An interesting case of synchronous endometrial and ovarian carcinomas analyzed through mismatch repair somatic tumor genetic testing

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I. Background

The simultaneous occurrence endometrial and ovarian carcinomas occur in 5% of endometrial cancer patients and 10-20% of ovarian cancer patients[1].

The diagnosis of the synchronous adenocarcinoma of the uterus and the ovary is challenging as they could represent two independent primary tumors or metastatic dissemination from one site to another and has important implications for prognosis and patient management.

II. Objectives

To present a case of a 55-year-old woman with synchronous endometrioid carcinoma with clear cell features and endometrial adenocarcinoma of the endometrium. Mismatch repair (MMR) somatic tumor testing using next-generation sequencing (NGS) was performed on both tumor samples and showed some evidence of clonal lineage.

III. Patient History

Previous test results provided by referring specialist:

FAMILY HISTORY

Has a paternal aunt who died at the age of 57 with reported ovarian or endometrial cancer.

TUMOR TESTING

Tumor A (Ovarian carcinoma)

IHC/MSI: IHC = loss of nuclear expression of *MSH2* and *MSH6* (intact nuclear expression of *PMS2*) and abnormal mutant-type *TP53* staining.

Tumor B (Endometrial carcinoma)

IHC/MSI: IHC = loss of nuclear expression of *MSH2* and *MSH6* (intact nuclear expression of *PMS2*).

GENETIC TEST RESULTS

Germline MMR: No germline pathogenic variants detected in *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHECK2*, *EPCAM* (deletion and duplication only), *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, *TP53* genes.

(Invitae Breast and Gyn Cancers Guidelines-Based Panel).

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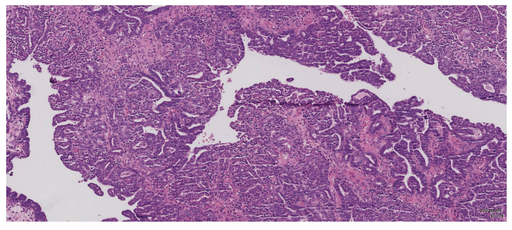
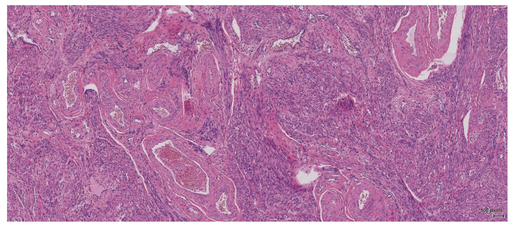
IV. Methods

***MLH1*/*MSH2*/*MSH6*/*PMS2*/*EPCAM* Somatic Tumor MMR Sequencing and Deletion/Duplication



Tumor A: Ovarian carcinoma



Tumor B: Endometrial adenocarcinoma

1. DNA extracted from FFPE slides
2. Sequence analysis of all coding exons and flanking intronic regions of up to 5 genes using NGS.

DNA corresponding to all *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* coding regions as well as 25 base pairs (bp) of non-coding flanking DNA was captured using DNA hybridization probes. Captured DNA was sequenced using Illumina sequencing technologies and processed using the Data-Driven Medicine (DDM) Bioinformatics pipeline (Sophia Genetics). Minimum NGS coverage is 1000X for all exons and ±25 bp of flanking intronic sequencing. All regions with coverage that does not meet this threshold are assessed by Sanger sequencing. All pathogenic, likely pathogenic and uncertain NGS variants are confirmed by Sanger sequencing.

3. Multiplex Ligation-dependent Probe Amplification (MLPA) is used to assess for large single or multi-exon deletions and duplications.

V. Results

Results from Impact Genetics Somatic MMR tumor testing:

Tumor A: Ovarian carcinoma

Detected in Tumor A	Detected in blood	Gene	Variant	Classification	Variant allele frequency
Yes	No	*MSH2*	c.2034T>A p.(Tyr678Ter)	Pathogenic	19.8%
Yes	No	*MSH2*	c.1216C>T p.(Arg406Ter)	Pathogenic	17.6%

No other reportable variants detected in *MSH2* and *MSH6*

Tumor B: Endometrial adenocarcinoma

Detected in Tumor B	Detected in blood	Gene	Variant	Classification	Variant allele frequency
Yes	No	*MSH2*	c.2034T>A p.(Tyr678Ter)	Pathogenic	8.7%
Yes	No	*MSH2*	c.1216C>T p.(Arg406Ter)	Pathogenic	7.8%

No other reportable variants detected in *MSH2* and *MSH6*

INTERPRETATION:

Both variants were confirmed by Sanger sequencing and were not detected in the patient's DNA from blood, consistent with the previously reported negative *MSH2* germline results for this patient.

The two variant alleles frequencies are consistent with the tumor cellularity present on the FFPE block of tumor A estimated to be less than 50% and tumor B, estimated to be less than 20%.

Given the low tumor cellularity of both tumor samples provided, copy number analysis by multiplex ligation-dependent probe amplification (MLPA) was not possible.

c.2034T>A (p.Tyr678Ter) nonsense variant: This variant has been described once in ClinVar (Accession ID: RCV000702976.1, by Invitae, last evaluated June 2018) and in the literature as a pathogenic germline variant associated with Lynch syndrome[5]. This substitution creates a nonsense variant which causes a premature termination codon.

c.1216C>T (p.Arg406Ter) nonsense variant: This variant has been described several instances in ClinVar (RCV000030238.4, RCV000677885.1, RCV000202291.4, RCV000162489.3, RCV000524334.2 and RCV000001825.2), InSight database and in the literature as a pathogenic germline variant causing Lynch syndrome. This substitution creates a nonsense variant which causes a premature termination codon.

VI. Conclusions

In the literature, data from recent NGS papers suggest that sporadic synchronous endometrial and ovarian carcinomas show evidence of clonality and that these tumors may constitute dissemination from one site to another[2,3]. However, the chronology of the development of these synchronous cancer remains unclear.

Similar results were then obtained in Lynch-related synchronous endometrial and ovarian carcinomas[4].

In this patient, the identification of the same *MSH2* somatic variants in both tumor types is suggestive of the presence of clonally related tumors, however, the analysis remains limited since on only two genes were sequenced in our assay.

Given that neither *MSH2* variant was detected in this patient's blood reduces the likelihood that this patient has Lynch syndrome.

VII. References

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VIII. Acknowledgements

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