METACHRONOUS MULTICENTRIC JUGULOTYMPANIC AND RETROPERITONEAL PARAGANGLIOMAS: A CASE REPORT AND REVIEW OF THE LITERATURE

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**ABSTRACT**

**Introduction:** Paragangliomas (PGLs) or extra-adrenal pheochromocytomas (PHEO) are rare neuroendocrine neoplasms originating from cells of the primitive neural crest. Head and neck PGLs represent nearly 20% of all PGLs. Retropertioneal localisations are rare and represent less than 2% of all PGLs, and are known to be exceptionally non-functional. **Case report:** In this article we report a case of a 46-year-old female who presented, in 2013, a jugulotympanic PGL for which radiotherapy was delivered. In 2016, a second PGL occurred in the retroperitoneum and was completely resected by surgery alone. 6 year follow up showed a stability of the jugulotympanic PGL and no retroperitoneal recurrence. **Conclusion:** Current knowledge of different management modalities is especially relevant for patients with multicentric PGL. Notably, potential benefits and risks of available treatment options should be taken into consideration for every individual patient in order to provide personalized care. Recently, genetic screening particularly SDH mutations has shown a positive impact in the management of this disease as well as in predicting survival outcomes.

**INTRODUCTION**

Paragangliomas (PGLs) or extra-adrenal pheochromocytomas (PHEO) are rare neuroendocrine tumours originating from neural crest-derived cells situated in the region of the autonomic nervous system ganglia (Feng, 2009 and Capatina, 2013). PGLs can be either sympathetic or parasympathetic in origin. Parasympathetic PGLs are mainly located in the head and neck and less frequently in the thorax and pelvis, and are usually non-functional. While sympathetic PGLs are often located along vertebrae and in pelvis, and usually secrete catecholamines (Barnes, 2004 and Benn, 2006). Head and neck PGLs represent nearly 20% of all PGLs (Mannelli, 2009), 0.6% of head and neck (H&N) tumors, and 0.03% of all tumors (Sykes, 1986). They arise most frequently from the carotid body (60% of cases), followed by jugular bulb (23%), vagus nerve (13%) and the tympanic branch of the glossopharyngeal nerve (6%) (Erickson, 2001). Retropertitoneal PGLs are rare and represent less than 2% of all PGLs, and are exceptionally nonfunctional (Ouaïssi, 2007). Multicentric PGLs can be found in 10% to 20% of sporadic cases, and in up to 80% of familial cases (Boedeker, 2005). In this report, we describe a rare case of metachronous jugulotympanic and retroperitoneal paragangliomas.
showed a solitary well-defined heterogeneous and hypervascular left sided retroperitoneal mass, located immediately lateral to the aorta and measured 42 millimeters in the great diameter (Figure 2).

The chest CT found no intra-thoracic lesion. Moreover, plasma free and 24-hour urine catecholamines and metanephrines were also normal. The tumor was completely resected through a midline laparotomy incision. On macroscopic examination the mass was yellow homogeneous and encapsulated, and measured 5 × 4 × 4 cm. The histological examination was in favor of a retroperitoneal paraganglioma (Figure 3). At 6 years of follow-up, periodic MRI shows a stability of the jugulotympanic PGL, and the abdominal/pelvic CT shows no sign of recurrence of the retroperitoneal location.

**DISCUSSION**

PGLs are rare tumors of the autonomic nervous system and are generally benign (about 70% of cases) (Lenders, 2005 and Loosli, 2014). The criteria of malignancy based on histopathology are not well defined and the only definition of malignancy is the presence of distant metastases (Suarez, 2013). Malignancy is most common in vagal PGs (Papaspyrou, 2012 and Szymanska, 1999). These tumors are classified into two categories: 1) Chromaffin cell tumors arising from the sympathetic system which are often known by catecholamines secretion and intra-adrenal location in 70% of the cases (PHEO) or more rarely extra-adrenal (PGL intrathoracic or abdominal), and 2) non-chromaffin cell tumors (cervical PGL: carotid glomus, jugulotympanic, vagal and laryngeal) arising from the parasympathetic system, rarely secreting, and clinically characterized by compressive symptoms of surrounding anatomical structures (Loosli, 2014). Multiple PGLs may occur synchronously or metachronously. Multicentric tumors occur in 10–20% of all head and neck PGLs (Papaspyrou, 2012; Thabet, 2001 and Lee, 2006). However, reports of much higher incidence of multiple tumors including 40 % for sporadic form and 80 % for familial variety, can be found in the literature (Szymanska, 2015; Gardner, 1996; Netterville, 1995; McCaffrey, 1994).

Genetic mapping of PGLs identified multiple susceptibility genes, including succinate dehydrogenases (SDHB, SDHC, SDHD, SDHAF2, SDHA), transmembrane protein 127 (TMEM127), Von Hippel-Lindau disease (VHL), RET (Rearranged during Transfection) in Multiple Endocrine neoplasia type 2 ( MEN2), neurofibromatosis type 1 (NF1) and myc associated factor X (MAX) (Currás-Freixes, 2015). Germinal mutations of succinate dehydrogenase (SDH) genes are responsible for 70% of familial cases; and about a third of head and neck PGLs, apparently sporadic, have also altered SDH genes. These genetic variants are responsible of one of the five SDH paraganglioma syndromes (1 to 5) (Cavenagh, 2018). PGL 1 is the most common paraganglioma syndrome in which 93% of patients develop extra-adrenal tumors of the head and neck encompassing 84% are parasympathetic, 56%
are multifocal, and only 4% have malignant behavior (Neumann, 2004). 24% of these patients will also develop phaeochromocytoma (Welander, 2011). The second most common mutation affects SDHB gene and is involved in paraganglioma syndrome 4, it is predominantly associated with extra-adrenal PGLs, with 78% of patients developing intra-thoracic or intra-abdominal extra-adrenal sympathetic PGLs. However, 25% of patients will also develop pheochromocytoma (Welander, 2013). There is higher morbidity and mortality than other paraganglioma syndromes with up to 79% of cases with metastasis (Venkatesan, 2011).

In a recent retrospective study, Buffet et al. analyzed the impact of genetic testing on the management and outcomes of patients with PGL and/or PHÉO. The studied population was divided into two groups: “genetic patients”, who were informed of their genetic status (SDHB, SDHD, SDHC, or VHL germline mutation) within the year following the first PPGL diagnosis, and “historic patients”, who only benefited from the genetic test several years after initial PPGL diagnosis. The results revealed that genetic patients had better follow-up than historic patients, with a greater number of examinations and a reduced number of patients lost to follow-up (9.6% vs 72%, respectively). During follow-up, smaller (18.7 vs 27.6 mm; P = 0.0128) new PGLs and metastases as well as lower metastatic spread were observed in genetic patients. Genetic patients who developed metachronous metastases had a better 5-year survival rate than historic patients (P = 0.0127). Hence, the authors suggest that early knowledge of genetic status had a positive impact on the management and clinical outcome of patients with a germline SDHx or VHL mutation (Buffet, 2019). Unfortunately, for reasons of unavailability genetic screening couldn’t be offered to our patient.

Our case report represents the particularity of the occurrence of two metachronous and multicentric PGLs, the first one in the retroperitoneal space which both were nonfunctional. To the best of our knowledge only one case-series reported a case with such association: in this report of 142 head and neck PGLs, Mediouni et al. reported 131 cases with benign PGLs, among them 26 patients had multiples PGLs (18 synchronous and 8 metachronous), with only one patient having a retroperitoneal metachronous PGL (Mediouni, 2014). Contrariwise, in a series of 175 head and neck PGLs 33 patients presented with multiple locations and none of them had a retroperitoneal PGL (Papaspyrou, 2010). Another series of 24 multicentric head and neck PGLs didn’t report any retroperitoneal case (Alvarez-Morujio, 2015). The other particularity is the rarity of nonfunctional retroperitoneal PGL. In fact, less than 2% of all PGLs arise in the retroperitoneum among which 40% are nonfunctional (Ouassili, 2007 and Fahmi, 2015). These tumors are often asymptomatic and are revealed in an advanced stage by compressive symptoms or detected incidentally by an imaging exam (Soufi, 2014). Pretreatment diagnostic modalities include radio-imaging techniques including USG, CT, MRI, 131I, MIBG and PET/CT (18F-FDG or 18F-DOPA) along with endocrine secretion analysis (Wen, 2010; Hemalatha, 2014; Taieb, 2014). Only CT, MRI and endocrine tests were affordable to our patient. The treatment of PGLs must be part of a multidisciplinary approach. Complete surgical resection represents the only curative treatment option for head and neck paragangliomas (Boedeker, 2005; Boedeker CC, 2004 and Kollert, 2006). However, for many tumors, eg. large and locally advanced jugular or jugulotympanic PGLs, the optimal management is controversial due to their specific anatomical location, the high rates of morbidity (cranial nerve injuries), and the risks of incomplete resection, which are the main arguments to advocate upfront radiation therapy (RT) (Taieb, 2014). In contrast to surgery, the aim of radiotherapy in H&N PGLs is to achieve long-term tumor control, but it is not considered as a curative treatment option (Hinerma, 2001 and Boyle, 1990). Until this time, there is no randomized trials comparing surgery to RT, however, many RT retrospective series have been published with local control rates exceeding 90% (Taieb, 2014; Dupin, 2014 and Gilbo, 2014). Complete surgery with no microscopic residue is also the only treatment that allows survival rates of more than 75% at five years in retroperitoneal PGLs. Resection is often challenging as these highly vascular tumors are frequently located near multiple vital blood vessels (Soufi, 2014; Fahmi, 2015 and Gannan, 2015). Preoperative treatment such as chemotherapy, RT or embolisation may be indicated for potentially unresectable tumors in order to reduce the tumor size. RT may also be used for inoperable tumors or for palliation purpose (Bryant, 1982). The 6 year follow up of our patient shows stability of the jugulotympanic PGL, no local recurrence in the retroperitoneum and no distant recurrence.

**Conclusion**

Multiple and multicentric PGLs are not uncommon and may occur synchronously or metachronously. However the association of a head and neck PGL with a non-functional retroperitoneal PGL is exceptional. The knowledge of the different modalities of management is especially relevant for patients with multicentric PGL, and the benefits and potential risks of all treatment options should be taken into consideration for every patient. Recently, genetic screening especially for SDH mutations has shown a positive impact on the management and prediction of clinical outcomes in this rare presentation.

**Conflict of interest:** The author reports no conflict of interest related to this case report.

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**REFERENCES**


