Surgical management of recurrent and extra-adrenal pheochromocytomas requiring vascular resection and reconstruction

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ABSTRACT

This case series highlights that extra-adrenal and recurrent pheochromocytomas can require en bloc vascular resection to achieve negative margins. Through this series of cases performed in a multidisciplinary fashion, we aim to highlight the technical aspects of these cases that can add to their complexity. Vascular invasion alone should not preclude an otherwise feasible oncologic resection. (J Vasc Surg Cases Innov Tech 2023;9:101202.)

Keywords: Paraganglioma; Pheochromocytoma; Vascular invasion; Vascular reconstruction

Pheochromocytomas are rare lesions with an annual incidence of 0.8 per 100,000 person-years, although this might be an underestimation given the large number of tumors diagnosed in autopsy series.[1] Paragangliomas, or extra-adrenal pheochromocytomas, represent the subset of these tumors located outside the adrenal medulla, most often at the organ of Zuckerkandl, which contains paired extra-adrenal chromaffin tissue at the level of the aortic bifurcation.[2] Extra-adrenal pheochromocytomas likely represent ≥15% of adult pheochromocytomas and ≥30% of pediatric pheochromocytomas. Also, up to one half of these tumors are estimated to be malignant.[3] Local invasion into the inferior vena cava or infrarenal aorta can present an added technical challenge in the resection of these lesions, and the rates of vascular invasion with these tumors have not been well-defined.

We describe our multidisciplinary experience with three cases of pheochromocytoma with vascular invasion that required en bloc vascular resection and reconstruction. With each case, we aimed to highlight the technical challenges that tumors in these locations pose. All patient data were de-identified. After discussion with our institutional review board, our research was determined to be reflective of our experience in our own practice and exempt from the requirement for institutional review board approval. All three patients provided written informed consent for the use of their de-identified patient information as part of a case series.

CASE REPORT

Patient 1. The first patient was a 73-year-old woman with a 5-cm mass located at the organ of Zuckerkandl incidentally noted on a computed tomography (CT) scan performed after a motor vehicle collision. Further imaging studies were performed preoperatively to delineate the anatomy. CT angiography of the abdomen and pelvis was performed, which revealed a 4.6 × 4.3 × 4.9-cm heterogeneously enhancing mass at the aortic and inferior vena cava (IVC) bifurcation (Fig 1). No clear plane was identifiable between the left common iliac vein and the tumor on the imaging study, although direct invasion was not apparent. Positron emission tomography (PET) magnetic resonance imaging with dotatate was also performed and again identified the ~5-cm necrotic paraganglioma with increased metabolic activity and no evidence of distant metastatic disease.

She subsequently underwent a biochemical workup, which revealed the following: chromogranin A, 504 ng/mL (range, 0-101.8 ng/mL), 24-hour urine metanephrines, 277 μg/d (range, 36-229 μg/d), 24-hour urine normetanephrines, 6630 μg/d (range, 95-650 μg/d), normal plasma metanephrine levels, and elevated plasma normetanephrine, 17.45 nmol/L (range, 0-0.89 nmol/L). The biochemical analysis findings were consistent with an extra-adrenal pheochromocytoma, and an alpha-blockade with doxazosin was appropriately initiated for ≥2 weeks preoperatively. Beta-blockade was initiated in the perioperative period to manage her heart rate, and she was admitted for prehydration before the day of surgery.

The patient was taken to operating room for planned exploration and resection of the lesion. Intraoperative exploration via midline laparotomy allowed for exposure of the retroperitoneum. The retroperitoneum was incised along the anterior surface of the aorta inferior to the inferior mesenteric artery, and this dissection was carried onto the right common iliac artery.

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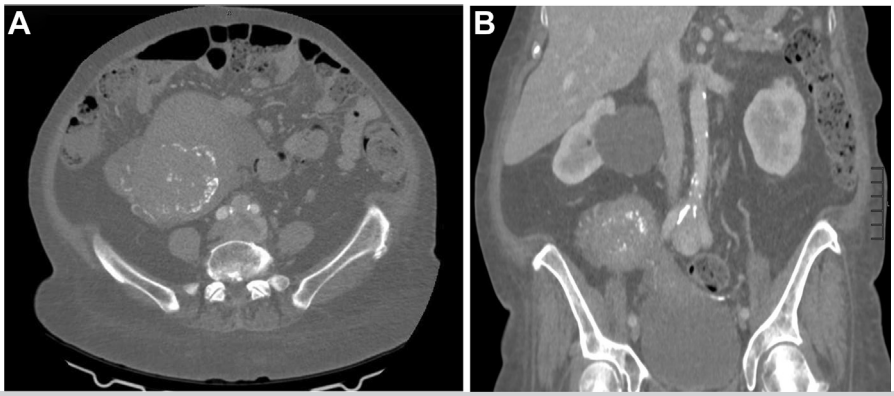

Fig 1. Axial **(A)** and coronal **(B)** images demonstrating tumor at the aortic bifurcation.

As the tumor dissection proceeded, it became apparent that the tumor was inseparable from a portion of the aortic bifurcation and would require resection of the distal aorta, its bifurcation, and the proximal common iliac arteries.

Control of the distal infrarenal aorta was achieved to allow for subsequent clamp placement. During dissection to achieve control of the right common iliac artery, a right common iliac vein injury occurred, which was initially controlled with digital tamponade. The injury was repaired formally using 4-0 Prolene suture, with improved exposure after resection of the aortic bifurcation. The aorta and common iliac arteries were clamped, and the tumor was resected en bloc with the aortic bifurcation and passed off the field. The reconstruction options included very short segment aortoiliac reconstruction, which is often technically difficult given the limited working space, and aortobifemoral reconstruction. An initial attempt was made to perform aorto-bi-iliac reconstruction with an end-to-end aortic anastomosis using a Dacron conduit; however, the limited working space proved challenging with a crimped result and nonpalpable femoral pulses. The decision was made to convert to aortobifemoral reconstruction using Dacron because the overall narrow pelvis made more distal exposure of the external iliac arteries more challenging, and bilateral groin incisions were created to expose and control the common femoral arteries and branches. A bifurcated Dacron graft was tunneled deep to the ureters in the retroperitoneum, and both distal anastomoses were fashioned end to side using Prolene suture. The proximal anastomosis was fashioned end to side off the prior Dacron graft because the aortic anastomosis was hemostatic and without stenosis. The patient was systemically heparinized during clamping until the reconstruction was complete. The patient had an uncomplicated postoperative course and has continued to take aspirin 81 mg daily.

The final pathologic examination revealed a 4-cm retroperitoneal paraganglioma with capsular invasion and focal tumor extension to the inked free margin, Ki-67 index of 3% with high cellularity and both large and irregular cell nests for a total grade of a moderately differentiated type, with a Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) score of 6. These features suggested increased malignant potential.[4] The scoring system is expanded further in the Discussion section. Additional assays were performed to assess for loss of succinate dehydrogenase (SDH) expression, although the findings were normal. Postoperative follow-up included a repeat PET dotatate scan, which demonstrated no residual retroperitoneal disease or metabolic activity. A right upper lobe, lateral segment, 1-cm lung nodule was present on imaging, suspicious for metastatic disease. Her plasma normetanephrines and metanephrines have remained normal since the surgery. Postoperative aortic duplex ultrasound demonstrated a patent graft with normal lower extremity ankle brachial indexes.

Patient 2. The patient was a 60-year-old man with a history of right adrenalectomy during childhood (age, ~9 years) for a reportedly benign tumor. He had presented with recent onset of hyperglycemia and hypertension that had been worsening during the past year. He was admitted to an outside hospital for dehydration and back pain. CT imaging performed at that time revealed a lobulated 8.8 × 8.6-cm enhancing mass in the surgical bed of the right adrenal gland extending into the retrocaval and aortocaval space, suspicious for recurrent pheochromocytoma or paraganglioma (Fig 2). The left renal vein and right renal artery appeared to be encased in tumor, and there was loss of the fat plane between the mass and IVC, without definitive invasion. Additional imaging with PET-CT was performed, which demonstrated intense uptake in the mass in close proximity to the IVC, right renal vessels, and left renal vein without evidence of lymph node involvement or metastatic disease.

The patient underwent a preoperative biochemical workup, which revealed a normal plasma metanephrine level and elevated plasma normetanephrines of 8724 pg/mL (normal, <148 pg/mL), consistent with a paraganglioma. Alpha-blockade with doxazosin was appropriately initiated, and he subsequently received beta-blockade with metoprolol 2 weeks before surgery.

The patient was taken to the operating room for planned exploration and resection via a chevron incision. The right colon

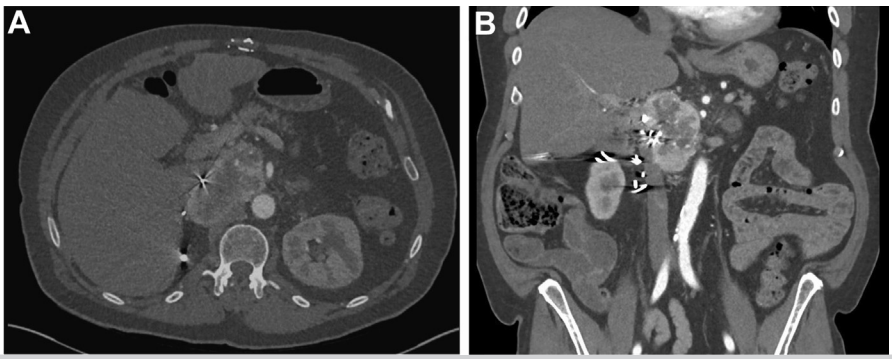

Fig 2. Axial **(A)** and coronal **(B)** images demonstrating recurrent pheochromocytoma in the right adrenal resection bed.

and duodenum were fully mobilized to expose the right retroperitoneum and IVC. The tumor appeared adherent to the IVC at the level of both renal veins and several centimeters both proximally and distally. The liver was fully mobilized, and the retrohepatic IVC, which appeared uninvolved, was controlled. The left renal vein was completely encased in tumor at its confluence with the IVC, although the more distal left renal vein, left gonadal vein, and left adrenal vein were free from involvement and carefully preserved. The right renal artery was dissected free from the tumor; however, the right renal vein appeared encased with tumor at its confluence with the IVC inferiorly and posteriorly. Given the extent of tumor involvement, resection en bloc with the IVC was deemed necessary. The left renal vein was divided using a vascular stapler, with care taken to preserve the left adrenal and gonadal veins. The patient was subsequently systemically heparinized, and the IVC and right renal artery and vein were clamped. A longitudinal venotomy was created to allow for visualization of any branch vessels requiring ligation or oversewing, and no backbleeding lumbar branches were encountered. The vena cava was then divided proximally and distally, and a portion of the IVC was divided around the right renal vein to allow for a button reimplantation. A nonbifurcated Dacron graft was selected for reconstruction using 4-0 Prolene suture in an end-to-end fashion proximally and distally. A side-biting clamp was placed to allow for excision of a small portion of the lateral wall of the Dacron graft, and the right renal vein anastomosis was completed end to side, with a total warm ischemic time of $<$1 hour (Fig 3).

Aside from a mild elevation in creatinine, the patient had an uneventful postoperative course. An intravenous heparin infusion was initially started and was titrated to therapeutic levels before conversion to an oral anticoagulant. His renal function normalized, and he receives anticoagulation therapy with apixaban for the prosthetic venous conduit. When using an autologous conduit, we often favor antiplatelet therapy alone; however, when using a prosthetic conduit, we favor lifelong anticoagulation therapy.

The final pathologic examination revealed an 8.8 $\times$ 8.5 $\times$ 4.4-cm soft tissue mass consistent with recurrent pheochromocytoma invading the left renal vein and IVC, with surgical margins free of tumor. However, 3 of 12 lymph nodes were positive for metastatic pheochromocytoma, and the Ki-67 proliferation index was $\sim$5%. An assay for loss of expression of SDH was performed, with normal findings.

Patient 3. The patient was a 45-year-old woman who initially presented to a cardiologist with progressive hypertension. She was lost to follow-up for several years but then presented to an endocrinologist who performed biochemical testing and ordered a CT scan of the abdomen and pelvis. The CT scan was notable for a 7.3 $\times$ 6.3-cm enhancing heterogeneous mass, suspicious for paraganglioma with encasement of the right common iliac artery and vein and compression of the distal IVC, without definitive invasion (Fig 4). No obvious metastatic disease was evident.

The biochemical analysis findings were notable for normal 24-hour urine epinephrine and dopamine but elevated 24-hour urine norepinephrine (1715 μg/24 hours; normal range, 0-135 μg/24 hours). The 24-hour urine metanephrines were elevated at 6368 μg/24 hours (normal range, 131-612 μg/24 hours). Phenoxybenzamine was appropriately initiated $\geq$2 weeks before surgery. Subsequently, beta-blockade was initiated.

She was brought to the operating room for exploration and resection via a midline laparotomy. The abdominal viscera were rotated to the patient's left, including mobilization of the proximal right colon and distal small bowel. The IVC and distal aorta were exposed, and proximal and distal control of the right common iliac artery and aorta were obtained. The IVC was controlled several centimeters above the confluence of the iliac veins. The tumor directly involved the right common iliac artery just distal to its origin from the aorta. After systemic heparinization, the artery was clamped proximally and distally. The artery was divided, keeping the involved segment en bloc with the tumor, which allowed for greater exposure of the common iliac veins. Additional dissection was necessary to free the tumor from the distal IVC and confluence of the iliac veins. During the course of the dissection, a longitudinal tear was created in the distal IVC. This was controlled using direct pressure and several 4-0 sutures. The tumor appeared to involve a small segment of the IVC, and a side-biting clamp was placed

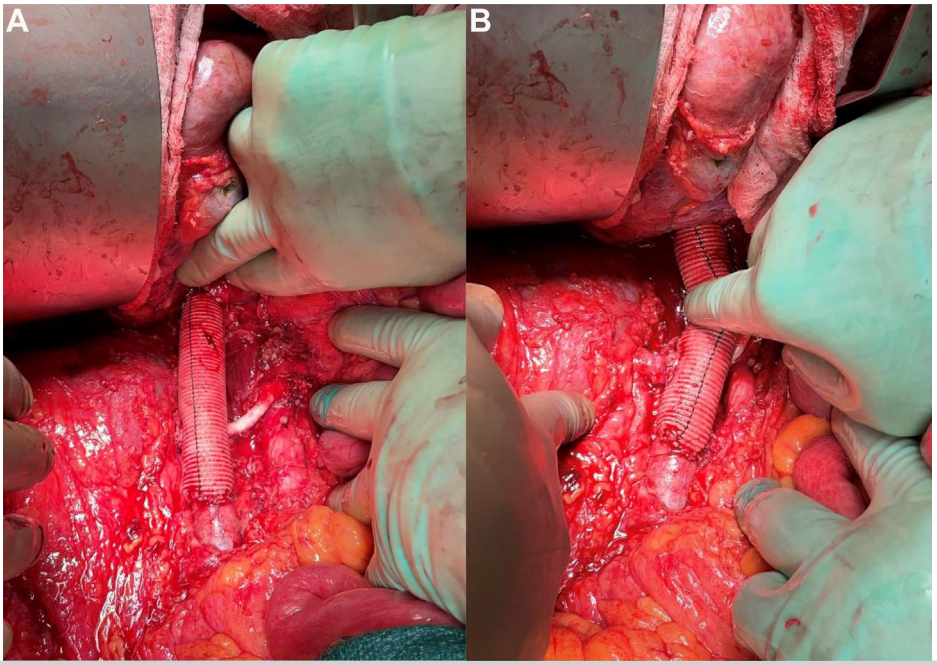

Fig 3. A and B, Intraoperative photographs of inferior vena cava (IVC) reconstruction with right renal vein reimplantation.

beneath this. The tumor, with a portion of the anterior wall of the IVC, was resected and passed off the field, and the IVC was repaired with additional Prolene suture. Attention was then turned to the right common iliac artery, and reconstruction was performed with an 8-mm ringed polytetrafluoroethylene graft in an end-to-end fashion. Her distal pulses remained palpable after completion of the reconstruction.

The patient's postoperative course was notable only for ileus, which persisted for ~1 week postoperatively, and she was subsequently readmitted with a partial small bowel obstruction, which was managed conservatively. She was instructed to take aspirin 81 mg daily.

The final pathologic examination revealed a 7.9 × 6.3 × 4.5-cm extra-adrenal pheochromocytoma with capsular invasion into surrounding adipose tissue. The surgical margins were free of tumor. The tumor demonstrated large, irregular cell nests with a Ki-67 index >3%. The GAPP score was 7 of 10, suggestive of high malignant potential (Fig 5).[4] An assay for SDH loss of expression was performed, with normal findings.

TECHNICAL PEARLS AND PITFALLS

Whenever exploration finds features suspicious or definitive for direct vascular invasion, those structures must be resected en bloc with the tumor in question. As with any vascular operation, proximal and distal control is critical to limit bleeding and allow for appropriate reconstruction. Obtaining vascular control of the common iliac veins can be treacherous, and injuries in that location often require division of the ipsilateral common iliac artery for adequate exposure and control. Short-segment aortoiliac reconstructions are also technically challenging, given the limited working space, and an aortobifemoral reconstruction might be more easily accomplished.

When evaluating perirenal IVC involvement, the left renal vein can be divided with impunity, provided the left adrenal and gonadal branches are preserved for venous drainage. Full mobilization of the liver can be necessary to expose and control the infrahepatic IVC above the renal veins. The renal vein can be reimplanted on the reconstructed IVC using a button technique. Also, whenever the renal vein is clamped for a prolonged period, the ipsilateral renal artery should also be clamped. The warm ischemia time must be kept to a minimum, as much as possible. Large caliber venous and arterial reconstructions can often be maintained using daily aspirin 81 mg, although smaller caliber, low-flow venous reconstructions could require therapeutic anticoagulation.

If more central and extensive involvement of the IVC is present, resection and reconstruction could require the use of venovenous bypass. These complex cases should always include a multidisciplinary discussion between a multispecialty surgical team and anesthesiology.

DISCUSSION

Catecholamine-secreting tumors are, overall, rare entities that present a significant operative challenge both from the perspective of being biochemically active and from possible involvement of adjacent vascular structures. Pheochromocytomas are neuroendocrine tumors that arise from chromaffin cells of the adrenal

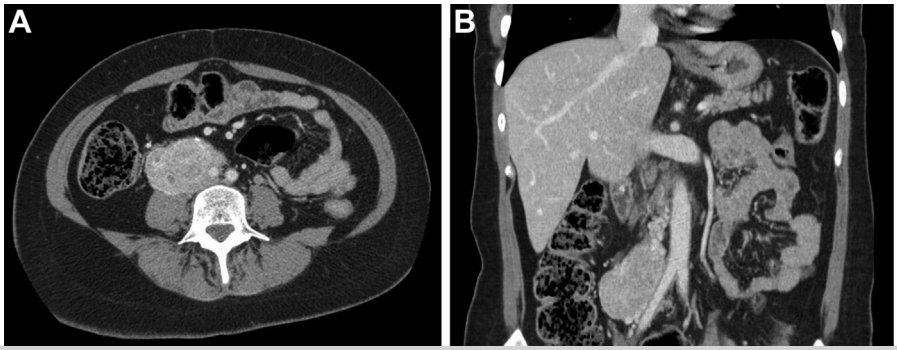

Fig 4. Axial **(A)** and coronal **(B)** images demonstrating tumor encasing the right common iliac artery.

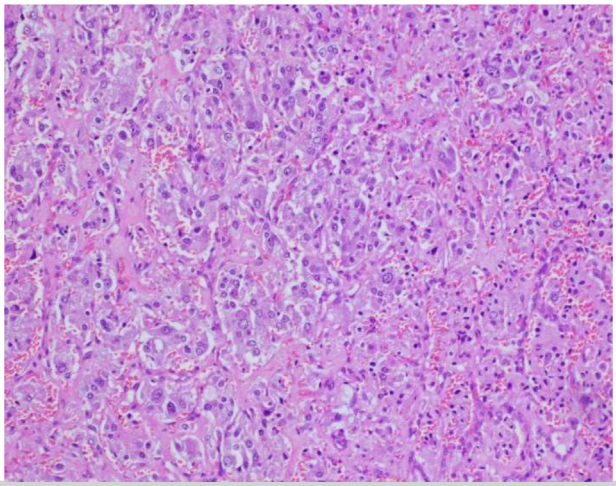

Fig 5. Histopathologic features of the extra-adrenal tumor showing classic nested, or zellballen, arrangement of cells (hematoxylin-eosin stain).

medulla or extra-adrenal paraganglia (paragangliomas), which release catecholamines. Most of these tumors (85%-90%) are intra-adrenal, and 5% to 29% of the tumors could be malignant, potentially more than double the classically reported 10%.[5,6] Radical surgical resection remains the only curative treatment, and vascular invasion, even in recurrent lesions, should not be considered a contraindication to resection. Appropriate preoperative preparation is crucial to mitigate the sequelae of massive catecholamine release due to intraoperative manipulation.

Alpha-blockade should be initiated for all patients ≥1 to 2 weeks before planned surgical resection, which helps to minimize intraoperative blood pressure lability and a hypertensive crisis. Once an alpha-blockade has been initiated and titrated to achieve orthostatic hypotension, additional beta-blockade could be necessary to treat reflex tachycardia.[7,8] These patients also become severely volume depleted and are often encouraged to increase salt and fluid consumption before surgery.[8] In our series, all three patients were preadmitted for intravenous hydration.

CT has a sensitivity of 93% to 100% for detecting adrenal pheochromocytomas and 90% for detecting extra-adrenal pheochromocytomas. CT also allows for determination of the relationship between the tumor and adjacent vascular structures.[9] Although a similar study has not been performed in humans, Schultz et al[10] demonstrated in dogs that the positive predictive value for contrast-enhanced CT for vascular invasion of adrenal masses was 100%, with a sensitivity of 92% and specificity of 100%. A careful review of preoperative imaging studies in multiple planes is necessary to assess for suggested or definite vascular invasion. As our case series illustrates, even when the finding of vascular invasion is not conclusive on preoperative imaging studies, it is likely present. Thus, the operative strategy must include a plan for en bloc vascular resection and reconstruction.

No standardized guidelines are available for monitoring vascular reconstructions in these settings. However, in nonobese patients, duplex ultrasound can be performed easily, limiting radiation and contrast exposure.

The choice of the conduit is ultimately at the discretion of the operating surgeon, although some literature support the possible superiority of ring-reinforced polytetrafluoroethylene compared with Dacron for IVC reconstruction, given lower incidence of thrombosis.[11,12] Ring support also prevents compression from adjacent structures. We did not select this conduit material for our patients, because we did not have the necessary size readily available.

Although vascular invasion represents a more locally advanced lesion, it might or might not correlate with the malignant potential of the lesion. As of 2017, the classification of pheochromocytomas and paragangliomas as malignant or benign has been replaced by a risk stratification system.[13,14] The GAPP is a novel tool allowing for prediction of the risk of metastasis and, ultimately, patient prognosis. The GAPP incorporates the histologic grade, cellularity, presence or absence of comedo necrosis, vascular or capsular invasion, Ki-67 index, and catecholamine type, for a total score of 0 to 10.[4]

Patients deemed to have pheochromocytomas or paragangliomas with high malignant potential should also

be evaluated with genetic testing because these tumors can be components of numerous syndromes, including multiple endocrine neoplasia type 2, von Hippel-Lindau disease, neurofibromatosis type 1, and familial paraganglioma.[15,16] Because the clinical course of patients with malignant pheochromocytomas and paragangliomas is heterogeneous, such risk stratification tools might allow for a more individualized approach to follow-up and surveillance.[17,18] All these patients warrant long-term follow-up given the prolonged period between the initial diagnosis and the appearance of metastatic disease.

CONCLUSIONS

Pheochromocytomas or paragangliomas with vascular involvement can be technically challenging to resect. Imaging studies should be carefully reviewed for evidence or suggestion of vascular invasion, and the operative strategy must include a plan for en bloc vascular resection and reconstruction with a multispecialty surgical team approach, because aggressive and complete surgical resection offers the only possibility of cure.

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