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Opportunities and Challenges in Laboratory Medicine

Soft Tissue Tumours
with MYXOID Stroma

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Outline of presentation

• Introduction
• Common tumours
• Diagnostic clues
• Differential diagnoses
• Take home messages
Introduction

• Soft tissue tumours may give diagnostic dilemma due to infrequently encountered in surgical pathology practice and their overlapping histologic features.
• This talk will focus on one of the common features; tumours with predominantly myxoid stroma.
• A heterogenous group of lesions having diverse clinical behaviours that range from reactive, benign, intermediate to sarcomas
• Differentiating myxoid soft tissue lesions require knowledge of the clinical and radiological findings.
• Immunohistochemistry analysis or molecular testing are helpful in some cases
**Introduction**

- Macroscopically, they have a variable gelatinous quality.
- Microscopically, the myxoid stromal matrix appears as amorphous material and may be confuse with oedema.
- In general, the superficial myxoid lesions are benign and the deep ones are malignant.
- Extensive sampling is critical for proper assessment of the lesions.
## Soft Tissue Tumours with MYXOID Stroma:
### Type of Tumours

<table>
<thead>
<tr>
<th>Benign</th>
<th>Intermediate</th>
<th>Malignant</th>
</tr>
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<tbody>
<tr>
<td>Ganglion cyst</td>
<td>Myoepithelioma</td>
<td>Myxofibrosarcoma</td>
</tr>
<tr>
<td>Intramuscular /cellular myxoma</td>
<td>Atypical myxoinflammatory fibroblastic Tumour</td>
<td>Myxoid liposarcoma</td>
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<tr>
<td>Juxta-articular myxoma</td>
<td>Ossifying fibromyxoid tumour</td>
<td>Extraskeletal myxoid chondrosarcoma</td>
</tr>
<tr>
<td>Dermal nerve sheath myxoma</td>
<td></td>
<td>Low grade fibromyxoid sarcoma</td>
</tr>
<tr>
<td>Superficial acral fibromyxoma (Digital fibromyxoma)</td>
<td></td>
<td>Myoepithelial carcinoma</td>
</tr>
<tr>
<td>Cutaneous myxoma</td>
<td>(Superficial angiomyxoma)</td>
<td></td>
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<tr>
<td>Deep aggressive angiomyxoma</td>
<td></td>
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<tr>
<td>1. Usual anatomic depth of tumour</td>
<td>Superficial (Dermal or Subcutis) VS Subfascial or deep-seated</td>
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<tr>
<td>2. Extent of myxoid stroma</td>
<td>Extensive or Variable</td>
<td></td>
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<tr>
<td>3. Presence of pleomorphism</td>
<td></td>
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<tr>
<td>4. Vascular pattern</td>
<td></td>
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<tr>
<td>5. Additional features e.g. bone shell</td>
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</tbody>
</table>
### APPROACH TO STTs WITH MYXOID STROMA

1. **Usual anatomic depth of tumour**

<table>
<thead>
<tr>
<th>Superficial (Dermal or Subcutis)</th>
<th>Subfascial or deep-seated</th>
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<td>Superficial acral fibromyxoma</td>
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<tr>
<td>(Digital fibromyxoma)</td>
<td>Low grade fibromyxoid sarcoma</td>
</tr>
<tr>
<td>Cutaneous myxoma (Superficial</td>
<td>Myxofibrosarcoma (1/3)</td>
</tr>
<tr>
<td>angiomyxoma)</td>
<td>Extraskeletal myxoid</td>
</tr>
<tr>
<td>Myoepithelioma</td>
<td>chondrosarcoma</td>
</tr>
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<td>Myxoid liposarcoma</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic T</td>
<td></td>
</tr>
<tr>
<td>Myxofibrosarcoma (2/3)</td>
<td></td>
</tr>
</tbody>
</table>
2. Extent of myxoid stroma

- Extensive
  - Intramuscular/cellular myxoma
  - Juxta-articular myxoma
  - Dermal nerve sheath myxoma
  - Cutaneous myxoma
  - Deep angiomyxoma
  - Myxofibrosarcoma
  - Myxoid liposarcoma
  - Extraskeletal myxoid chondrosarcoma
  - Myxoinflammatory fibroblastic T

- Variable
  - Superficial acral fibromyxoma
  - Ossifying fibromyxoid tumour
  - Low grade fibromyxoid sarcoma

- Variable
  - Ganglion cyst
  - Myoepthelioma/Myoepithelial carcinoma
### APPROACH TO STTs WITH MYXOID STROMA

#### 3. Presence of pleomorphism
- Myxofibrosarcoma
- Myoepithelial carcinoma
- Myxoinflammatory fibroblastic T

#### 4. Distinctive vascular pattern
- Curvilinear: Myxofibrosarcoma
- Arcades of blood vessels: Low grade fibromyxoid sarcoma
- Thin-walled, plexiform, branching capillaries (crow’s feet / chicken-wire): Myxoid liposarcoma

#### 5. Additional features e.g. bone shell
- Ossifying fibromyxoid tumour
# MYXOID TUMOURS

<table>
<thead>
<tr>
<th>SOFT TISSUE</th>
<th>AGE</th>
<th>SEX</th>
<th>COMMON SITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular myxoma</td>
<td>40-70</td>
<td>F&gt;M</td>
<td>Thigh, shoulder, buttocks, arm</td>
</tr>
<tr>
<td>Deep aggressive angiomyxoma</td>
<td>20-60</td>
<td>F, M</td>
<td>Pelviperineal, inguinoscrotum, retroperitoneal</td>
</tr>
<tr>
<td>Ossifying fibromyxoid tm</td>
<td>Adult</td>
<td>M&gt;F</td>
<td>Thigh, head &amp; neck, trunk</td>
</tr>
<tr>
<td>Mixed tumour/myoepithelioma</td>
<td>Child, Adult</td>
<td>M=F</td>
<td>Limb, limb girdle, trunk, head &amp; neck</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>Young adult</td>
<td>M=F</td>
<td>Proximal extremities &amp; trunk, other sites</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>50-70</td>
<td>M&gt;F</td>
<td>Limbs &amp; limb girdle (Sup – 50%)</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma (EMC)</td>
<td>Adult (M=50)</td>
<td></td>
<td>Proximal extremities &amp; limb girdle (thigh). Trunk, head &amp; neck, paraspinal, abdomen, &amp; pelvis</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>30-40</td>
<td>M=F</td>
<td>Extremities (IM of thigh 2/3)</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>Middle age</td>
<td>M=F</td>
<td>Distal extremities</td>
</tr>
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</table>
Intramuscular/cellular myxoma

- Most common benign myxoid neoplasm
- Middle-aged adult
- F > M
- Slow-growing, painless, deep-seated mass
- Proximal extremities especially thigh
- Sporadic (most lesions)
- Syndrome (Mazabraud Syndrome; +Fibrous dysplasia/ McCune-Albright Syndrome; + fibrous dysplasia, cutaneous hyperpigmentation and endocrine abnormality
- Mutation of GNAS1 gene
Intramuscular/cellular myxoma

- Hypocellular
- Abundant myxoid stroma (may appear frothy)
- +/- Foamy histiocytes resembling lipoblasts
- Poorly vascularized but scattered capillaries or thicker-walled vessels are present.

**Cellular myxoma:**
Increase cellularity & vascularity but cells are similar

- CD34 (+, often)
- Low risk of local recurrence

Sparse small, bland cells, with oval nuclei, inconspicuous nucleoli & small amounts of palely eosinophilic cytoplasm.
Intramuscular/ cellular Myxoma

Differential Diagnoses

1. Low-grade myxofibrosarcoma
   (elderly, mostly superficial lesions, curvilinear blood vessels, contains atypical pleomorphic cells – nuclei with coarse chromatin, multilobated nuclei, multinucleated tumour cells)

2. Myxoid Liposarcoma
   Monomorphous cell but rich in delicate capillary network

*These sarcomas have metastatic potential
Juxta-articular myxoma

- Reactive process – related to injury
- Male > Female (5th – 6th decades)
- Adjacent to large joints
  - Knee (85%), shoulder, elbow, hip, ankle
- Infiltrative lesion
- Histologically, the cells are similar to intramuscular myxoma
- CD34 & SMA (+, variable)
- S100 (-)
- Lack of GNAS1 gene mutation
- Local recurrence in 35% of cases
LOW GRADE FIBROMYXOID SARCOMA

- Young adults and children
- Male = Female
- Deep-seated lesion
- Painless mass, slow growing
- Proximal extremities, common intramuscular
- Other sites: trunk, mesentery, lung, small intestine, tongue
- Late local recurrence and metastasis. (Metastasis to the lungs and pleura).
- Long term follow-up
Alternating myxoid zones and heavily hyalinized stroma
Bland spindle cells with nuclear hyperchromasia and irregular nuclear outline
Short fascicular and whorling growth pattern
Arcades of small vessels with perivascular sclerosis

Courtesy of AJSP 2017; 22: 94-101

+/- Giant collagen rosettes (hyalinised centre) surrounded by fibroblasts
Molecular studies:

- t(7;16) - a fusion of FUS-CREB3L2
- t(11;16) - a fusion of FUS-CREB3L1

LOW GRADE FIBROMYXOID SARCOMA

EMA

MUC 4 +
LOW GRADE FIBROMYXOID SARCOMA

Differential diagnoses

1. Nodular fasciitis
2. Neurofibroma
3. Benign fibrous histiocyтома

*No alternating stromal pattern or nuclear hyperchromasia

4. Fibromatosis: Hypocellular and not hyalinised. The nuclei are hypochromatic and they have stellate shape cytoplasm (β- Catenin + in most cases)
Myxofibrosarcoma

6th decade and above
Commonly a superficial tumour
Extremities (limbs & limb girdle)
Rare on trunk, head & neck
hand & feet)
Retroperitoneum & abdominal
cavity are not a primary site

Spread along vessels and fascial
plane (Local recurrence > 50%)

Metastasis to the lung or bone

No specific IHC
Myxofibrosarcoma

Myxoid areas

Solid areas

High grade

Pseudolipoblast

Low-grade

Intermediate-grade
Differential diagnosis depends on depth of tumour

1. A deep-seated low-grade myxofibrosarcoma
   i. Low-grade fibromyxoid sarcoma
      (the cells are quite bland – not pleomorphic)
   ii. Myxoid liposarcoma
      (monomorphic cells, signet-ring lipoblasts, and
      arborizing capillaries – lack in pleomorphism &
      perivascular condensation)
      Pitfall: Pseudolipoblasts
Differential diagnosis

2. A superficial low-grade myxofibrosarcoma
   i. Cutaneous myxoma
   ii. Myxoid variant of a DFSP (the cells are hyperchromatic but are uniform in shape and size. Also lack of alternating hypocellular & hypercellular areas. CD34 +)

3. High-grade myxofibrosarcoma
   i. Dedifferentiated liposarcoma
      Retroperitoneum: Favours Dediff Liposarcoma
      Dediff Liposarcoma: MDM2 +, CDK4+ IHC
Myxoid Liposarcoma

- 10% of soft tissue sarcoma
- Young adults (30s & 40s)
- Rare in children
- Slow-growing, painless
- Deep-seated, extremities (thigh & buttocks)
- Local recurrence & metastasis (50%)
- Metastasis to bone & other soft tissue sites (retroperitoneum, opposite extremity, axilla, etc) rather than lung

Wide local resection
Radiotherapy - ↓ local recurrence
Chemotherapy – after local recurrence & metastasis
Myxoid Liposarcoma

Uniform oval mesenchymal (non-lipogenic) cells

Variable no. of small signet-ring lipoblasts

Delicate, arborizing, crow’s feet or chicken-wire capillary vasculature

Myxoid stroma
Pools of stromal/extracellular mucin appear like microcystic or pseudoacinar

**High-grade myxoid liposarcoma:**
- >5% round cell component

**t(12;16)- FUS-DDIT3 fusion – 90%
  t(12;22)- EWSR1-DDIT3**

High-grade: Hypercellular, primitive round cell morphology with hyperchromatic nuclei, vesicular chromatin
Myxoid Liposarcoma

Differential diagnosis

1. **Intramuscular myxoma**
   (paucicellular, no true lipoblast. Note: This distinction can be difficult on small biopsy specimen)

2. **Well-differentiated liposarcoma with myxoid change**
   (more pleomorphism, MDM2+, CDK4+)

3. **Myxofibrosarcoma**
   (older adult, mostly superficial, cells are more pleomorphic, perivascular condensation)
Myxoid Liposarcoma

Differential diagnosis

4. Extraskeletal myxoid chondrosarcoma
(older age group, cells in cords and nests, eosinophilic cytoplasm, hypovascular, lack of plexiform vasculature. Note: more aggressive & need wider excision)
Cutaneous myxoma (Superficial angiomyxoma)

Trunk, head & neck, extremities and subcutis
Entrapped adnexal structures (25%)
Sporadic (middle-aged)
Syndromic (young adult)
- Carney complex (cutaneous & cardiac myxoma, skin hyperpigmentation & endocrine abnormalities)

Lobular growth, with scattered bland cells in a myxoid and collagenous stroma
Blood vessels +++
Neutrophils ++
Local recurrence is common

Differential diagnosis of cutaneous myxoma:
1. Superficial acral fibromyxoma (SAF)

Painful lesion
Young adult
Solitary, dome shape, polypoid, dermal-based lesions on fingers, toes, palm, sole & periungual

The cells are arranged in fascicles or storiform pattern, moderate cellularity
Numerous thin-walled vessels
Mast cells +++
CD34+, EMA +/-
Recurrence – 1/3 of cases

Courtesy of Diag Histopathol 2015:21:11:438-444
Differential diagnosis of cutaneous myxoma:
2. Neurothekeoma

Younger patients
Dermis & Subcutis
Head & neck, upper extremities
Multinodular with myxoid matrix and peripheral fibrosis
Spindled or epithelioid mononuclear cells arranged in whorled pattern, variable atypia, giant cells +/-
Local recurrence: rare

CD 10
NSE
D2 - 40
S100 -  HMB45 -  NKI-C3 +
Male = Female (young adult)
Distal extremities & fingers
Dermis with extension into subcutis
Multilobulated separated by fibrous tissue
Schwannian cells with pseudoinclusion
S100 (+++), GFAP (+)
Local recurrence up to 45%

Differential diagnosis of cutaneous myxoma:
3. Dermal nerve sheath myxoma

Courtesy of Diag Histopathol 2015:21:11:438-444
Ossifying fibromyxoid tumour

Shell of lamellar bone

Subcutaneous mass
Ossifying fibromyxoid tumour

Adult, M > F
Extremities, trunk, head & neck
Subcutis or intramuscular
Well-circumscribed, multinodular
(4-5 cm) with incomplete shell of bone
Variable fibromyxoid stroma

Criteria for malignancy:
1. High nuclear grade or high cellularity &
2. The mitotic count is >2/50HPF
Ossifying fibromyxoid tumour

S100 (+: 70-90%), Desmin (+: 50%)
EMA(+: 10%)

Differential diagnosis:

1. Soft tissue myoepithelioma
   (more intratumoral heterogeneity, S100 +, EMA +, Keratin +, GFAP+, EWSR1 in 50% of cases)

1. Extraskeletal myxoid chondrosarcoma (more abundant myxoid stroma, spindled to epithelioid cell, S100 + in <20%, Desmin -)
Take home messages

• The presence of myxoid stroma can be seen in many tumours and may pose a diagnostic challenge, in particular, in needle biopsy specimen with abundant myxoid matrix and low cellularity

• Intramuscular or cutaneous myxoma have bland spindled cells and paucicellular.

• Low-grade fibromyxoid sarcoma has more collagenous stroma, demonstrating myxoid and collagenous zones and is MUC4 positive.
Take home messages

- **Myxoid liposarcoma** has characterized plexiform branching capillaries with uniform non lipogenic mesenchymal cells and scattered lipoblasts.
- **Myxofibrosarcoma** has elongated curvilinear vessels, perivascular condensation of tumour cells with prominent nuclear pleomorphism
- Differentiating myxoid soft tissue lesions requires correlation of clinical, radiological and histological findings, in particular, the patient’s age, the site of the lesion, the depth of the lesion, histological features, and vascular pattern.
References
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Thank you