherapy has been required following this procedure [10,43].

Conclusion

Laryngeal paragangliomas, although rare pathological entities, demonstrate a specific interest for oncologists and onco-surgeons, due to their biological behavior and also to the recently introduced therapeutic agents, such as somatostatin. Close multidisciplinary approach based on the particular oncological status of each patient is of paramount importance.

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