Familial adrenocortical carcinoma in association with Lynch syndrome

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Abstract

Context: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with a poor prognosis. Although the majority of childhood ACC arises in the context of inherited cancer susceptibility syndromes, it remains less clear whether a hereditary tumour predisposition exists for the development of ACC in adults. Here, we report the first occurrence of familial ACC in a kindred with Lynch syndrome due to a pathogenic germline *MSH2* mutation.

Case: A 54-year-old female, with a history of ovarian and colorectal malignancy, was found to have an ACC. A detailed family history revealed her mother had died of ACC and her sister had previously been diagnosed with endometrial and colorectal cancers. A unifying diagnosis of Lynch syndrome was considered, and immunohistochemical analyses demonstrated loss of MSH2 and MSH6 expression in both adrenocortical carcinomas (proband and her mother), and in the endometrial carcinoma of her sister. Subsequent genetic screening confirmed the presence of a germline *MSH2* mutation (resulting in deletions of exons 1-3) in the proband and her sister.

Conclusion: Our findings provide strong support for the recent proposal that ACC should be considered a Lynch syndrome associated tumour and included in the Amsterdam II clinical diagnostic criteria. We also suggest that screening for ACC should be considered in cancer surveillance strategies directed at individuals with germline mutations in DNA mismatch repair genes.

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine cancer with an incidence of less than 1 case per million individuals per year (1). The majority of childhood ACC occurs in patients with familial cancer susceptibility syndromes such as Li-Fraumeni syndrome (LFS), but whether a hereditary tumour predisposition exists for the development of ACC in adults is less clear (1). Whilst the majority of ACC in adulthood are sporadic, increasing evidence supports association between adult ACC and inherited cancer susceptibility syndromes including LFS, Multiple Endocrine Neoplasia type 1 and Lynch syndrome (LS)(1). However, given the low prevalence of ACC, ascertaining whether this cancer is a *bona fide* syndrome-associated malignancy is challenging.

Lynch syndrome is an autosomal dominant familial cancer syndrome caused by pathogenic germline mutations in one of several DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6* or *PMS2),* and associated with an estimated lifetime colorectal cancer risk of 80% (2). LS is also associated with an increased risk of several extra-colonic tumours (endometrial, stomach, small intestinal, hepatobiliary, urinary tract), which are therefore included as part of the Amsterdam II clinical diagnostic criteria for LS (2). In addition to these recognised cancers, previous reports have described a number of rare, non-classical cancers, including adrenocortical carcinoma (ACC), in patients with LS. Given the low prevalence of ACC it remains uncertain whether it is a true LS-associated tumour or arises independent of the primary genetic defect, although a recent study involving 114 subjects with primary ACC and 135 probands from MMR gene-positive kindreds has provided important evidence for the former (3).

Here, we provide additional evidence to implicate ACC as a LS-associated cancer with the first description of an intergenerational (mother-to-daughter) occurrence of ACC in a family with LS due to a germline MSH2 mutation. We therefore propose that ACC be included in clinical diagnostic criteria for LS and considered in cancer surveillance recommendations for individuals with germline mutations in DNA MMR genes.

Case History

In 2001, the proband (Patient III:2), a 54-year old female, presented to her local hospital with right loin pain, lethargy and weight loss. She had previously undergone a hysterectomy and bilateral salpingo-oopherectomy for ovarian cancer at age 44 years and endoscopic removal of a malignant colonic polyp at age 47 years. Clinical examination revealed right loin tenderness but was otherwise unremarkable with no evidence of catecholamine, glucocorticoid, mineralocorticoid or androgen excess. Abdominal ultrasonography demonstrated a right suprarenal lesion and subsequent computed tomography (CT) confirmed the presence of a 14 cm mass arising from the right adrenal gland. There was no evidence of extra-adrenal disease. Biochemical investigations excluded phaeochromocytoma and confirmed a non-secretory adrenal lesion.

The patient underwent a laparoscopic right adrenalectomy and nephrectomy to remove a 14 x 10cm adrenal mass. Pathological examination of the resected specimen showed an adrenocortical tumour with adrenal capsular invasion, areas of confluent necrosis and possible vascular invasion **(Figure 2A (a) and (b))**. The tumour was composed of lobules of oncocytic cells separated by fibrous septae. The tumour cells showed focal marked nuclear pleomorphism with bizarre nuclear forms. The mitotic index was 1/50hpf. Immunohistochemically, tumour cells were positive for vimentin and melan A and negative for calretinin, inhibin, S100, cytokeratin, carcinoembryonic antigen (CEA), chromogranin A, neurofilament (NFP) and synaptophysin. Collectively, these features were in keeping with an oncocytic adrenocortical carcinoma based on Lin-Weiss-Bisceglia criteria (4,5).

Adjunctive mitotane therapy (maximum tolerated dose: 500mg thrice daily) was commenced with concurrent hydrocortisone replacement (10mg twice daily). To date the patient has

received regular clinical, biochemical and radiological surveillance with no evidence of disease recurrence.

The proband's sister (Patient III:1) had no significant personal medical history until age 36 years when she was diagnosed with an adenocarcinoma of the descending colon which required a left hemicolectomy. At age 47 years she was diagnosed with endometrial carcinoma following investigations for intermenstrual bleeding, and treated by radical hysterectomy.

An underlying familial cancer syndrome was suspected and a more detailed family history revealed that the proband's maternal aunt (Patient II:3) and grandfather (Patient I:1) had both been diagnosed with colorectal cancer **(Figure 1)**. Importantly, the certificate of death for the proband's mother (Patient II:2) stated metastatic adrenocortical carcinoma as the cause of death. Given the rarity and difficulty in establishing malignancy of adrenocortical tumours, the histology of the resected adrenal tumour was re-evaluated which, confirmed the original diagnosis of primary adrenocortical carcinoma **(Figure 2A(c))**.

In accordance with the Amsterdam II criteria and revised Bethesda criteria the family fulfilled diagnostic requirements for Lynch syndrome and further immunohistochemistry was performed on both ACCs (Patients III:2 and II:2) and the endometrial tumour (Patient III:1) to determine MMR protein expression status **(Figure 2B)** (2). In all analysed tumours expression of MLH1 and PMS2 was retained whilst nuclear staining for MSH2 and MSH6 were absent, consistent with a LS phenotype. Further germline genetic testing was undertaken by multiplex ligation dependent probe amplification (MLPA) analysis in the proband and her sister and revealed a heterozygous deletion of exons 1, 2 and 3 of the *MSH2* gene. Further genetic testing also identified the mutation in the proband's son (Patient IV:5), daughter (Patient IV:4) and niece

(Patient IV:2). In accordance with the Chompret testing criteria, *TP53* germline mutations were excluded in the proband (6). The unavailability of genomic DNA from the proband's mother (Patient II:2) precluded further genetic study.

Discussion

ACC is not currently included in the diagnostic criteria for Lynch syndrome. However, our description of familial ACC arising in the context of a germline *MSH2* mutation supports the recent proposal that ACC should be considered a LS-associated tumour (3). Currently, the diagnosis of LS requires patients/kindreds to fulfil the Amsterdam or revised Bethesda criteria, with demonstration of absent MMR protein expression on tumour immunohistochemistry and/or microsatellite instability (MSI) genotyping supporting the diagnosis (2). Genetic testing for germline mutations in MMR genes is reserved for individuals with tumours that demonstrate MSI or absent MMR protein expression, or those deemed at-risk based on computational prediction models (2).

Isolated cases of ACC arising in single patients of families with LS and germline mutations in DNA MMR genes *(MLH1, MSH2, MSH6)* have been previously reported, but given their rarity, determining whether these tumours were coincidental or part of the LS tumour profile has remained controversial (3,7,8). Compelling evidence supporting ACC as a LS-associated cancer was recently provided by Raymond and colleagues who found that LS prevalence among patients with primary ACC was significantly higher (3.2%) than in the background population (0.2%), and comparable to the prevalence of LS in colorectal (2-4%) and endometrial cancer (1-5%) (3). Moreover, the prevalence of ACC in LS was increased compared with the general population. Given that ACC is typically an aggressive malignancy, with limited treatment options for advanced disease, recognising association of this tumour with LS has important clinical implications. Specifically, improved awareness and recognition of the syndrome and entry into appropriate systematic cancer surveillance programmes would be anticipated to lead to earlier diagnosis and timely intervention in order to reduce LS-related morbidity and mortality.

IHC analysis of tumour MMR proteins is often performed concomitantly with MSI to improve clinical sensitivity in the evaluation for LS. In our case, IHC analysis for LS-related tumours was informative and identified loss of MSH2 and MSH6 expression in the ACC and endometrial tumours analysed from affected patients with the germline MSH2 mutation. In contrast with colorectal tumours, which demonstrate high MSI, previous reports have consistently found that ACC tumours have low MSI in patients with LS, and on this basis MSI testing was not performed in our patient (3). Whilst a molecular basis for this discrepancy between tumour types remains unclear, it has been proposed that in some tumours, possibly due to tissue-specific factors, the consequences of MMR deficiency occur in the latter stages of carcinogenesis thereby preventing detectable accumulation of MSI. Further, currently used MSI tests have been optimised for colorectal cancers and are less sensitive for MSI detection in other tumour types. Therefore, low MSI does not necessarily exclude a diagnosis of LS and, for both sporadic and familial ACC, IHC analysis of MMR proteins should be considered the first-line molecular screening strategy, even in individuals without other LS-associated lesions, with germline genetic testing pursued in the absence of one or more MMR proteins. Currently, there are no established biochemical or radiological screening guidelines for those at-risk of ACC. We have adopted an empirical approach in the offspring of our proband, combining periodic surveillance MRI imaging MRI with serum and urinary steroid profiling. It remains to be seen whether this is a clinically cost-effective approach.

In summary, we report the first description of familial ACC in conjunction with a germline *MSH2* mutation and provide support for MMR genes as candidates in hereditary ACC. We advocate ACC be now included in clinical diagnostic criteria for LS and considered in cancer surveillance strategies for individuals with germline mutations in DNA MMR genes. Moreover,

in the absence of clinical management guidelines for ACC surveillance in patients with inherited cancer syndromes, including LS, we recommend individualised screening protocols coupled with ongoing clinical vigilance.

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Figure Legends

Figure 1.

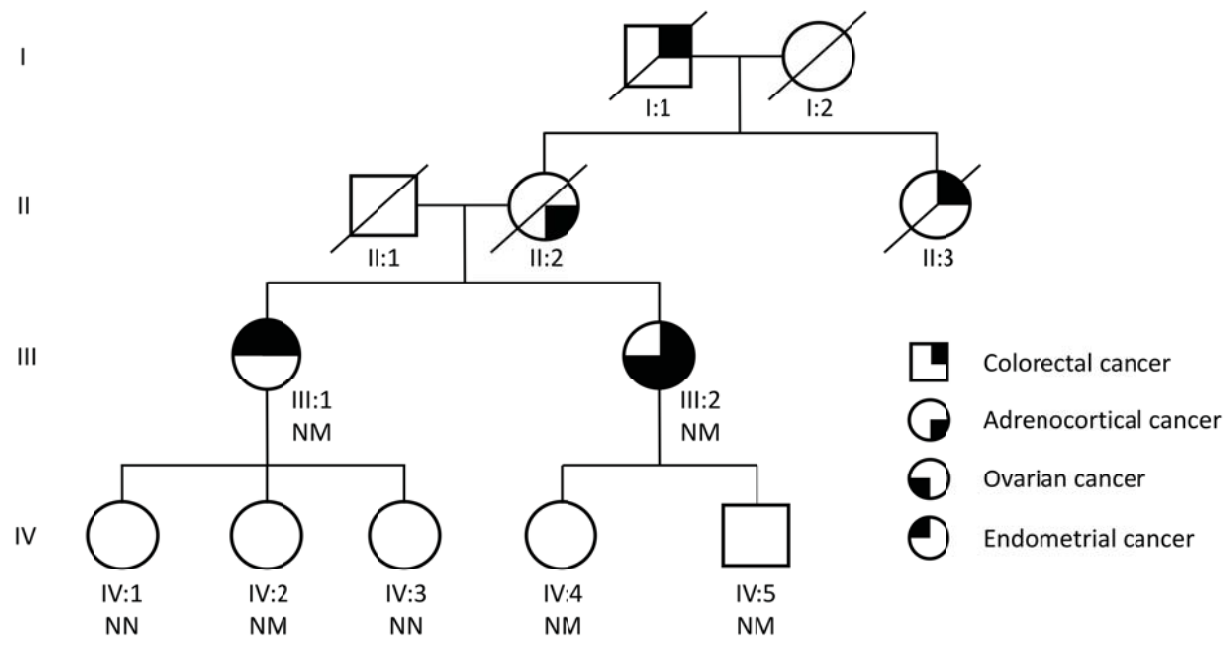
Pedigree of family with the germline *MSH2* mutation. NN represents wild-type individuals and NM denotes carriers of the mutation.

Figure 2.

(A) (a) High magnification image of H&E stained photomicrograph demonstrating confluent tumour necrosis (arrowhead) in ACC from patient II:2. (b) Medium magnification image demonstrating capsular invasion (arrowhead) in ACC from patient II:2. (c) Medium magnification image of ACC from patient III:2 demonstrating atypical nuclei, mitotic activity and areas of necrosis.

(B) Immunohistochemical analyses of MLH1, PMS2, MSH2 and MSH6 protein expression in adrenocortical carcinomas (ACC) resected from Patients II:2 (a,b,c,d) and III:2 (e,f,g,h), and endometrial tumour resected from Patient III:1 (i,j,k,l) (x400). All analysed tumours retained expression of MLH1 (a,e,i) and PMS2 (b,f,j) (short arrowhead) but expression of MSH2 (c,g,k) and MSH6 (d,h,l) was absent (solid arrow) with adjacent normal stromal cells exhibiting positive staining (dashed arrow).

260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Colorectal cancer
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Ovarian cancer
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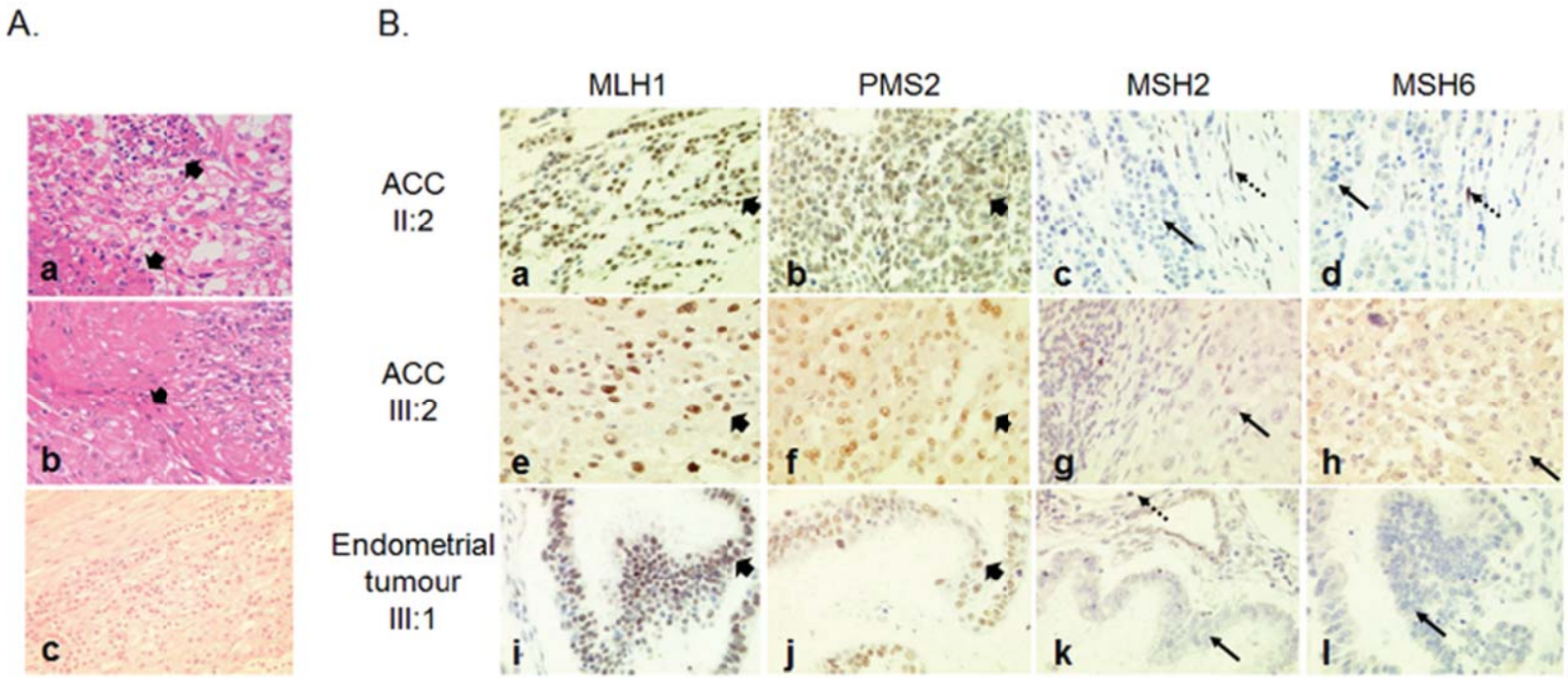
A.
B.
MLH1
PMS2
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