Familial Adenomatous Polyposis (FAP)

Johnathan W. Cain, DO
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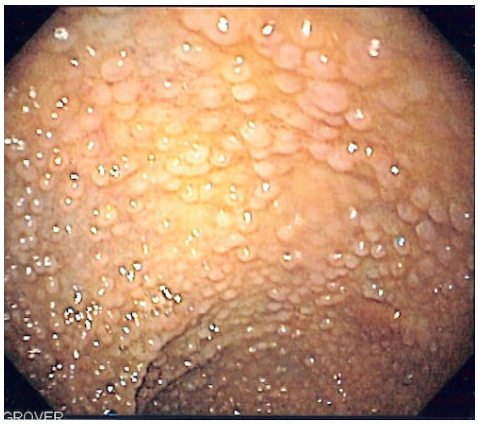
Table of Contents

Pathophysiology

Genetic Mutation [1]

- Mutation in the APC Gene
  - APC: Adenomatous Polyposis Coli
  - Tumor Suppressor Gene
- Autosomal Dominant


FAP on Colonoscopy [8]

Incidence [2]

- Incidence: 1/8,300 Births
- Accounts for < 1% of All Colorectal Cancer Cases

Presentation

- Hallmark is **100's-1,000's of Colorectal Polyps** [3]
- 100% Lifetime Risk of Colorectal Cancer
- 70-80% of Tumors Occur in the Left Colon [4]

Histology

- Numerous Sessile Polyps Throughout the Colon
- Generally ≤ 1 cm
- Various Histologic Features, Similar to Sporadic Colorectal Cancers [5]
- The Adenomas Themselves are More Abundant but Do Not Have an Individually Higher Risk of Malignancy

Timing and Progression

- Onset of Polyps: [6]
  - 50% by Age 15
  - 95% by Age 35
- Average Age of Colorectal Cancer Diagnosis: 35-40 [7]

Extracolonic Manifestations

Duodenum Polyps

- Incidence: 30-70% [3]
- Second Most Common Site of Adenomas [3]
- Second Most Common Cause of Death [9]
- Predilection for the Ampulla and Periampullary Region [10]
- Spigelman Staging of Duodenal Polyps in FAP [11]
  - Stage 0: 0 Points
  - Stage I: 1-4 Points
  - Stage II: 5-6 Points
  - Stage III: 7-8 Points
  - Stage IV: 9-12 Points

Factor	0 Points	1 Point	2 Points	3 Points
Number of Polyps	0	1-4	5-20	> 20
Polyp Size	No Polyps	1-4 mm	5-10 mm	> 10 mm
Histology	No Adenomas	Tubular Adenoma	Tubulovillous Adenoma	Villous Adenoma
Dysplasia	None	Low Grade	NA	High Grade

Stomach Polyps

- Incidence: 30-88% [3,12]
- Most Commonly Benign Fundic Gland Polyps (FGPs) [3]
- 60% Sporadic but 40-80% Have > 100 Polyps [13]

Desmoid Tumors

- Incidence: 21% [14]
- Generally Benign with Low Risk of Distant Metastases [14]
- Locally Aggressive with High Recurrence Rates [3,14]
- Third Most Common Cause of Death in FAP [15]
- Intraabdominal/Mesenteric Fibromatosis is the Most Common Subtype [16]

Osteomas

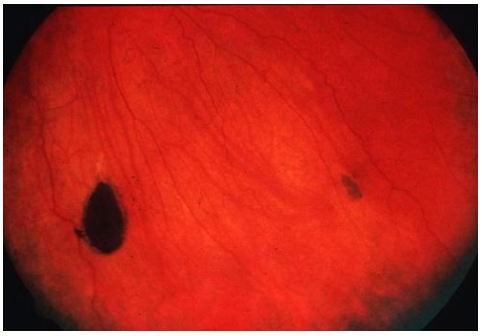
- Incidence: 65-80% [3]
- Most Common in the Frontal Bones [17]
    - Can Also Affect the Mandible, Maxilla, or Long Bones
- Range in Size from Slight Thickening to Large Palpable Masses [3]

Brain Tumors

- 3x Overall Increased Risk [18]
- Associated Tumors: [18]
    - Medulloblastoma – Most Common (13x Increased Risk)
    - Astrocytoma
    - Less Commonly: Ependymoma, Pinealblastoma, Ganglioglioma
- Most Commonly Develop During Childhood [18]
- Previously Described as Turcot Syndrome – Now Only Considered a Part of the FAP Spectrum

Congenital Hypertrophy of Retinal Pigment Epithelium (CHRPE)

- Incidence: 90% [19]
- The Most Common and Earliest Extraintestinal Manifestation of FAP [20,21]
- Described as At Least One Dark Pigmented Lesion with a Halo in the Retina [22]
- No Malignant Potential [23]



CHRPE [24]

Dental Abnormalities

- Incidence: 30-75% [25]
- Include Impacted Teeth, Tooth Ankylosis, Missing Teeth, Supernumerary Teeth, Hypercementosis, or Compound Odontomas [25,26]

Other Less Common Associations [3]

- Thyroid Cancer
- Nasopharyngeal Angiofibroma
- Benign Skin Tumors
    - Epidermal Cyst
    - Fibroma
    - Lipoma
    - Pilomatricoma
- Hepatoblastoma
- Pancreatic Cancer
- Adrenal Tumors

Variations

Classical FAP

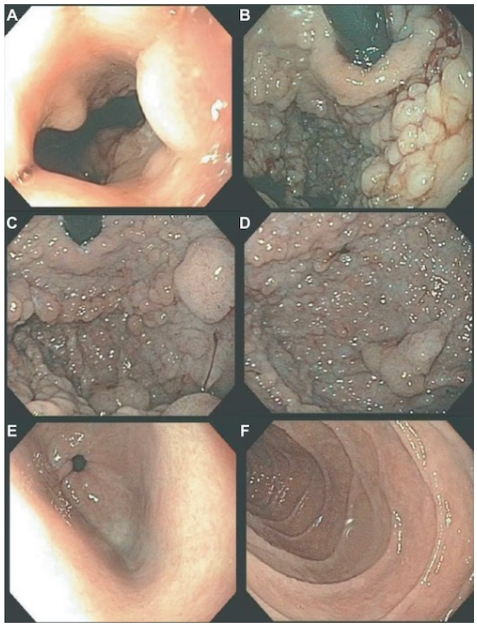
- FAP as Described Above

Attenuated FAP (AFAP)

- Less Aggressive Phenotypic Variant
- Develop Fewer Polyps; Defined as < 100 Polyps (Oligopolyposis) [27]
- Later Age of Diagnosis [28]
- Later Age of Onset of Colorectal Cancer: Average Age 55 [29]
- Lower Risk of Colorectal Cancer (70-80%) [29,30]
- Extracolonic Manifestations are Less Frequent [27]

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)

- Defined as > 100 Polyps in the Proximal Stomach [27,31]
- Polyps are Restricted to the Body and Fundus [31]
    - Spares the Antrum [31]



GAPPS on Upper Endoscopy: (A) GE Junction, (B) Cardia, (C) Fundus, (D) Body, (E) Spared Antrum, (F) Spared Duodenum [31]

- Predominantly Benign Fundic Gland Polyps (FGPs) [31]
    - Some Have Regions of Dysplasia with High Risk of Cancer
- No Evidence of Colorectal or Duodenal Polyps [27]

Historical Variants

- *Gardner's Syndrome*: FAP with Extracolonic Manifestations
- *Turcot's Syndrome*: FAP with Brain Tumors
- *Originally Described Colonic Polyposis with Extracolonic Manifestations but Gardner's Syndrome and Turcot's Syndrome are Now Considered a Part of the FAP Spectrum [32]

Diagnosis and Screening

Diagnosis

- Clinical Diagnosis Can Be Clear on Colonoscopy
    - Flexible Sigmoidoscopy Alone is Often Sufficient
- Primary Diagnosis is Made by an APC Gene Mutation
- Patients with a Family History of FAP Should Undergo Genetic Counseling/Screening by Age 10-12 [33]

Colonoscopy

- High-Quality Colonoscopy Starting at **Age 10-15 Years** [34]
- **Repeat Every Year** [34]
- Flexible Sigmoidoscopy May Be Considered Based on patient and Family preference or Clinical Judgment [34]
    - Risk for Missing Transverse or Right-Sided Colon Polyps

Upper Endoscopy

- Start Screening at **Age 20-25** [34]
    - Start Immediately if Any Colon Polyps are Seen
- Repeat Endoscopy Based on Spigelman Stage [34]
    - Stage 0: Every 3-5 Years
    - Stage I: Every 2-3 Years
    - Stage II: Every 1-2 Years
    - Stage III: Every 6-12 Months
    - Stage IV: Expert Surveillance Every 3-6 Months

Other Screening Considerations

- May Also Consider Screening with Thyroid Ultrasound Every 2-5 Years Starting in Late Teenage Years [34]
- No Specific Guidelines for Desmoid Tumor or Brain Tumor Surveillance

Surgical Management

Indications for Colectomy

- Absolute Indications (2015 ACG Guidelines): [35]
  - Documented or Suspected Colorectal Cancer
  - Significant Symptoms
- Relative Indications (2015 ACG Guidelines): [35]
  - Multiple Large Adenomas > 6 mm
  - Significant Increase in Adenoma Number on Consecutive Exams
  - Adenoma with High-Grade Dysplasia
  - Inability to Adequately Survey the Colon Because of Multiple Diminutive Polyps
- Consider Prophylactic Colectomy if Otherwise Not Indicated [36]
  - Exact Timing is Debated
  - Most Patients Undergo Surgery Between Ages 15-25 Years [36]

Surgical Options

- *Total Abdominal Colectomy with Ileorectal Anastomosis (TAC/IRA)*
  - Spares Rectum
  - Advantages:
    - Technically Easier
    - Lower Risk of Complications
    - No Risk for Sexual or Bladder Dysfunction
    - No Permanent Stoma
  - Highest Risk of Metachronous Cancer in the Remaining Rectum (5-25% Future Risk)
  - Generally Contraindicated for Severe Rectal Disease or if the Patient is Not Reliable for Follow-Up Surveillance
  - Requires Flexible Proctoscopy Every 6-12 Months [34]
- *Total Proctocolectomy with Ileal Pouch Anal Anastomosis (IPAA)*
  - Resects the Majority of the Rectum – More Complex Operation
  - Advantages:
    - Lower Risk of Metachronous Cancer than TAC/IRA
    - No Permanent Stoma
  - Risk for Sexual or Bladder Dysfunction and Possible Fecal Incontinence
  - Requires Flexible Pouchoscopy Every 6-12 Months [34]

- *Total Proctocolectomy with End Ileostomy*
    - Requires a Permanent Stoma
    - Risk for Sexual or Bladder Dysfunction
    - Requires Flexible Endoscopy of Ostomy Every Year [34]

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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