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Adrenal pheochromocytoma in a patient with Lynch Syndrome

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ABSTRACT

Lynch Syndrome (LS), or hereditary non-polyposis colorectal cancer, is the most common cause of hereditary colorectal cancer. There are well described extra-colonic manifestations of LS, including gynecologic and upper urinary tract malignancies. Other extra-colonic manifestations of LS are less understood. Here we present an unusual case of a functional adrenal pheochromocytoma in a 31-year old man with LS.

1. Introduction

Lynch Syndrome (LS) is one of the most common hereditary cancer syndromes, with a reported carrier incidence as high as 1 in 300 people in the United States. LS is caused by germline mutations of the mismatch repair genes MLH1, MSH2, MSH6, or PMS2 and increases the lifetime risk of developing a constellation of malignancies including colorectal, endometrial, and genitourinary cancers, among others. While adrenocortical carcinoma has been associated with LS, pheochromocytoma is not traditionally recognized as a known extra-colonic manifestation of LS.[1] Instead, pheochromocytomas have been associated with other hereditary syndromes, including von Hippel-Lindau syndrome, multiple endocrine neoplasia II, neurofibromatosis type I, and other genetic predispositions arising from mutations in the SDH gene complex. Here we present a unique case of adrenal pheochromocytoma arising in a 31-year-old male with LS.

2. Case presentation

A 31-year-old male was referred to urology for a 3.4 cm right adrenal mass. This was originally diagnosed 2 years earlier during an emergency room visit for an episode of anxiety and chest pain. Per the patient's report, his blood pressure at the time was elevated with systolic pressures in the 160s, and a CT scan revealed a 2.6 cm right adrenal mass. He was discharged with a beta blocker and a urology referral, but was lost to follow up and transitioned to an angiotensin-converting enzyme inhibitor by his primary care physician. He presented for an initial urology consultation in 2021, endorsing frequent anxiety attacks, headaches, palpitations and chest pain.

The patient's medical history is remarkable for LS, diagnosed in 2014 on testing performed in the setting of a family history of LS. Both he and his mother share a germline mutation in *MSH6* (p.S602). He has an extensive family history of early onset gynecologic cancers in his maternal relatives. He has no personal oncologic history, with a colonoscopy performed in 2018 revealing a lipoma and 2mm adenoma that were removed.

In January of 2021 he had an MRI of the abdomen that showed an indeterminate 3.4 cm right adrenal mass with T2 hyperintensity and without signal loss on chemical shift imaging (Fig. 1). The differential diagnosis included a functional or non-functional adenoma, pheochromocytoma, or, given his history of LS, adrenocortical carcinoma or a secondary metastasis. He then underwent a dedicated four-phase CT scan, which confirmed a heterogeneously enhancing, 4 cm nodule in the right adrenal gland (Fig. 2). Given his history of LS, a chest CT was also performed and revealed no pulmonary lesions.

His physical examination was unrevealing.

He underwent a functional adrenal laboratory evaluation that revealed normal electrolytes and:

- Plasma metanephrine **288** (ref <57 pg/mL)
- Plasma normetanephrine **379** (ref <148 pg/mL)
- Total plasma metanephrines **667** (ref <205 ng/mL)
- 24-h urine metanephrine **2041** (ref 36–190 mcg/24 hour)
- 24h urine normetanephrine **1307** (ref 35–482 mcg/24 h)
- Total 24h urine metanephrines **3348** (ref 115–695 mcg/24h).
- Adrenocorticotropin (ACTH) level 56 (ref 6–50 pg/mL)
- Plasma renin 4.98 (ref 0.25–5.82 pg/mL)
- Serum DHEA-sulfate 346 (ref 106–464 μg/dL)

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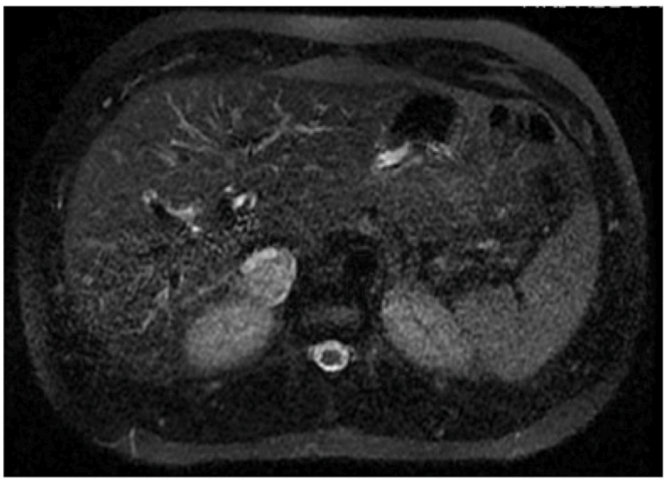

Fig. 1. Abdominal magnetic resonance imaging (MRI) demonstrates a well-circumscribed, T2-hyperintense 2.2 × 3.1 × 3.4 cm right adrenal mass without signal loss on chemical shift imaging. Shown in axial view.

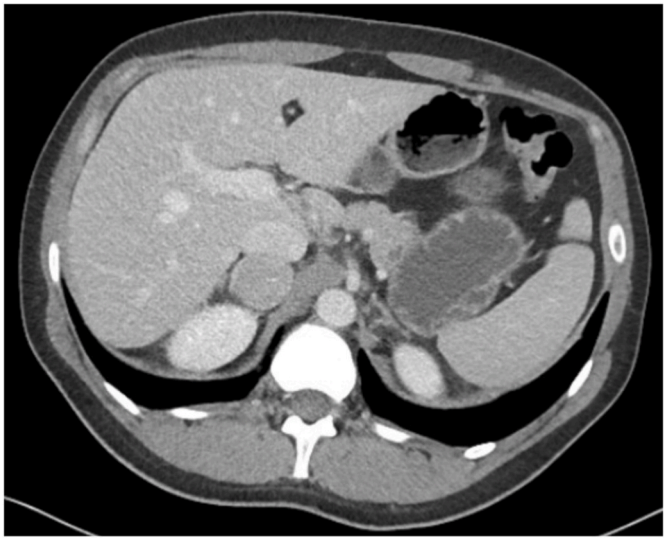

Fig. 2. Contrast-enhanced abdominal computed tomography (CT) scan reveals a heterogeneously enhancing, 3.0 × 3.3 × 4.0 cm nodule in the right adrenal gland, with 66.7% absolute washout and 41.2% relative washout. Shown in axial view on venous phase.

- Serum aldosterone 5 (ref 2–9 ng/dL)
- Serum cortisol 22.9 (ref 6–23 μg/dL).

Given his laboratory evaluation suggestive of pheochromocytoma, he was recommended to undergo a right robotic-assisted radical adrenalectomy, to which he consented.

He was referred to endocrinology for operative preparation and was prescribed doxazosin to be started at 1mg daily and titrated every 2–3 days to maintain a pre-operative blood pressure goal of <140/90. Additionally, he was instructed to start atenolol 25mg daily following at least 4 days of continuous alpha blockade through the morning of surgery. He was also counseled to increase his salt and fluid intake pre-operatively.

He underwent an uneventful robotic right adrenalectomy in March 2021 with no intraoperative hemodynamic changes encountered throughout the case. He remained hemodynamically stable off all anti-hypertensive medications following the operation and was discharged on post-operative day one. His plasma metanephrines were rechecked

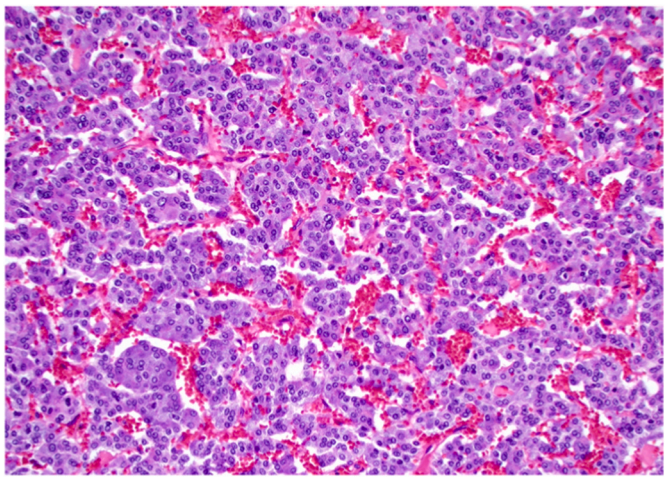

Fig. 3. Histopathology of resected pheochromocytoma. Histologic sections demonstrated characteristic nests of cells (zellballen) embedded in a richly vascular sustentacular network. The tumor cells had abundant amphophilic cytoplasm with speckled chromatin. (200× magnification).

2.5 weeks following surgery and had completely normalized. He recovered uneventfully from surgery and remains asymptomatic and normotensive off all medications.

Final pathology revealed a benign 4.0 cm pheochromocytoma confined to the adrenal gland with negative margins (Fig. 3). Given his history of MSH6-deficient LS, mismatch repair (MMR) immunohistochemical analysis was conducted on the tumor and showed that MLH1, PMS2, MSH2, and MSH6 expression all remained intact. Immunostain for SDHB was also retained.

3. Discussion

The lifetime risk of urologic cancer in patients with LS is 4–5%. Although endocrine cancers are not classically associated with LS, these patients may be at increased risk of harboring adrenocortical carcinomas. For patients with LS, The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) recommends colonoscopy every 2 years starting at age 20–25, daily aspirin, yearly urine analysis at 25–30, helicobacter testing and upper endoscopy every 3–5 years after age 40, a yearly neurologic exam at 25–30, and additional gynecologic screening recommendations for female patients. There is no formal recommendation for routine cross sectional imaging.[2,3]

Known hereditary syndromes associated with pheochromocytomas include VHL, MEN2, and NF1. Neuroendocrine tumors have not been described as known extracolonic manifestation of LS. Only two other cases have reported pheochromocytoma in patients with LS, including a 52-year-old woman with LS and a pheochromocytoma harboring mutations in *MSH2* and *MSH6*, and a 33-year-old male with LS incidentally found to have a pheochromocytoma.[4,5]

4. Conclusion

In summary, we present the unusual case of a 31-year-old with LS and a growing right adrenal mass with markedly elevated plasma and urine metanephrines, found to have a pheochromocytoma. Robotic resection of his mass resolved his symptoms and resulted in normalization of his blood pressure and metanephrines. Our case further highlights the paramount role for multidisciplinary care and screening protocols for patients with LS.

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Consent

Written, informed consent was obtained from the patient presented herein for presentation of his case.

Declaration of competing interest

The authors report no conflicts of interest.

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None.

Abbreviations

MRI	magnetic resonance imaging
CT	computerized tomography
Ref	reference range
ICU	intensive care unit
MMR	mismatch repair
MLH1	mutL homolog 1
PMS2	PMS1 Homolog 2
MSH2	mutS homolog 2
MSH6	mutS homolog 6
ACC	adrenocortical carcinoma
Men2	Multiple endocrine neoplasia type 2
VHL	Von Hippel-Lindau
NF1	Neurofibromatosis Type 1

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