Case 4:
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Clinical History
A 52 year old woman presented with recurrent haemoptysis. CT thorax revealed a left upper lobe mass. On bronchoscopy a 'fleshy' tumour was identified. Brushings were called 'suspicious for malignancy', and the patient was referred for surgical resection.
Differential Diagnosis

- Inflammatory myofibroblastic tumour / sarcoma
- Extraskeletal myxoid chondrosarcoma
- Angiomatoid 'malignant' fibrous histiocytoma
- Primary pulmonary myxoid sarcoma

Inflammatory myofibroblastic tumour

- Tumour with (myo)fibroblastic differentiation; of intermediate biological potential; characteristically associated with a prominent inflammatory infiltrate
- Predilection for children, adolescents & young adults
- Broad anatomic distribution

- Histology:
  - Several histologic patterns
  - Plump spindle-cells in myxoid-collagenous background
  - Ganglion-like myofibroblasts
  - Inflammation

Immunohistochemistry:

- (+/-) ALK, ROS1, smooth muscle actin, desmin, keratin (focal)

Molecular:

- ALK
- ATIC, CAGE, CLTC, EML4, FYN, RANBP2, SEC31L1, TPM3, TPM4
- ROST, PDGFRβ, ETV6
- Others…
Differential Diagnosis

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Extraskeletal myxoid chondrosarcoma

- Malignant mesenchymal neoplasm of uncertain histogenesis
- Typically adults
- Predominates in deep soft tissue extremities

- **Histology:**
  - Cords-clusters-reticular pattern
  - Uniform spindle-ovoid cells
  - May have round-epithelioid cells with high-grade
  - Prominent myxoid stroma

- **Immunohistochemistry:**
  - (+/-) S100, CD117, synaptophysin

- **Molecular:**
  - NR4A3
    - EWSR1, FUS, TAF15, TCP12, TFG

- **RT-PCR:**
  - \( EWSR1-\text{CREB1} \)
Differential Diagnosis

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Angiomatoid fibrous histiocytoma

- Histology:
  - Pseudocapsule with prominent lymphoplasmacytic cuff
  - Pseudoangiectatic spaces; haemosiderin deposition
  - Syncytial pattern
  - Bland nuclei with open chromatin
  - Occasionally: myxoid, reticular, pleomorphic
  - Immunohistochemistry:
    - (+) EMA, desmin, CD68, CD99, ALK*
  - Molecular:
    - EWSR1-CREB1 (>90%)
    - EWSR1-ATF1
    - FUS-ATF1

*Angiomatoid fibrous histiocytoma is a mesenchymal neoplasm of intermediate biologic potential, generally affecting adolescents and young adults. It frequently arises in superficial soft tissue but may also occur in viscera, including the endobronchial region. Up to 10% may recur locally, and metastasis is rare.*
Primary Pulmonary Myxoid Sarcoma

- Mesenchymal neoplasm of intermediate biologic potential
- Predominantly early-mid adulthood
- Cough / haemoptysis
- Largely endobronchial
- Rare (< 20 reported cases)
- 20 % metastasis

Histology:
- Reticular to lace-like pattern
- Spindle-polygonal cells
- Variable atypia
- Prominent myxoid stroma
- Patchy inflammation; lack prominent lymphoplasmacytic cuff
- Occasionally peripheral fibrosis / fibrous pseudocapsule

Immunohistochemistry:
- (+/-) SMA (focal/weak), EMA (focal/weak); (-) desmin, keratin

Molecular:
- EWSR1-CREB1
- EWSR1-X
- X-X

Differential Diagnosis
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Diagnosis
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Discussion
- Primary pulmonary myxoid sarcoma and angiomatoid fibrous histiocytoma appear to have many overlapping attributes:
  - Clinical; morphologic; immunohistochemical; molecular
  - Multi-institutional collaborations required to characterize extent of overlap:
    - Biologic potential
    - Does morphology of PPMS occur outside lung?
    - Will PPMS be found to have EWSR1-ATF1, FUS-, CREM-, others?
  - Essential to clearly convey to clinician(s) diagnostic challenges, and potential risk of aggressive behaviour
Summary: Potential Pitfalls

- Morphology:
  - Primary pulmonary myxoid sarcoma overlaps with multiple entities of varying malignant potential (e.g., inflammatory myofibroblastic tumour, extraskeletal myoid chondrosarcoma, angiomatoid 'malignant' fibrous histiocytoma, myoepithelioma, others)

- Immunohistochemistry:
  - Scope of immunophenotypes may not be adequately reflected for rare tumours, particularly soft tissue neoplasms (e.g., desmin, keratin, & ALK)
  - Variability in immunohistochemical protocols (e.g., clones, platforms, protocols)

- Molecular biology:
  - *EWSR1* is promiscuous
  - Methodological considerations (expanding role for RT-PCR, NGS, NanoString, Nanopore etc)

References