# GLEE Club: a series of three cases

Victoria van Winden

PathWest Laboratory Medicine WA

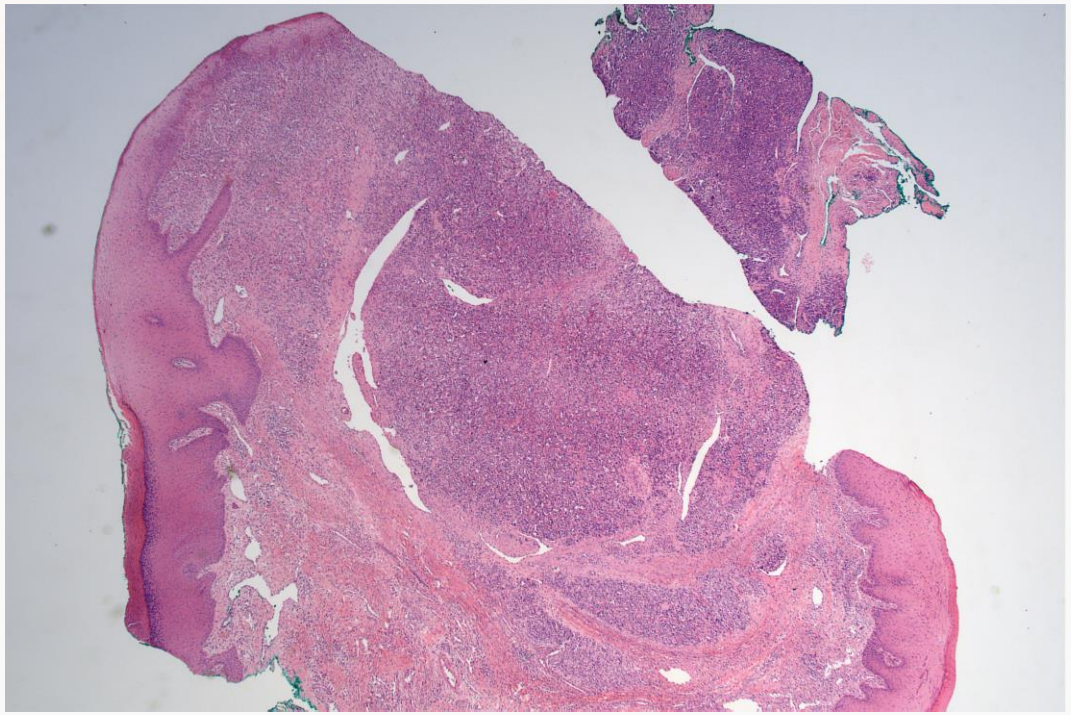
# Disclosure of Relevant Financial Relationships

I have no relevant financial relationships to report.

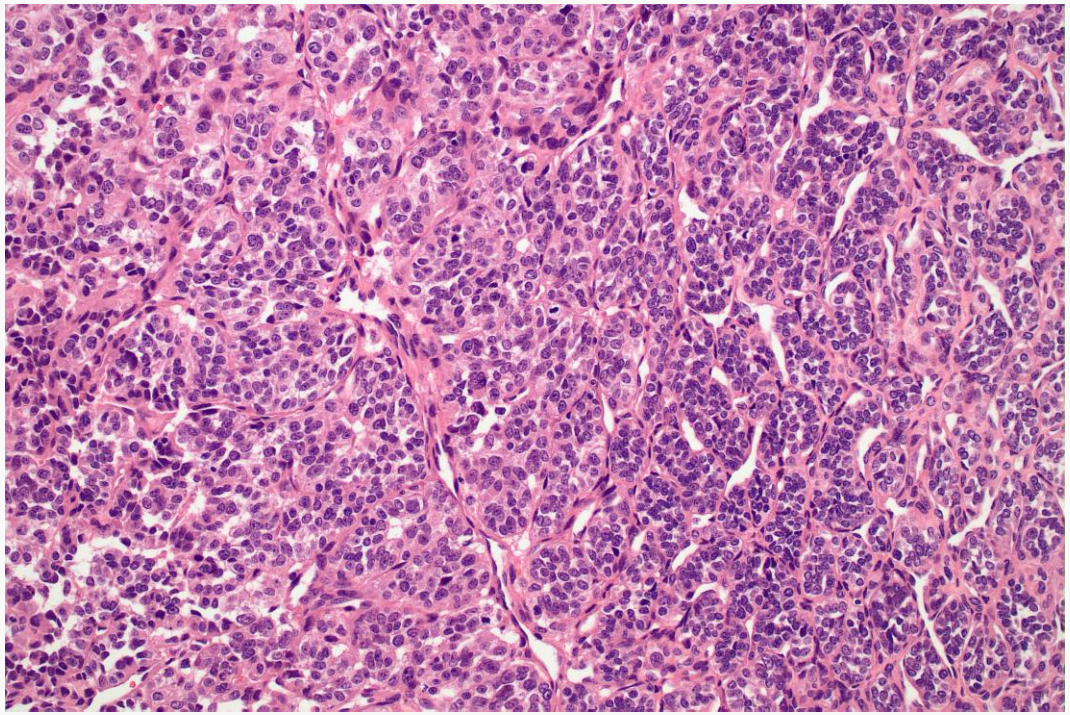
# Case 1

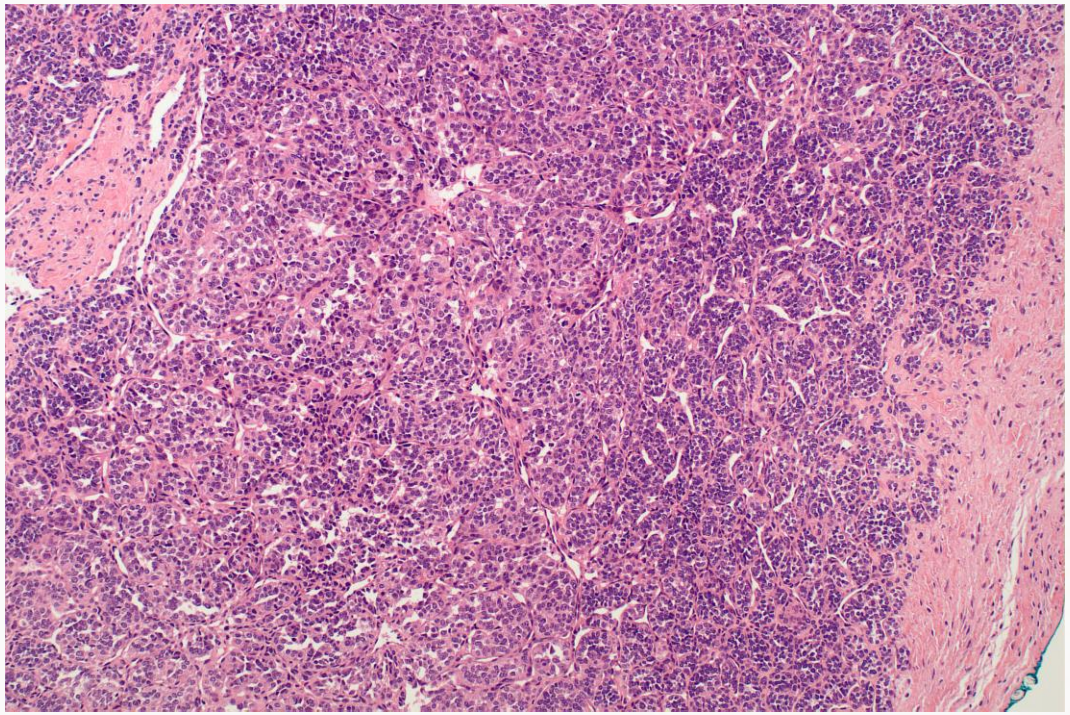
- 11-year-old male
- Growing non-tender swelling on the tip of his right thumb

# Case 1: Right thumb lesion, HE

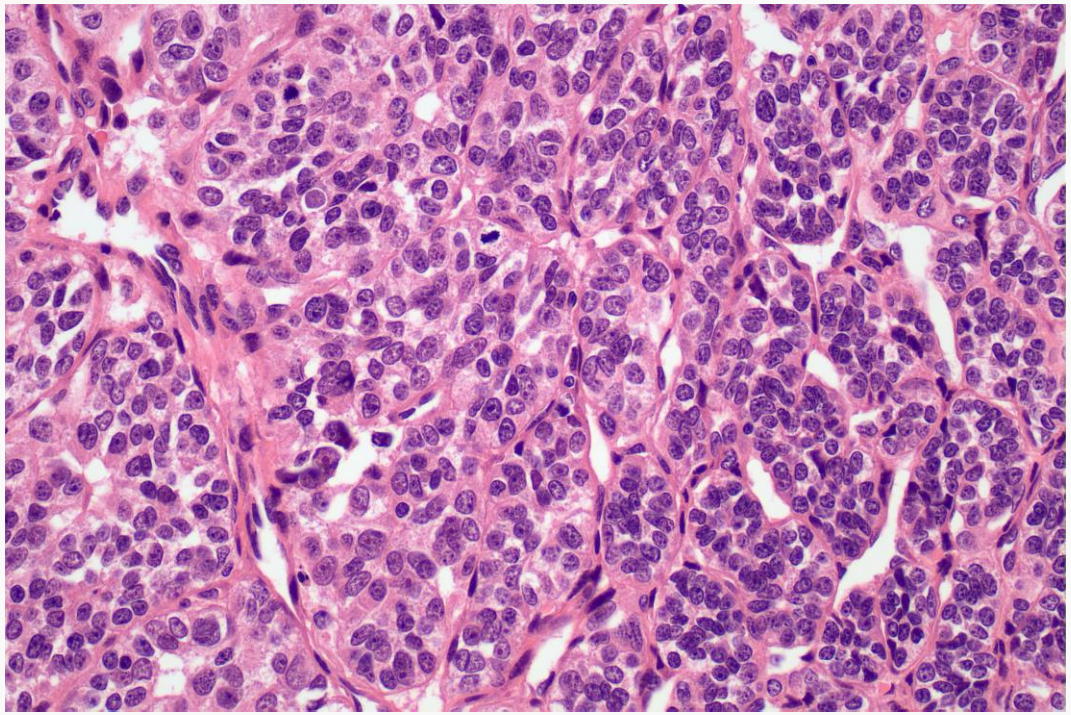


# Case 1: Right thumb lesion, HE





# Case 1: Right thumb lesion, HE



# Case 1: Diagnosis?

- Pericytoma
- Glomus tumour
- Paraganglioma
- NET
- Synovial sarcoma

# Case 1: Right thumb lesion, IHC

## Positive

- CD99 (membranous)
- CD56

## Negative

- Cytokeratins
- Chromogranin, synaptophysin
- SMA
- Desmin
- S100
- SOX10
- CD34

# Case 1: Right thumb lesion, FISH

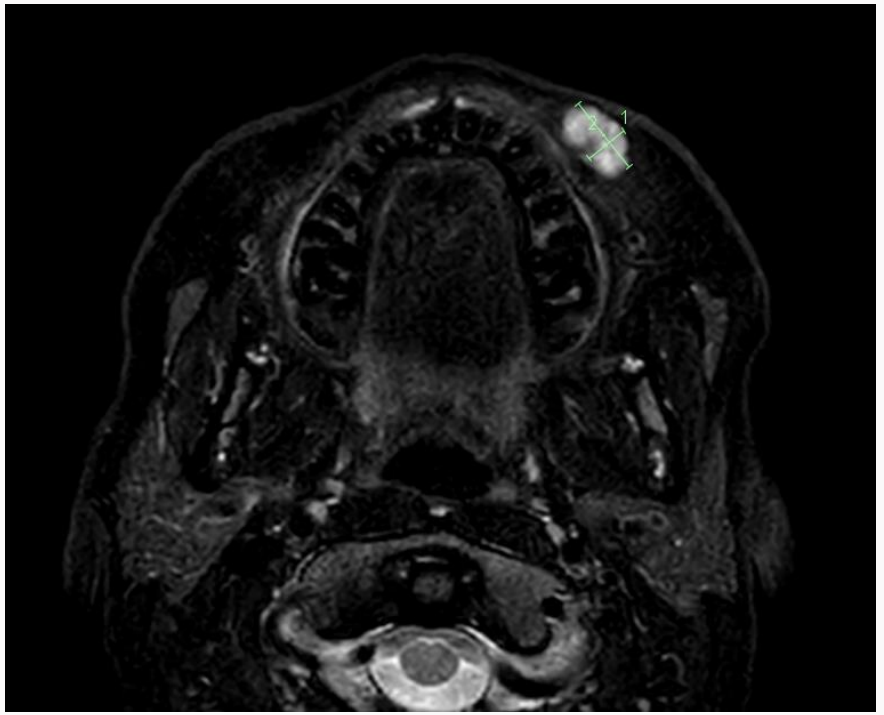
NO disruptions detected in:

- EWSR1
- FUS
- SS18

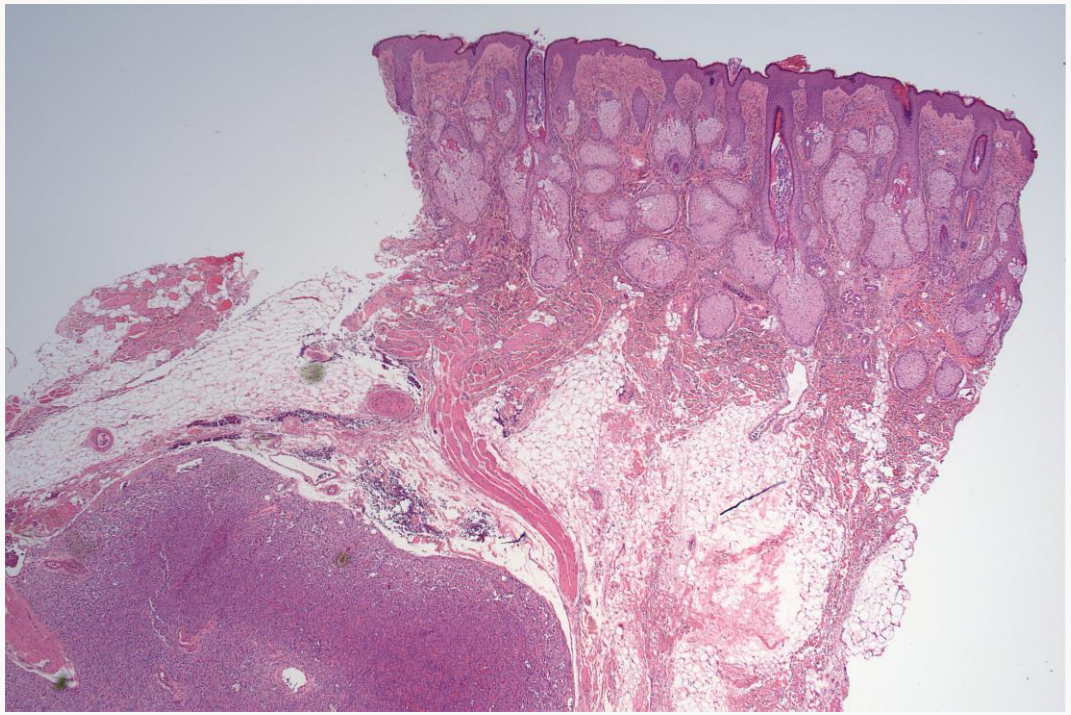
# Case 2

- 23-year-old female
- Subcutaneous left cheek lump in the nasolabial region
- Ultrasound: highly vascular lobulated hypoechoic subcutaneous mass ?AVM
- MRI: 16mm well-circumscribed markedly hypervascular subcutaneous lesion in the left cheek. No large feeding vessels seen.

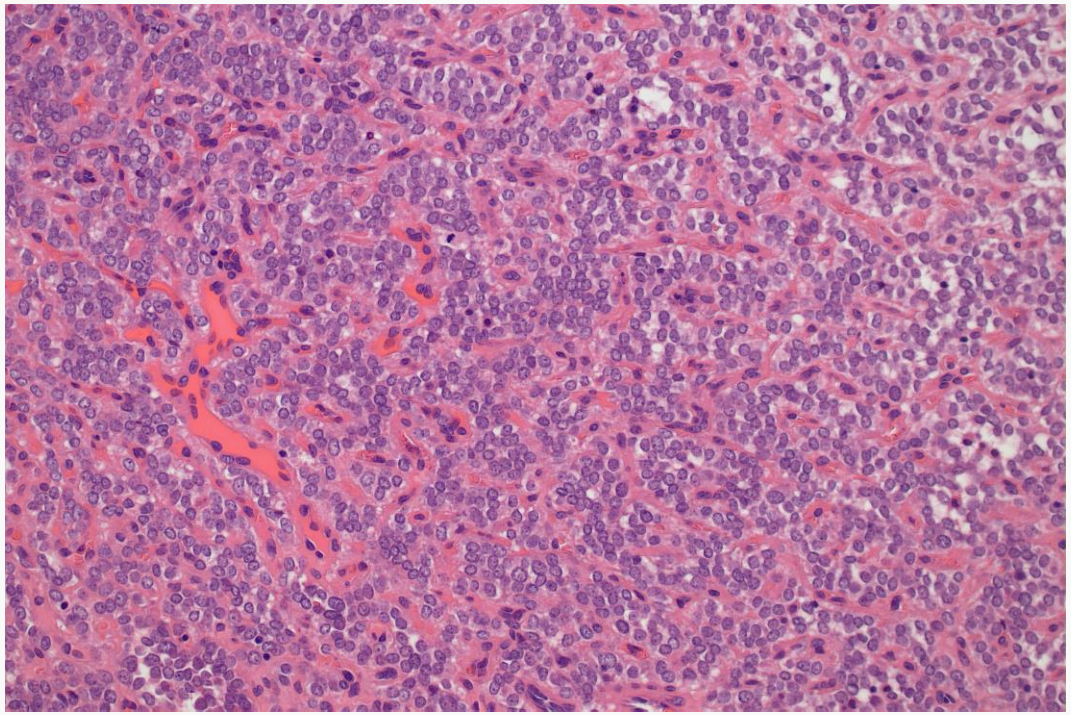
# Case 2: Left cheek lump, imaging



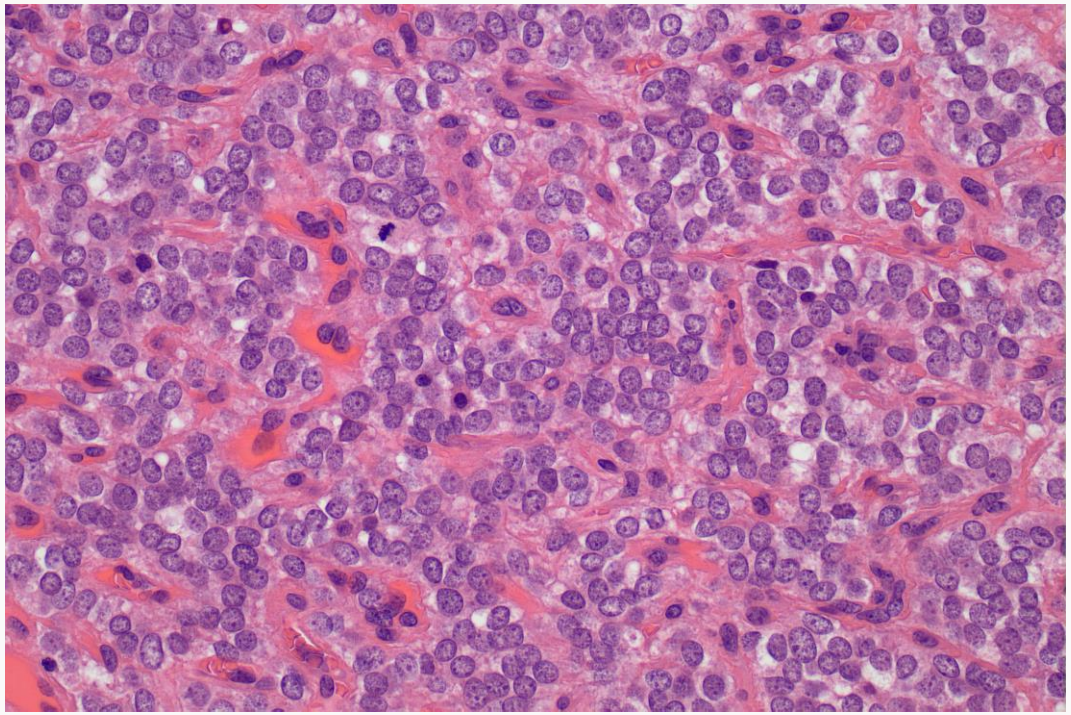
# Case 2: Left cheek lump, HE



# Case 2: Left cheek lump, HE



# Case 2: Left cheek lump, HE



# Case 2: Diagnosis?

- Pericytoma
- Paraganglioma
- NET
- Solitary fibrous tumour
- GIST

# Case 2: 2020 Left cheek lump, IHC

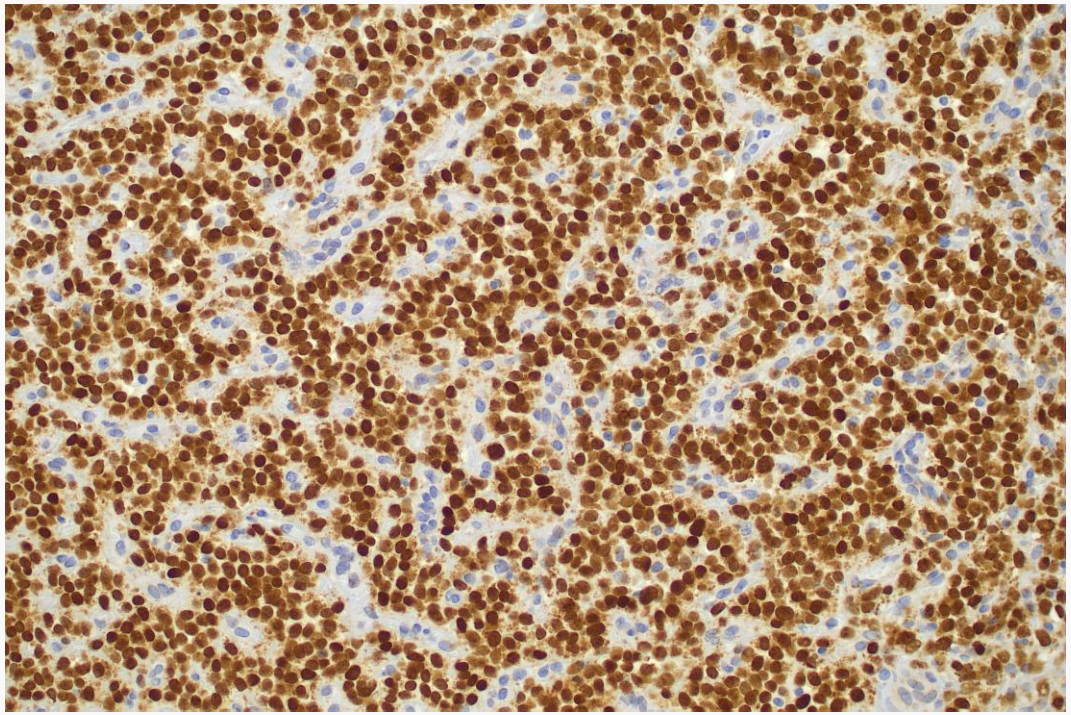
## Positive

- CD34
- STAT6

## Negative

- Cytokeratins
- CD31, ERG
- SMA
- SOX10
- S100
- CD117
- GFAP
- Chromogranin, synaptophysin

# Case 2: 2020 Left cheek lump, STAT 6 IHC



# Case 2: Left cheek lump, FISH

EWSR1 disruption not detected

SS18 disruption not detected

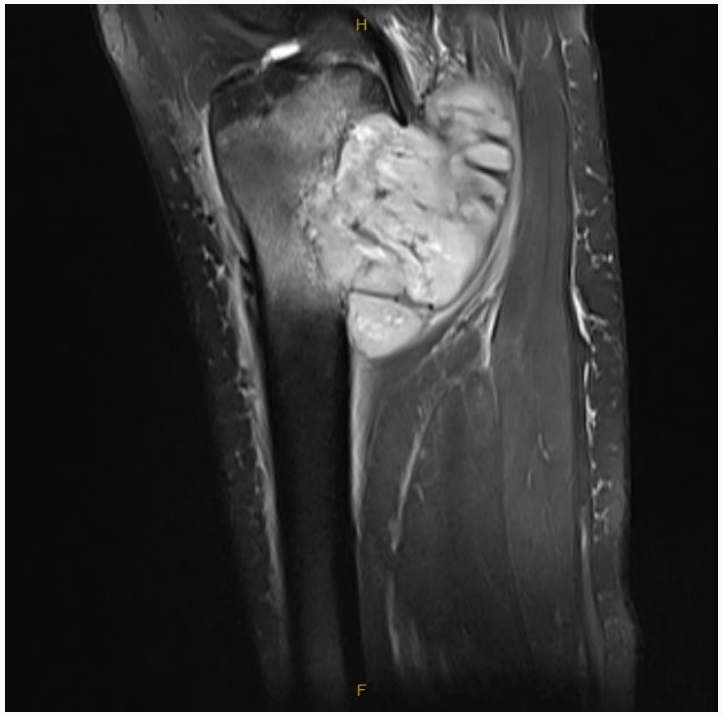
FUS disruption not detected

CIC disruption not detected

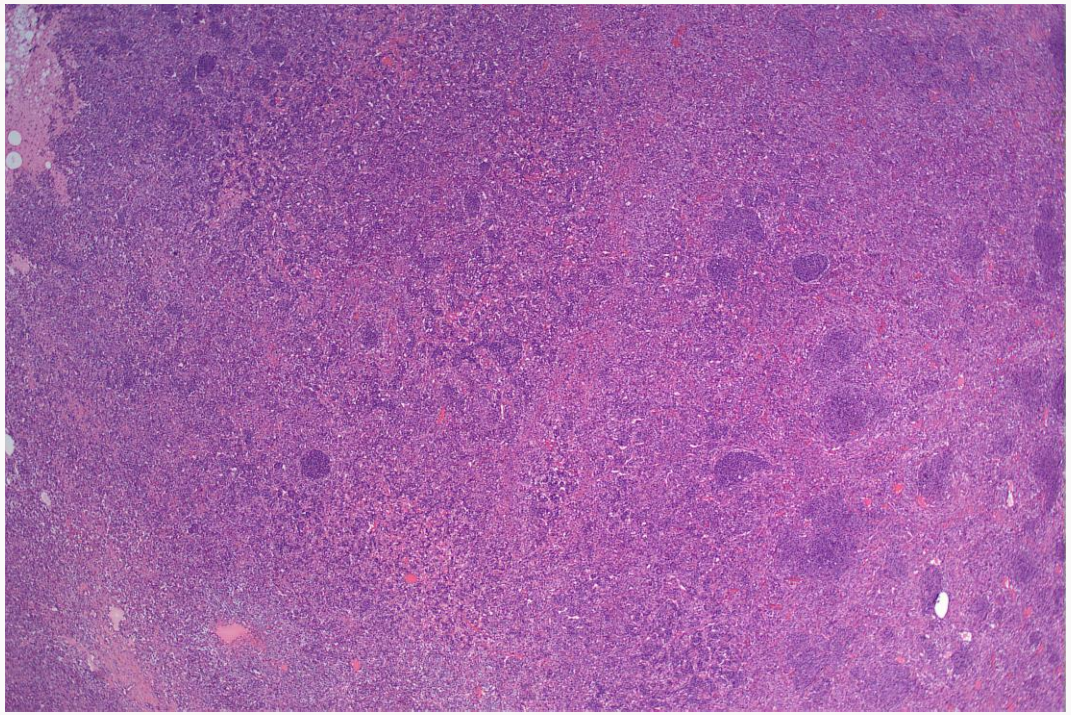
# Case 3: Left knee mass

- 25-year-old female
- Medial knee pain with tenderness and swelling

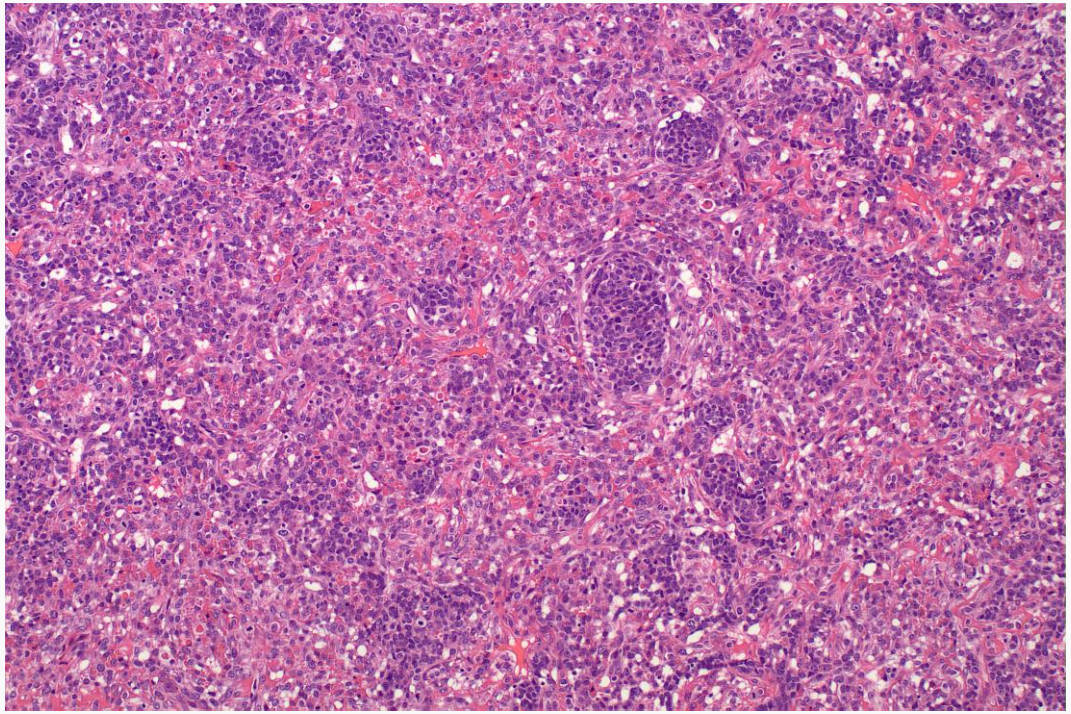
# Case 3: Left knee, MRI

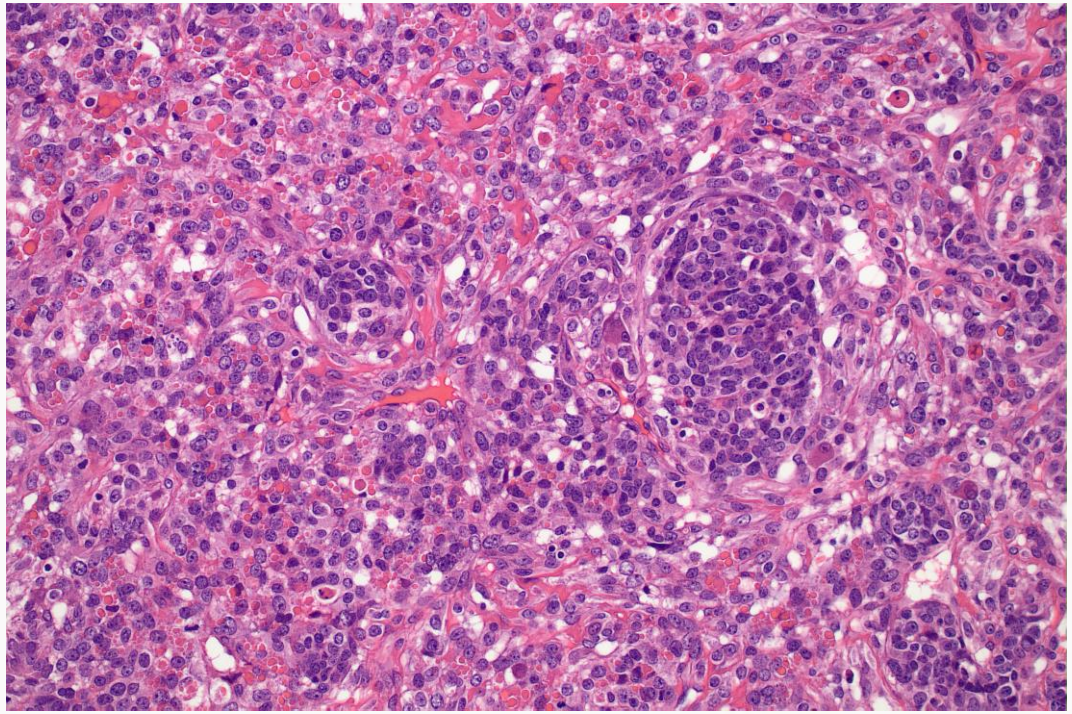


# Case 3: Left knee open incisional biopsy, HE

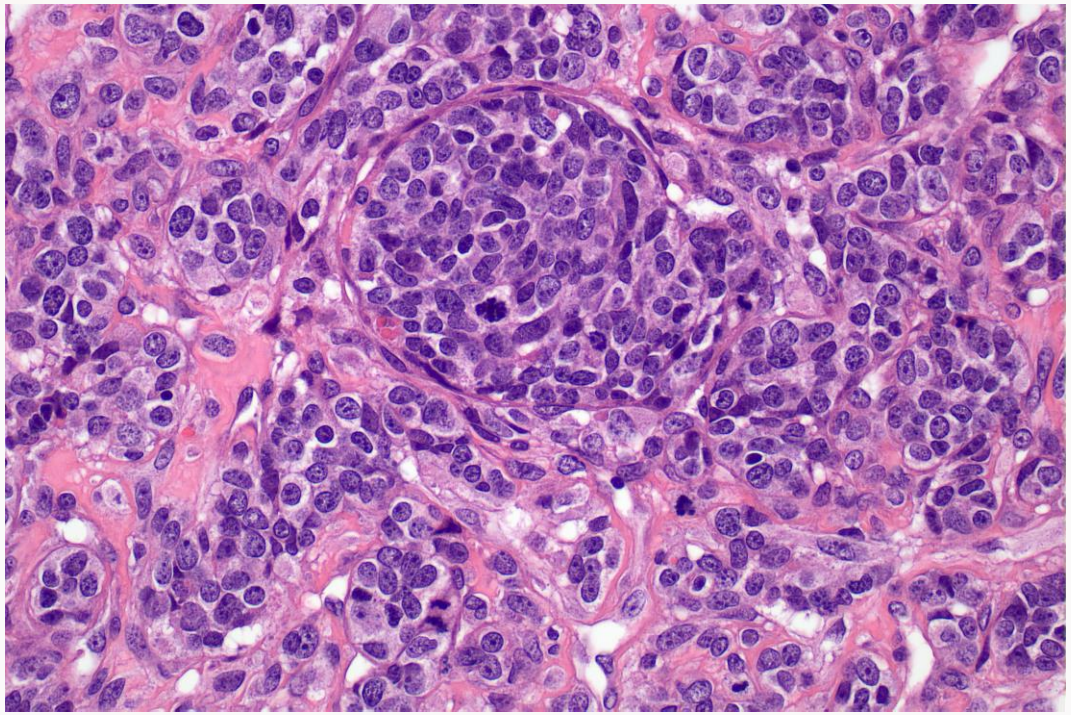


# Case 3: Left knee open incisional biopsy, HE





# Case 3: Left knee open incisional biopsy, HE



# Case 3: Diagnosis?

- Ewing sarcoma
- Osteosarcoma
- Mesenchymal chondrosarcoma
- Alveolar RMS
- Biphasic synovial sarcoma
- PEComa
- Myoepithelioma

# Case 3: Left knee, IHC

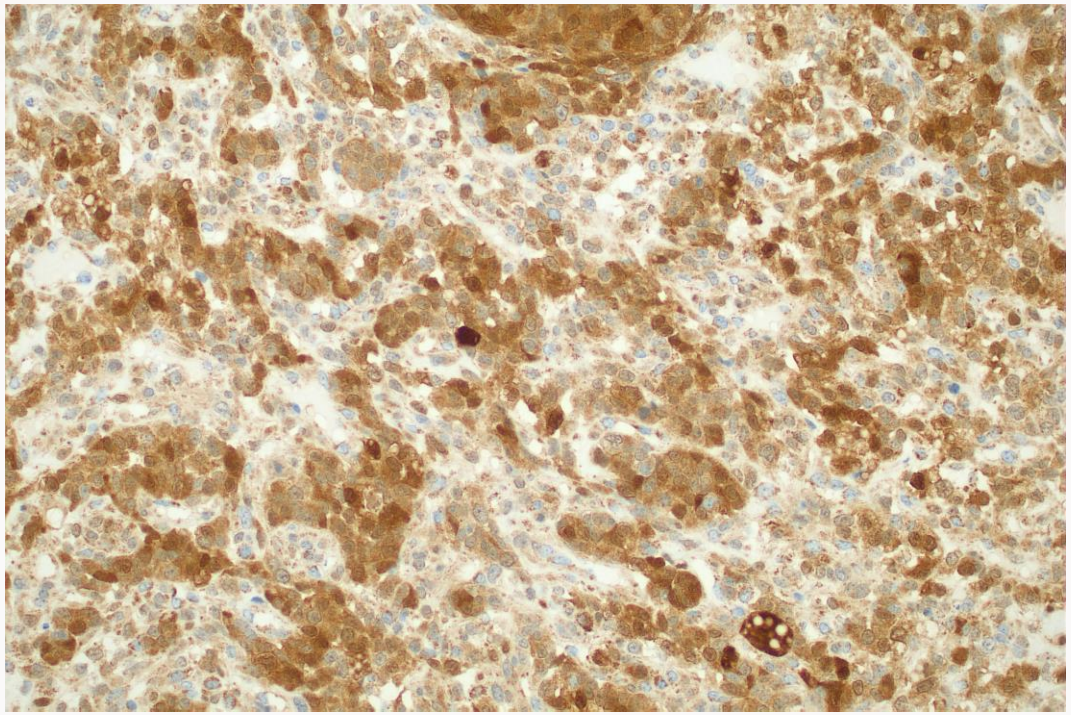
## Positive

- CD99 (patchy, membranous)
- Fli 1 (variable intensity)
- SATB2
- NKX3.1
- STAT6

## Negative

- Cytokeratins
- S100
- Desmin
- SOX10
- Myogenin and MyoD1
- CD34
- ERG
- WT1

# Case 3: Left knee open incisional biopsy, STAT6



# Case 3: Left knee, FISH

MDM2 amplification DETECTED

EWSR1 disruption not detected

NCOA2 disruption not detected

SS18 disruption not detected

# What is the diagnosis (or diagnoses)?

- Morphological similarities between all 3 cases
- Immunophenotypic variability
- Variable FISH findings

# Literature review

**A Distinct Malignant Epithelioid Neoplasm with *GLI1* Gene Rearrangements, Frequent S100 Protein Expression and Metastatic Potential: Expanding the Spectrum of Pathologic Entities with *ACTB1/MALAT1/PTCH1-GLI1* Fusions**

Cristina R Antonescu[1], Narasimhan P Agaram[1], Yun-Shao Sung[1], Lei Zhang[1], David Swanson[2], and Brendan C. Dickson[2]

**GLI1-Amplifications Expands the Spectrum of Soft Tissue Neoplasms Defined by *GLI1* Gene Fusions**

Narasimhan P. Agaram[1], Lei Zhang[1], Sung Yun-Shao[1], Samuel Singer[2], Todd Stevens[3], Carlos N. Prieto-Granada[3], Justin A. Bishop[4], Benjamin A. Wood[5], David Swanson[6], Brendan C. Dickson[6], Cristina R. Antonescu[1]

**GLI1-Altered Soft Tissue Tumors of the Head and Neck: Frequent Oropharyngeal Involvement, p16 Immunoreactivity, and Detectable Alterations by *DDIT3* Break Apart FISH**

Doreen N. Palsgrove[1,8] · Lisa M. Rooper[2] · Todd M. Stevens[3] · Christina Shin[4] · Douglas D. Damm[5] · Jeffrey Gagan[1] · Julia A. Bridge[6] · Lester D. R. Thompson[7] · Prasad R. Koduru[1] · Justin A. Bishop[1]

Distinctive Nested Glomoid Neoplasm

*Clinicopathologic Analysis of 20 Cases of a Mesenchymal Neoplasm With Frequent GLI1 Alterations and Indolent Behavior*

*David J. Papke Jr, MD, PhD,* Brendan C. Dickson, MD, MSc,†‡ Andre M. Oliveira, MD, PhD,§ Lynette M. Sholl, MD,* and Christopher D.M. Fletcher, MD, FRCPath**

GLI1 Immunohistochemistry Distinguishes Mesenchymal Neoplasms With *GLI1* Alterations From Morphologic Mimics

*Paige H. Parrack, MD, Adrian Mariño-Enríquez, MD, PhD, Christopher D.M. Fletcher, MD, FRC.Path, Jason L. Hornick, MD, PhD, and David J. Papke Jr, MD, PhD*

# *GLI1*-altered mesenchymal tumours

- A group of neoplasms characterised by fusions or amplifications involving GLI1, having:
  - similar morphology
  - a variable immunophenotype

# *GLI1*-altered mesenchymal tumours

## Molecular pathology

- GLI1
  - Glioma-associated oncogene homologue 1
  - Location: 12q13.3
  - Transcription factor that plays a critical role in the Hedgehog signaling pathway
- Two mechanisms of alteration:
  - GLI1 fusions (2/3 of cases)
  - GLI1 amplifications (1/3 of cases)

# *GLI1*-altered mesenchymal tumours

## Molecular pathology

- GLI1 fusions:
  - Results in promoter swapping
  - Multiple identified fusion partners (ACTB, MALAT1, PTCH1, APOD, DERA, SYT, NCOR2, HNRNPA1, TXNIP, NEAT, PAMR1)
- GLI1 amplification
  - Co-amplified with nearby genes such as DDIT3 (12q13), CDK4 (12q14.1), MDM2 (12q15), STAT6 (12q13.3-14.1), HMGA2

# *GLI1*-altered mesenchymal tumours

## Clinical features

- Propensity to occur in  younger to middle aged adults
- No significant sex predilection
- Most soft tissue (deep and subcutaneous), rarely bone
- Diverse anatomic sites:
  - 1/3 head and neck
  - Extremities and trunk
  - Visceral

# *GLI1*-altered mesenchymal tumours

## Macroscopic features

- Circumscribed, nodular or multinodular
- Solid, solid and cystic
- Median size 4 cm

# *GLI1*-altered mesenchymal tumours

## Microscopic findings

- Relatively well-circumscribed, lobulated
- Nests separated by an arborising capillary network
- Monomorphic round epithelioid cells
- Vesicular chromatin
- Small central or inconspicuous nucleoli
- Moderate pale eosinophilic cytoplasm
- Variable mitotic rate (<1->30/10 hpf)
- Tumour necrosis uncommon

# *GLI1*-altered mesenchymal tumours

## Microscopic findings

- GLI1 amplified cases tend to be more cellular with more cytological atypia, including cases with clearly sarcomatous cytomorphology
- Described cytomorphology in GLI1 amplified cases include:
  - Spindle cell
  - Biphasic spindled and epithelioid
  - Rosette formation

# *GLI1*-altered mesenchymal tumours

## Immunohistochemistry = variable

- In GLI1 fusion cases S100 most consistent (~50% of all cases, focal or diffuse)
- Overall CD56 most consistently expressed
- Variable expression of EMA, cyclin D1, CD10, BCL-2, BCOR, and D2-40
- In GLI1 amplified cases STAT6 expression can be seen (a frequently co-amplified gene)
- SOX10 always negative

# *GLI1*-altered mesenchymal tumours

## Testing

- GLI1 IHC
  - 91% sensitivity
  - 98% specificity
  - Both fused and amplified tumours
  - Nuclear and cytoplasmic, OR just nuclear
- STAT6, CDK4 and MDM2 IHC expression as surrogates for GLI1 amplification

# *GLI1*-altered mesenchymal tumours

- GLI1 FISH (break apart or amplification)
- FISH for DDIT3, MDM2, CDK4, and HMGA2 amplification
  - GLI1 and DDIT3 are neighbouring genes (12q13.3 and 12q13) separated by only 50kb
  - Telomeric bacterial artificial chromosomes used for GLI1 also interrogate DDIT3
  - DDIT3 FISH can be used as a surrogates for GLI1 alterations
  - FISH for MDM2, CDK4 and HMGA2 can be used as a surrogate for GLI1 amplified cases as frequently co-amplified genes
    - CDK4 90% of cases
    - MDM2 80% of cases
    - HMGA2 5/5 cases tested

# *GLI1*-altered mesenchymal tumours

## Prognosis

- ~38% of patients develop locoregional recurrence or distant metastasis
- Sites of metastasis:
  - Lymph nodes
  - Lung
  - Distant soft tissues
  - Bone
  - Liver
  - Brain

# Back to our series…

# Case 1: Right thumb lesion

FISH testing*:

- **GLI1 gene fusion DETECTED**
- Break apart AND amplification of the telomeric portion of the gene
- None of the recognised partners tested (ACTB, MALAT1 or PTCH1) were abnormal

**= “Malignant epithelioid neoplasm with GLI1 fusion”**

*FISH testing performed at Memorial Sloan Kettering Cancer Centre courtesy of Prof. C Antonescu

# Case 2: Left cheek lump

GLI1 IHC*:

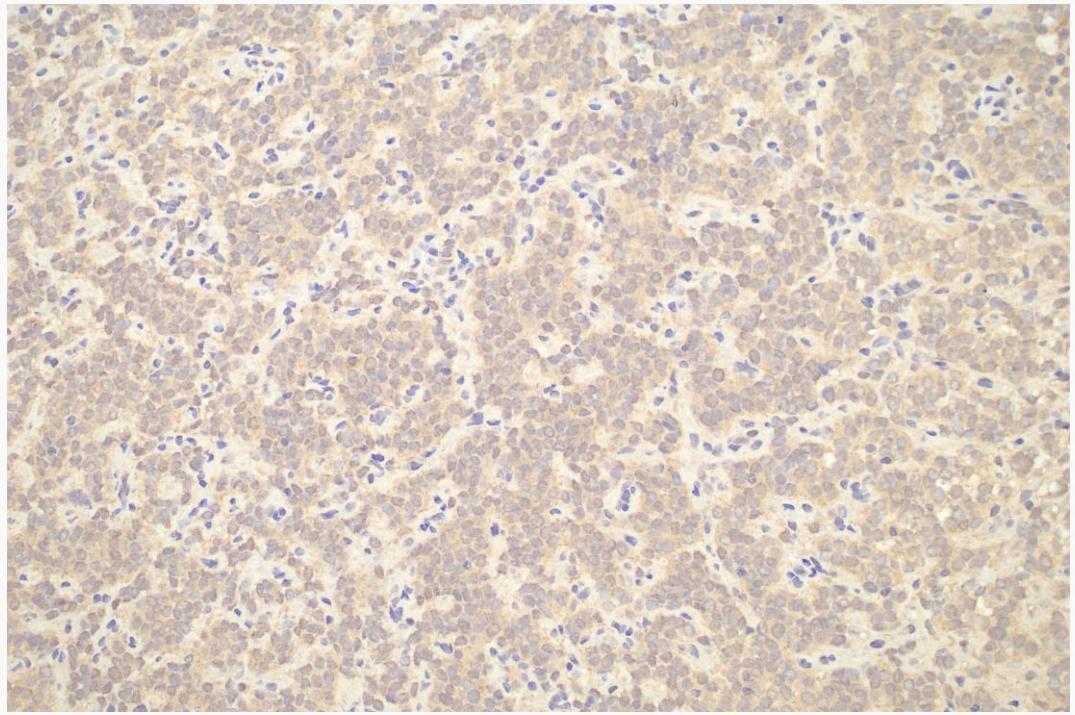
- NEGATIVE

FISH testing:

- DDIT3 disruption detected

**“Mesenchymal tumour with GLI1 alteration favoured”**

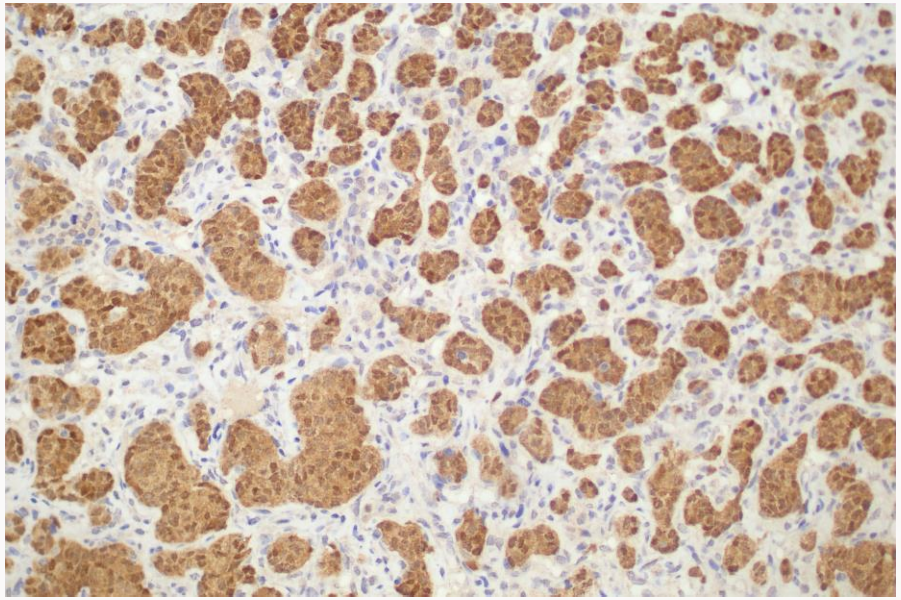
*performed at Royal North Shore Hospital courtesy of Prof. Anthony J Gill



# Case 3: Left knee mass

GLI1 IHC:

- POSITIVE



FISH testing:

- MDM2 amplification detected
- DDIT3 amplification detected

**“GLI1-altered epithelioid mesenchymal neoplasm”**

*performed at Royal North Shore Hospital courtesy of Prof. Anthony J Gill

# Future research

- Are GLI1 altered neoplasms with with nested glomoid morphology distinct from other GLI1 altered neoplasms? Do GLI1 alterations just infer a nested phenotype?
  - Plexiform fibromyxoma
  - Gastroblastoma
  - Pericytoma with t(7;12)
  - Liposarcomas
- Are GLI1 fused tumours different (phenotypically, prognostically) to GLI1 amplified tumours?
- Can atypical features be defined to predict metastatic potential?
- Can SHH pathway inhibitors be used in advanced cases?

# References


1. Agaram NP, Zhang L, Yun-Shao S, Singer S, Stevens T, Prieto-Granada CN, et al. GLI1-Amplifications Expands the Spectrum of Soft Tissue Neoplasms Defined by GLI1 Gene Fusions. Mod Pathol. 2019 Nov;32(11):1617–26.

2. Antonescu CR, Agaram NP, Sung YS, Zhang L, Swanson D, Dickson BC. A Distinct Malignant Epithelioid Neoplasm with GLI1 Gene Rearrangements, Frequent S100 Protein Expression and Metastatic Potential: Expanding the Spectrum of Pathologic Entities with ACTB1/MALAT1/PTCH1-GLI1 Fusions. Am J Surg Pathol. 2018 Apr;42(4):553–60.

3. Cloutier JM, Kerr DA. GLI1-Altered Mesenchymal Tumors. Surgical Pathology Clinics. 2024 Mar;17(1):13–24.

4. Jiahan L, Rongjun M, Weng LI, Lin Y, Qianming B, Zhou X, et al. GLI1-altered mesenchymal tumor: a clinicopathological and molecular analysis of ten additional cases of an emerging entity. Virchows Archiv. 2022 May;480(5):1087–99.

5. Kerr DA, Cloutier JM, Margolis M, Mata DA, Rodrigues Simoes NJ, Faquin WC, et al. *GLI1*-Altered Mesenchymal Tumors With *ACTB* or *PTCH1* Fusion: A Molecular and Clinicopathologic Analysis. Modern Pathology. 2024 Feb 1;37(2):100386.

6. Palsgrove DN, Rooper LM, Stevens TM, Shin C, Damm DD, Gagan J, et al. GLI1-Altered Soft Tissue Tumors of the Head and Neck: Frequent Oropharyngeal Involvement, p16 Immunoreactivity, and Detectable Alterations by DDIT3 Break Apart FISH. Head Neck Pathol. 2022 Aug 6;16(4):1146–56.

7. Papke DJ, Dickson BC, Oliveira AM, Sholl LM, Fletcher CDM. Distinctive Nested Glomoid Neoplasm: Clinicopathologic Analysis of 20 Cases of a Mesenchymal Neoplasm With Frequent GLI1 Alterations and Indolent Behavior. American Journal of Surgical Pathology. 2023 Jan;47(1):12–24.

8. Parrack PH, Mariño-Enríquez A, Fletcher CDM, Hornick JL, Papke DJ. GLI1 Immunohistochemistry Distinguishes Mesenchymal Neoplasms With GLI1 Alterations From Morphologic Mimics. American Journal of Surgical Pathology. 2023 Apr;47(4):453–60.

9. Zhong H, Xu C, Chen X, Guo X, Yang S. GLI1-altered epithelioid soft tissue tumor: A newly described entity with a predilection for the tongue. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2022 Jul;134(1):e14–22.

# Acknowledgements

Dr Daniel Wong

A/Prof Peter Robbins

Dr Shona Hendry

A/Prof Benjamin Wood

Dr Chris Van Vliet

Dr Ben Allanson and the Diagnostic Genomics Department at PathWest

A/Prof Benhur Amanuel and the Department of Molecular Pathology at PathWest

Prof. Anthony J Gill

Prof. C Antonescu

# Thank you

Contact: Victoria.VanWinden@health.wa.gov.au