Desmoid Tumor: Pathobiology and Treatment

Desmoid Tumor Research Foundation
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Overview of Sarcomas

• “Incidence”: 11,000/year in USA
  – 1% of cancers in adults
  – 15% of cancers in pediatric malignancies

• Not restricted to any organ site

• Resemble connective tissue with mesenchymal origin
  • Bone and cartilage
  • Blood vessels, lymphatics
  • Skeletal and smooth muscle
  • Fat
  • Neural crest and perineural cells
Sarcomas can occur anywhere in the body

- Lower Extremity: 31% (1400 cases)
- Visceral: 18% (797 cases)
- Abdominal: 15% (687 cases)
- Upper Extremity: 13% (555 cases)
- Trunk: 10% (468 cases)
- Other: 12% (59 cases)

Total cases: 4496

Courtesy of M. Brennan MSKCC
Classification of Sarcomas by Lineage of Differentiation

- Adipocytic: Liposarcoma
- Myogenic: Leiomyosarcoma, Rhabdomyosarcoma
- Vascular: Angiosarcoma, Hemangioendothelioma
- Neural: Ewing/PNET, MPNST
- Fibroblastic: Synovial Sarcoma, Fibrosarcoma, Desmoid, Myofibroblastic, Myxofibrosarcoma, Endometrial Stromal Sarcoma
- Chondrocytic: Chondrosarcoma
- Osteogenic: Osteosarcoma
- Unclassifiable
Approach to Patients with Sarcomas

• Multidisciplinary Teamwork Required
  – Specialty expertise in multiple fields e.g. surgery, pathology, medical oncology, radiation oncology, psychosocial support, plastic and reconstructive surgery, physical therapy

• Definitive referral center disease
Choosing the Optimal Primary Management of a Newly Diagnosed Localized Sarcoma

• Pathology review is often critical

• Every patient is unique
  – Complex decisions based on anatomic site, tumor behavior, co-morbid factors, etc.
Same Issues Apply to Desmoid Tumor

- Pathology review is often critical
- Every patient is unique
  - Complex decisions based on anatomic site, tumor behavior, co-morbid factors, etc.
• Fibroblastic monoclonal proliferation arising from musculo-aponeurotic structures, constituted by spindle cells in a collagen matrix, without atypical, pleomorphic or hypercromatic nuclei typical of malignancy.

• 0.2-0.4/100,000

Li et al., Hum Pathol 1996
Alman et al., Diagn Mol Pathol, 1997
• Fibroblastic monoclonal proliferation arising from musculo-aponeurotic structures, constituted by spindle cells in a collagen matrix, without atypical, pleomorphic or hypercromatic nuclei typical of malignancy.

Scar formation that the body isn’t turning off
Desmoid Tumor/
Aggressive Fibromatosis

- Not a cancer, but can cause morbidity and mortality
- 95% Sporadic
- 5% FAP-Associated (Familial Adenomatous Polyposis = Gardner syndrome)
Gardner Syndrome

- Autosomal dominant syndrome (50% chance of passing it on to children)
- 1000s of bowel polyps and high risk of colon cancer if colon is not removed
- Mutation in FAP "tumor suppressor gene" in all cells in body
- 10% lifetime risk of desmoid tumors
Desmoid tumor: a disease opportune for molecular insights

D. Kotiligam¹, A.J.F. Lazar², R.E. Pollock³ and D. Lev¹

SITES:

FAP-Associated

- Intra & extra abdominal: 27%
- Extra-abdominal other sites: 8%
- Abdominal wall: 20%
- Intra-abdominal: 45%
Follow up of 897 FAP patients

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<td>Colorectal cancer</td>
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<td>3 (6.3)</td>
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<td>3 (10.3)</td>
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<td></td>
<td></td>
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<td>7 (14.6)</td>
<td>2 (6.9)</td>
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<td>12 (1.5)</td>
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<td>1 (2.1)</td>
<td></td>
<td></td>
<td>2 (0.9)</td>
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<tr>
<td>Total</td>
<td>790</td>
<td>48</td>
<td>30</td>
<td>29</td>
<td>107</td>
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Sporadic Desmoid

- 85% of the cases harbor a mutation in \textit{CTNNB1}, encoding for $\beta$-Catenin protein
- Occurs just in the tumor cells; not in normal tissue
- Not hereditary
- Rarer \textit{APC} (chromosome 5) deletion in \textit{CTNNB1 WT} tumors may occur
Desmoid tumor: a disease opportune for molecular insights

D. Kotiligam\textsuperscript{1}, A.J.F. Lazar\textsuperscript{2}, R.E. Pollock\textsuperscript{3} and D. Lev\textsuperscript{1}

[Diagram showing the Wnt signaling pathway with key annotations:]

- **Missing in FAP**
- **Mutated in sporadic desmoid**
- **Cell Growth**
SITES:

Sporadic Desmoid

- Abdominal wall: 25%
- Lower extremity: 23%
- Pelvic girdle: 5%
- Intra-abdominal: 5%
- Head & Neck: 10%
- Upper extremity: 10%
- Scapular girdle: 22%
- Abdominal wall: 25%
- Lower extremity: 23%
- Pelvic girdle: 5%
- Intra-abdominal: 5%
- Head & Neck: 10%
- Upper extremity: 10%
- Scapular girdle: 22%
Most common sites

- 22%
- 29%
- 24%
Threatening locations
Management

• Observation
  – Some spontaneously recede
  – Some grow and then stop growing

• Surgery
  – Only known curative therapy
  – Role of “margins”?
  – Need to balance consequence of disease with consequence of surgery
Management - 2

• Radiation Therapy
  – Unclear role for “positive margins”
  – Can be helpful for unresectable and growing or symptomatic disease
Management - 3

• Medical Treatment
  – NSAIDs (eg Sulindac)
  – Hormonal Therapy (eg tamoxifen)
  – Targeted therapy (imatinib/Gleevec)
  – Chemotherapy
    • Liposomal doxorubicin (Doxil)
    • Methotrexate and Vinblastine (Velban)

• Need to determine need for and goals of treatment!
Clinical Study Designs

• **Retrospective Case Series**
  – “In the last 10 years we treated 30 patients with drug X. Looking back at their medical records, here is what happened to the tumors.”
  – Require Institutional Review Board approval for medical record review (with or without signed consent of patient)
  – Biased by case selection and lack of direct comparator
Clinical Study Designs

• Prospective Studies
  – Enrollment of patients as research subjects/participants in study of drug(s)
  – Requires permission of IRB and often the FDA
  – Requires signed informed consent of patient
Types of Prospective Studies

• Phase I
  – New drug or combination of drugs
  – Designed primarily to test safety and toxicity, and to establish appropriate dose
  – Often multiple (or any) tumor types
  – Enroll very small numbers of patients at one dose level; if safe, increase dose in new group of patients
  – Everyone gets drug but may not be at effective (too low) or safe (too high) dose
  – Frequent visits for safety evaluation and determination of drug blood levels
Types of Prospective Studies

• Phase II
  – Designed primarily to test efficacy of drug
  – Dose determined from prior Phase I studies
  – Often one tumor type
  – Enrolls moderate number of patients
  – Everyone gets drug
  – Everyone gets same dose of drug
  – Outcome measured as “response rate” or “progression free survival (PFS)”
Types of Prospective Studies

• **Phase III**
  - Designed primarily to *test if one treatment is better than another*
  - One tumor type
  - Enrolls large number of patients
  - Requires national/global effort for rare disease
  - Everyone gets drug
  - Everyone gets same dose of drug
  - Outcomes: “Response rate”, “PFS”, “Overall Survival”, or “Hazard Ratio”
  - If positive results, can lead to FDA approval
Recent Very Promising Retrospective Study
(Drs. Gounder, Maki, and others; Memorial Sloan-Kettering Cancer Center)

- **Sorafenib (Nexavar)**
  - Oral medicine
  - Blocks key pathways in many tumors
  - Approved for treatment of kidney and liver cancers
  - Side effects can include high blood pressure, painful rash on hands/feet, diarrhea, nausea, fatigue, low blood counts, and others
Activity of sorafenib against desmoid tumor/deep fibromatosis (DT/DF)


Departments of Medicine, Pathology, and Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY
Sorafenib and DT/DF

CELLULAR PROPERTIES:
-- Sorafenib inhibits VEGFR, PDGFR, KIT, RET and RAF.
-- Exhibits anti-angiogenic, antiproliferative and/or pro-apoptotic effects.

INDEX CASE:
-- 19 year old female with progressive and symptomatic supraclavicular desmoid that was initially resected, however recurred within 24 months and deemed unresectable.
-- Imatinib was unavailable for this patient. She was started on Sorafenib 400 mg BID through an expanded access program from the manufacturer.
-- Symptomatic relief of pain and improvement in shoulder mobility within weeks of starting; the tumor has been only stable by MRI at 24 months, however.

GOAL:
We herein report our retrospective experience of 14 DT/DF patients treated with sorafenib.

Gounder et al. ASCO 2010
Sorafenib:

**INDICATION:**
-- Progression by imaging: 12, stable scans but worsening pain: 2 and maximum benefit in 1 patient who had received prior doxorubicin.

-- 10/14 pts with prior chemotherapy (median 3 lines) started on sorafenib after a median of 17.5 mo after initial presentation.
-- 4/14 pts had first-line therapy with sorafenib after a median of 4 mo (1-12) after initial presentation.

**DURATION**
-- Sorafenib was given for a median of 14 months (range 2 – 24) mo.

**DOSE**
-- Patients were started at a median dose of 400 mg PO daily, decreased for symptoms.
-- Symptoms included: included hand-foot syndrome, fatigue, rash, a sensation of scalp burning, hypertension, mild alopecia and diarrhea.
-- Severity of symptoms were not quantified.
Pt #1: Pre- and Post MRI w/ contrast

7/9/09: Post Gadolinium (popliteal surface)

12/11/09: Post Gadolinium

Gounder et al. ASCO 2010
RECEIST Response (BLUE)
Signal Change (RED and GREEN)

Percent Change from baseline

Individual Patients: 1 - 14

= Abd/RP

Gounder et al. ASCO 2010
Conclusions

• Desmoid Tumors are caused by mutations in the APC/beta-catenin pathway
• Although not strictly cancers, desmoids can cause significant illness or death
• Treatment plans must be individualized and can include observation, surgery, radiation, and medical therapy
• A variety of medical therapies can be effective, and promising new treatments are coming!
THANK YOU!