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CASE REPORT

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Paraganglioma masquerading as a primary liver lesion: A rare entity discovered during surgery

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Abstract

A 54-year-old woman with controlled hypertension presented with abdominal pain and weight loss. Imaging revealed a 6.6 cm liver lesion. During resection, she became severely hypertensive and diagnosis was paraganglioma. Hepatic paragangliomas are exceedingly rare but must be considered in the differential of abdominal mass even without typical clinical symptoms.

KEYWORDS

abdominal, hypertension, liver, neuroendocrine, paraganglioma, tumor

1 | INTRODUCTION

Paragangliomas are rare neuroendocrine tumors that arise from the extra-adrenal chromaffin cells of the sympathetic and parasympathetic ganglia. Paragangliomas are classified into two groups; head and neck tumors which arise from the parasympathetic nervous system and do not produce catecholamines and sympathetic paragangliomas which occur along the axis of the body from the skull base to the pelvic floor and produce catecholamines.[1,2] The most common locations for paragangliomas are the retroperitoneal space (55.2%), head/neck (25.6%), bladder (5.6%), and mediastinum (3.2%).[3] The liver is a rare location for paragangliomas with only a handful of cases

reported in the literature.[3-16] Diagnostic imaging can be used to detect the presence of a paraganglioma but findings are nonspecific and overlap with tumors of other tissue origin. We present a rare case of primary hepatic paraganglioma that was diagnosed during surgical resection. Undiagnosed paragangliomas have an extremely high mortality rate in the operating room, up to 60%, so this rare diagnosis cannot be missed.[17]

2 | CASE REPORT

A 54-year-old woman presented to the Emergency Department with 3 weeks of dull, diffuse abdominal pain associated with bloating and early satiety. Review of systems was positive for fatigue, night sweats, and a 5 lb unintentional weight loss over approximately 4 weeks. She denied palpitations, anxiety, headaches, hot flashes, or tremors. Past medical history was significant for obesity, diet-controlled hyperlipidemia, and well-controlled hypertension with only one antihypertensive agent. Her only medication was low-dose hydrochlorothiazide, and she denied usage of over-the-counter supplements. On physical examination, vital signs were unremarkable with a heart rate of 80 beats per minute and blood pressure of 125/87. Abdominal examination revealed tenderness to palpation of the right upper quadrant but no guarding or rebound tenderness. Bowel sounds were normal. Laboratories revealed normal blood counts, liver, and renal function. Contrasted CT abdomen and pelvis demonstrated a 6.6 cm heterogeneous and hypervascular mass in the caudate lobe of the liver exerting mass effect on the IVC and left hepatic vein. Subsequent multiphasic abdominal MRI demonstrated a T2 hyperintense lesion with punctate foci of T1 hyperintensity, suggesting intralesional hemorrhage, or dense protein deposits (Figure 1). Dynamic contrasted imaging showed avid arterial enhancement with delayed washout. Excision was recommended over biopsy due to the risk of bleeding and seeding the surrounding tissue with biopsy. On the day of surgery, the patient's blood pressure was well controlled, 127/85. She tolerated thoracic epidural placement and induction of general anesthesia without issue. The patient remained hemodynamically stable with incision and exposure of the tumor. Upon manipulation of the mass, however, she became acutely hypertensive with systolic blood pressures to the low 200 s. Elevated blood pressure was initially treated by increasing volatile anesthetic, propofol, and fentanyl due to a concern for poor pain control or an inadequate depth of anesthesia. When these treatments did not sufficiently lower blood pressure, the patient was treated with intravenous nitroglycerin, esmolol, and labetalol to rapidly treat hypertensive emergency.[18] These therapies successfully

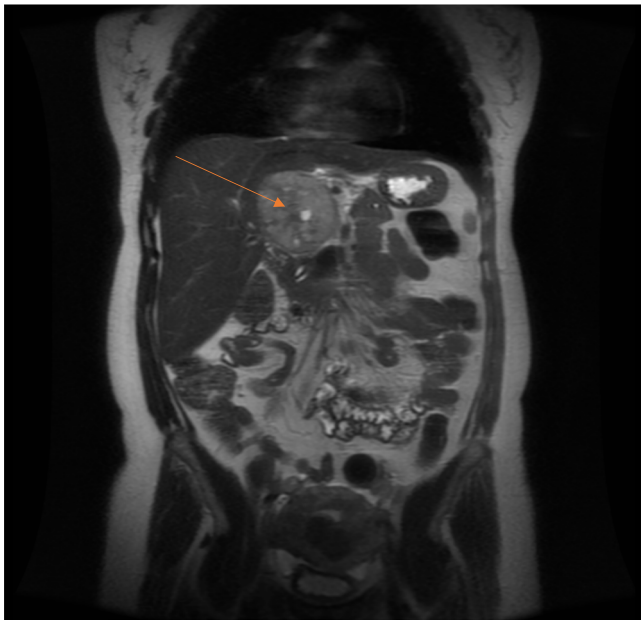

FIGURE 1 Abdominal MRI revealing a T2 hyperintense 6.6 cm liver lesion exerting mass effect on the inferior vena cava and the left hepatic vein

improved blood pressure to 150 s systolic. As surgery progressed, it was noted that when manipulation of the tumor ceased, blood pressure improved. This finding along with the fact that blood pressure responded to alpha and beta blockade, and severely increased blood glucose levels (up to 400 mg/dl requiring insulin infusion) led the anesthesia team to reach the working diagnosis of a catecholamine secreting tumor. Blood pressure remained labile throughout the case until the mass was completely excised. As the surgeon isolated the mass from its blood supply, the patient became acutely hypotensive requiring intravenous phenylephrine and over 6 L of crystalloid fluid resuscitation. Postoperatively, the patient was transferred to the surgical intensive care unit on a phenylephrine infusion. Pathology displayed nested architecture and a prominent vascular background (Figure 2) with synaptophysin and chromogranin immunopositivity consistent with a paraganglioma. While the presence of metastasis is the only definitive indicator of a malignant paraganglioma, this lesion was felt to be benign as the tumor was moderately differentiated using a histologic scoring system and contained necrosis and Ki-67 labeling of 1% (Figure 3). There were no other obvious lesions on chest/abdomen/pelvic imaging to suggest metastatic disease. Immediately postoperatively, 24 h urine metanephrines were obtained and returned significantly elevated with normetanephrine predominance consistent with a paraganglioma. 24 h urine normetanephrine was 952 mcg/24 h (82–500), and 24 h urine metanephrine was 350 mcg/24 h (45–290). The patient did well clinically and metanephrines returned to

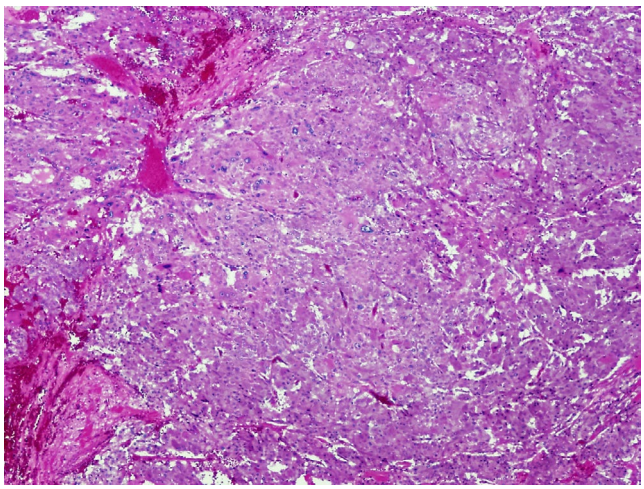

FIGURE 2 Hematoxylin and eosin stain of the mass (40×) displaying nested architecture and a prominent vascular background with synaptophysin and chromogranin immunopositivity consistent with paraganglioma

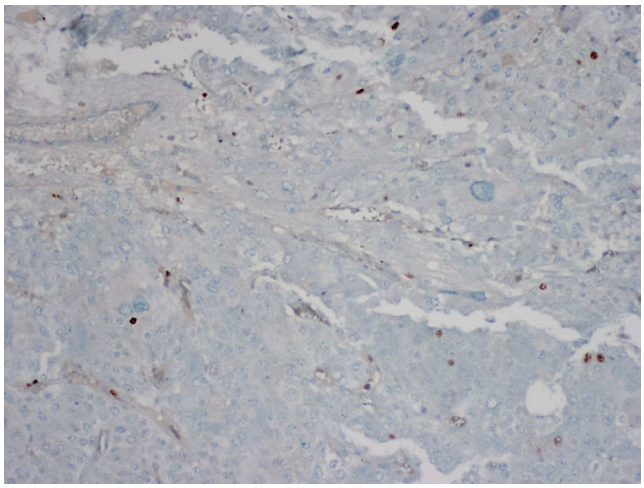

FIGURE 3 Ki-67 stain of the mass showing necrosis and Ki-67 labeling of 1% which favors a benign lesion

normal 6 weeks postoperatively. Serum normetanephrine was 41 pg/ml (0–145), metanephrine was <10 pg/ml (0–62). At long-term follow-up, the patient continued to do well clinically and showed no evidence of paraganglioma recurrence.

3 | DISCUSSION

Our case highlights a hepatic paraganglioma which is a rare condition that should be considered in the differential of an abdominal mass, even in patients without typical symptoms. Paragangliomas are rare tumors with a prevalence of 0.2%–0.6% in patients with hypertension.[1] These tumors are typically associated with poorly controlled or resistant hypertension. However, as in this patient, up to half of the individuals with pheochromocytomas or paragangliomas are normotensive or have paroxysmal hypertension that is not seen on routine screening. Other common symptoms of paragangliomas are headaches, palpitations, pallor, and piloerection. The recommended screening tests are the measurement of circulating catecholamine metabolites (plasma-free metanephrines or urinary fractionated metanephrines). Patients with functional paragangliomas typically exhibit metanephrine levels >4 times upper limit of normal. Other conditions can cause more mild elevations in metanephrines such as obesity, obstructive sleep apnea, and medications. Common medications that can falsely elevate plasma and urine metanephrines include acetaminophen, labetalol, sotalol, methyldopa, tricyclic antidepressants, buspirone, phenoxybenzamine, MAO inhibitors, sympathomimetics, cocaine, sulfasalazine, and levodopa. These conditions should be considered, and interfering medications avoided when screening for paraganglioma. Current practice guidelines recommend screening for paraganglioma in patients with typical symptoms of catecholamine excess, particularly if paroxysmal, an adrenal incidentaloma with or without hypertension, hereditary predisposition, or syndromic features suggesting these tumors, and previous history of paraganglioma.[1] In this case, the patient did not have typical signs, symptoms, or history for paraganglioma so diagnosis was felt to be very unlikely.

Imaging revealed a 6.6 cm heterogeneous and hypervascular mass in the caudate lobe of the liver exerting mass effect on the IVC and left hepatic vein on CT abdomen/pelvis. Multiphasic abdominal MRI showed a T2 hyperintense lesion with punctate foci of T1 hyperintensity, suggesting intralesional hemorrhage or dense protein deposits (Figure 1). Dynamic contrasted imaging showed avid arterial enhancement with delayed washout.

T2 hyperintensity, heterogenous attenuation, mass effect, intralesional calcifications, fat, and/or hemorrhage can be seen in both benign and malignant lesions. When these features are visualized in a lesion located in the liver, the differential includes hepatic adenoma, hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma, cholangiocarcinoma, hemangioma, or metastatic lesion. Abdominal paragangliomas, which are typically located in the infrarenal area near the origin of the inferior mesenteric artery in the location of organs of Zuckerkandl and appear as paraaortic soft tissue masses with homogeneous enhancement or central areas of low attenuation on contrast-enhanced CT scan. Typically HU are >10. Punctate calcification or focal areas of high attenuation caused by acute hemorrhage may be seen in some tumors. They are commonly hypointense or isointense compared

with the liver parenchyma on T1-weighted MRI images and are markedly hyperintense on T2-weighted MR images. CT and MRI are helpful in delineating presence and anatomic significance of a mass but less helpful in determining its origin.[19] Functional imaging with ^{123}I-MIBG or GA^{68}DODATATE is more sensitive and specific, especially for differentiated lesions. ^{18}F-FDG PET/CT can be used to detect metastatic disease. In this case, the features of a liver lesion and paraganglioma overlapped but due to the location, a primary liver lesion was the most likely diagnosis.

Treatment for paraganglioma is surgical resection. Due to the high-risk nature of this surgery, an experienced surgical team and proper pre-operative preparation of the patient are necessary. These preparations are also necessary before any procedures, such as endoscopy or biopsy that could irritate the tumor and cause large catecholamine release. Mortality without surgical pre-treatment has been reported as high as 60% but with appropriate pre-operative medical management, mortality reduces to 0–6%.[17] Preparation for surgery includes adequate alpha blockade and hydration to minimize hypertensive crisis and subsequent severe hypotension following tumor resection. Prior to surgery, alpha-adrenergic blocker is given for at least 7 days pre-operatively to normalize blood pressure. The alpha blockade prevents vasoconstriction caused by activation of the alpha receptors due to excess circulating catecholamines. This vasodilation can cause a compensatory tachycardia or tachyarrhythmia in some patients. Beta adrenergic blockade can be used in this situation to normalize heart rate but it is critical to recognize that beta adrenergic blockers should never be started prior to appropriate alpha blockade due to risk of severe hypertension. If there are contraindications to beta adrenergic blockers, calcium channel blockers can be an alternative. Careful hemodynamic monitoring is critical intraoperatively and postoperatively. For the surgery itself, a laparoscopic procedure is preferred since it has been shown to decrease postoperative morbidity.[1,20,21]

All paragangliomas have malignant potential. Pathologic scoring systems[22,23] and radiographic features can suggest malignant paraganglioma but there is no single risk-stratification tool that is recommended in the current literature.[24] Pathologic features for a malignant paraganglioma include capsular/periadrenal adipose invasion, increased cellularity, necrosis, tumor cell spindling, increased/atypical mitotic figures, and nuclear pleomorphism. In this case, radiographic features include large size (≥ 4–6 cm), irregular shape, necrosis, calcifications, hemorrhage, attenuation ≥10 HU on non-contrast CT, absolute washout ≤60%, and relative washout ≤40%. On MRI, malignant lesions appear hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. FDG avidity on PET scan is also indicative of dedifferentiation and malignancy.[25,26] Despite these features, only on visualizing metastases where chromaffin tissue is not normally found can confirm malignancy. As metastatic lesions can occur decades after resection, long-term follow-up is critical. In addition to malignant potential, all patients with paraganglioma should be referred for genetic counseling given the high rate of underlying genetic syndromes that accompany these rare tumors.[1]

This case highlights the need for recognition and a high index of suspicion for paraganglioma in the differential of any abdominal mass. Abdominal paragangliomas are typically located in the infrarenal area near the origin of the inferior mesenteric artery in the location of the organs of Zuckerkandl; only a handful of liver paragangliomas have been reported in the literature. In addition, paragangliomas typically present with features of poorly controlled or episodic hypertension, palpitations, headache, sweating, or piloerection. Clinical practice guidelines recommend screening for paraganglioma in patients with typical symptoms or history of this condition. However, due to high perioperative mortality rates without proper pre-operative treatment, we recommend considering this diagnosis even in asymptomatic individuals, in those without history of a catecholamine secreting tumor, and in any patient with an abdominal mass. In this case, fortunately diagnosis was recognized swiftly by the Anesthesia team and treated aggressively. Medical and surgical teams should be aware that primary hepatic paragangliomas can occur and understand the proper perioperative management of this condition.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

Michelle E. Miller performed literature review and wrote the majority of the case report. Nicole O. Vietor, endocrine staff of record, provided care for patient postoperatively and wrote endocrine portions of the case report. Edward J. Park delivered anesthesia care during surgery and co-wrote anesthesia section of case report. Shane P. Sweeney wrote pathology sections of case report and provided pathology images. Matthew Katz wrote radiology sections of case report and provided radiologic images. Robert C. Vietor delivered anesthesia care during surgery, co-wrote anesthesia section of case report and revised the case report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

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