Lynch syndrome-associated endometrial cancer
(a practicing pathologist’s perspective)

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Outlines

• Introduction
• Molecular genetics
• Significance of diagnosing LS
• LS diagnosis and screening tests
• Screening strategies:
  – Tumor morphology and topography
  – Universal screening
Introduction

• Lynch syndrome (LS) is a hereditary predisposition to develop certain types of cancers (e.g., CRC, endometrial and ovarian cancer)

• As a result of a germline mismatch repair (MMR) gene mutation in $MLH1$, $PMS2$, $MSH2$, or $MSH6$ genes

• Autosomal dominant
Cancer Risks in Lynch Syndrome

% with cancer

Colorectal 78%
Endometrial 43%
Stomach 19%
Biliary tract 18%
Ovarian 9%

Age (years)

Estimate:
Uterine cancer rates may be TWICE those of colon cancer rates in women.
<table>
<thead>
<tr>
<th></th>
<th>Endometrial CA</th>
<th>Colorectal CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>45-55 yrs</td>
<td>35-45 yrs</td>
</tr>
<tr>
<td>DNA MMR Mutations</td>
<td>hMSH6 &gt; hMSH2 &gt; hMLH1</td>
<td>hMLH1 = hMSH2 &gt; &gt; hMSH6</td>
</tr>
<tr>
<td>MSI-H Rate</td>
<td>70%</td>
<td>99%</td>
</tr>
<tr>
<td>Family history</td>
<td>30%</td>
<td>80%</td>
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LS and EC

• Endometrial carcinomas (ECs) show frequent DNA MMR abnormalities in ~20%:
  - Sporadic (~75%): *MLH1* promoter methylation
  - LS (~25%): Germline mutations DNA MMR genes
    • Overall 2-5% of all EC are LS-related
Molecular Genetics

Chr 2
- MSH6
- MSH2

Chr 3
- MLH1

Chr 7
- PMS2
Molecular Genetics

Obligatory

MutSα

MutLα

MSH2, MSH6

MLH1, PMS2

Obligatory
Addition of nucleotide repeats
Why we should screen for LS?

• Women with LS have equal or higher risk of endometrial cancer, compared to CRC ~40-60%
• Sentinel malignancy >50%
• Personal risk for synchronous or metachronous tumors; screening for CRC can reduce the risk of death by 65%
• Implications for family members
Diagnosis of LS

• The most direct method of documenting a LS defining mutation is gene sequencing
  – Expensive
  – Time consuming
  – Needs patient’s consent

• Other ways to select for genetic testing
  – DNA MMR IHC for MLH1, MSH2, MSH6, and PMS2
  – MSI analysis:
    • Not as sensitive as IHC
  – MLH1 promoter methylation analysis
    • To distinguish epigenetic inactivation of MLH1
DNA MMR immunohistochemistry (IHC)

- Loss of expression of any marker (4-marker panel):
  - 91% sensitive and 83% specific for MSI-H
    - *hMSH6* mutation


Practically speaking...

- Loss of expression of MSH2 and/or MSH6 indicates DNA-MMR gene mutation
  - Highest risk for Lynch syndrome

- Loss of expression of MLH1 and/or PMS2 may indicate DNA-MMR gene mutation
  - Lower risk for Lynch syndrome
IHC-MMR

• Familiar methodology (but requires training)
• Quick turn-around
• Can pinpoint genes of interest for sequencing
• Relatively inexpensive*


IHC-MMR

• Problems:
  – Weak internal positive controls
    • Low proliferative activity
  – Weak, equivocal signal in tumor cells (MLH1)
    • Transcriptional silencing vs missense mutation vs nonsense mutation
Reporting MMR IHC

Pathology Addendum

Results of immunohistochemical staining for DNA mismatch repair proteins are as follows:

- **MLH1**: Staining present in tumor
- **MSH2**: Staining absent in tumor
- **MSH6**: Staining absent in tumor
- **PMS2**: Staining present in tumor

Conclusion: Immunohistochemical staining results suggest abnormal MSH2 and/or MSH6 protein expression. Clinical correlation is suggested.
Regulatory issues

– Is consent needed for MMR IHC?

– Clinicopathologic correlation
  • IHC reporting
  • Assure all targeted patient samples are tested
  • Assure all relevant patients are referred for counseling

– Genetics evaluation
  • MSI vs methylation vs mutation analysis
Whom we should screen?

- Detection of patients at risk for LS has relied upon assessment of a variety of features such as young age, FH or PH (Amsterdam II criteria and the revised Bethesda guidelines)
- In EC this lacks sensitivity and specificity
- Hampel et al study 2006:
  - 6 of 10 patients were under age of 50y
  - 7 of 10 patients did not meet Amsterdam criteria or revised Bethesda guidelines

Tumor morphology and topography

- Tumor characteristics frequently seen in ECs with DNA Mismatch repair (DNA MMR) abnormalities:
  - Lower uterine segment origin
  - Peritumoral and tumor infiltrating lymphocytes
  - Undifferentiated/dedifferentiated carcinoma
  - Synchronous ovarian clear cell carcinoma
  - Tumor heterogeneity (mixed tumors, hybrid tumors?)
  - ? Non endometrioid, mixed histology in young patients

Tumor morphology and topography

- **Tumor heterogeneity:** 2 or more morphological patterns (frequently of different grade), each at least 10%, juxtaposed but not mixed
  - **Mixed histology:** 2 or more distinct histological types

- **Undifferentiated ca:** Solid sheets of round or polygonal cells with vesicular chromatin, without evidence of gland formation

- **TIL:** >40 lymphocytes /10 HPF within the tumor

- **Peritumoral lymphocytes:** readily identifiable lymphoid aggregates from scanning power

- **LUS:** Tumor is confined grossly to LUS
Dedifferentiated adenocarcinoma

*MLH1* hypermethylation
39 year old with *MLH1* mutation
50 year old with high grade EC with ambiguous morphology

*MSH2* mutation
62 year old with mixed histology

**MSH6 mutation**

- Clear cell
- Serous
- Endometrioid
47 year old with “mixed serous and endometrioid carcinoma”
Patient had *MSH2* mutation
Endometrial tumor

Synchronous Ovarian clear cell carcinoma

MSH6 loss
49 year old with IA endometrioid adenoca & synchronous ovarian endometrioid adenoca
Endometrial tumor
PMS2 mutation
MELF Pattern of Invasion

• Microcystic elongated fragmented, described by Murray et al, seen in ~15% of EC, and associated with LVI

• In our study cases 75% of myoinvasive tumors had MELF pattern of invasion
  - More frequent in patients with MLH1/PMS2 loss (82%) vs MSH2/MSH6 (66%). \( P=0.08 \)

MELF Pattern of Invasion: A Frequent Finding in Endometrial Carcinoma with DNA Mismatch Repair Abnormalities

Lynch syndrome screening tests in uterine cancer patients >50 y depends on clinical and tumor morphology criteria: evidence against universal testing

- Retrospectively performed MMR IHC on all EC patients aged >50 y, who lacked BG criteria and lacked TM-MMR
- Among 182 EC patients, 4 had MLH1/PMS2 loss (3 had \textit{MLH1} promoter hypermethylation) and 1 had MSH6 loss
- They concluded that in EC patients >50y, universal screening by MMR IHC is questionable

Endometrial Carcinomas

**All <50 years age**

- **IHC-MMR**
  - IHC-MMR retained
  - No suspicion: no further testing
  - Clinical suspicion high: alternative test

**≥50 years age**

1. **Tumor characteristics**
2. **Personal/family history**

- **Loss of IHC-MMR**
  - **MLH1/PMS2 loss**
    - MLH1 promoter methylation
      - present: Sporadic EC
      - absent: Gene mutation analysis
  - **MSH2/MSH6 loss**

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Loss of IHC-MMR

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2. Personal/family history

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MLH1 promoter methylation

present
Sporadic EC

absent
Gene mutation analysis

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MLH1 promoter methylation

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absent

Sporadic EC

Gene mutation analysis

LS screening strategies

• Universal screening
  – Will detect all patients at risk for LS
  – Reasonable approach for centers that are unfamiliar with the morphologic and topographic features

  Ryan et al. Cancer 2012; 118:681-688

  – It has obvious monetary implications

• Testing all patients < 60 y
LS screening strategies: Universal screening

Universal screening

• 76 EC patients with mutation proven LS were included
• This study also show poor sensitivity of AC and rBG (58% and 36%)
• 39% were >50y
• Morphologic features in MSI-H: 44%
• Cohort?

Ryan et al. Cancer 2012; 118:681-688
Take home messages

- Recognizing which patients have LS-associated EMC allows surveillance for and prevention of colon cancer

- Differences with LS associated colon cancer

- EC with DNA MMR abnormalities show characteristic morphologic and topographic features

- Similar to colon cancer, DNA MMR IHC screening of endometrial cancers is effective
  - Selected approach (age, morphology and clinical criteria)
  - Generous age cut-off (e.g. 60 y)
  - Universal screening

Questions?