Adrenal Cortical Carcinoma Associated With Lynch Syndrome: A Case Report and Review of Literature

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Objective: Adrenocortical carcinoma (ACC) is a rare malignancy with poor prognosis. ACC was reported in 3.2% patients with Lynch syndrome (LS), however no particular case-detection strategies have been recommended.

Participants: We report a case of a 65-year-old woman who was incidentally discovered with a large adrenal mass during work-up of postmenopausal uterine bleeding. She was recently diagnosed with MSH6 germline mutation after her sister presented with uterine carcinoma in the setting of LS.

Results: Whereas the patient was asymptomatic for overt hormonal excess, biochemical work-up confirmed glucocorticoid autonomy and androgen and estrogen excess. Urine steroid profiling was suggestive of ACC. Adrenalectomy confirmed an oncocytic ACC with focal extracapsular extension into the periadrenal adipose tissue with a Ki-67 of 15% and a peak mitotic count of 40/50 high-power fields.

Conclusion: ACC can be the only manifestation of LS. A best case-detection approach for ACC in the asymptomatic patient with LS is unclear, however urine steroid profiling could be considered.

Adrenal cortical carcinoma (ACC) is a rare malignancy with an incidence of one to two per one million individuals per year but represents ~13% of adrenal tumors >4 cm in referral endocrine centers [1]. ACC occurs most frequently in the fifth to sixth decade of life and demonstrates a female-to-male predominance of 2.5 to 1. Although most ACCs are sporadic, these can also occur as part of an hereditary syndrome, such as Li-Fraumeni syndrome, multiple endocrine neoplasia type 1, Beckwith–Wiedemann syndrome, familial adenomatosis, neurofibromatosis type 1, Carney complex, and Lynch syndrome (LS) [2]. Despite the large tumor size on presentation, approximately one-half of patients with ACC is discovered incidentally (42%), with a smaller proportion of patients presenting with hormonal excess (31%) or with symptoms of mass effect (20%) or discovered during cancer-staging imaging for another malignancy (6%) and during evaluation of B symptoms (1%) [3]. Early discovery is key to assure a better prognosis.

Abbreviations: ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; LS, Lynch syndrome.
LS-hereditary nonpolyposis colorectal cancer is an autosomal-dominant hereditary cancer predisposition syndrome caused by germline pathogenic variants in any of DNA mismatch repair genes [4], including MLH1, MSH2, MSH6, and PMS2 [5]. Patients with LS demonstrate a substantial lifetime risk of developing colorectal (80%) and endometrial cancer (60%) [4, 6]. Germline pathogenic variants in the MSH6 gene account for ~18% of LS cases [7]. Association of ACC with LS has been reported only in several case reports and one small prospective study, totaling 12 patients (Table 1) [5, 8–14].

1. Case Report

A 65-year-old woman with a past medical history of hypertension presented for evaluation of a recently developed vaginal bleeding. Transvaginal ultrasound demonstrated endometrial thickening and two uterine fibroids. The patient was treated with dilation and curettage of endometrial hyperplasia, and pathology was benign. Incidentally, on the same initial ultrasound, a large heterogeneous mass within the right upper quadrant of the abdomen was also noted. To investigate this finding further, an abdominal CT scan was performed and revealed a heterogeneous right adrenal mass, 6.0 × 5.1 × 7.8 cm (Fig. 1A). The patient was referred to the Mayo Clinic for further evaluation of the right adrenal mass.

Notably, as a result of a recent diagnosis of LS in the patient’s sister, our patient was tested positive for familial pathogenic variant in MSH6. A recent colonoscopy was normal.

A. Investigations

During evaluation in the adrenal clinic, the patient was mostly asymptomatic, although she did complain of some fatigue, loss of appetite, and a 3-pound weight loss over the prior 2 weeks (which she thought was a result of anxiety related to the recent diagnosis of the adrenal mass). On physical examination, she did not have Cushingoid features, acne, or hirsutism. Her blood pressure was 135/83 mmHg, and no clinical features suggestive of primary hyperaldosteronism, such edema or hypokalemia, were present. Biochemical work-up was negative for pheochromocytoma but demonstrated evidence of androgen excess, elevated serum steroid precursors, and estrogen excess, which could have explained the patient’s recent uterine bleeding (Table 2). In addition, the patient demonstrated evidence of adrenocorticotropic hormone (ACTH) independent cortisol excess based on abnormal cortisol concentrations after 1 mg overnight dexamethasone administration, along with low ACTH and elevated 24-hour, urine-free cortisol (Table 2). Urine multisteroid profiling was performed and was highly suspicious for ACC (Table 2). Based on the clinical, biochemical, and imaging presentation, ACC was suspected, and adrenalectomy was recommended.

B. Treatment

Patient was treated with an open right adrenalectomy. Final pathology demonstrated a 9.2 × 5.9 × 4.8-cm adrenal oncocytic ACC (Fig. 1B) with focal extracapsular extension into periadrenal adipose tissue, a Ki-67 index of 15%, and a peak mitotic count of 40 mitoses in 50 high-powered fields. Surgical margins were negative for tumor. Postoperatively, the patient was treated with glucocorticoid-replacement therapy, and treatment with mitotane was started 6 weeks after surgery.

C. Outcome and Follow-Up

During the subsequent 26-months of follow-up, the patient remains in remission: imaging demonstrates no evidence for local recurrence or metastatic disease. In addition, patient’s serum and urinary steroid biomarkers are within normal ranges.
Table 1. Previous Reports of Patients With LS and ACC

| Studies | Age | Sex | MSH Type | Microsatellite Stability | Mode of Discovery | Tumor Size, mm | Adrenal Hormone Excess | Treatment | Mitotic Count | Outcome | Criteria |
|---------|-----|-----|----------|--------------------------|------------------|----------------|----------------------|-----------|---------------|---------|----------|
| [8]     | 44  | M   | NR       | NR                       |NR                | NR             | NR                   | NR        | NR            | Died of disease | NR       |
| [9]     | 65  | F   | MSH2     | MSS                      | Cushingoid features | NR             | ACTH-independent Cushing | S         | 130/50 HPF    | Died of disease | Didn’t meet Amsterdam criteria |
| [10]    | 34  | M   | MSH2     | MSS                      | Symptoms of hypertension and hypokalemia (possible primary hyperaldosteronism leading to imaging) | 40 | NR (possible primary hyperaldosteronism) | S | NR | Died of disease | Met Amsterdam criteria II |
| [11]    | 60  | F   | MSH2     | MSS                      | Follow-up MRI for breast cancer | 51 | NR | S | NR | Alive | Met Amsterdam criteria |
| [5]     | 29  | M   | MSH2     | MSS                      | Flank pain | NR | NR | S | 20/50 HPF | Alive | NR |
| [12]    | 52  | M   | MSH2     | MSS                      | Genetic evaluation | NR | NR | NR | NR | Alive | Met Amsterdam criteria I |
| [13]    | 47  | M   | MLH1     | MSS                      | Genetic evaluation | NR | NR | NR | NR | Alive | Met Amsterdam criteria I |
| [14]    | 39  | M   | MSH6     | MSS                      | Genetic evaluation | NR | NR | NR | NR | Alive | Met Amsterdam criteria II |
| [13]    | 42  | F   | MSH2     | MSS                      | Genetic evaluation | NR | NR | NR | NR | Alive | Met Amsterdam criteria II |
| [13]    | 23  | F   | MSH2     | MSS                      | Genetic evaluation | NR | NR | NR | NR | Alive | Met Amsterdam criteria II |
| [13]    | 54  | F   | MSH2     | NR                       | Lion pain, weight loss, and lethargy | 140 | None | S | 1/50 HPF | Alive | Met Amsterdam criteria II |
| [14]    | 68  | M   | MSH2     | NR                       | Abdominal pain | 41 (Extra adrenal) | S | 2/10 HPF | Alive | Met Amsterdam criteria II |
| This study | 65  | F   | MSH6     | NR                       | Incidental discovery | 92 | Androgen, estrogen excess | S | 40/50 HPF | Alive | NR |

Abbreviations: ACTH, adrenocorticotropic hormone; F, female; HPF, high-power field; M, male; MSS, microsatellite stable; NR, not reported; S, surgical.
2. Discussion

We present a rare case of a patient with LS whose only presentation was incidentally discovered ACC. Outside from ACC, she had no other manifestations of LS at the time of this case report.

Only 13 cases (including our case) have been reported so far in the literature (Table 1). The median age of presentation was 47 years (range: 23 to 68), and 46% were women. The first association of ACC with LS was described in the “N family” of two large Midwestern kindreds by H. T. Lynch in 1966 [8]. Proband from the N family died at age 44 from ACC, whereas his siblings presented with multiple primary colon carcinomas, endometrium carcinomas, and other cancers [8]. Later, three other case reports demonstrated an association of ACC with LS in patients with the \textit{MSH2} germline mutation [5, 10, 11]. In 2013, a prospective study of 114 patients with ACC demonstrated a 3.2% prevalence of LS, which is higher than in the general population (0.2%) and comparable to the prevalence of LS in patients with colorectal cancer and endometrial cancer (1% to 5%) [12]. In this study, five of 114 patients with ACC and LS had \textit{MSH2} (in three patients), \textit{MSH6} (one patient), and \textit{MLH1} (one patient) germline mutations, with four patients demonstrating microsatellite stability. More recently, two more case reports published in 2016 and 2018 [13, 14] again showed association between LS and ACC with \textit{MSH2} germline mutation.

It is challenging to diagnose ACC early in an asymptomatic phase, before substantial growth and metastases occur. The diagnosis of ACC is based on clinical presentation and imaging characteristics of adrenal mass (Hounsfield units $>10$, size $>4$ cm, and heterogeneous). In patients with a genetic predisposition of ACC (such as Li-Fraumeni syndrome, Beckwith–Wiedemann syndrome, multiple endocrine neoplasia type 1, familial adenomatous

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{(a, left) Axial CT image and (right) coronal CT image showing a 6.0 $\times$ 5.1 $\times$ 7.8-cm right adrenal mass (arrows). (b) Gross pathology serial cut sections of a 9.2-cm right ACC.}
\end{figure}
polyposis, neurofibromatosis 1, and LS), the incidence of ACC, although much higher than the general population, is still low to warrant serial imaging. Steroid profiling (Fig. 2) is an attractive alternative that could help diagnose ACC much earlier in the natural history of the disease [15]. In our patient, steroid profiling confirmed our suspicion of ACC after discovery of adrenal mass [16]. Whereas in this case, steroid profiling did not change our management,

Table 2. Results of Biochemical Testing Demonstrate Androgen-, Estrogen-, and Corticotrophin-Independent Cortisol Excess

| Laboratory Test                               | Before Surgery | 1 Mo After Surgery | Reference Range |
|-----------------------------------------------|----------------|--------------------|-----------------|
| Urine-free cortisol, μg/24 h                  | 68             | N/A                | 3.5–45          |
| ACTH, pg/mL                                   | <5             | N/A                | 7.2–63          |
| Serum                                         | 13             | N/A                | <1.8            |
| 8 AM Serum cortisol following Aldosterone ng/dL| 20             | N/A                | ≤21             |
| Renin plasma activity, ng/mL/h                | 2              | N/A                | 0.6–3.0         |
| Androstenedione, ng/dL                        | 151            | N/A                | 30–200          |
| DHEA sulfate, μg/dL                           | 403            | <15                | <15–157         |
| 17-Hydroxyprogesterone, ng/dL                 | 167            | <40                | <51             |
| 17-Hydroxypregnenolone, ng/dL                 | 888            | <16                | 31–455          |
| Total testosterone, ng/dL                     | 30             | <7                 | 8–60            |
| Estradiol, pg/mL                              | 113            | <10                | <10 (Postmenopausal) |

Abbreviations: DHEA, dehydroepiandrosterone; N/A, not available.

Figure 2. Urine steroid profiling. HRAM, high resolution, accurate mass.
after appropriate validation, this test could be offered as a case-detection, noninvasive, and radiation-free test to patients at high risk for ACC. Surgical resection is the mainstay of treatment of ACC with a goal to achieve a microscopic tumor clearance (R0) resection. Further management depends on the stage of ACC and prognostic markers derived from pathology examination.

3. Conclusion

In summary, we present a patient with LS whose only manifestation was ACC, adding to the available literature of only 12 cases. We also demonstrated that steroid profiling could serve as a noninvasive diagnostic and potentially as a case-detection tool for patients at risk for ACC.

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References and Notes

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol.* 2016;175(2):G1–G34.

2. Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM, Jolly S, Miller BS, Giordano TJ, Hammer GD. Adrenocortical carcinoma. *Endocr Rev.* 2014;35(2):282–326.

3. Ñíguez-Ariza NM, Kohlenberg JD, Delivanias DA, Hartman RP, Dean DS, Thomas MA, Shah MZ, Herndon J, McKenzie TJ, Arlt W, Young WF Jr, Bancos I. Clinical, biochemical, and radiological characteristics of a single-center retrospective cohort of 705 large adrenal tumors. *Mayo Clin Proc Innov Qual Outcomes.* 2017;2(1):30–39.

4. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med.* 2003;348(10):919–932.

5. Karamurzin Y, Zeng Z, Stadler ZK, Zhang L, Ouansafi I, Al-Ahmadie HA, Sempoux C, Saltz LB, Soslow RA, O’Reilly EM, Paty PB, Coit DG, Shia J, Klimstra DS. Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: a report of new cases and review of the literature. *Hum Pathol.* 2012;43(10):1677–1687.

6. Stoffel E, Mukherjee B, Raymond VM, Tayob N, Kastrinos F, Sparr J, Wang F, Bandipalliam P, Syngal S, Gruber SB. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology.* 2009;137(5):1621–1627.

7. Houleberghs H, Goverde A, Lusseveld J, Dekker M, Bruno MJ, Menenkamp AR, Spaander MCW, Wagner A, Hofstra RMW, Te Riele H. Suspected Lynch syndrome associated MSH6 variants: a functional assay to determine their pathogenicity. *PLoS Genet.* 2017;13(5):e1006765.

8. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large midwestern kindreds. *Arch Intern Med.* 1966;117(2):206–212.

9. Berends MJ, Cats A, Hollema H, Karrenbeld A, Beentjes JA, Sijmons RH, Mensink RG, Hofstra RM, Verschueren RC, Kleibeuker JH. Adrenocortical adenocarcinoma in an MSH2 carrier: coincidence or causal relation? *Hum Pathol.* 2000;31(12):1522–1527.

10. Broaddus RR, Lynch PM, Lu KH, Luthra R, Michelson SJ. Unusual tumors associated with the hereditary nonpolyposis colorectal cancer syndrome. *Mod Pathol.* 2004;17(8):981–989.

11. Medina-Arana V, Delgado L, González L, Bravo A, Díaz H, Salido E, Riverol D, González-Aguilera JJ, Fernández-Peralta AM. Adrenocortical carcinoma, an unusual extracolonic tumor associated with Lynch II syndrome. *Fam Cancer.* 2011;10(2):265–271.

12. Raymond VM, Everett JJN, Furtado LV, Gustafson SL, Jungbluth CR, Gruber SB, Hammer GD, Stoffel EM, Greenson JK, Giordano TJ, Else T. Adrenocortical carcinoma is a Lynch syndrome-associated cancer. *J Clin Oncol.* 2013;31(24):3012–3018.

13. Challis BG, Kandasamy N, Powles AS, Koulouri O, Annamalai AK, Happerfield L, Marker A, Arends MJ, Nik-Zainal S, Gurnell M. Familial adrenocortical carcinoma in association with Lynch syndrome. *J Clin Endocrinol Metab.* 2016;101(6):2269–2272.
14. Wright JP, Montgomery KW, Tierney J, Gilbert J, Solórzano CC, Idrees K. Ectopic, retroperitoneal adrenocortical carcinoma in the setting of Lynch syndrome. *Fam Cancer*. 2018;17(3):381–385.

15. Bancos I, Arlt W. Diagnosis of a malignant adrenal mass: the role of urinary steroid metabolite profiling. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(3):200–207.

16. Hines JM, Bancos I, Bancos C, Singh RD, Avula AV, Young WF, Grebe SK, Singh RJ. High-resolution, accurate-mass (HRAM) mass spectrometry urine steroid profiling in the diagnosis of adrenal disorders. *Clin Chem*. 2017;63(12):1824–1835.