I. Background

The simultaneous occurrence endometrial and ovarian carcinomas occur in 5% of endometrial cancer patients and 10-20% of ovarian cancer patients. 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 endometroid 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 from 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).

Tumor B (Endometrial carcinoma)

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

GENETIC TEST RESULTS

Somatic Tumor MMR Sequencing

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

V. Results

Results from Impact Genetics Somatic MMR tumor testing:

Tumor A: Ovarian carcinoma

<table>
<thead>
<tr>
<th>Detected in Tumor A</th>
<th>Detected in blood</th>
<th>Gene</th>
<th>Variant</th>
<th>Classification</th>
<th>Variant allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>MSH2</td>
<td>c.2034T&gt;A p.(Tyr678Ter)</td>
<td>Pathogenic</td>
<td>19.8%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>MSH2</td>
<td>c.1216C&gt;T p.(Arg406Ter)</td>
<td>Pathogenic</td>
<td>17.6%</td>
</tr>
</tbody>
</table>

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 allele 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.

Tumor B: Endometrial adenocarcinoma

<table>
<thead>
<tr>
<th>Detected in Tumor B</th>
<th>Detected in blood</th>
<th>Gene</th>
<th>Variant</th>
<th>Classification</th>
<th>Variant allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>MSH2</td>
<td>c.2034T&gt;A p.(Tyr678Ter)</td>
<td>Pathogenic</td>
<td>8.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>MSH2</td>
<td>c.1216C&gt;T p.(Arg406Ter)</td>
<td>Pathogenic</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

No other reportable variants detected in MSH2 and MSH6

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. 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 (RCV00030238.4, RCV000677885.1, RCV000202291.4, RCV000162489.3, RCV000524334.2 and RCV000018252.2), 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. 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.

VII. References


VIII. Acknowledgements

Special thanks to our pathologist Dr. M. Treloar for reviewing the slides and to Dr. Ian Fraley for continuing to support our interpretation efforts and acting as our expert medical adviser for the MMR somatic test offered by Impact Genetics/Dynacare.

Additional thank you to Franny Jewett for continuous support and to the Impact Genetics team in Bowmanville Ontario.