Lynch Syndrome/ Hereditary Nonpolyposis Colon Cancer (HNPCC)

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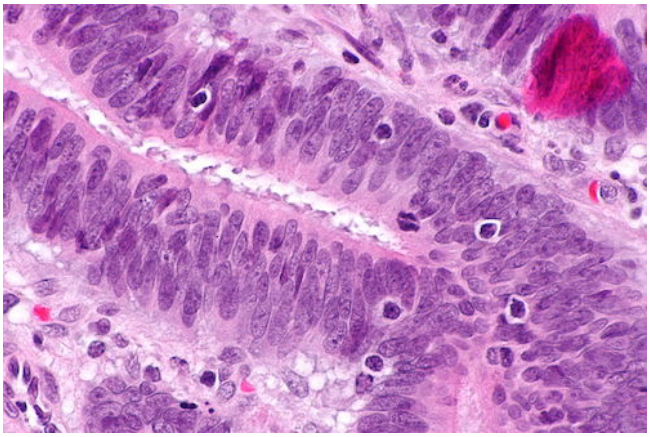
Pathophysiology

Colorectal Cancer

- The Most Common Cause of Hereditary Colorectal Cancer [1]
- Lifetime Risk: 20-80% Depending Mutation & Associated Risk Factors [2]
- Accounts for 3-5% of All Colorectal Cancers [2,3]
- Cancer Occurs at a Younger Age than Sporadic Cancers [4]
    - Average Age 45-60 Years [5]
- Most Common in the Right Colon (Sporadic Cancers are Most Common on the Left) [5]
- Propensity for Synchronous and Metachronous Colorectal Cancers [5]



Tumor-Infiltrating Lymphocytes, Suggestive of Microsatellite Instability (MSI) as Seen in Lynch Syndrome [9]

Genetic Mutations

- Autosomal Dominant
- Mutation in DNA Mismatch Repair (MMR) Genes
    - Include: MLH1, MSH2, MSH6, or PMS2 [6,7]
        - MLH1 and MSH2 are the Most Common (60-80%) [5]
    - Can Also Be Caused by Deletions in the Non-MMR EpCAM Gene – Causes Epigenetic Silencing of MSH2 [5]
- Cause **Microsatellite Instability** (Genetic Hypermutability) [2,5]
- Incidence: 1/279 Births [8]
- 20% are Sporadic Mutations

Types

- *Type I*: Colorectal Cancer with No Extracolonic Malignancy
- *Type II*: Colorectal Cancer with Extracolonic Malignancy

Extracolonic Manifestations

Endometrial Cancer

- Most Common Extracolonic Malignancy (40-60%) [2]
- Accounts for 5% of All Endometrial Cancers [10]
- Median Age of Diagnosis: 48 Years [11]
- Endometrioid Adenocarcinoma is the Most Common Type (92%) [12]

Ovarian Cancer

- Incidence: 1-38% [2]
- Earlier Age of Onset: 42-49 Years [13]

Other Less Common Associations [2,14]

- Urinary Tract Cancers (Kidney, Ureter, Bladder) (1-18%)
- Stomach Cancer (1-13%)
- Small Bowel Cancers (1-6%)
- Pancreatic Cancer (1-6%)
- Hepatobiliary Cancer (1-4%)
- Brain Tumors (1-3%)
- Breast Cancer
- Skin Cancers

Diagnosis and Screening

Diagnosis

- Clinical Diagnosis Suspected Based on the Amsterdam Criteria
- Diagnosis Confirmed by Genetic Screening

Amsterdam Criteria (1990) [15]

- Criteria:
  - ≥ 3 Relatives with Histologically Verified **Colorectal Cancer**, One of Whom is a First-Degree Relative of the Other Two
  - ≥ 2 Generations are Involved
  - ≥ 1 Cancer Case Was Diagnosed Before Age 50
  - FAP Must Be Excluded
- *Criteria are Remembered as the "3-2-1 Rule"
- Sensitivity 61% and Specificity 67% [16]

Amsterdam II Criteria (1999) [17]

- Criteria:
  - ≥ 3 Relatives with Histologically Verified **Lynch Syndrome-Associated Cancer**, One of Whom is a First-Degree Relative of the Other Two
  - ≥ 2 Generations are Involved
  - ≥ 1 Cancer Case Was Diagnosed Before Age 50
  - FAP Must Be Excluded
- *Criteria are Remembered as the "3-2-1 Rule"
- Sensitivity 78% (Increased) and Specificity 61% [16]

Revised Bethesda Criteria [18]

- Criteria Used to Determine the Need to Test Colorectal Tumors for MMR Deficiency and/or MSI
- Criteria:
  - Colorectal Cancer Diagnosed in a Patient Who is < 50 Years of Age
  - Presence of Synchronous, Metachronous Colorectal, or Other HNPCC-Associated Tumors, Regardless of Age
  - Colorectal Cancer with the MSI-H Histology Diagnosed in a Patient Who is < 60 Years of Age
  - Colorectal Cancer Diagnosed in One or More First-Degree Relatives with an HNPCC-Related Tumor, with One of the Cancers Being Diagnosed Under Age 50 Years
  - Colorectal Cancer Diagnosed in Two or More First- or Second-Degree Relatives with HNPCC-Related Tumors, Regardless of Age
- Sensitivity 94% and Specificity 25% [16]
- Has Largely Been Replaced by Universal Screening for MMR Deficiency and/or MSI in Colorectal and Endometrial Cancers

Screening [19]

- High-Quality Colonoscopy Starting at Age 20-25
    - Repeat Every 1-2 Years
- Upper Endoscopy Starting at Age 30-40
    - Repeat Every 2-4 Years
- Consider Endometrial Biopsy Starting at Age 30-35
    - Repeat Every 1-2 Years
    - *No Proven Benefit to Endometrial or Ovarian Cancer Screening [19]

Surgical Management

Therapeutic Colectomy

- Indications: Colorectal Cancer or Unresectable Adenomas
- *Colon Cancer*: Total Abdominal Colectomy with Ileorectal Anastomosis (TAC/IRA) is Generally Preferred [20]
    - May Consider Segmental Colectomy in Select Circumstances
    - Requires Surveillance with Flexible Proctoscopy or Repeat Colonoscopy Every Year [21]
- *Rectal Cancer*: Consider Total Proctocolectomy vs Segmental Resection
    - Total Proctocolectomy Done with End Ileostomy or Ileal Pouch Anal Anastomosis (IPAA)
    - Segmental Resections: Low Anterior Resection (LAR) and Abdominoperineal Resection (APR)

Prophylactic Colectomy

- Prophylactic Colectomy Generally Not Performed
- Possible Prophylactic Indications: [21]
    - Colon Technically Difficult to Navigate
    - Unable to Comply with Screening Recommendations
    - Severe Psychological Distress Due to Fear of Developing Colorectal Cancer
    - Families with Early Onset or Severe Penetrance of Colorectal Cancer
    - Females Already Undergoing Hysterectomy for Uterine Cancer

Prophylactic Total Hysterectomy and Bilateral Salpingo-Oophorectomy (TH-BSO)

- Effective at Preventing Endometrial and Ovarian Cancers
- Indicated for Females After Age 40 or Once Childbearing is Complete [22]

Other Prophylactic Measures

- Aspirin – May Reduce the Incidence of Colorectal Cancer [23,24]
- Oral Contraceptives – Used to Prevent Gynecologic Cancers (Debated) [25]

Other Colorectal Cancer and Polyposis Syndromes

Syndromes

- *Familial Adenomatous Polyposis (FAP)*
- *Lynch Syndrome*
- *Juvenile Polyposis Syndrome (JPS)/Familial Juvenile Polyposis*
- *MUT Y Homolog (MUTYH)-Associated Polyposis (MAP)*
- *Peutz-Jeghers Syndrome (PJS)*
- *Serrated Polyposis Syndrome (SPS)*
- PTEN Hamartoma Tumor Syndromes: (PHTS)

Comparisons

- *See Familial Colorectal Cancer and Polyposis Syndromes

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