Malignant Vagal Paraganglioma

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Abstract Paragangliomas are rare, typically benign neuroendocrine tumors that represent a small portion of head and neck tumors. A small percentage of these are known to have malignant potential. They arise from the carotid body, jugular bulb or vagus nerves. There is limited literature discussing the management of malignant vagal paragangliomas. We present a case of a 25 year old female with a left malignant vagal paraganglioma. The following case presentation will describe the presentation, classic radiologic findings, and management of a malignant vagal paraganglioma along with a review of the literature.

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History

A 25 year-old female reported to the emergency department for evaluation of a severe headache. An avid singer, she incidentally complained of difficulty with vocal range and stamina over several months. Family history was negative for head and neck cancer. Physical exam revealed fullness with mild generalized erythema of both the left posterior nasopharynx and the oropharynx. On palpation of the left oropharynx there was no discrete mass, however, the patient endorsed mild tenderness on palpation. Flexible fiberoptic laryngoscopic exam revealed normal bilateral true vocal fold motion and appearance. No cervical lymphadenopathy was appreciated and cranial nerves II–XII were intact.

Radiographic Features

Computed tomography (CT) identified a $6 \times 4 \times 3$ cm left post-styloid parapharyngeal space avidly enhancing mass (Fig. 1). Magnetic resonance imaging (MRI) confirmed a mass within the left parapharyngeal space that was isointense on T1, slightly hyperintense on T2, and showed multiple flow voids with gadolinium enhancement. The mass was posterior to the carotid bifurcation and antero-lateral to the internal jugular vein. Radiographic findings were highly suspicious for a vagal paraganglioma or nerve sheath tumor. Urine catecholamines, vanillylmandelic acid (VMA) panel and thyroid function studies were all within normal limits. Succinyl dehydrogenase (SDH) gene testing was negative.

Fig. 1 *Left image* coronal post-contrast CT demonstrating an avidly enhancing mass within the carotid space extending from slightly posterior to the carotid bifurcation superiorly to the skull base without intracranial extension. *Top right image* axial post-contrast CT showing left post-styloid parapharyngeal mass. Note the splaying of

the internal and external carotid arteries and apparent obliteration of the internal jugular vein. *Bottom right image* T1 post-gadolinium MRI showing isointense, left parapharyngeal space mass with apparent flow voids

The patient was offered surgical excision or radiation therapy, and she elected to proceed with surgical excision. Pre-operatively she underwent angiography, balloon occlusion testing of the left common carotid artery, and embolization of the tumor's main blood supply. Following her embolization, she developed left 10th and 12th cranial nerve deficits.

Surgical intervention included a trans-cervical, trans-mandibular excision of the left post-styloid parapharyngeal space mass originating from the vagus and also grossly involving the hypoglossal nerve. Both nerves were sacrificed during the procedure. Additionally, left selective neck dissection of levels I–III and left true vocal fold injection medialization were performed.

Diagnosis

The main tumor specimen demonstrated varying patterns of morphology showing expansive areas of sclerosis separating vague islands and scattered collections of individual tumor cells. The tumor proved to involve both the surgically identified Vagus and Hypoglossal nerves (Fig. 2). Large sheets of metastatic tumor were seen to

Fig. 2 Broad bands of dense connective tissue separate individual and groups of tumor cells which involved Vagus and Hypoglossal nerves

overrun lymph nodes (Fig. 3) and consisted of the classic organoid pattern of enlarged, ovoid cells with occasional hyperchromatic nuclei contained within granular, eosinophilic cytoplasm. Varying degrees of an organoid, nesting or “zellballen” pattern were identified (Fig. 4). Large areas

Fig. 3 A metastatic focus of tumor within a cervical lymph node that demonstrated the characteristic “Zellballen” histologic pattern separated by thin septae. Note the delicate vascularity

Fig. 4 Tumor involving a resected cervical lymph node appearing in a clustered, nesting pattern

of degeneration and necrosis were also present. Confirmation of the diagnosis was done through immunohistochemical means by utilizing s100 protein (Fig. 5 left) which outlined delicate, peripherally placed sustentacular cells not readily observable solely with hematoxylin and eosin staining methods. Neurosecretory granules contained within chief cells were strongly highlighted with the neuroendocrine marker synaptophysin (Fig. 5 right).

Discussion

Parangliomas (PGs) are rare neuroendocrine tumors derived from neural crest cells that arise from paraganglia and uncommonly show malignant behavior. They account for 0.6 % of all head and neck tumors [1]. In the head and

neck, they arise from the carotid body, jugular bulb or vagus nerves. PGs typically have a benign clinical behavior; however, up to 19 % can be malignant [2]. Less than 5 % of head and neck PGs originate from the vagus nerve [3]; however, vagal paragangliomas (VP) are the most likely to be malignant [2]. These tumors present a management challenge in the head and neck due to their close relation to vital neck and skull base structures.

PGs in the head and neck are associated with the parasympathetic nervous system and are typically non-secretory [4]. This is in contrast to thoracic and abdominal paraganglia, which are associated with the sympathetic nervous system and are typically secretory.

PGs can present in multiple locations including the carotid body, vagus nerve, jugular bulb, and the tympanic branch of the pharyngeal artery [4]. Carotid body tumors are the most common PGs of the head and neck and are more often found in men. Vagal PGs are more commonly found in women [4]. Patients with PGs in the head and neck more often present with a neck mass, and most patients are asymptomatic until the tumors are large enough to compress adjacent structures, resulting in cranial nerve deficits and airway compression [1, 2, 5]. Twenty-four hour urine testing for catecholamines or plasma testing for catecholamines will typically be negative in head and neck tumors given the non-secretory nature of these paragangliomas. However, it is still important to obtain these tests to rule out the presence of an adrenal paraganglioma (pheochromocytoma) or other functional paraganglioma in the patient.

While 65 % of PGs are sporadic, the remainder are inherited [10]. Mutations within four subunits of the succinyl dehydrogenase gene, as well as mutations within the SDHAF2 gene are associated with hereditary PGs [11]. The inheritance pattern and penetrance of these mutations is still not fully understood [11]. Familial PG syndromes present at a younger age; these patients are more likely to have multiple PGs and pheochromocytomas [5]. Therefore, patients with more than one of the following characteristics should undergo genetic testing: age <50, multiple tumors, extra-adrenal tumors, family history, metastatic tumors, elevated dopamine or elevated methoxytyramine [11]. Immunohistochemistry may also be used on resected tumors to indicate if a patient has these mutations [11].

CT and MRI with angiography provide valuable information to aid diagnosis and preoperative planning [6]. Vagal PGs tend to cause anterior displacement of the internal and external carotid arteries, as seen in this case. When large, these may splay the carotid bifurcation, a finding more typically seen with carotid body tumors. Typically, lesions are avidly contrast enhancing on CT and MRI, reflecting their vascular nature. The classic MRI feature of flow voids gives the tumor a “salt and pepper”

Fig. 5 Previously inconspicuous sustentacular cells outlining the clustered “zellballen” are highlighted with s100 immunostain (*left*) and neurosecretory granules within the cytoplasm of chief cells are

highlighted by a synaptophysin immunostain (*right*) within the main body of tumor

appearance. 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy can be used to detect occult or metastatic PGs [6].

Histologic features of PGs include chief cells surrounded by sustentacular cells in a “nest of cells” pattern [6]. Atypical histologic findings such as cytologic atypia, mitotic activity, necrosis, and infiltrative growth are not predictors of malignancy in isolation as, they can be seen in tumors that behave in clinically benign fashion. When present, they do suggest a higher risk of malignant behavior [6]. However, malignancy is classically defined by the gross or microscopic evidence of regional or distant metastatic disease [1, 3, 8].

Optimal treatment for malignant vagal PGs is not clear due to their rare occurrence, but surgical resection followed by radiation therapy is most commonly described [2]. Five-year survival rates are approximately 80 % for PGs with lymph node metastases and 12 % with distant metastases [2].

Radiation therapy has been offered as a primary treatment modality, and some studies demonstrate success with local control [7]. Mendenhall described postoperative radiation therapy using 60–70 Gy at 2 Gy per once-daily fractionation as their preferred therapy following resection [2]. Surgical resection may require sacrifice of CN X and poses a risk of damage to surrounding vasculature and cranial nerves [3]. It is important to discuss the clinical implications of these deficits preoperatively.

Nerve sheath tumors, specifically a schwannoma (also referred to as neurilemoma), were included in the clinical differential diagnosis for our patient due to their ability to have a similar presentation in this location. Schwannomas are benign tumors composed of schwann cells that produce myelin [9]. In the head and neck most of these tumors present in the parapharyngeal space and arise from CN X [9]. They may also involve CNs IX, XI, XII, sympathetic chain, and brachial or cervical plexus. Histologic characteristics of

schwannomas include alternating Antoni A and B regions, which is distinctly different from PGs. Imaging characteristics of schwannomas include enhancement, however, not to the degree of paragangliomas. Displacement of the common or internal carotid artery is also characteristic of these tumors. They do not demonstrate flow voids [9]. Treatment consists of surgical resection, and nerve preservation is often achieved.

Postoperatively our patient underwent positron emission tomography—computed tomography (PET CT), which showed no evidence of distant disease. Additionally a 123I-MIBG scan was performed and demonstrated no abnormal foci of MIBG activity. Following completion of her workup, she underwent postoperative radiation therapy with 5600 cGy to the tumor bed and left neck with a 600 cGy tumor bed boost. She tolerated this well and was disease free at her 8 month follow-up.

In summary, PGs are slow growing tumors which typically demonstrate benign clinical behavior. Malignant PGs can only be diagnosed by demonstrating metastatic disease. Management of malignant PGs is challenging and can include surgical intervention alone or with the addition of adjuvant radiation therapy. Genetic testing is available to assess whether these patients carry the familial variant of the disease and it allows for the screening of family members.

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