Adrenal pheochromocytoma in a patient with Lynch Syndrome

Katherine M. Rodriguez, Kelly T. Harris, Nirmish Singla

Department of Urology, The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, USA

ARTICLE INFO

Keywords:
Pheochromocytoma
Lynch syndrome
Adrenal
Mismatch repair

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. 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 colono-scopy 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/24h)
- 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)

* Corresponding author. Departments of Urology and Oncology The James Buchanan Brady Urological Institute The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Park 213, Baltimore, MD, 21287, USA.
E-mail address: Nsimgla2@jhmi.edu (N. Singla).

https://doi.org/10.1016/j.eucr.2022.102015
Received 25 December 2021; Received in revised form 17 January 2022; Accepted 23 January 2022
Available online 3 February 2022
2214-4420/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license
Given his laboratory evaluation suggestive of pheochromocytoma, he was referred to endocrinology for operative preparation and was prescribed doxazosin to be started at 1 mg 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 25 mg 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 preoperatively.

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 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.

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. 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.

Funding

This research did not receive any specific grant from funding.
agencies in the public, commercial, or not-for-profit sectors.

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.

Acknowledgements

None.

Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| 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 |

References

1. Sehgal R, Sheahan K, O’Connell PR, et al. Lynch syndrome: an updated review. Genes. 2014;5(3):497–507.
2. Berg AO, Armstrong K, Botkin J, et al. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11(1):35–41.
3. Gupta S, Provenzale D, Llor X, et al. NCCN guidelines insights: genetic/familial high-risk assessment: colorectal, version 2.2019: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2019;17(9):1032–1041.
4. Riff BP, Katona BW, Wilkerson M, et al. HNPCC-associated pheochromocytoma: expanding the tumor spectrum. Pancreas. 2015;44(4):676.
5. Mojtová E, Hanajíková J, Hamidová O, et al. An incidental finding of pheochromocytoma in a 33-year-old patient with Lynch syndrome. Vnitr Lek. 2020;66 (5):80–84.