Evaluation and Management of HNPCC

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Lynch Syndrome
Historical Background

• First described by Aldred Warthin in 1913
• In 1966, Henry Lynch reported two large families with hereditary CRC
• Over the years, hundreds of families with the same pattern of cancer occurrence have been described
• In 1988, Amsterdam criteria were put forward
• Early 1990s the mutant gene (MMR gene) was discovered
Lynch Syndrome

• The most frequent hereditary CRC syndrome
• Autosomal dominant inheritance
• Germline mutations in MMR genes (MLH1, MSH2, MSH6 and PMS2)
• Early age of onset of multiple colonic tumors and polyps
• Extra-colonic tumors (endometrium, stomach, urothelial, small intestine, hepatobiliary, prostate and ovary)
Diagnosis of HNPCC

• Frequently underestimated
• Phenotypic features are not very evident
• Implications:
  • Inadequate treatment
  • Inadequate follow up after treatment
  • Inadequate surveillance of family members
Diagnosis of HNPCC

- Suspicious family history
- Suspicious pathology features of tumors
- Genetic testing
The family history
Amsterdam criteria

- Three relatives with histologically confirmed CRC
- One relative first degree to the other two
- Three successive generations
- One cancer diagnosed under the age of 50 y
- FAP excluded
The family history
Betheseda criteria

• Amsterdam criteria fulfilled
• Two or more HNPCC related cancers in one individual (including colonic and extracolonic cancers)
• Individual and first degree relative with either CRC and/or extracolonic cancer and/or colorectal polyp
• Cancer diagnosed at age less than 45 and adenoma less than 40
• Individual with CRC or endometrial cancer less than 45
• Individual with right sided undifferentiated cancer less than 45
• Signet ring cancer less than 45
• Adenoma at less than 40
Drawbacks of Family History

- Missing information
- Scattered family members
- Unknown family members and illegal relations
- Young family members not developing tumors
Suspicious Pathology Features

- Right sided tumors
- Multiple tumors
- Tumor-infiltrating lymphocytes
- Crohn’s like infiltrates
- Aggressive histology
- Good prognosis
Genetic Testing
Identification of MMR Gene Mutation

• The ideal test
• Crucial to extend molecular analysis of family members and surveillance
• Difficult to identify the mutation
  • Genetic heterogeneity
  • Variable clinical features among HNPCC families
• The technique is costly and time-consuming
Microsatellite Instability (MSI)

- MMR gene mutations results in MSI
- Detected in tumor tissue by immune-histochemistry and PCR
- The MSI-H detected in approximately 86% of HNPCC cases
- Recommended in patients with suspicious family history
- May be recommended in all CRC patients because of its Important prognostic and predictive value of response to chemotherapy and immunotherapy
MsPath and PathScore scoring system

- Scoring systems based on clinicopathologic features have been used to standardize the prediction of HNPCC patients.

- Used to identify the probability of MSI-H presence in CRCs.

- 95% specificity.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Criteria</th>
<th>MsPath</th>
<th>PathScore</th>
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</thead>
<tbody>
<tr>
<td>Tumor locations</td>
<td>Right-sided</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Grade</td>
<td>Well differentiated</td>
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<td>1.2</td>
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<tr>
<td></td>
<td>Moderately differentiated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>0.6</td>
<td>1.2</td>
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<tr>
<td>Histologic type</td>
<td>Mucinous differentiated</td>
<td>1.1</td>
<td>0.5</td>
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<tr>
<td></td>
<td>Mucinous carcinoma</td>
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</tr>
<tr>
<td></td>
<td>&gt;50%, or signet ring, or medullary carcinoma</td>
<td></td>
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<tr>
<td>Dirty necrosis</td>
<td>Absent</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Crohn-like reaction</td>
<td>Present</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes</td>
<td>Present</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes</td>
<td>Present</td>
<td></td>
<td>1.3</td>
</tr>
</tbody>
</table>

Total scores are calculated by the sum of score of positive criteria.
The Patient

• Segmental resection vs Subtotal colectomy
  • Decreases risk of subsequent CRC (4% and 9% after 10 and 25 y in extended surgery vs 20% and 47% after standard resection)
  • Easier endoscopic surveillance
  • Adequate quality of life
  • It provides no survival benefit

• The role of total proctocolectomy

• Prophylactic oophorectomy, hysterectomy
The Mutation Carriers

• Risk reducing surgery
  • Total colectomy
  • Total hysterectomy with bilateral salpingo-oophorectomy

• Regular surveillance for colon and gynaecologic cancer
Family Members of Known HNPCC Patients

• Screening starting at age of 25 y or 10 y before the age of the youngest member of the family at the time of CRC diagnosis
  • Total colonoscopy each year (1-2 years)
  • Endometrial aspiration biopsy, transvaginal ultrasound, cervical smear, two-handed pelvic examination (no consensus)
Gastric, small bowel, pancreatic, urinary, prostate, breast

• Benefit of surveillance for most extracolonic cancers is still unknown
• Programs are not standardized
• Surveillance for these cancers should be performed in a research setting
• Results of long-term surveillance should ideally be collected and evaluated at a regional or national or international LS registry.
Other Issues

• Taking into consideration the current limitations of available evidence
  • Assisted reproduction and PND
  • Prophylactic regular aspirin