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Case Report

An Adrenal Mass in a Patient with Lynch Syndrome

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1. Abstract

Adrenocortical cancer (ACC) is a rare malignancy (estimated annual incidence 0.7 to 2.0 cases per million individuals worldwide) with a poor prognosis. In contrast, Lynch Syndrome (LS) is a much more commonly encountered hereditary syndrome that predisposes individuals to colon cancer and multiple other malignancies. Recently ACC has been described as a LS associated malignancy. Identifying associations between LS and other malignancies such as ACC is impor-tant as it promotes identification of individuals not already diagnosed with LS, may influence decisions to screen families, and may impact screening or evaluation of otherwise nonsuspicious findings (i.e. an adrenal nodule) in patients at risk.

2. Introduction

Lynch syndrome (LS) describes a subset of patients with germline mutations in DNA mismatch repair (MMR) genes (most commonly *MLH1*, *MSH2*, *MSH6*, and *PMS2*) that account for 2-4% of all colorectal cancers [1, 2] with varying phenotypes de-pending on specific mutation. Patients with LS have an estimated lifetime risk of 80% for developing colorectal cancer and an in-creased risk for other extracolonic malignancies, including endo-metrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, and small intestinal cancers.[2] Recently adrenocor-tical cancer (ACC), a rare and aggressive malignancy, has been associated with LS [3-7], although the low prevalence of ACC makes it difficult to attribute causality.

3. Case

A male in his 30s with a family history of colon cancer in mul-tiple first degree relatives underwent colonoscopy for evaluation of persistent diarrhea and was found to have a moderately dif-ferentiated adenocarcinoma of the distal transverse colon. Pre-operative staging did not demonstrate evidence of metastatic disease. He underwent a laparoscopic-assisted partial colectomy, with resection of a T2N1, stage IIIb moderately differentiated ad-enocarcinoma with loss of expression of MSH2 and MSH6. Con-firmatory genetic testing demonstrated a deletion of the MSH2 gene, consistent with Lynch Syndrome. Six weeks after surgery, a staging PET-CT demonstrated a metabolically active left ad-renal nodule (1.3 x 1.0 cm, SUV 8.6) without evidence of addi-tional disease. High resolution CT imaging identified enhance-ment and washout characteristics incompatible with a benign adenoma (Figure 1A and B). Biochemical evaluation excluded a hormonally functional adrenal tumor. Image-guided fine needle aspiration biopsy of the nodule demonstrated adrenal tissue with atypical cells, but failed to render a conclusive diagnosis. Immu-nostaining on the biopsy specimen was positive for calretinin, weakly positive for inhibin, and negative for CDX-2 and CK20; estimates of the Ki-67 proliferation index were high (32%). The patient was started on adjuvant FOLFOX therapy for treatment of his colorectal cancer and later referred for surgical evaluation of the adrenal mass. Following completion of therapy, repeat im-aging demonstrated an increase in the size of the adrenal mass to 1.7 x 1.2 cm.

The patient underwent an uncomplicated open left adrenalec-tomy for a clinical suspicion of a primary adrenal malignancy. Pathologic examination showed adrenocortical carcinoma (ACC) with oncocytic features, measuring 1.5 x 1.4 x 1.2 cm, confined to the adrenal gland with surgical margins free of tu-mor. The mitotic rate was 10 per 50 high power fields with severe nuclear atypia and a ki-67 index of 32%, supporting the malig-nant diagnosis. Immunostaining for MSH2 and MSH6 demon-strated loss of protein expression consistent with the pattern ob-served in the patient's initial colorectal cancer.

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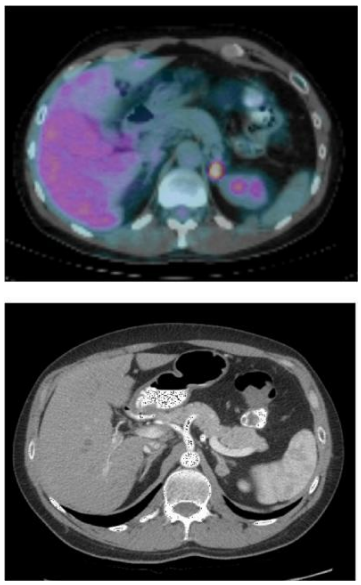

Figure 1: A PET-avid left adrenal mass (arrow, A), measuring 1.3 x 1.0 cm on contrasted CT (arrow, B).

4. Discussion

This case report describes a young man with colorectal cancer and concomitant adrenocortical cancer. In both tumors immunohistochemistry demonstrated loss of protein expression of MSH2 and MSH6, consistent with a diagnosis of LS and suggestive of a relationship between ACC and LS.

To date, the largest study evaluating a link between LS and ACC characterized 94 patients with ACC who underwent subsequent genetic counseling – 3 were found to have LS, for a syndrome prevalence of 3.2% amongst patients with ACC.[7] This is significantly higher than the prevalence of 0.72 per million individuals amongst the general population [7,8]. The same group also retrospectively evaluated 135 probands with LS and identified two more patients with a personal history of ACC; both had MSH2 germline mutations. Of these five patients, ACC tumor tissue was available for analysis in four, with two demonstrating loss of MSH2/MSH6 protein expression (both with MSH2 germline mutations), one demonstrating loss of MLH1/PMS2 expression (MLH1 germline mutation in family), and one patient with a MSH6 germline mutation demonstrating intact protein expres-sion [7]. It is possible the latter patient had a sporadic ACC. Oth-er case reports in the literature identify MSH2 mutation as the common denominator in LS associated ACC[4,6], as observed in this patient. While difficult to assess due to the rarity of the disease, the association between MSH2 germline mutation and ACC should be further examined. The oncocytic classification of our patient's tumor makes this report unique amongst the other reports of LS-associated ACC. Typically characterized by abun-dant eosinophilic and granular cytoplasm due to the high number of mitochondria, the high mitotic rate and nuclear atypia in this report meet the Lin-Weiss-Bisceglia criteria for oncocytic malignancy[9]. Estimates of survival for patients with oncocytic ACC are favorable, with a median survival of 58 months in one series of 13 patients [10]. To our knowledge this is the first report that associates an oncocytic adrenocortical carcinoma with LS. Currently our patient is alive and well without evidence of either colon or adrenal cancer after X months of follow-up

Although a PET-avid adrenal lesion in patients with known malignancy is concerning for metastasis, a primary adrenal tumor should be excluded. Pheochromocytomas are characteristically PET avid, and atypical adenomas can also demonstrate PET avid-ity. However, in the setting of LS, a primary ACC should be con-sidered with a higher index of suspicion, as highlighted by this case, especially in the setting of normal plasma metanephrines and relatively rapid enlargement. Although infrequent, recogni-tion of an association between rare cancers like ACC and LS may promote identification of families and individuals at risk, influ-ence screening decisions, and may heighten suspicion of new adrenal nodules in the patient with LS. The current study lends support to the available data supporting ACC as a LS associated malignancy.

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