TAWAM HOSPITAL
IN AFFILIATION WITH JOHNS HOPKINS MEDICINE

What could be behind a non-immune Hydrops?

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History of presenting illness

How did the story begin…

- 3 months old male infant
- Presented to the ER with 2 days history of progressing decreased activity, lethargy and poor feeding
- Was discharged 6 days back, after being treated for acute bronchiolitis with superadded pneumonia, discharged on Cefprozil

Physical examination

- Had low grade fever
- Hemodynamically stable
- Noticed to have a cardiac murmur
- Mild abdominal distension
- Significant bilateral scrotal swelling with normal skin appearance
- Flat Hemangioma at lower back with ill-defined borders

Continue history

- In the ER the patient underwent full septic work-up because of the presentation and was started on ceftriaxone

- Over the next 48 hours, patient demonstrated clinical improvement and was treated for the diagnosis of partially treated meningitis

Continue history

- Past medical/surgical history:
  - Had bilateral inguinal repair in the private sector few weeks earlier
  - Following with GI service for possible diagnosis of protein losing enteropathy

- Antenatal:
  - Mild pleural effusion, hydrocele and mild ascites of 8 mm detected at 18 weeks and 22 weeks of gestation

Continue history

- Postnatal:
  - Admitted to NNU for tachypnea and ruling out sepsis
  - Postnatal US:
    - No pleural effusion visualized on either side except for mild ascites

- Family history:
  - Parents are first degree cousins
  - Both parents are from highly Consanguineous families
  - Has five other siblings, two with same perinatal presentation
    - One died few hours after birth

What was happening in the hospital during this admission?

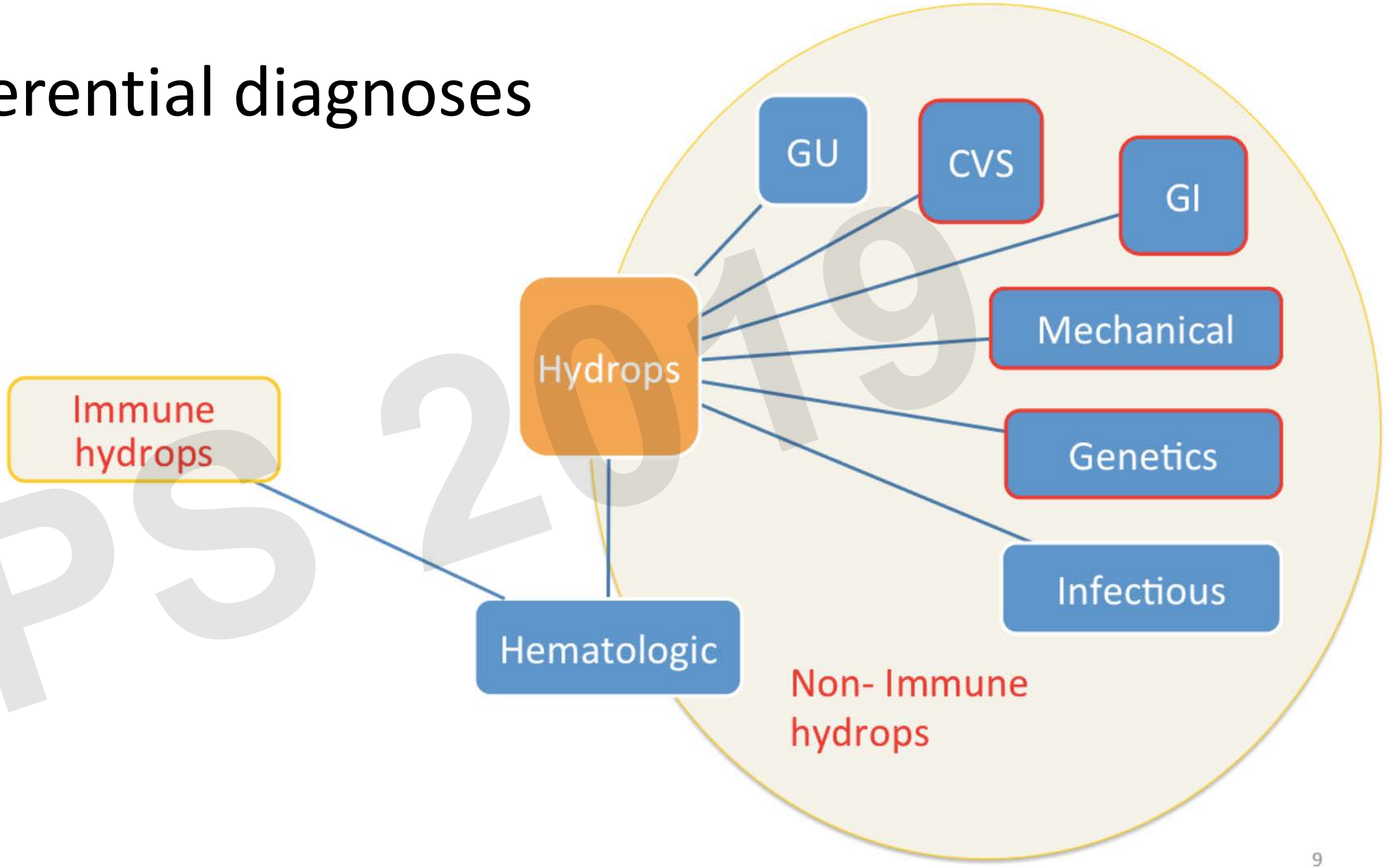
- Patient was noticed since admission to have significant bilateral Hydrocele
- Was noticed in two occasions to have a **bulging mass** in the right inguinal area (although was operated few weeks earlier)
- A scrotal US was done and confirmed **bilateral hydrocele with patent processus vaginalis and persistent inguinal hernia**
- Surgeons were involved since admission, and they decided to re-intervene for correction!

Continue hospital course

- Surgery day…
  - Patient underwent Bilateral inguinal hernia repair
  - Bilateral Hydrocelectomy

- Intraoperatively the surgeons have noticed **white fluid (chylous)** coming from the abdominal cavity !!!

Differential diagnoses

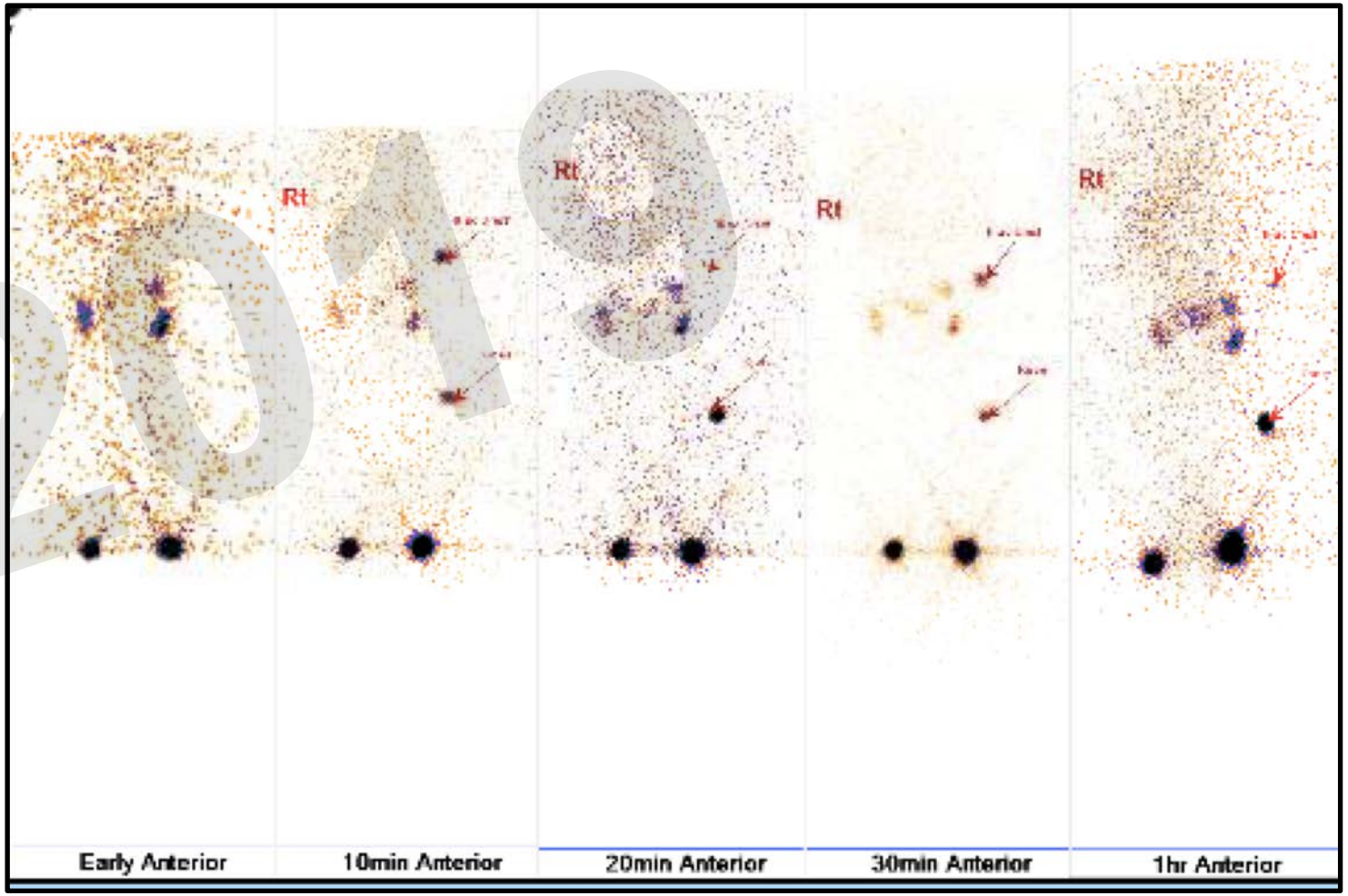


Investigations

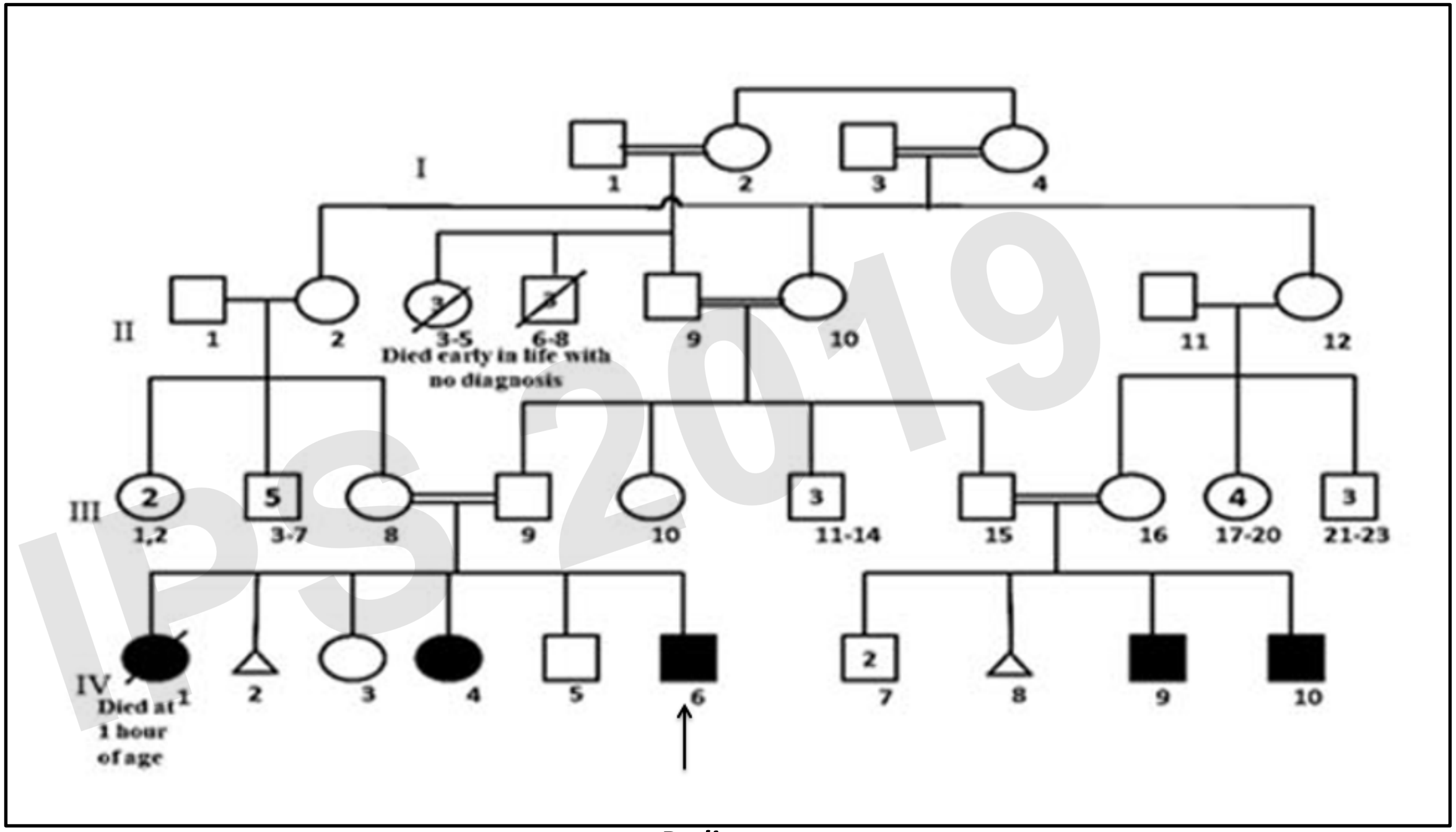
- General chemistry:
  - Normal Electrolytes
  - LFT showing **hypoalbuminemia** (Albumin 11 g\L)
  - Normal Lipid profile
- Blood count
  - Normal CBC and differentials
- Immunology:
  - Normal immunoglobulins
  - Normal lymphocytes subset
- Ascetics fluid:
  - **Low cholesterol** (0.82 mmol\L) , **High Triglyceride** (11.9mmol\L)

Continue investigations

- Lymphoscintigraphy
  - Mild paucity of right-sided inguinal group of lymph nodes.
  - No evidence of obstructed or impaired lymphatics on either sides.
- ECHO:
  - Small PFO



Lymphoscintigraphy



Pedigree

Continue investigations

- Karyotyping was done and reported normal
- Whole exome sequence was done and showed
  *"Variant mutation of **THSD1-protein**"*
- The sister's WES was reviewed again and the genetic variant was also detected

Description of patient phenotype

- Hydrops: Pleural effusion, ascites and Hydrocele
- Bilateral inguinal hernia
- Distinctive features: Prominent forehead, depressed nasal bridge,
- Hyperteloresim
- Hemangioma
- Protein losing enteropathy

Phenotypes of patients relatives…

Older sibling	Cousin	Cousin
Siste		
Bilateral p effusions and		es with thorax, fusion
PDA, PFO		D
		ease
	Hypoalbuminemia	Distinctive features
4 capillary hemangiomas	Distinctive features	Hypoalbuminemia and hypogammaglobinemia
	Multiple erythematous macules	

Non immune hydrops
Congenital cardiac anomalies
Hemangiomas
Gastrointestinal disorder, Malabsorptive

Reviewing literatures

Mutation in this gene was recently reported to cause NIHF (shamseldin et al.2015)

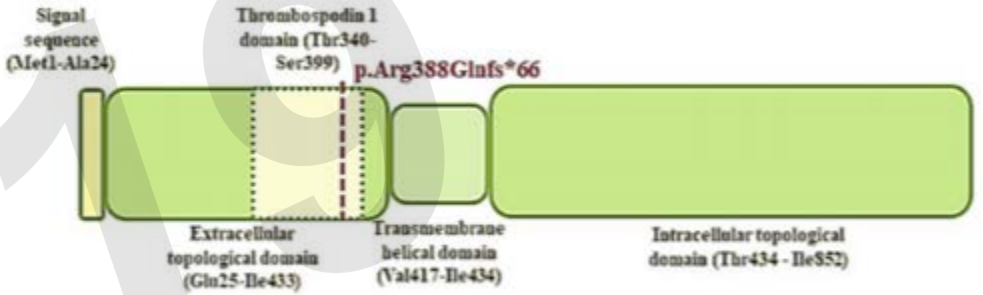
- Two highly consanguineous families in Saudi Arabia with 3 siblings in the first and 2 in the second
- The reported indies had the same mutation
- All indies had NIHF with variable phenotypes, two of them had lymphedema that was not reported in out study, and none had cardiac nor GI involvement

Reviewing literatures

- In 2016, Santiago et al, has identified 6 sporadic and 2 familial mutations in 18 middle-aged to elderly patients diagnosed with intracranial hemorrhage, compared to out study, family history was non remarkable for strokes, brain hemorrhage, or sudden death

About the gene

- The gene was first coded in 2006 and mapped in the human genome in 2016
- Highly expressed in endothelial cells as a cell surface protein that carries the thrombospondin1 protein
- Extracellular domain in the N-terminal region
- Intracellular domain in the C-terminal site



Thrombospondin 1 domain, contains the protein with variation “p.Arg388Glnfs*66”

Take home massage

- Etiologies of Non-immune hydrops fetalis are variant, Cardiovascular causes form 40%
- Genetic and metabolic causes of NIHF are increasing owing to advanced technologies in diagnosis
- Detailed history is a key factor for diagnosis, pediatricians should always report full and detailed history
- Family history is a cornerstone in the process of diagnosis, with it -itself- we can rule in and rule out diagnoses

Resources

- Dc, W., Takayanagi, S., Hiroyama, T., Yamazaki, S., Nakajima, T., Morita, Y., Nakauchi, H. (2012). Genetic marking of hematopoietic stem and endothelial cells: Identification of the Tmtsp gene encoding a novel cell surface protein with the thrombospondin-1 domain. Blood, 107(11), 4317–4325.
- Santiago-Sim, T., Fang, X., Hennessy, M. L., Nalbach, S. V., Depalma, S. R., Lee, M. S., Kim, D. H. (2016). THSD1 (Thrombospondin Type 1 Domain Containing Protein 1) Mutation in the Pathogenesis of Intracranial Aneurysm and Subarachnoid Hemorrhage. Stroke, 47(12), 3005–3013. https://doi.org/10.1161/STROKEAHA.116.014161.
- Takayanagi, S., Hiroyama, T., Yamazaki, S., Nakajima, T., Morita, Y., Usui, J., Nakauchi, H. (2006). Genetic marking of hematopoietic stem and endothelial cells: identification of the Tmtsp gene encoding a novel cell surface protein with the thrombospondin-1 domain. Blood, 107, 4317–4325.
- Abdelrahman HA, Al-Shamsi A, John A, et al. A recessive truncating variant in thrombospondin-1 domain containing protein 1 gene THSD1 is the underlying cause of nonimmune hydrops fetalis, congenital cardiac defects, and haemangiomas in four patients from a consanguineous family. Am J Med Genet Part A. 2018;18.