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Multiple Recurrent Paraganglioma in a Pediatric Patient with Germline *SDH-B* Mutation

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ABSTRACT

Magnetic Resonance Imaging (MRI) and fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) are recognized approaches for locating paragangliomas. Recently, gallium-68 DOTA-octreotate (DOTATATE) scans have shown promise detecting neuroendocrine tumors missed by FDG-PET and MRI. 13-year-old male with SDH-B mutation presented with symptoms of paraganglioma and elevated catecholamines. MRI did not demonstrate the T2 hyper intense signal typical of paraganglioma and pheochromocytoma; FDG-PET scan did not reveal increased foci of uptake. DOTATATE scan revealed a signal consistent only with residual adrenal tissue. Resection of the right adrenal bed revealed paraganglioma. Following surgery, no further symptoms were reported and biochemical tests normalized.

Introduction

Succinate Dehydrogenase B (*SDHB*) is part of a family of genes that codes for the Krebs cycle enzyme *succinate dehydrogenase*. Mutations in these genes are associated with development of paragangliomas, pheochromocytomas, and renal cell carcinoma (RCC).[1] Paragangliomas are extra-adrenal tumors of sympathetic and parasympathetic ganglion that, like pheochromocytomas, are derived from neural crest cells and have the ability to secrete catecholamines. This may cause symptoms including headaches, sweating, palpitations, hypertension, and behavior changes.

Approximately 10–20% of cases are diagnosed during childhood, and most cases are functional in nature with clinical symptoms related to catecholamine hypersecretion and/or tumor mass effect.[2] Both MRI and computed tomography (CT) can identify tumor location after biochemical diagnosis. Functional imaging, such as fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans, are highly sensitive and specific for detecting metastatic disease in patients who have biochemically confirmed paraganglioma.[3] Gallium-68 DOTA-octreotate (DOTATATE) scans are superior in detecting somatostatin-avid malignancies, including neuroendocrine tumors.[4] Surgical resection, with long term surveillance is standard treatment for these tumors.

Case presentation

A 13-year-old boy presented to the National Institutes of Health (NIH) with recurrent headaches, occasional chest pain, and hypertension. His past medical history was significant for a previous right total adrenalectomy at age 11 at an outside institution for biochemically active pheochromocytoma associated with germline SDHB alteration. His presenting symptoms at that time were consistent hypertension of 155/115, episodic headaches, and non-exertional chest pain. Elevated serum and urine catecholamines were found; and an MRI revealed a 2.5 cm right adrenal mass with no evidence of metastatic disease. He underwent an uncomplicated laparoscopic right radical adrenalectomy.

After surgery, his symptoms and catecholamines normalized until age 13, when he re-presented with headaches and chest pain similar to his previous episode. Laboratory testing again revealed

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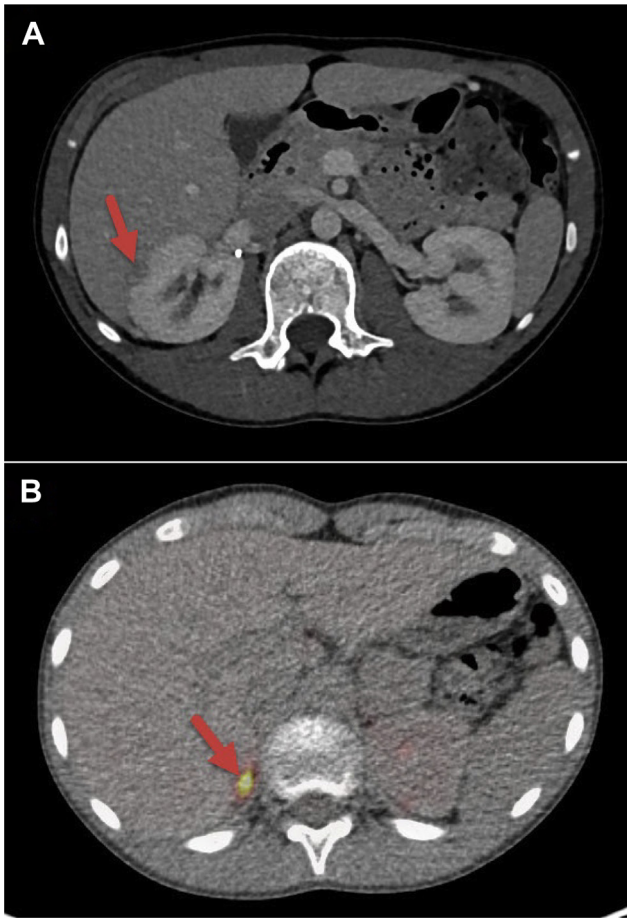

Figure 1. (A) DOTATATE PET/MRI at time of relapse reveals an upper pole capsular renal mass and (B) Enhancing artifact in the right adrenal bed despite history of previous total adrenalectomy. Red arrow shows enhancing lesion identified on imaging.

elevated catecholamines. He underwent a full-body CT, and an MRI of the abdomen and pelvis which revealed an enhancing soft-tissue artifact in the right adrenal bed and a 1.6 cm renal cortical mass (Fig. 1A). DOTATATE scan revealed signal in the right adrenal bed suggestive of residual right adrenal tissue rather than recurrent tumor (Fig. 1B). DOTATATE scan demonstrated increased uptake in the right renal mass seen on CT and MRI. He elected to undergo a robotically assisted right partial nephrectomy and resection of the right adrenal site at the Urologic Oncology Branch at the NIH.

The patient underwent alpha blockade and catecholamine-synthesis inhibition for 2 weeks prior to the procedure. Intraoperatively, suspicious nodular lesions were found along the inferior vena cava, underneath the liver, and in the right adrenal bed. Frozen section of the paracaval tissue revealed multiple small neuroendocrine tumors. The paracaval lesions were not identified on any of the preoperative imaging. Additional nodules were identified and resected between anterior Gerota's fascia and the liver capsule as well as throughout the right adrenal fossa.

Final pathology revealed paraganglioma in the right residual adrenal tissue and multiple nodules of hyperplastic paraganglia along the periadrenal and adjacent renal fibroadipose tissue (Fig. 2). Interestingly, the right renal mass was also a paraganglioma with no invasion to renal parenchyma. The renal tumor and hyperplastic paraganglia were positive for synaptophysin and chromogranin immunohistochemistry staining which are markers for neuroendocrine tumors. Ki67 proliferation index was higher than 5% (intermediate).

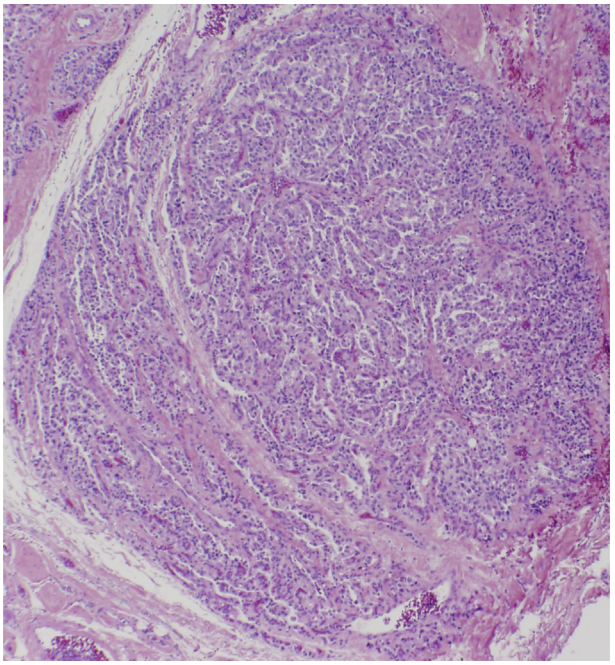

Figure 2. Paraganglioma. Spindle cells growing in a characteristic Zellballen pattern.

Discussion

This patient's FDG PET scan did not identify the paragangliomas in this patient. However, it was noted that there was extensive brown fat present, which may have obscured the detection of the paraganglioma using this imaging modality. However, the DOTATATE scan also failed to conclusively demonstrate any of the paraganglioma, except for some equivocal findings in the right adrenal fossa. The paracaval lesions were essentially invisible on all the imaging modalities; This illustrates the need a low threshold of suspicion when evaluating equivocal soft tissue lesions in symptomatic SDHB patients. It also highlights the shortcomings of current imaging techniques in children where brown fat may obscure small paragangliomas.

The renal mass identified on MRI (Fig. 1A) was initially suspected to be renal cell carcinoma (RCC). Patients affected with germline mutations of the *SDHB* gene are at risk for the development of RCC and, it is recommended that patients with this mutation undergo annual surveillance in order to identify and treat these lesions early. Germline *SDHB* mutation may result in aggressive RCC and early surgical resection of solid renal masses is recommended.[5] Active surveillance for SDHB-related renal masses is not recommended.[5] Since it was suspected the artifact embedded within the right adrenal bed would be a remnant chromaffin tumor, the therapeutic goal was to achieve definitive treatment with complete surgical resection. Surprisingly, the pathology of the surgically removed kidney lesion also demonstrated paraganglioma with no invasion outside of the tumor capsule or into the renal parenchyma. This case demonstrates a rare location of a paraganglioma, occurring adjacent to the renal parenchyma. Partial adrenalectomy is often recommended for other hereditary adrenal tumors, such as VHL-related pheochromocytomas.[5] However, given this local recurrence after a radical adrenalectomy, this approach may not be suitable for SDH-related pheochromocytomas and paragangliomas.

On 3-month follow up, the patient was normotensive and reported no headaches or chest pain. Additionally, his serum and urine catecholamines and metanephrines were within normal limits. The clinical improvement and biochemical normalization,

along with an uncomplicated surgical course. Lifelong surveillance is recommended for SDHB-related tumors.

To our knowledge, this is the first case report on the management of a symptomatic pediatric SDHB patient with robotically-assisted partial nephrectomy and local resection of a paraganglioma. Furthermore, this case highlights the significance of thorough intraoperative inspection for suspicious tissue in a previously treated SDHB patient with biochemical and symptomatic recurrence, despite an MRI or FDG PET scan failing to conclusively identify recurrent paraganglioma.

Conflict of interest

No competing financial interests exist.

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