Mélie SARREAU. CHU Bordeaux
Sophie COLLARDEAU-FRACHON. CHU Lyon

EXTENSIVE PRENATAL LYMPHANGIOMA in the setting of PIK3CA-RELATED OVERGROWTH SPECTRUM: about 2 cases

DEFINITION

Cystic lymphangioma :

- A rare benign lesion (tumor or malformation?), usually occurs in childhood
- Composed of cystic lymphatic dilation of variable sizes.
- Isolated or combined with other abnormalities such as vascular malformation or soft tissue hyperplasia→ look for a syndrome.
- Neck most often involved. Abdomen and lower limbs <10%
- Prenatal risk depends on its location.
- Rarely an indication of TOP (termination of pregnancy)

=> Rarely a reason for fetopathological examination since imaging/echography is very pathognomonic

=> Rare studies and case reports of genetic investigations of lymphangioma following post-mortem examination

Keppler-Noreuil et al. Am J Med Genet C Semin Med Genet. 2016;172:402- 421.

PRENATAL EXAMINATION

2 similar fetal cases last year!
With TOP for ultrasound anomalies

CASE 1:

Maternal Antecedent :G1P0

Consanguinity: 0

22 years old

CASE 2:

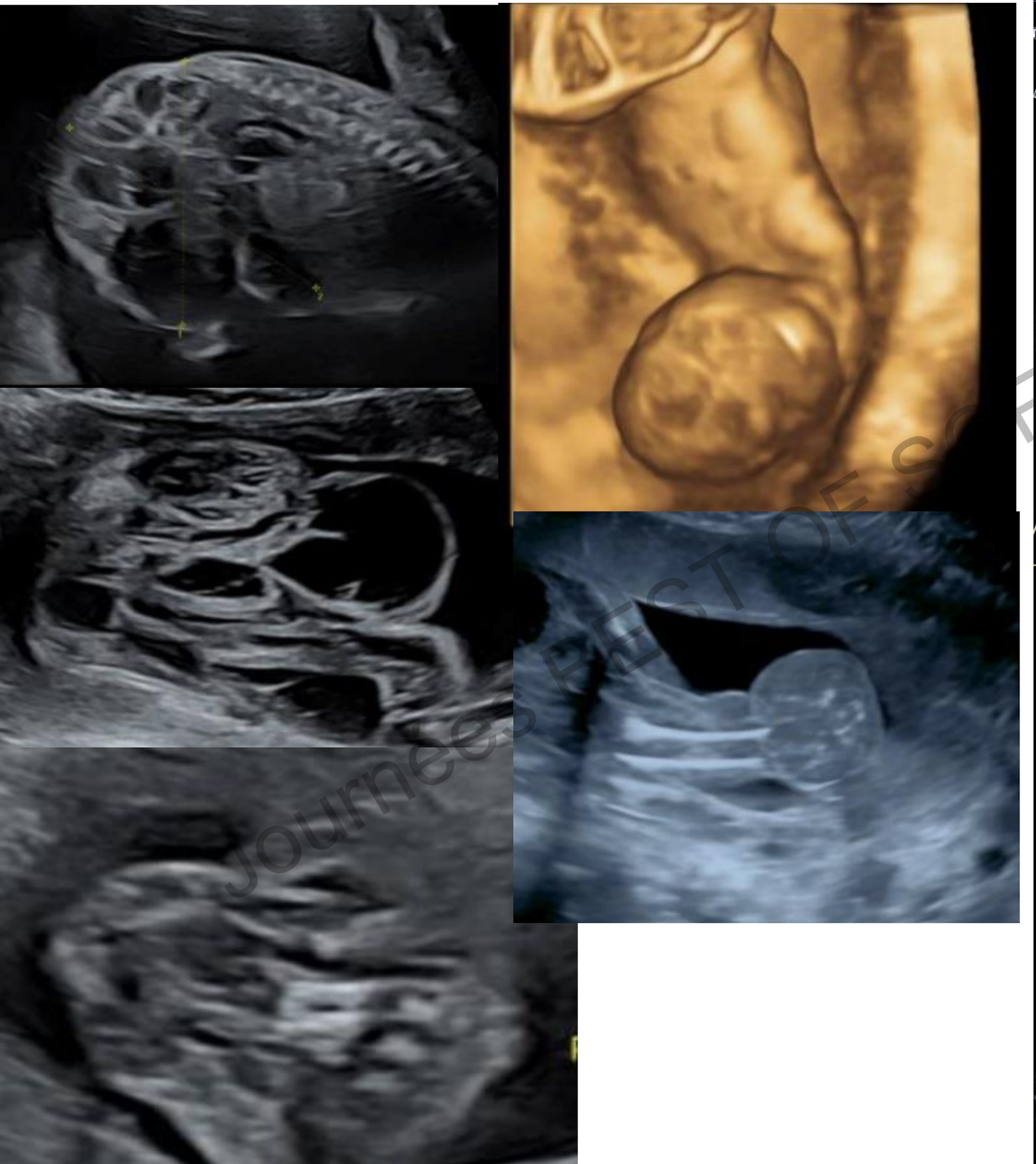
Maternal Antecedent: G2P1

Consanguinity : 0

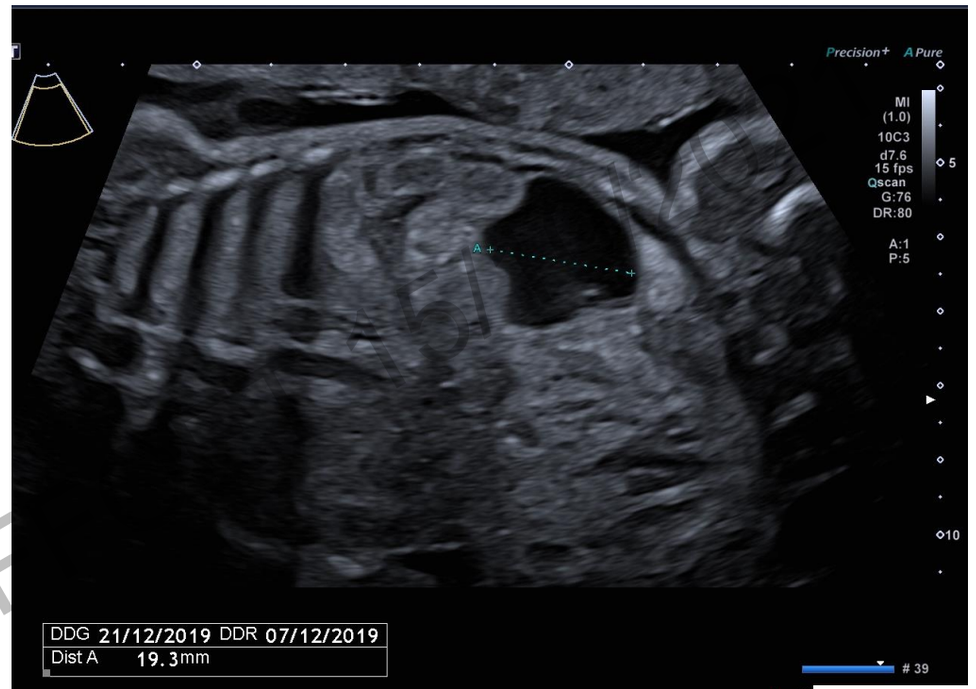
29 years old

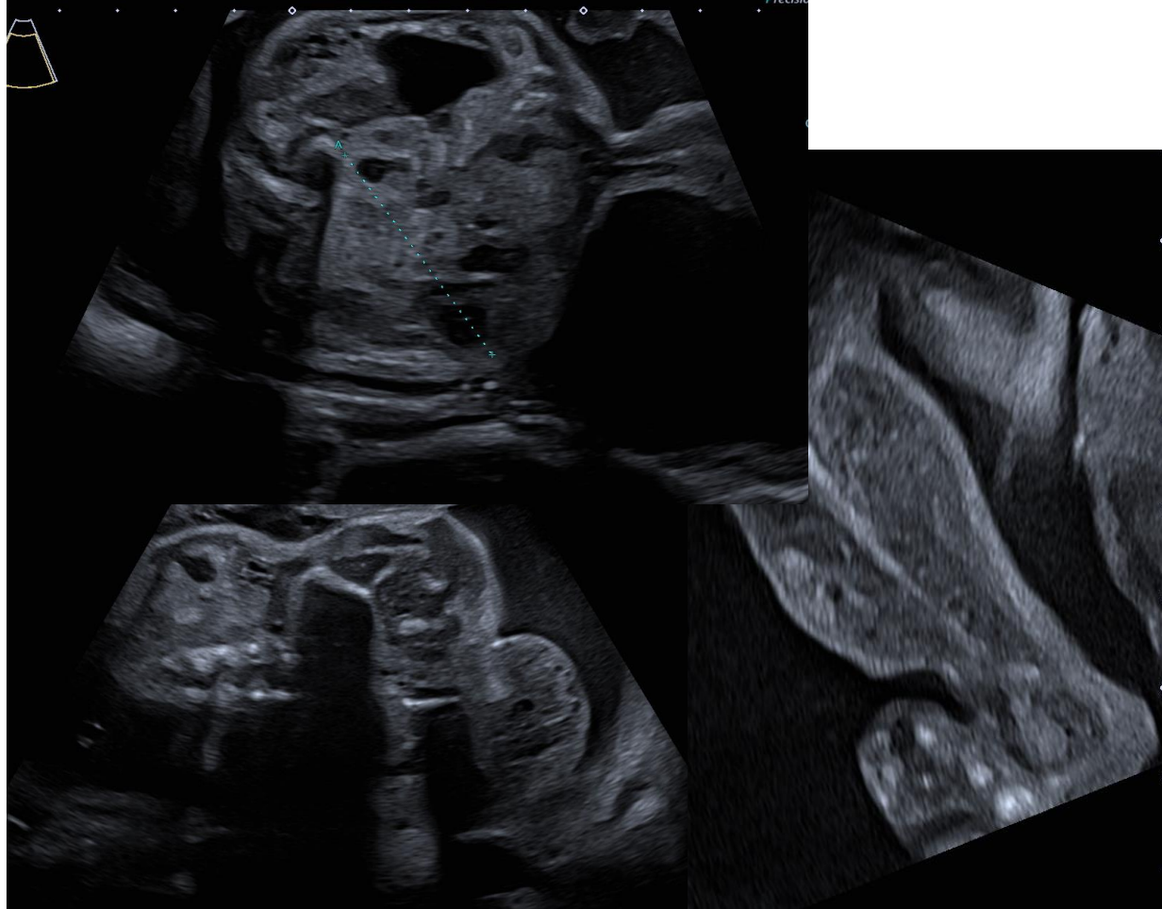
PRENATAL EXAMINATION - ULTRASOUND

Case 1: 23 + 4 GW (Dr F. Coatleven)



Case 2: 24+5 GW (Pr L. Guibaud)



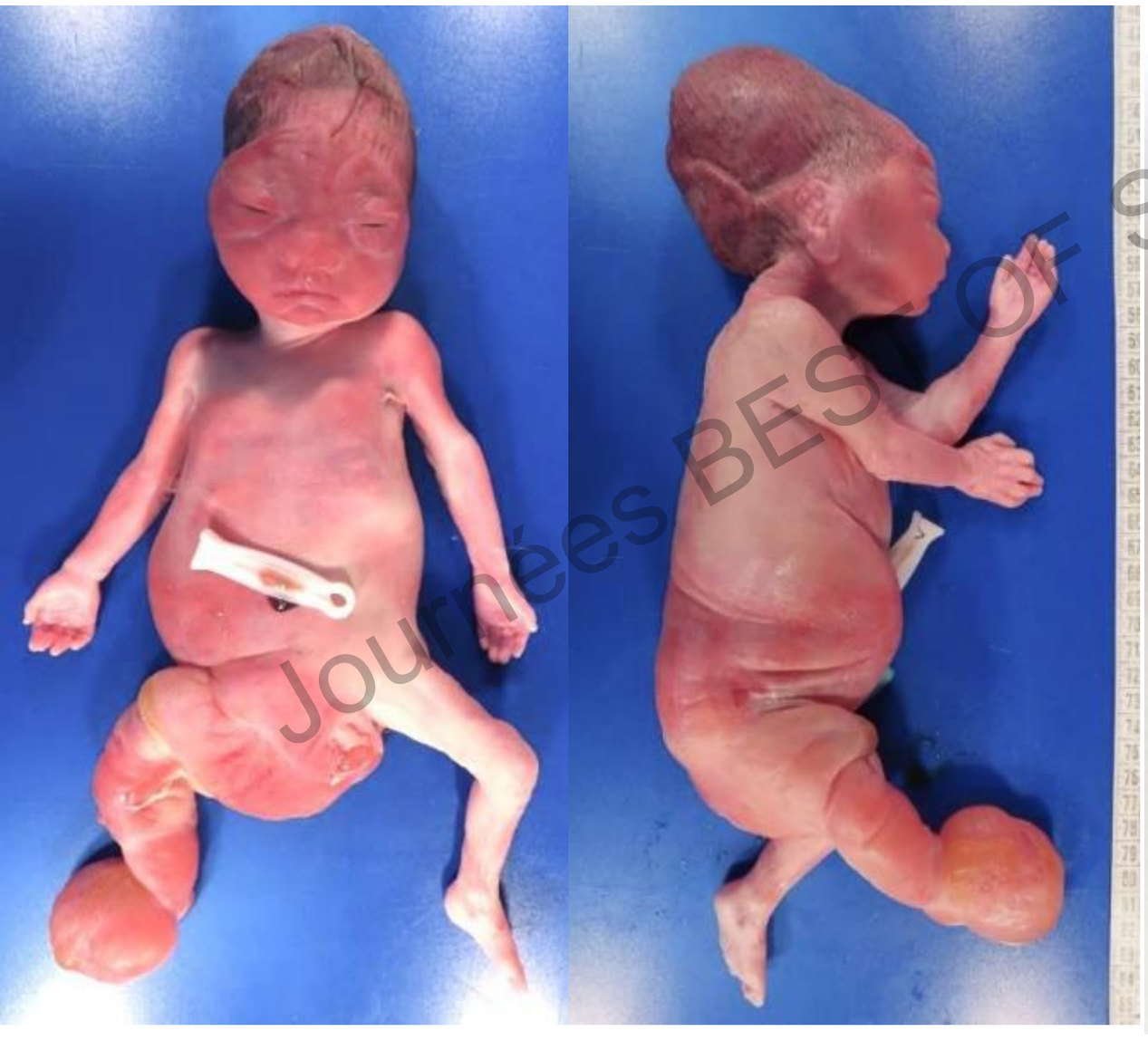


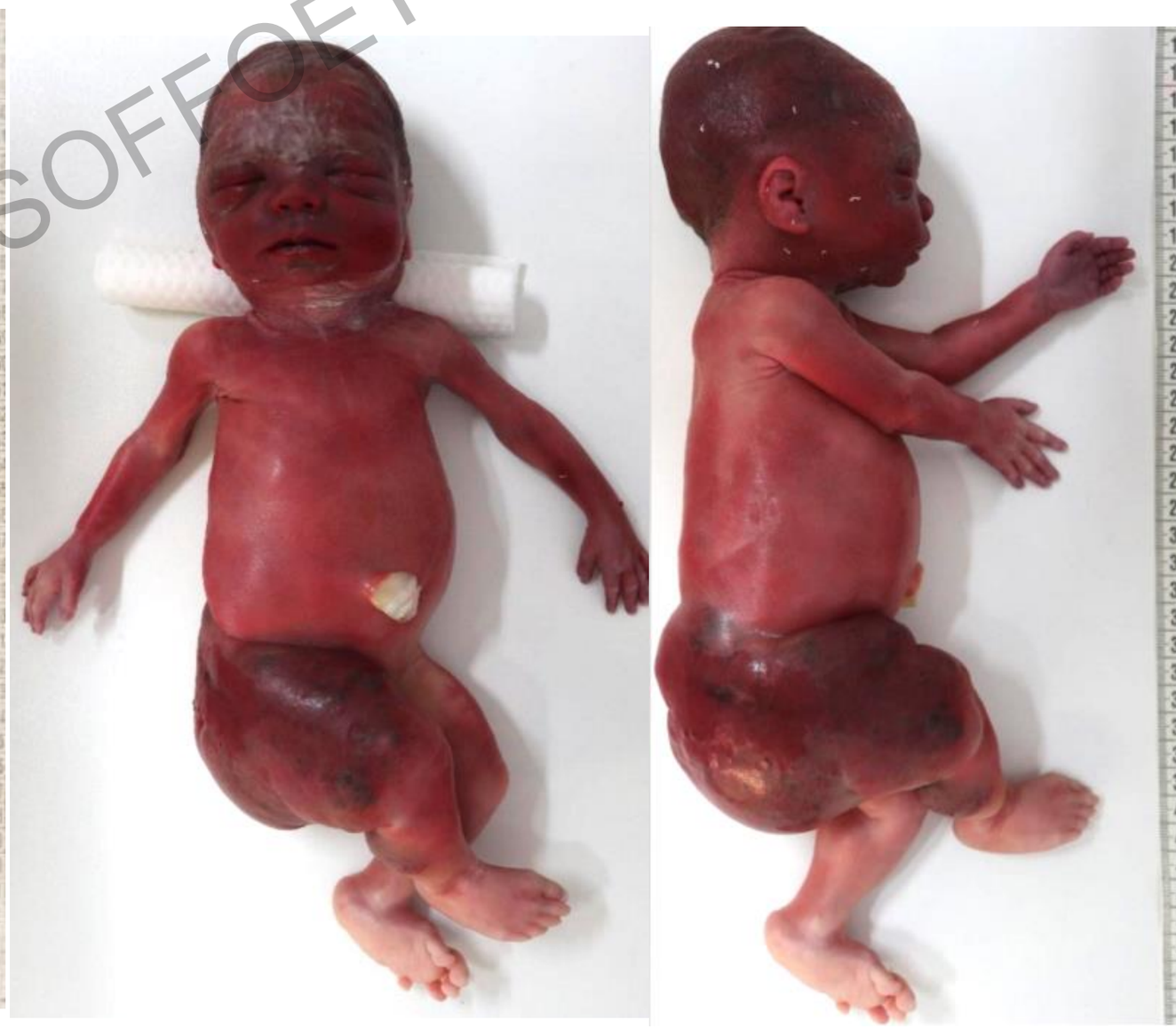
EXTERNAL EXAMINATION

Case 1:TOP 25+1GW, male, 966g.

Case 2:TOP 25+2GW, female 1100 g

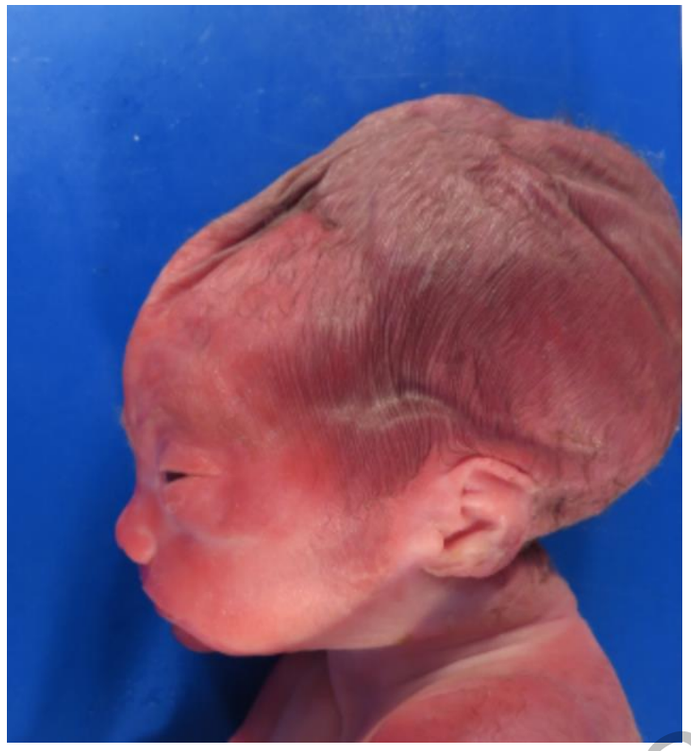
Hemihypertophy involving the right lower limbs, pelvis and abdomen

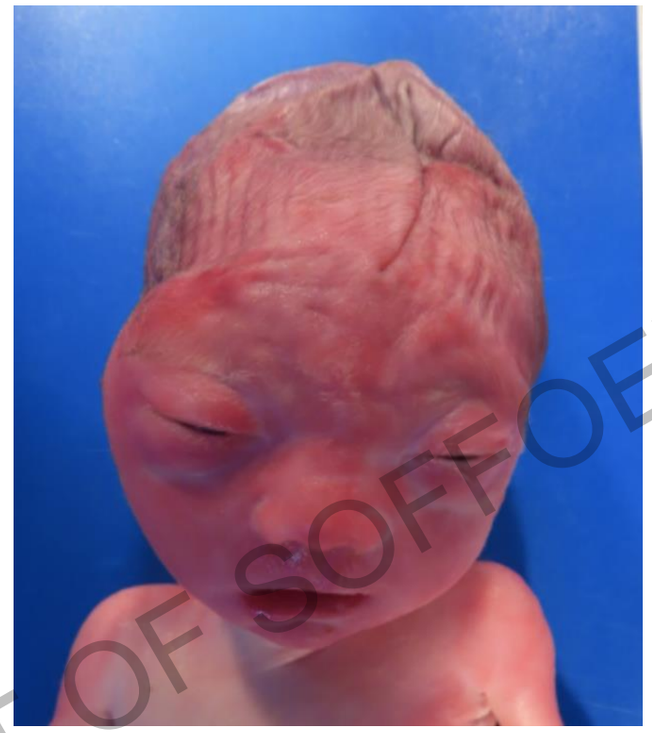




EXTERNAL EXAMINATION

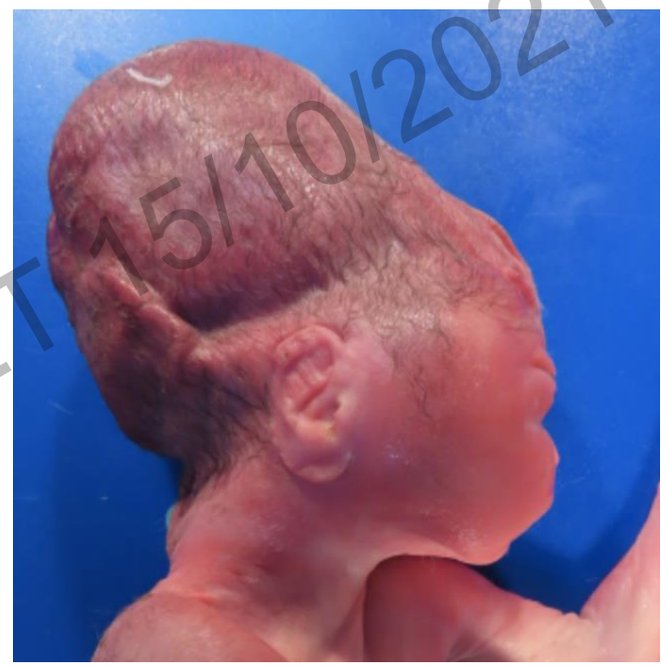
Case 1:

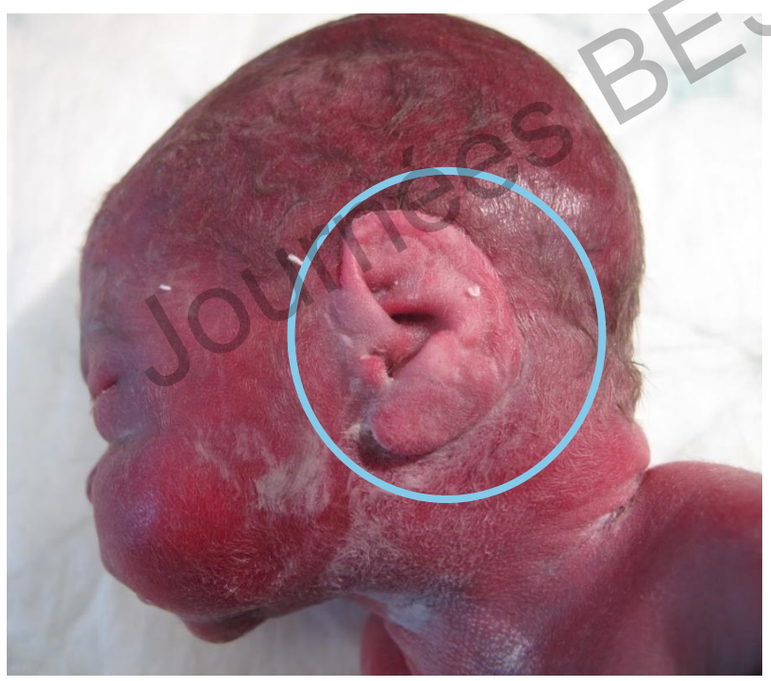


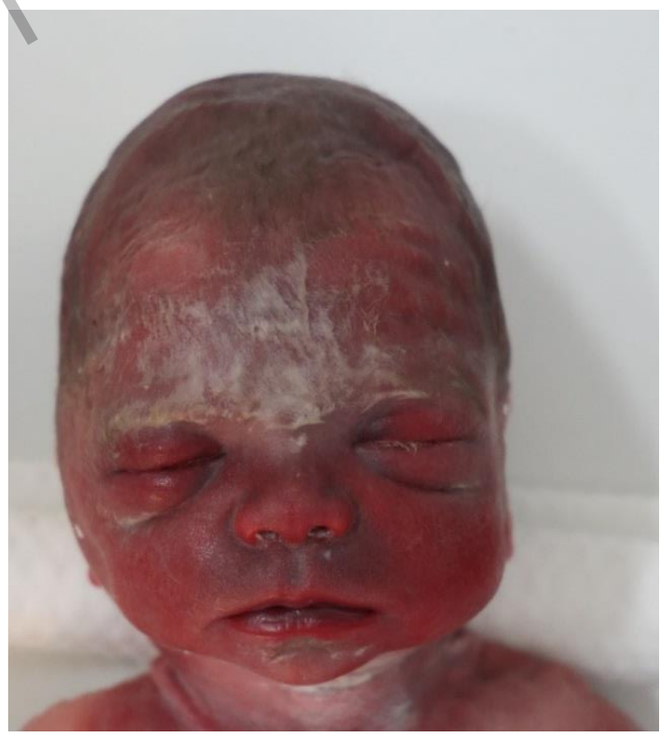


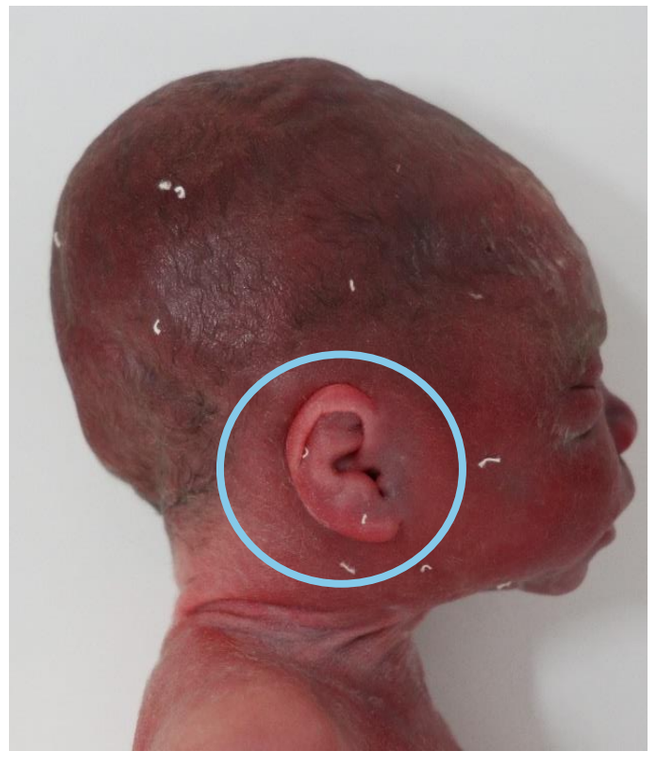
Case 2:

Asymmetrical ear size



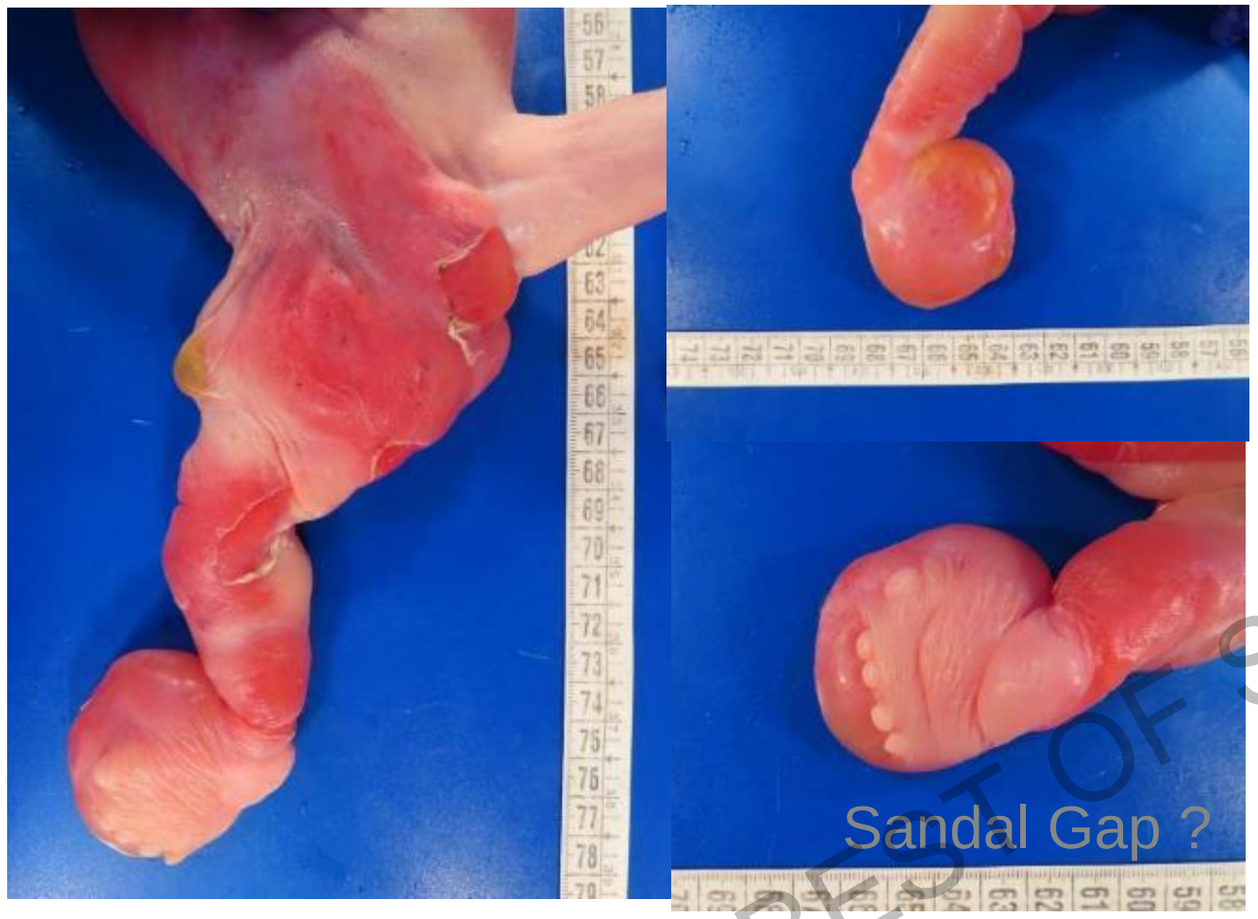




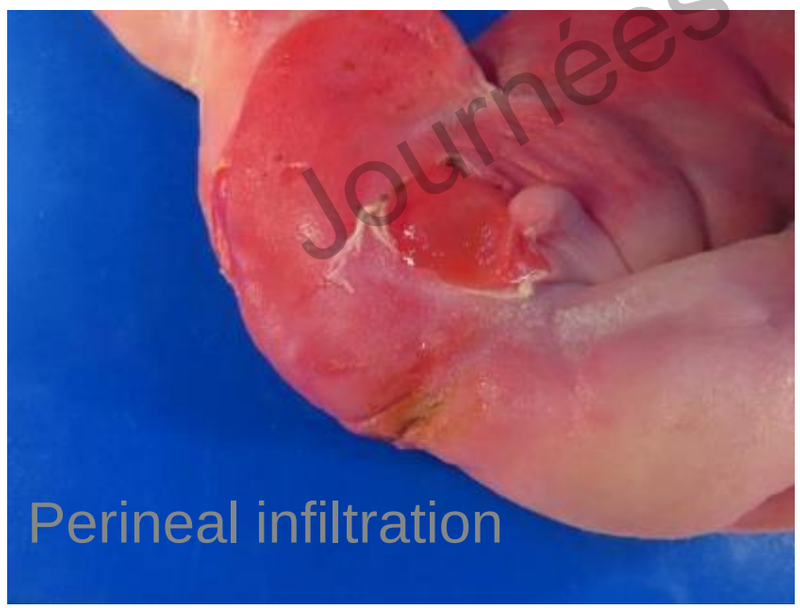


EXTERNAL EXAMINATION

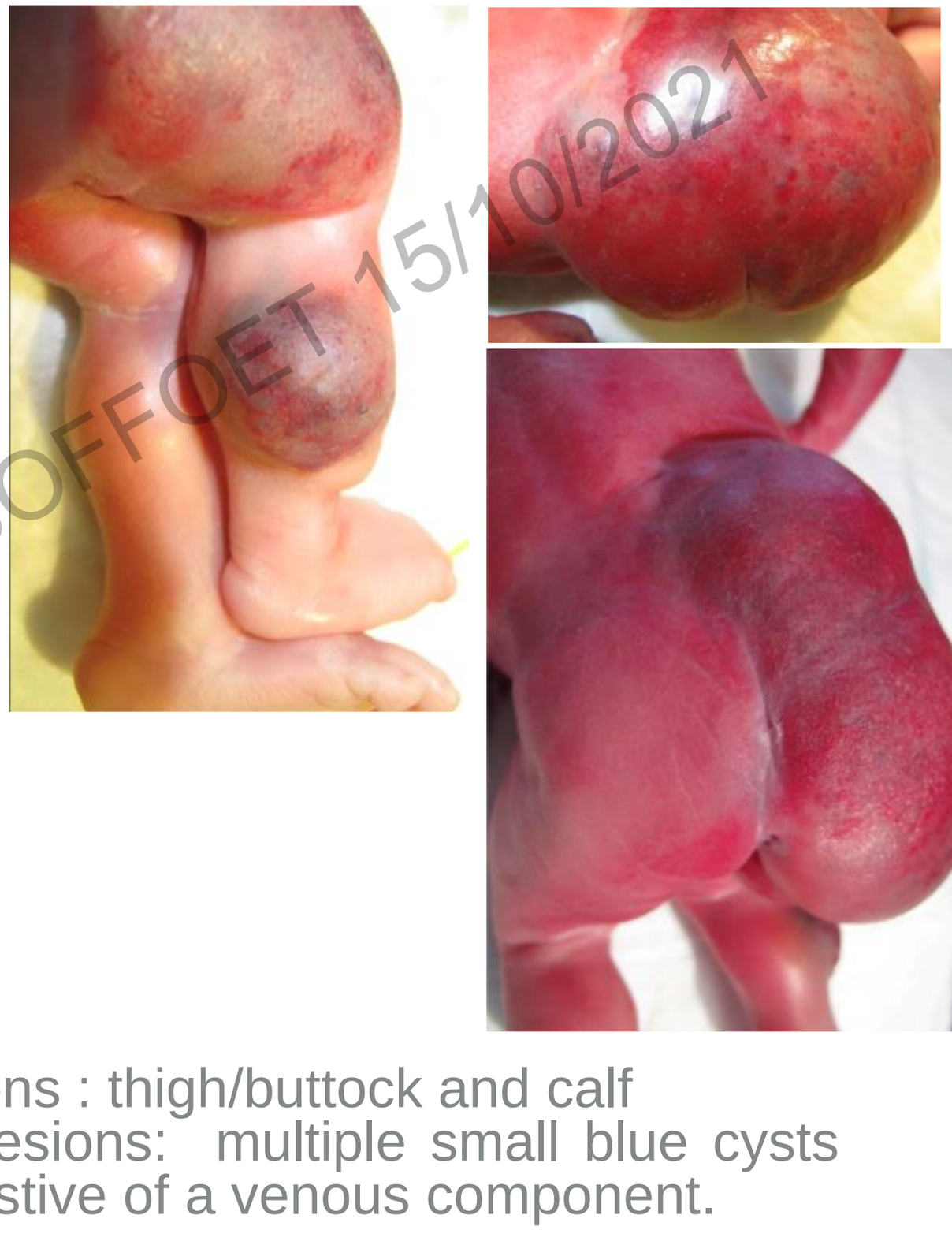
Case 1:



One large and extensive lesion with edema



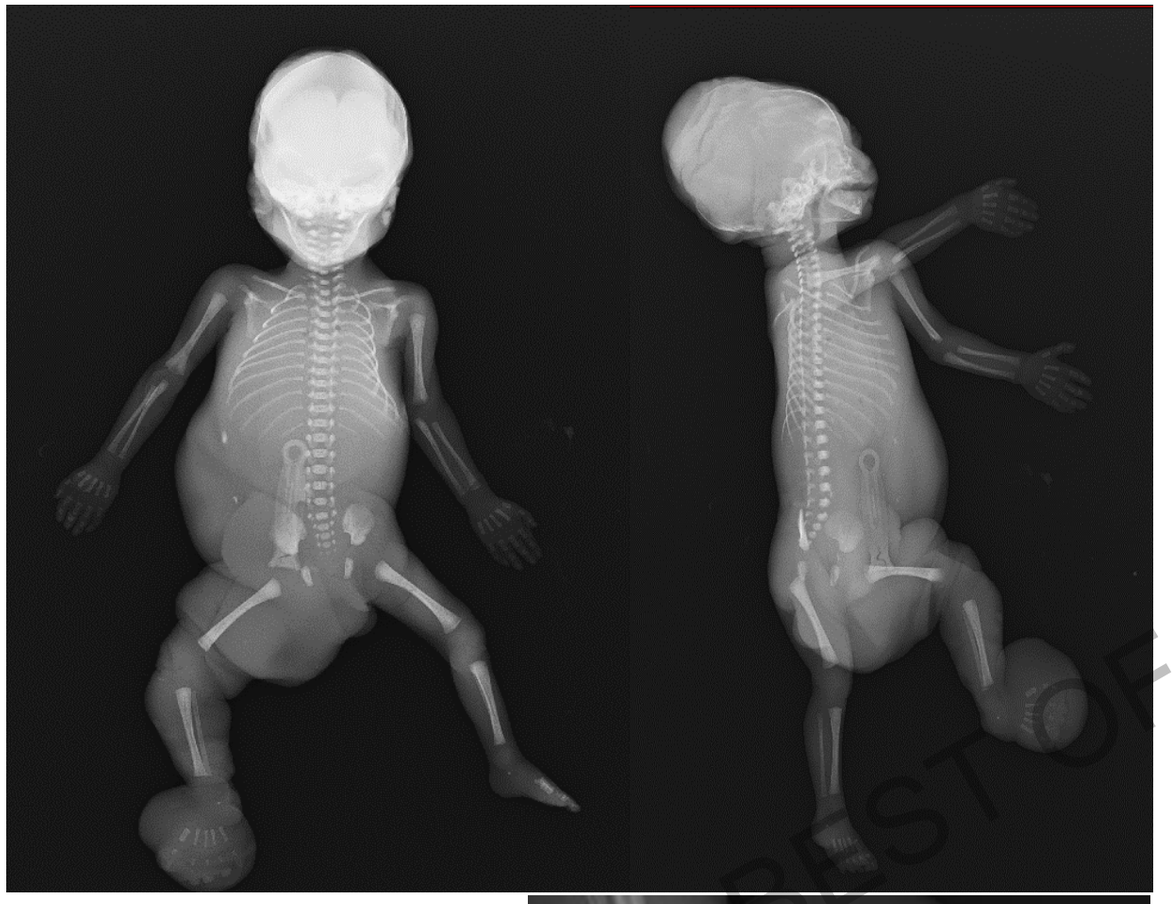
Case 2:

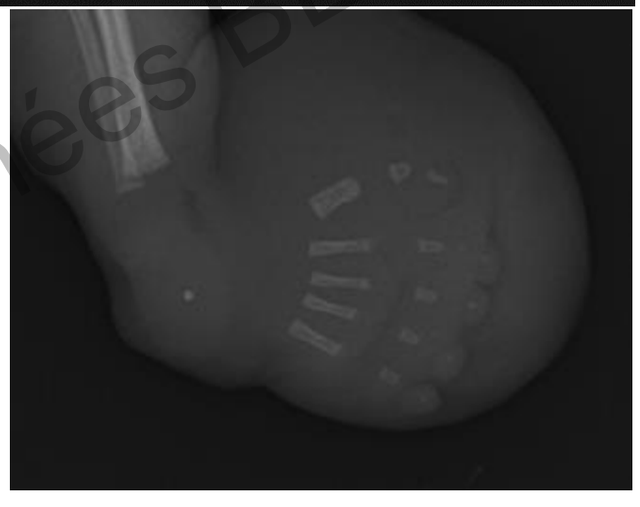


2 lesions : thigh/buttock and calf
Both lesions: multiple small blue cysts suggestive of a venous component.

RADIOGRAPHY

Case 1:





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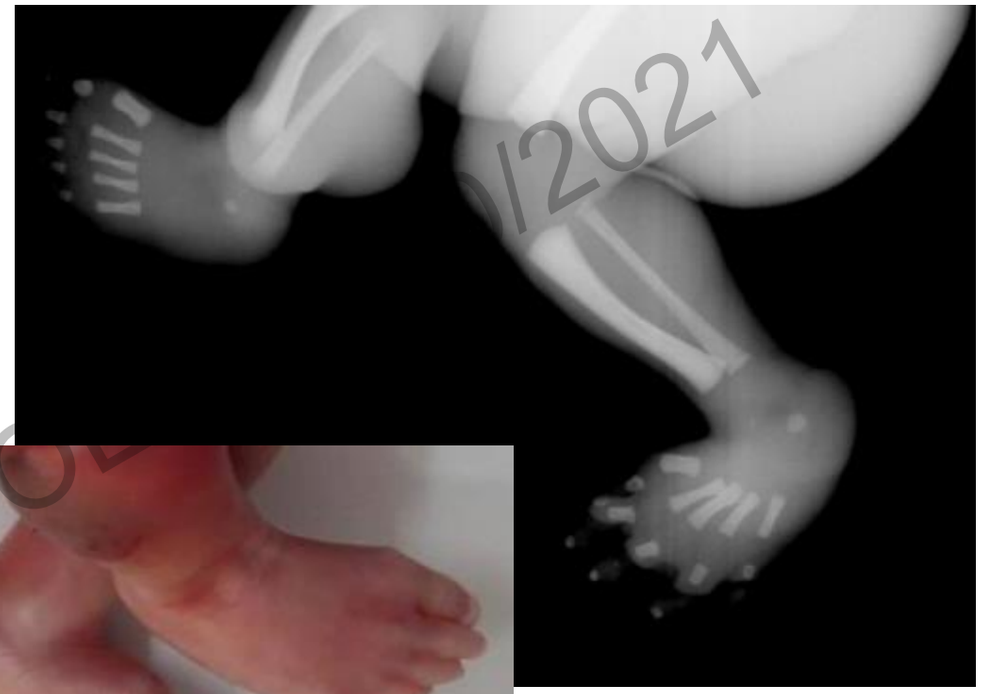
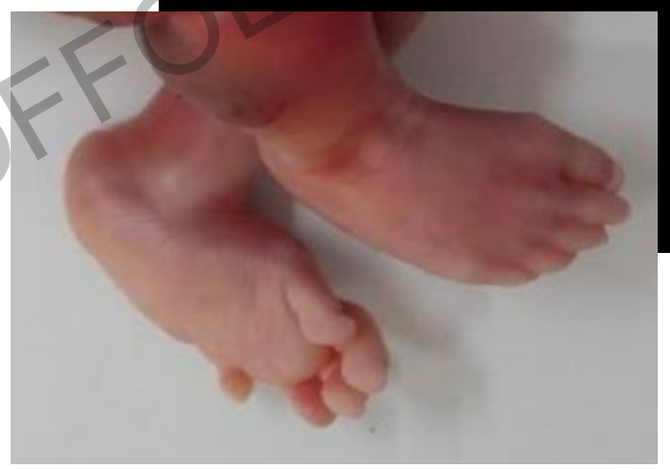


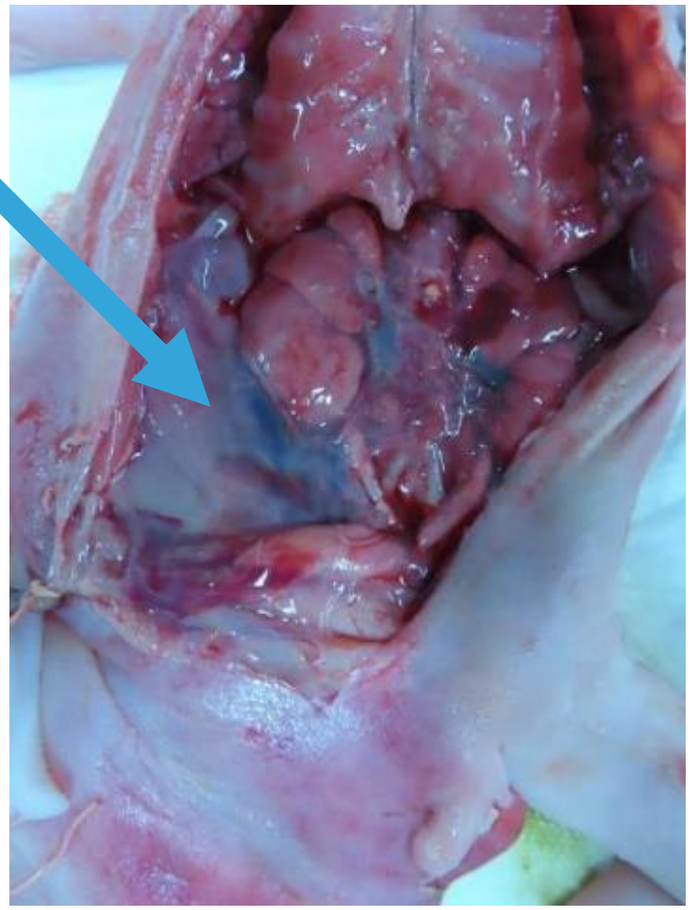


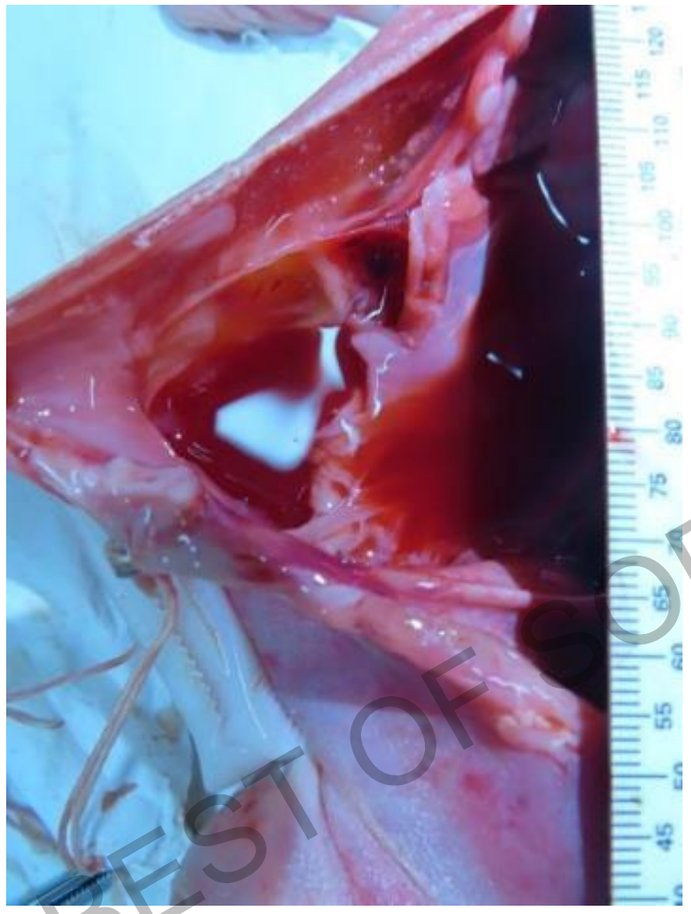
- Equine varus feet
- Abnormal low implantation of the 5th toe, with no nail
- Sandal gap between the 1st and the 2nd toe
- Abnormal presence of an astragale ossification point

No bone or squelettal anomalies, sandal gap difficul…

INTERNAL EXAMINATION

Case 1:





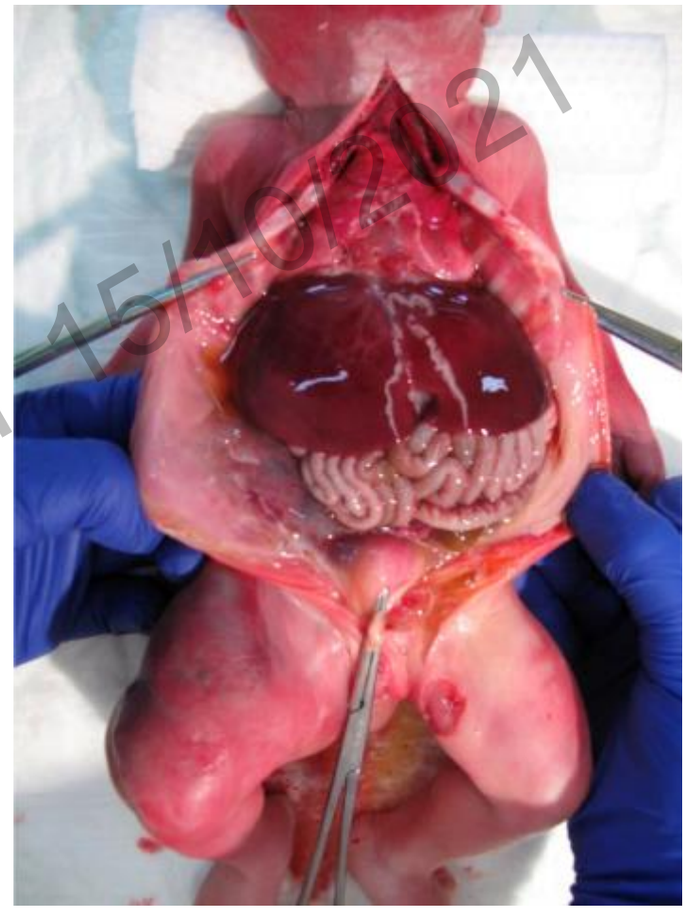
- Extension to the perineum, peritoneal cavity and retroperitoneum up to the renal compartment,

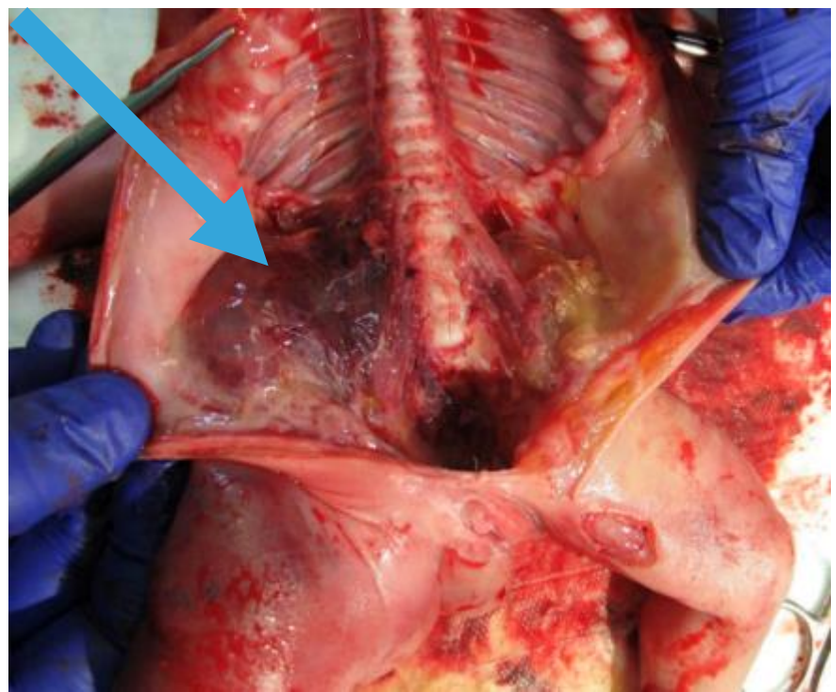
- Englobing the uretere without repercussions on the kidneys (no hydronephrosis)

- Infiltration of muscle (psoas and abdominal wall), hypodermis and cutaneous tissue

Multicystic appearence on cut sections

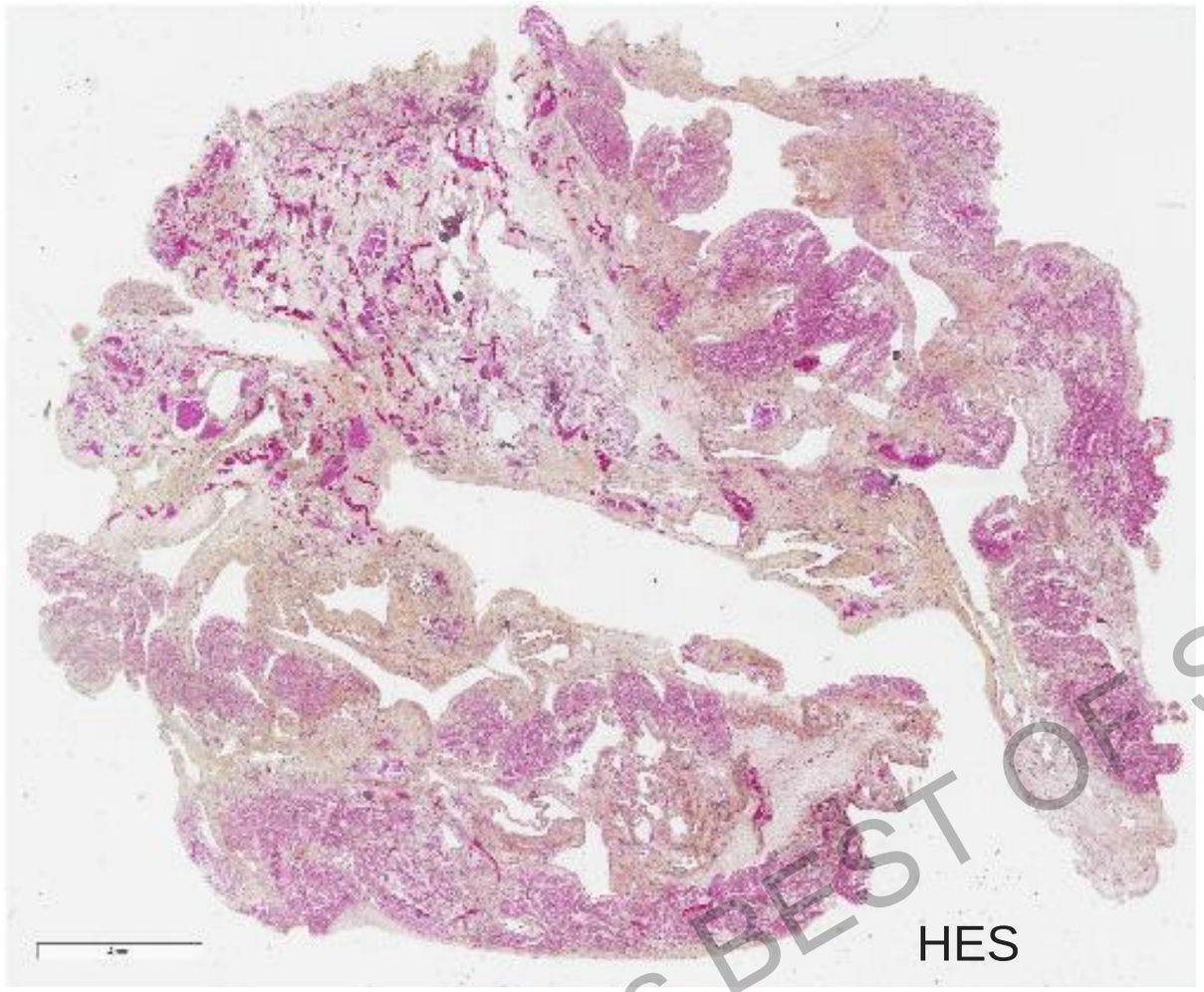
Case 2:





HISTOLOGY

Cases 1 & 2:

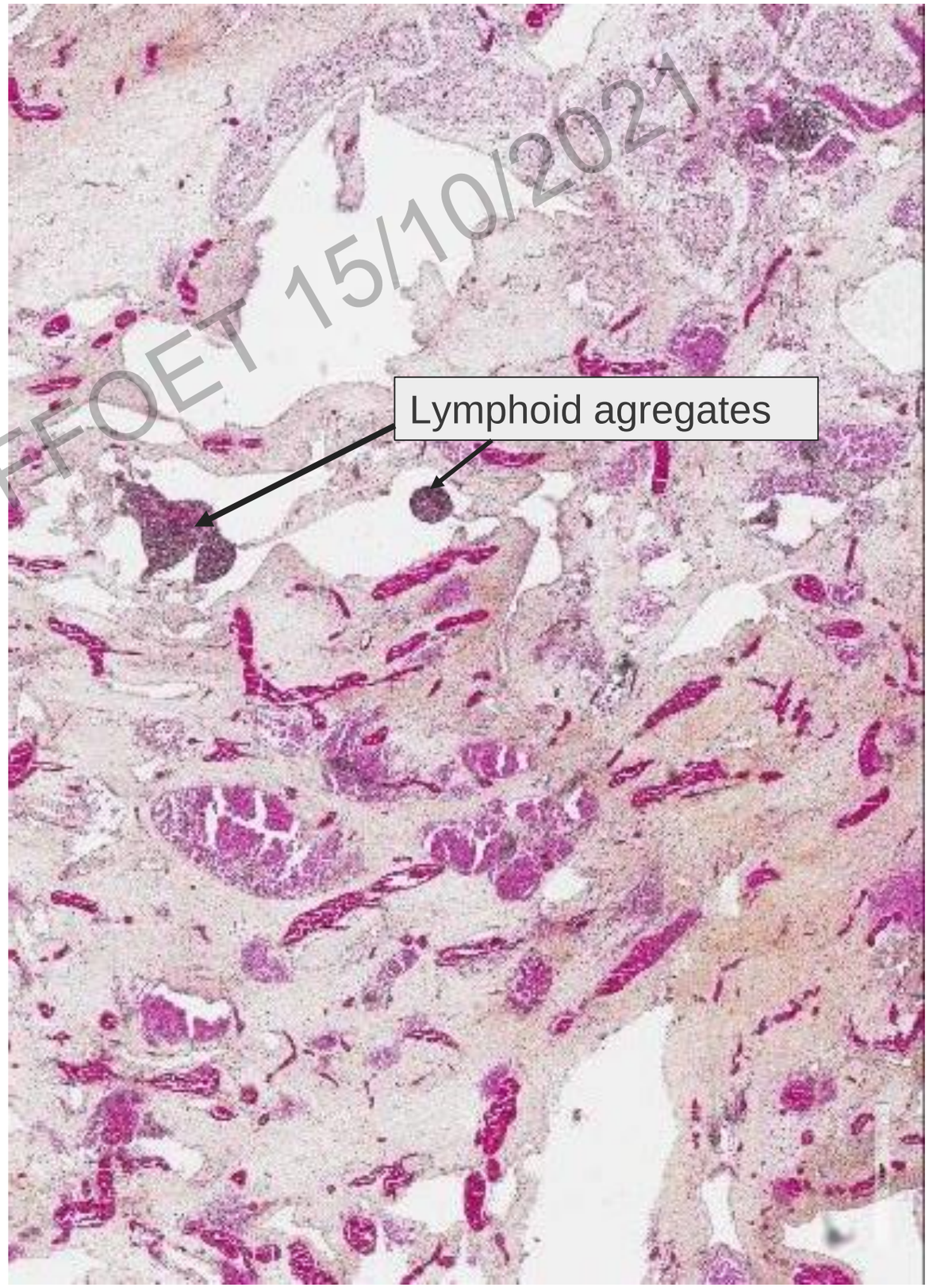


- Micro & macro cystic vascular structures
Communicate more or less with each other

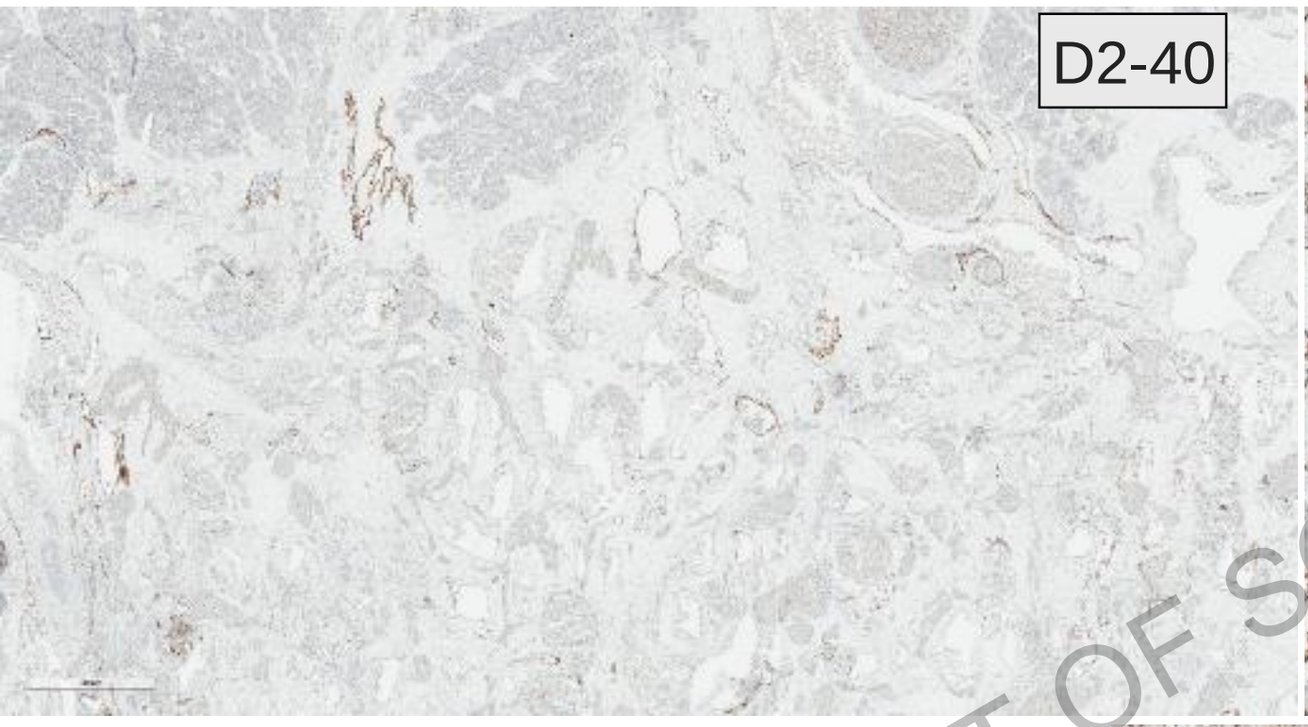
- Some lymphatic with lymphoid agregates and bundles of smooth muscle fibers in their wall

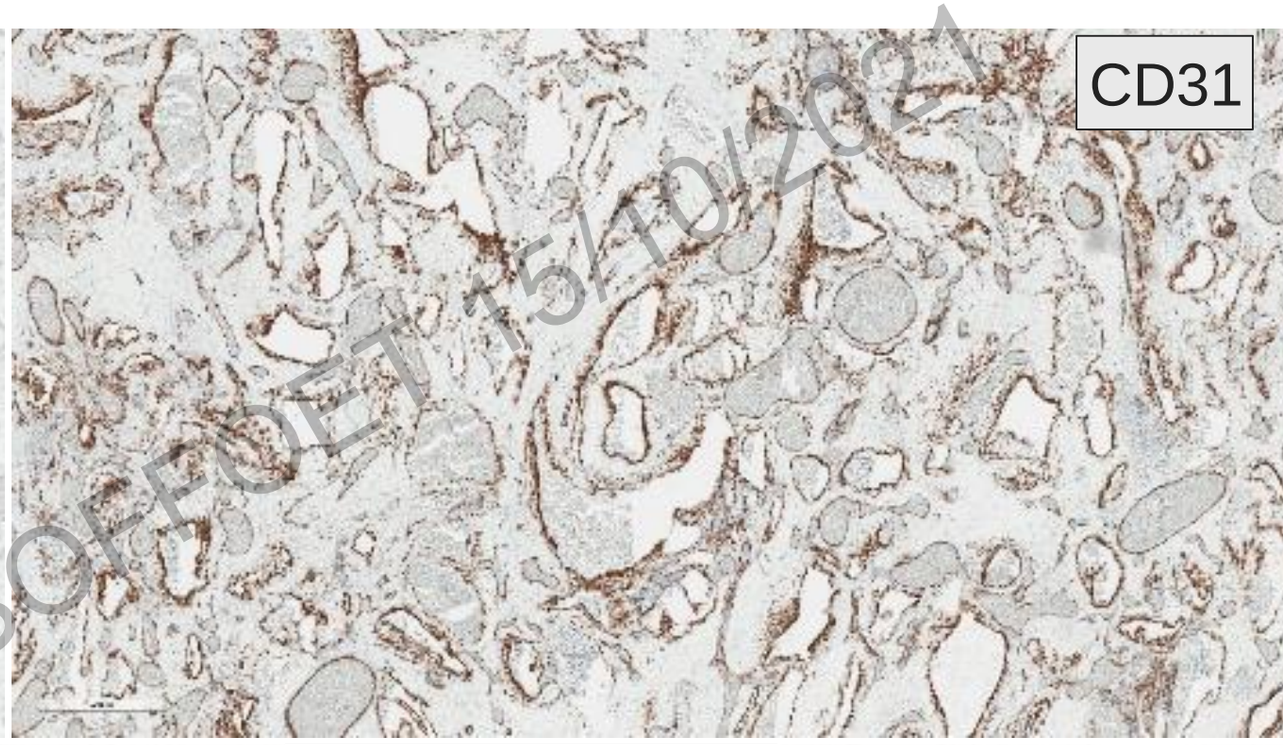
- Some veins

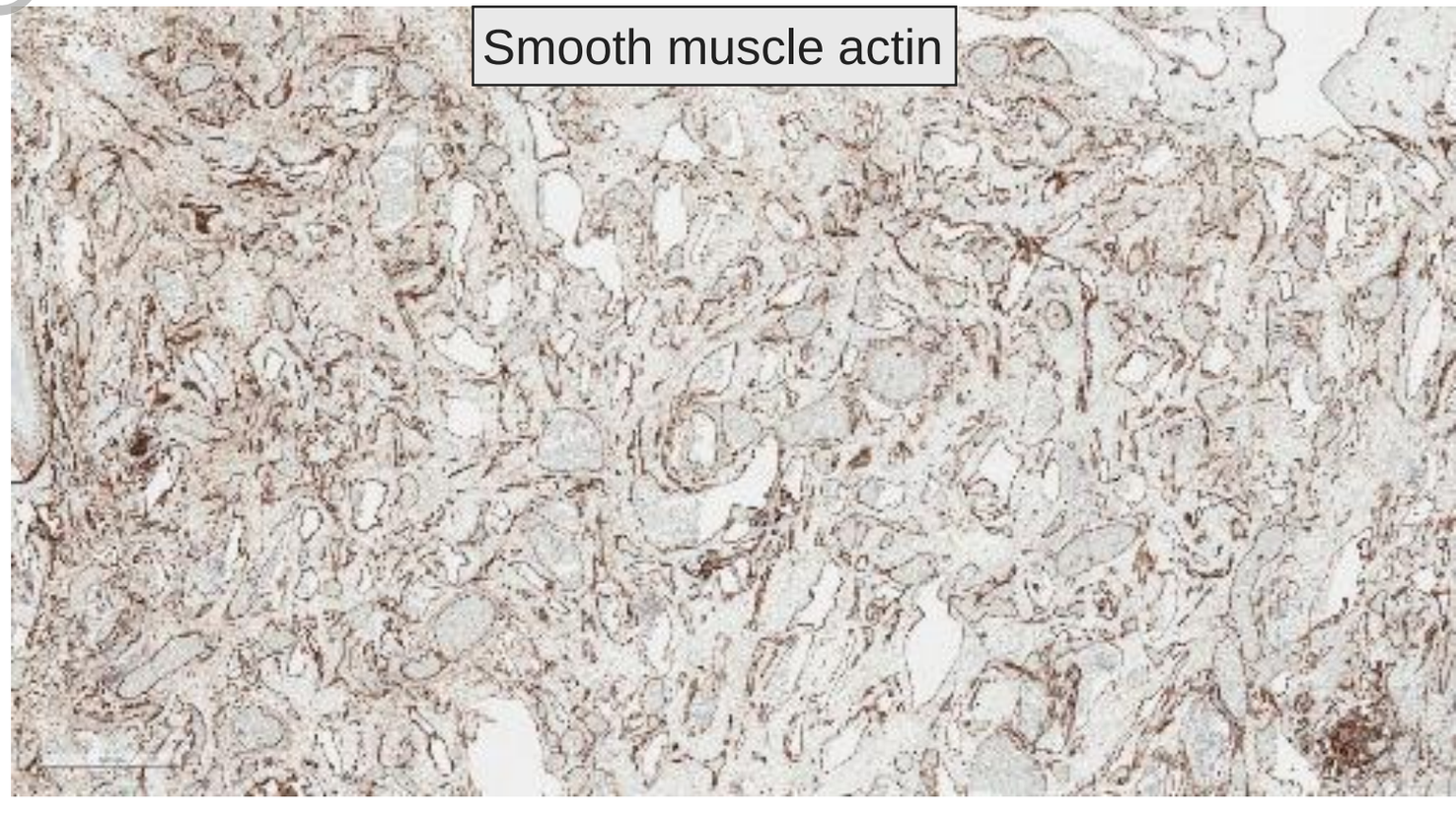
- Associated with veins and excess of soft tissue component: fat or collagen fibrous tissue which replace muscle



Cases 1 & 2:







D2-40 is expressed on endothelium of lymphatic strcutures
CD31 is diffusely expressed
Smooth muscle actin underlines muscle : all around the vein and focally in lymphatic wall

PIK3CA Mutations in both cases: 3q26,32

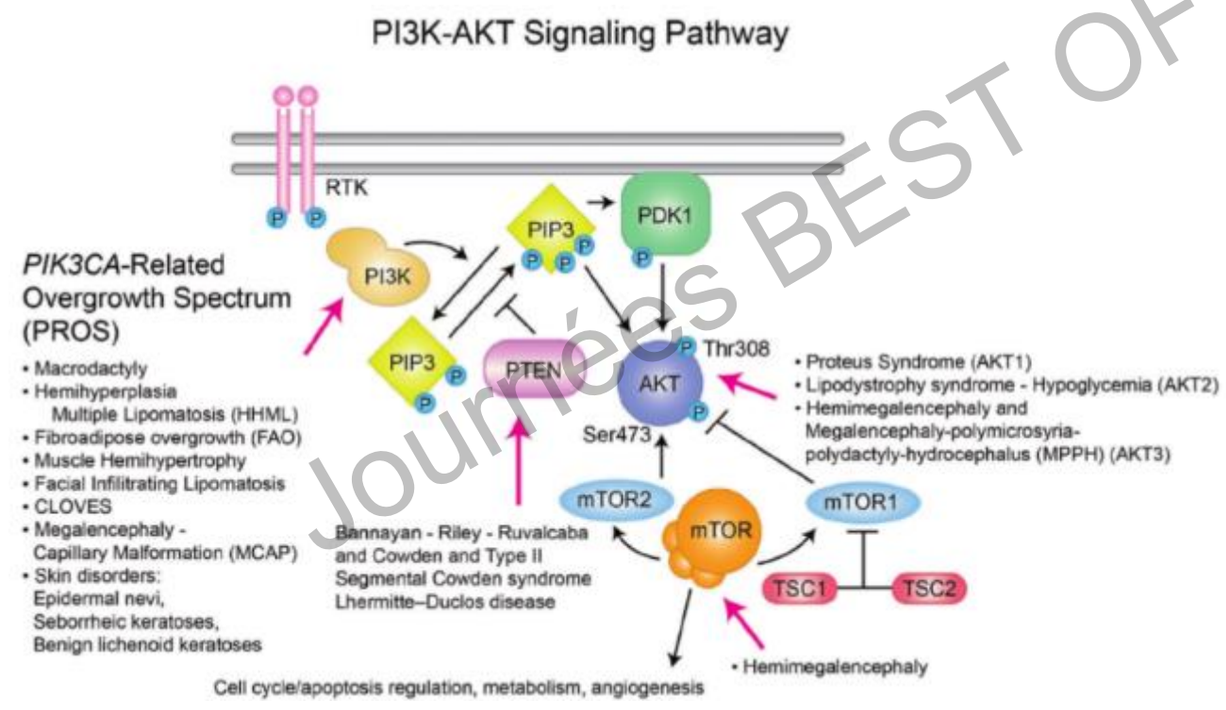
(Dr PP Bringuier, deparment of pathology, Hopital Femme-Mère-Enfant, Lyon)

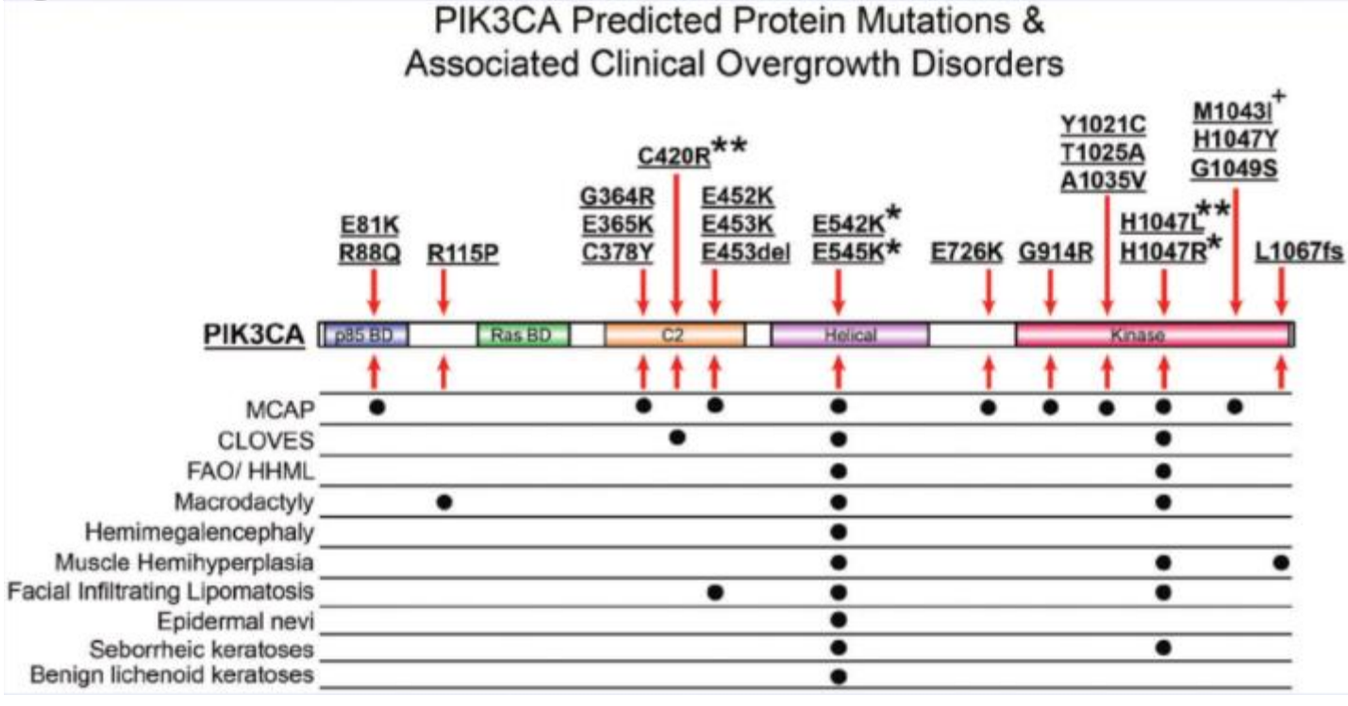
Case 1:

Activated mutation
c,3140A>G; p.His1047Arg
Exon 21: freq 4,65 % on FFPE

Case 2:

Activated mutation
c.1624G>A; p.Glu542Lys
Exon 10: 10% on FFPE





Keppler-Noreuil KM, Rios JJ, Parker VER, Semple RK, Lindhurst MJ, Sapp JC, Alomari A, Ezaki M, Dobyns W, Biesecker LG. 2015. PIK3CA-related overgrowth spectrum (PROS): Diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet Part A 167A:287–295.

PROS: PIK3CA-RELATED OVERGROWTH SPECTRUM

Large overlap of syndromes +++, large phenotypic variability.

Overgrowth disorders with hemihypertrophy (vascular and soft tissue hyperplasia)

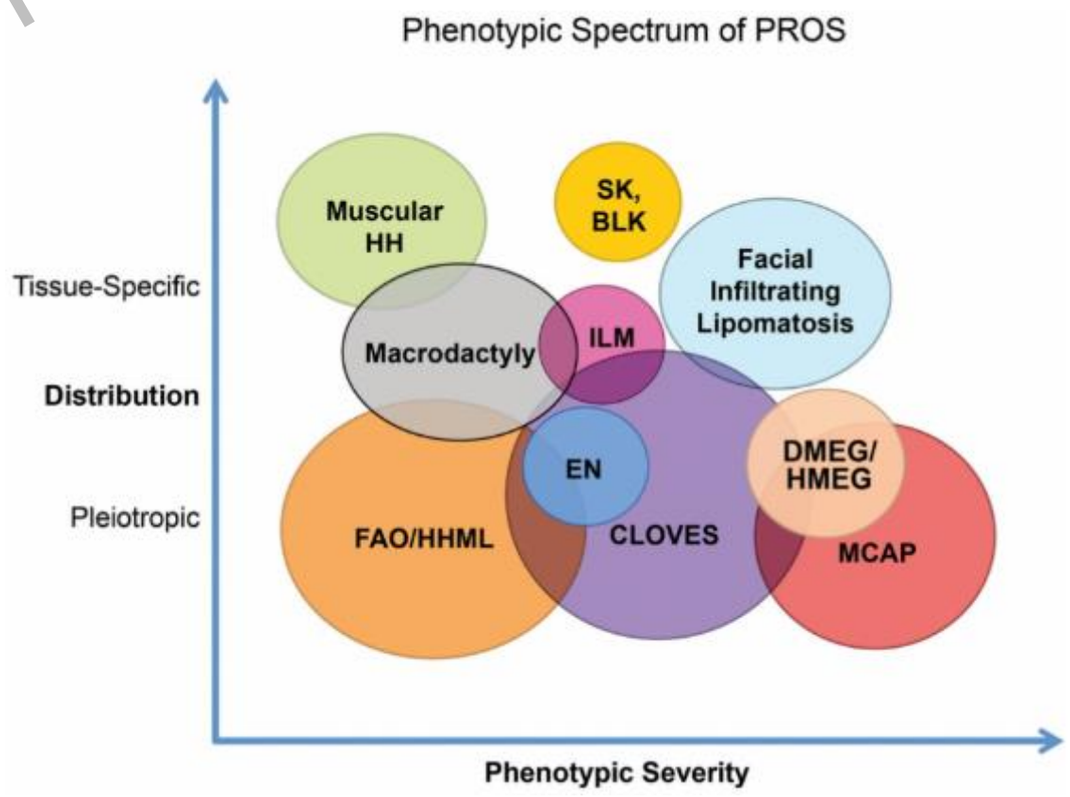
Somatic mutations in mosaic, post zygotic, 5-45% depending on the studies and tissues.

Various clinical presentations depending on the location or the type of predominant disease.

- **CLOVES:** "Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis / Skeletal / Spinal anomalies“

- **Klippel-Trenaunay (KTS):** vascular malformation, planar angioma, soft tissue or bone hypertrophy

- **MCAP**: Megalencephaly - CApillary-malformation - Polymicrogyria



Health Autority

Keppler-Noreuil KM, Rios JJ, Parker VER, Semple RK, Lindhurst MJ, Sapp JC, Alomari A, Ezaki M, Dobyns W, Biesecker LG. 2015. PIK3CA-related overgrowth spectrum (PROS): Diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet Part A 167A:287–295.

DIFFENTIAL DIAGNOSIS

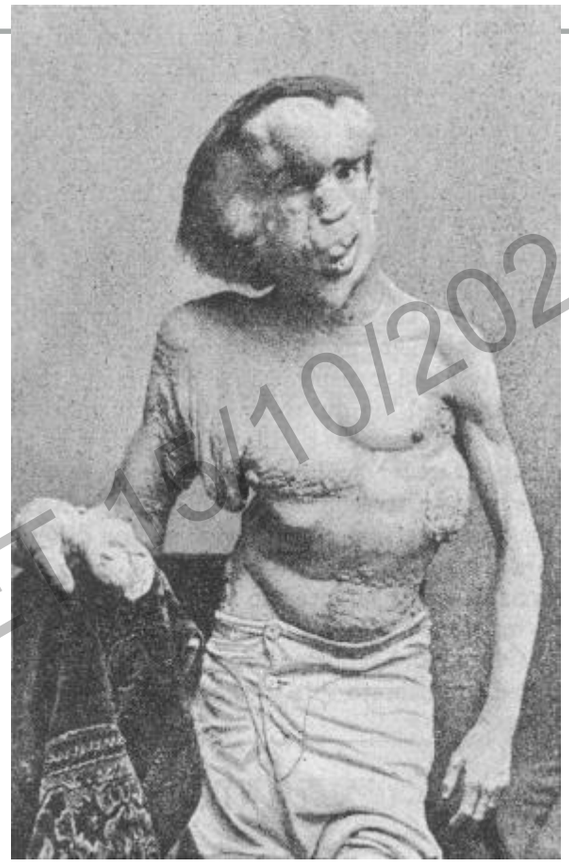
- **Proteus syndrom** : main differential diagnosis of CLOVES syndrome, severe, progressive and asymmetric segmental hypertrophy. (AKT1 mosaic gene).

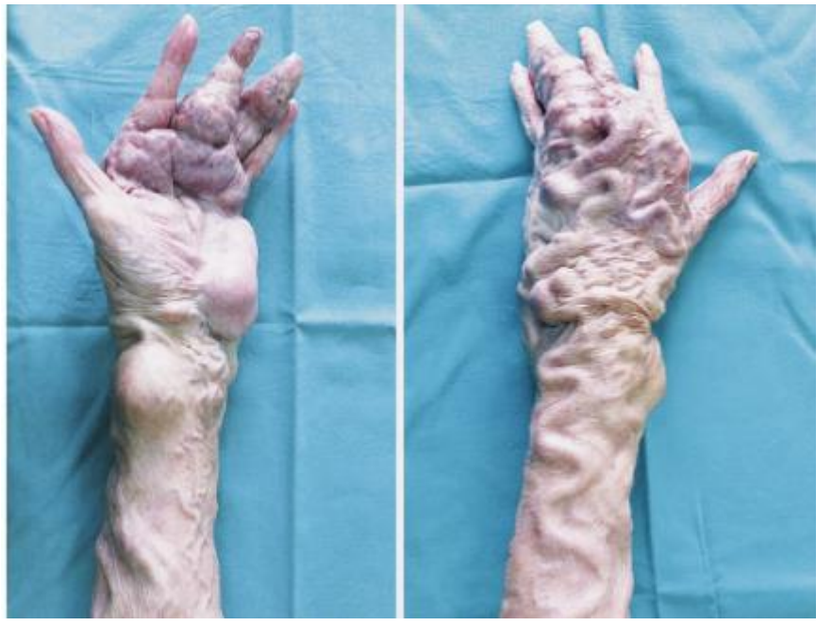
- **Parkes-Weber syndrom** (high-flow hypertrophic vascular malformation) and capillary malformation-arteriovenous malformation syndrome (CM-AVM) are differential diagnoses of KTS, linked to autosomal dominant germline mutations in the RASA1 gene or the EPHB4 gene.

- **PTEN gene** can be differential diagnoses of CLOVES syndrome:

✓ **SOLAMEN syndrom**, variant of Cowden syndrome, characterized by segmental hypertrophy, lipomatosis, the presence of arteriovenous malformations and epidermal nevi

✓ **Bannayan-Riley-Ruvalcaba syndrome,** characterized by macrocephaly, developmental delay, multiple lipomatosis, intestinal hamartomatous polyposis, pigmented macules of the penis, and sometimes capillary malformations.





French Health Autority. Hypertrophyc syndrom linked to PIK3CA (PROS) without cerebral pathology. CLOVES and Kklippel trnaunay syndroms. syndrom

POSTNATAL / PRENATAL PRESENTATION AND DIAGNOSIS

- Many study with genetic diagnosis in adults:

**Peng et al. Prenat Diagn. 2006;26:825-30. Taiwan*
Retrospective analysis of prenatal and perinatal presentations of KTS, for the purpose of prenatal counseling. 2 institutional cases and 19 cases from the literature with KTS presenting antenatal.
**Alomari. Clin Dysmorphol. 2009;18:1-7. USA*. First series of 18 patients with CLOVES syndrome with descriptive study but no diagnosis.

- More often bibliography with post natal babies born with lymphangioma with clinical and genetic diagnosis in pediatrics:

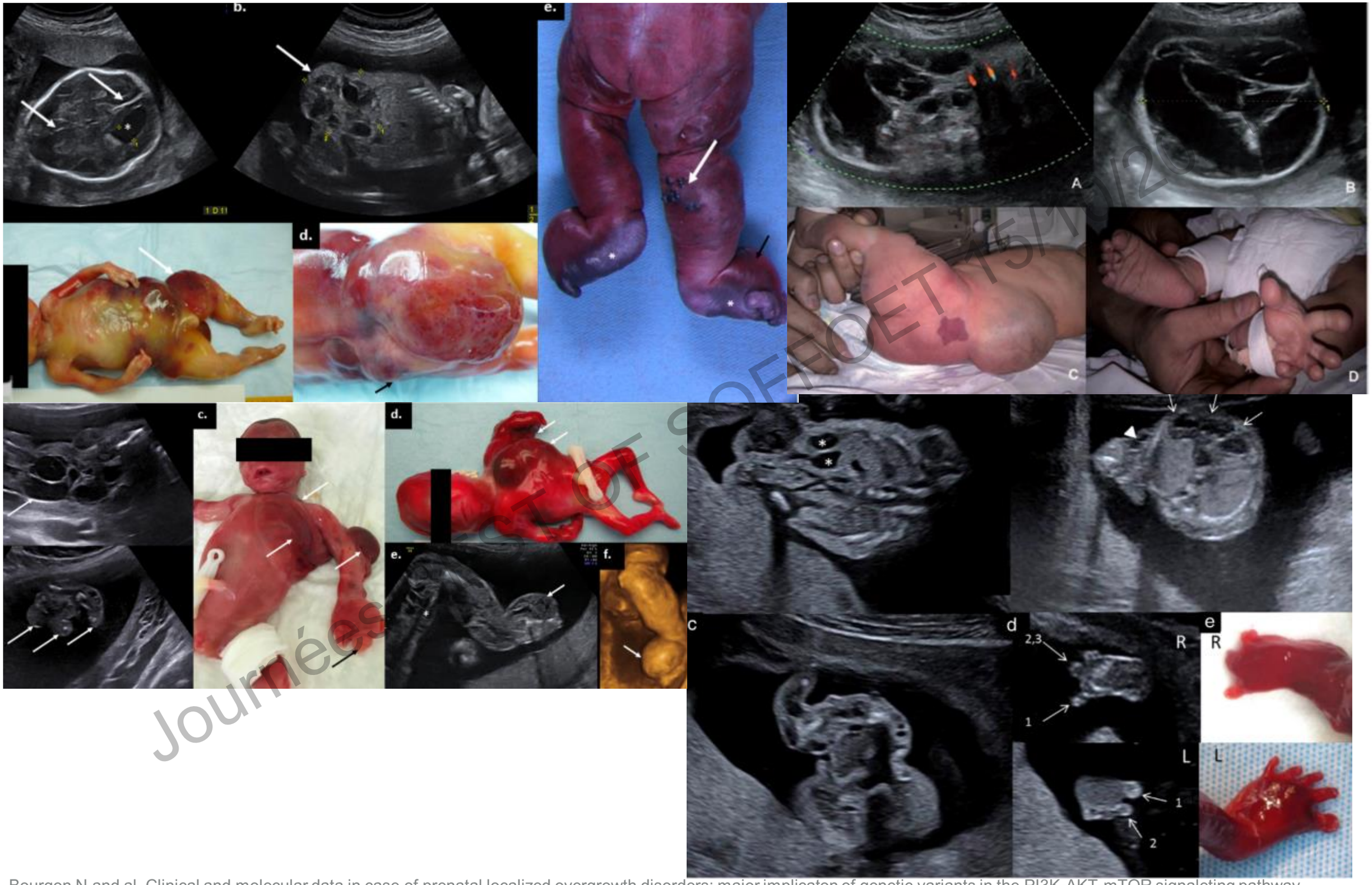
Luks J Pediatrics: Most people at Boston Children's Hospital with an isolated lymphatic malformation (16/17) or KTS (19/21), or fibro-adipose vascular anomaly (5/8) or CLOVES (31/33), had a PIK3CA somatic mosaic.

- More often prenatal diagnosis of polymalformative syndrom or MCAP and post natal and post mortem PLOS:

Recently in first trimester: *De Graer C and Al. Novel features of PIK3CA-related Overgrowth Spectrum: lesson form an aborted fetus presenting de novo constitional PI3CA mutation. Eur J Med Genet 2020; 63: 103775*

- Rare case reports of lymphangioma with prenatal features and post natal or post mortem examination and genetic analyses: *Bourgon and Al 2020*

PRENATAL PRESENTATION



- Bourgon N and al. Clinical and molecular data in case of prenatal localized overgrowth disorders: major implicaton of genetic variants in the PI3K-AKT-mTOR signaleting pathway.
- De Graer C and Al. Novel features of PIK3CA-related Overgrowth Spectrum: lesson form an aborted fetus presenting de novo constituional PIK3CA mutation. Eur J Med Genet 2020; 63: 103775
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- Fraissenon and al. Ultrasound Obst Gynecol 2020;56:780-81.

PRENATAL DIAGNOSIS CHALLENGES

Rare prenatal diagnosis of PROS in the settings of extensive lymphangioma.

Fetal PROS probably underestimated.

Currently PD is not an indication in lymphangioma.

How to consider the PD now?

- Molecular confirmation of PIK3CA mutations on prenatally obtained samples is challenging because of somatic mosaicism:

**Emrick L and al. Prenatal diagnosis of CLOVES syndrome confired by detection of a mosaic PIK3CA mutation in cultures amniocytes. Am J Genet A. 2014; 10: 2633-2637*

**Lalonde et al. Mol Genet Genomic Med. 2019;7:e536.*

- Are the same variants implied in prenatal case ? Are there more severe?

Interest of a PD ?

Prognosis:

neuro handicap in case of MCAP

depends on location (cervical lymphangioma can be life–threatening)

Importance of diagnosis for therapeutic and prognostic approaches in lymphagiomas?

CONCLUSION

- Several variants of PIK3CA mutations / Great phenotypic variability with several entangled syndrome. PROS
- Somatic mosaic mutations which are not equally present in organs but which are best represented on lesional tissue.

- Rare cases diagnosed on post-mortem fetal tissue:

- Prenatal diagnosis (DP) : NGS on cultured amniocytes, regardless of the fetal phenotype and the time of the amniocentesis with best results for prenatal US findings suggestive of CLOVES or MCAP.

⇒Should we propose a PD for lymphangiomas?
⇒Criteria to justify TOP in the future?
⇒Therapeutic interest post natal? In utero ?

- Clinical trial on PIK3CA treatments/ Inhibiting factor form PIK3CA
=> EPIK-P1 (but embryologically toxic on animals) therefore contraindicated during pregnancy.

To help physicians in prenatal descriptions of fetal phenotypes and guide molecular testing before or after birth, hence improving prenatal counselling.

BIBLIOGRAPHY - ACKNOWLEDGMENT

- Thanks to Sophie Collardeau Frachon for helping in genetic etiology of my case and to share her case for presenting today!
- Thanks to Foetopathology CHU Bordeaux team !

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