59th AANP DIAGNOSTIC SLIDE SESSION 2017
CASE 2017-06

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No financial disclosures

Clinical history

- A 35-year-old G3P2 at 20w5d of gestation
- A genetic sonogram - multiple congenital anomalies including macrocephaly, parallel lateral ventricles, choroid plexus cysts, nuchal thickening, frontal bossing, midfacial hypoplasia, hypertelorism, bell-shaped chest, multiple echogenic intracardiac foci and bilateral clubfeet
- Termination at 22w5d of gestation
- Autopsy performed

Weights and Measurements

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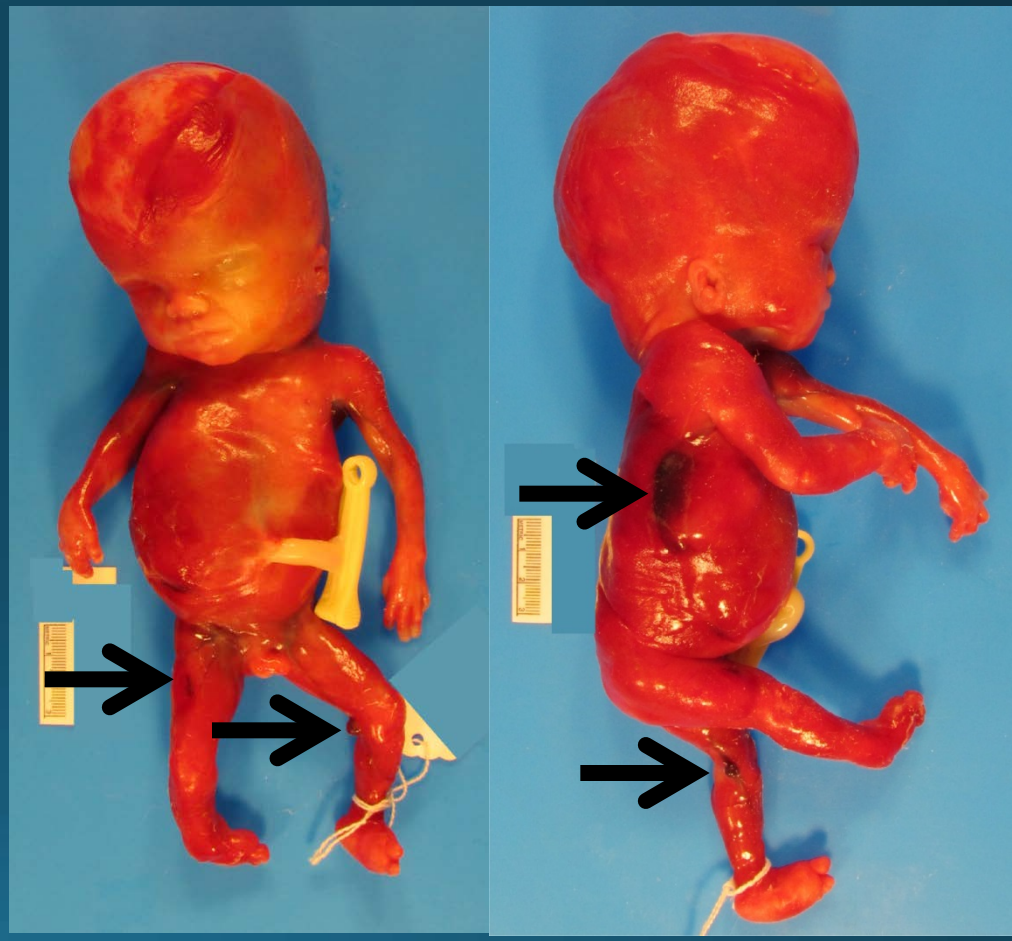
- Body weight: 526 g
- Length: 32.0 cm
- Foot length:
  - Right: 2.9 cm
  - Left: 3.4 cm

Expected (22 weeks gestation)

- 461 g +/- 122 g
- 28.0 cm +/- 2.0 cm
- 3.9 cm +/- 0.3 cm

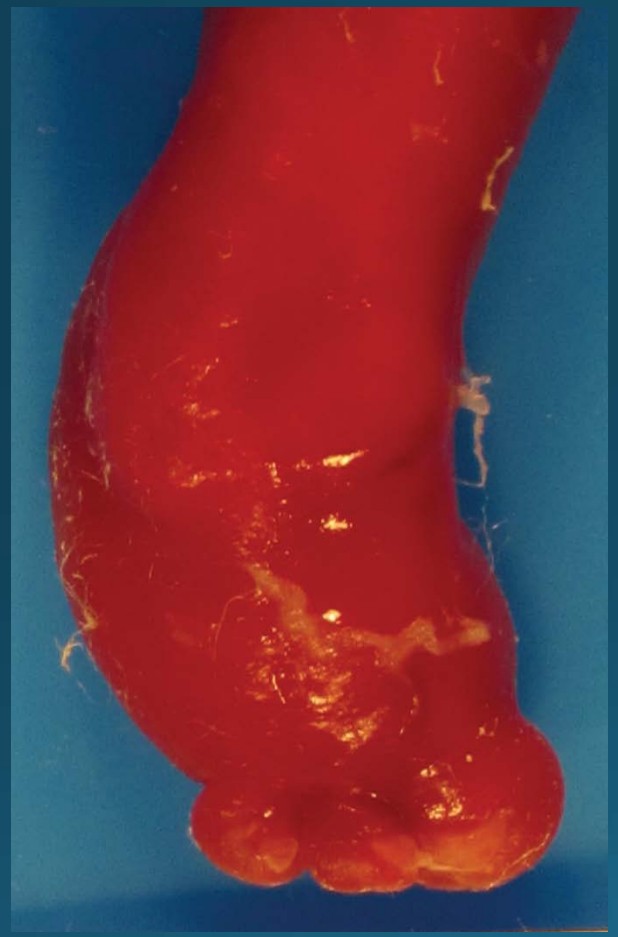
Malformations

- Dolichocephaly, low nasal bridge, long face, anteverted nostrils
- Cutaneous vascular malformations right thorax and both legs (Black arrows)

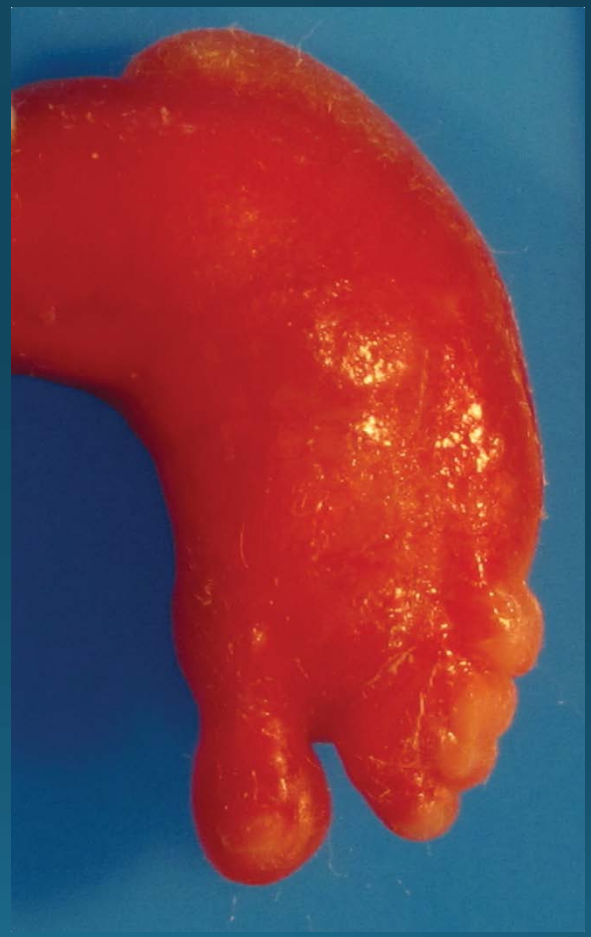


Malformations:

Clubbed feet

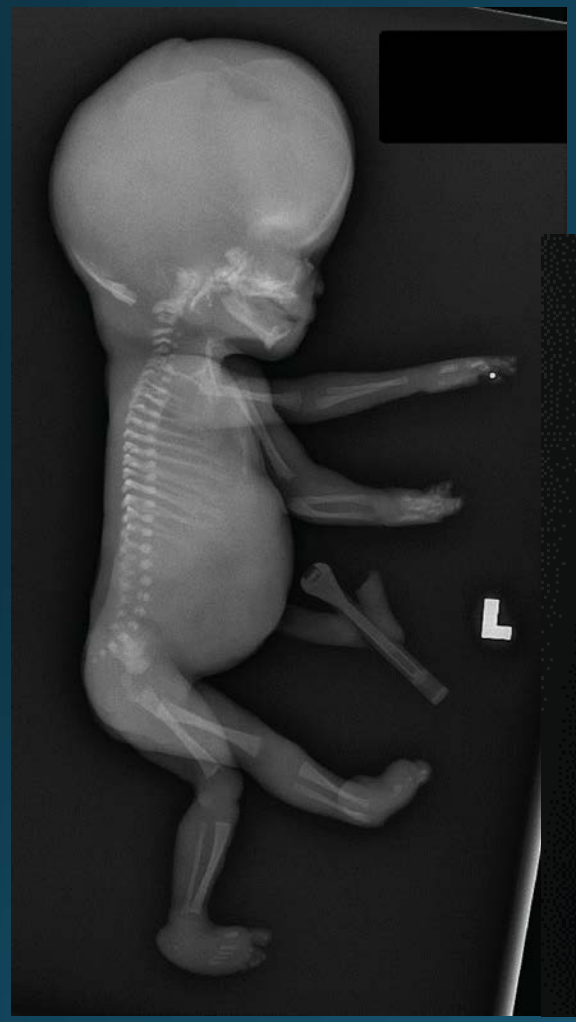


Right foot with 3 toes

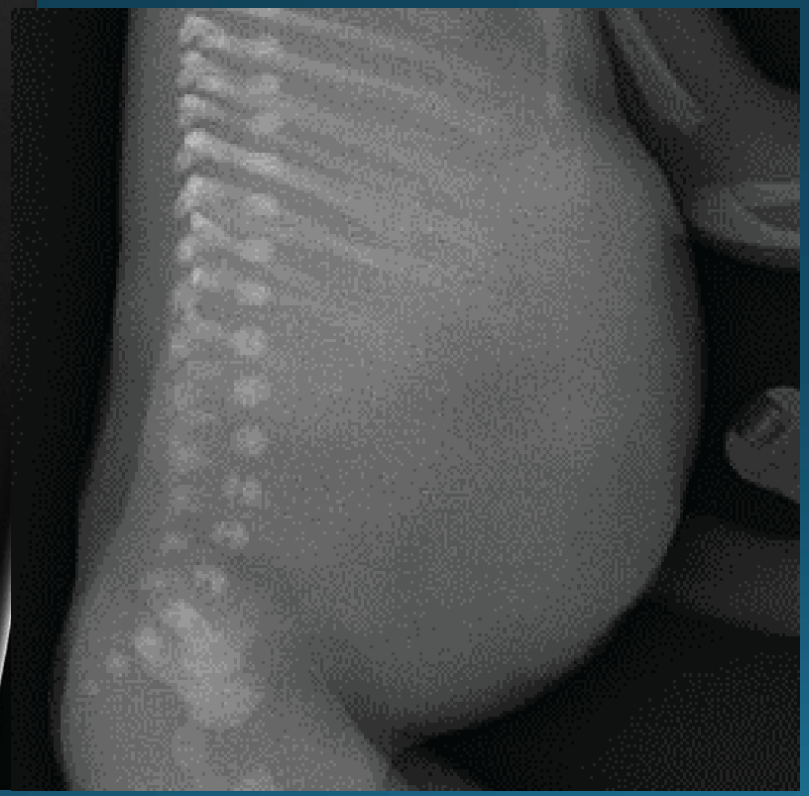


Left foot with 2-3-4 syndactyly

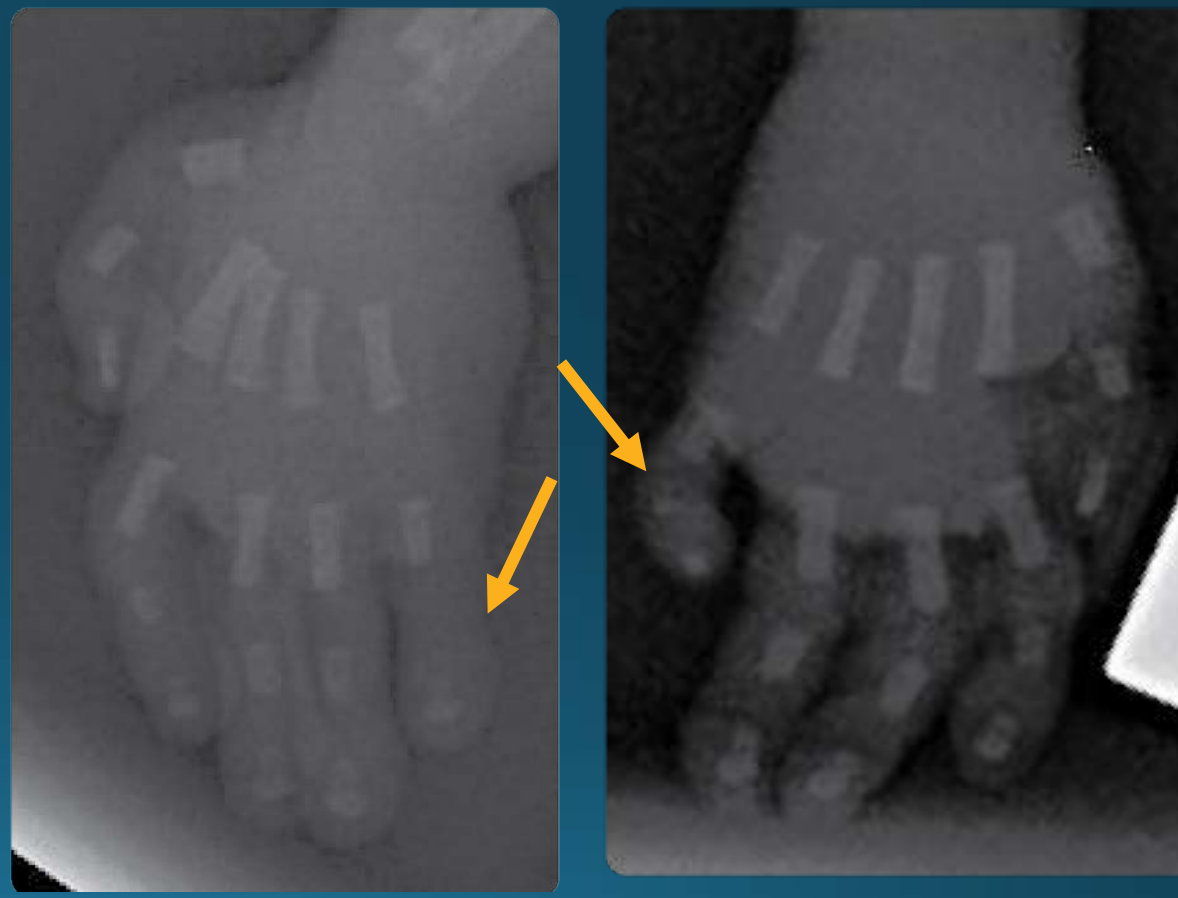
Post-mortem X-rays:



Enlarged Skull, frontal bossing, 11 ribs



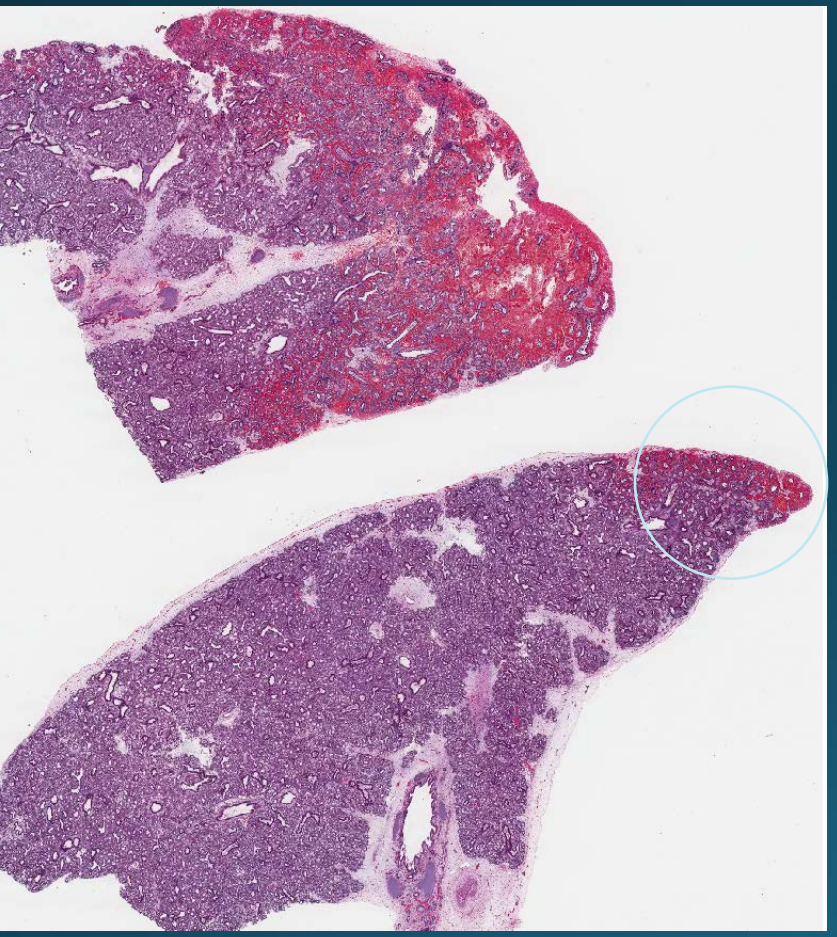
Lumbar vertebral bodies with clefting



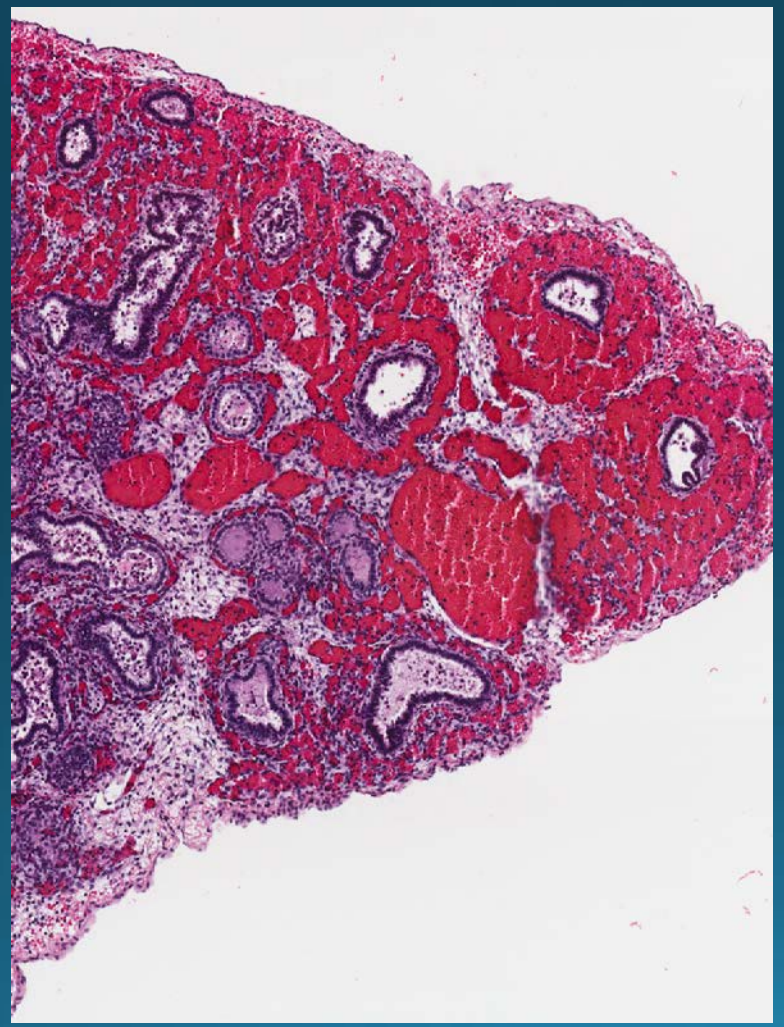
Absent/Poorly formed mid-phalanx 5th fingers

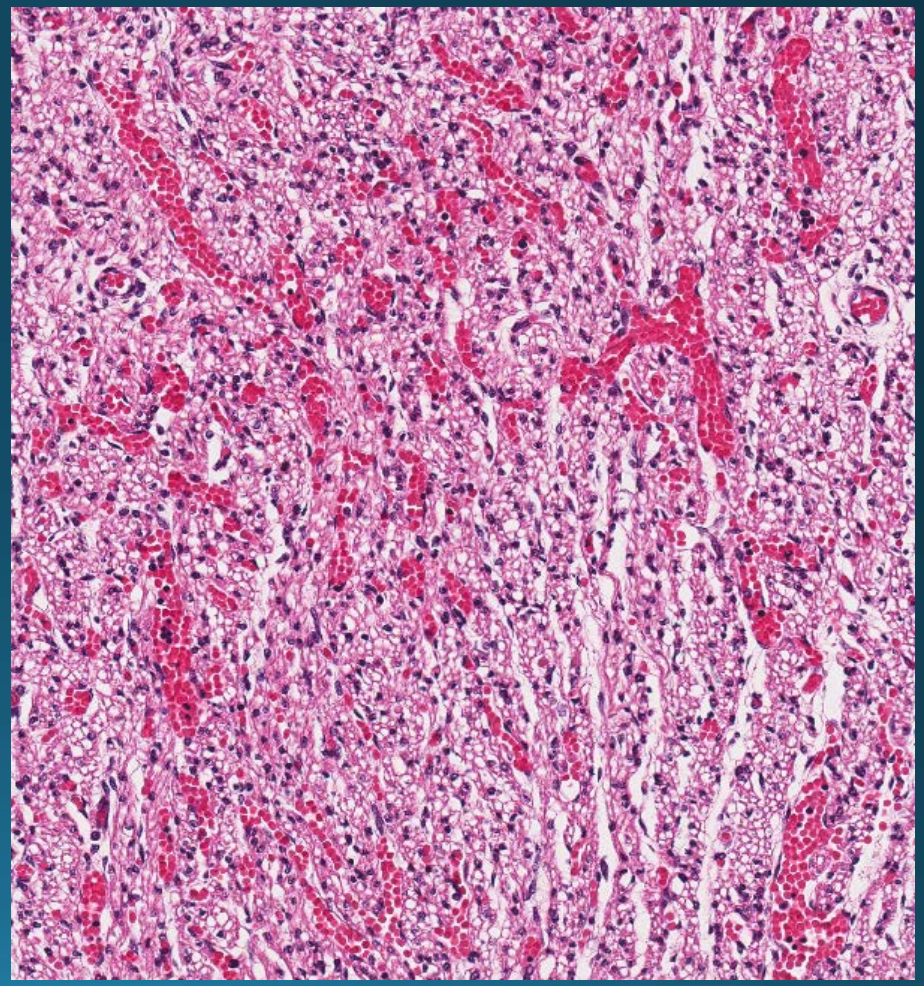
Capillary malformations:

Lung

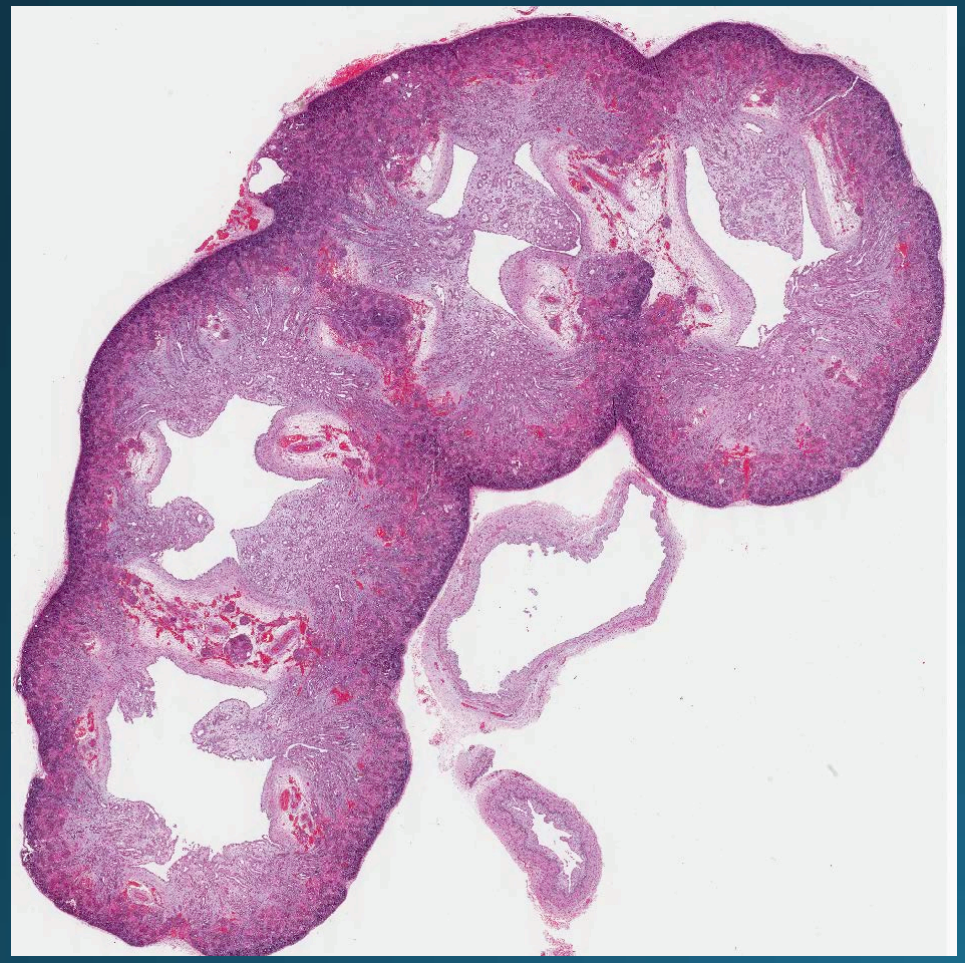


Heart

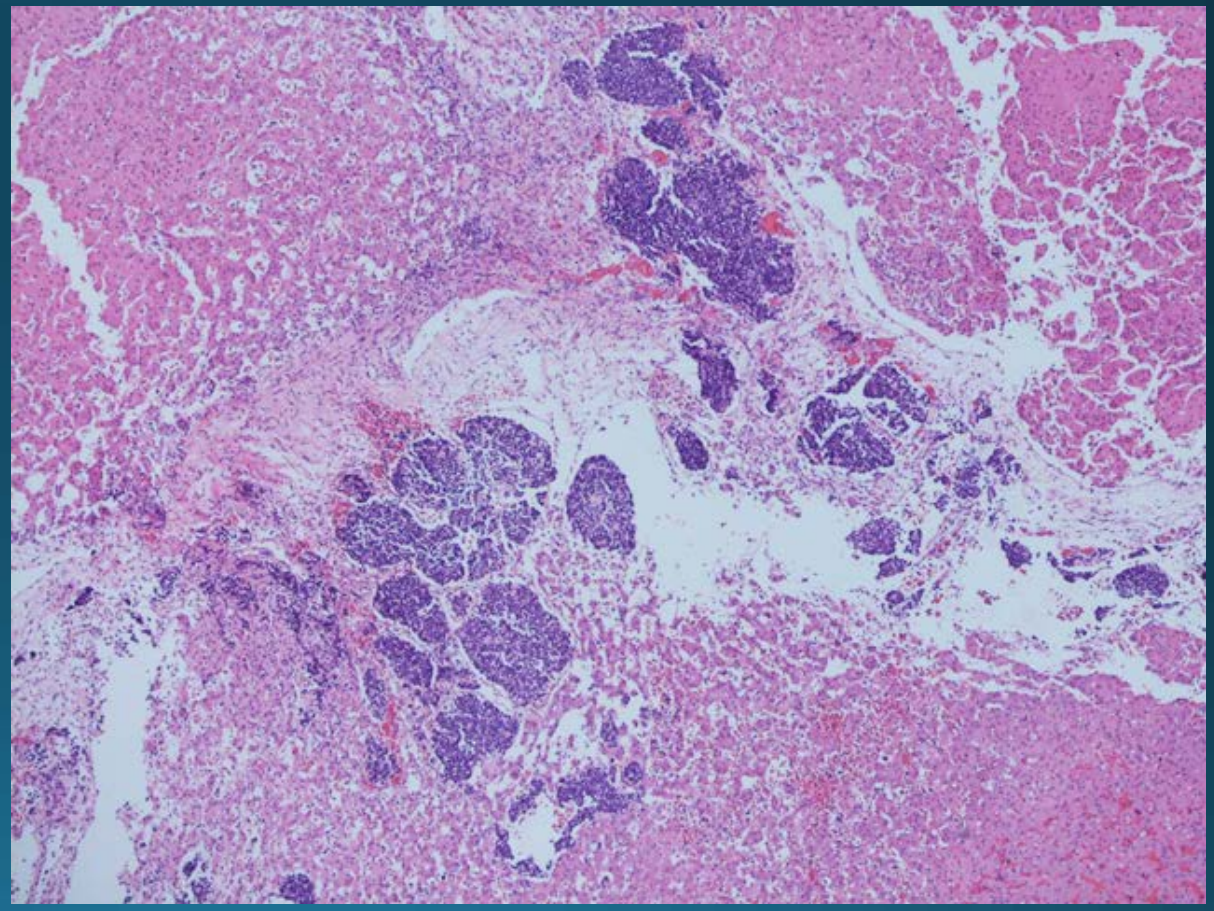




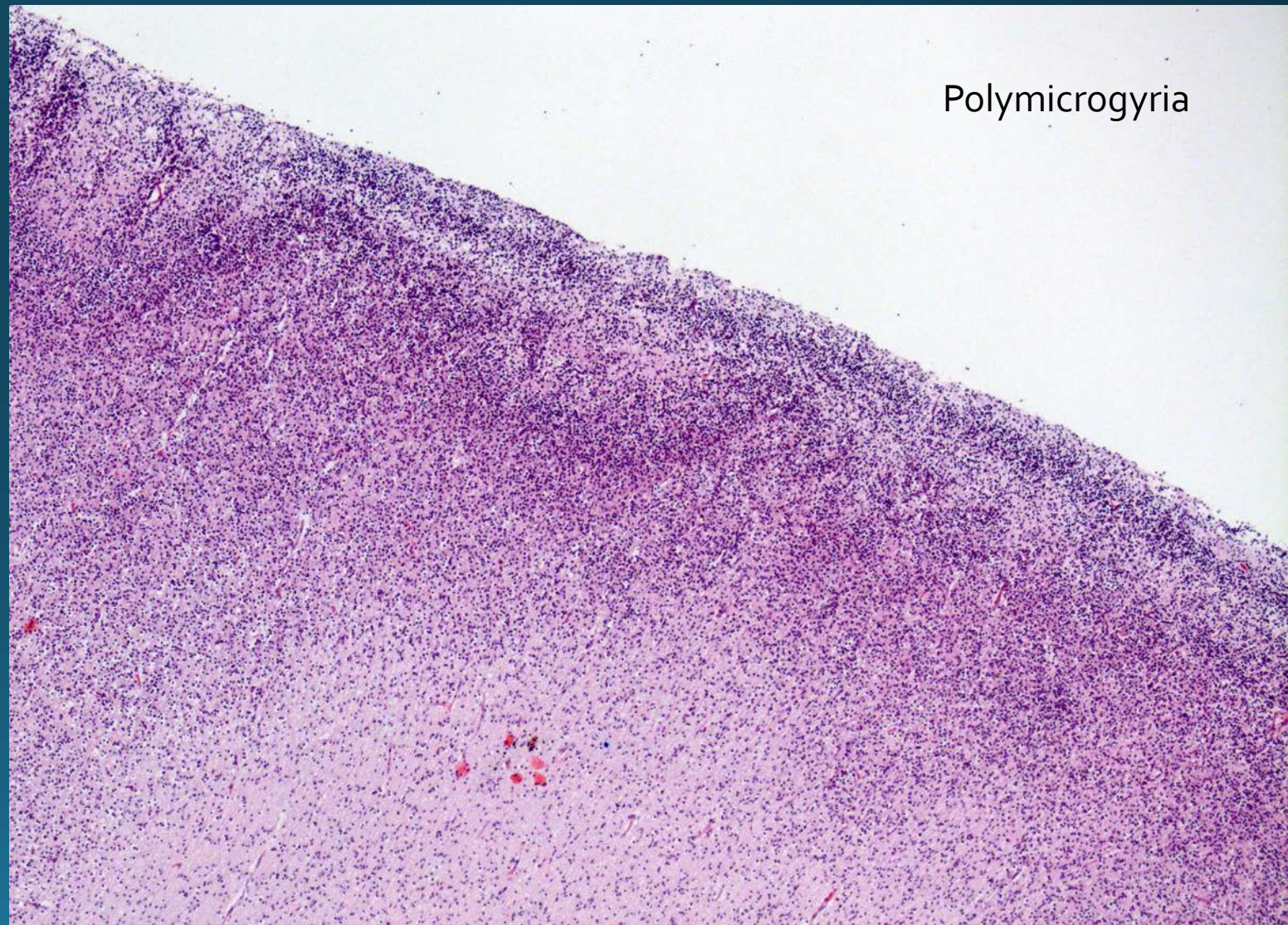
Right Kidney with Hydronephrosis



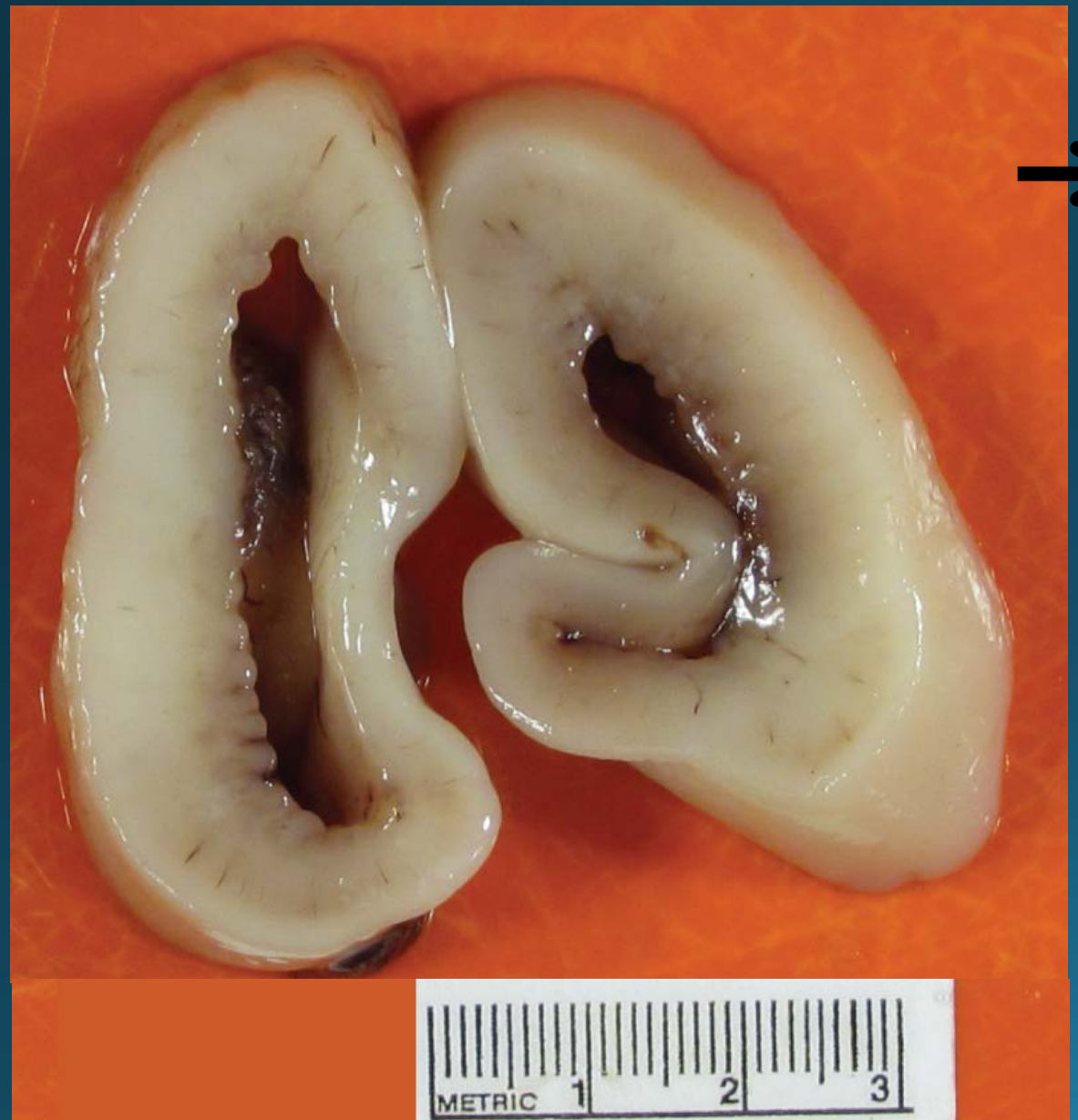
Left Adrenal Gland with Neuroblastoma In Situ

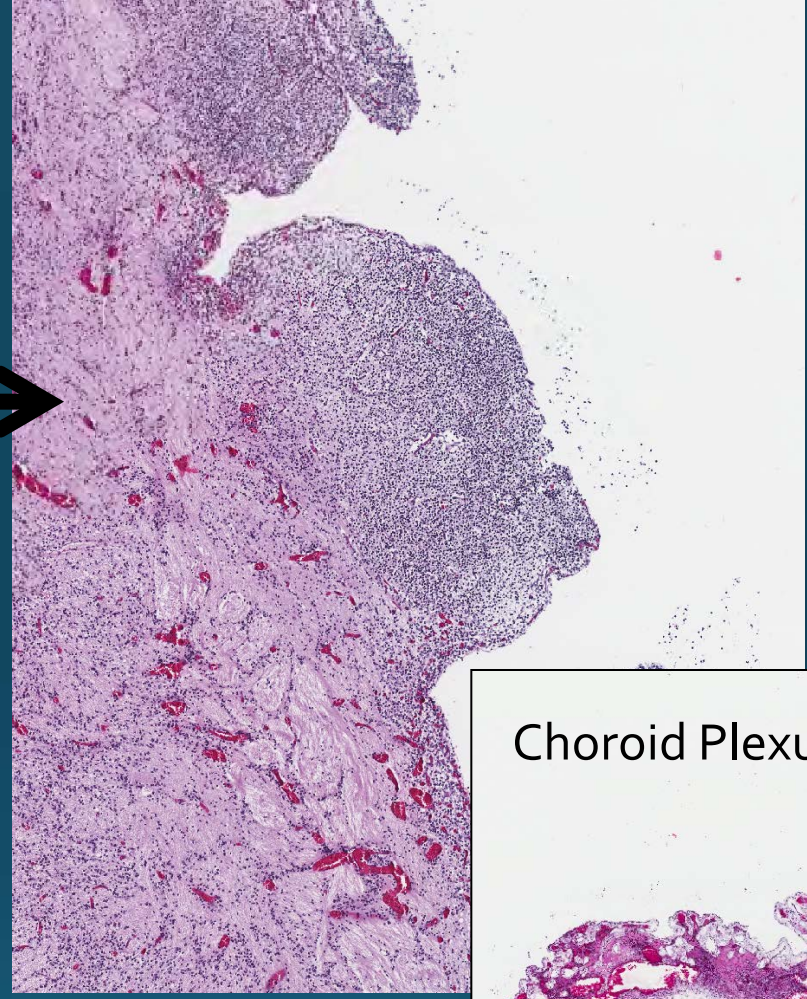


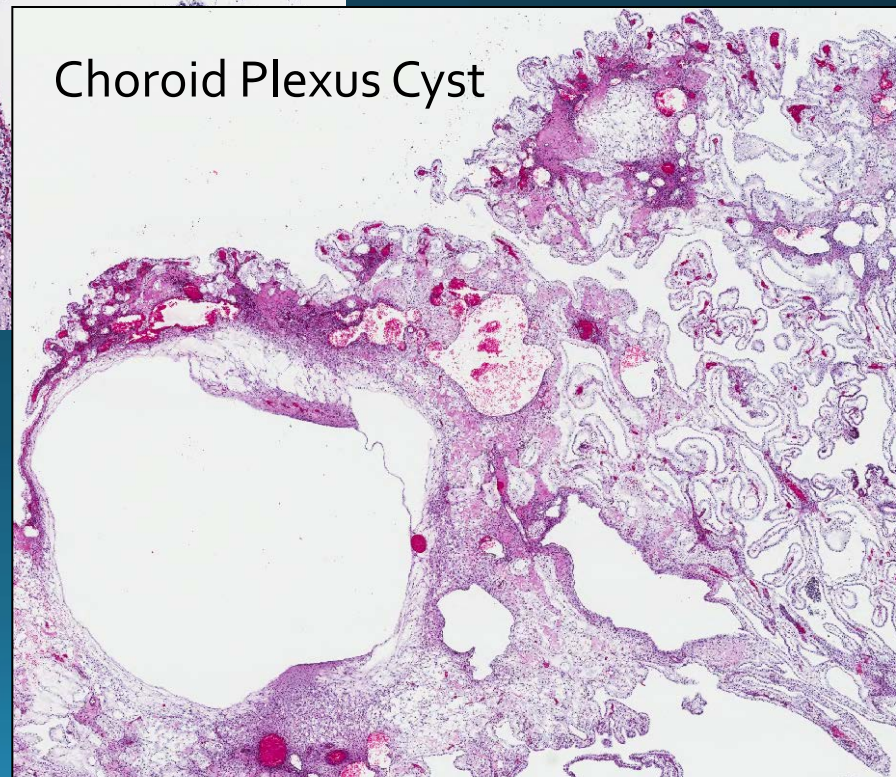
Autopsy: Brain
Brain weight: 154 g (Expected: 65.4 g @22 wk)



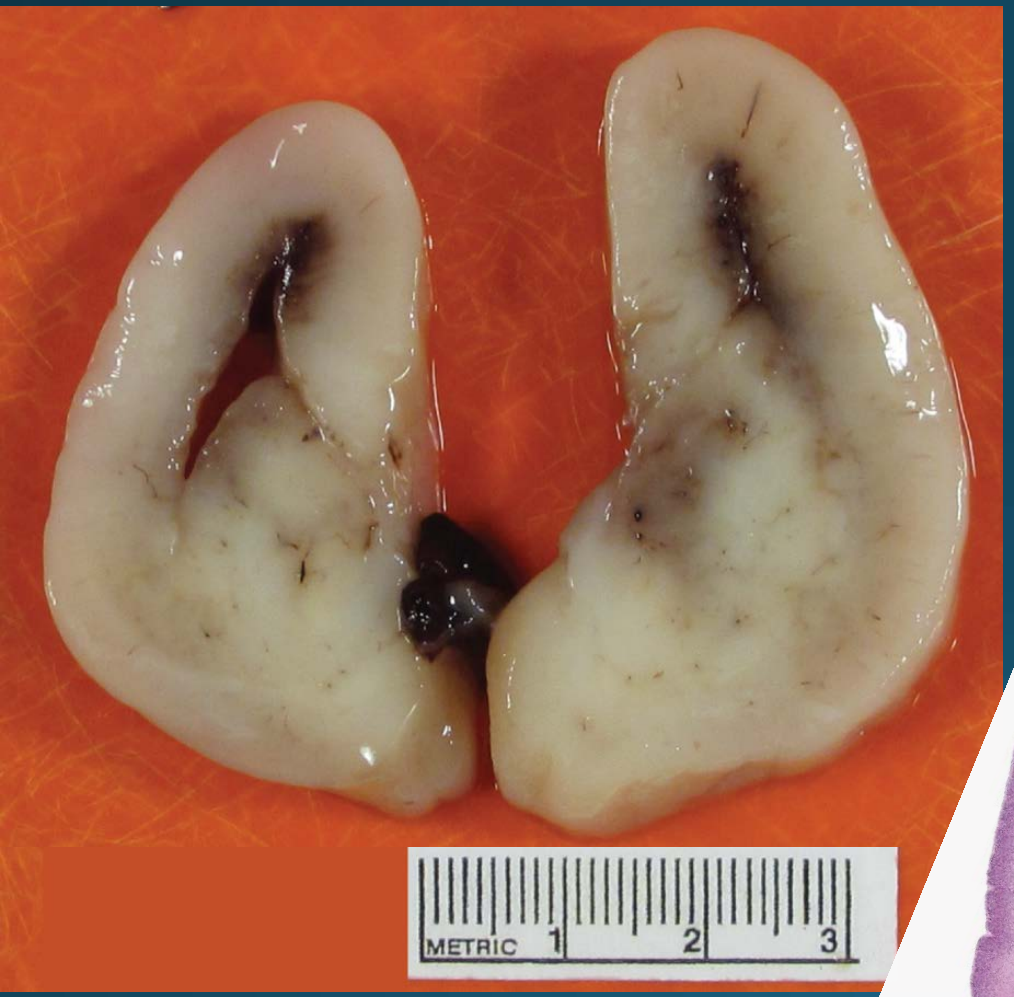
Nodular Ventricular Surface

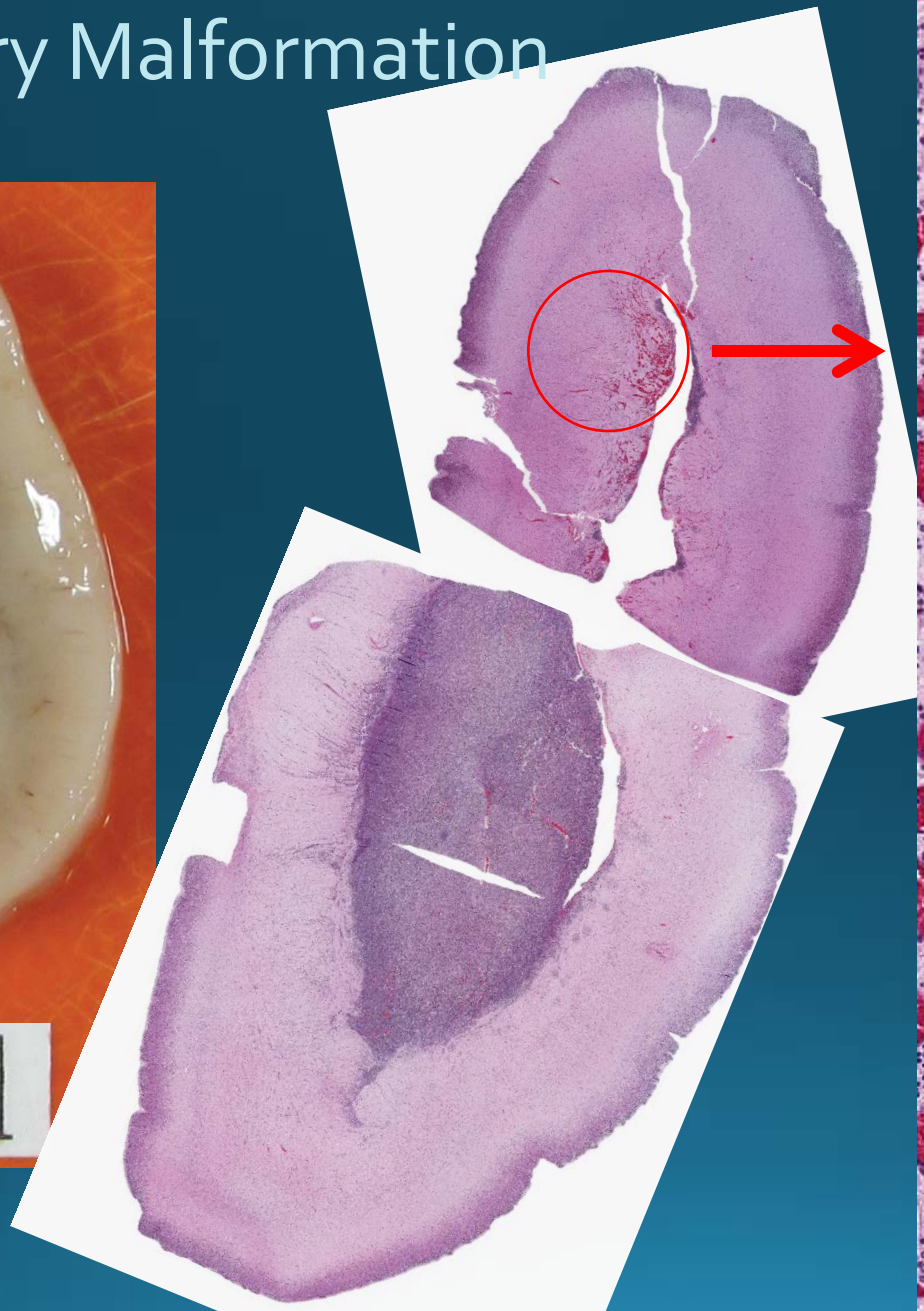


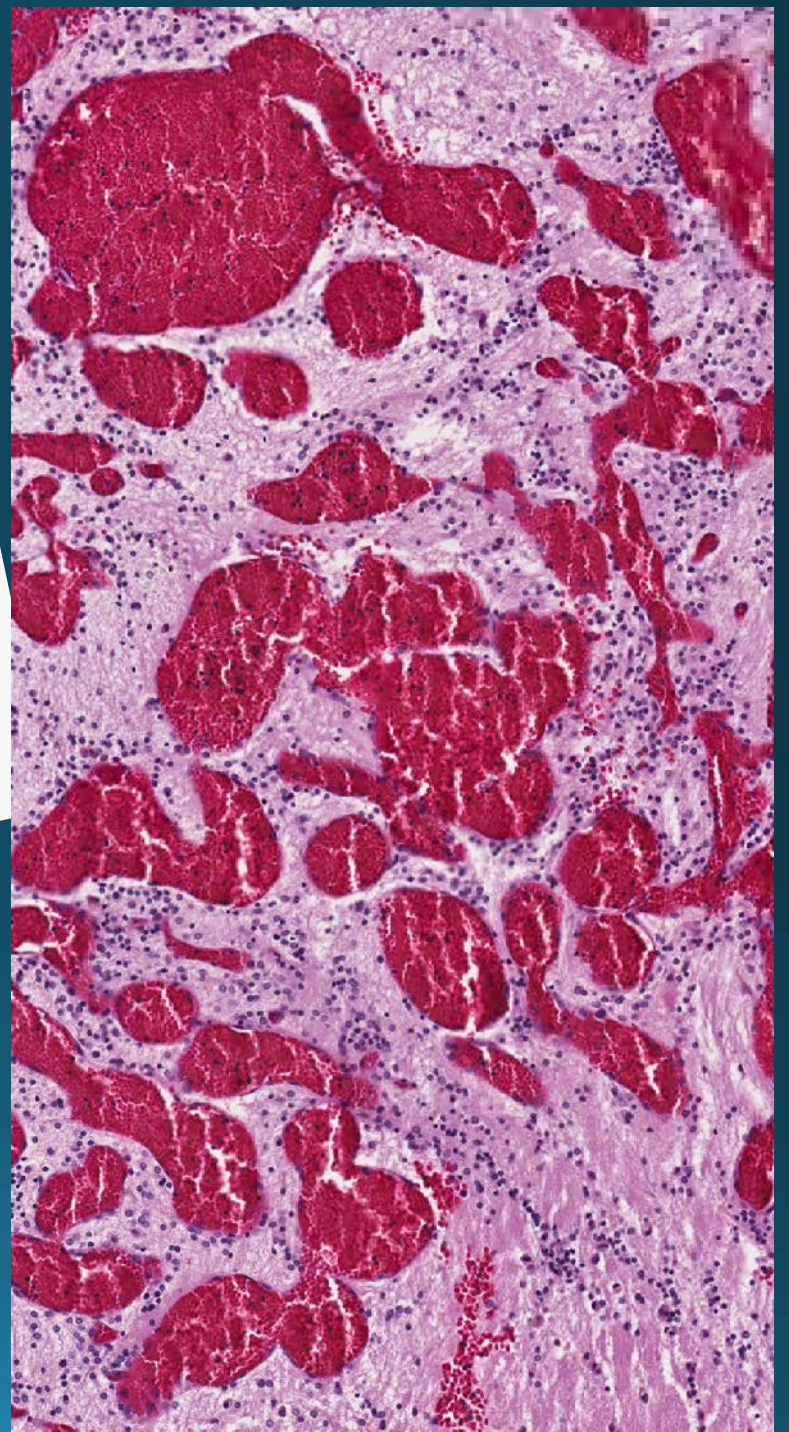




Massively Enlarged Germinal Matrix Periventricular Capillary Malformation







Differential diagnosis?

Genetic testing

CLINICALLY RELEVANT INTERPRETATIONS

Interpretations of variants that are deemed clinically significant are listed here.

Variants Detected	Interpretation
AKT1 p.E17K	A pathogenic, nonsynonymous ***AKT1* p.E17K** mutation was identified at near heterozygous frequency in the sequenced tissue. *AKT1* encodes a serine-threonine protein kinase which, when activated, helps to regulate critical signaling pathways involved in proliferation, differentiation and cell survival. This single nucleotide variant results in the replacement of a glutamic acid with a lysine residue at codon 17. This variant occurs in a highly conserved amino acid residue located within the N-terminal pleckstrin homology (PH) domain of the protein and interacts with the kinase domain to maintain AKT in an inactive state. This variant has been shown to be centrally involved in the molecular etiology of Proteus syndrome in which somatic, activating alterations in***AKT1* p.E17K** have been described (Lindhurst MJ, *et al.*; N Engl J Med; 2011 Aug 18;365(7):611-9). Lindhurst et al. (2011) found

Indication:	Overgrowth disorder, prenatal onset, facial dysm, 3 toes right foot, syndactyly toes 3/4/5 on left	**Date Ordered:**	
Specimen Quality:	Adequate	**Date Accessioned:**	

REVIEW STATUS: Final

TEST PERFORMED

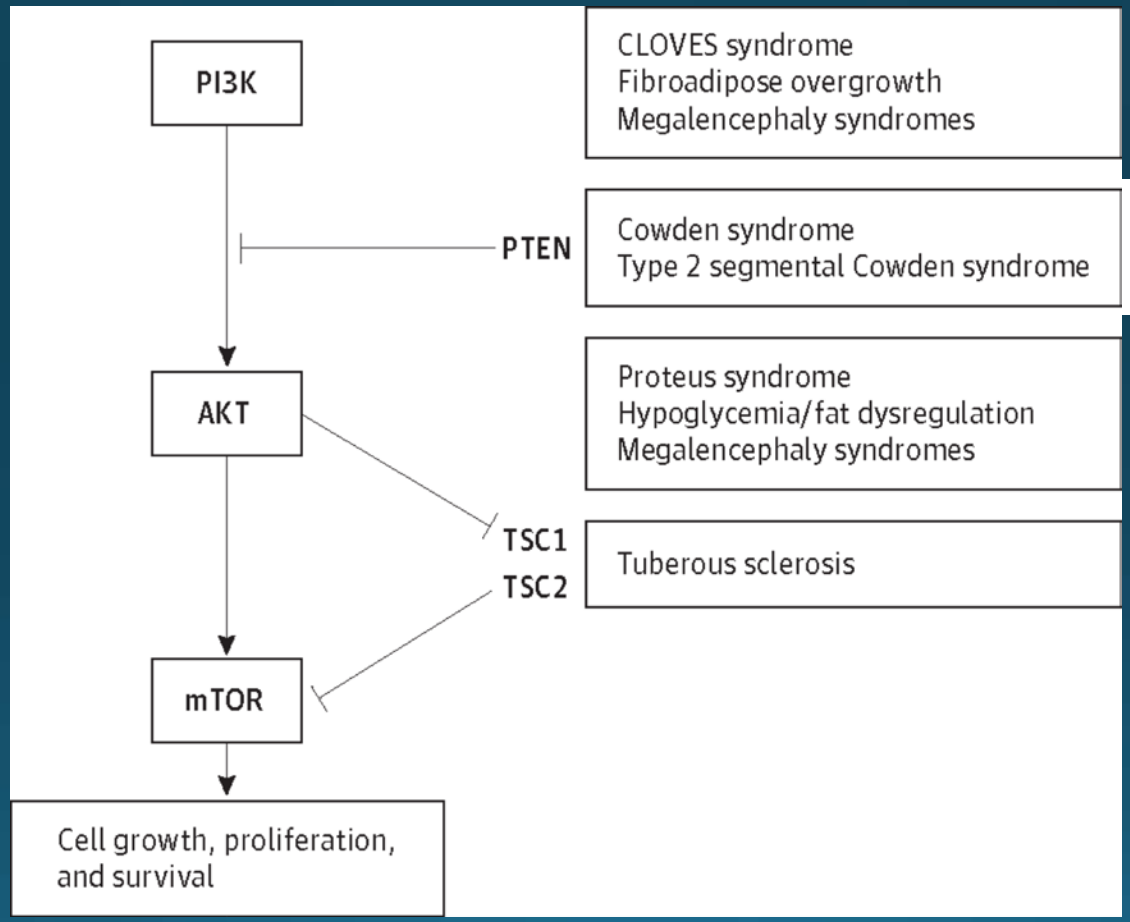
Somatic Overgrowth Gene Set - Targeted next-generation sequencing was performed on this FFPE sample biopsied from the left temporal lobe in this patient with multiple malformation syndrome with early overgrowth. See Test Details for more information.

CLINICALLY RELEVANT RESULTS SUMMARY

Variants that are deemed clinically significant are listed here.

Variants Detected	Pathogenic	Likely Pathogenic
AKT1 p.E17K	✓	

Discussion: Genetic pathway PI3K-**AKT**-mTOR Signaling Pathway



Bannayan-Riley-Ruvalcaba syndrome

CLOVES indicates congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies.

JAMA Dermatol. 2014;150(9):990-993. doi:10.1001/jamadermatol.2013.10368

Diagnosis

Proteus Syndrome due to AKT1 pE17K mutation.

- Facial anomaly
  - Dolichoencephaly
  - frontal bossing,
  - midfacial hypoplasia,
  - Hypertelorism
  - low nasal bridge,
  - anteverted nostrils
- Systemic vascular malformations
- Brain anomaly
  - Megalencephaly
  - Cobblestone cortex
  - Periventricular nodular heterotopia
  - Massively enlarged germinal matrix
  - Multiple capillary malformations
  - Focal polymicrogyria
  - Choroid plexus cyst

Discussion: Proteus syndrome (PS)

- Proteus syndrome is a complex condition characterized by asymmetric overgrowth of tissue types derived from all three germ layers (bones, skin, neural and other tissues)
- Incidence: < 1 in 1 million people worldwide
- Named by Wiedemann; derived from the Greek god, Proteus (ability to constantly change his shape)

Discussion:

- Clinical presentation of PS
  - Highly variable
  - Joseph Merrick, "The Elephant Man"
    -most well-known case of Proteus syndrome

Sculpture by Paul Kamoda in 1990s

References

- Biesecker L. G., Happle R., Mulliken J. B., et al.: Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet 1999; 84(5): 389–395.
- Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet 2006; 14(11): 1151–1157.
- Ogrodnik M, S Krzysztof, J Sergiusz. Neurological manifestations of Proteus syndrome – review of the literature. Vol. 24/2015, nr 49
- Dietrich R. B., Glidden D. E., Roth G. M., et al.: The Proteus syndrome: CNS manifestations. Am J Neuroradiol 1998; 19(5): 987–990.