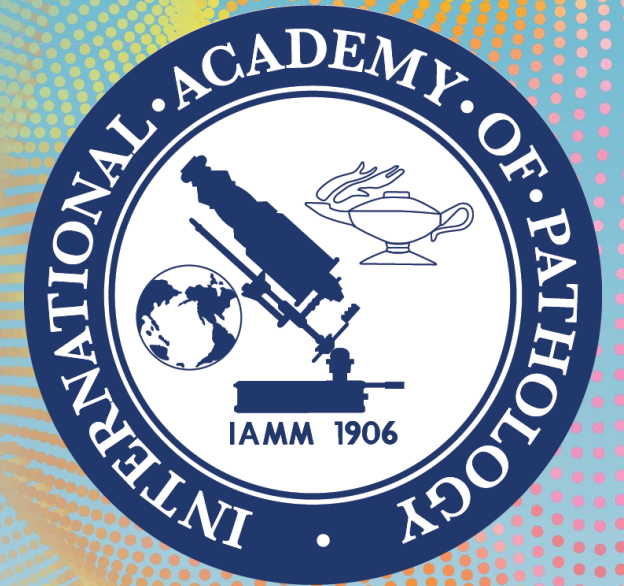


Paediatric primary non-Langerhans cell histiocytoses of the CNS with associated molecular alterations: A review of three cases

Amber Louw

PathWest Laboratory Medicine



Presentation prepared by : Dr Amber Louw and Dr JM Dyke (PathWest Neuropathology)



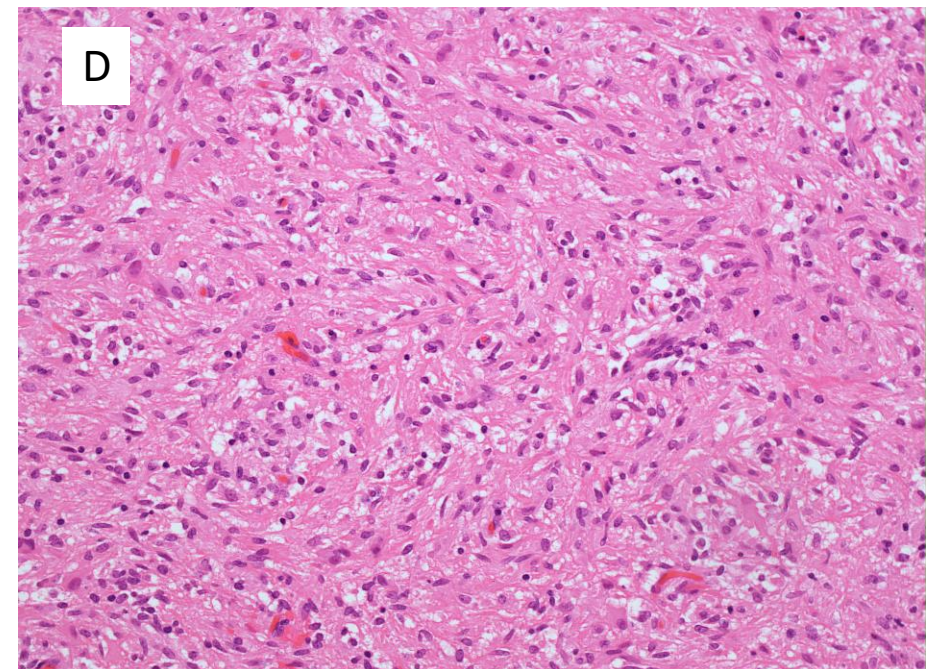
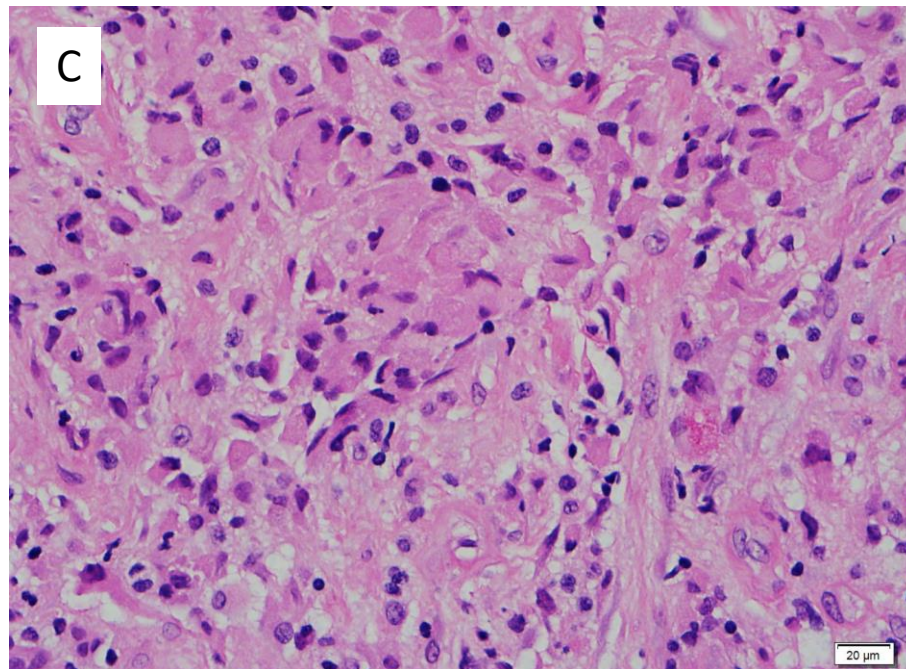
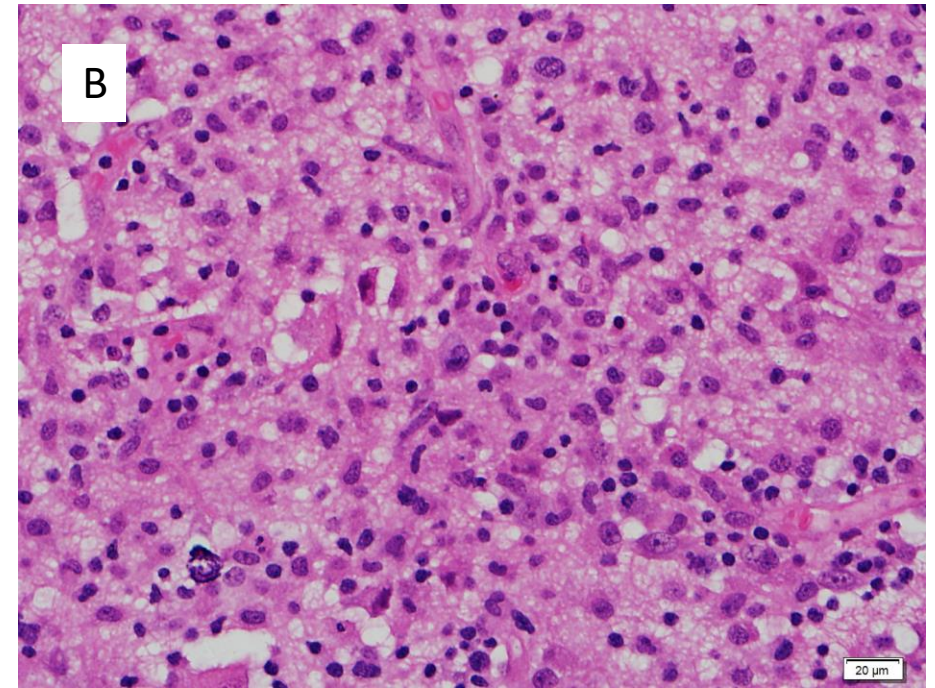
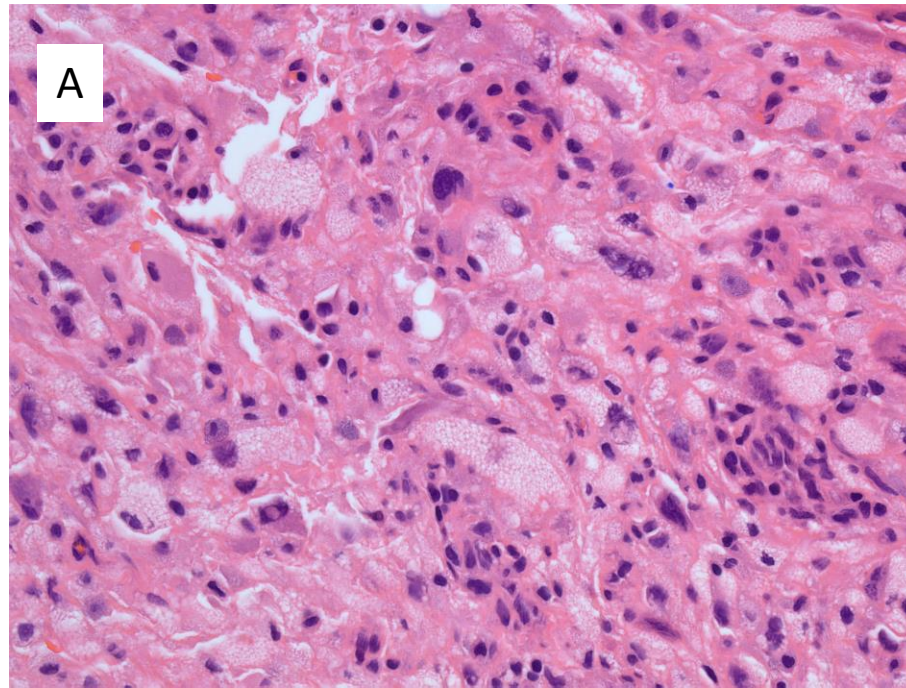
The 48th Annual Scientific Meeting *of the*

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Disclosure of Relevant Financial Relationships

No relevant financial relationships

**Which of these
is the odd-one
out?**



Contents

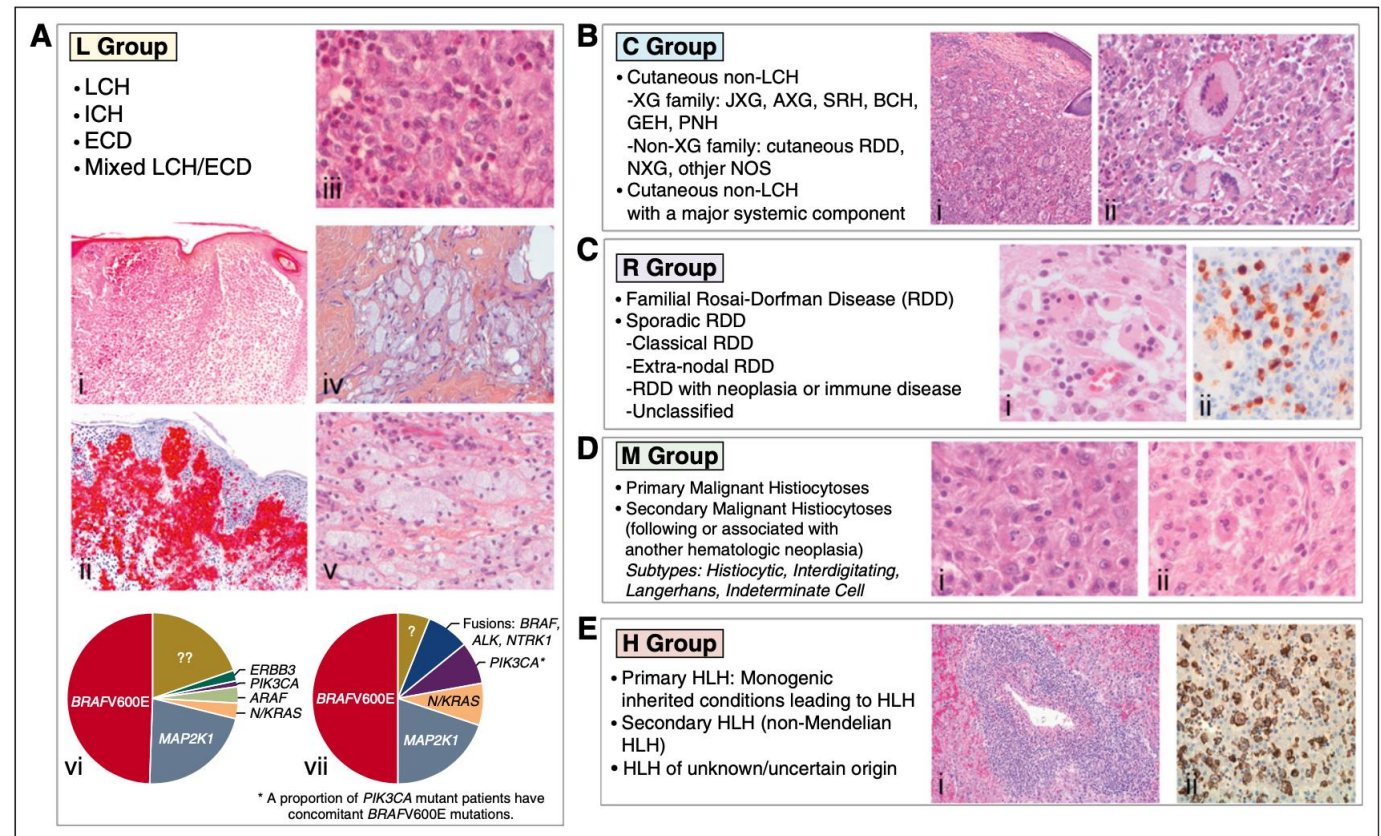
- Introduction
- Case 1
- Case 2
- Case 3
- Conclusion

Introduction

- Heterogenous and complex group of lesions
- Derived from monocyte phagocyte system
 - >100 entities described
- Classification
 - Broadly into Langerhans cell histiocytosis (LCH) or non-LCH disorders
 - Histiocyte Society classification
 - Clinical, pathological and molecular features
 - WHO Haematolymphoid Tumours
 - Cell lineage

Introduction

- Histiocyte Society classification
 - Clinical, pathological and molecular features



Introduction

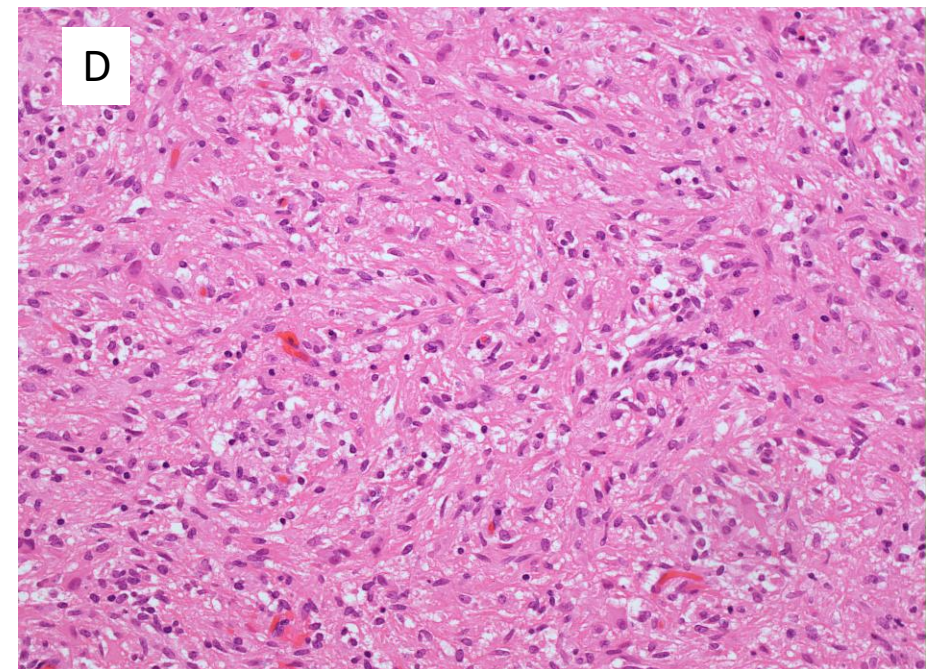
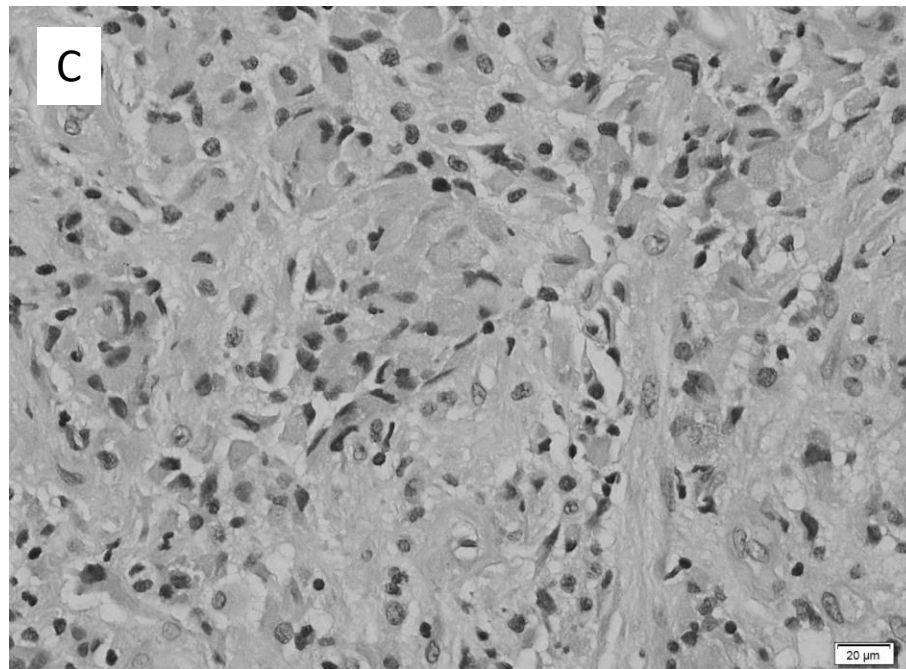
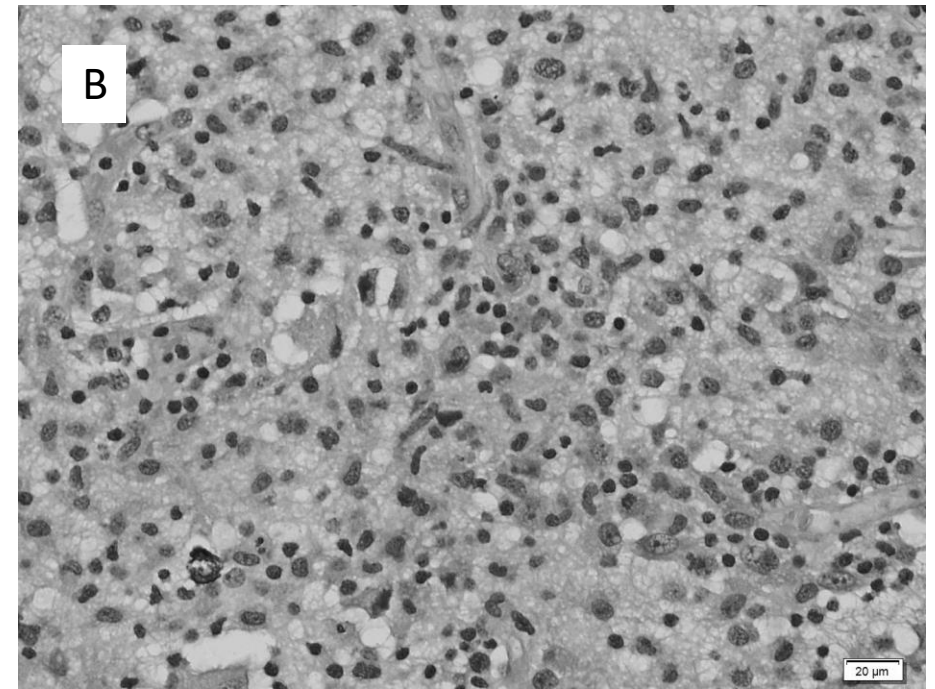
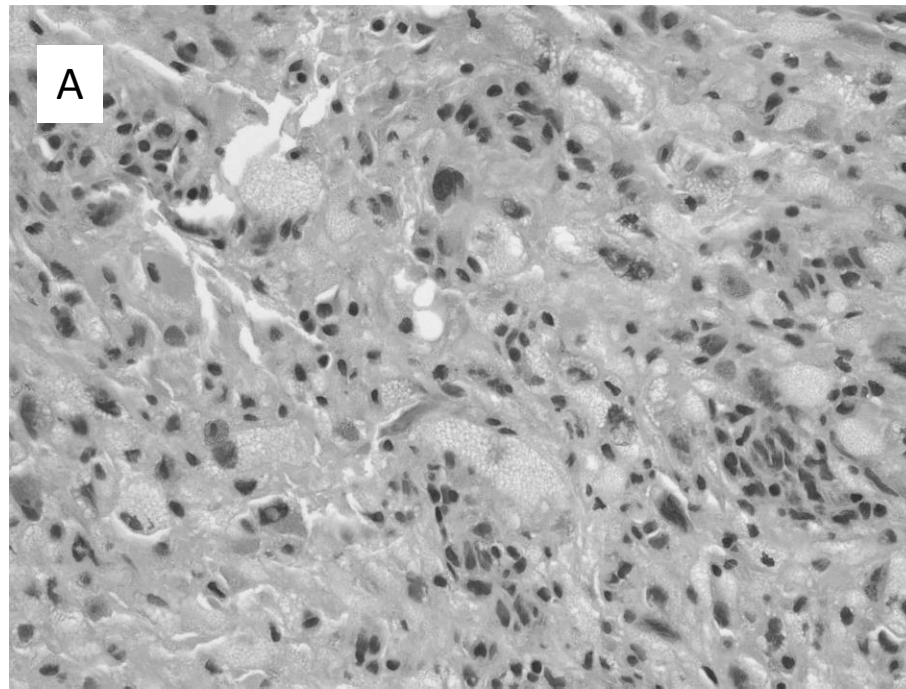
- WHO Haematolymphoid Tumours
 - Cell lineage

Cell lineage	Disorders
Plasmacytoid dendritic cell neoplasms	Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms	Langerhans cell neoplasms <ul style="list-style-type: none">- Langerhans cell histiocytosis- Langerhans cell sarcoma Other dendritic cell neoplasms <ul style="list-style-type: none">- Indeterminate dendritic cell tumour- Interdigitating dendritic cell sarcoma
Histiocyte/macrophage neoplasms	Histiocytic neoplasms <ul style="list-style-type: none">- Juvenile xanthogranuloma- Erdheim-Chester disease- Rosai-Dorfman Disease- ALK-positive histiocytosis- Histiocytic sarcoma

Introduction

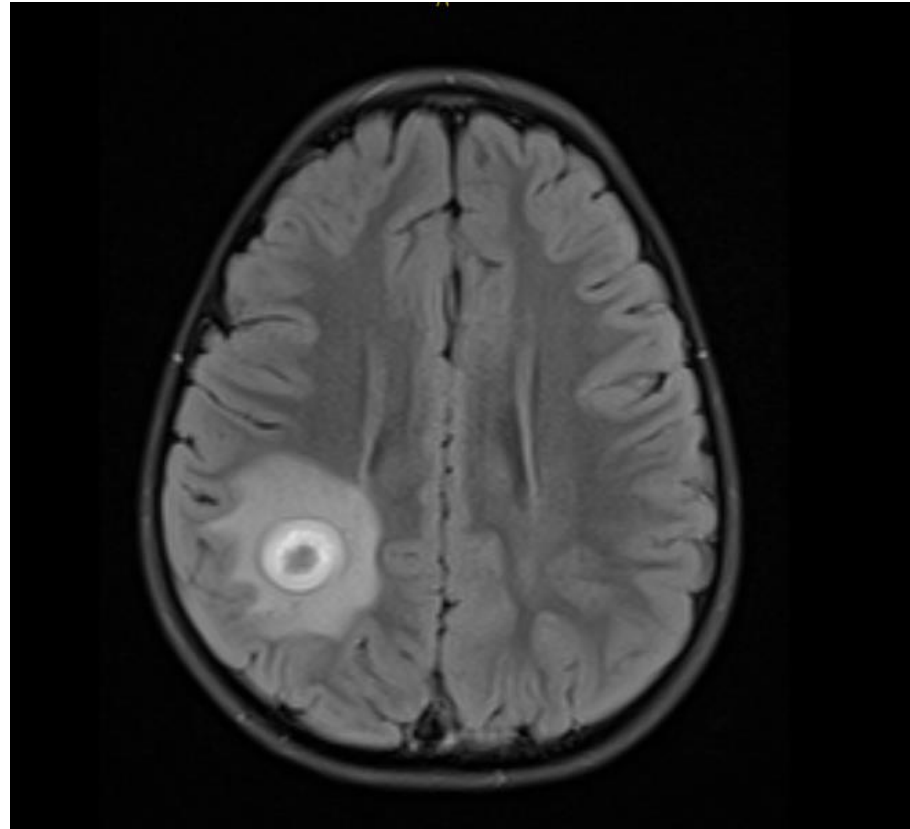
- Central nervous system (CNS) involvement can occur as part of systemic disease or as single organ/isolated disease
- Brain parenchyma and/or meninges
- Challenging diagnosis
 - Overlap between neoplastic and non-neoplastic disorders
- Activating mutations in MAPK/ERK pathway and *PIK3CA* and fusions involving *BRAF*, *NTRK1* and *ALK* identified in some histiocytoses

Case 1



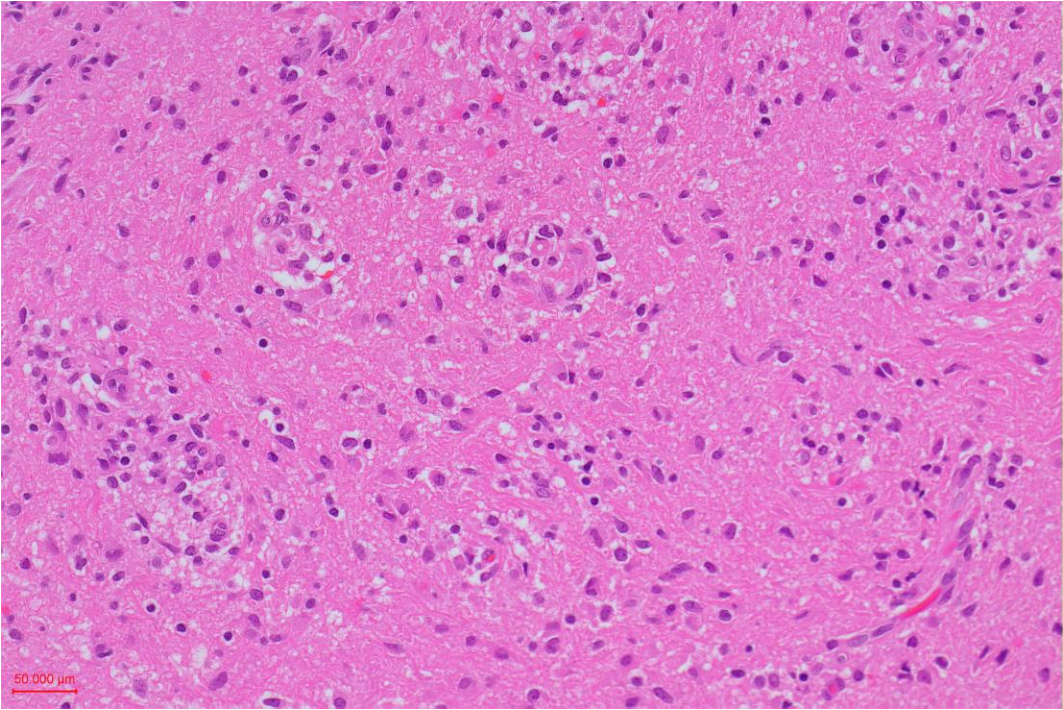
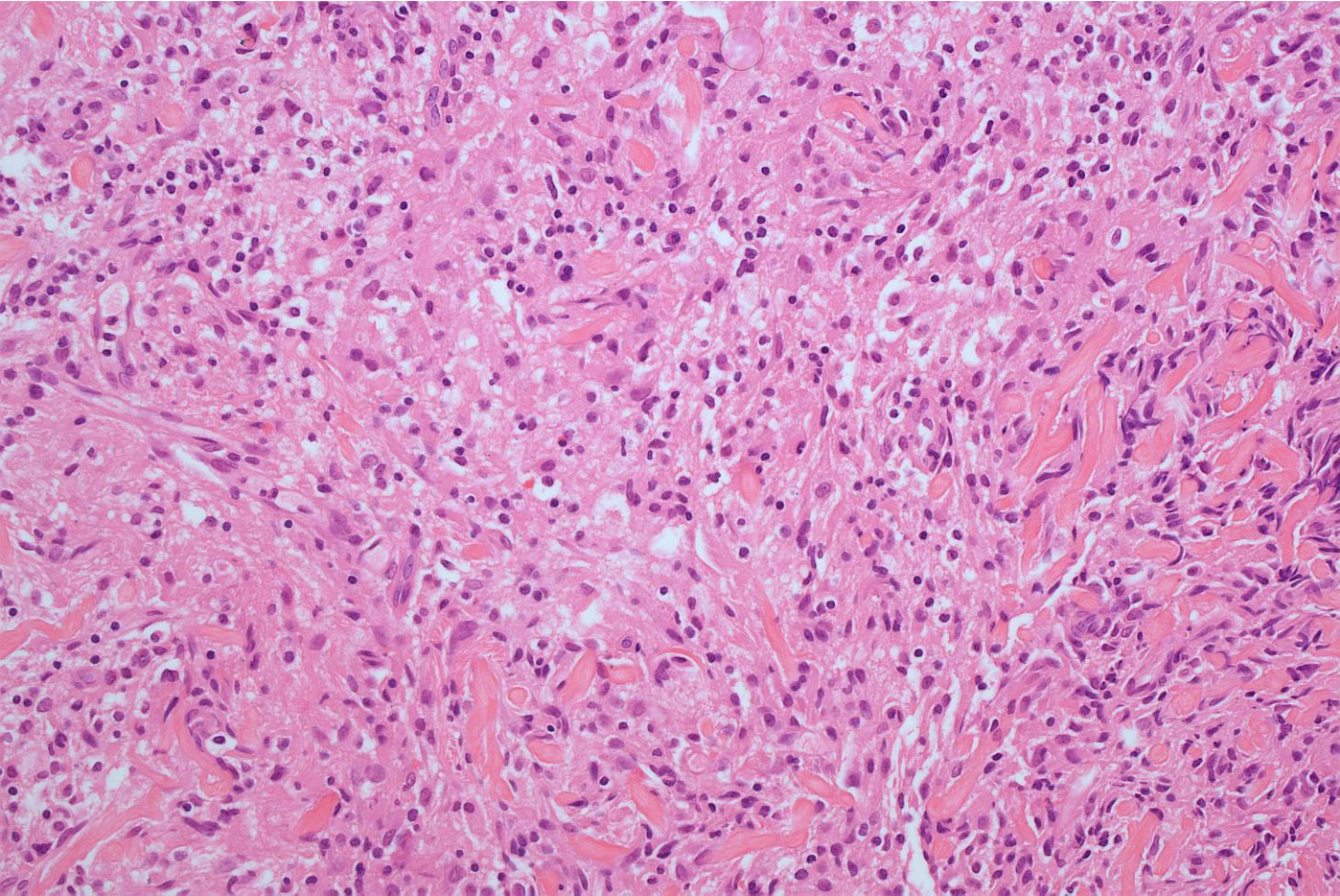
Case 1

- 4yo girl
- Generalised seizures
- MRI brain – 20mm thick walled enhancing lesion in right parietal lobe with marked surrounding T2/FLAIR high signal parenchymal abnormality extending into adjacent deep white matter



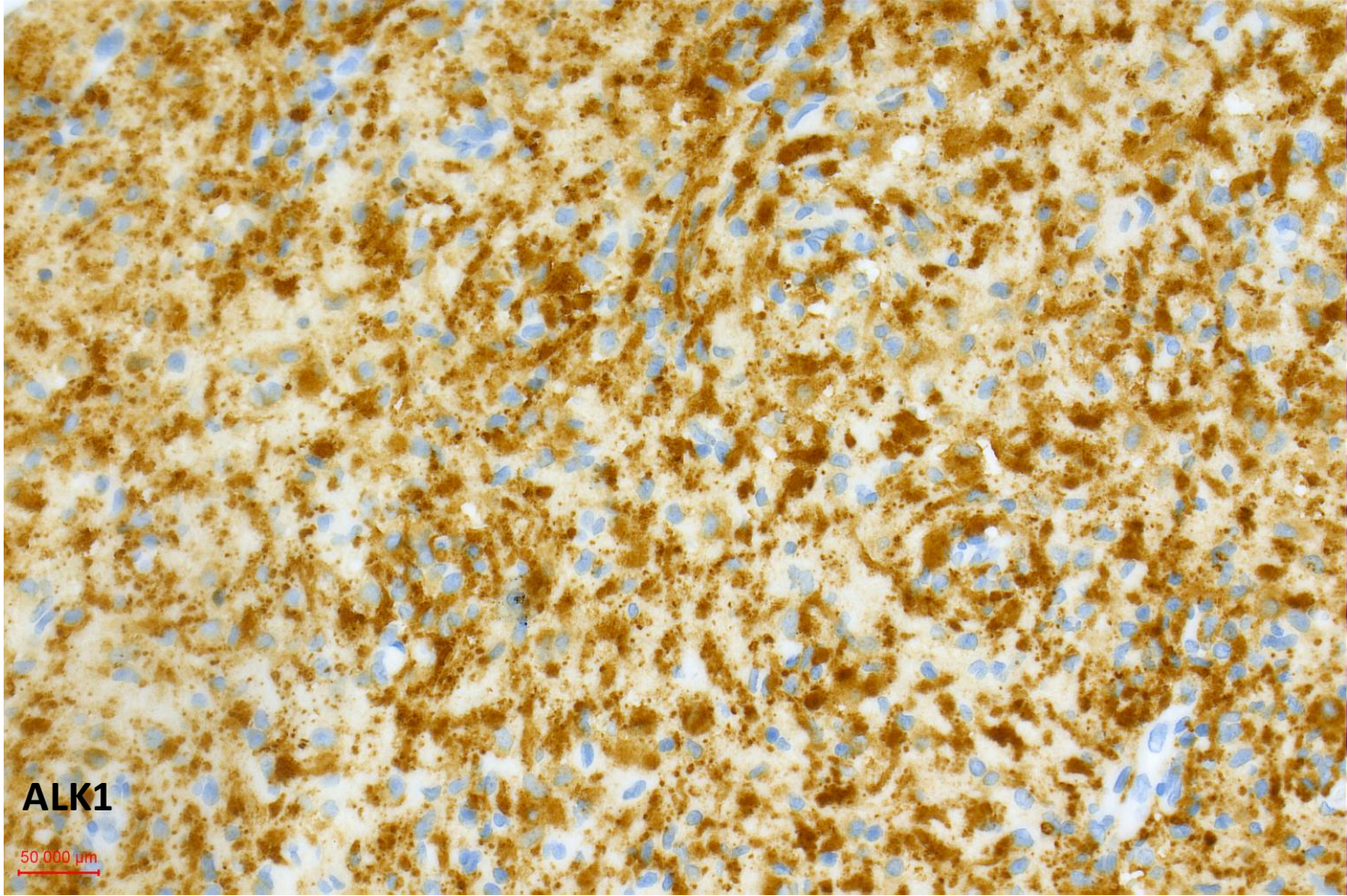
T2 FLAIR

Case 1



x200

Case 1



x200

Case 1

- *ALK1* disruption detected by:
 - Fluorescence in situ hybridisation (FISH) -
 - *ALK1* disruption at 2p23 in 47% of nuclei
 - Targeted NGS
 - TruSight Tumor 170 gene panel (Illumina, USA)
 - *ALK-KIF5B* fusion
 - No abnormalities in *TP53*, *BRAF*, *MAP2K1*, *PIK3CA* or *NRAS*

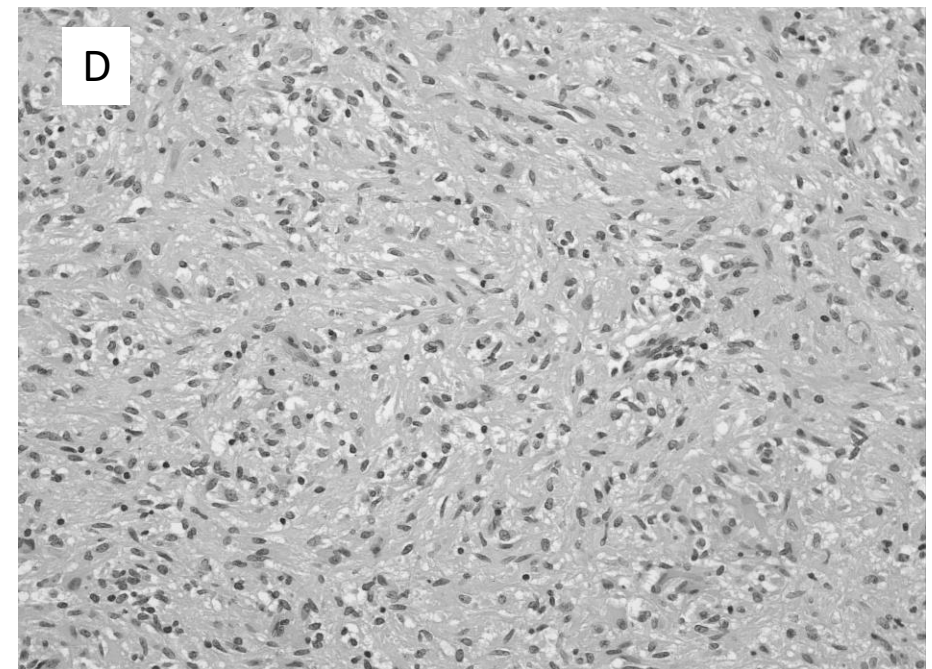
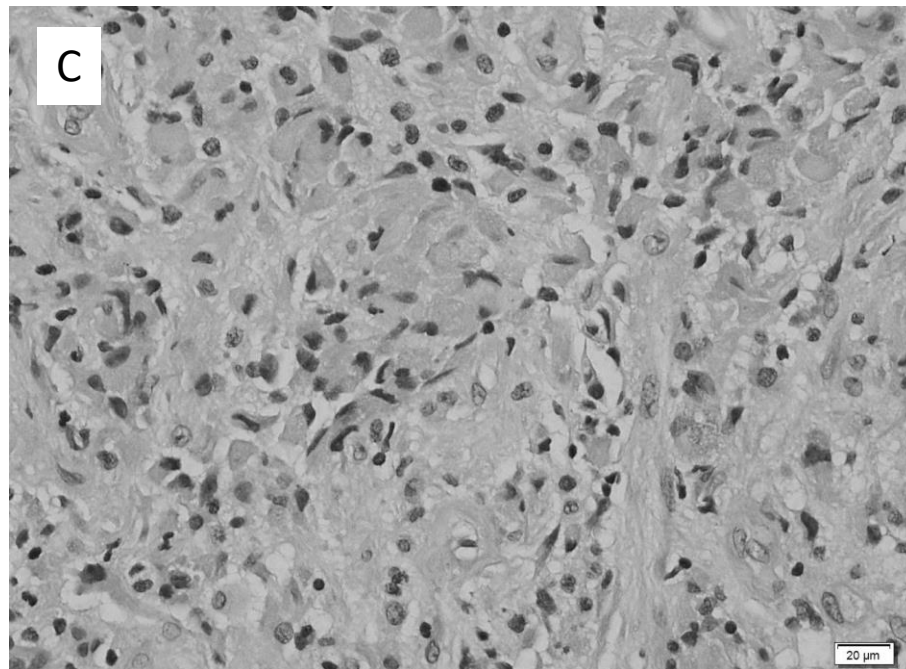
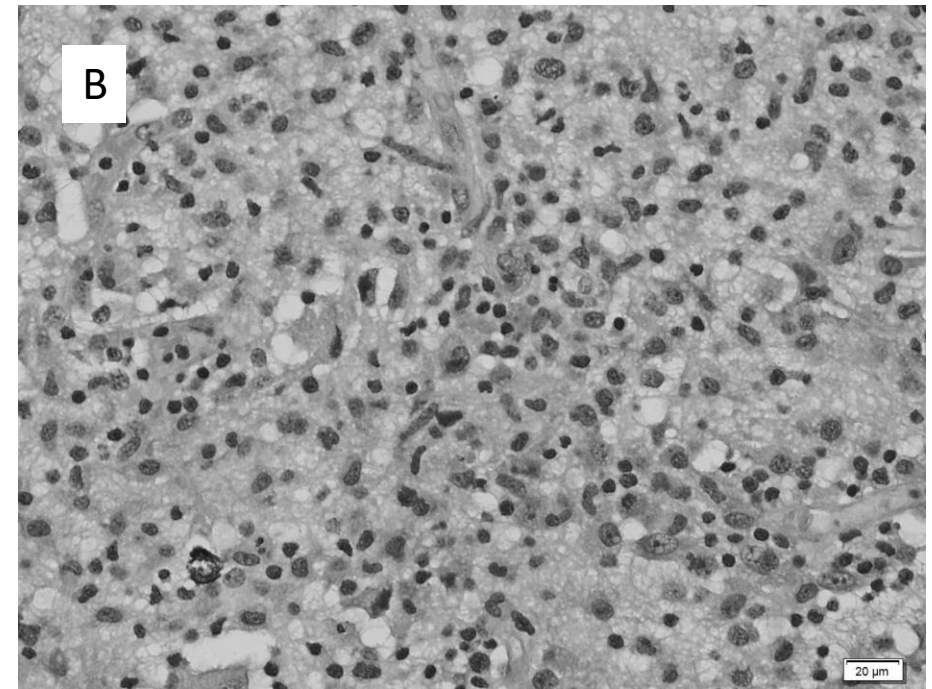
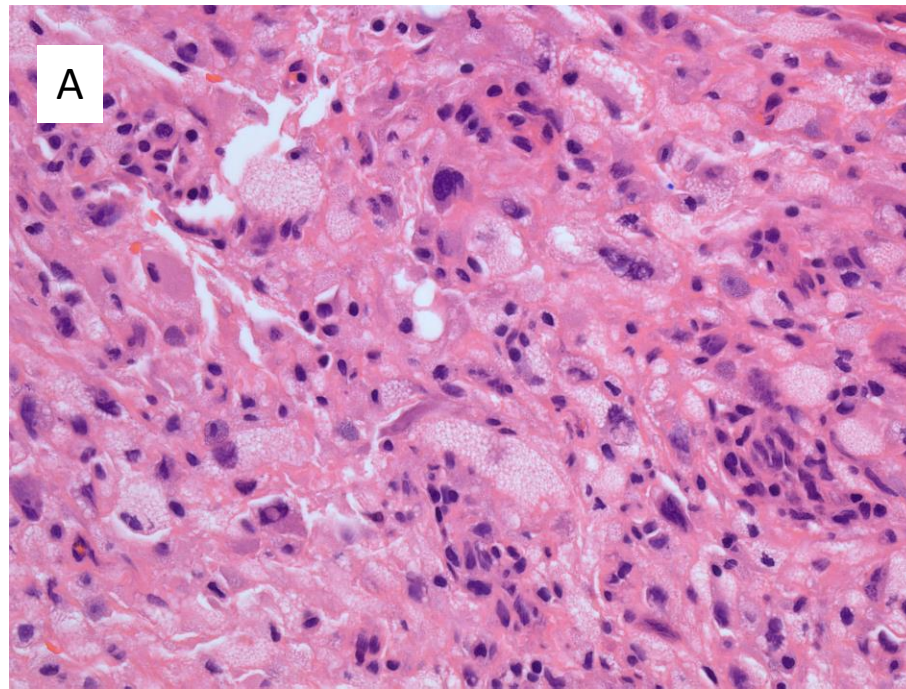
Case 1

- Diagnosis
 - Non-Langerhans cell histiocytosis with ALK-KIF5B fusion (ALK positive histiocytosis)
- Progress
 - GTR achieved at surgery; no adjuvant therapy.
 - No recurrent or metastatic disease at neuroimaging follow-up 36mths after resection.

ALK-positive histiocytosis

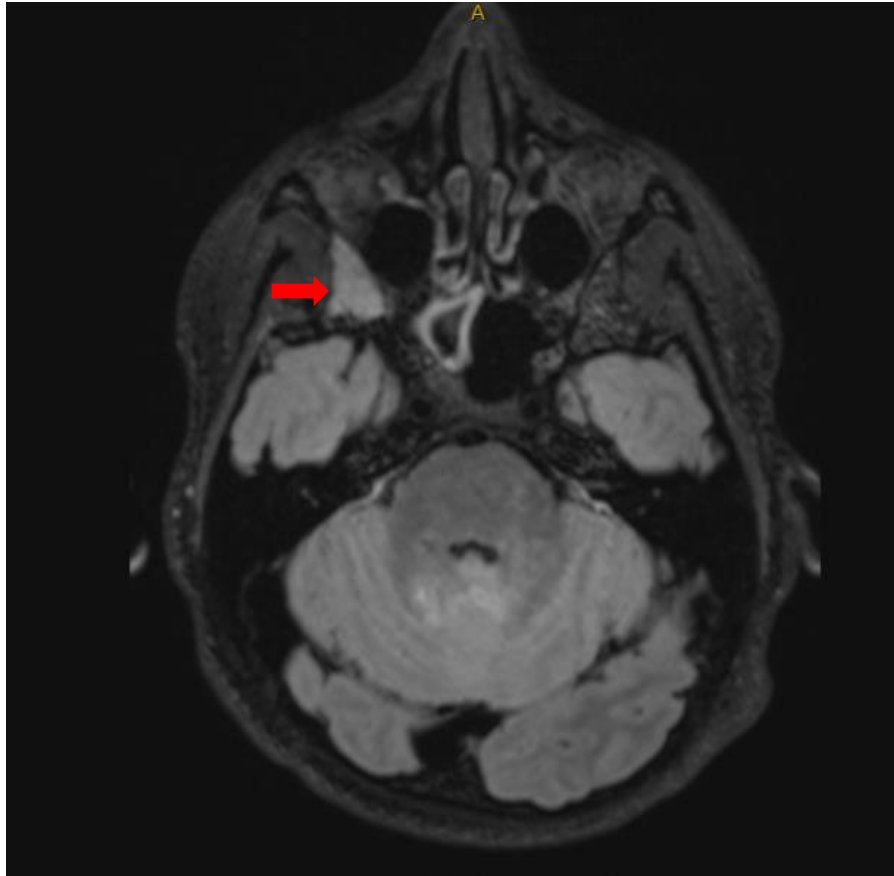
- Single or multisystem disorder
- ALK positive immunohistochemistry secondary to *ALK* translocations
– usually *ALK-KIF5B*
- Bland histiocytes – epithelioid, foamy or spindled
- Recent study has shown durable responses to ALK inhibition, including in those with CNS involvement

Case 2



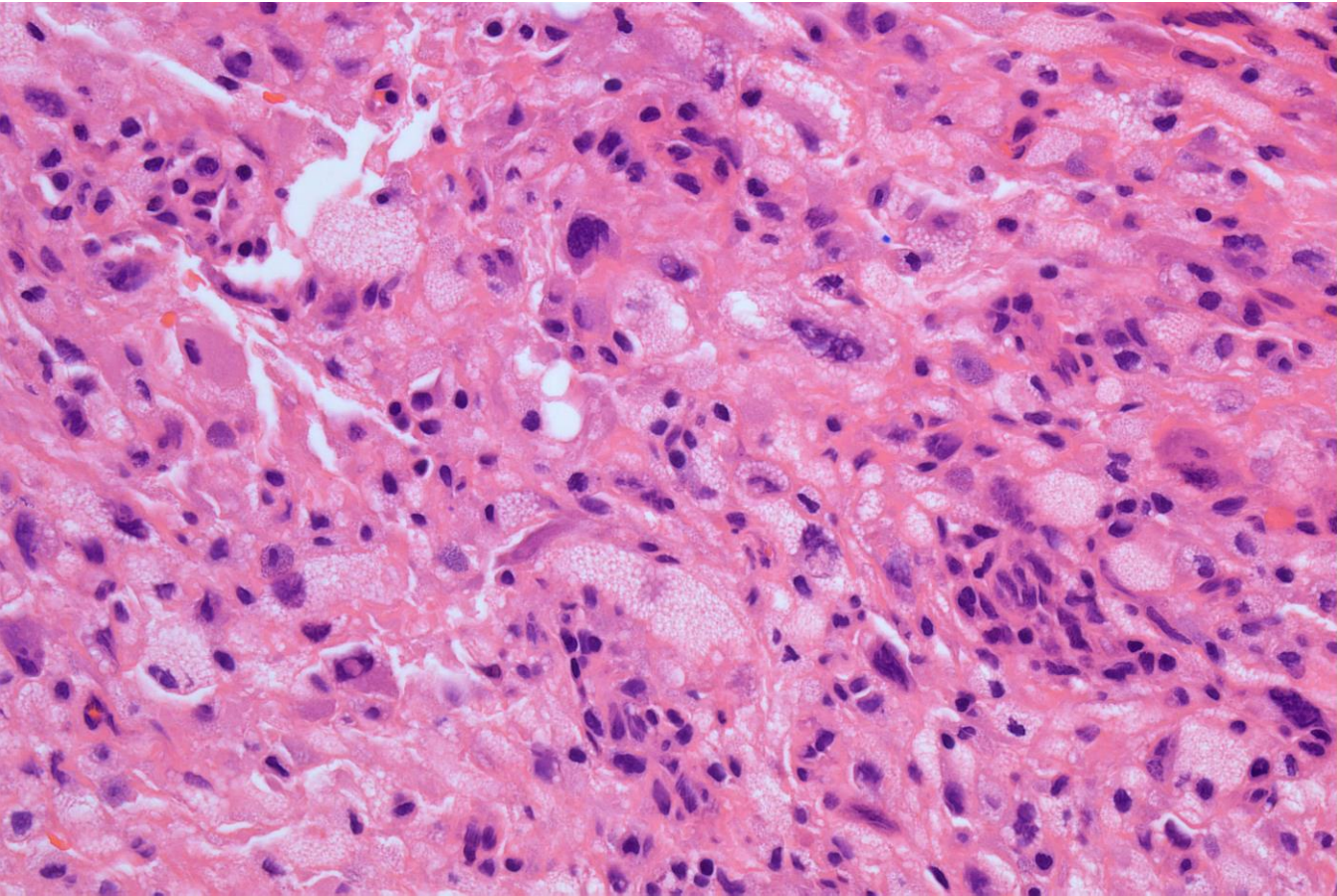
Case 2

- 16yo male
- Known NF1
- MRI brain - right greater sphenoid wing expansile T2 hyperintense lesion 24 x 16 x 22mm

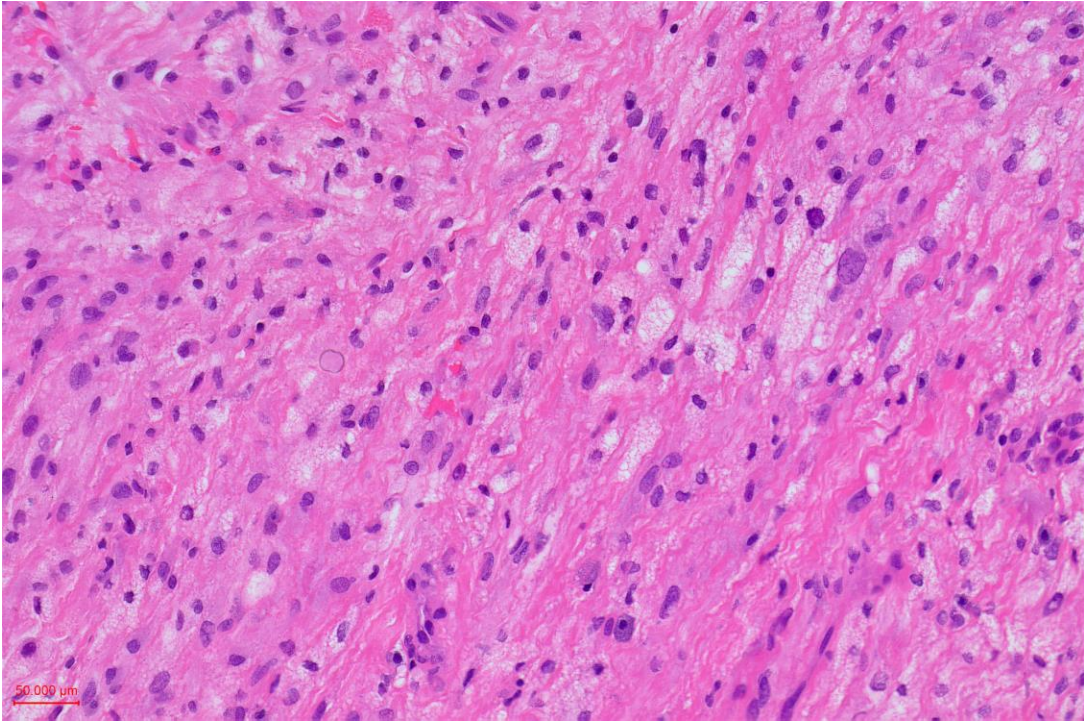


T2 FLAIR

Case 2

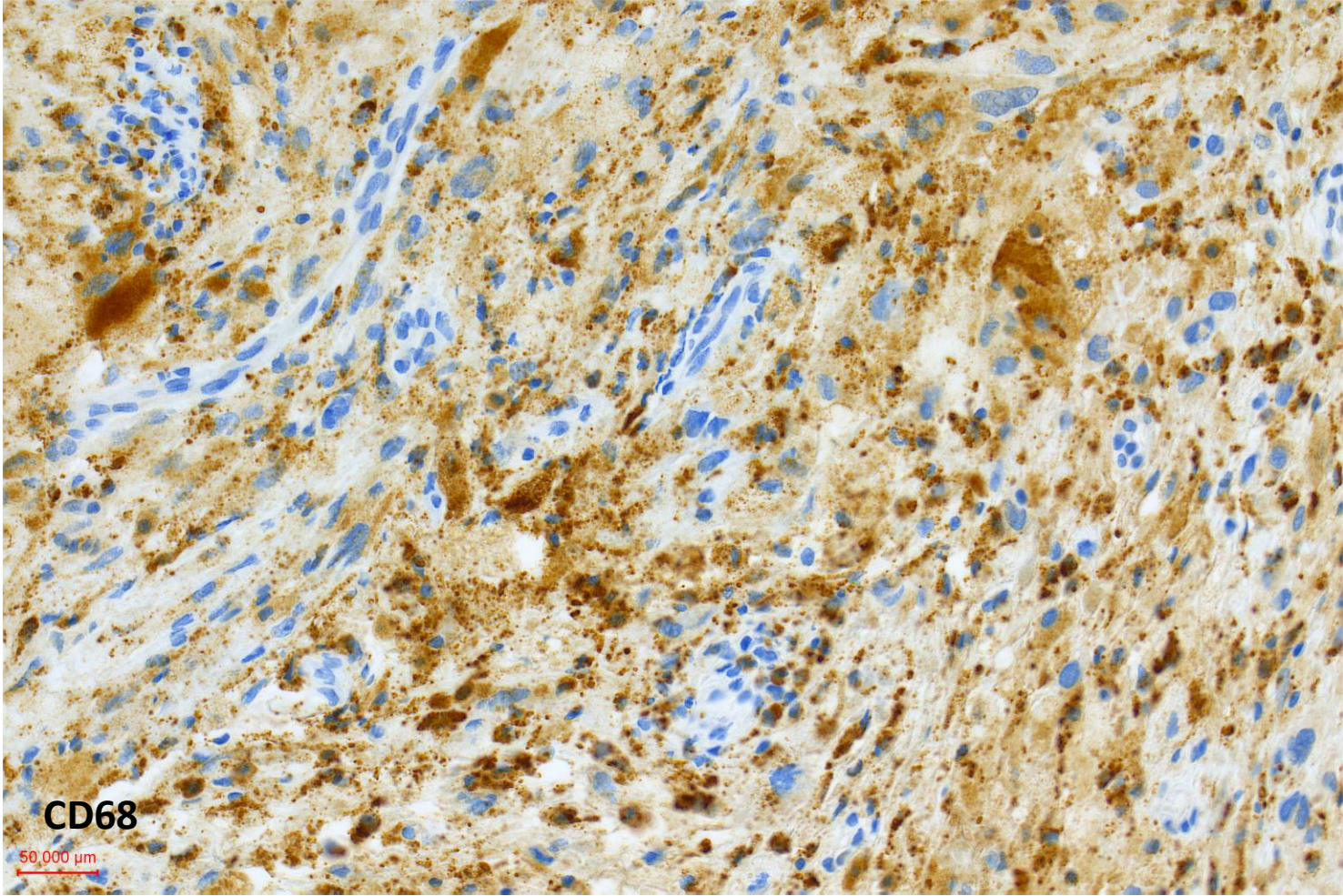


x400



x200

Case 2



x200

Case 2

- A custom 33 gene panel on NGS Illumina MiSeq platform detected a *TP53* splice site variant (VAF 22.4%)
 - No variants detected in other genes including *BRAF*, *MAP2K1*, *PIK3CA*, *KRAS* or *NRAS*

Case 2

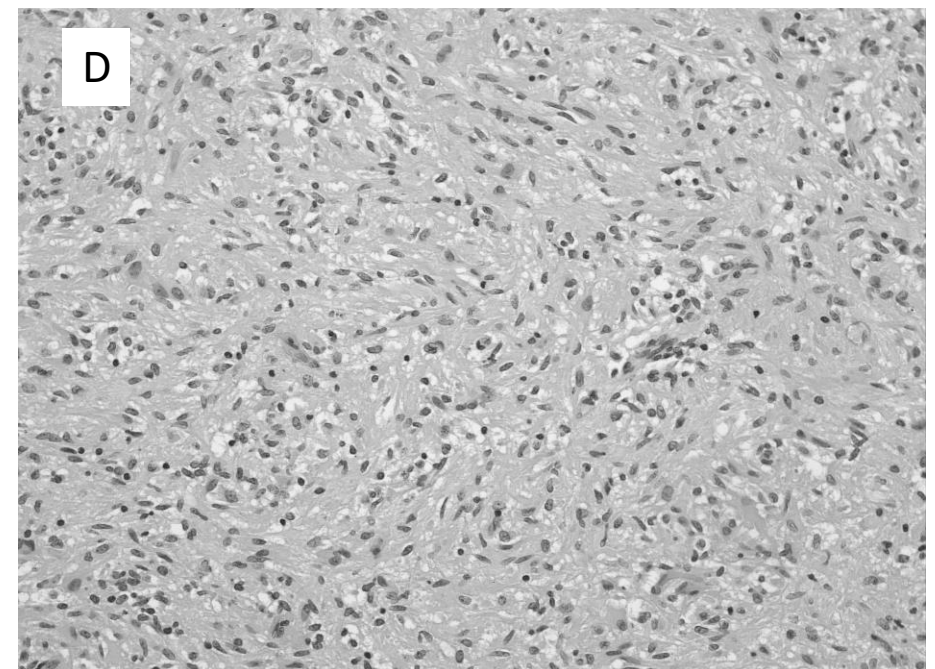
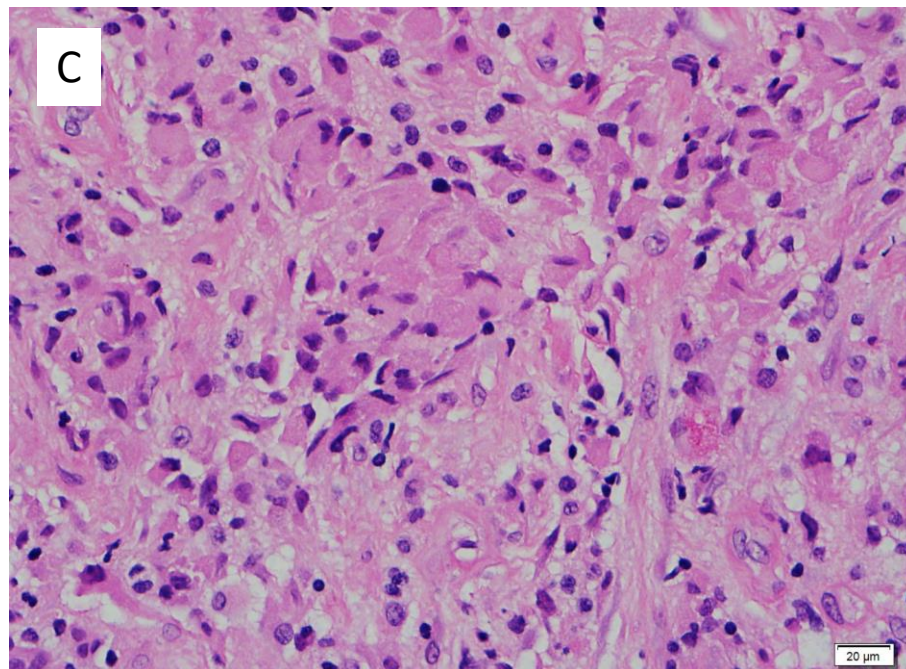
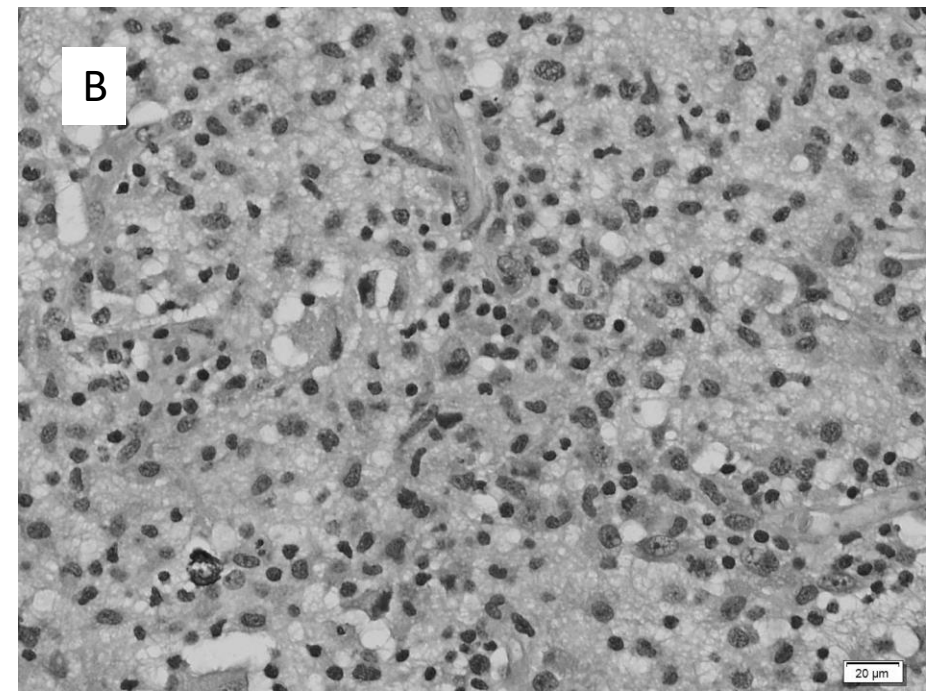
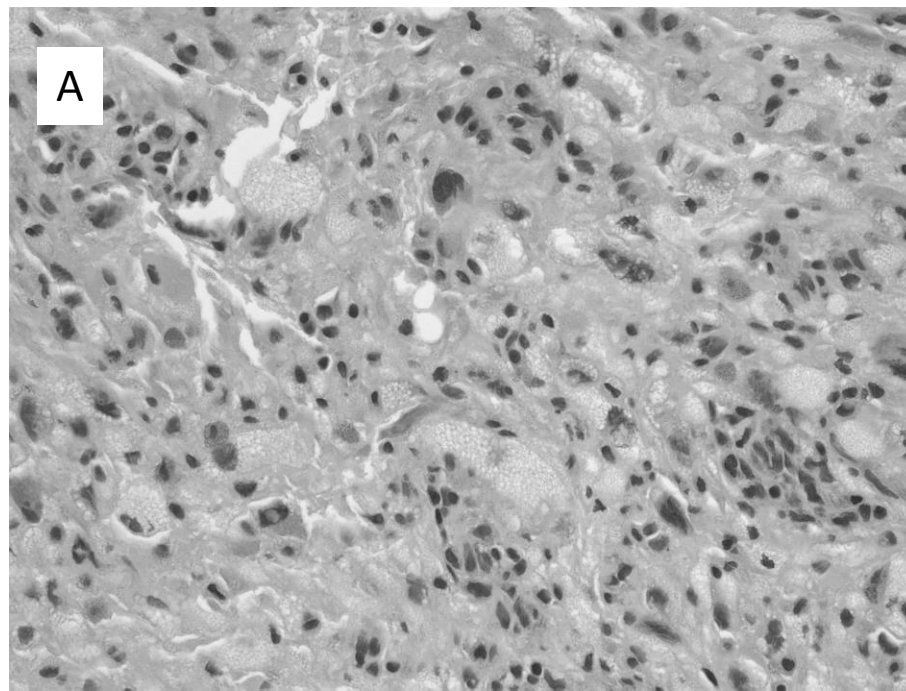
- Diagnosis
 - Non-Langerhans cell histiocytosis, most in keeping with juvenile xanthogranuloma (JXG)
- Progress
 - Diagnostic biopsy only performed.
 - No disease progress on neuroimaging surveillance at 30mths after Bx.

Juvenile xanthogranuloma

- Neoplastic histiocytic proliferation
- CNS involvement is described
- JXG occurs more frequently in children with NF1

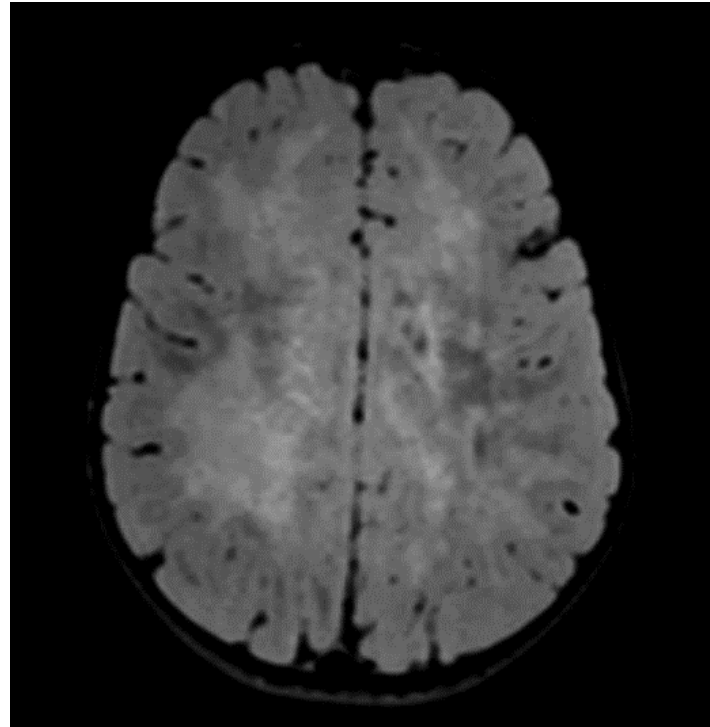
- This patient had no cutaneous involvement
- Studies have reported a higher risk for juvenile myelomonocytic leukaemia (JMML) in those with both NF1 and JXG

Case 3



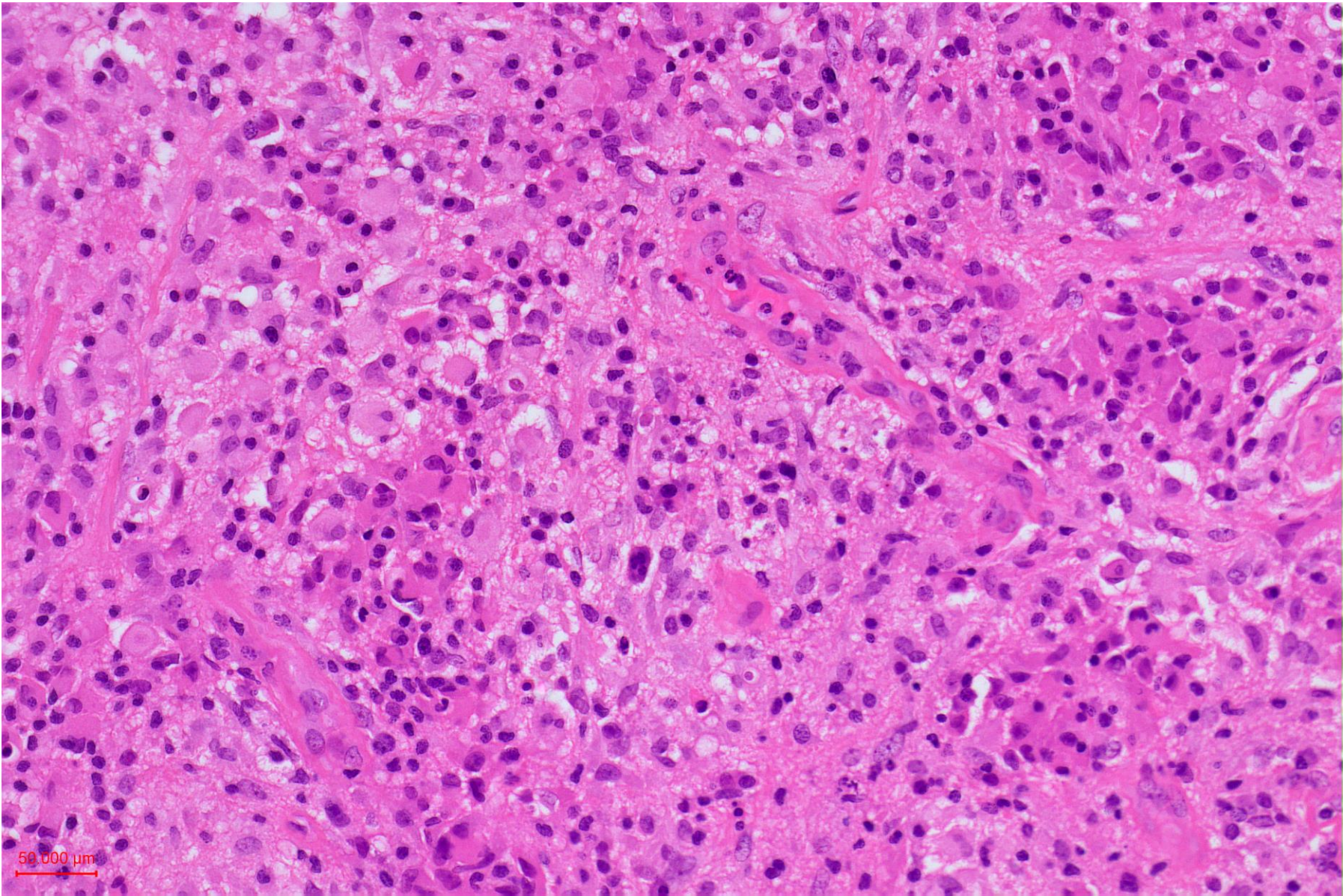
Case 3

- 3 yo female
- Weight loss, failure to thrive, multiple pituitary endocrinopathies
- MRI brain – diffuse T2 hyperintense white matter signal abnormality supra- and infra-tentorially
- No extracranial disease on systemic imaging



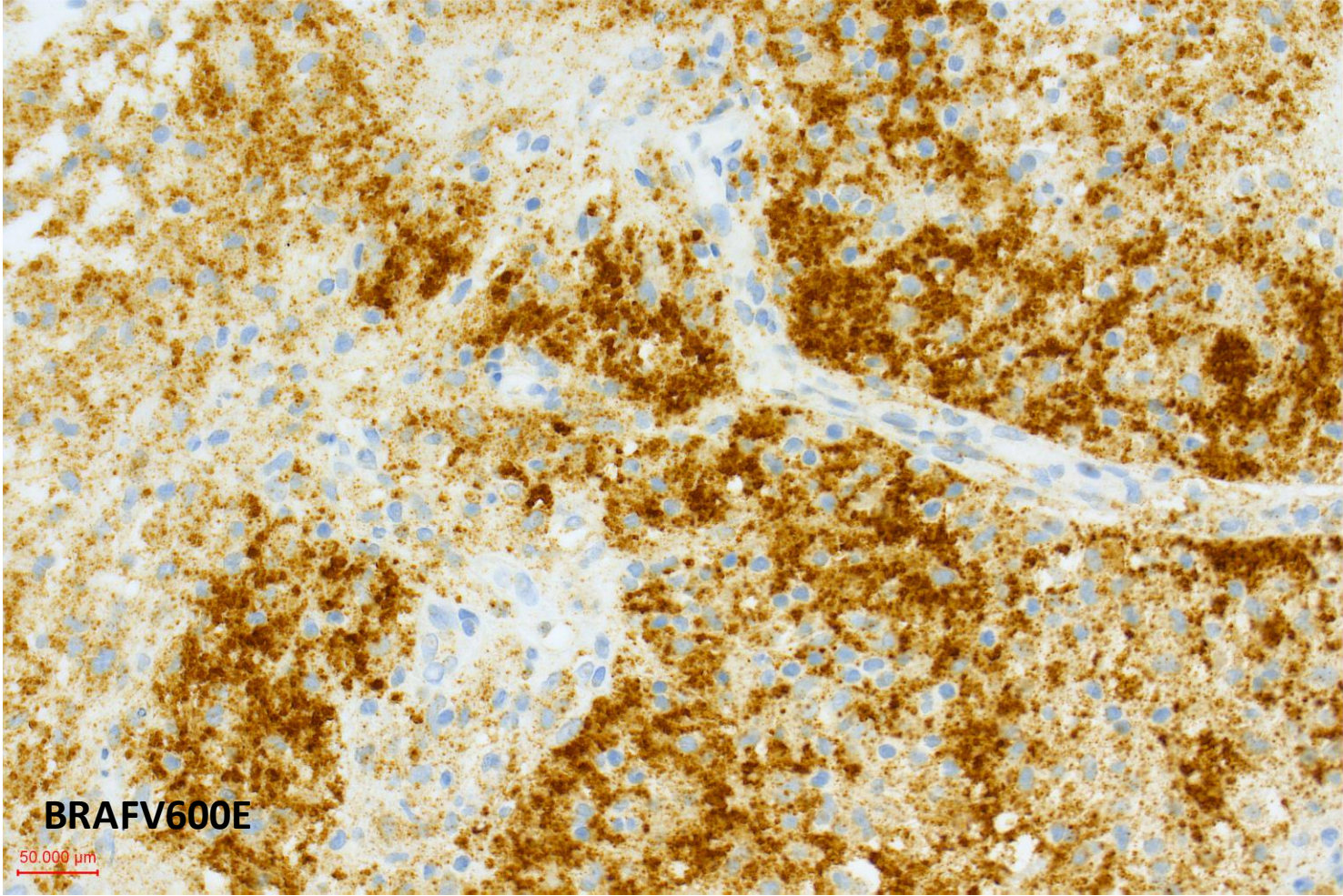
T2 FLAIR

Case 3



x200

Case 3



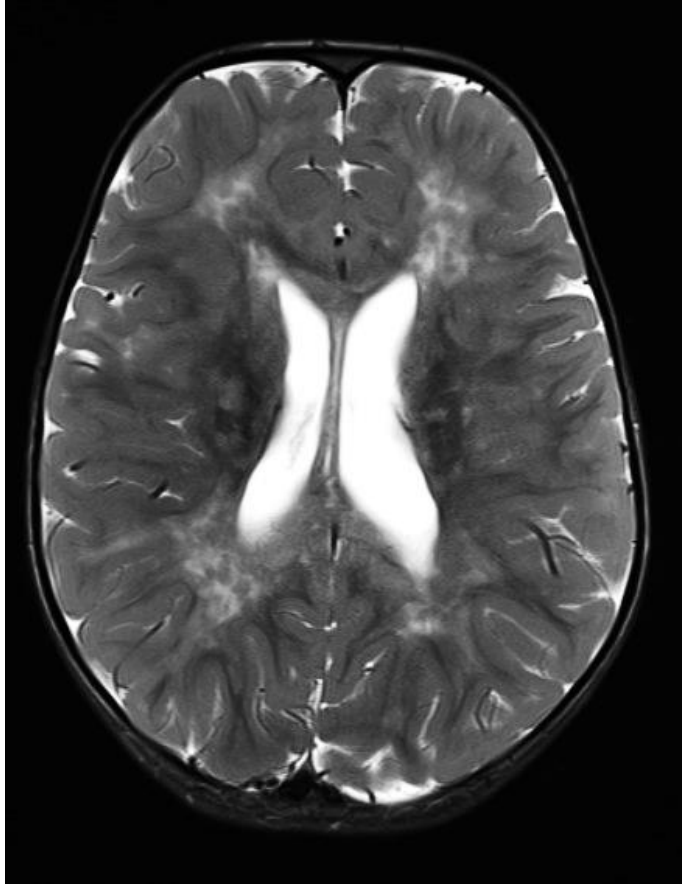
x200

Case 3

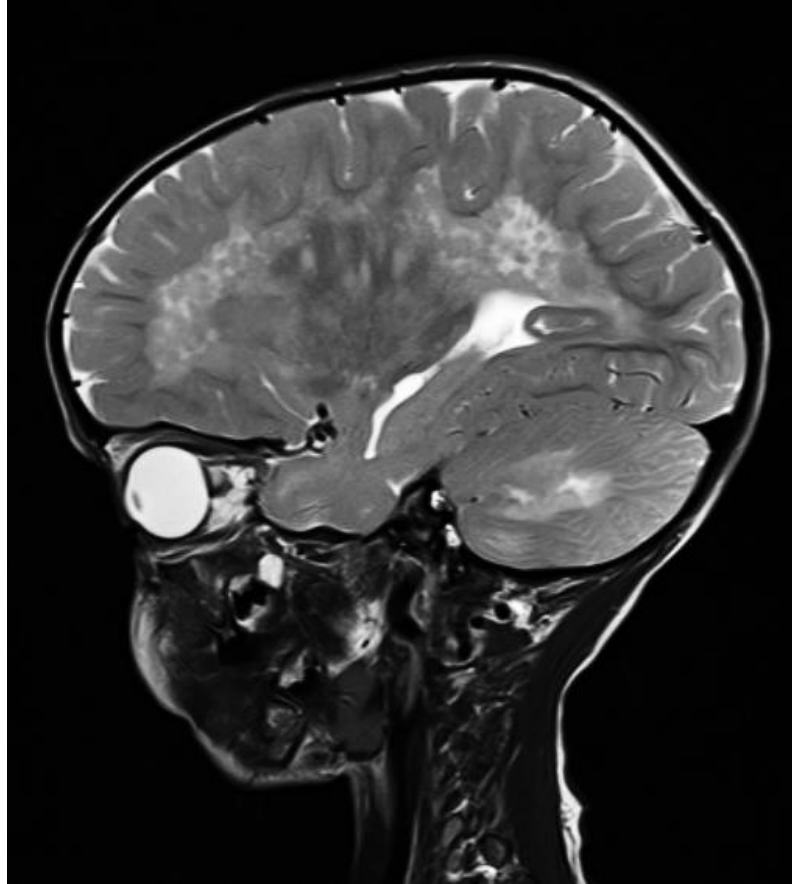
- A BRAF V600E mutation (VAF 18.5%) was confirmed on the TruSight Oncology 500 gene panel (Illumina, USA)

Case 3

- Diagnosis
 - Non-Langerhans cell histiocytosis with *BRAF V600E* mutation, most in keeping with Erdheim-Chester histiocytosis
- Progress
 - Dabrafenib therapy – resolution of CNS neuroimaging findings within 6/12 of therapy commencement; clinical improvement.
 - Stable min residual disease on neuroimaging at 29mths post dabrafenib commencement.

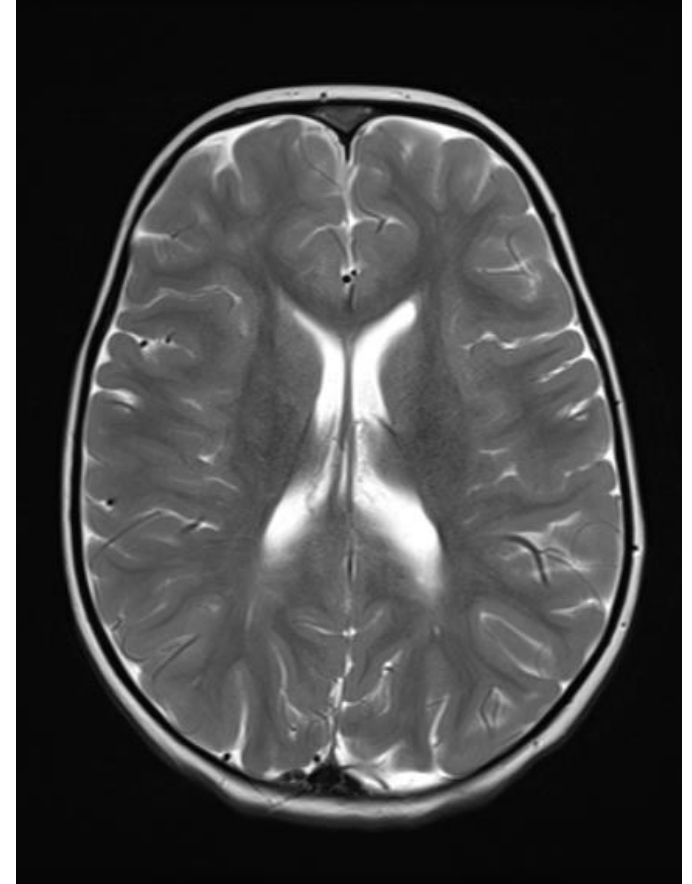


Sept 2021



Sept 2021

Post treatment with
Dabrafenib- ongoing



Feb 2024

Erdheim Chester disease

- Falls under the “L” (Langerhans) group
- Both ECD and LCH demonstrate clonal mutation in genes of the MAPK pathway
- More common in adults, is reported in children
- Infiltration of foamy mononucleated histiocytes
 - ECD vs LCH can be distinguished by CD1a
- Treatment with BRAF inhibitors has been shown to have an anti tumour effect in patients with ECD or LCH

Immunohistochemistry

	CD68	CD163	S100	CD1a	BRAF VE1	ALK1
ALK+ histiocytosis	Positive	Strong positive	Positive	Neg	Neg	Strong positive
JXG	Strong positive	Strong positive	Neg	Neg	Neg	Neg
ECD	Strong positive	Strong positive	Neg	Neg	Strong positive	Neg

Positive	Positive
Strong positive	Strong positive

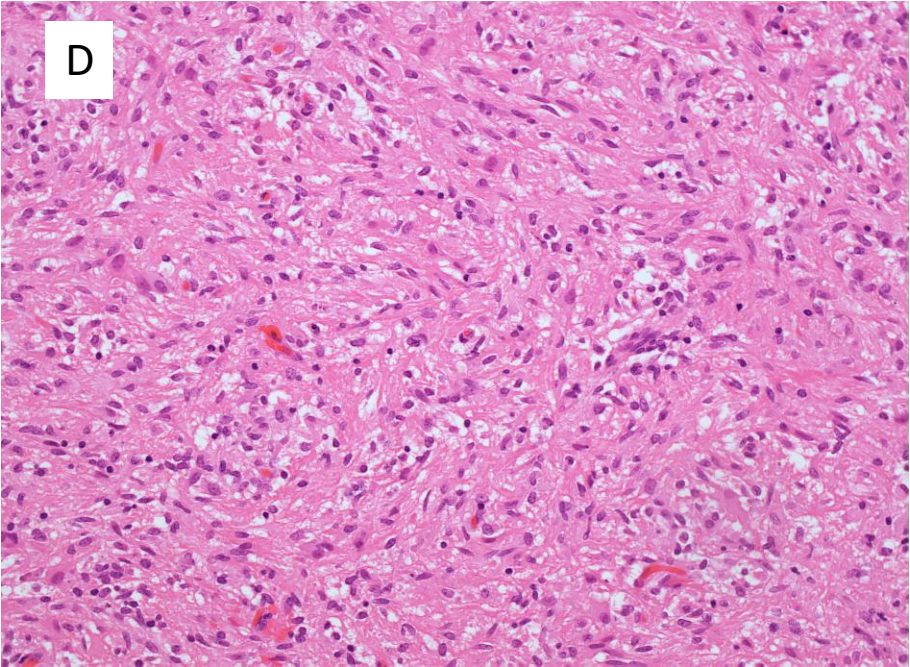
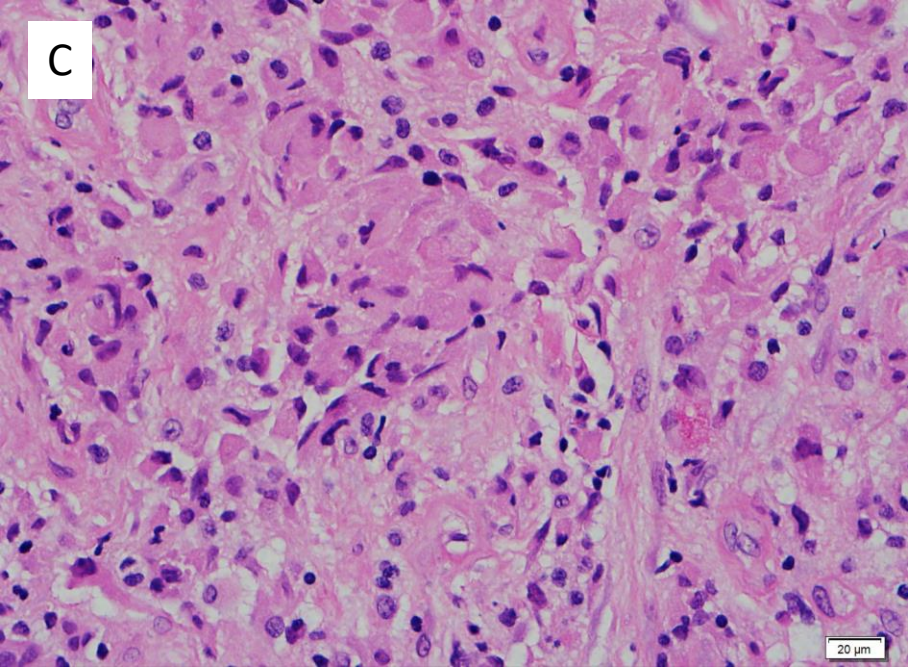
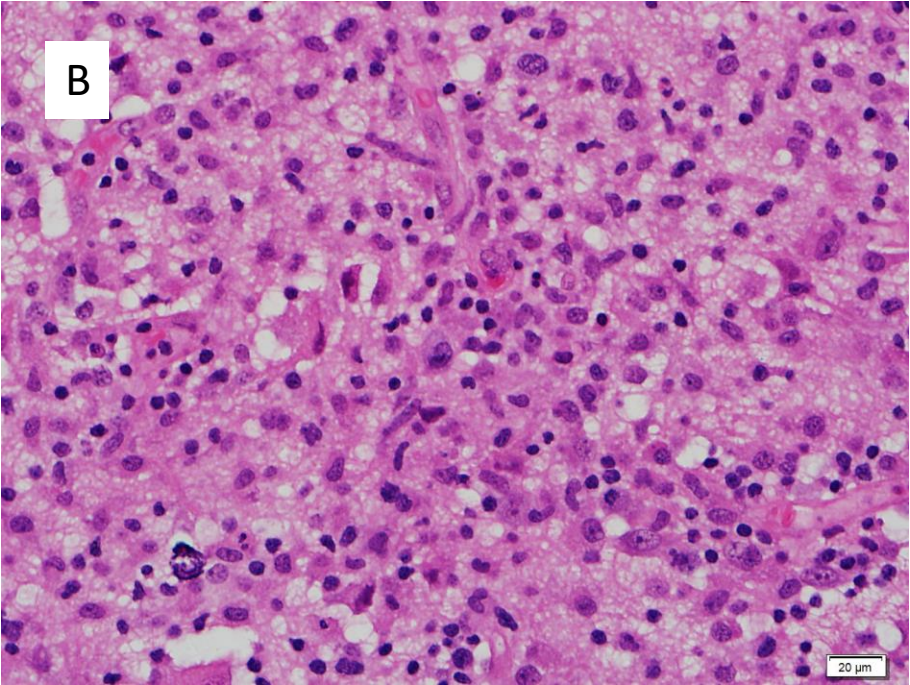
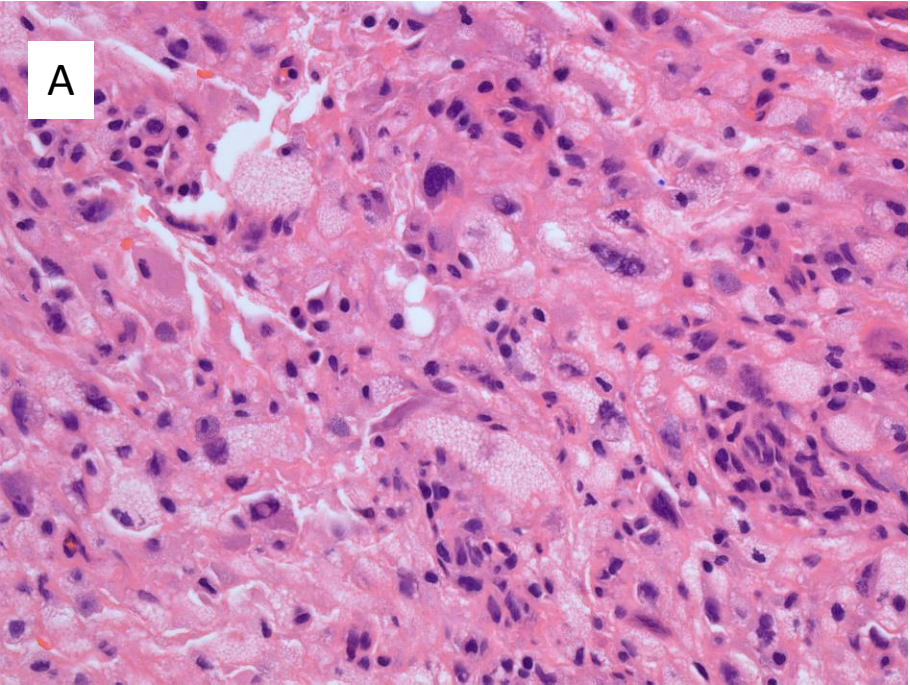
Primary CNS Histiocytoses – practical points

- Histiocytic CNS infiltrates are more likely to be non-neoplastic than neoplastic.
 - Implications for tissue triage at time of intraoperative assessment, especially for small biopsy samples
- Microscopic tumour morphology is of limited utility in assisting with selection of ancillary investigations or final diagnosis.
- A standardised approach is recommended for workup of suspected CNS histiocytic neoplasms.
- Use of DNA methylation analysis for assistance with diagnosis not as clear-cut as for glial neoplasms
 - NGS panel and/ or RNA fusion panel of greater utility than DNA methylation analysis.

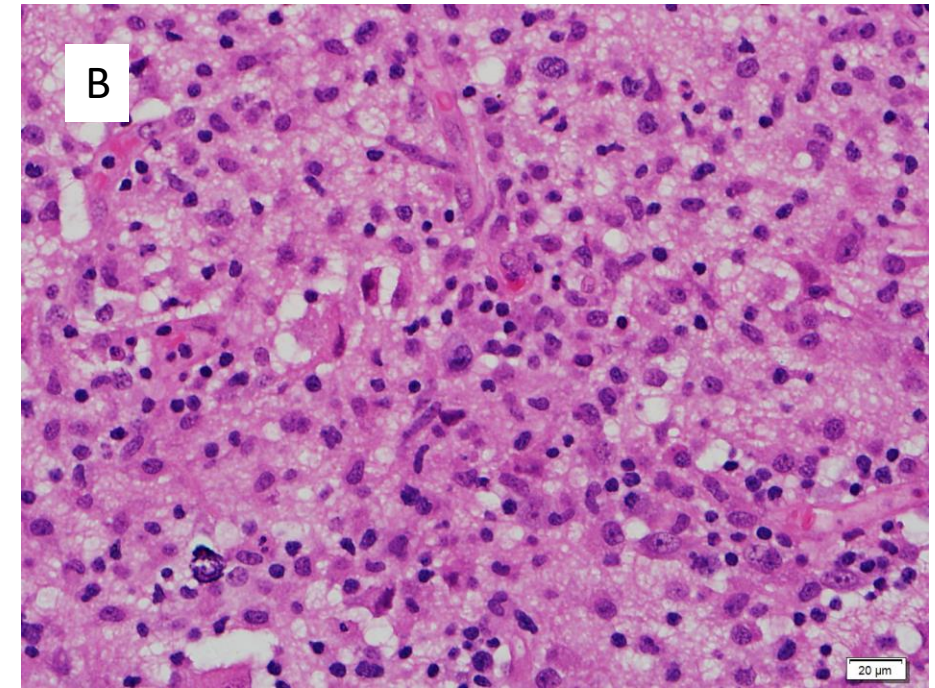
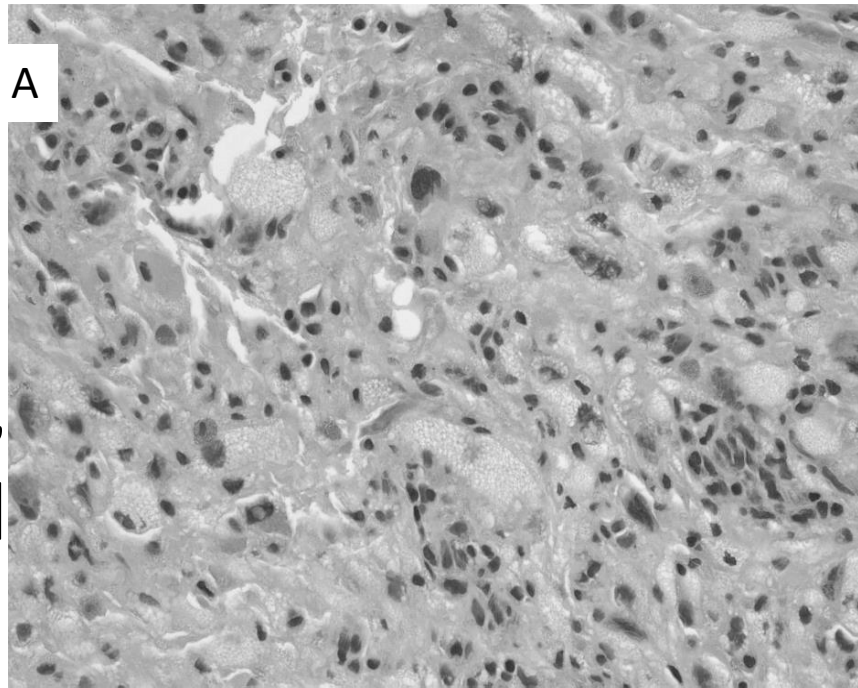
PathWest approach to CNS Histiocytosis work-up

- IHC: CD68 (KP1), CD163, S100, CD30, CD1a, Langerin, BRAF (VE1), ALK1
- Cytogenetics: FISH – ALK breakapart; BRAF breakapart; NTRK1, NTRK2, NTRK3 breakapart probes
- NGS: Ampliseq 33 gene panel includes relevant targets – BRAF, MAP2K1, PIK3CA
- If Required - After discussion with managing clinician and with patient consent: TSO500 (includes RNA fusion targets)

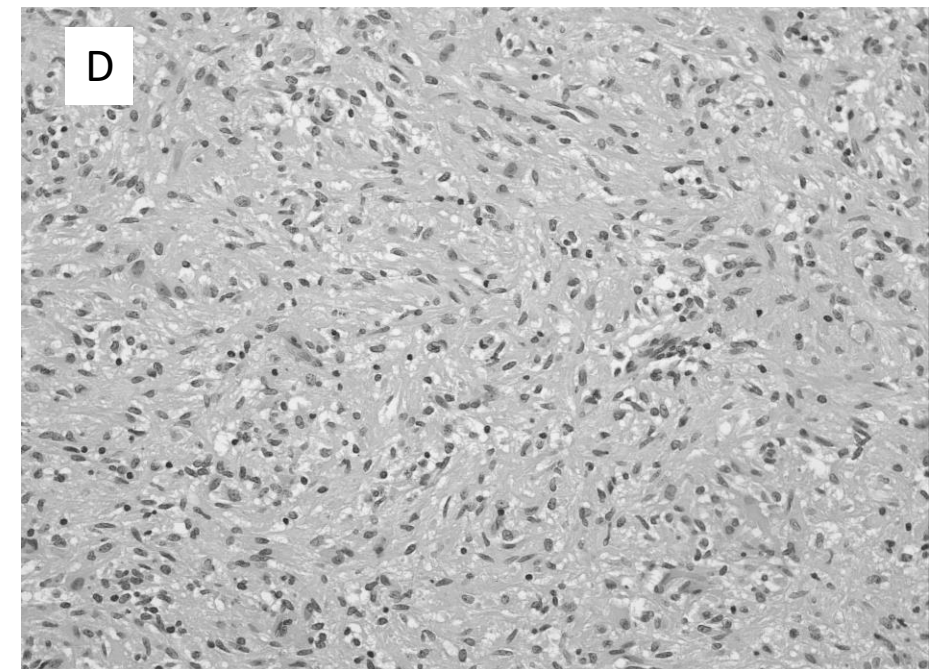
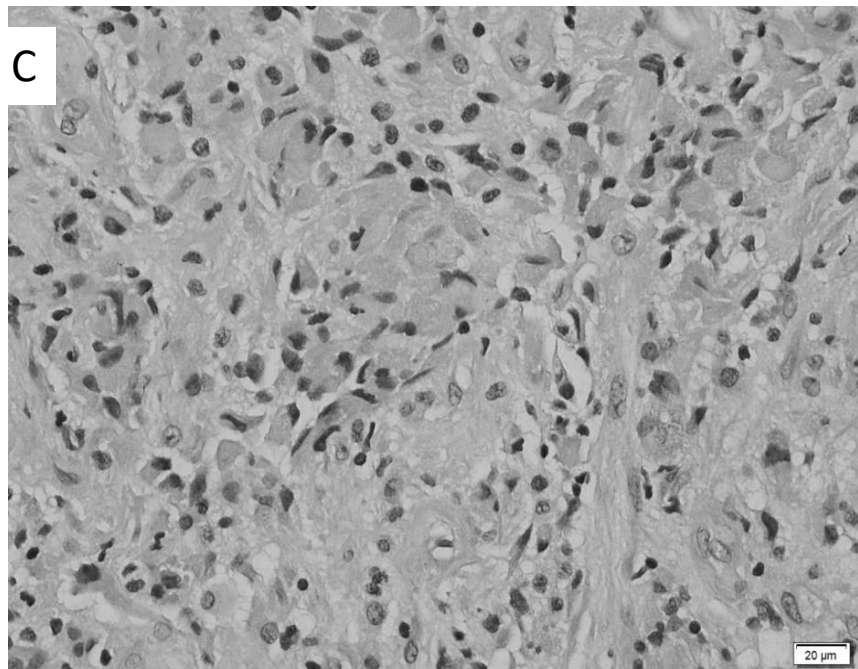
Which of these is the odd-one out?



**Right frontal lobe
tumour in a 6yoM,
with CNS-confined
disease:**



**ALK-positive ALCL,
lymphohistiocytic
variant**



Thank you

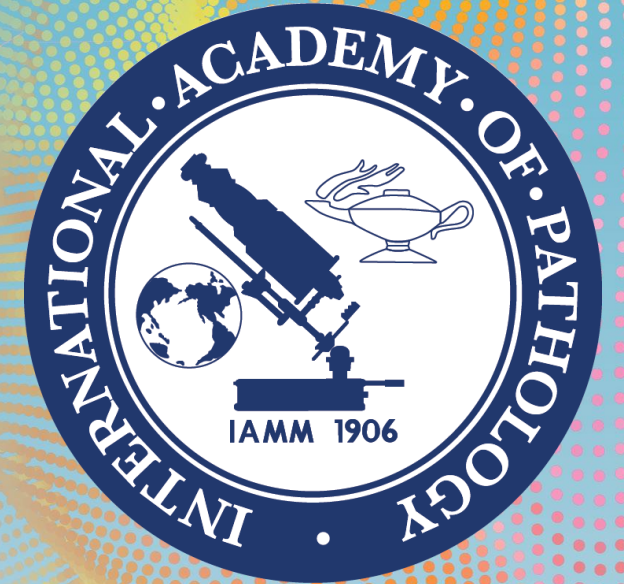
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Dr Chris van Vliet

Dr Alexandra RW Kang

Dr Vicki Fabian

Dr Benhur Amanuel



The 48th Annual Scientific Meeting *of the*

Australasian Division of the
International Academy of Pathology

References

Emile JF, Abia O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. Jun 2 2016;127(22):2672-81. doi:10.1182/blood-2016-01-690636

WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2024 [cited 2024 05 28]. (WHO classification of tumours series, 5th ed.; vol. 11). Available from: <https://tumourclassification.iarc.who.int/chapters/63>.

Cohen Aubart F, Idhah A, Emile JF, et al. Histiocytosis and the nervous system: from diagnosis to targeted therapies. *Neuro Oncol*. Sep 1 2021;23(9):1433-1446. doi:10.1093/neuonc/noab107

Kemps PG, Picarsic J, Durham BH, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. *Blood*. 2022;139(2):256-280. doi:10.1182/blood.2021013338

Dehner LP. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. *Am J Surg Pathol*. May 2003;27(5):579-93. doi:10.1097/00000478-200305000-00003

Picarsic J, Pysher T, Zhou H, Fluchel M, Pettit T, Whitehead M, Surrey LF, Harding B, Goldstein G, Fellig Y, Weintraub M, Mobley BC, Sharples PM, Sulis ML, Diamond EL, Jaffe R, Shekdar K, Santi M. BRAF V600E mutation in Juvenile Xanthogranuloma family neoplasms of the central nervous system (CNS-JXG): a revised diagnostic algorithm to include pediatric Erdheim-Chester disease. *Acta Neuropathol Commun*. 2019 Nov 4;7(1):168. doi: 10.1186/s40478-019-0811-6. PMID: 31685033; PMCID: PMC6827236.

Raygada M, Arthur DC, Wayne AS, Rennert OM, Toretsky JA, Stratakis CA. Juvenile xanthogranuloma in a child with previously unsuspected neurofibromatosis type 1 and juvenile myelomonocytic leukemia. *Pediatr Blood Cancer*. 2010 Jan;54(1):173-5. doi: 10.1002/pbc.22297. PMID: 19785027; PMCID: PMC2783853.

Pan Z, Kleinschmidt-DeMasters BK. CNS Erdheim-Chester Disease: A Challenge to Diagnose. *J Neuropathol Exp Neurol*. 2017 Dec 1;76(12):986-996. doi: 10.1093/jnen/nlx095. PMID: 29096034.

