

Cytological features of ROS1 rearranged Pulmonary Inflammatory Myofibroblastic tumour - Case discussion

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Disclosure of Relevant Financial Relationships

No relevant financial relationships.

Overview



Case discussion

Clinical information
Imaging features



Cytological features

Histology correlation
Background
Differential diagnoses



Molecular testing

FISH
Sequencing



Literature review and discussion

Mutations
Clinical behaviour



Conclusion

Clinical outcome
Key points

Case details

Adult male, 30s

Incidentally detected left endobronchial lesion on CT

Past medical history of melanoma excision >3 years prior

Current smoker with a significant pack/year history

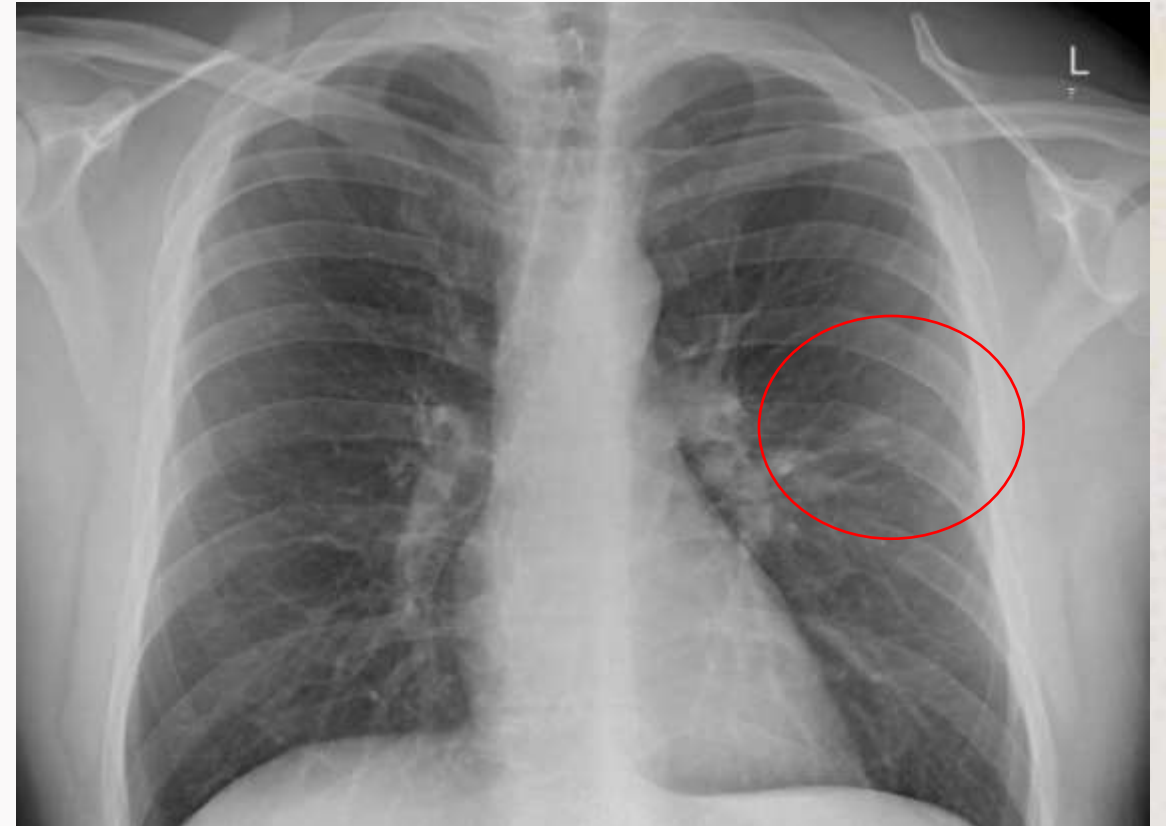
Imaging findings

XR: Minor ground glass density left mid zone

CT: "Linear peribronchovascular reticular solid radial opacity in LLL, some reaching pleural surface"

mixed reticular and ground glass change

PET: faint lower level activity SUV <2

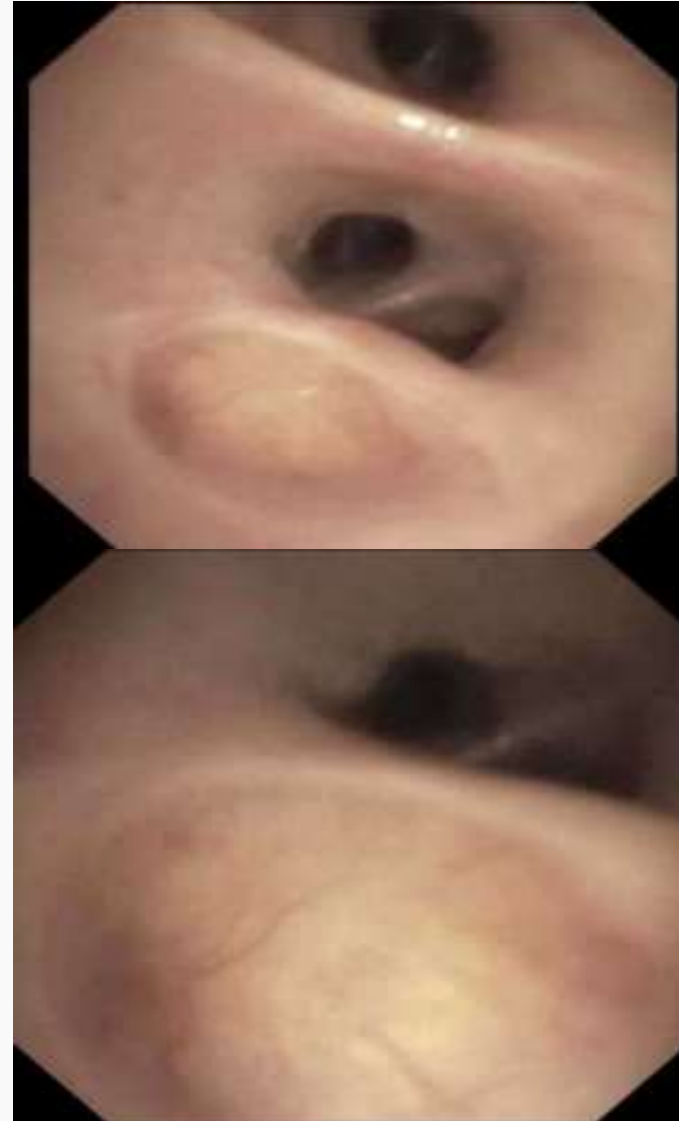


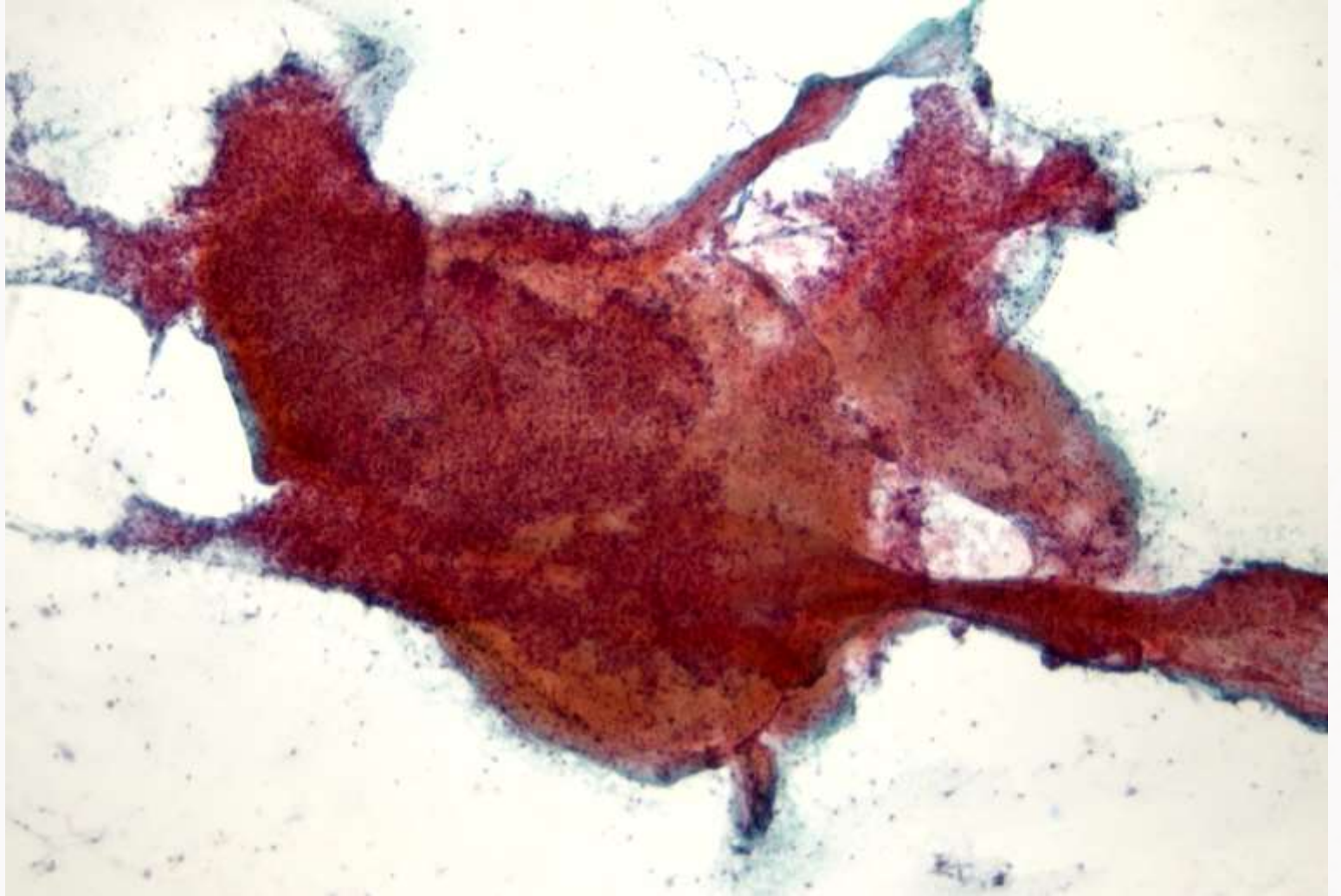
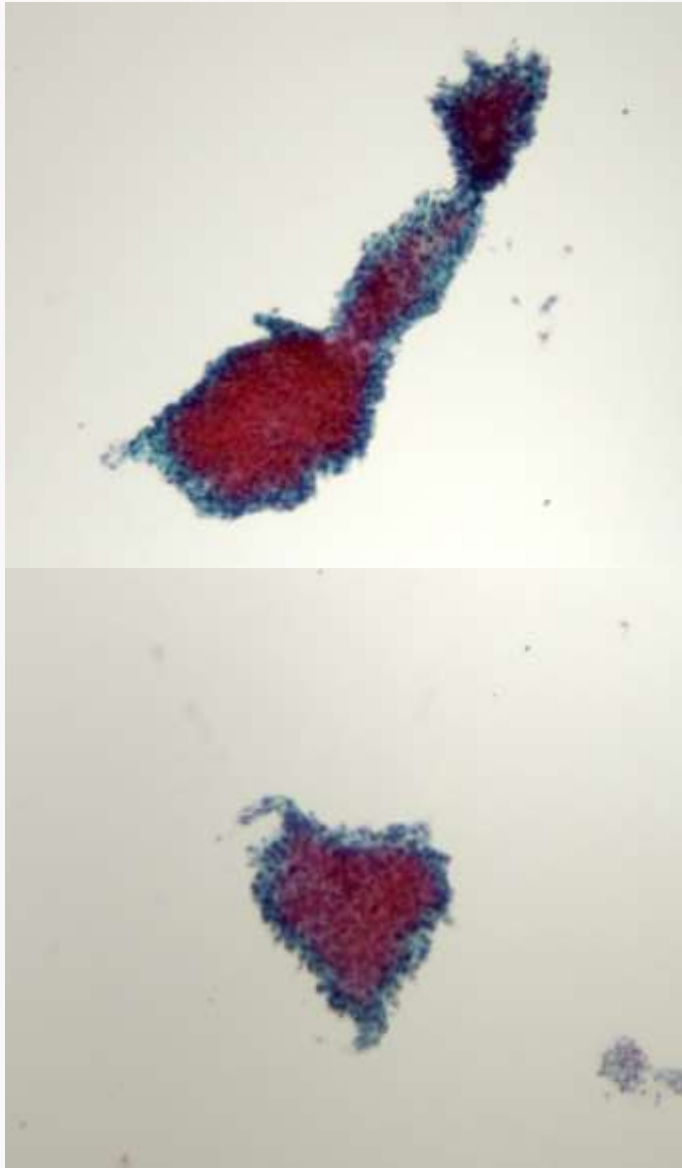
Bronchoscopy

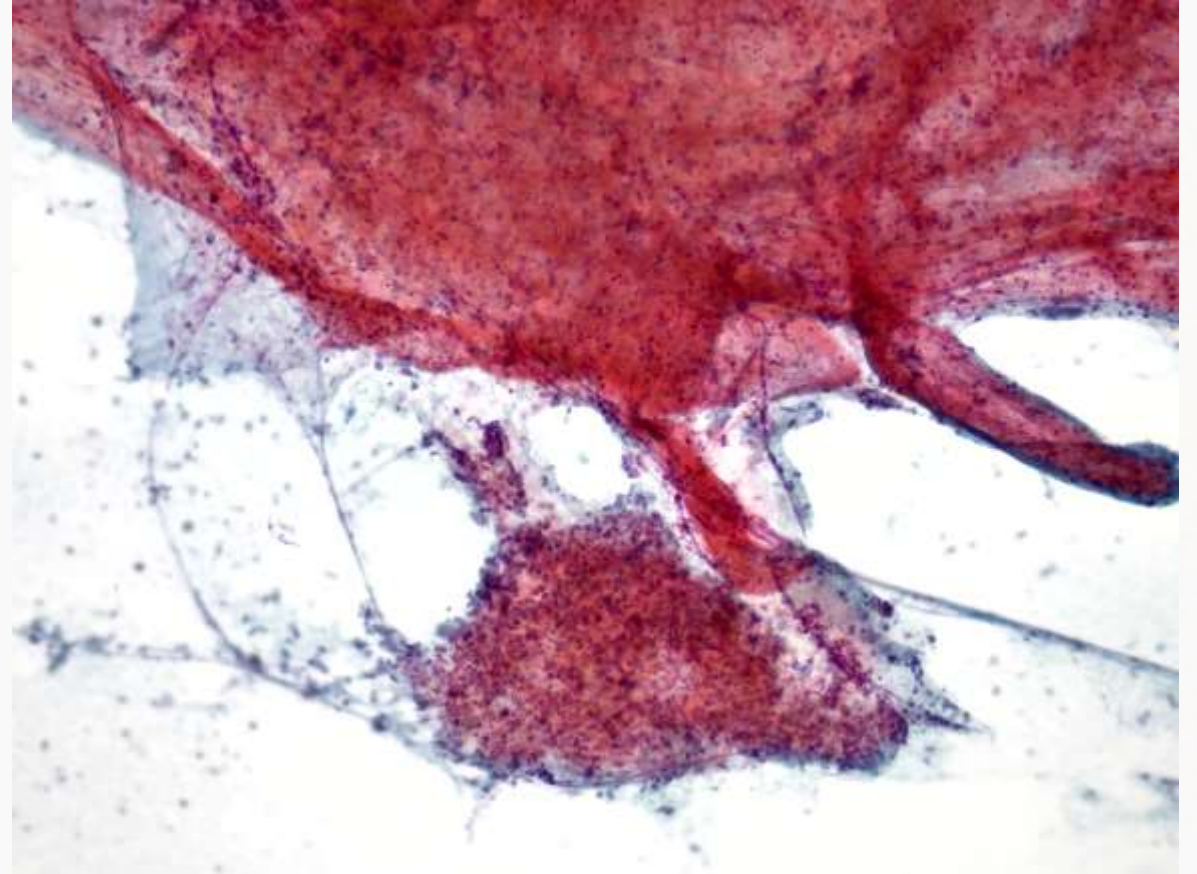
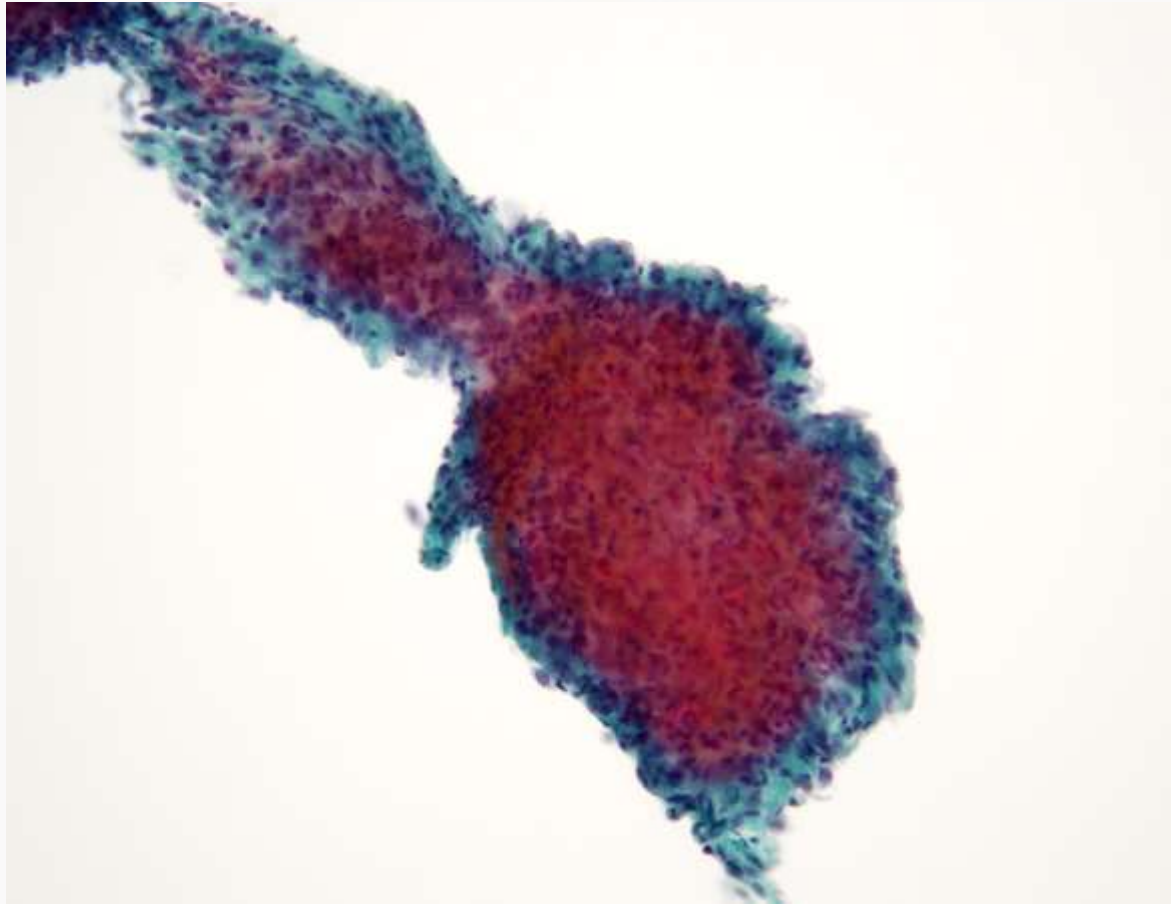
Underwent bronchoscopy and biopsy with bronchial brushings/washings.

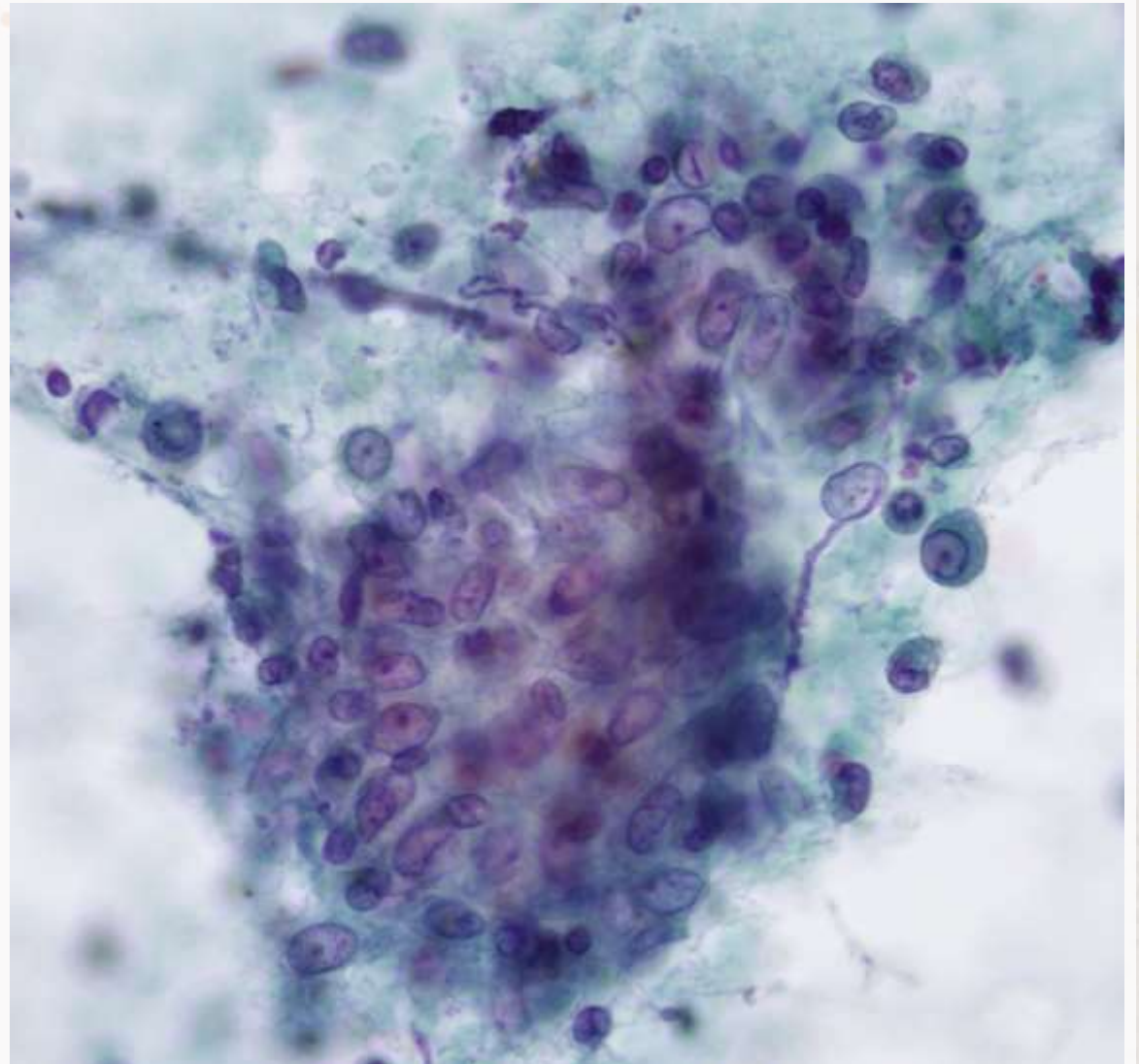
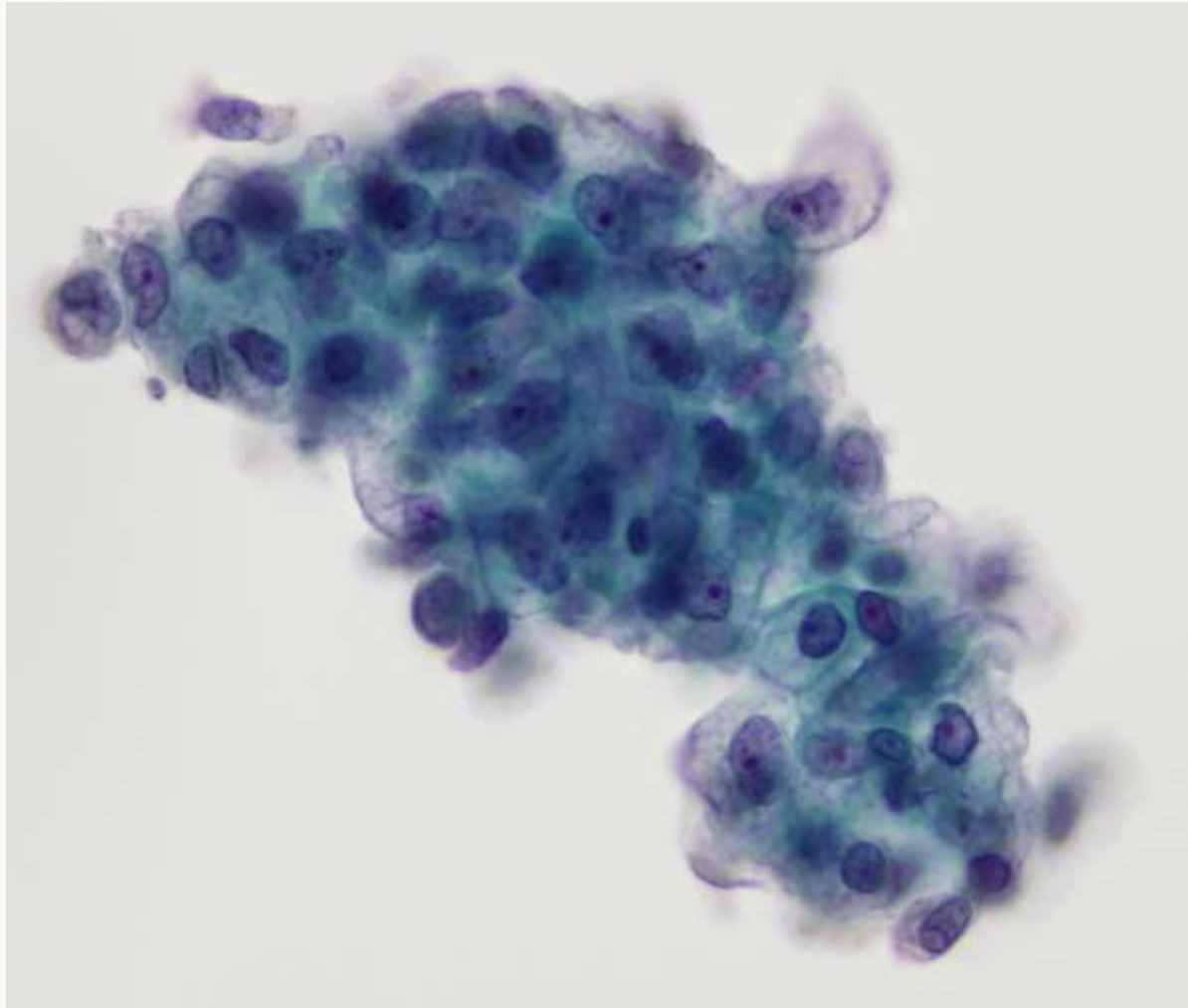
Clinical history:

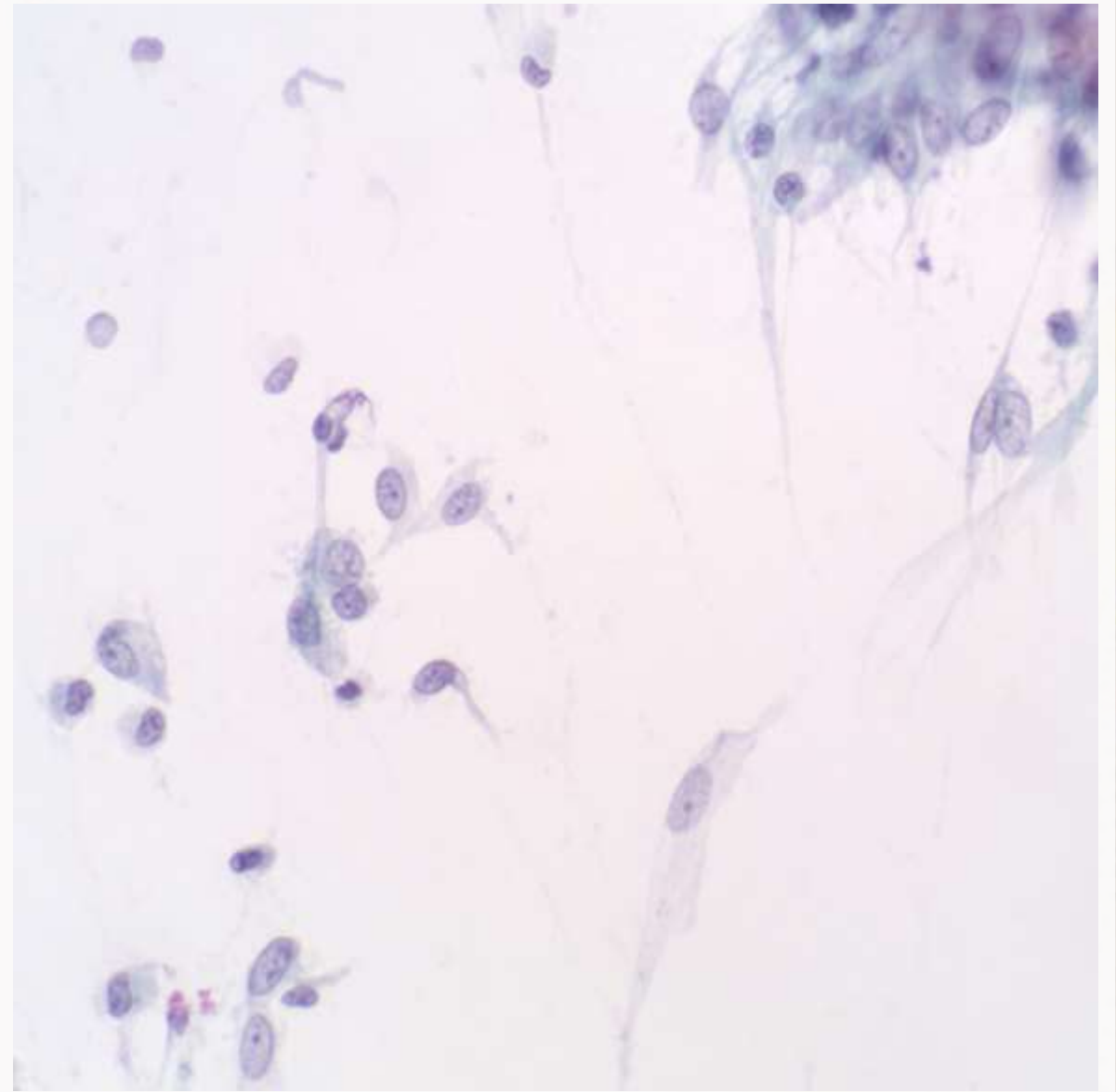
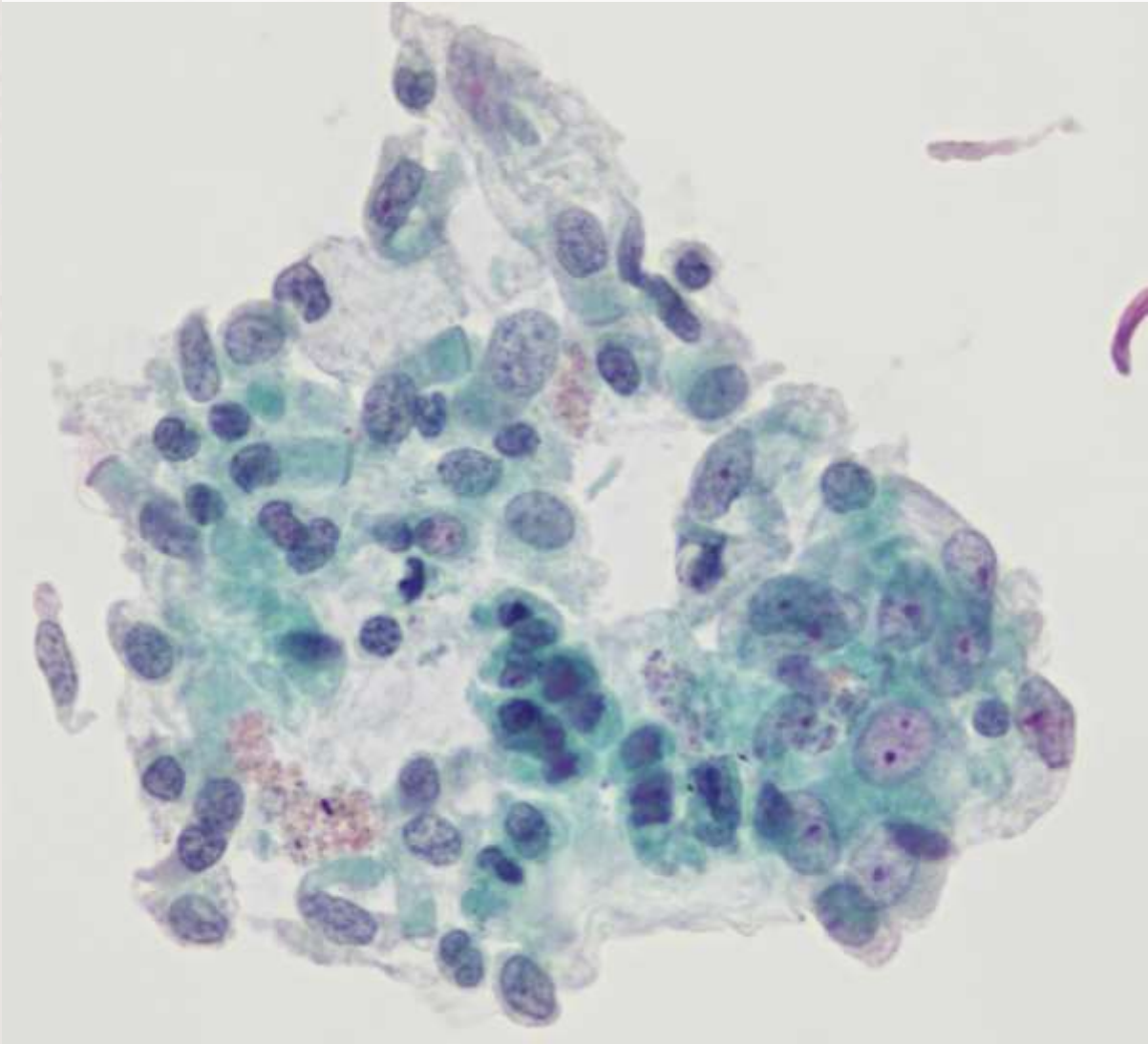
- Morphological appearance of a carcinoid tumour.



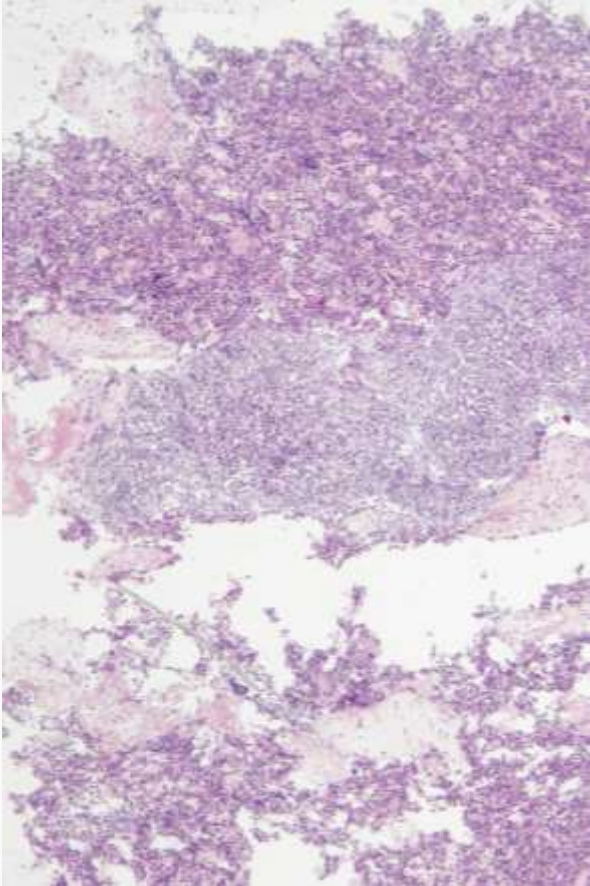




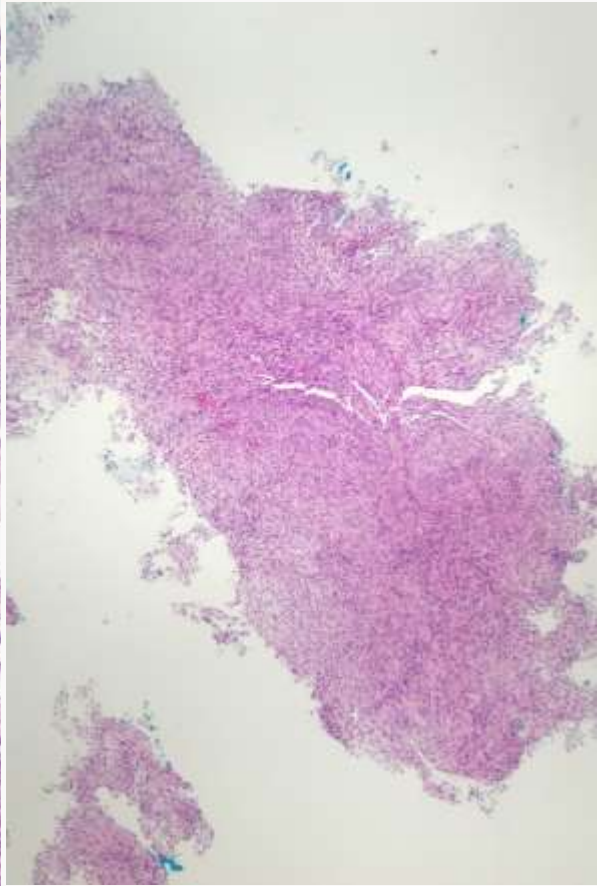




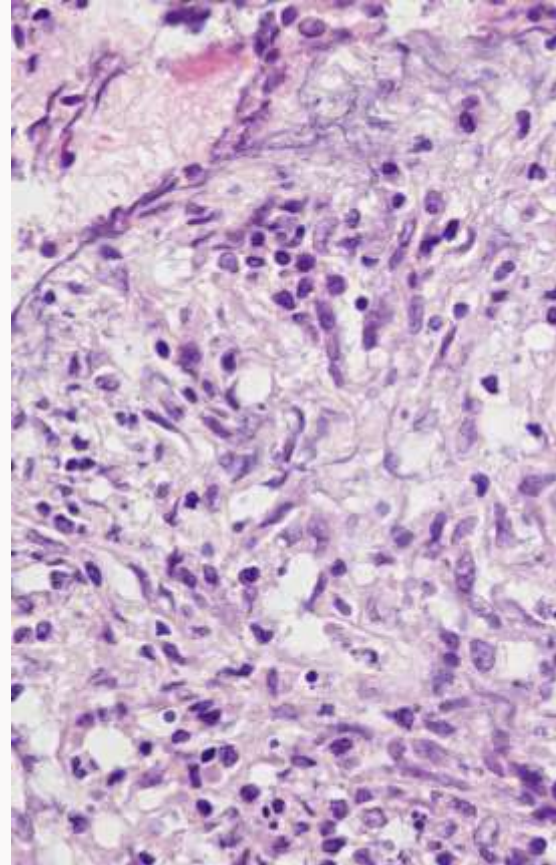
Cell block 4x



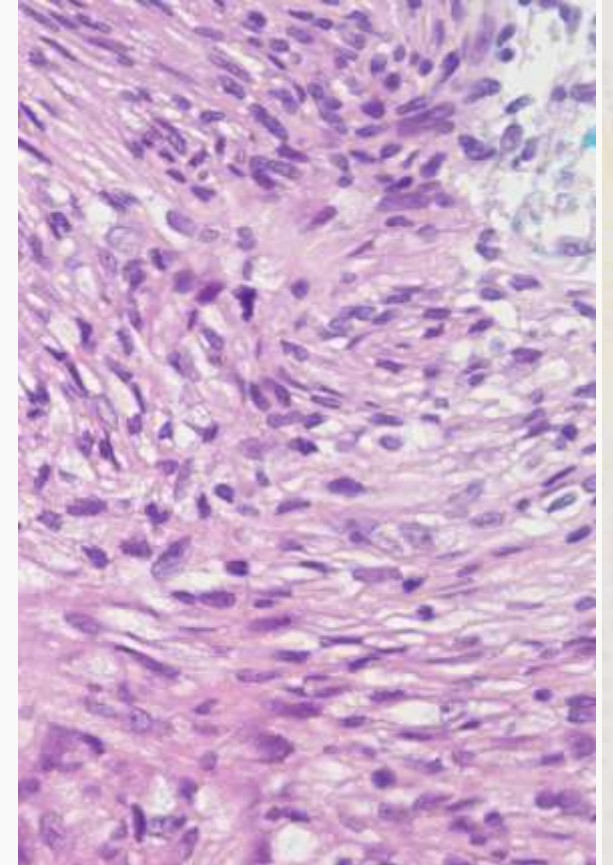
Biopsy 4x



Cell block 40x



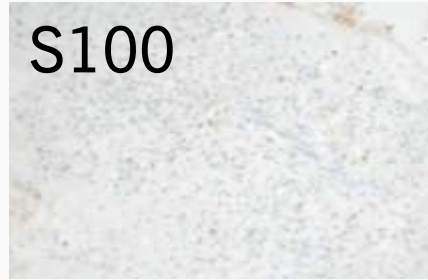
Biopsy 40x



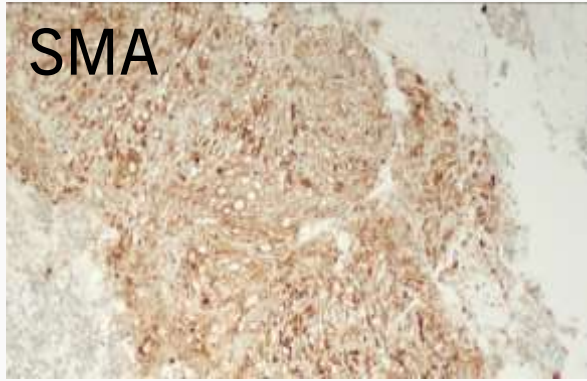
Cell block

- AE1/AE3 +(weak) S100-
- SMA+ROS1+DESMIN dot-like

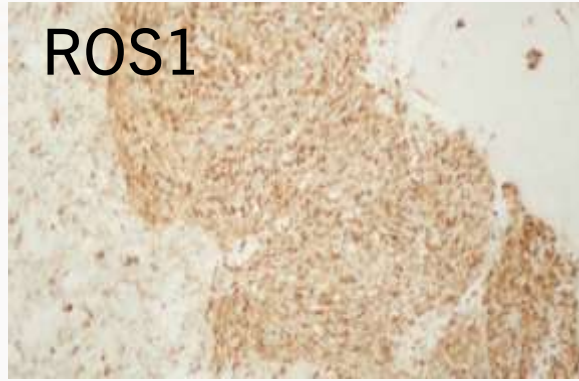
S100



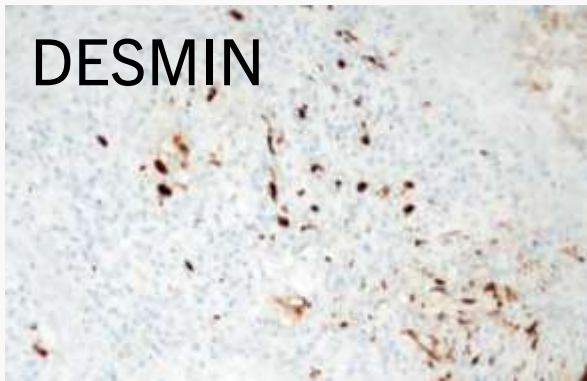
SMA



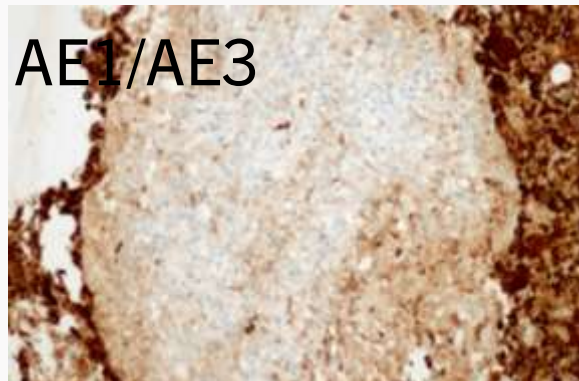
ROS1



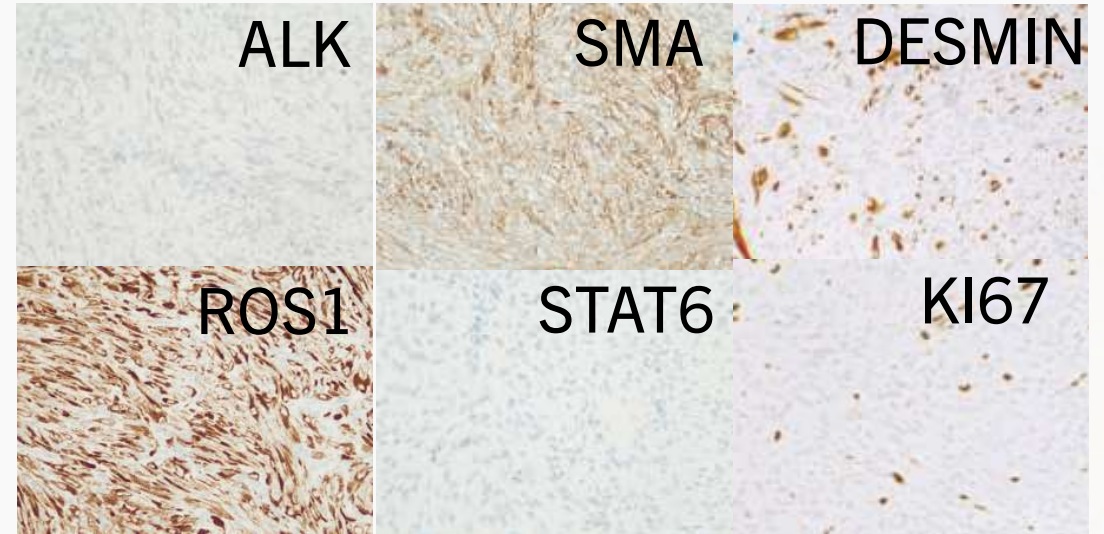
DESMIN



AE1/AE3



Biopsy IHC



Positive:

- SMA, desmin dot-like, ROS1⁺⁺, granular cytoplasmic CD68, D2-40, CD99
- MTAP/BAP1 (retained) PHH3 increased

Negative

- Neuroendocrine markers, TTF1, S100, SOX10, AE1/AE3, p63, CD34, STAT6, SSTR2, PR, CD21, CXCL13, CD1a, ERG, EBV, HHV8, ALK1, BRAF V600E IgG/IgG4,

Inflammatory Myofibroblastic Tumour

- Historically:
 - "wastebasket" diagnosis- spindle cell proliferation with inflammatory cell infiltrate, thought to be reactive/inflammatory
 - plasma cell granuloma, inflammatory pseudotumour, inflammatory fibrosarcoma, etc
- Identification of Anaplastic lymphoma kinase (ALK) and other gene rearrangements:
 - Neoplastic process
- Predilection for children and young adults
- Ultrastructural features of myofibroblastic cells
- IMT remains a heterogenous group of entities.

Behaviour

Typically non-aggressive, however aggressive variants are described.

- Epithelioid morphology and increased mitoses confer greater risk
 - “Epithelioid inflammatory myofibroblastic sarcoma” – typically intra-abdominal/pelvic
- ~20% recur or show aggressive behaviour
- Metastasis rare

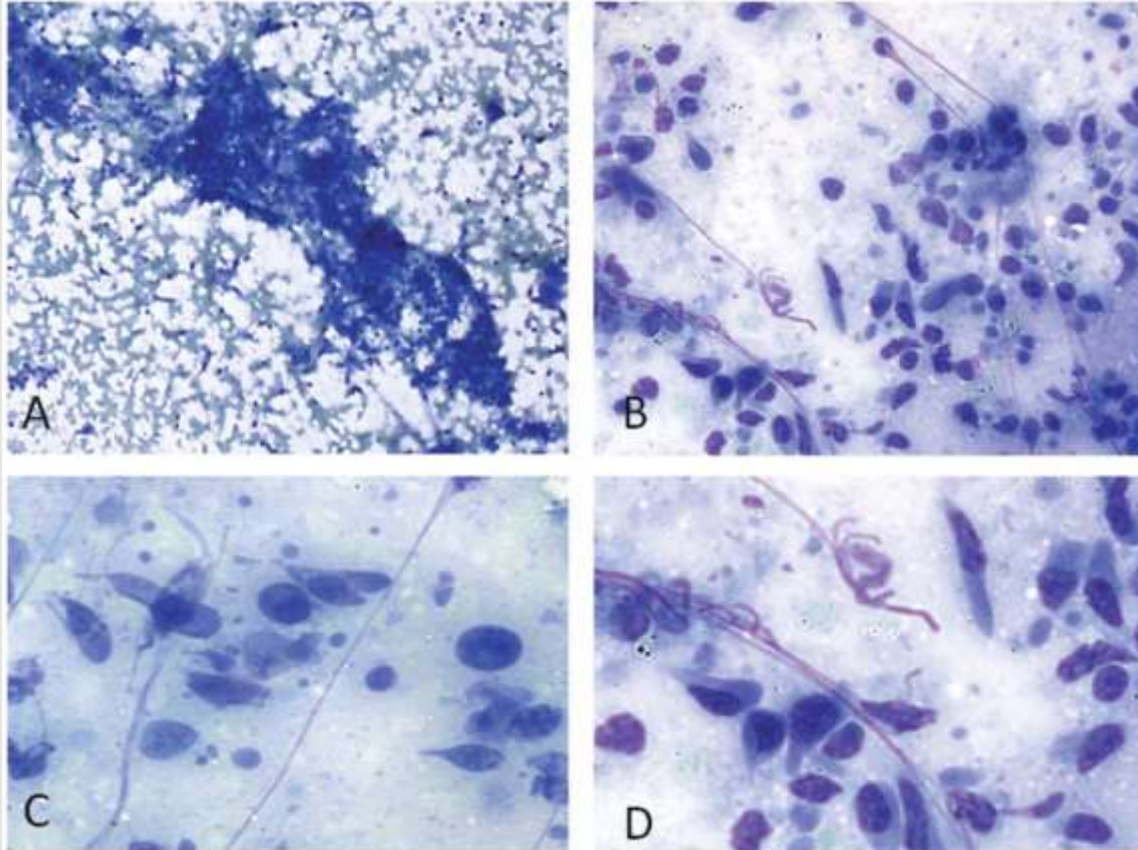
Lesions are typically solitary, and excision is generally curative.

Spontaneous regression rarely reported

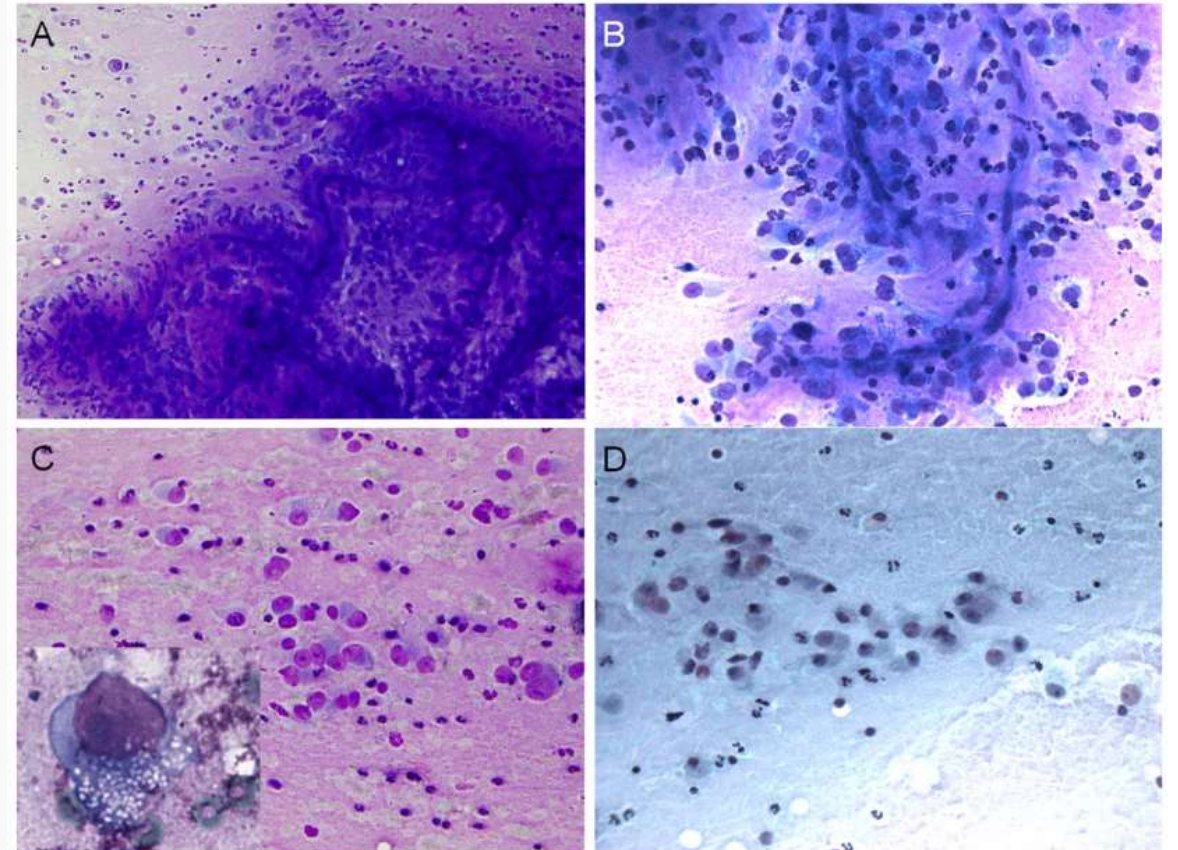
IMT Diagnosis: Morphology

- Key criteria are:
 - Monomorphic fascicular proliferation of spindled cells with inflammatory infiltrate
 - myxoid, hypercellular or hypocellular fibrous patterns described
 - Pulmonary cases may be more likely to show lymphoplasmacytic rather than neutrophilic infiltrate
 - Stoll, L. M. & Li, Q. K. Cytology of fine-needle aspiration of inflammatory myofibroblastic tumor. *Diagnostic Cytopathology* **39**, 663–672 (2011):
 - 20 cases: 15% IMT, 60% atypical spindle cell proliferation, 25% inflammation and fibrosis
 - “...**coffee bean like** or bipolar in shape. The **chromatin is vesicular and evenly distributed** with **one to multiple small nucleoli**. The nuclear membranes are smooth. The cytoplasm was relatively dense with tapered ends; resembling myofibroblasts”
- Diagnosis requires ancillary studies

IMT Diagnosis: Morphology



Stoll, L. M. & Li, Q. K. Cytology of fine-needle aspiration of inflammatory myofibroblastic tumor. *Diagn. Cytopathol.* **39**, 663–672 (2011).



Lee, J.-C. *et al.* Cytopathologic features of epithelioid inflammatory myofibroblastic sarcoma with correlation of histopathology, immunohistochemistry, and molecular cytogenetic analysis. *Cancer Cytopathology* **123**, 495–504 (2015).

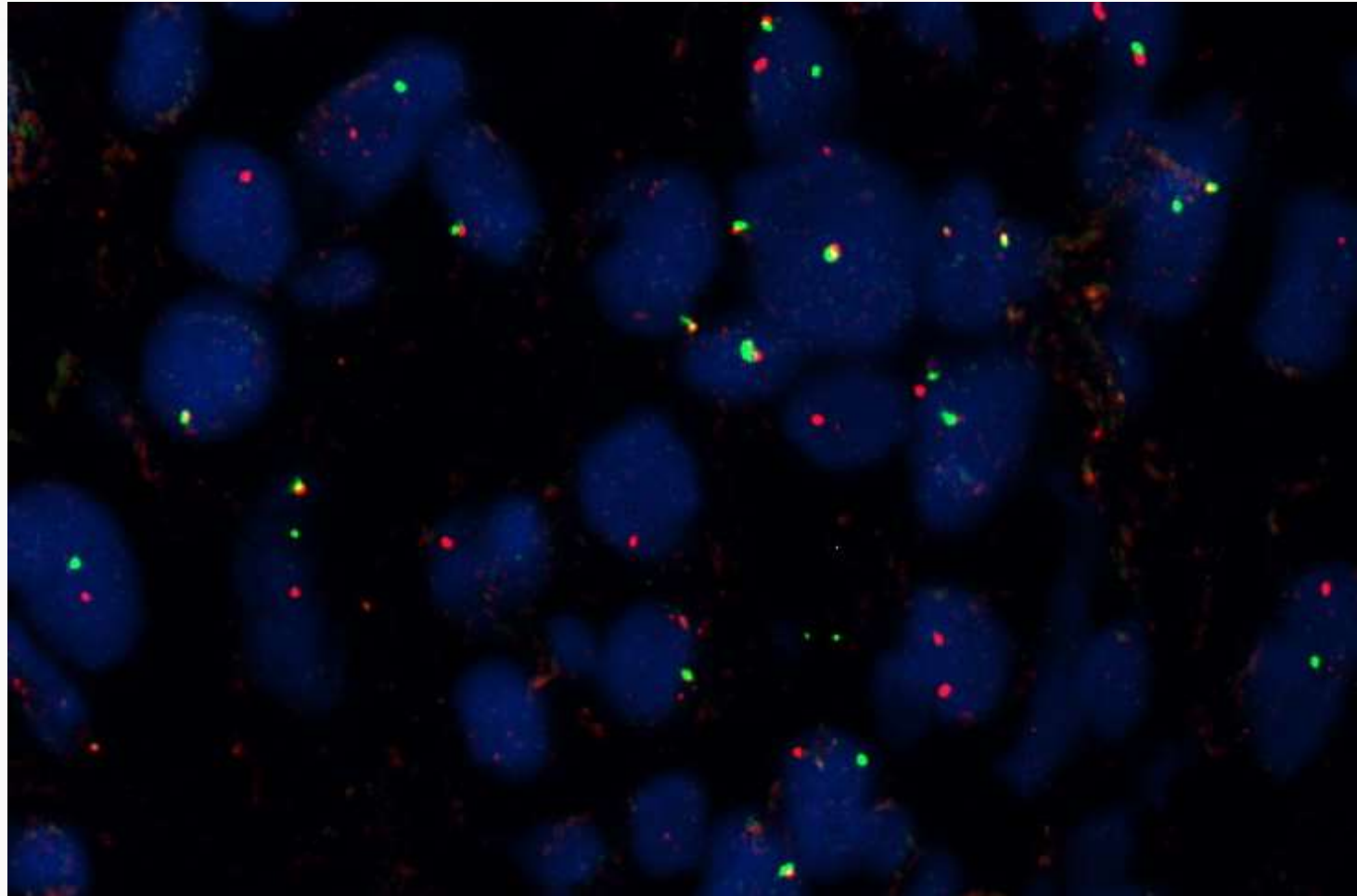
IMT Diagnosis: Ancillary tests

- Myofibroblastic differentiation
 - SMA positive, variable staining for calponin, MSA, and desmin
- Exclusion of other entities
 - **Melanoma**
 - **IgG4-related sclerosing disease,**
 - **Solitary fibrous tumour,**
 - **Meningioma**
 - **Langerhans cell histiocytosis**
 - Spindle cell carcinoma,
 - Sarcomatoid-variant anaplastic large-cell lymphoma,
 - Rhabdomyosarcoma,
 - IMT-like dedifferentiated liposarcoma

IMT Diagnosis: Ancillary tests

- Gene rearrangements
 - ALK rearrangements in 50%
 - ROS1(10%), ETV6, NTRK3, RET and PDGFRB also described
 - Variants generally bear no specific morphology, though ALK and ROS1 immunohistochemical staining pattern is associated with certain rearrangements
 - EIMS: Typically *RANBP2-ALK* fusion
- FISH
- Molecular testing

ROS1 FISH



66% break apart signals

Vysis ROS1 break apart probe
(Abbott)

Sequencing

Oncomine precision assay thermofisher scientific (A46291)

- ALK, ROS1, METexon14, NTRK1, NTRK2, NTRK3, RET
- **NOT DETECTED**

Sequencing

Limited data

- Approximately 50% of ROS1 rearranged IMTs likely have TFG–ROS1
- Remaining 50% may have YWHAE–ROS or another unspecified fusion partner

CCDC6-ROS1.C5R35.1
CD74-ROS1.C4R33.NGS
CD74-ROS1.C6R32.COSF1202

CD74-ROS1.C6R34.COSF1200
CD74-ROS1.C6R35.COSF1478
CD74-ROS1.C7R34

CEP85L-ROS1.C8R36
CLIP1-ROS1.C19R36
CLTC-ROS1.C31R35
ERC1-ROS1.E11R36

EZR-ROS1.E10R33
EZR-ROS1.E10R34.COSF1267
EZR-ROS1.E10R35

GOPC-ROS1.G4R36.COSF1188
GOPC-ROS1.G8R35.COSF1139
HLA_A-ROS1.H7R34
KDEL2-ROS1.K5R35

KDEL2-ROS1.K5Rintron34
LRIG3-ROS1.L16R35.COSF1269
MSN-ROS1.M9R34
MYO5A-ROS1.M23R35

NCOR2-ROS1.N7R36
NFKB2-ROS1.N13R36
PPFIBP1-ROS1.P9R35
PWWP2A-ROS1.P1R36
SDC4-ROS1.S2R32.COSF1265
SDC4-ROS1.S2R34
SDC4-ROS1.S4R32.COSF1278
SDC4-ROS1.S4R34.COSF1280

SHTN1-ROS1.K11R36

SLC34A2-ROS1.S13R32.COSF1259
SLC34A2-ROS1.S13R33
SLC34A2-ROS1.S13R34.COSF1261
SLC34A2-ROS1.S13R36
SLC34A2-ROS1.S4R32.COSF1196
SLC34A2-ROS1.S4R34.COSF1198
SLC34A2-ROS1.S4R35

TFG-ROS1.T4R35
TFG-ROS1.T5R35
TMEM106B-ROS1.T3R35

TPM3-ROS1.T3R36
TPM3-ROS1.T7R35.COSF1273
YWHAE-ROS1.Y4R36
ZCCHC8-ROS1.Z2R36
ZCCHC8-ROS1.Z3R36

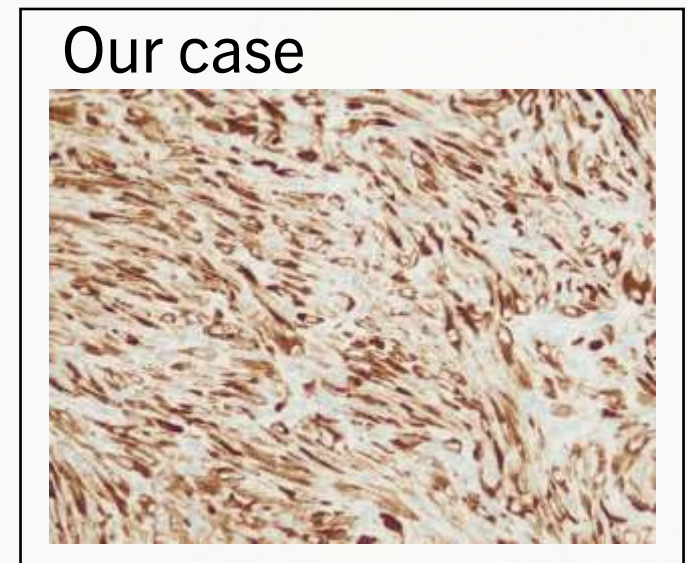
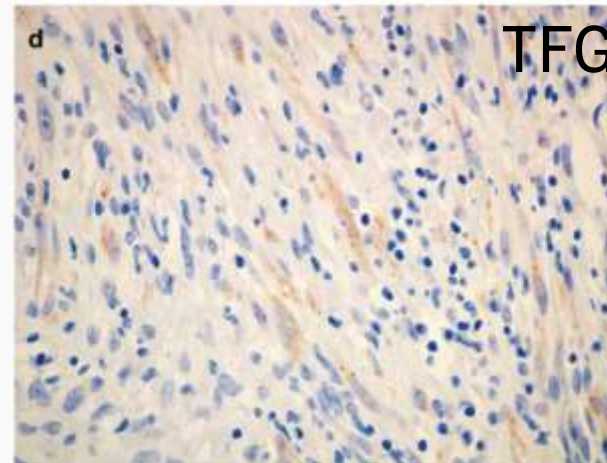
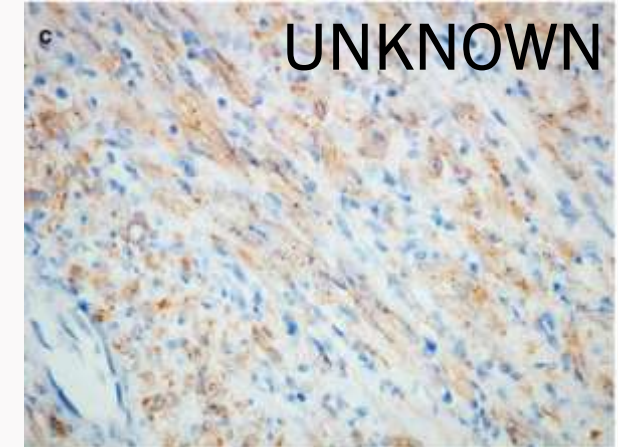
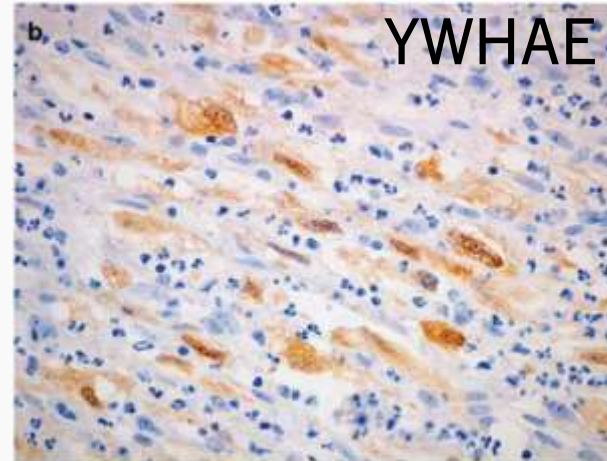
Hornick *et al.* 2016 described 3x ROS1 rearranged cases.

- YWHAE-ROS1,
- TFG-ROS1,
- Unknown fusion with positive fish and IHC

YWHAE–ROS1: diffuse cytoplasmic and nuclear expression of ROS1

TFG–ROS1: diffuse cytoplasmic and dot-like expression of ROS1

Unknown-ROS1: diffuse dot-like cytoplasmic staining



Hornick, J. L., Sholl, L. M., Dal Cin, P., Childress, M. A. & Lovly, C. M. Expression of ROS1 predicts ROS1 gene rearrangement in inflammatory myofibroblastic tumors. *Modern Pathology* **28**, 732–739 (2015).

Outcome

- Patient monitored with close follow up, repeat imaging, trial of steroids
- Stable on 6 month imaging
- Mass mostly resolved on 12 month CT scan

Summary

- IMT of the lung has distinct prognostic and management implications, however is a heterogenous entity
- Cytological features are non-specific but should prompt further investigation
- Ancillary studies (cell block or biopsy) required - diagnosis of exclusion
- ALK, ROS1 and molecular testing

Acknowledgements

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