Three Day Old Male With Acute Kidney Injury Following Post Circumcision bleeding

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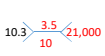
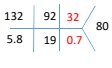
History and Physical exam

- 3 day old male
- 38 weeks (18 year old G2P1 mother, outside hospital)
- Birth weight 2.4 kg.
- Maternal illicit drug use and maternal thrombocytopenia (Platelets131,000/mm^3).
- DOL#3: Circumcision >> Significant Bleeding >> Transferred to the local NICU.
- BP was low. Otherwise normal
- Dry clots in circumcision's site

Laboratory

- Blood& urine culture
- TORCH screen





Differential Diagnosis at the outside hospital

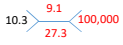
1- Neonatal sepsis with DIC
2- Neonatal autoimmune & alloimmune thrombocytopenia.
3- Congenital TORCH infection

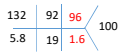
Outside Hospital : Initial Management

- Blood products
- Local hemostatic measures
- Empiric antibiotics (Gentamicin and ampicillin)
- IVIG with Solumedrol.
- No improvement was noted

Outside Hospital: Clinical Course

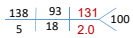
- No coagulation studies were done
- Blood products daily (packed RBCs X 4; platelets X 4, and cryoprecipitate X 1. No FFP)
- Hypertension.
- Worsening AKI and Fluid overload. Maintained good urine output.
- Respiratory distress and recurrent apnea
- Chest X-ray: Cardiomegaly and pulmonary edema.
- Echo: Left-sided heart failure > > > milrinone infusion.
- Blood and urine cultures negative. TORCH screening was negative





Clinical Course

- DOL#8,
- Transferred to UTSW Children's Medical Center
- Physical examination at admission:
  - Vitals: BP=113/75 mmHg, HR=190 bpm, RR= 60 breaths/min on 4 L/min O_2.
  - Patient was in acute respiratory distress.
  - Bruises on arms and legs.
  - Edema
- Patient was intubated and ventilated due acute respiratory failure shortly after admission.
- Lab evaluation:
- PT/INR: 24.3/2.1
- PTT=36.5



Has your differential diagnosis changed?

What further investigations would you order?

Labs on admission

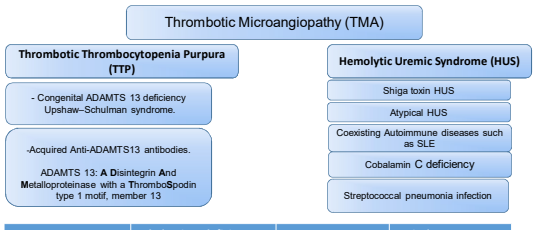
PT/INR*	PTT	Haptoglobin	LDH	Smear	C3	C4	Urinalysis	Renal sonogram	Echo
13.3/1.0	35	Undetectable <8 mg/dl(8-198)	2669 u/l (178-629)	Schistocytes	42 mg/dl (60-196)	12 mg/dl (13-24)	3+ proteinuria Large blood	Hydronephrosis grade2. No thrombosis	Heart failure

Differential Diagnosis

- Congenital Coagulopathy
- Neonatal sepsis with DIC
- Thrombotic microangiopathies

- **Congenital Coagulopathy**: Common with post circumcision bleeding.
  - Normally most factors are low in the first few months of life.
  - Most factors have half-life for 12-72 hours.

- **Disseminated intravascular coagulopathy (DIC):** sepsis, pregnancy complications such as asphyxia or meconium aspiration, trauma, malignancy.



ADAMTS 13	Cobalamin C deficiency screening	CXR	Typical HUS
59% Normal >67%	Negative	No pneumonia No effusion	Age No diarrhea

Diagnosis

Atypical HUS

Management: Initial

- PD
- Eculizumab at DOL#17
  - 300 mg x1 then,
  - 150 mg q2 weeksx2
  - 150 mg q4 week

Atypical HUS

- Rare genetic disease.
- Incidence rate ~0.11 cases per million pediatric population per year
- Clinical diagnosis based on a combination of mechanical hemolytic anemia with schistocytes on smear, consumptive thrombocytopenia, and acute kidney injury (AKI).
- Cardiac and neurologic involvement 20%.
- Dysregulation of complement alternative pathway.
- ~40-70% have triggering events…Trauma and infections
- ~ 30% of cases present with diarrhea
- Vast majority of children need renal replacement therapy at presentation
- High risk of ESRD
- Low C3 in 30% cases.
- Genetic analysis is positive in 60-70% of cases.

Atypical HUS

Genetic analysis:

1- Confirmation: 60-70% of cases.
2- Prognosis: Specific mutations with clinical outcomes and response to therapy
3- Family counseling
4- Kidney and liver transplantation: Factor B and C3.

TMA functional Panel	TMA genetic panel
Low C3, C4, factor B and I High soluable MAC (C5b-C9) Factor H autoantibodies: negative	Negative

Treatment

Plasma-Based therapy

- Morbidity and mortality
- Not efficient in all patients
- Often fails to rescue kidney function

Kidney with/without liver transplantation

Immunosuppressuion

- Factor H autoantibodies

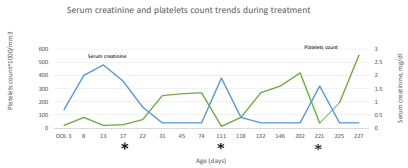
Eculizumab

- 2011, EMA and FDA
- An anti–complement component 5 humanized antibody.
- High effectiveness
- Easy administration
- No guidelines of dosage and frequency in neonates and small infants<5 kg.
- High risk of meningococcal infection
- Cost & availability

Summary of case reports treated with Eculizumab

Author	Genetic testing	Presentation	Age at first dose	Eculizumab dosing	Follow up
Michaux et al 2014	CFH mutation	11 days Vomiting Hypertension Cardiac dysfunction	Unclear	300 mg weekly x 2 doses then, biweekly x 2 months then, every 3 weeks	24 month: Normal kidney functions
Ariceta et al 2012	Negative	3 days Hyperbilirubinemia Thrombocytopenia Anemia	39 days	300 mg x 1 then, 150 x1, 300 mg q 3 week	14 months: No relapses. Mild proteinuria
Sharma et al 2014	CFH mutation	28 days Gross hematuria Hypertension	35 days	300 mg weekly x2 then, q 3 weeks	11 months: No relapses
Anastaze et al 2015	Negative	18 days Seizures	20 days	300 mg weekly x 2then. 300 mg/ 3 week	24 months: No relapses and normal neurologic exam.
Our case 2016	Negative	3 days Post circumcision bleeding	17 days	300 mg x1 then, 150 mg biweekly x2 then, 150 mg/4 weekly (relapse), 300 mg /3 weeks.	12 months: 2 relapses. Nephrotic syndrome. Normal kidney functions. Eculizumab dose :300 mg biweekly,

Follow up



Can we discontinue the treatment?

Author	Population	Complement abnormality	SCr at start, mg/dl	SCr at stop mg/dl	Relapse	Last SCr 22 months
Fakhouri et al 2016	38 cases >18 y: 29 case <18 y: 9 case	CFH: 11 case MCP: 8 C3: 1 CFI: 1 Anti CFH Ab:1 No gene: 16	Adult: 7.9 Child: 1.9 On dialysis: 18/38	Adult:1 Child: 0.4	CFH:8/11 MCP: 4/8 No variant: 0/16	Adult: 1 Child:0.44
Ardissino et al 2014	10 cases >18 y: 3 < 18 y:7	CFH: 3 Anti-CFH: 2 CFI:3 MCP:1 CFHR3/R1:1			CFH: 3/3 Others: 0/7	

- Nephrotic syndrome at 10 months of age
- Kidney biopsy in Feb 2017: collapsing FSGS

TMA-related collapsing glomerulopathy

Author	Population	TMAs causes	TMA-FSGS	TMAa outcomes			
					No FSGS	CG	Other FSGS
Boub et al 2016	N=2030 native kidney biopsies. TMA= 53(2.3%) C/B=48/5	HTN = 21 ACP = 9 Drugs= 7 Others= 9 Unknown= 7	N=33/50 (62.3%) CG=19/33 (57.6%) Other FSGS= 14/33	ESRD	1/18	7/18	4/14
				Proteinuria g/day	0.28	0.87	0.69

What do you recommend for treatment of TMA-related collapsing glomerulopathy?

Conclusion

- aHUS is still clinical diagnosis which is a challenge in newborns who present with atypical presentation.
- Eculizumab is a drug of choice for aHUS, and the outcome of aHUS is changed from one of the most severe and disabling kidney diseases to being a curable disease with a specific treatment. However, as with all other medications, risks and side effects in particular meningococcal infection may occur.
- Number of factors could be used to decide whether to discontinue or not discontinue the treatment, in particular, the assessment of risk of relapse, Also other factors should be consider such as (age, kidney function recovery, native or transplanted kidney, the presence of severe extrarenal manifestations, and the willingness of the patient.
- Collapsing glomerulopathy could develop in TMAs, and has bad outcomes.

Thank you

Raymond Quigley, MD