

Secreting Paraganglioma of the Organ of Zuckerkandl with Extensive Degenerative Necrosis

Dhouha Bacha¹, Fatma Medhioub², Wael Ferjaoui^{2*}, Lassad Gharbi², Ahlem Lahmar¹, Sana Ben Slama¹ and Saadia Bouraoui¹

¹Department of Pathology, Mongi Slim University Hospital, Faculty of Medicine of Tunis, Tunisia; ²Department of General Surgery, Mongi Slim University Hospital, Faculty of Medicine of Tunis, Tunisia

Corresponding author:

Dr Wael Ferjaoui, Department of General Surgery, Mongi Slim University Hospital, Faculty of Medicine of Tunis, Tunisia, Tel: +216 52430099, E-mail: farjaouiwael4@gmail.com

Abstract

We report a case of a secreting paraganglioma developed on the organ of Zuckerkandl. Paragangliomas are tumors that arise from tissue of the extra adrenal sympathetic nervous system. They may or may not produce catecholamines. One of the most uncommon complications of adrenal paragangliomas is the extensive necrosis within the tumor that is said to be associated with the attacks of alternating hypertension and hypotension due to catecholamine release. To our knowledge, this is the first cases of a secreting paraganglioma of the organ of Zuckerkandl with a large central area of necrosis.

Keywords: Paraganglioma; Hypertension; Lumpectomy; Coagulative necrosis; Immunohistochemistry

Introduction

Pheochromocytomas are neuroendocrine tumors that arise within the adrenal medulla. Subsets of this tumor family that arise from extra adrenal sympathetic nervous system tissue are referred to as paragangliomas (PGLs). They may arise in the sympathetic or parasympathetic paraganglia. Parasympathetic PGLs are located especially in the head and neck and have dopamine as a main product, whereas sympathetic PGLs secrete epinephrine and are located basically in the abdomen and pelvis. [1,2] One of the most common sites of the sympathetic PGLs is the organ of Zuckerkandl (OZ). [3] These tumors are yet rare with a highly variable clinical presentations making the diagnosis challenging. However, timely diagnosis and appropriate treatment are crucial to prevent severe complications.

Massive catecholamine release causing an extensive tumor necrosis is an infrequent complication of sympathetic PGL. [4]

Herein, we report a case of an extensive necrosis complicating a PGL of the OZ. A detailed histopathological analysis was performed.

Case Presentation

A 29-year-old man developed acute-onset episodic headaches and palpitations. He had no personal or family history of cardiovascular disease. At physical examination, his blood pressure was 220 over 120 mmHg. Otherwise, no thyroid struma, chest rates, heart murmurs, abdominal tenderness or mass, and no peripheral edema were noted. An electrocardiogram showed a normal sinus rhythm, with a heart rate of 65 beats/minute. Chest X-ray showed no abnormalities with a cardiothoracic ratio of 46 %. Laboratory investigations showed normal findings (complete blood count, serum electrolytes, liver and renal functions). Episodic symptoms disappeared within 3 days under antihypertensive treatment. He did not take his treatment correctly and no further exploration was carried out.

He returned 3 months later with a right flank pain. Abdominal computed tomography (CT) revealed a 5 cm heterogeneous mass within the retroperitoneum, between infrarenal abdominal aorta and inferior vena cava [Figure 1]. Other headache and palpitation episodes occurred but this time associated with low blood pressure (40/25 mm Hg).

Elevated urinary normetanephrine levels were noted (44.43 µmol/L). Metanephrine levels were normal (1.85 µmol/L).

According to clinical presentation, biological and CT scan findings, a paraganglioma was highly suspected preoperatively.

He was put on alpha-blockers. After equilibration of his blood pressure, a complete surgical excision of the mass has been decided through a median infra-umbilical laparotomy.

Peroperatively, there were no peritoneal implants, vessel infiltration nor regional adenomegaly.

A solid cystic 6 cm-mass was found directly at the aortic bifurcation. It was adherent to the inferior vena cava and to the right of the aorta but it was freed with surgical dissection with a total bleeding of less than 100 cc and a surgical time of 150 min [Figure 2].

On gross examination, the surgical specimen displayed a 6 × 4.5 × 4 cm, encapsulated tumor, with both firm and pasty consistency zones. The cut surface was red-brownish and showed hemorrhage areas [Figure 3 and Figure 4].

Hematoxylin and eosin-stained showed a well-circumscribed and encapsulated tumor with a large coagulative necrosis (about

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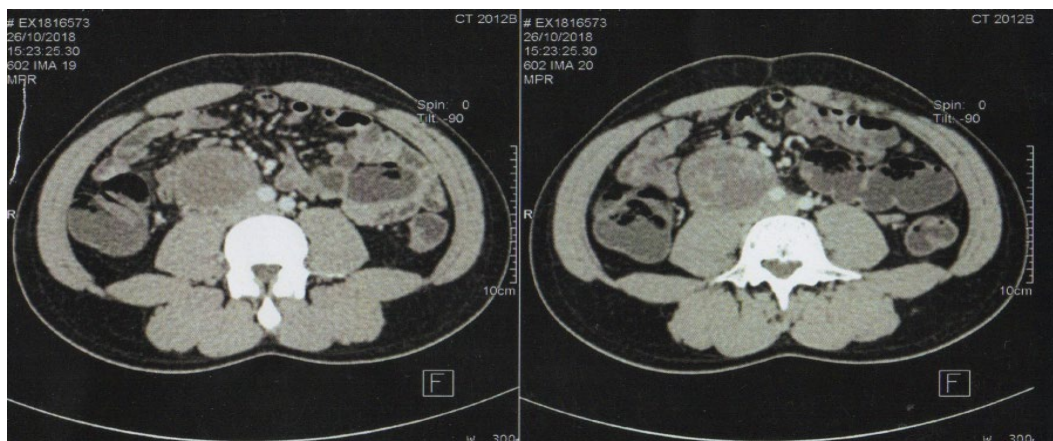


Figure 1: Abdominal computed tomography showing a 5 cm heterogeneous mass within the retroperitoneum, between infra renal abdominal aorta and inferior vena cava.

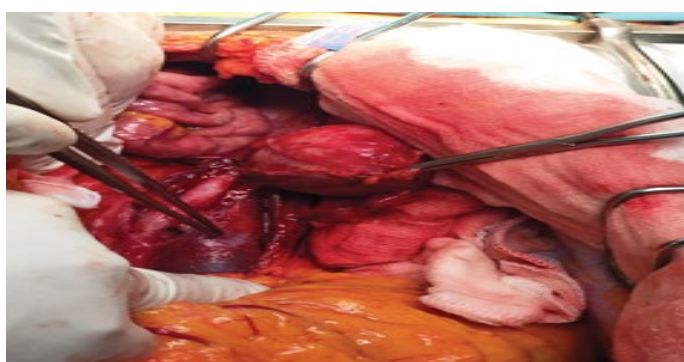


Figure 2: A solid cystic 6 cm-mass located at the aortic bifurcation, adherent to the inferior vena cava and to the right of the aorta.



Figure 4: The cut surface was red-brownish and showed hemorrhage areas.



Figure 3: The surgical specimen displayed a 6 × 4.5 × 4 cm, encapsulated tumor, with both firm and pasty consistency zones.

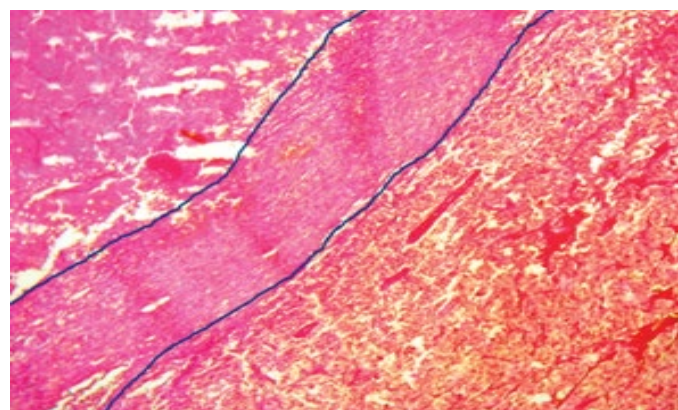


Figure 5: Viable and necrotic tumor areas separated by fibrous septa (between two lines). (Haematoxylin and Eosine 40x).

60% of tumor surface). Cellularity was moderate and tumor cells were polygonal, arranged in sheets and lobules surrounded by a delicate capillary network generating typical “zellballen” [Figure 5 and Figure 6]. They had an abundant and eosinophilic cytoplasm. Although nuclear pleomorphism was present, mitotic activity was low (<1 mitosis/10 high power fields). There was no vascular nor capsular invasion. Immunohistochemical study revealed diffuse and strong expression of chromogranin and synaptophysin and a negative staining with cytokeratin. Ki-67 labeling index was less than 1%.

Postoperative course was uneventful. He was discharged in a stable state. The 2-year follow-up revealed resolution of any palpitations and his blood pressure was well controlled.

Discussion

The organ of Zuckerkandl (OZ) was first described in 1901 by Emil Zuckerkandl.^[5] It comprises of a small mass of chromaffin cells derived from neural crest located along the aorta from the inferior mesenteric artery to aortic bifurcation. It is believed to be of greatest importance during the early gestational period as a homeostatic regulator of blood pressure, secreting catecholamines. Then, it undergoes atrophy and degenerative changes with increased stroma formation and decreased catecholamine content.^[6] By adulthood, distinct microscopic groups of extra adrenal chromaffin cells endure and have the potential to develop into tumors.^[7]

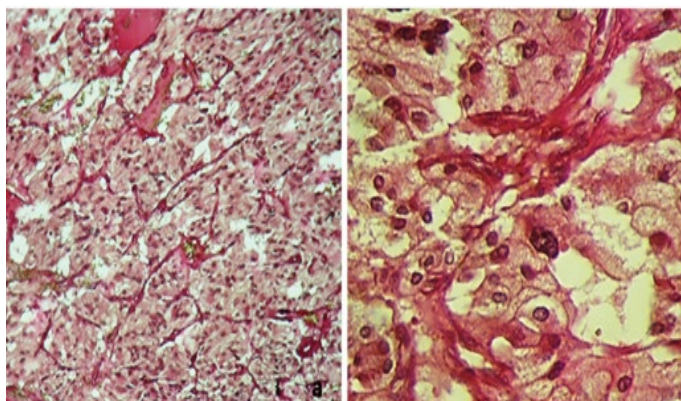


Figure 6: (a) Tumor cells are arranged in a “zellballen” pattern, separated by a delicate capillary network (Haematoxylin and Eosine 100x), (b) Polygonal tumor cells with abundant cytoplasm and a relatively pleomorphic nuclei (Haematoxylin and Eosine 200x).

There are two types of tumors that may occur in the OZ: neuroblastomas which occur exclusively in children^[8] and paragangliomas. The first documented case of PGL of OZ was in 1902.^[9] Currently, more than a century later, there are at least 135 reported cases in the world literature^[10]. They develop at any age with a highest incidence among young adults between 21 and 40 years old and an equal sex distribution.^[10,11] Pediatric onset paragangliomas are almost always hereditary even in the absence of a family history, that’s why a genetic testing should be offered for all pediatric patients with paragangliomas.^[12] At least 30% of paragangliomas are known to be hereditary, a proportion that has increased with the discovery in 2012 of 10 susceptibility genes that are: *VHL*, *RET*, *NF1*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *TMMEM127*, *MAX*.^[13]

Clinical presentations vary depending on their functionality. In fact, 60% of these tumors are functional, i.e., secrete catecholamine causing therefore hypertension which can be sustained or paroxysmal, as in our case.^[14] According to the World Health Organization (WHO) criteria, 74% of patients with paragangliomas of the OZ have hypertension.^[15] High blood pressure can be accompanied by episodic headaches, palpitations and sweating. This classic triad is seen in less than 25% of patients.^[16] At least one component of the triad occurs in approximately 50% of patients.^[16] Patient may also present with sudden attacks of alternating hypertension and hypotension, as was the case with our patient.^[17] Rarely, if a paroxysm is sufficiently severe, a hypertensive crisis or myocardial infarction may occur.^[18]

Non-functioning tumors, clinically silent with non-elevated catecholamine levels account for 43% of PGLs.^[19] Non-specific symptoms that can mimic many other conditions can be presented. Sometimes, they are related to local tumor development causing abdominal pain, mass and heaviness. Bowel, neurological and vascular signs may reveal a locoregional invasion.^[20] Sometimes, the diagnosis can be made in front of metastases or as part of a hereditary disease. Despite the highly variable clinical presentation, approximately 10% of paragangliomas are discovered incidentally at imaging performed to evaluate patients with unrelated symptoms.^[13]

The diagnosis relies on biochemical evidence of excess catecholamine production. Current guideline recommend that initial testing should include measurements of urinary or plasma metanephrines, metabolites of catecholamines. They are used because their metabolism is relatively constant unlike catecholamines. Normetanephrine and vanillylmandelic acid levels are also assessed. Patients with paragangliomas in the OZ have elevated normetanephrine only but not elevated metanephrine as it was in our case. It is because phenyl ethanolamine N-methyl transferase, the enzyme required for converting normetanephrine to metanephrine is not expressed in paragangliomas as it is in the adrenal medulla.^[21]

As for imaging studies, abdominal and pelvic CT or MRI is usually performed first. They have similar success.^[22] MRI classically shows an enhancing mass with high T2-weighted signal intensity in approximately one third of cases.^[23] Other findings may include cystic change, necrosis hemorrhage and calcifications. In most cases, functional imaging by ¹²³I-MIBG scintigraphy also plays an important part as it has excellent sensitivity and specificity and may help detect primary or metastatic tumors that could be missed on CT/MRI. In our case, the MIBG scintigraphy wasn’t performed. Currently, newer modalities of functional imaging (⁶⁸GA-DOTATATE PET/CT, ¹⁸F-FDOPA PET/CT) offer greater sensitivity but they are not yet widely available.^[23]

Surgical resection is the treatment of choice for paragangliomas as for pheochromocytomas. It is the only possibility for a cure. It is performed preferably laparoscopy. Walz et al. have shared their experience with 27 PGLs treated by laparoscopy and they recommend a retroperitoneoscopic approach for tumors that are caudal to the renal vessels, and transabdominal laparoscopy for PGLs situated cranial to those vessels.^[24] However, if the tumor is greater than 6 cm, as was the case with our patient, or there is a high-risk of malignancy, an exploratory laparotomy is required. We begin by searching for peritoneal implants, regional pathologic adenomegaly and ectopic location of chromaffin cells. Retroperitoneal access requires the mobilization of the right colon. Once the tumor is found, its relationships with the neighboring vessels should be studied. Complete excision is required. Before the operation, patients are pretreated with alpha-blockers to reduce mortality and surgical complications.^[25] If tachyarrhythmias develop, beta-adrenergic antagonists should be added to the regimen.^[10] The main concern intraoperatively is catecholamine release due to the tumor manipulation leading to a hypertensive episode. Postoperatively, blood pressure should be monitored. It is recommended plasma and/or urine metanephrines be rechecked 2-4 weeks postoperatively. A normal level indicates a successful resection.

The preoperative arterial embolization has been described mainly in cervical PGLs as its use in abdominal PGLs can expose to intestinal ischemia and liberation of catecholamines into the blood torrent which can induce a hypertensive crisis. It is reserved especially to hypervascularized and larger PGLs to debulk the tumor and reduce the surgical time and the intraoperative bleeding or to the ones that cannot be excised to diminish the effects of excessive secretion of catecholamines.^[26]

Chemotherapy and radiation therapy have also been used as treatment option. Chemotherapy is considered for patients with metastatic or unresectable tumors and for neoadjuvant therapy for large bulky primary PGLs to facilitate an eventual resection.^[27] Radiation therapy has been used to reduce the tumor size and to palliate the symptoms and has shown positive results when it is directed at the tumor bed and spinal metastases.^[28] Chemotherapy has been used for mainly palliative purpose in malignant disease.^[27]

A particularity in our case is the presence of an extensive necrotic center within the tumor. In fact, the catecholamine-induced vasoconstriction of the tumor vessels causes a chronic ischemia and then acute infarction occurs in the tumor resulting in the extensive necrosis.^[29] Subsequently, fluctuating catecholamine release from the infarcts causes repeated attacks of alternating hypertension and hypotension which accelerates the progression of the extensive necrosis. Many previous cases of extensive necrosis in adrenal pheochromocytoma showed spontaneous remission of catecholamine crisis even before the surgical removal of the tumor.^[4,30-32] These same cases reported that patients with tumor extensive necrosis often present with abdominal pain,^[4,30-32] as it was with our patient. Most cases of spontaneous large necrosis of adrenal pheochromocytoma were shown to be benign,^[4,32] but malignant cases have also been reported.^[30] The 2017WHO classification defined malignant pheochromocytoma by the development of metastasis. PGLs are malignant in 10 to 40% of the cases.^[18] However, the categories of benign and malignant pheochromocytomas have been eliminated for an approach based on risk stratification. The Pheochromocytoma of the Adrenal gland Scaled Score (PASS) was established in 2002 and it provides a threshold for predicting metastatic risk.^[33] But this score applies only to pheochromocytomas and is not intended for use in extra-adrenal paraganglioma. Therefore, a new score, the Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) was developed in Japan in 2014.^[34] It classifies pheochromocytomas and paragangliomas into a three-tiered grading system providing an assessment of both risk of metastasis and patient survival. It is based on histological features, Ki-67 immunohistochemistry, and hormone data. The GAPP score of our patient is 1 which means the tumor is well-differentiated. Additional risk factors including tumor size >5 cm and SDHB mutation or loss of immunohistochemical expression of SDHB were also mentioned.^[34] Kimura showed that the combined use of GAPP and SDHB immunohistochemistry is useful to predict tumor metastasis and patient prognosis. In fact, the reported risk of metastasis and 5-year-old survival rates are respectively 3.6% and 100% for well-differentiated tumors as in our case, 60% and 66.8% for moderately differentiated type and 88.2% and 22.4% for poorly differentiated tumors.

Unfortunately, even with confirmed successful resections by pathology, 11% of patients return with either a recurrence or metastases, usually within liver, lungs and bone.^[10] Metastatic lesions have a poor prognosis with a 5-year survival rate of 36% according to one study.^[28-34]

Conclusion

The paraganglioma of the organ of Zuckerkandl has a wide variety of clinical presentation. Recognizing the signs and making the appropriate diagnosis is crucial because patients who are undiagnosed can suffer severe consequences of hypertensive crises including heart attacks, strokes and even death. This case highlights the need to consider spontaneous tumor infarction due to catecholamine fluctuating release as a rare but severe complication of these tumors. To our knowledge, this is the first case of a secreting paraganglioma of the organ of Zuckerkandl with a large central area of necrosis.

Competing Interests

The authors declare that they have no competing interests.

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