Familial Adenomatous Polyposis and Associated Mesenchymal Tumors

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Familial Adenomatous Polyposis (FAP)

- Multiple premalignant colorectal polyps, strong tendency for progression to adenocarcinoma
- Average age of onset for intestinal adenomas ~ 25 years
- ~100% lifetime risk of colonic polyposis and intestinal adenocarcinoma
- Germline APC mutation at 5q21-22
- Incidence 1/7,000 to 1/30,000
- 2/3 familial, 1/3 sporadic

Gardner Syndrome

- Described in 1950’s as autosomal dominant familial colorectal polyps and carcinomas with other tumors: Epidermoid cysts Osteomas Dental anomalies Desmoid-type fibromatosis
- 2017: Gardner-type FAP
Gardner Syndrome, APC, and Desmoids

Gardner, 1950  Cancer of the lower digestive tract in one family group
Gardner, 1952  Surface lumps or tumors on the head and body are associated with carcinoma
Gardner, 1953  Surface tumors are “hard” and “soft”, some with childhood onset
Gardner, 1960  Fibromatosis in Gardner syndrome; early childhood fibromas in offspring

Gardner Syndrome, APC, and Desmoids

Naylor, 1979  29% of Gardner Syndrome patients have desmoids
Caspari, 1995  Desmoids are associated with specific APC mutations
Li, 1996  Desmoids are clonal
Clark, 1997  Early childhood desmoids reported in a family with APC mutations at codon 1464

FAP-Associated Soft Tissue Tumors

• Definite:
  Desmoid-type fibromatosis
  Gardner fibroma

• Possible:
  Juvenile nasopharyngeal fibromatosis
  Embryonal rhabdomyosarcoma

Gardner Fibroma: WHO 2013 Definition

Gardner fibroma is a plaquelike proliferation of thick, haphazardly arranged collagen bundles with interspersed fibroblasts and is associated with Gardner-type FAP.

Gardner Fibroma: Clinical Features

• Poorly defined mass
• Age:
  30% 1st year
  80% 1st decade
  20% 2nd to 6th decades
• Males and females equally affected
• Superficial and deep soft tissue sites:
  72% back, paraspinal region, chest wall
  14% head/neck and trunk, including mesentery
  14% extremities
• FAP in 70%
• Family history of desmoids in 10%

Paraspinal mass, young child
**Gardner Fibroma: Macroscopic Features**

- Plaquelike mass
- Soft, rubbery, or firm
- White or tan with yellow flecks
- Usually 1-10 cm in greatest dimension
- Margins difficult to discern

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**Gardner Fibroma: Microscopic Features**

- Patternless hypocellular proliferation of coarse collagen fibers
- Inconspicuous bland fibroblasts
- Sparse mast cells
- White or tan with yellow flecks
- Entrapped adipose tissue, muscle fibers, nerves
- Difficult to discern from normal fibrous tissue or a scar, especially in the dermis and subcutis
Gardner Fibroma: Genetics

- Germline APC mutation, sporadic or familial
- Gardner fibroma in absence of FAP: a different manifestation of APC mutation, another mutation, or something as yet unidentified?
- No evidence as yet for CTNNB1 mutation

Gardner Fibroma: Outcome and Prognosis

- Benign, but beware!
- High risk for desmoid-type fibromatosis: concurrent or subsequent desmoid in 50%
- Strong association with FAP: 70%
- Family history of desmoids or soft tissue tumors: 10%
- Sentinel lesion for APC mutation in the patient and family: evaluation and surveillance essential
- Lack of consensus on optimal treatment for fibroma
**Gardner Fibroma: Unresolved Questions**

- Overgrowth, malformation or neoplasm?
- To what extent does surgical resection increase the risk of desmoid?
- What is the optimal clinical management?
- How can under-recognition be addressed?
- Are genes other than \( APC \) involved?

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**Desmoid-Type Fibromatosis: Definition**

Desmoid-type fibromatosis is a locally aggressive (myo)fibroblastic neoplasm that usually arises in deep soft tissues and is characterized by infiltrative growth and a tendency toward local recurrence, but lacks metastatic potential.

-WHO, 2013

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**Desmoid-Type Fibromatosis: General Features**

- Rare: 0.2-0.4/100,000 population/year
- 40% in first 2 decades
- Peaks in 3rd decade and at 4-5 years of age
- 60% of childhood fibrous tumors
- 10-25% arise in patients with FAP

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**FAP-Associated Desmoids**

- 10-15% of FAP patients develop one or more desmoids: >800 fold increased risk
- Desmoids occur at a younger age in FAP
- Female predilection for desmoids in FAP
- Intrafamilial phenotypic variations

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**Sites for FAP-Associated Desmoids**

- Site predilections in general:
  - Intra-abdominal (pelvis, mesentery)
  - Surgical scar tissue after colectomy
- Sites for children with FAP:
  - Extra-abdominal sites
  - Limb girdles
  - Proximal extremities
Desmoid-Type Fibromatosis: Macroscopic Features

- Hard, spherical or ovoid mass
- White or tan
- 5-10 cm in greatest dimension, sometimes much larger
- Infiltrative margins
- May merge with Gardner fibroma at periphery

Desmoid-Type Fibromatosis: Microscopic Features

- Broad morphologic spectrum, many patterns
- Sweeping fascicles of elongated, slender spindle or stellate cells
- Delicate or dilated blood vessels along edges of fascicles
- Variable cellularity, mitotic rate, myxoid change, stromal collagen, mast cell infiltrate
- No significant atypia or hyperchromasia
Desmoid-type fibromatosis

Genetic Aberrations in Desmoids
- 5q22.2 loss/deletion
- 6p21-21.2 or 6q15- q23.3 loss
- 8q and 20q gains/trisomies
- Constitutional APC mutation
- Rare MUYTH mutations?
- Sporadic mutations: APC, CTNNB1, AKTI, BRAF

Genetic Aspects of Pediatric Desmoids
- CTNNB1 mutations are more frequent (64-66%) than APC mutations (16-18%)
- Children whose desmoids are CTNNB1 mutation-negative should be tested for germline APC mutations and offered genetic counseling
- AKTI and BRAF mutations in rare cases
- No data on MUYTH mutations

APC Mutations in FAP-Associated Desmoids
- FAP-associated desmoids have more intratumoral genetic aberrations (losses of 5q22.2, 6q15-q22.3, 13q14.11-q34) in addition to the APC mutation
- Desmoids are more frequent if the APC mutation is beyond codon 1399
- 20% of FAP patients test negative for an APC mutation
3/24/2017

FAP-Associated Desmoids

- APC mutation
  - Inhibition of Beta-catenin phosphorylation and proteosomal degradation

Sporadic Desmoids

- CTNNB1 mutation
  - APC mutation
  - Beta-catenin accumulates in cytoplasm and translocates to nucleus
  - Nuclear beta-catenin binds transcription factors and induces target gene transcription, with activated Wnt signaling
  - Altered regulation of tissue remodeling
  - Altered target gene expression (induced WT1, repressed IGFBP-6) with cellular proliferation

Desmoid-Type Fibromatosis:
Treatment Options

- Emerging approach: observation
- Surgery
- Pharmacotherapy
  - Chemotherapy
  - Anti-estrogens
  - NSAIDs
  - Interferon-alpha
  - Targeted treatments
- Cryotherapy
- Radiotherapy (sarcoma risk)

Desmoid-Type Fibromatosis:
Outcome and Prognosis

- Local recurrence rate 33-68%
- 20% with multiple recurrences
- Higher recurrence risk if young age, intralesional excision, mesenteric site, Gardner-type FAP
- Death rate <2% for non-FAP desmoids
- Risk of sarcoma in irradiated desmoid

Desmoid-Type Fibromatosis:
Morbidity and Mortality in FAP

- Higher tendency for recurrence in a shorter time, especially if there is co-existing Gardner fibroma
- Early colectomy may increase risk of intra-abdominal desmoid
- Less responsive to chemotherapy
- Higher risk of death due to desmoids in 10-30% (vs. <2% for sporadic desmoids)
- Death due to complications of aggressive growth and involvement of vital structures

Additional Considerations

- Detection of Gardner fibroma in association with a desmoid
- Distinction between Gardner fibroma and a hypocellular desmoid with abundant collagen
- Risk of post-irradiation sarcoma in the site of a desmoid
- Other manifestations of Gardner-type FAP
- APC mutation-negative Gardner fibroma and desmoid
Under-Recognition of Gardner Fibroma

- Retrospective review of desmoids revealed that 4% of cases were Gardner fibromas
- 24-37% of desmoid specimens also contain a Gardner fibroma
- High recurrence risk in general for desmoids in extremities, deep soft tissue of back and chest wall, head, neck
- 4-fold higher recurrence risk for desmoids with Gardner fibromas in superficial soft tissue of chest wall and back, abdominal wall and cavity
- Shorter recurrence-free survival for desmoids with Gardner fibroma: 3.2 vs. >25 years

*Cates et al, 2014; Goldstein et al, 2015

Comparative Features of Gardner Fibroma and Desmoid

<table>
<thead>
<tr>
<th>Desmoid</th>
<th>Gardner Fibroma</th>
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<tbody>
<tr>
<td>Nodule</td>
<td>Plaque</td>
</tr>
<tr>
<td>Whorled</td>
<td>Rubbery</td>
</tr>
<tr>
<td>Fascicles</td>
<td>Patternless</td>
</tr>
<tr>
<td>Cellular</td>
<td>Hypocellular</td>
</tr>
<tr>
<td>Prominent vessels</td>
<td>Hypovascular</td>
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<tr>
<td>Fibrillar collagen</td>
<td>Matted collagen</td>
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<tr>
<td>Mitoses</td>
<td>No mitoses</td>
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<tr>
<td>SMA, MSA, Desmin</td>
<td>CD34</td>
</tr>
</tbody>
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Gardner fibroma and desmoid

What is this?

Desmoid and Gardner fibroma

Smooth muscle actin at the interface between Gardner fibroma and desmoid
Post-Irradiation Sarcoma and Desmoid
- Very rare (no data specific for FAP)
- Years from irradiation to sarcoma: 3-18
- Types: UPS, osteosarcoma, fibrosarcoma
- Not always derived from the primary desmoid
- Histologic clues:
  - Zonal necrosis
  - Hypercellularity
  - Severe nuclear atypia
  - Increased mitotic activity

What Else to Look for in the Young? Extra-Intestinal Manifestations of APC
- Malformations: dental abnormalities
- Benign tumors: osteomas, epidermoid cysts, nasopharyngeal angiofibroma, Gardner fibroma, desmoid-type fibromatosis
- Cancer: hepatoblastoma, rhabdomyosarcoma, medulloblastoma, thyroid carcinoma
- CHRPE: congenital hypertrophy of retinal pigment epithelium

What About Gardner Fibroma and Desmoid in the Absence of APC Mutation or FAP?
- False-negative APC mutation testing (imperfect sensitivity)
- Other conditions:
  - Attenuated APC
  - Familial desmoids with APC mutation, but no polyps
- Undetected APC abnormalities:
  - Somatic mosaicism for APC
  - Large 5q deletion
  - Epigenetic modification of APC promoter 1B region
- Alternative mutations: MUYTH, AKT, BRAF?

Back to the Patient: Take Action!
- Consider the possibility of an APC mutation in the child and/or family
- Obtain a thorough physical exam, medical history, and family history
- Consider a genetic counseling evaluation
- If no evidence of APC/FAP, consider CTNNBI and possibly other mutation analysis of the desmoid tissue and/or APC mutation testing of the patient
- If an APC mutation is present, initiate surveillance and prevention: colorectal polyps and carcinoma can arise as early as the 1st decade
Practice Points

- Gardner fibroma and desmoid-type fibromatosis are sentinel lesions for APC mutation/Gardner-type FAP in young patients and their families
- Gardner fibroma can be a difficult diagnosis due to its hypocellular, collagenized histology
- Patients with Gardner fibroma require ongoing follow-up for colorectal tumors and desmoid-type fibromatosis
- Under-recognition of Gardner fibroma is an opportunity to educate clinicians and colleagues

Practice Points

- Desmoid-type fibromatosis is a locally aggressive, non-metastasizing neoplasm that can affect children, adolescents and adults
- Desmoids in FAP patients are more likely to recur and have higher mortality
- Evaluation for FAP and/or APC mutation and long-term follow-up and surveillance are necessary: details vary according to the situation
- Treatment options vary, but current evidence favors a conservative approach for both Gardner fibroma and desmoid-type fibromatosis

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“There is a bright future for complexity, what with one thing leading to another.”
E.B. White