Indolent Soft tissue tumors

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Malignant
(Locally Agg.)

Rarely meta.

(Malignant
(Can be graded as Gr. I-III)

Non-meta.

DFSP, SFT, KS, Infantile FS… etc

Demoid-type fibromatosis,
Plamary fibromatosis, … etc

Intermediate
(Should not be graded)

Lipoma, leiomyoma,
glomus tumor, … etc

Benign

Malignant

Locally Agg.

Benign
Benign ≠ never metastatic

- in mesenchymal neoplasms: extremely rare < 1/50,000
- No histological difference between non-metastatic and metastatic lesions

Deep “Benign” Fibrous Histiocytoma: Clinicopathologic Analysis of 69 Cases of a Rare Tumor Indicating Occasional Metastatic Potential


Metastases occurred in 2 patients (<5%), both with tumor-related mortality

- WHO: classified as benign
Indolent soft tissue tumors - I

Discrepancies

**WHO classification** vs. **ICD-O**

- Ossifying fibromyxoid tumor (rarely metastasizing) vs. (88420)
- Diffuse type tenosynovial GCT (benign) vs. (88021)
- Epithelioid hemangioma (benign) vs. (rarely metastasizing)

**WHO classification**

- Soft tissue vs. bone

*Bone: local recurrent tendency*
Indolent soft tissue tumors -II

• major categories of tumor differentiation
  ➢ Adipocytic, fibroblastic/myofibroblastic, fibrohistiocytic

• tumor depth-dependent nomenclature
  ➢ atypical intradermal smooth muscle neoplasm vs. leiomyosarcoma
  ➢ atypical lipomatous tumor vs. well-differentiated liposarcoma

• overrepresentation of tumors of uncertain differentiation

• overrepresentation of tumors with specific genetic alterations
  ➢ mutation, amplification, gene fusion, or deletion
Indolent (locally aggressive) tumors - III

**non-metastasizing**

- **Fibroblastic/myofibroblastic**
  - giant cell fibroblastoma
  - desmoid-type fibromatosis
  - palmar/plantar fibromatosis
  - lipofibromatosis

- **Adipocytic**
  - atypical lipomatous tumour (WDLPS)
    - dedifferentiated LPS
  - atypical spindle cell lipomatous tumor*

- **Fibrohistiocytic**
  - tenosynoival giant cell tumor, diffuse-type
    - malignant TSGCT

**rarely metastasizing**

- **Fibroblastic/myofibroblastic**
  - dermatofibrosarcoma protuberans
    - fibrosarcomatous, pigmented
  - solitary fibrous tumour
    - malignant
    - dedifferentiated
  - inflammatory myofibroblastic tumour
    - epithelioid IMFsarcoma
  - low-grade myofibroblastic sarcoma
    - infantile fibrosarcoma
    - myxoinflammatory fibroblastic sarcoma
      (atypical MIF tumor)

- **Fibrohistiocytic**
  - plexiform fibrohistiocytic tumour
  - giant cell tumor of soft tissue

Gene fusion  Missense mutation  Amplification  Deletion
### Indolent (locally aggressive) tumors - III

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Indolent (locally aggressive) tumors-IV

**non-metastasizing**

- **Vascular**
  - Kaposiform hemangioendothelioma

- **Pericytic**
  - glomangiomatosis
  - myofibromatosis

- **Nerve sheath**
  - melanotic schwannoma

- **Uncertain differentiation**
  - pleomorphic hyalinizing angiectatic tumour
  - hemosiderotic fibrolipomatous tumour

- **Smooth muscle**
  - atypical intradermal smooth muscle neoplasms

**rarely metastasizing**

- **Vascular**
  - retiform hemangioendothelioma
  - papillary intralymphatic angioendothelioma
  - composite haemangioendothelioma
  - pseudomyogenic haemangioendothelioma
  - *Kaposi sarcoma*
    - epithelioid HE---malignant!

- **Uncertain differentiation**
  - angiomatoid fibrous histiocytoma
  - ossifying fibromyxoid tumour
    - malignant OFMT
  - myoepithelioma/mixed tumor, NOS
    - myoepithelial CA/ malignant mixed tumor
  - phosphaturic mesenchymal tumour, benign
    - malignant PMT
  - atypical fibroxanthoma

- **Smooth muscle**
  - atypical intradermal smooth muscle neoplasms

- **gene fusion**
- **missense mutation**
- **amplification**
- **deletion**
Indolent tumor entities may variably progress to sarcomas

- **Desmoid fibromatosis**
  - extremely rare, only after radiation

- **tenosynoival giant cell tumor, diffuse-type**
  - malignant TSGCT

- **inflammatory myofibroblastic tumour**
  - epithelioid inflammatory myofibroblastic sarcomas

- **dermatofibrosarcoma protuberans**
  - fibrosarcomatous DFSP

- **solitary fibrous tumour**
  - malignant SFT, dedifferentiated SFT
Desmoid-type fibromatosis

- **aggressive, non-metastasizing** myofibroblastic neoplasm
- **clinical presentation**
  - $F \equiv > M$
  - extra-abdominal cavity:
    - *abdominal wall* (female predominance, pregnant or postpartum)
    - *external trunk, thigh, head & neck*
  - Intra-abdominal cavity:
    - *retroperitoneum, mesentery*, or *pelvis*
  - **FAP/Gardner syndrome** (<10%):
    - colonic adenoma polyposis, mesenteric fibromatosis
Desmoid-type fibromatosis

- extensively infiltrative growth with tendency toward recurrence
Desmoid-type fibromatosis

- Prominent myxoid stroma in intraabdominal fibromatosis

✓ key differential Dx

Fibromatosis (mesenteric) vs. low-grade fibromyxoid sarcoma

β-catenin vs. MUC4
Desmoid-type fibromatosis

- **Wnt/β-catenin signaling mutations**
  - *CTNNB1 exon 3* on 3p21 (sporadic, 88%) or *APC* on 5q21-22 (familial)
  - 80% nuclear β-catenin (+)

*Adapted from Current Opinion in Oncology 2009, 21:352-359*
**Desmoid-type fibromatosis**

- **Wnt/β-catenin signaling mutations**
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Adapted from *Current Opinion in Oncology* 2009, 21:352–359
• variation in natural course:
  ✓ rapid recurrence, stabilization, or regression
• watchful waiting: progression (22%, 6/27)
• PFS: \( \leq 37 \) y, > 7 cm, extra-abdominal
• surgery-associated high morbidity
✓ relentless recurrent or technically demanding primary sites
• radiation therapy: reported effective for local control in 80%
• extremely rare radiation-induced sarcomas in fibromatosis (n<10)
• cell origins of sarcomas
✓ malignant transformation of *CTNNB1*-mutated fibromatosis cells
✓ wild-type normal cells lying in the radiation field
Diffuse-type Tenosynovial Giant Cell Tumor

- **Presentation:**
  - median age: 35 y (1st-7th decades),
  - slight *female* predominance
  - MRI: low signal on T1 and T2
  - **around large joints** mostly,
    - knee (75%), hip (15%), ---,
    - temporal mandibular joint*.
  - **extra-articular:**
    - bursae, tendon sheath
  - **intra-articular:**
    - a.k.a “pigmented villonodular synovitis”
  - **high local recurrence:** 20-50%
  - **joint destruction**
Diffuse-type Tenosynovial Giant Cell Tumor

- Pathology: locally aggressive neoplastic proliferation of synovial origin
  - multinodular and/or villous infiltrative growth
  - heterogeneous cell population
- synoviocte-like mononuclear cell (neoplastic cells, desmin-positive)
- giant cells, siderophages, foamy cells and lymphoplasmatic infiltrates
DDx of diffuse-type Tenosynovial CT

GCT of bone, soft tissue recurrence

- Prior history of osseous GCT
- H3F3A seq (mainly G34W)
  - H3F3A mutant-specific IHC
DDx of diffuse-type Tenosynovial CT

**GCT of bone, soft tissue recurrence**

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**GCT of soft tissue**

- Uniform mononuclear cells
- Evenly distributed giant cells
- No mutated H3F3A thus far

*Modern Pathology (2017), 728–733*
DDx of diffuse-type Tenosynovial CT

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- Prior history of osseous GCT
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**Malignant tenosynovial GCT**
- Altered architectural patterns
- Pleomorphic, spindle, epithelioid cells
- *CSF1* rearrangement

*Modern Pathology* (2017), 728–733
Molecular pathogenesis of diffuse-type tenosynovial GCT

Imatinib acts on cells of the monocyte/macrophage lineage with M-CSFR

Imatinib induces tumor regression in patients with advanced TSGCT

Trials by using other tyrosine kinase inhibitors (e.g. nilotinib and sunitinib) is under investigation in advanced TSGCT (NCT01261429 and NCT01207492).
Targeting CSF1R

RG7155 Ab

Targeting Tumor-Associated Macrophages with Anti-CSF-1R Antibody Reveals a Strategy for Cancer Therapy

Cancer Cell 25, 846–859, June 16, 2014

PLX3397 inhibitor

Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor

Malignant Diffuse-type Tenosynovial Giant Cell Tumors
A Series of 7 Cases Comparing With 24 Benign Lesions
With Review of the Literature

Chien-Feng Li, MD,* Jun-Wen Wang, MD,† Wen-Wei Huang, MD,‡ Chi-Chen Hou, MD,§
Shih-Cheng Chou, MD,‖ Hock-Liew Eng, MD,¶ Ching-Nan Lin, MD,*
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benign
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UPS

malignant

MFS

desmin

FS

GCT
**M-TSGCT** is a distinct sarcoma with recurrent losses at 15q22-24 *CSF1* rearrangement and overexpression.

DFSP: Most Prevalent Cutaneous Intermediate Sarcoma

Chromosome 17
COL1A1 exons 6 to 47

Chromosome 22
PDGFB exon 2

COL1A1:PDGFB

PDGFB Dimer

PDGFR

Intracellular Signals

PDGFB rearrangement

J Clin Oncol. 2009; 27(34): 5800-5807
Common histological variants vs. mimics of DFSP

Dermatofibroma (fibrous histiocytoma)

DFSP
Histological variants vs. mimics of DFSP

myxoid DFSP vs. LG myxofibrosarcoma (myxofibrosarcoma) vs. Sclerotic DFSP vs. SFT
Histological variants vs. mimics of DFSP

myxoid DFSP vs. LG myxoFS  
Sclerotic DFSP vs. SFT  
giant cell fibroblastoma vs. ALT or pleoLP
Fibrosarcomatous DFSP: an adverse variant

- increased metastasis, similar recurrence
- mostly primary de novo
- nodular, interface in-between

- herringbone-like sweeping bundles
- increased atypia and mitosis
- CD34 loss, p53 overexpression
A tumor at gastric wall

CD34

CD117

PDGFB rearrangement
Molecular and Clinical Analysis of Locally Advanced Dermatofibrosarcoma Protuberans Treated With Imatinib: Imatinib Target Exploration Consortium Study B2225

Response of metastatic dermatofibrosarcoma protuberans to imatinib. Computed tomography scan of thorax of patient 9 at baseline and after 3 months of imatinib therapy at 400 mg twice daily.

8 locally advanced lesions: 4 with CR; 4 with PR
2 metastatic lesions: 1 with PR; 1 with SD

J Clin Oncol. 2009; 27(34): 5800-5807
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