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Management of SHDB positive patient with metastatic bilateral giant retroperitoneal paragangliomas

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ABSTRACT

Paragangliomas are rare neuroendocrine tumors that can vary in size and metabolic activity. We report a case of giant bilateral malignant retroperitoneal paragangliomas (PGL) in a patient with germline succinate dehydrogenase B (SDHB) mutation. This patient, who presented in an emaciated and debilitated state, was managed with adrenergic blockade followed by radical primary surgery. After being metabolically and radiographically disease free for 4 years, he underwent salvage resection for recurrent retroperitoneal disease and palliative radiation to a site of solidary vertebral metastasis. We review incidence and prognosis of metastatic PGL.

1. Introduction

Paragangliomas (PGLs) are rare (2–8 cases/million) neuroendocrine tumors which arise from the chromaffin cells of extra-adrenal autonomic paraganglia. Approximately 40% of PGLs have a hereditary risk factor, with mutations in the succinate dehydrogenase SDH gene complex (SDHA, SDHB, SDHC, SDHD) being the most common.[1] Paragangliomas tend to have a benign phenotype, but up to 30% of patients can present with or develop metastatic lesions. Here we present a case of a patient with very rare bilateral malignant retroperitoneal giant PGLs in whom genetic testing revealed an SDHB mutation.

2. Case presentation

A previously healthy 57-year-old male presented for evaluation of worsening fatigue, significant unintended weight loss (30lb), and persistent tarry stools. On evaluation, the patient was noted to be severely hypertensive (220/95 mmHg). Cross-sectional imaging revealed large bilateral retroperitoneal (RP) masses, wherein the right sided mass (17.7cm) encased the vena cava and the left sided mass (10.5cm) encased the left renal vasculature (Fig. 1). Elevated plasma free metanephrines and an iodine-123-MIBG scan were indicative of the diagnosis of giant PGLs (Fig. 1).

Following catecholamine blockade with alpha blockers in the form of phenoxybenzamine and metyrosine, the patient underwent radical resection of the left RP mass. Given the vasculature of the left kidney was completely encased by tumor, the kidney and tumor were resected en-block and the tumor was resected off of the vasculature ex-vivo. The kidney had two renal arteries, and subsequently auto transplant into left external iliac artery and vein was performed.

Staged resection of the right RP mass was performed 4 months later, which required en-bloc resection of the right kidney and IVC. An IVC graft was utilized in reconstruction (Fig. 2). The left auto-transplanted kidney failed to concentrate urine due to non-patency of the lower pole renal artery and the patient became dialysis dependent soon after right-sided surgery. Genetic testing revealed a Succinate dehydrogenase [ubiquinone] iron-sulfur subunit (SDHB) mutation, prompting familial testing.

The patient was followed with serial plasma free metanephrines as well cross-sectional imaging and remained radiographically and metabolically disease free for 4 years. The patient was approved to proceed with living donor renal transplantation; however, repeat imaging just prior to transplant revealed a large RP retrocrural recurrence (10.5 × 9.6cm) (Fig. 3). This recurrence was metabolically silent.

Biopsy of the RP mass was consistent with PGL. Fluorodeoxyglucose positron emission tomography (FDG-PET) staging demonstrated a

Abbreviations: Succinate dehydrogenase, (SDH); Succinate dehydrogenase B subunit, (SDHB); Paraganglioma, (PGL).

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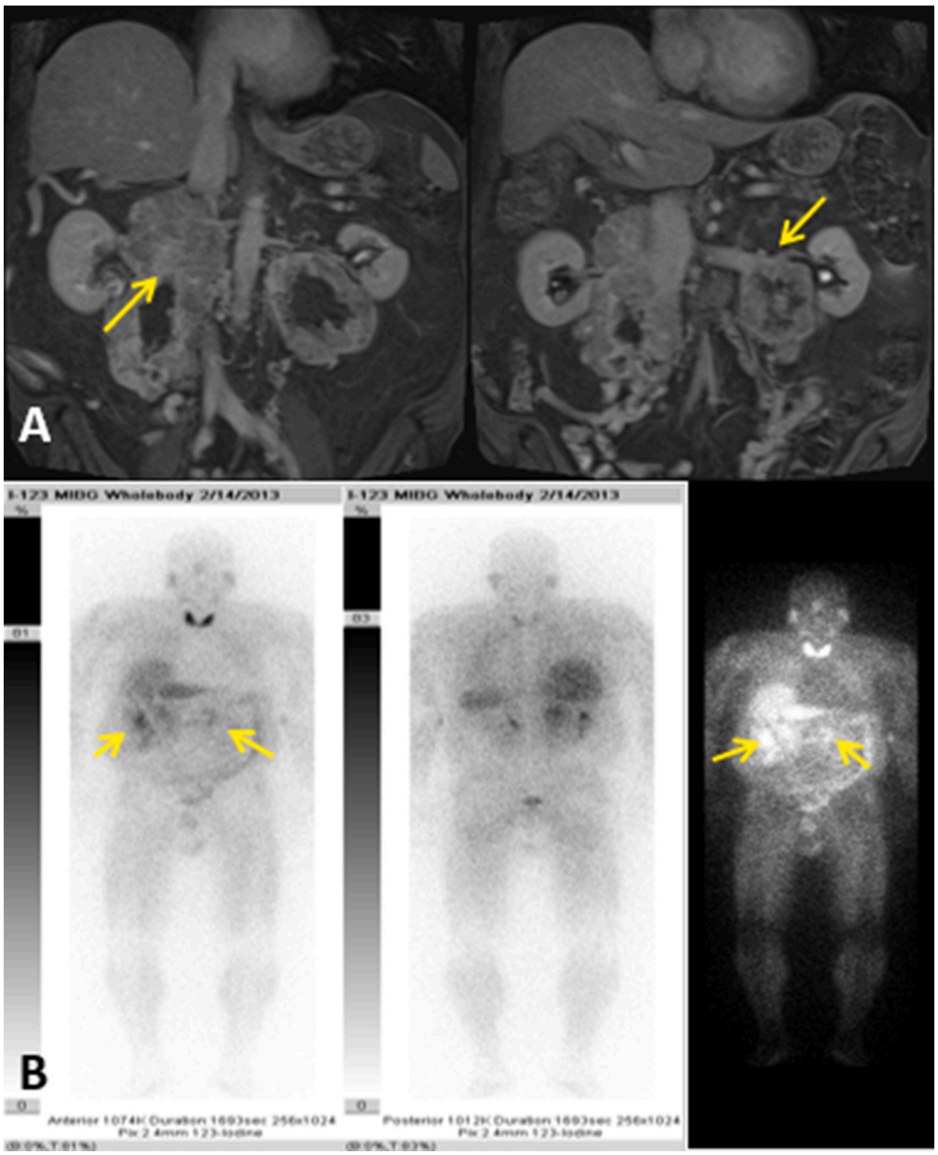

Fig. 1. (A) Cross sectional CT imaging demonstrating large bilateral retroperitoneal (RP) masses (arrows highlight IVC and left renal vein invasion).(B) Iodine −123 MIBG Scan demonstrating uptake of radiotracer by the RP masses consistent with paraganglioma.

metastasis to the T1 vertebral body (Fig. 3). The patient underwent palliative radiation to the solidary vertebral metastasis, followed by resection of the recurrent RP PGL. Pathology was consistent with PGL.

Within one year of the salvage resection, MIBG-scan and MRI revealed lesions in the right RP surgical bed, enlarging RP lymph nodes, as well as metastatic disease of the liver. In conjunction with medical oncology, MIBG and Lutetium Lu-177-dotatate therapy were discussed, however the patient was not felt to be a candidate citing his ongoing renal insufficiency and need for dialysis. Ultimately, the patient elected palliation over systemic chemotherapy.

3. Discussion

We report the management of a patient with a SDHB mutation presenting with bilateral giant RP paragangliomas (PGLs). The size cutoff defining a giant PGL is not well described, and experience with these tumors has been derived mostly from case studies.[2] The incidence of giant RP PGLs is unknown, and largely their behavior can be inferred from literature describing metastatic PGL, as reports of localized giant PGLs have limited follow up. To our knowledge, this is the first report of bilateral giant PGL.

Malignancy in PGL is defined by presence of metastases in sites where chromaffin tissue is normally absent, such as lymph nodes, liver, lungs, and bones. Metastatic PGL is rare, with an estimated incidence of 93 cases per 400 million persons, in the United States.[3] The most common sites of PGL metastasis are lymph nodes, bone, liver, and lungs.[4] The development of metastasis in PGL cannot be predicted reliably by any histologic or pathologic marker, however presence of somatic mutations and primary tumor size appear to be two critical clinical factors.[5]

PGL hereditary status influences metastatic potential, as patients with Neurofibromatosis 1 (NF1), Multiple endocrine neoplasia (MEN), or Von Hippel-Lindau (VHL) mutations rarely develop metastasis, whereas patients with SDHB mutations develop metastases at a rate of as high as 50–97%.[4] In larger series of metastatic PGL, it is reported that approximately 25% of SDHB patients will harbor metastatic disease at presentation.[5]

With respect to size of the primary tumor, data suggest that larger primary PGL size is an independent risk factor for development of metastatic disease. In various studies, cut-off sizes of 4.5, 5, and 6cm have been used to demonstrate this increased risk of future metastatic

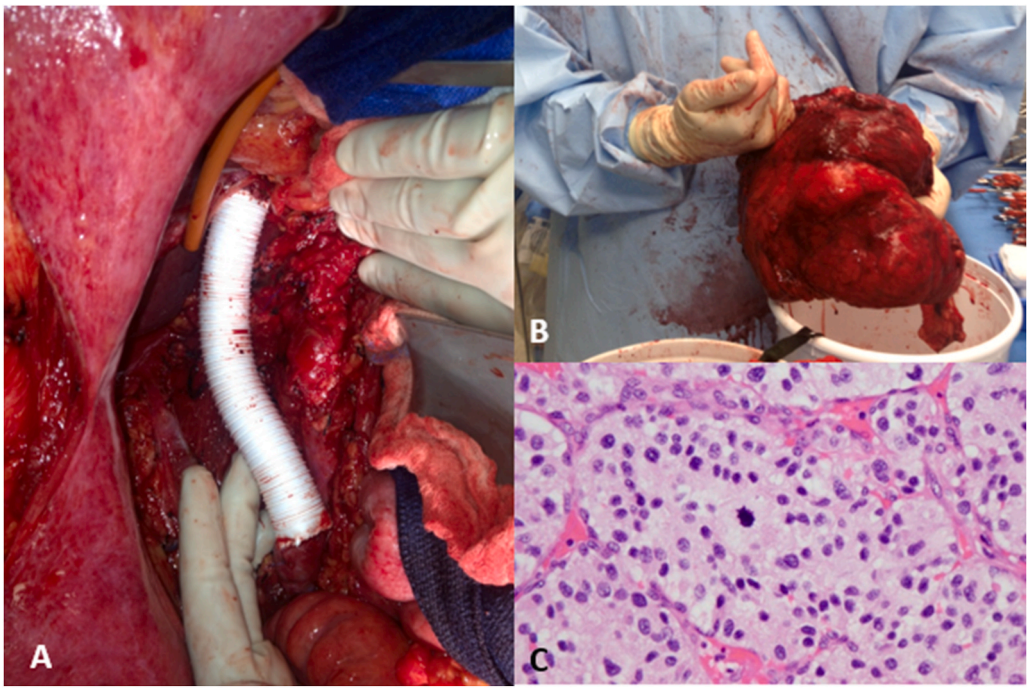

Fig. 2. (A) Intraoperative image of enbloc resection of right kidney with subsequent IVC graft.(B) surgical team holding R-sided specimen with finger in resected vena cava to show its relationship to mass.(C) Diagnosis of malignant PPGL was established from pathologic analysis revealing lympho-vascular invasion and a high mitotic index (10 mitoses/30 high power fields).

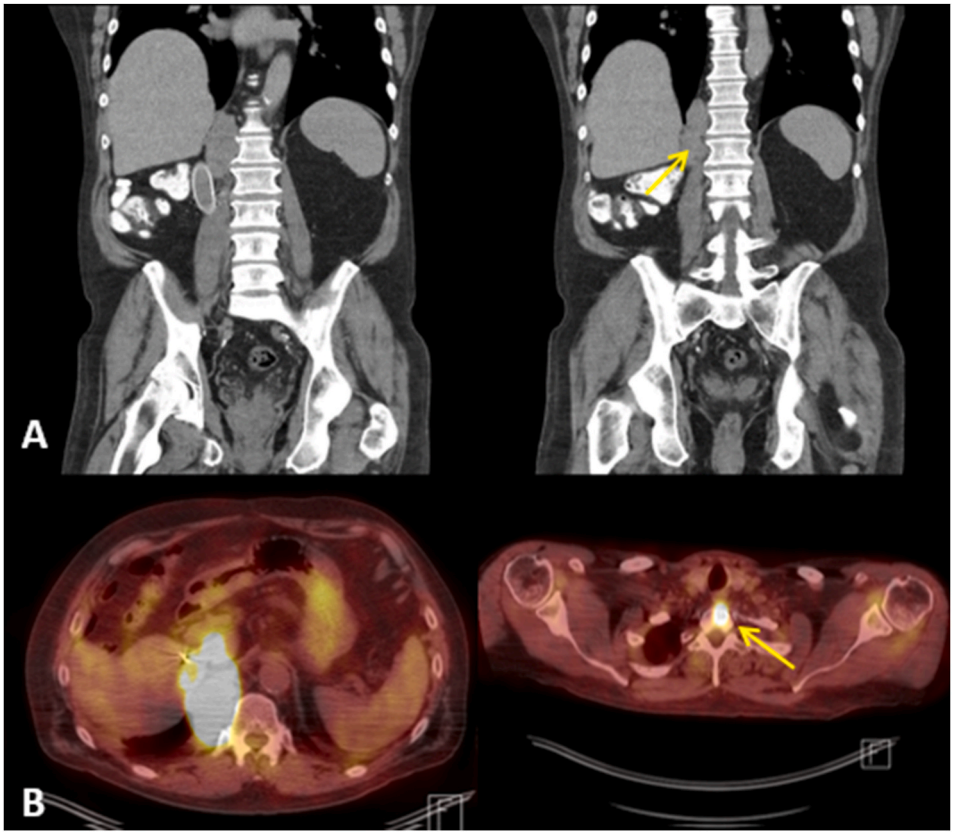

Fig. 3. (A) Surveillance CT scan demonstrating retrocrural recurrence (Arrow).(B) PET/CT confirmed recurrance and solidary metastasis to T1 vertebral body(Arrow).

disease.[5]

Overall, metastatic disease develops at a median time of 5.5 years from initial diagnosis for all-comers with PGL. Meanwhile, in patients with SDHB mutations, reported 5 year and 10 year overall survival is 91.8 and 75.5%.[5]

The current standard of care for PGL is for a complete surgical resection or the primary and/or metastatic sites, if possible. In giant paraganglioma, given the increased involvement of local structures (such as adjacent vasculature, great vessels, or organs), referral to a tertiary center is paramount in providing adequate index resection.

Given the overall paucity of literature on giant paragangliomas, continued collaboration and follow up is necessary to determine factors such as neoadjuvant and adjuvant management of these patients to aid in mitigation of recurrence and metastatic events.

4. Conclusion

In summary, we present a case of a 57 year old SHDB + patient who was found to have bilateral giant retroperitoneal malignant PGLs, requiring bilateral radical resection with subsequent recurrent and metastasis. PGLs are variable in their clinical course, however size and presence of SHDB mutation are risk factors for an aggressive and metastatic course. Giant paragangliomas represent both a surgical and a therapeutic challenge, and disruption in current care paradigms are needed.

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Declaration of competing interest

None.

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