Evaluation and Management of HNPCC

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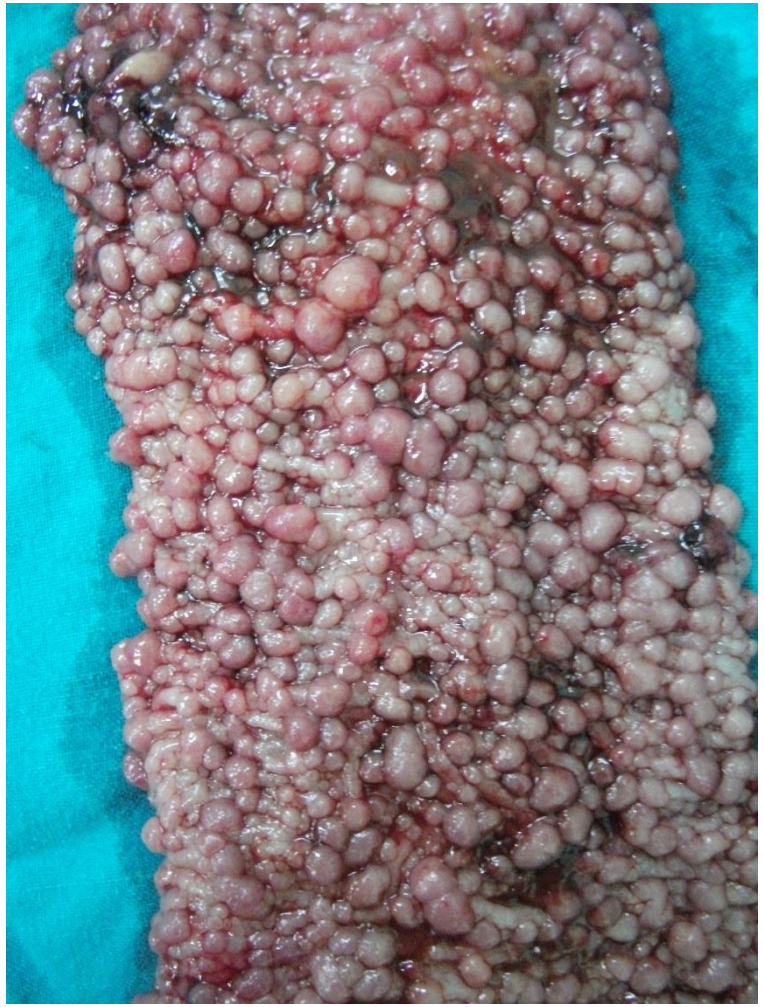
Lynch Syndrome
Historical Background

- 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

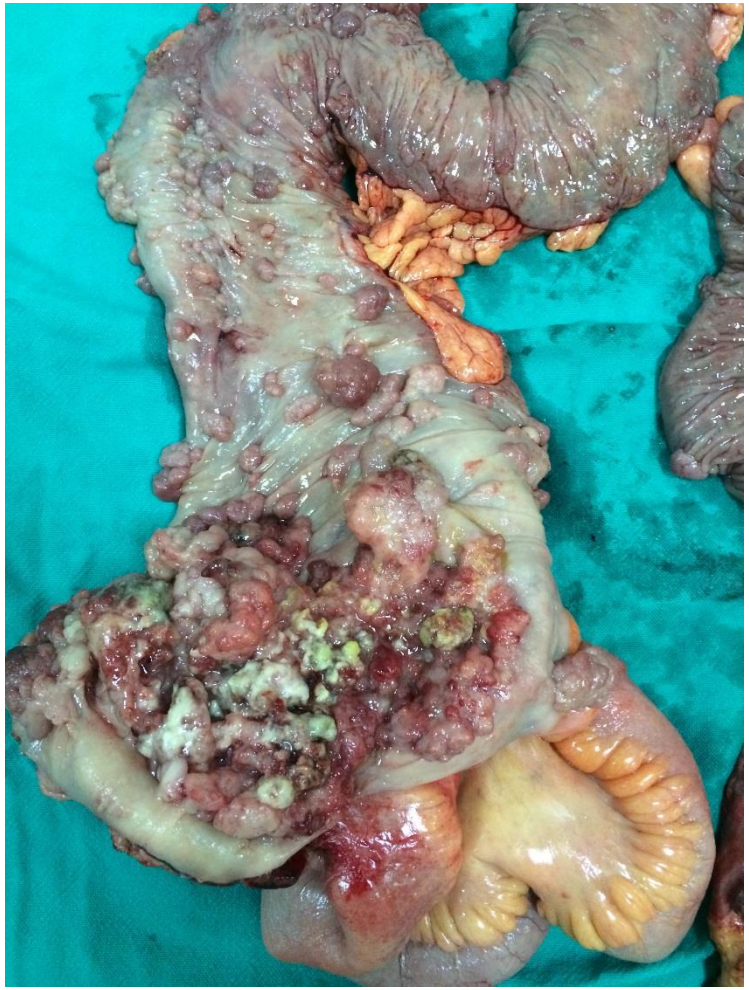
Lynch Syndrome

- 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.

Feature	Criteria	MsPath	PathScore
Tumor locations	Right-sided	1.6	0.8
Age	<50	0.7	1.1
Grade	Well differentiated	0	1.2
	Moderately differentiated	0	0
	Poorly differentiated	0.6	1.2
Histologic type	Mucinous differentiated		0.5
	Mucinous carcinoma >50%, or signet ring, or medullary carcinoma	1.1	
Dirty necrosis	Absent	0	0.6
Crohn-like reaction	Present	0.5	0.8
Tumor infiltrating lymphocytes ≥1	Present	2.1	
Tumor infiltrating lymphocytes >2	Present		1.3

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