ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 07, pp.5473-5477, July, 2019

DOI: https://doi.org/10.24941/ijcr.35708.07.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

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

***[1]Fouad El Mejjatti, [2]Rim Ouajdi, [3]Rachid Jabi, [4]Mohamed Mouhoub, [5]Tijani El Harroudi, [1]Ali Sbai and [1]Loubna Mezouar**

[1]Department of Radiation Oncology, University Hospital Center of Oujda, Morocco
[2]Department of Radiology, University Hospital Center of Oujda, Morocco
[3]Department of General Surgery, University Hospital Center of Oujda, Morocco
[4]Anatomic Pathology Laboratory of Dr. Berkia, Oujda, Morocco
[5]Department of Surgical Oncology, University Hospital Center of Oujda, Morocco

ARTICLE INFO

Article History:
Received 19th April, 2019
Received in revised form
24th May, 2019
Accepted 27th June, 2019
Published online 31st July, 2019

Key Words:
Paragangliomas, Multicentric, Jugulotympanic, Retroperitoneal.

Corresponding author:
Fouad El Mejjatti

ABSTRACT

Introduction: Paragangliomas(PGLs) are rare neuroendocrine neoplasms originating from cells of the primitive neural crest. Head and neck PGLs represent nearly 20% of all PGLs. Retroperitoneal localisations are rare and represent less than 2% of all PGLs, and are known to be exceptionally nonfunctional. **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.

***Citation: Fouad El Mejjatti, Rim Ouajdi, Rachid Jabi, Mohamed Mouhoub, Tijani El Harroudi, Ali Sbai and Loubna Mezouar,* 2019.** "Metachronous multicentric jugulotympanic and retroperitoneal paragangliomas: a case report and review of the literature", *International Journal of Current Research*, 11, (07), 5473-5477.

INTRODUCTION

Paragangliomas (PGLs) or extra-adrenal pheocormocytomas (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). PGLscan be either sympathetic orparasympathetic 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). Retroperitoneal 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% offamilial cases (Boedeker, 2005). In this report, we describe a rare case of metachronousjugulotympanic and retroperitoneal PGLs.

Case Report

A 46-year-old female with no history of hypertension or any other personal or familial medical backgroundpresentedto our department in 2013 with right side hearing loss, tinnitus and otorrhea. The clinical examination has shown a white pulsatile mass obstructing the external auditory meatus. MRI showed a lytic process of the petrous part of the temporal boneand the jugular foramen evoking a jugulotympanicglomus tumor (Figure 1). A chest, abdominal and pelvic CT didn't show any other lesions. Plasma free and 24-hour urine catecholamines and metanephrines were normal. The biopsy of the mass was considered too risky due to its high vascularization, and therefore surgical resection was not provided. A 3D conformal radiation therapy was performed with a total dose of 50.4 Gy (28 fractions of 1.8 Gy, 5 fractions per week). An MRI was realized 3 months following this treatment and showed stable desease. 3 years later, in 2016, an abdominal CT with contrast

showeda 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).

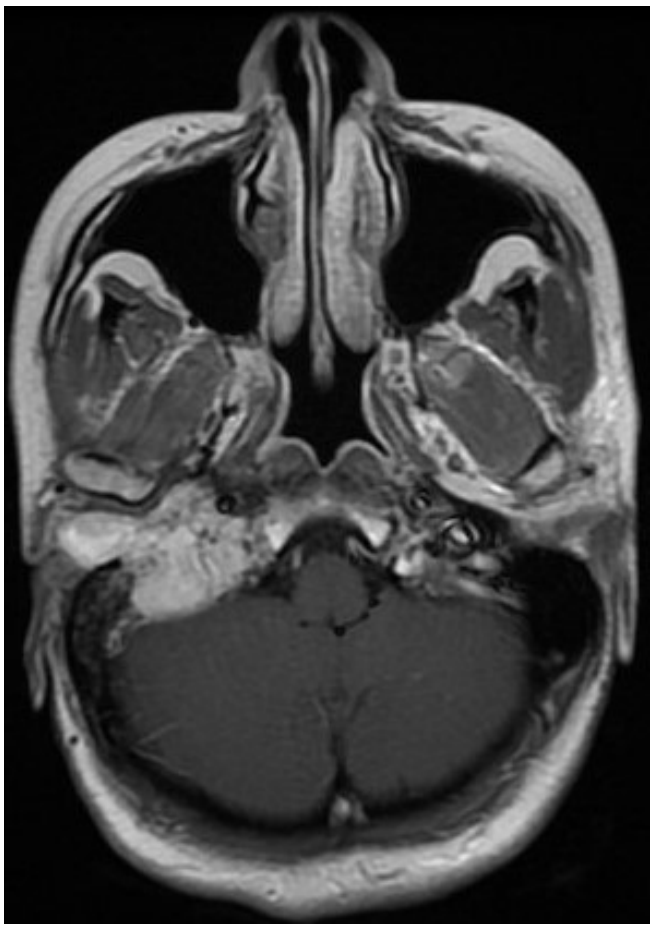

Figure 1. MRI: jugulotympanicparaganglioma

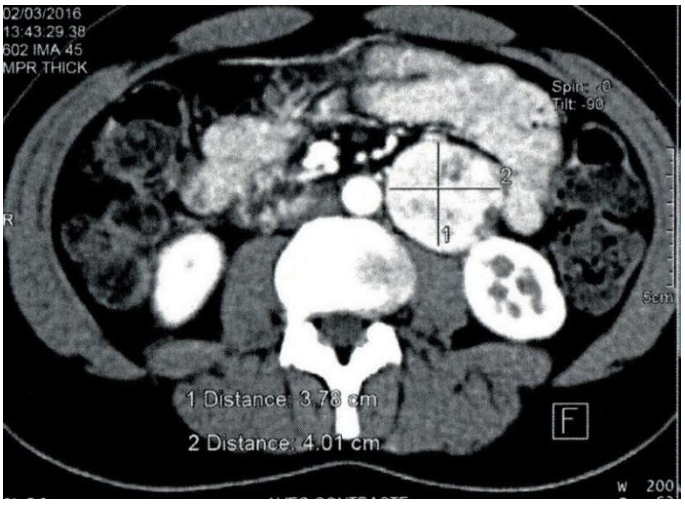

Figure 2. CT scan: retroperitonealparaganglioma

The chest CT found no intra-thoracic lesion. Moreover, plasma free and 24-hour urine catecholaminesand metanephrineswere 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 examinationwas 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.

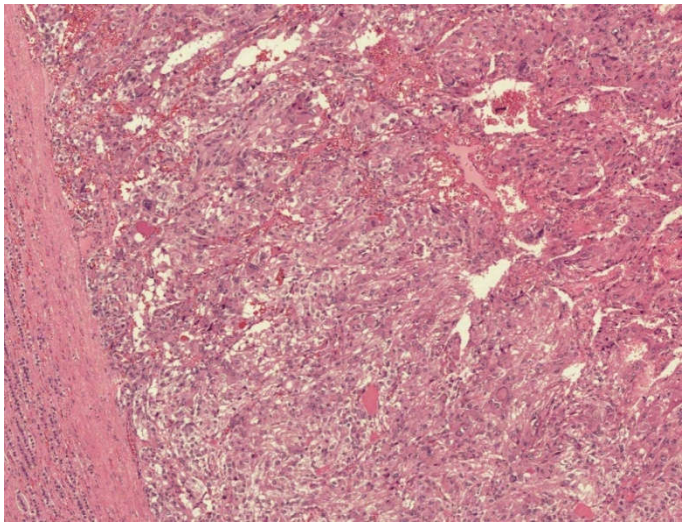

Figure 3. Microphotography showing an encapsulated proliferation made of nests of neoplastic cells

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 tumorsarising 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 PHEO. 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 positiveimpact 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 reportrepresents the particularity of the occurrence of two metachronousand multicentric PGLs, the first one inH&N (jugulotympanic) and the second in retroperitoneal space which both werenonfunctional. 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-Morujo, 2015). The other particularity is the rarity of non functionalret roperitoneal PGL. In fact, less than 2% of all PGLs arise in the retroperitoneumamong which 40% are nonfunctional (Ouaïssi, 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, I 131, MIBG and PET/CT (18F-FDG or 18F-DOPA) along with endocrine secretion analysis (Wen, 2010; Hemalatha, 2014; Taïeb, 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 morbidities (cranial nerve injuries), and the risks of incomplete resection, which are the main arguments to advocate upfront radiation therapy (RT) (Taïeb, 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 trialscomparing surgery to RT, however, many RT retrospective series have been published with local control rates exceeding 90% (Taïeb, 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.

Funding sources: none.

REFERENCES

Alvarez-MorujoRJ, Aristegui Ruiz M.A, PolettiSerafini D, et al. Management of multicentricparagangliomas: Review of 24 patients with 60 tumors. HEAD & NECK 2015; 267-276. Wiley Online Library; DOI : 10.1002/hed.23894.

Barnes L, Tse LLY, Hunt JL & Michaels L 2004. Tumours of the paraganglionic system WHO Classification of Tumours, Volume 8 IARC WHO Classification of Tumours. Geneva: WHO press.

Benn DE, Gimenez□Roqueplo AP, Reilly JR, Bertherat J, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J ClinEndocrinolMetab 2006;91:827□36.

Boedeker CC, Ridder GJ, Neumann HP, Maier W, Schipper J. Diagnosis and management of cervical paraganglioma: the Freiburg experience [in German]. Laryngorhinootologie 2004;83:585–592.

Boedeker CC, Ridder GJ, Schipper J. Paragangliomas of the head and neck: diagnosis and treatment. Fam Cancer 2005;4:55–59.

Boyle JO, Shimm DS, Coulthard SW. Radiation therapy for paragangliomas of the temporal bone. Laryngoscope 1990;100:896–901.

Bryant R.L, Stevenson D.R, Hunton D.W, et al. Primary malignant retroperitoneal tumors. *Am. J. Surg*. 144 (1982) 646–649.

Buffet A, Ben Aim L, Leboulleux S, et al. Positive Impact of Genetic Test on the Management and Outcome of Patients With Paraganglioma and/or Pheochromocytoma. *J ClinEndocrinolMetab,* April 2019; 104(4):1109–1118. doi: 10.1210/jc.2018-02411.

Capatina C, Ntali G, Karavitaki N, and Grossman A.B. The management of head-and-neck paragangliomas. Endocrine-Related Cancer (2013) 20, R291–R305.

Cavenagh T, Patel J, Nakhla N, et al. Succinate dehydrogenase mutations: paraganglioma imaging and at-risk population screening, Clinical Radiology 2018. doi: 10.1016/j.crad.2018.11.004.

Currás-Freixes M, Inglada-Pérez L,Mancikova V,et al. Recommendations for somatic and germline genetic testing of single pheochromocytoma and paraganglioma based on findings from a series of 329 patients. *J Med Genet* 2015; 52:647–656. doi:10.1136/jmedgenet-2015-103218.

Dupin C, Lang P, Dessard-Diana B, et al. Treatment of Head and Neck Paragangliomas With External Beam Radiation Therapy. *International Journal of Radiation Oncology. Biology. Physics* 2014; Volume 89; Number 2 ; 353-359.

Erickson D, Kudva YC, Ebersold MJ, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. *J ClinEndocrinolMetab.* 2001;86(11): 5210–5216.

Fahmi Y, Elabbasi T, Khaiz D, et al. Paragangliomeretropéritonéal: à propos d'un cas et revue de literature (retroperitoneal paraganglioma: report of a case and literature review). *Pan African Medical Journal.* 2015; 21:298 .doi:10.11604/pamj.2015.21.298.6564.

GannanE, van Veenendaal P, Scarlett A, Ng M, et al. Retroperitoneal non-functioning paraganglioma: A difficult tumourtodiagnose and treat. International Journal of Surgery Case Reports 17 (2015) 133–135.

Gardner P, Dalsing M, Weisberger E, Sawczuk A, Miyamoto R. Carotid body tumors, inheritance, and a high incidence of associated cervical paragangliomas. *Am J Surg* 1996; 172:196–199.

Gilbo P, G. Morris C, J. Amdur R, et al. Radiotherapy for Benign Head and Neck Paragangliomas: A 45-Year Experience. Cancer 2014; 3738-3743. *Wiley Online Library.* DOI: 10.1002/cncr.28923.

Hemalatha. A. L, AvadhaniGeeta K, Anoosha. K, Ashok. K.P, Rajani Deepa M. Extra- Adrenal Silent Retroperitoneal Paraganglioma: Report of a Rare Case. *Journal of Clinical and Diagnostic Research.* 2014 Nov, Vol-8(11): FD06-FD07.

Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Antonelli PJ, Cassisi NJ. Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomusvagale. Head Neck 2001;23:363–371.

Kollert M, Minovi AA, Draf W, Bockmuhl U. Cervical paragangliomas tumor control and long-term functional results after surgery. Skull Base 2006;16:185–191.

Lee KY, Oh YW, Noh HJ, et al. Extraadrenalparagangliomas of the body: imaging features. *Am J Roentgenol* 2006; 187(2):492–504.

Lenders JWM, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366:665-75.

Loosli N, Kohler Ballan B, Pechère-Bertschi A, Karenovcs W, Triponex F. Pheochromocytoma and paraganglioma : basics for the general practitioner. *Rev Med Suisse* 2014; 10 : 1650-5.

Mannelli M, Castellano M, Schiavi F, et al. Clinically guided genetic screening in a large cohort of italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. *J Clin Endocrinol Metab.* 2009; 94(5):1541–1547.

McCaffrey TV, Meyer FB, Michels VV, Piepgras DG, Marion MS. Familial paragangliomas of the head and neck. Arch Otolaryngol Head Neck Surg 1994; 120:1211–1216.

Mediouni A, Ammari S, Wassef M, et al. Histoire naturelle des paragangliomesmalins de la tête et du cou. Analyse comparative (Malignant head/neck paragangliomas. Comparative study). Annalesfrançaisesd'oto-rhino-laryngologie et de pathologiecervico-faciale 131 (2014) 145–151.

N. Feng, W.Y. Zhang, X.T. Wu.Clinicopathological analysis of paraganglioma with literature review, *World J. Gastroenterol* 15 (June (24)) (2009)3003–3009.

Netterville JL, Reilly KM, Robertson D, Reiber ME, Armstrong WB, Childs P. Carotid body tumors: a review of 30 patients with 46 tumors. Laryngoscope 1995; 105:115–126.

Neumann HP, Pawlu C, Peczkowska M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDH D gene mutations. JAMA 2004; 292:943e51.

Ouaïssi M, Sielez nieff I, Pirrò N, Payan MJ, Chaix JB, Consentino B, Sastre B. Paragangliome non sécrétantrétropéritonéal : À propos d'une observation (nonfunctional retroperitoneal paraganglioma : a cse report). Gastroentérologie Clinique et Biologique. 2007; 31(3): 307-308. PubMed |Google Scholar.

Papaspyrou K, Mewes T, Rossmann H et al. Head and neck paragangliomas: report of 175 patients (1989–2010). Head Neck 2012; 34:632–637. doi:10.1002/head.21790.

Papaspyrou K, Mewes T, Rossmann H, et al. Head and neck paragangliomas: report of 175 patients (1989–2010). HEAD & NECK 2012; 632-637. Wiley Online Library; DOI: 10.1002/hed.21790.

Soufi M, Benamr S, Chad B. Paragangliomerétropéritonéal non secrétant: une cause rare d'occlusionintestinale haute (non secreting retroperitoneal paraganglioma: a rare cause of upper intestinal obtruction). *Pan African Medical Journal*. 2014; 18:312 doi:10.11604/ pamj.2014.18.312.5140.

Suarez C, Rodrigo JP, Boedeker CC et al. Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy. Head Neck 2013; 35:1195–1204. doi:10.1002/hed.22976.

Sykes JM, Ossoff RH. Paragangliomas of the head and neck. *Otolaryngol Clin North Am.* 1986;19(4):755–767.

Szymanska A, Szymanski M,·Czekajska□Chehab E, Gołabek W,· Szczerbo□Trojanowska M. Diagnosis and management of multiple paragangliomas of the head and neck.Eur Arch Otorhinolaryngol 2015; 272:1991–1999. DOI 10.1007/s00405-014-3126-z.

Taïeb D, Kaliski A, Boedeker C, et al. Current Approaches and Recent Developments in the Management of Head and Neck Paragangliomas. Endocrine Reviews, October 2014, 35(5):795–819.

Thabet MH, Kotob H. Cervical paragangliomas: diagnosis, management and complications. J LaryngolOtol 2001; 115:467–474.

Venkatesan AM, Trivedi H, Adams KT, et al. Comparison of clinical and imaging features in succinate dehydrogenase-positive versus sporadic paragangliomas. Surgery 2011; 150:1186e93.

Welander J, Soderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. EndocrRelat Cancer 2011;18:R253e76.

Wen J, Li HZ, Ji ZG, et al. A decade of clinical experience with extra adrenal paragangliomas of retroperitoneum: Report of 67 cases and a literature review. *Urol Ann.* 2010;2:12-16.

****