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Case Report
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Extra-Adrenal Silent Paraganglioma: An Old Foe

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Abstract

Extra-adrenal paragangliomas are rare neuroendocrine tumors arising from chromaffin cells located in areas where par ganglia normally occur. They usually present with symptoms of catecholamine excess, however, a significant proportion of cases are asymptomatic or present with non-specific symptoms. One such variety comprises the silent or normotensive paraganglioma. We present a case of a 50 year-old female who presented with abdominal pain. On Magnetic Resonance Imaging (MRI) a well demarcated mass was found on the posterior abdominal wall, closely related to the abdominal aorta and the left kidney. During surgery to remove the mass, hemodynamic fluctuations were encountered, which were able to be managed promptly. Here we highlight the non-specific presentation of a silent paraganglioma leading to diagnostic dilemma and its potentially catastrophic consequences. We also focus on the lack of specific non-invasive preoperative diagnostic characteristics which are necessary for patient safety and suggest the routine assessment of the much under-utilized catecholamine profile in the preoperative evaluation of lesions localized in the potential sites of occurrence of paragangliomas, especially in patients presenting with non-specific symptoms.

Keywords: Paraganglioma; Pheochromocytoma; Extra-adrenal; Neuroendocrine tumor; Catecholamine; Hypertensive crisis

Introduction

Paragangliomas are rare neuroendocrine tumors that may arise at any location where chromaffin tissues are normally located. They are termed paragangliomas regardless of their location, apart from those that arise from adrenals, when they are termed pheochromocytoma. When they arise in locations other than the adrenals, they are termed extra-adrenal paragangliomas. Common extra-adrenal locations include carotid body, jugular foramen and aortic bifurcation [1].

Classical presentation of paragangliomas is characterized by symptoms of catecholamine excess including headaches (usually paroxysmal), palpitations diaphoresis and episodic hypertension. However, these symptoms are only seen in those cases where the tumors are functional, i.e., those that secrete catecholamines. A significant proportion of cases (upto 55%) are non-functional or clinically do not manifest hormone activity (silent) and hence, present with vague symptoms, mostly related to compression of local structures [2].

These silent paragangliomas pose a diagnostic challenge to the surgeon, delaying or misleading management and, rarely, contributing to fatal outcomes due to complications such as hypertensive crisis, pulmonary edema, cardiac ischemia and arrhythmias [1]. In this article we report such a case of a silent extra-adrenal paraganglioma.

Case Presentation

A previously healthy 50 year-old female presented with a 20-day history of left-sided abdominal pain associated with nausea, vomiting and episodic headaches. Physical examination was unremarkable. Laboratory tests also did not reveal any abnormalities. MRI of the abdomen showed a well demarcated, mass approximately of size 6.5 cm × 6.9 cm × 5.9 cm, on the posterior abdominal wall, lying antero-inferiorly to the left kidney, closely related to the abdominal aorta, from which it was receiving blood supply via a small branch. It demonstrated hypo intensity on T1 and hyper intensity on T2-weighted images, restricted diffusion on DWI and gradual enhancement after gadolinium contrast (Figures 1-4). Venous drainage was seen to be by a small vein leaving the lesion at its postero-lateral aspect, eventually draining into the splenic vein.

An exploratory laparotomy was undertaken and the abdomen was entered via a left paramedian incision. An encapsulated, approximately 8 cm × 8 cm × 6 cm, soft mass was found within the colonic mesentery in the left lower abdomen. It was adjacent to the abdominal aorta on its medial

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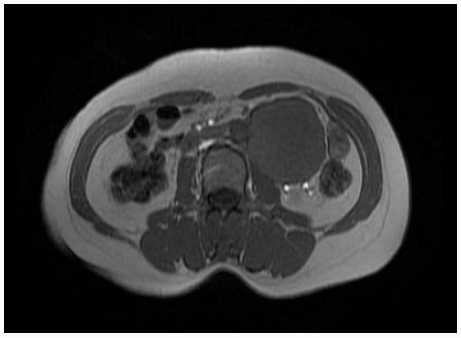

Figure 1: Axial T1 weighted MRI showing a large hypo intense mass in the posterior abdominal wall.

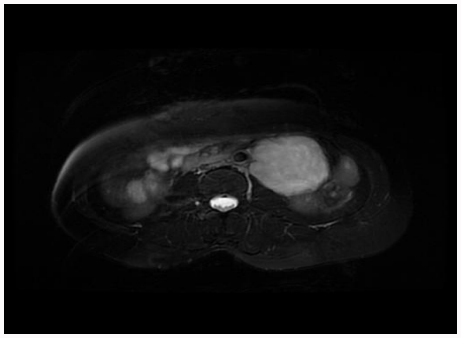

Figure 2: Axial T2 weighted MRI showing a large hyper intense mass in the posterior abdominal wall, lying antero-inferiorly to the left kidney.

aspect and adherent to the upper segment of the left ureter on its lateral aspect. During extrusion of the mass, the patient's blood pressure shot up to 250/120 mmHg, which was managed with sodium nitroprusside. This was followed by a brief episode of hypotension which was managed and fluids, epinephrine and norephinephrine. A diagnosis of extra-adrenal paraganglioma was considered. The mass was removed in its entirety. During the operative period, no further unpredicted events occurred. Postoperatively, it was decided to keep the patient under observation in the intensive care unit. During her period in the ICU, investigations did not reveal any cardiac damage or other end-organ damage. After 36 hrs, she was transferred back to the ward. No further untoward events occurred during the course of hospital stay. She was discharged on postoperative day 6.

Histopathology confirmed the diagnosis of paraganglioma (Figure 5). No vascular and capsular invasion or necrosis within the tumor stroma was noted. Immunohistochemistry was positive for synaptophysin and chromogranin A, negative for valentine and S-100 protein, Ki-67 expression was <1% and mitoses was rare.

There were no complications over 5 months of follow up.

Discussion

Paragangliomas are rare tumors that can occur in all locations where paraganglia are normally found in the human body. They can be of parasympathetic or sympathetic type. Parasympathetic paragangliomas occur mainly in the head and neck, whereas sympathetic paragangliomas occur in the thorax and abdomen [3,4]. Sympathetic paragangliomas can further be classified as functional or non-functional depending on whether they produce catecholamines or not, respectively.

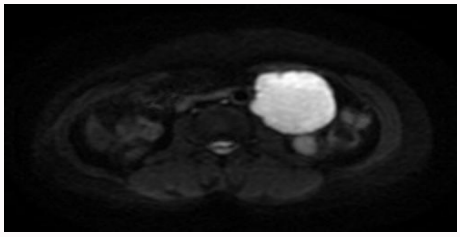

Figure 3: DWI showing significant restricted diffusion.

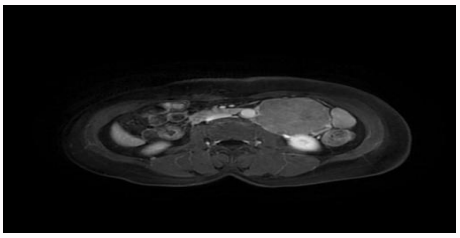

Figure 4: Axial post-contrast MRI showing homogenous enhancement of the mass.

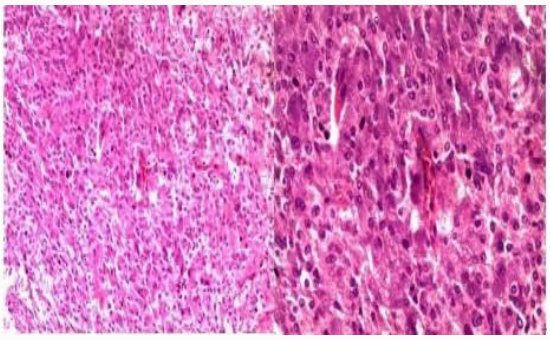

Figure 5: Histopathology of the specimen showing nesting of tumor cells. Surrounding capillaries are infrequently seen.

Functional paragangliomas may be smaller in size due to the fact that they are diagnosed relatively early and easily because of their endocrine symptoms [5]. The most common presenting symptoms are episodic hypertension, episodic headache, diaphoresis and tachycardia, however, patients may also frequently experience flushing, anxiety, panic attacks and palpitations [2]. There have also been reports of functioning paragangliomas presenting as ventricular arrhythmias [6], deep vein thrombosis [7], acute pancreatitis [8] and secondary diabetes [9].

Non-functional paragangliomas are much more difficult to diagnose and they most often present as abdominal mass [5]. They may be comparatively larger in size and have uncommon symptoms, particularly related to compression of adjacent organs [2]. They may also present as back pain [10], abdominal pain [11] or remain asymptomatic.

In this case report, we also want to emphasize that because paragangliomas have variable biological activity and secretary profile, they should not be classified simply as functional and non-functional [12]. A more dangerous entity is perhaps a secretary normotensive paraganglioma, like the one we report here - clinically silent and manifest only when mechanically or pharmacologically provoked. Our patient presented with non-specific symptoms and did not have any history of hypertension or previous episodes suggestive

of catecholamine excess. Laboratory test results did not show any evidence of latent organ dysfunction. Preoperative identification and timely management of silent paragangliomas is truly a challenge for surgeons, as intraoperative life-threatening complications may catch the surgical team unprepared with the potential for fatal consequences [1].

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are most often used as imaging modalities, however, 123I-Meta-Iodobenzylguanidine (MIBG) and Fluorine-8-L-Dihydrophenylalanine (18F-DOPA) Positron Emission Tomography (PET) are considered more specific for diagnosis [3,5,13,14]. These imaging modalities are usually not adopted by economically challenged patients such as ours. In addition to economic concerns, the fear of radiation exposure also deters patients from utilizing these modalities. This points to the need of inexpensive, safe and readily available specific diagnostic tests and diagnostic markers. Although catecholamine profile (plasma catecholamines, urine catecholamines, plasma free metanephrines and urine metanephrines) can be easily obtained and is recommended in the symptomatic patients and adrenal incidentalomas [4], in silent or non-functioning extra-adrenal tumors such as in our patient, whether or not to routinely obtain catecholamine profile is still at the discretion of the physician as no clear guidelines regarding biochemical analysis in asymptomatic patients are available at present. However, owing to the potential for catastrophic consequences, we believe that this test should be a part of routine assessment for silent tumors that, particularly on imaging, fit the profile of paragangliomas.

Additionally, there are no unique imaging characteristics of paragangliomas and differences are frequently encountered between imaging and intraoperative findings [5]. In general, extra-adrenal paragangliomas are found close to the aorta, renal vessels and vena cava. As highlighted by Xiao et al., specific imaging characteristics such as presence of tortuous blood vessels inside the tumor, tumor in close proximity to the renal blood vessels and aorta, could be used as criteria specific for paragangliomas [5]. Indeed, in that study, the authors showed that the rate of misdiagnosis on imaging could be drastically reduced if such criteria are adhered to. However, for such criteria to be reliable enough to be routinely implemented, large scale and multicentered studies are essential.

Percutaneous biopsy is an option for more accurate diagnosis but is usually precluded owing to the location of the tumors and the risk of catecholamine crisis occurring during the procedure. Hence, we don't feel that this is a feasible option for regular use.

Histopathological analysis is the only way of accurately diagnosing paragangliomas. Features specific to paragangliomas include highly vascular appearance and chief cells or chromaffin cells arranged in well-defined nests, separated by fibrovascular septa ("zellballen" appearance). Immunohistochemistry also aids in the diagnosis [2]. Our patient's tumor was positive for neuroendocrine markers synaptophysin and chromogranin A. Other markers specific for paragangliomas include neuron specific enlace, S-100 protein.

The distinction between benign and malignant paragangliomas is also difficult. There are no specific molecular, cellular or histological markers that can reliably diagnose malignancy [15]. Immunohistochemical markers, although used widely, are deemed unreliable for distinguishing malignant paragangliomas. Some markers associated with malignant paragangliomas include Ki-67, S-100 and HSP90 [3]. Our patient was negative for S-100, Ki-67 expression was low (<1%). Some histological predictors of malignancy include confluent tumor necrosis, vascular invasion, coarse modularity and high mitotic activity [16]. Vascular invasion was not seen and mitoses was rare in our patient. The finding of local invasion during surgery or of metastatic lesions (the presence of chromaffin tissue in sites usually devoid of chromaffin tissues) is considered the only reliable identifying feature of malignant paragangliomas [15,16]. Long-term follow up of cases with candidate immunohistochemical markers, imaging and histopathological markers should be done to rule out malignancy in absence of other lesions [15].

Surgical resection is the only option for cure due to its malignant potential. Surgery is usually challenging because of the relatively inaccessible location, close proximity to large vessels and the potential of occurrence of hemodynamic fluctuations, especially in pre-operatively asymptomatic cases. Although randomized controlled trial data are lacking to support decision making on preoperative management of asymptomatic normotensive paragangliomas, the Endocrine Society recommends preoperative hemodynamic control with alpha-adrenoceptor antagonists as the first choice [4]. Although alpha blockade has its own risks in orthostatic and prolonged post-operative hypotension and so on, we concur with the Endocrine Society guidelines because the possible consequences in a non-optimized patient far outweigh these risks. Other options for pre-operative blood pressure control are calcium channel blockers and metyrosine, but evidence is still lacking regarding their use [12].

Another concern that we put forward is, when a diagnosis is reached only during the operation itself, should the operation be temporarily abandoned until the patient can be better optimized or should the operation be continued and the ensuing hemodynamic instability be managed "as it unfolds"? What parameters aid in making this decision? There are no definitive answers to these questions. In our patient, the hemodynamic consequences were fortunately not as grave as others have reported [1,17].

Conclusion

Extra-adrenal normotensive paragangliomas are still a diagnostic challenge for surgeons. The recognition of possibility of the tumor is the most important step in the diagnosis and hence, a high index of suspicion and preparedness for crisis is required for the successful management of the patient. Through this case report, we raise the concern that the diagnosis of silent or normotensive paragangliomas is still worryingly dependent on the physician's knowledge and experience. There is a need for specific protocols in such cases, as these tumors are rare and not every physician will come across one in his/her practice. The issue of whether or not to test for catecholamine markers and metanephrines routinely in tumors located along the known potential sites for paragangliomas needs to be looked into. We also highlight the need for more specific diagnostic markers and more specific imaging criteria for the timely diagnosis of silent or normotensive paragangliomas. Moreover, specific questions about intraoperative decision making also need to be addressed.

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