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Case 2

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Clinical history

- Mother primigravida, high BMI
- Normal antenatal scans
- Reduced fetal movements 48h before delivery at 40+4 weeks
- Caesarean section due to profound & prolonged bradycardia
- Male 4kg born in poor condition
- HR 80bpm, spontaneous breathing at 6 minutes, O_2 sats 80%
- Cooling but he developed severe HIE
- PPHN & diffuse cardiac hypertrophy
- Intensive care withdrawn on day 2

	Current case	Range for GA	Best fit
Gestation	40	40	41
Birth weight	4002	2472-3372	2425-3625
Body weight	4213	2472-3372	2425-3626
Crown-heel	55.2	43.6-53.0	43.5- 53.3
Crown-rump	39	32.4-38.0	32.9-39.1
Toe-heel	8.5	6.9-8.5	7.1-8.7
Femur	7.9	7.2-7.8	7.2-7.9
Humerus	7	6.3-7.0	6.3-7.1
Head circ.	34	33-37	33.5-37.5

Weights in g; measurements in cm

Organs	Current case		Range for GA			Range for BW			
Heart	32.5	↑ ↑	14.8	-	26	21.1	-	31.9	Lung: BW
R. Lung	62.1			-			-		0.027
L. Lung	51.1			-			-		
(combined)	113.2	↑ ↑	21.9	-	67.3	47	-	84.6	N>0.015 for< 28wks
Liver	136.2	✓ ↓	92.1	-	163.7	148	-	220	N>0.012 for> 28wks
Pancreas	6.0	↑ ✓	2.3	-	4.9	3.1	-	6.3	
Spleen	15.8	↑ ✓	7.1	-	13.7	10.5	-	16.3	Brain: liver
Thymus	6.0		4.5	-	14.5	7.8	-	15.2	2.7
R. Kidney	25.7			-			-		Normal = 3
L. Kidney	27.3			-			-		
(combined)	53		15.8	-	38.8	24.9	-	45.1	Fetus: placenta
Adrenals	8.0		4.7	-	10.7	6.7	-	14.1	NA
Brain	368		277	-	435	357	-	461	
Placenta	NA	↑ ✓	390	-	643		-		

Weights in g


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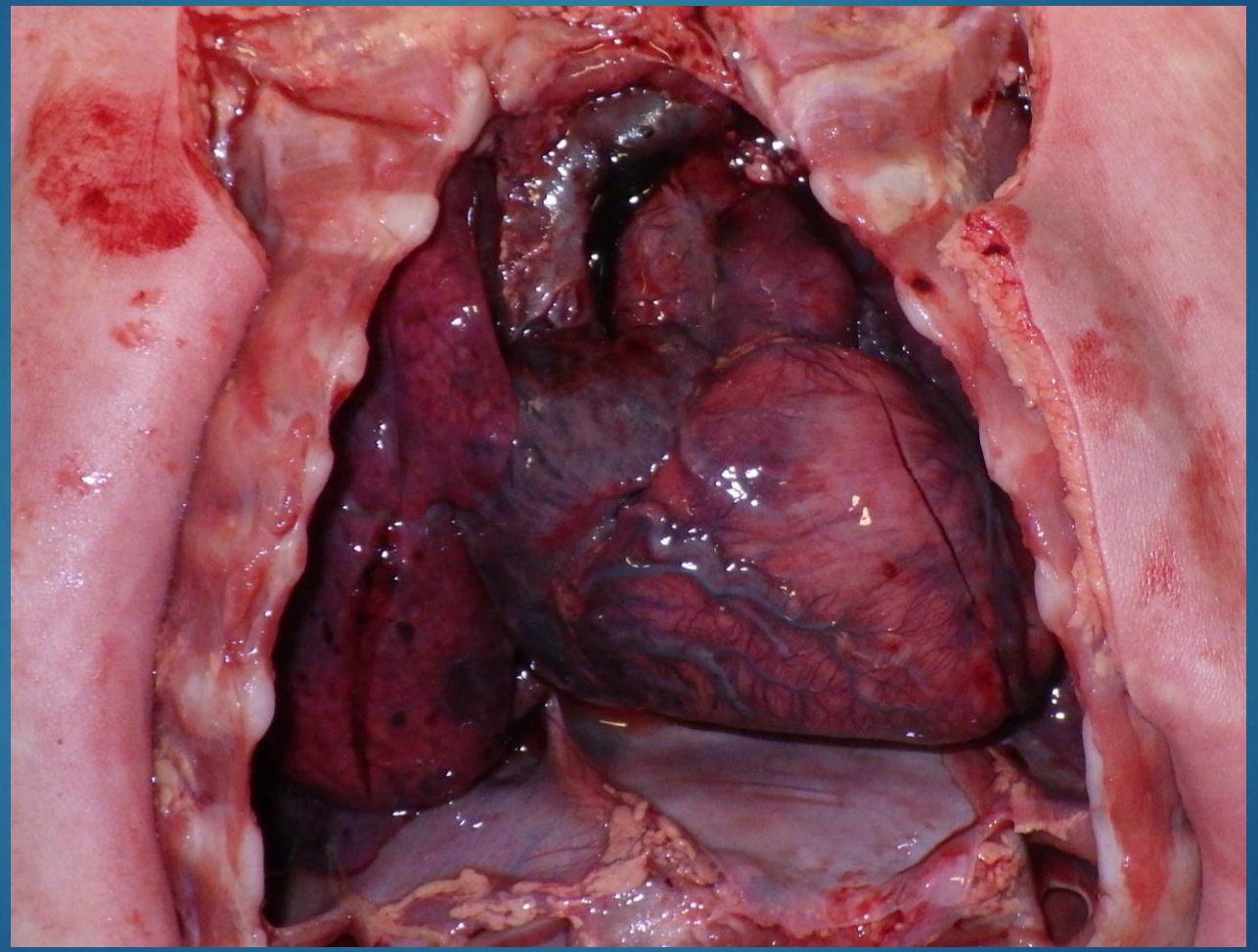
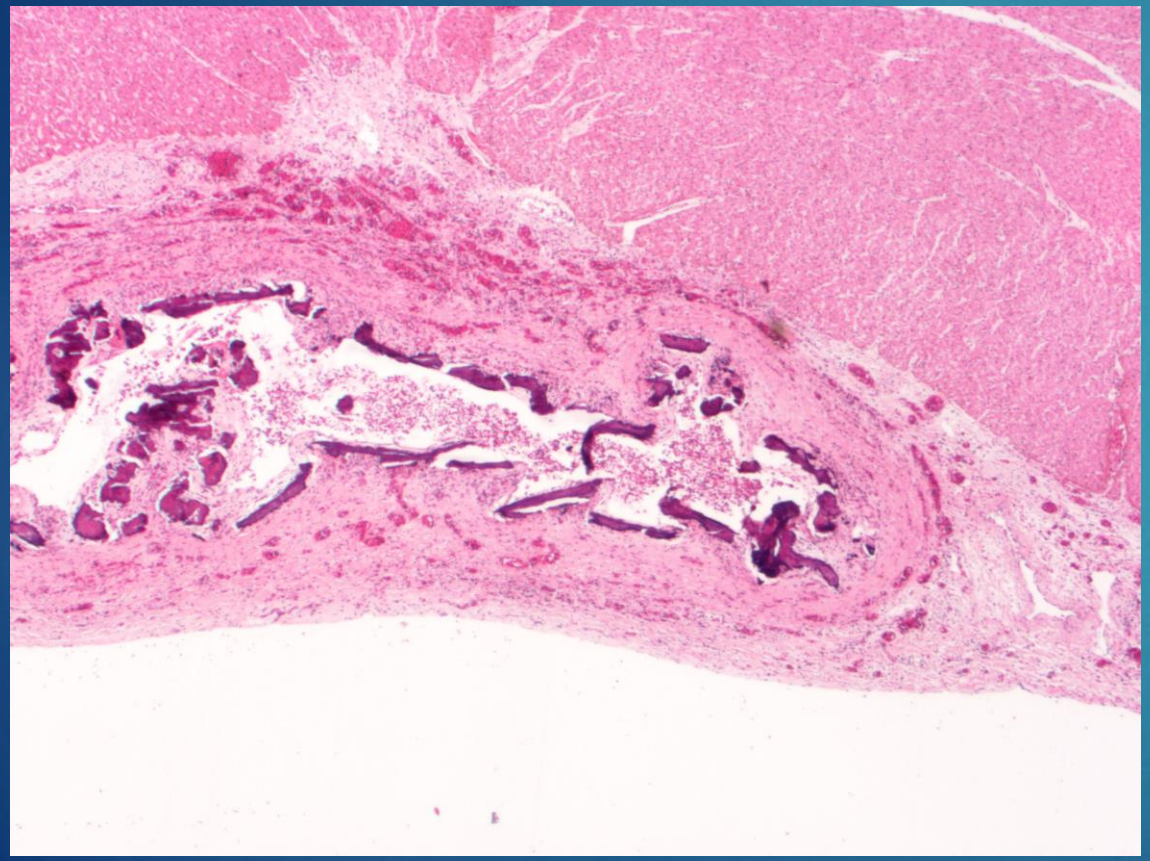
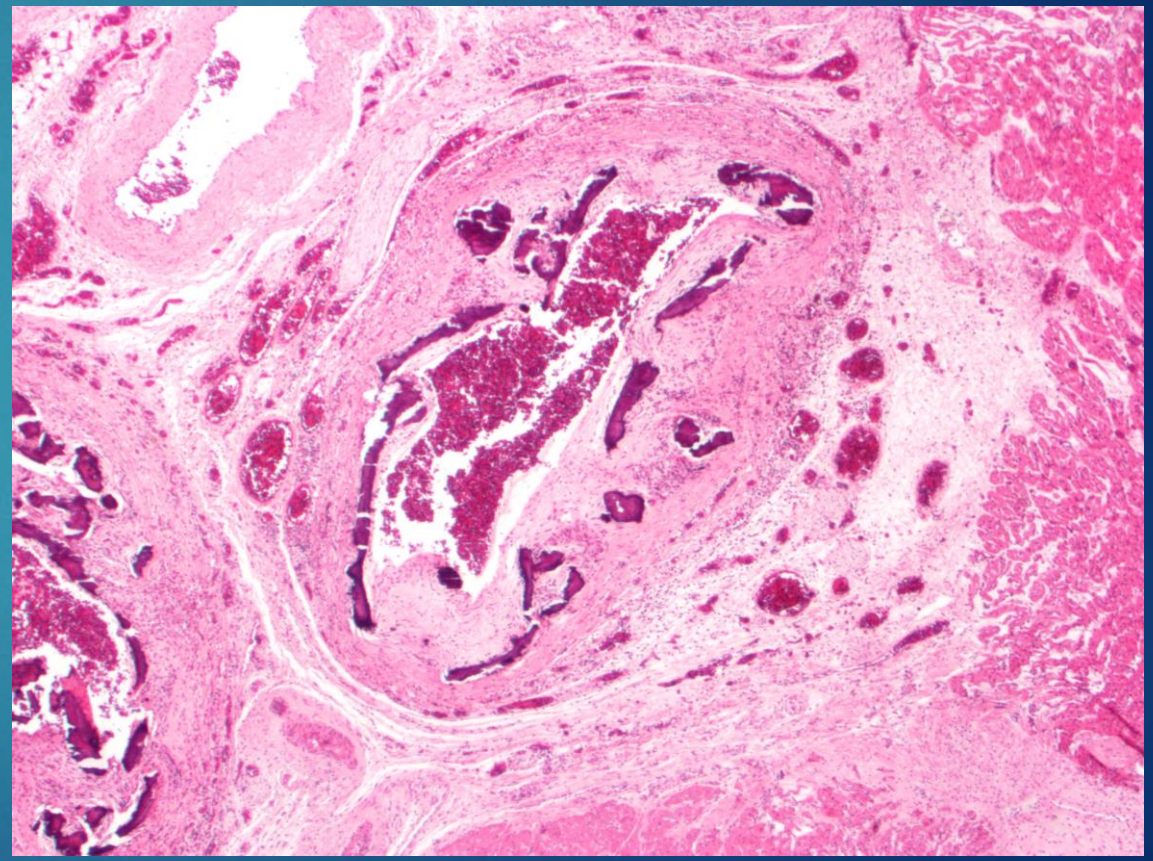
Heart

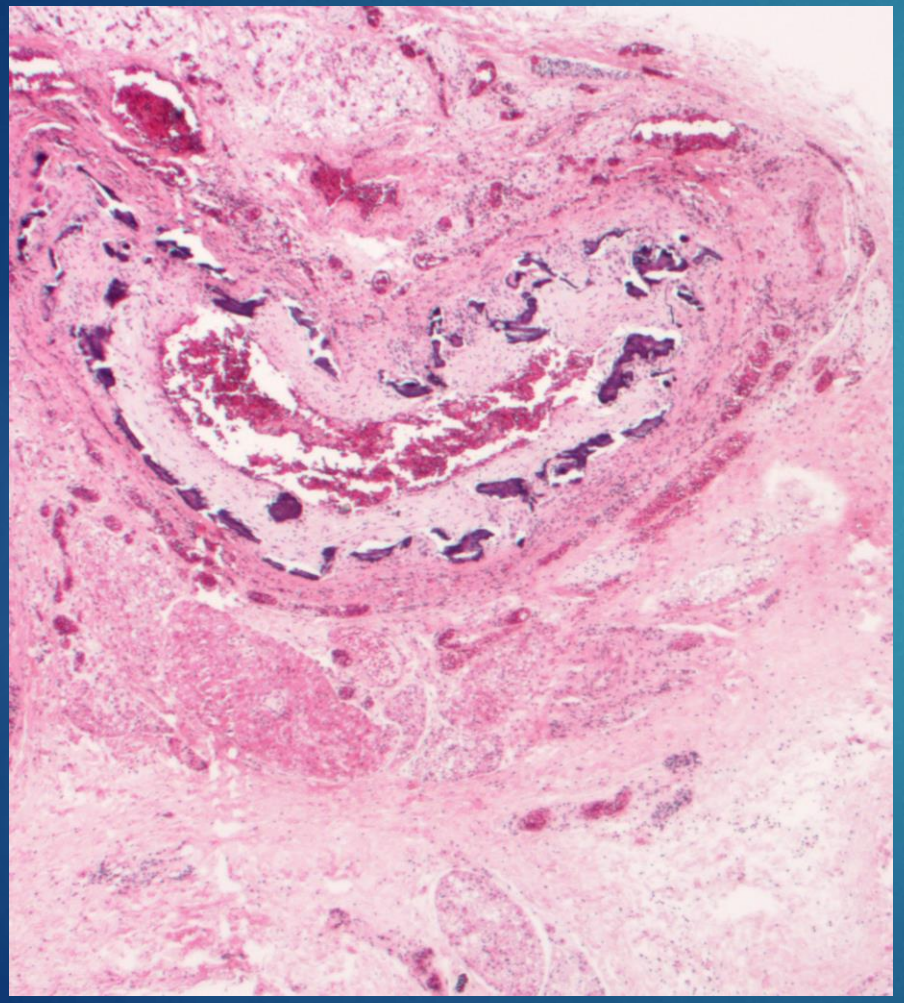


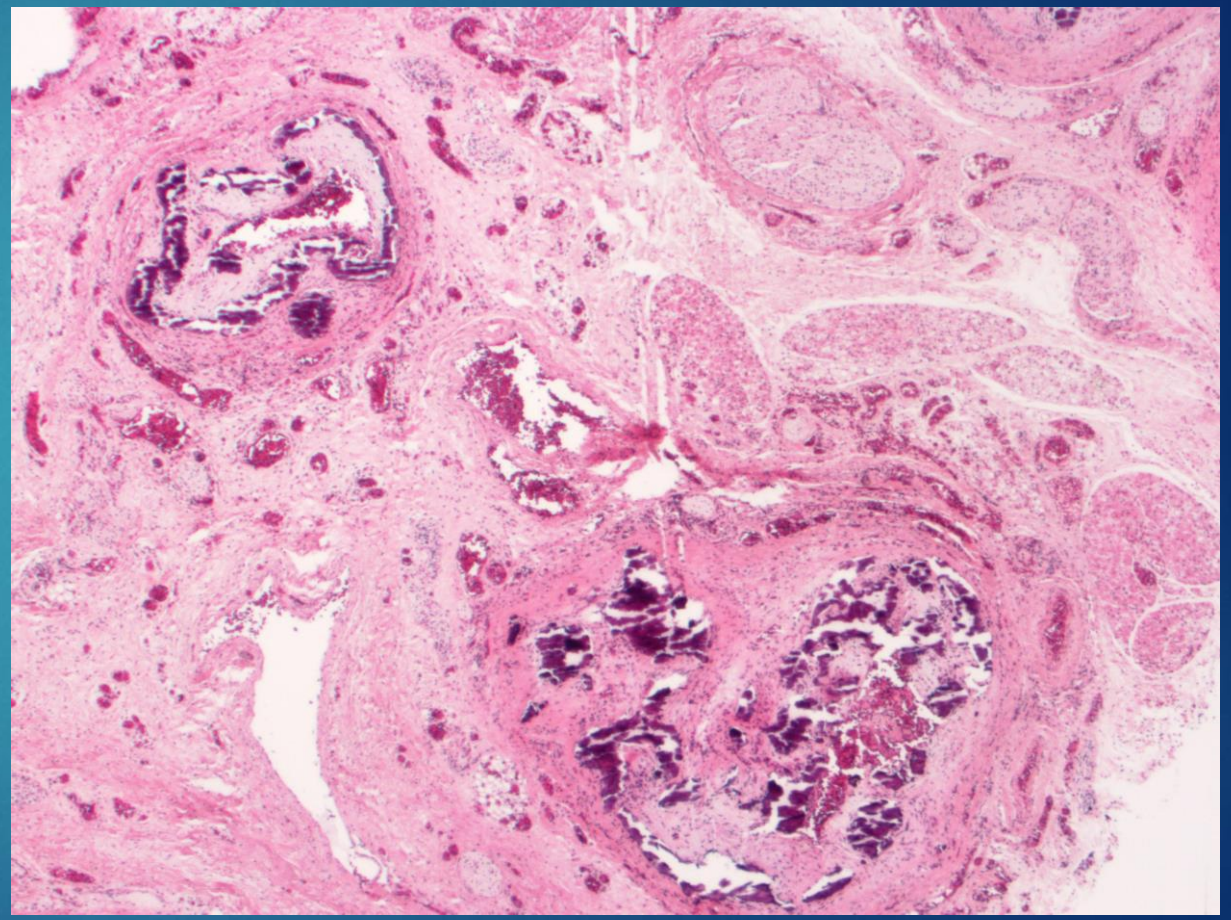
Histology coronary arteries



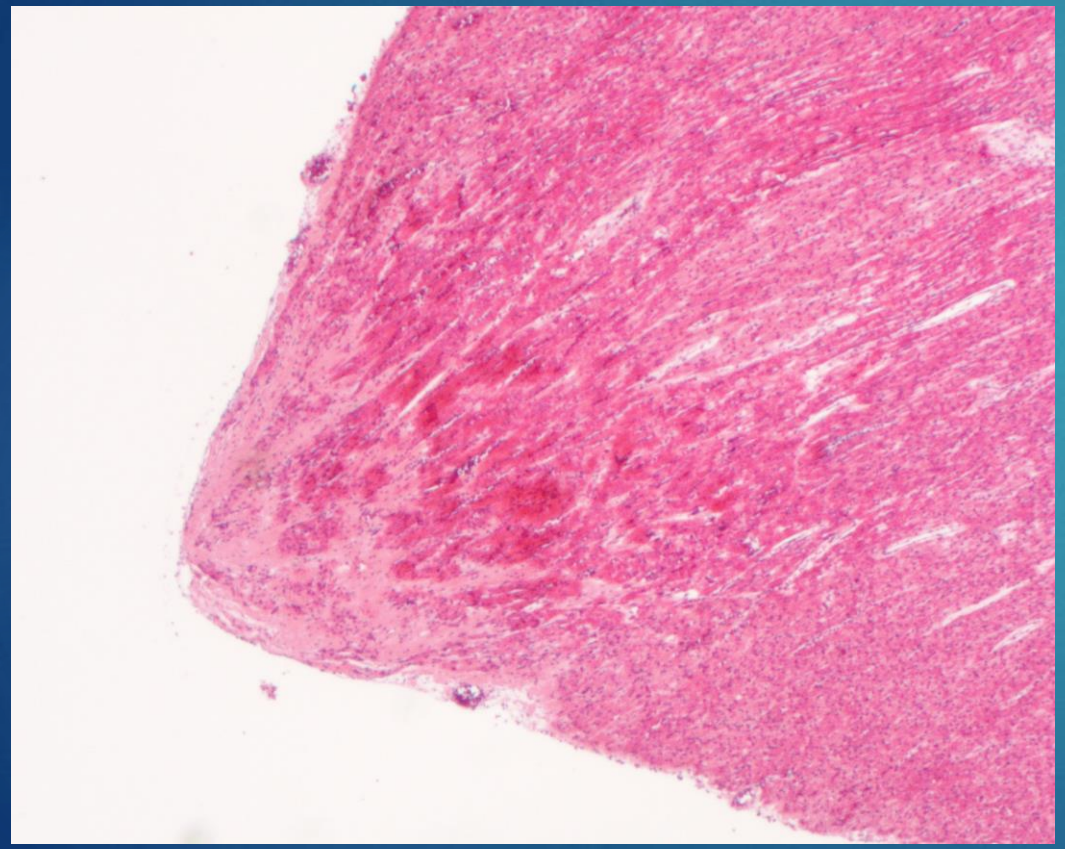


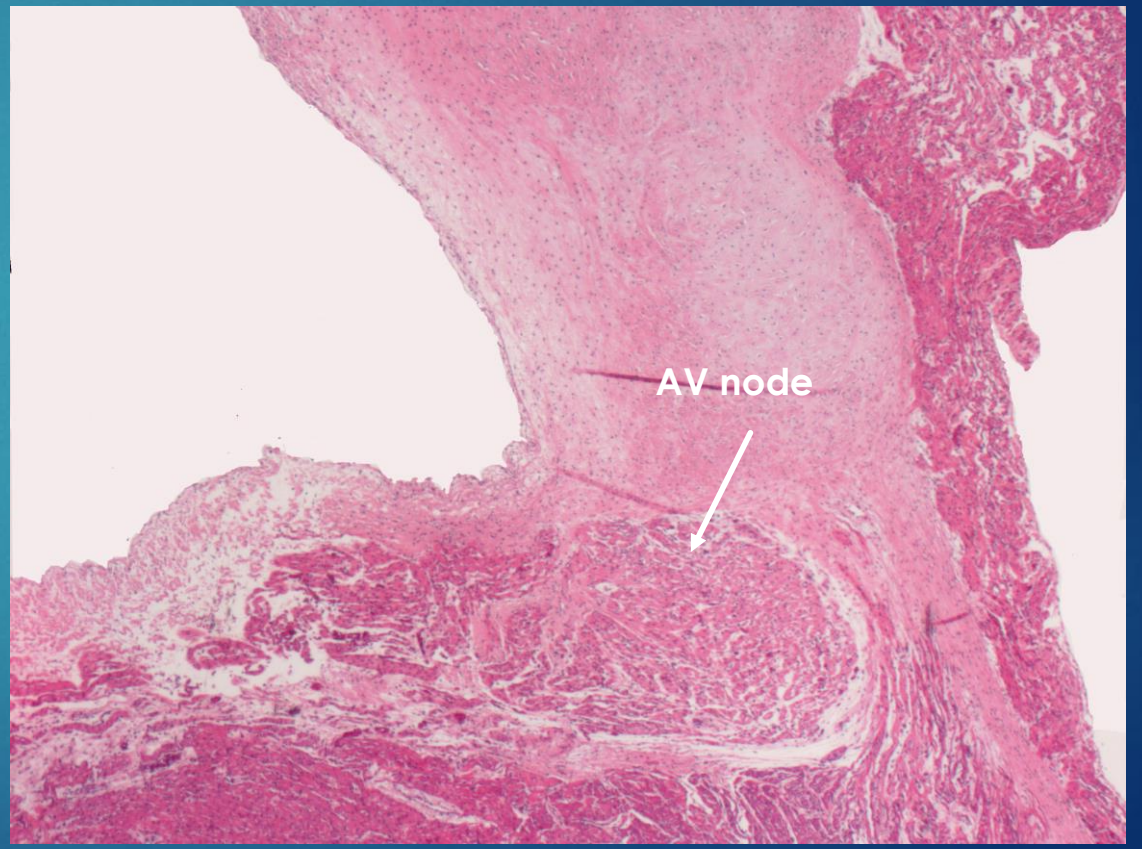
Carotid artery and branches



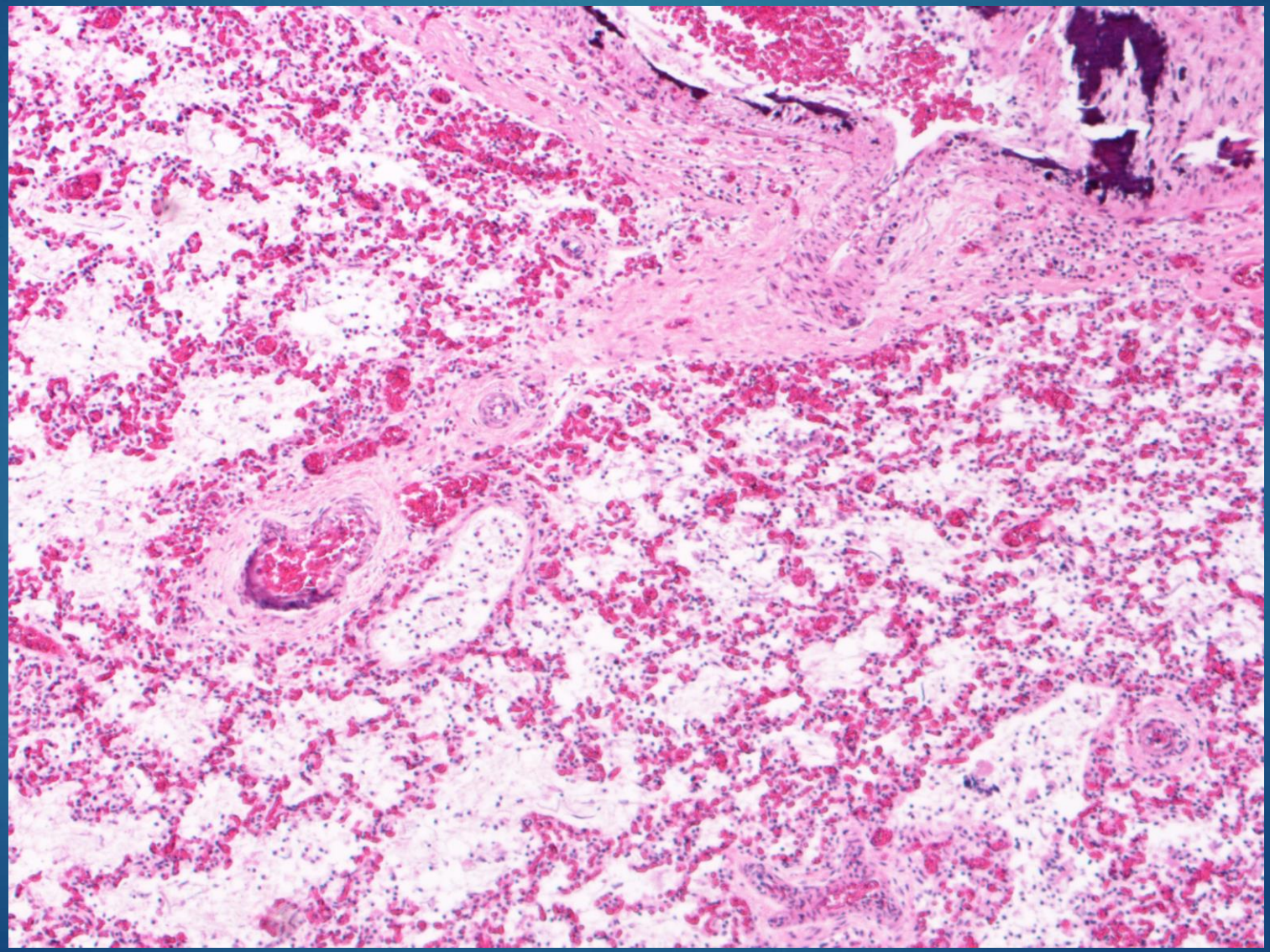


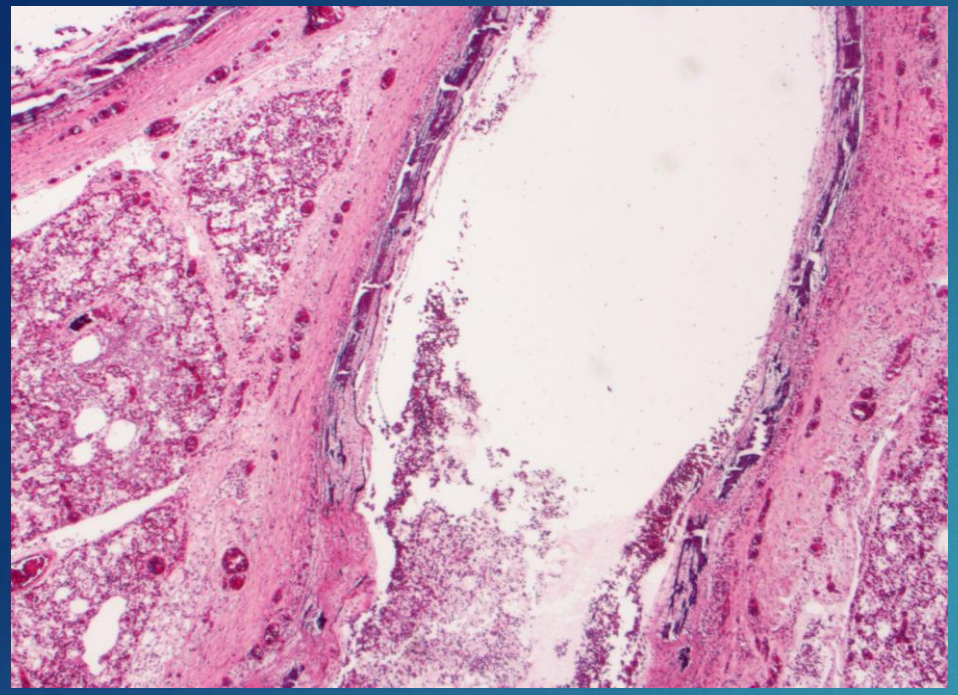
Infarct in papillary muscle

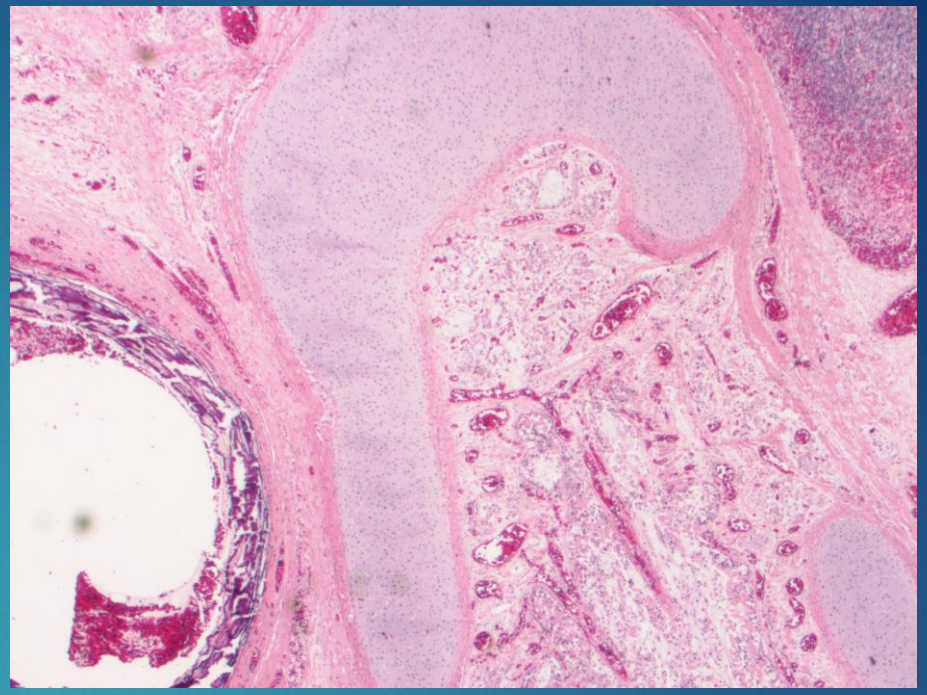


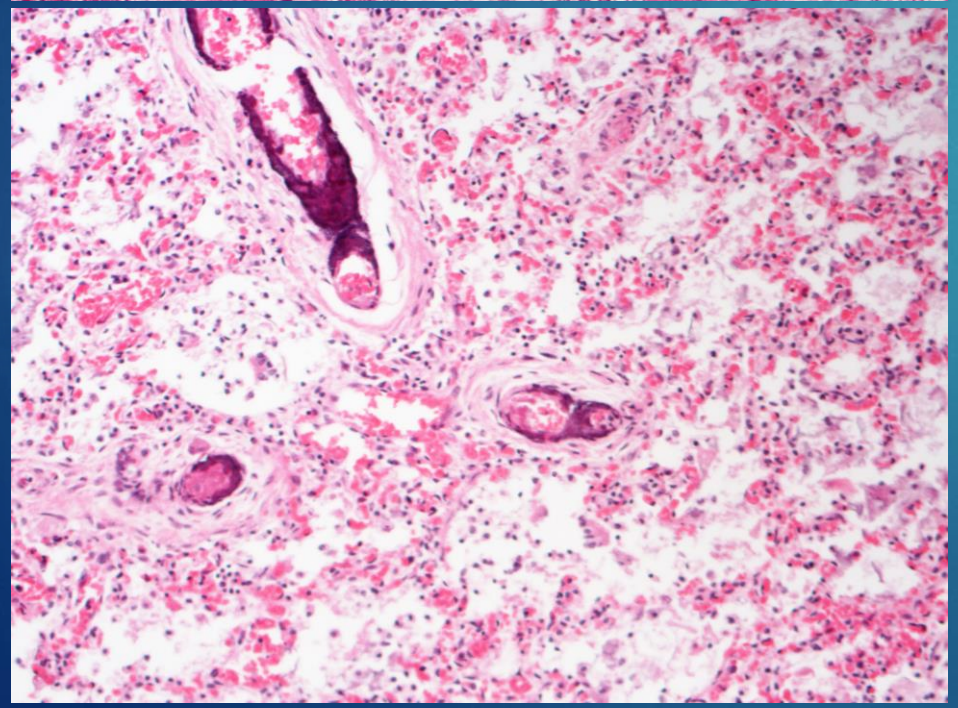


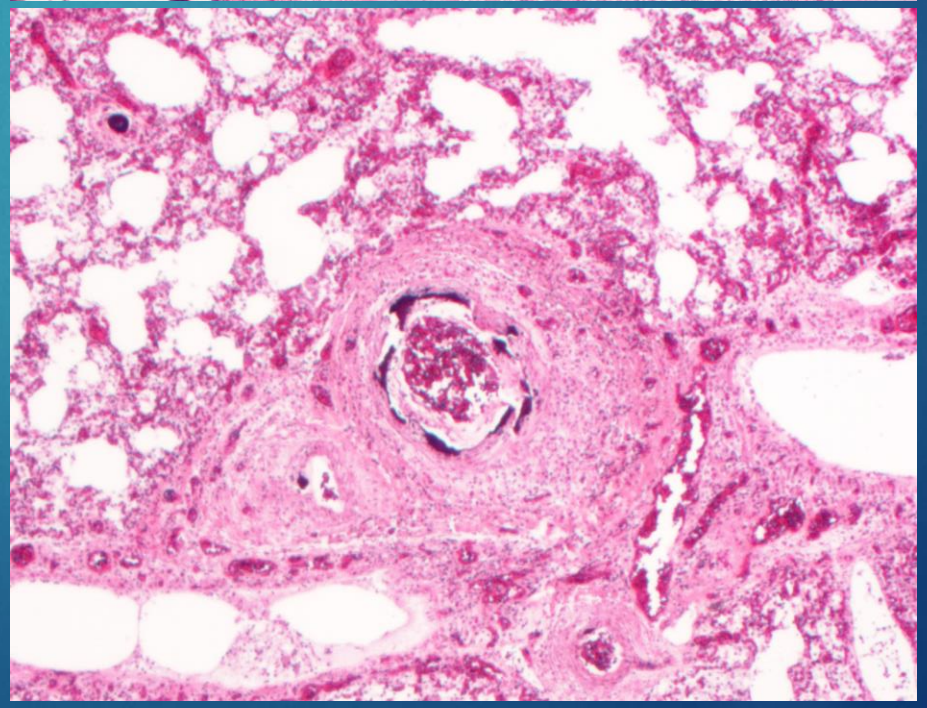
Lungs



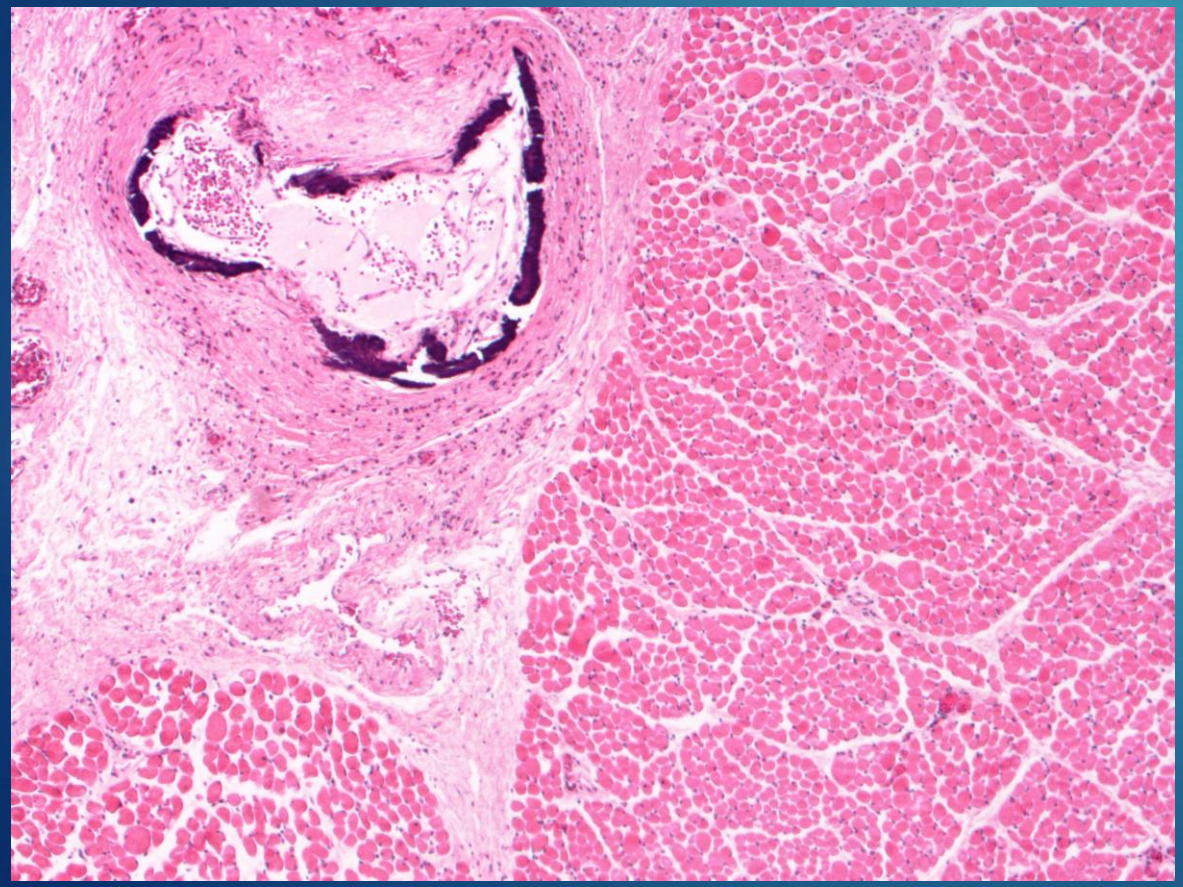


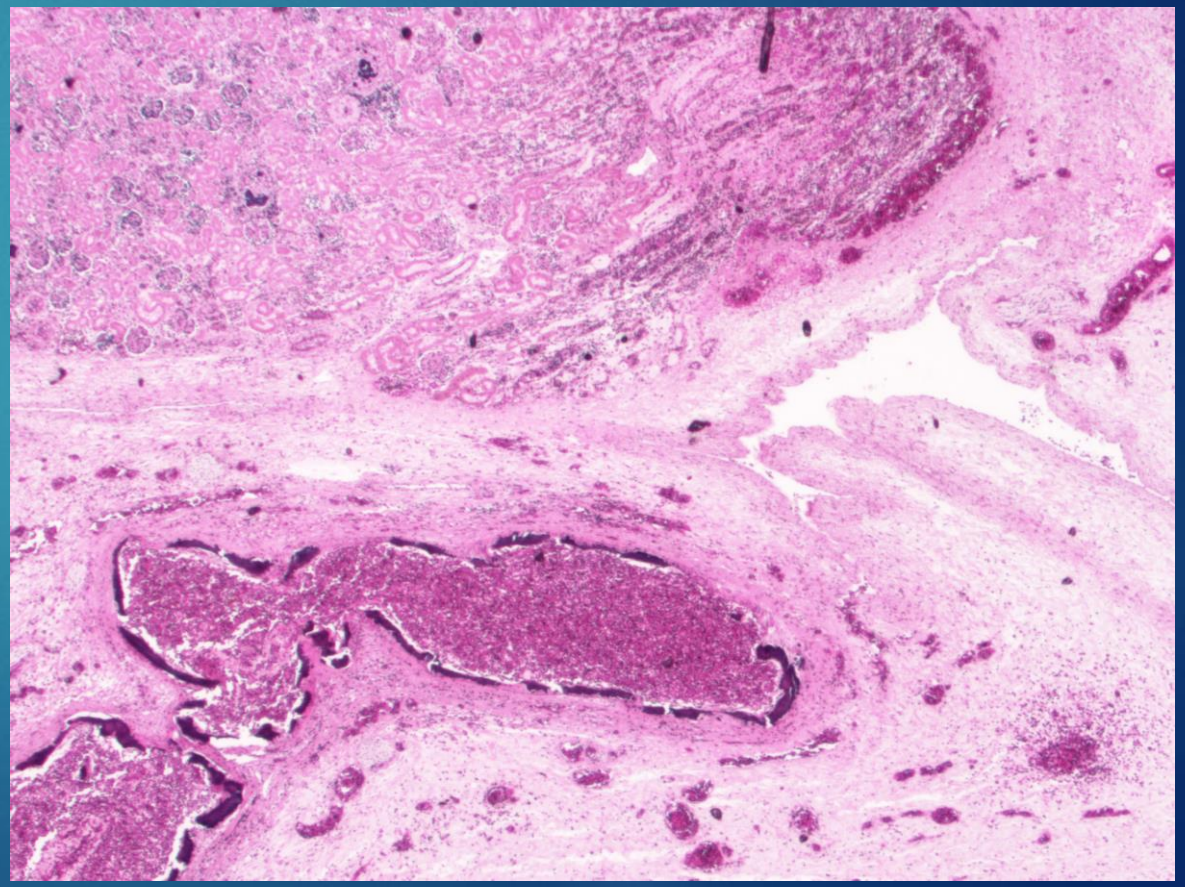




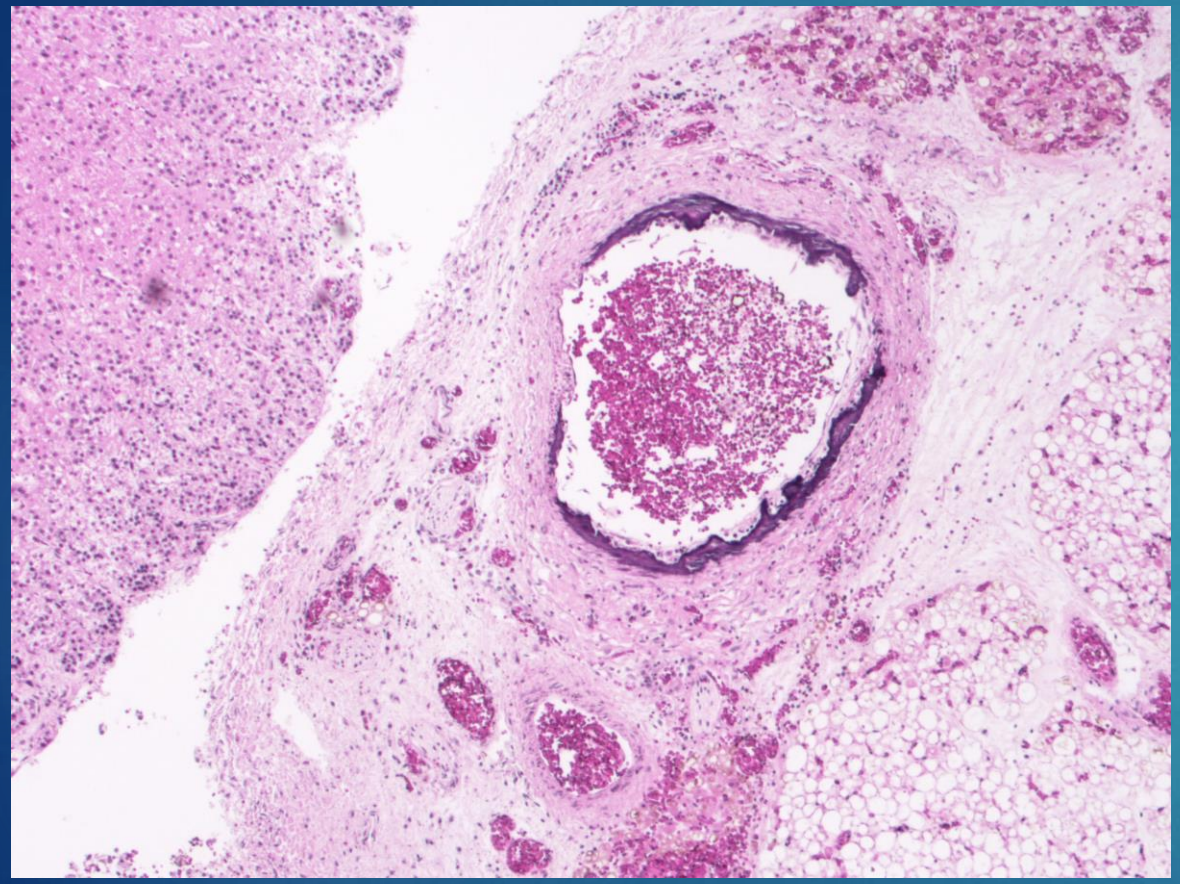


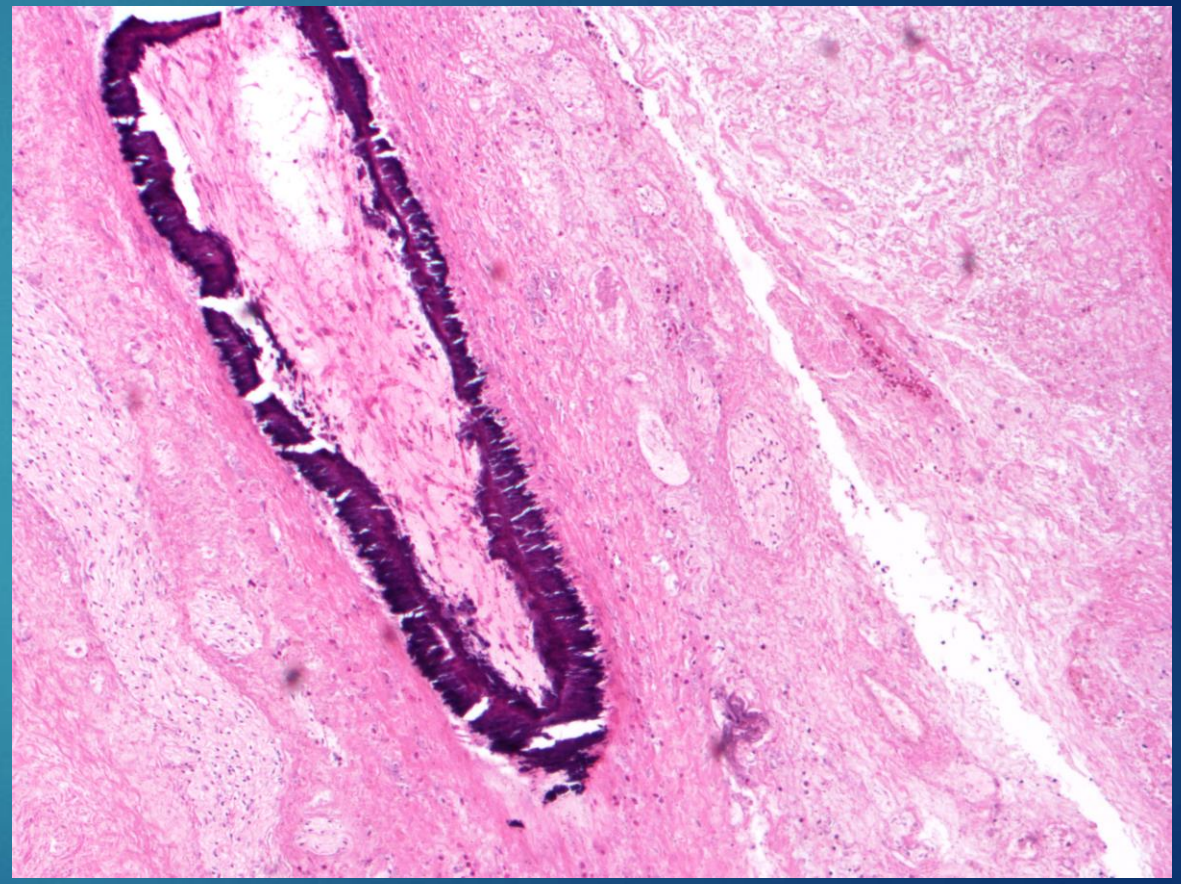
Descending aorta and renal arteries



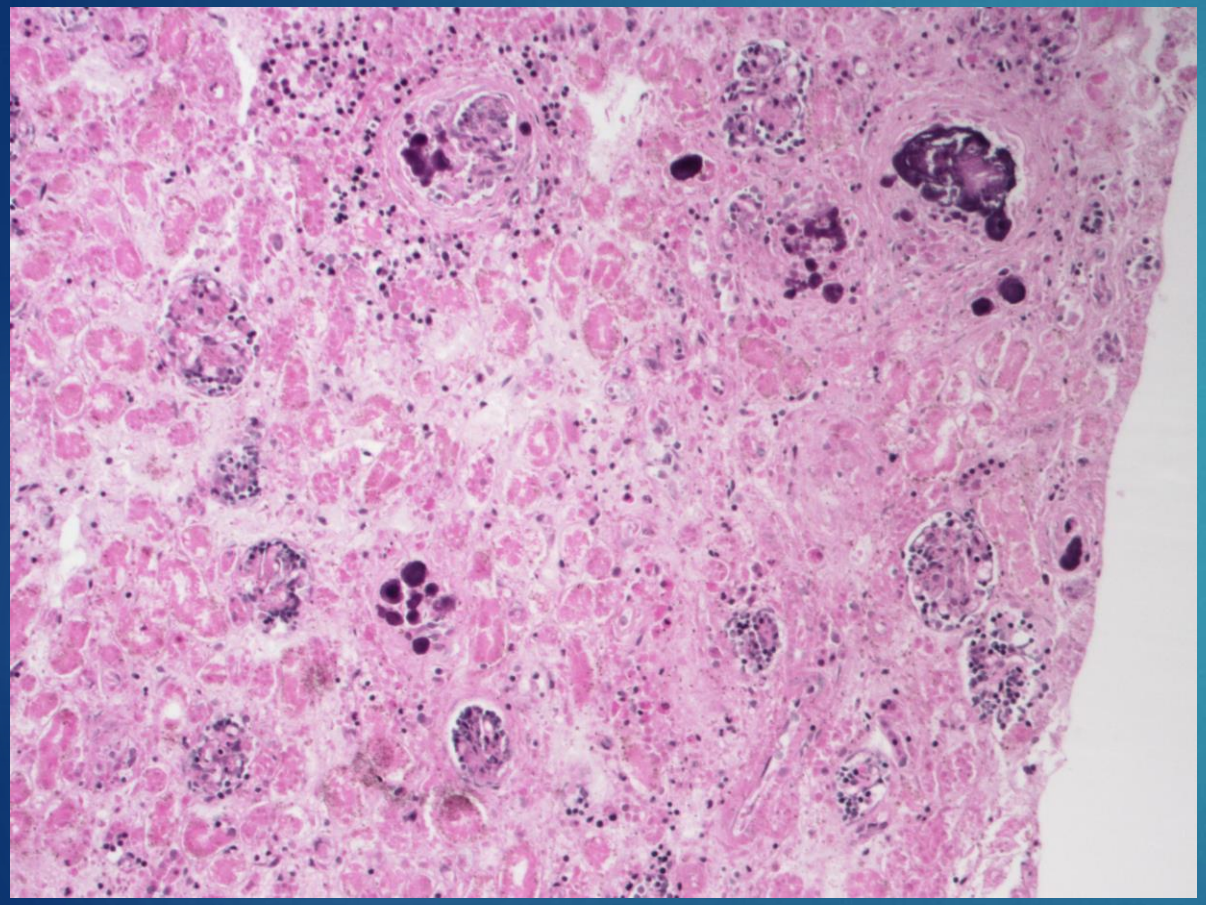


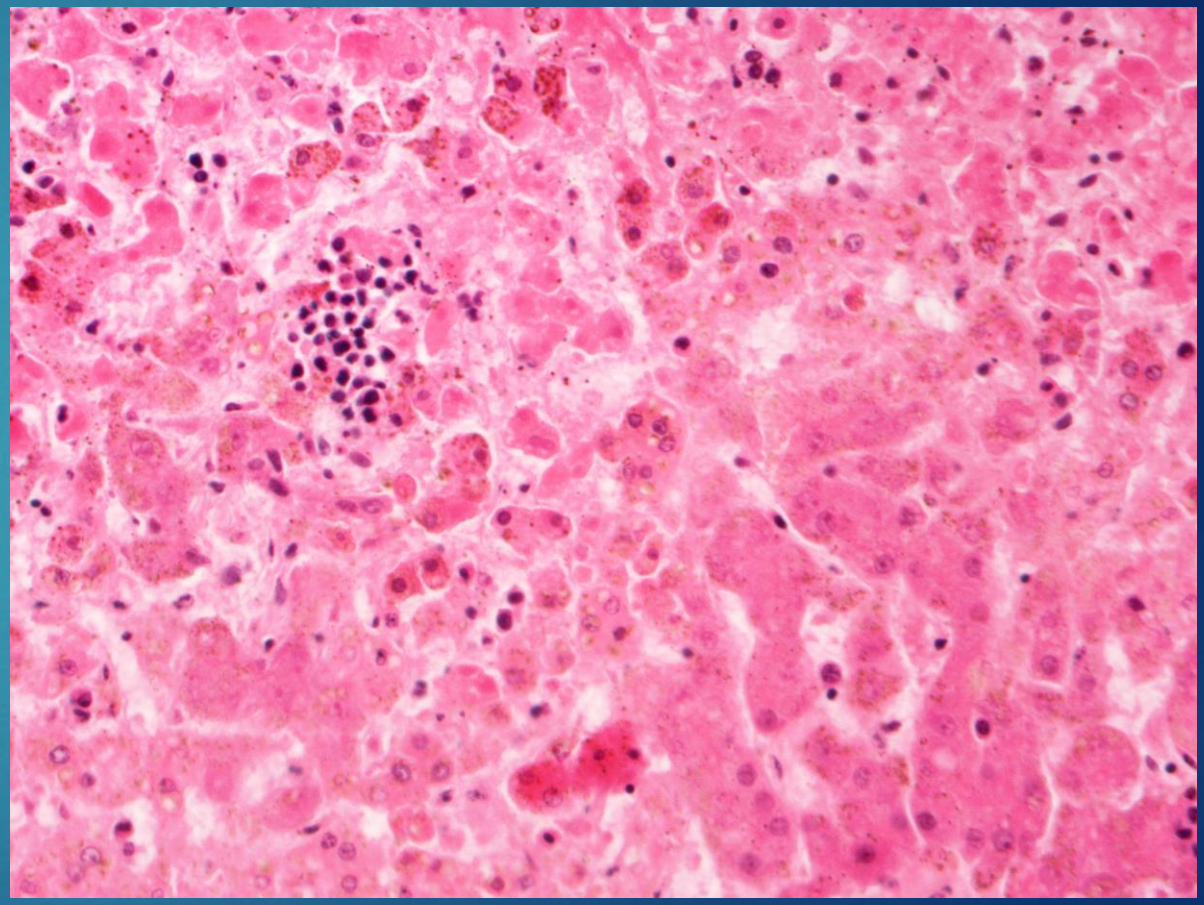
Adrenals and pancreas



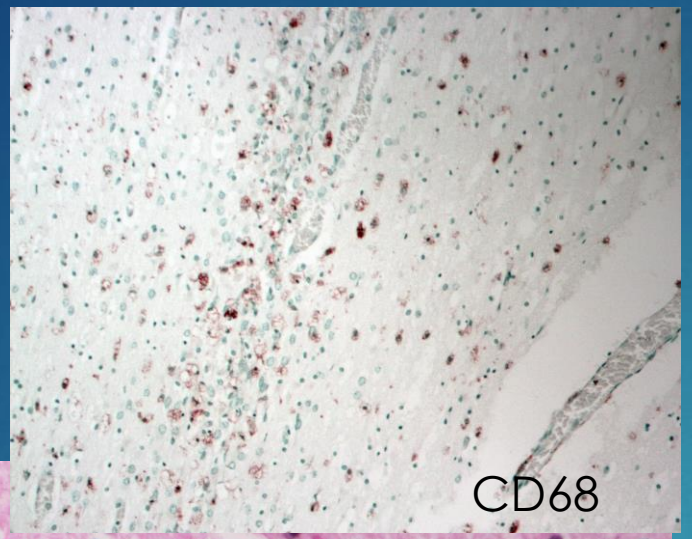


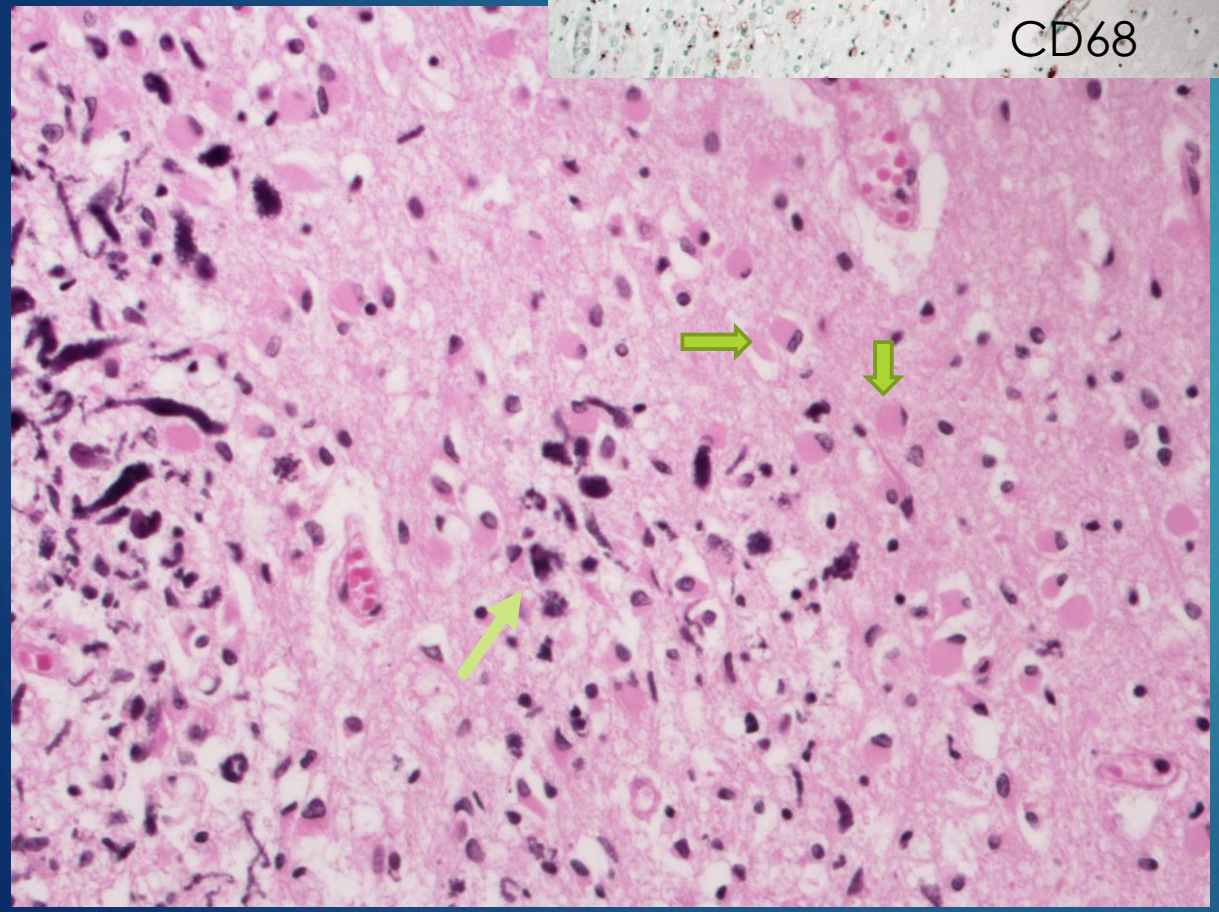
Kidney and liver

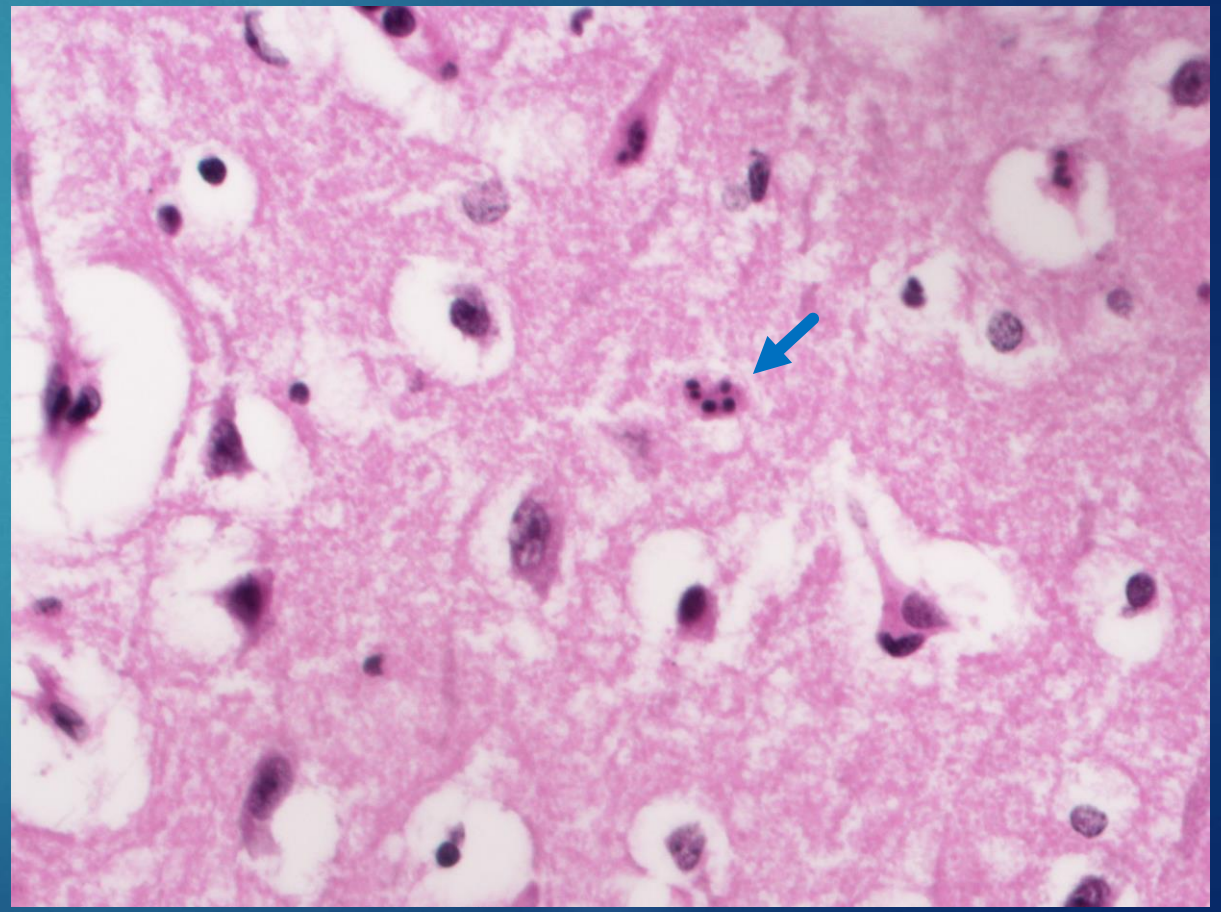




Brain







Diagnosis

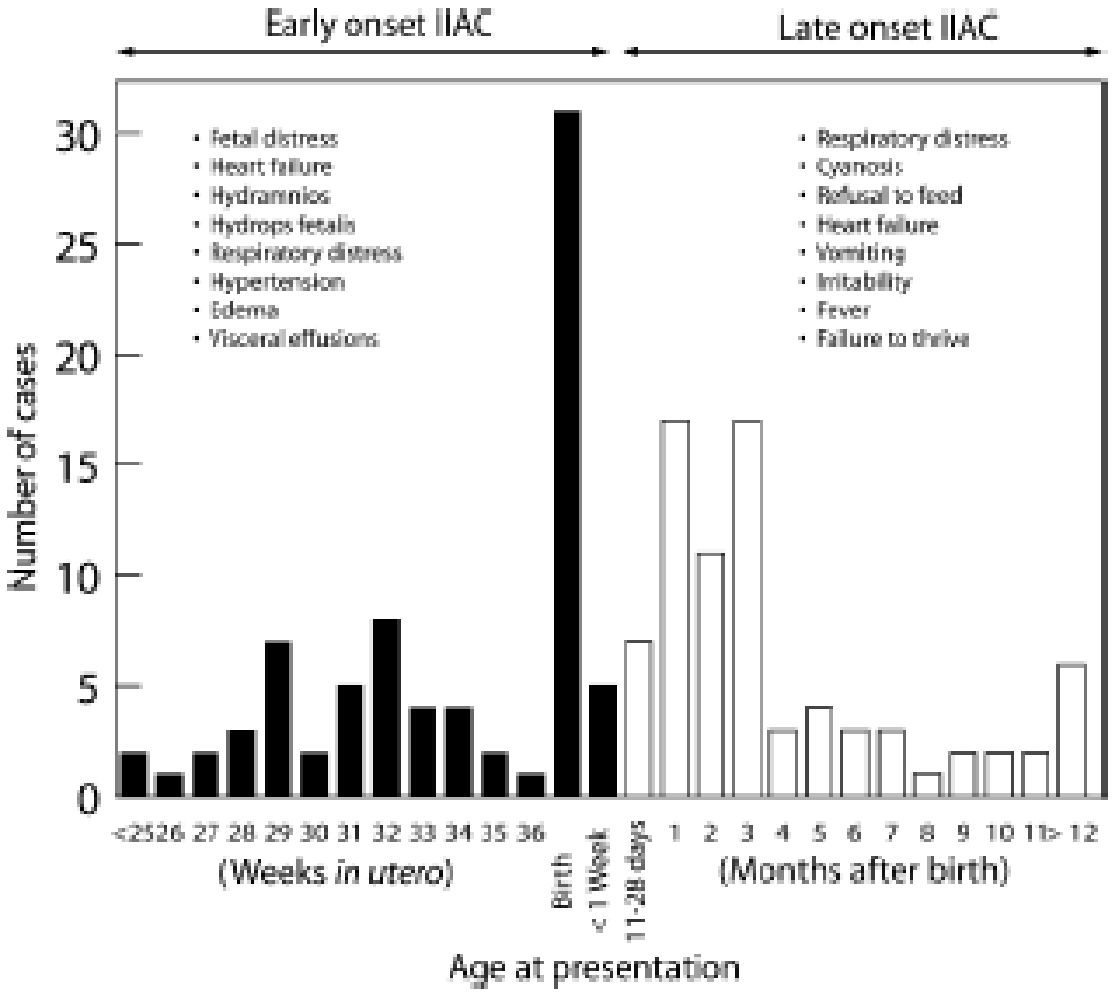
Generalized idiopathic arterial calcification of infancy (GACI)

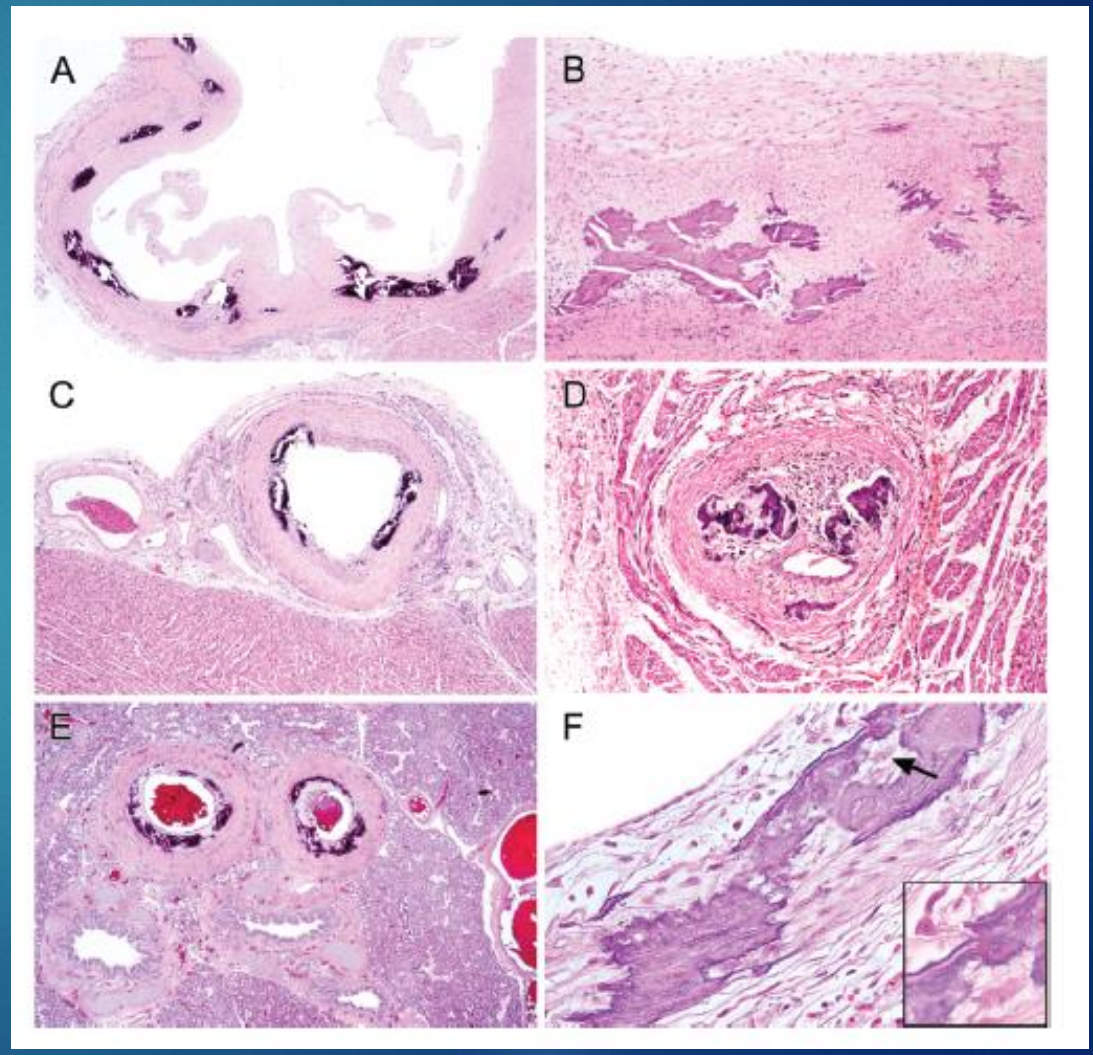
GACI

- Rare autosomal recessive disorder
- Diffuse calcification with hydroxyapatite deposits in the media's elastic lamina of large and medium sized arteries associated with intimal proliferation → arterial stenosis
- Antenatal USS may show hydrops and calcification (from 18/40)
- Depending on severity infants may present with IUD, NN heart failure, arterial hypertension and death within the first 6 months of life in 60-80%
- Spontaneous regression and survival to adulthood
- Biphosphonates (synthetic analogs of pyrophosphate) block conversion of Ca+ into hydroxyapatite & calcifications disappear
- *ENPP1* enzyme replacement therapy successful in mice (2018)

Idiopathic Infantile Arterial Calcification: The Spectrum of Clinical Presentations

Curtis R. Chong[1*] and Grover M. Hutchins[2] Pediatric and Developmental Pathology 11, 405–415, 2008



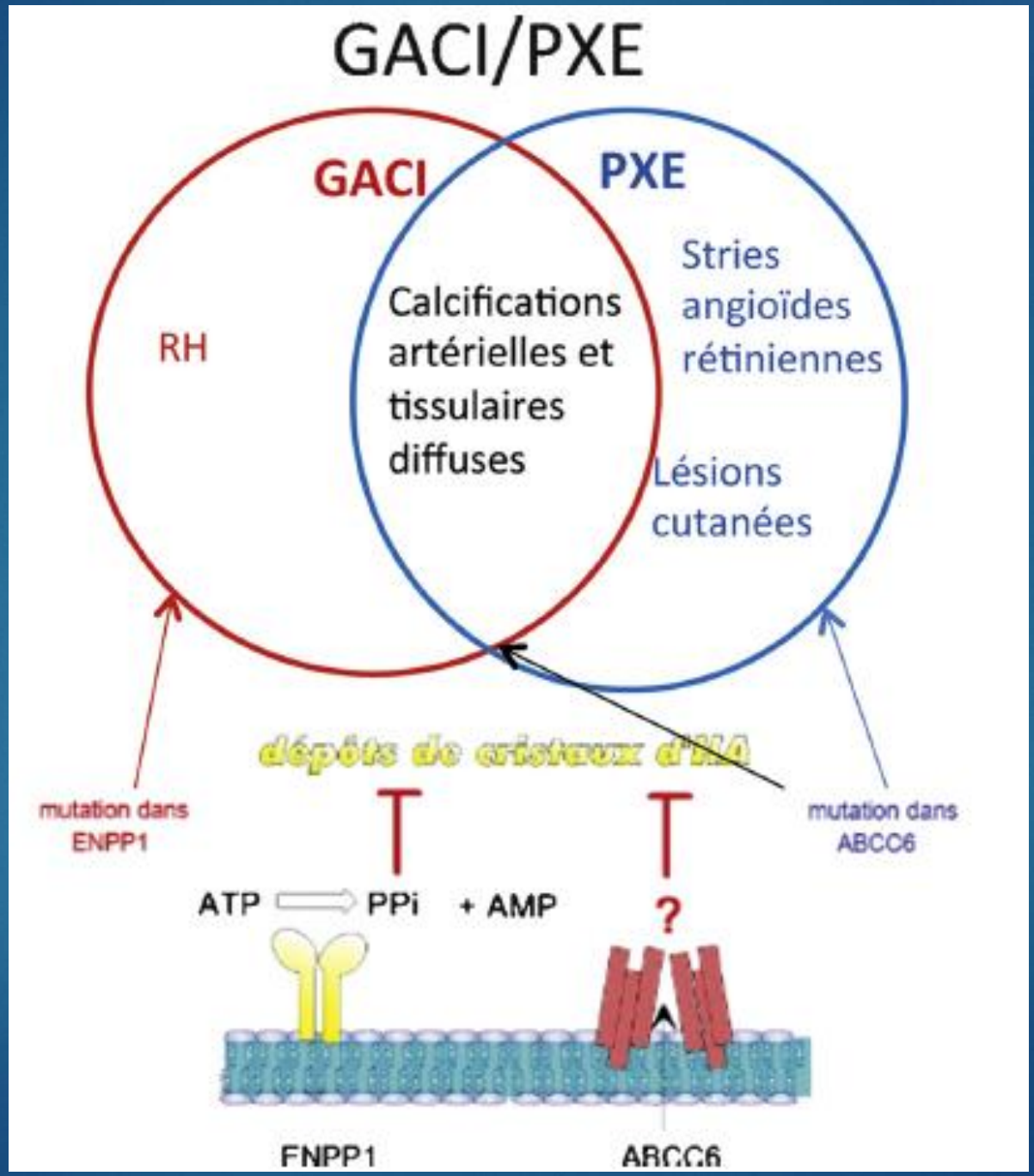


Genetics

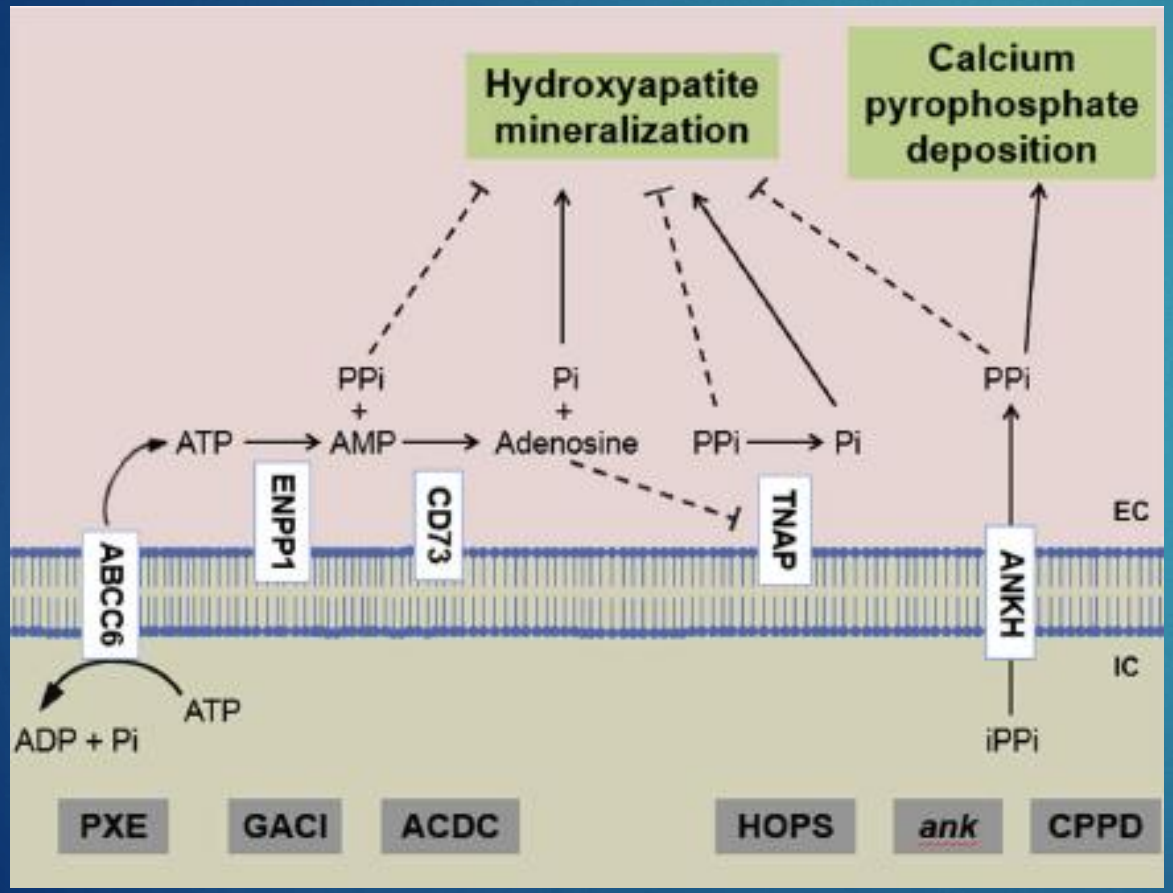
- 70%: Several inactivating mutations of the *ENPP1* gene which encodes ectonucleotide pyrophosphatase/phosphodiesterase 1 (PP1), a potent calcification inhibitor
- 30%: inactivating mutations of *ABCC6* gene encoding an ATP-binding efflux transporter responsible for PXE (pseudoxanthoma elasticum)
- AR hypophosphatemic rickets may also be associated with inactivation mutations of *ENPP1* & may alleviate symptoms of GACI

GACI and PXE

- PXE: multisystemic ectopic mineralization disorder, late onset, progressive clinical manifestations in skin, eyes and CV system
- Genotypic overlap between PXE and GACI
- Several families with GACI have *ABCC6* mutations. In one family one sibling died of GACI and another develop PXE 25 years later
- Recent study: 92 GACI patients
  - 3 patients treated with biphosphonates presented later with clinical features of PXE had *ENPP1* mutations
  - 14 patients (of 28 with no disease causing *ENPP1* mutation) had *ABCC6* mutations

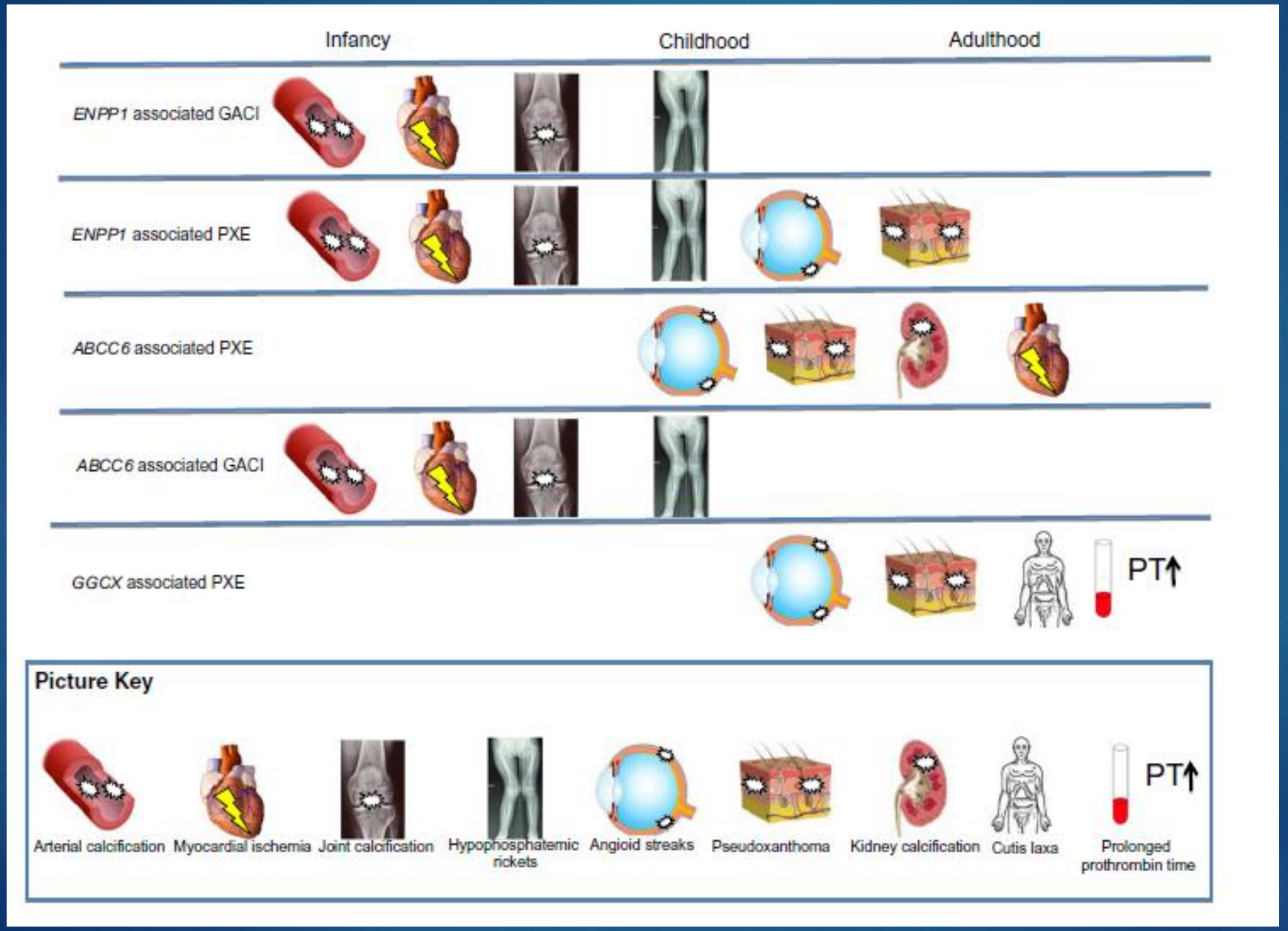

GACI/PXE
GACI
PXE
RH
Calcifications artérielles et tissulaires diffuses
Stries angioïdes rétiniennes
Lésions cutanées
dépôts de cristaux d'HA
mutation dans ENPP1
mutation dans ABCC6
ATP
PPi
+ AMP
?
ENPP1
ABCC6

Mechanism of mineralization



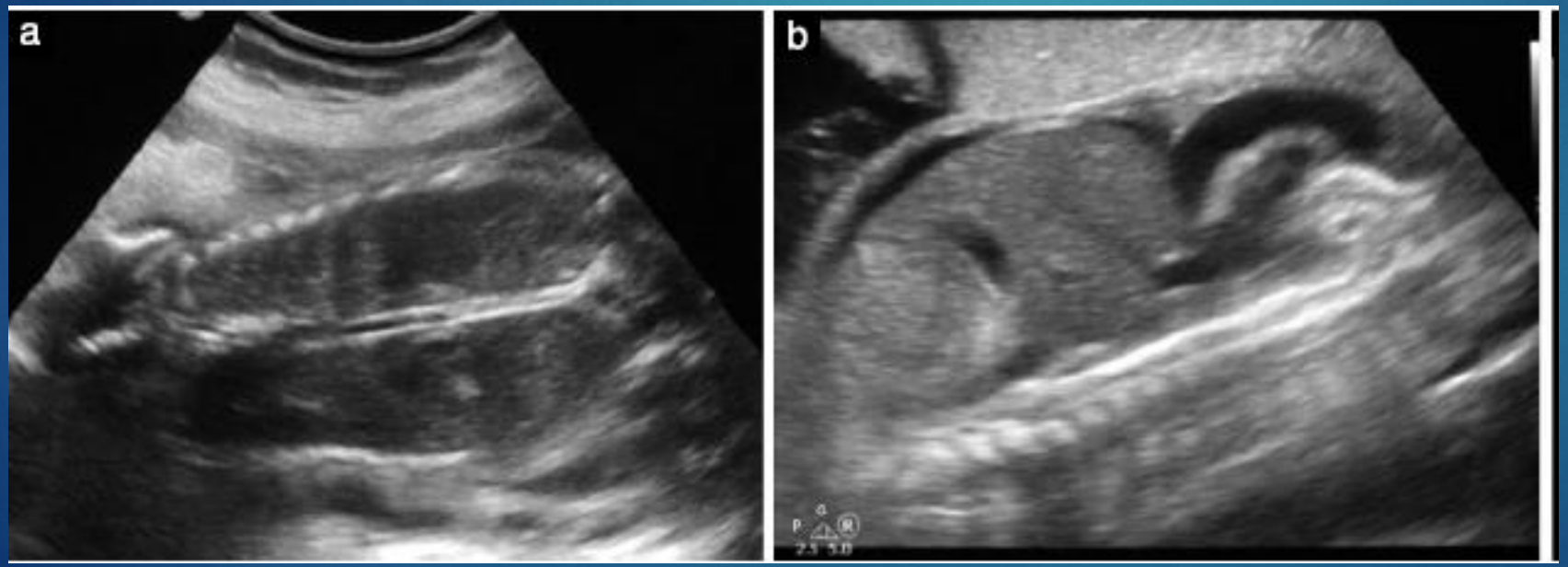
- *ABCC6* mediates ATP release from hepatocytes to the extra cellular space where ATP is converted into Ppi and AMP by *ENPP1*
- CD73 converts AMP to Pi & adenosine (inhibitor of tissue nonspecific alkaline phosphatase (TNAP) which hydrolyzes Ppi to Pi
- Deficiencies in *ABCC6, ENPP1* and CD73 lead to reduce plasma PPi levels and PPi/Pi ratios therefore promoting hydroxyapatite mineralization in peripheral tissues

Spectrum of the disease



Prenatal diagnosis of idiopathic infantile arterial calcification with hydrops fetalis

F. K. NASRALLAH*, H. BAHO†, A. SALLOUT* and M. QURASHI† *Ultrasound Obstet Gynecol* 2009; **34**: 601–604



Case report

Generalized arterial calcification of infancy—Findings at post-mortem computed tomography and autopsy

Ferdia Bolster *, Zabiullah Ali, Pamela Southall, David Fowler

Thank you

With thanks to Mo Haini

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