

Case example: TMA

GS became ill with diarrhea, fever and severe abdominal cramps at the age of 18 months while visiting Israel with her physician father.

Medical consultation verified above - fragmented RBC and ↓ platelets (< 75K) noted. Normal renal function and urinalysis. Rx: oral rehydration therapy (ORT); recovered and returned to the USA

2 1/2 years. similar event; developed acute renal failure which responded to fluid Rx.

3 1/2 years: another episode; saw nephrologist; laboratory- MAHA (microangiopathic hemolytic anemia) & ↓ platelets. When platelets normal; renal biopsy performed.

Case continued

3 1/2 - 12 years - no episodes

12 years: episode of severe abdominal cramps, fever, diarrhea, some ↓ in urine output, MAHA, ↑ haptoglobin,

Family had moved to Los Angeles; seen by nephrologist and hematologist - Rx I.V. heparin and fresh frozen plasma - rapid recovery

Subsequently father gave subcutaneous heparin and aborted episodes

12-20 years: multiple minor events - all resolved with subcutaneous heparin, at home

20 years: traveled to New York; became ill and required dialysis - with recovery, Cr 2.0 ; 2 years later required chronic dialysis

Questions: before Dr. Cohen presents his findings, how many think that the patient has HUS? TTP? No difference between the 2?

A

For the pathologist: are the morphologic findings *disease-specific* or fit in to an overall classification?

Are there diagnoses associated with symptom complex that can be excluded by biopsy?

Are the biopsy findings reversible?

After it was learned that the episodes recurred did that alter the interpretation?

Case analysis

1. Illness began in childhood without apparent antecedent infection; negative family history
2. 1st attack followed diarrheal illness - no culture & subsequent episodes were not triggered by infection
3. Recurrent episodes throughout 1st 2 decades
4. Renal function remained normal until age 20
5. No clinical evidence of secondary disorders
6. Studies to define pathogenesis - not available
 - A) ↓ to absent protease von Willebrand cleaving enzyme
 - B) ↓ to absent Factor H - stabilizer of alternate complement pathway (↓ C)

Management of patient

Identified after early episodes as TMA

Residual renal function remained normal - use of

Subcutaneous heparin unorthodox, made possible physician parent - Rx not evaluated but apparently prevented renal damage and significant recurrences

Traditionally would have received FFP and/or PE

Conjecture: if she had not become ill away from home and encountered delay in intervention would she have avoided chronic dialysis

THROMBOTIC MICROANGIOPATHIES TMA

“Thrombotic microangiopathies are microvascular occlusive disorders characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia and mechanical injury to erythrocytes”.

TSAI: 2002

HEMOLYTIC UREMIC SYNDROME

Described in 1955 by Gasser

5 fatal pediatric cases; with acute renal failure, microangiopathic hemolytic anemia (MAHA) and thrombocytopenia
Diarrheal form D+

During the next decades investigations for etiology revealed enteropathogens - especially E coli - 0157:H7 associated with contamination -

Risk factors for poor outcome

Very young or very old age; prolonged anuria
Hypertension; CNS Symptoms, ↑ WBC

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

Systemic clumping of platelets mediated by ultra large multimers of von Willebrand Factor (ULvWF) → ↓ platelets (<20,000)

Clinical pentad: ↓ platelets , MAHA ,acute renal failure (ARF), fever and neurologic symptoms

Practical: clinical suspicion, ↑ LDH (lactic dehydrogenase), ↓ platelets, ↑ Burr cells suggesting MAHA

GUIDELINES FOR TTP: DIAGNOSIS LABORATORY FINDINGS *

Hemagram, smear, coagulation studies, direct Coombs test, urinalysis, serum chemistries: renal, liver function & electrolytes

Desirable: HIV , Hepatitis C

Clinically unavailable: *ADAMTS 13* - vWF cleaving enzyme - deficient/absent in active TTP

* Brit J Haemat: 2003

TTP TREATMENT : GUIDELINES cont

Plasma exchange (PE): daily & > 2 days remission, (mortality has decreased from 80% to 10 - 30 %)

Remission defined as > 150,000 platelets and improved clinical and laboratory findings

Replacement solutions: controversial

Fresh frozen plasma (FFP) - rationale - supply missing enzyme

Cryoprecipitate

TTP:TREATMENT GUIDELINES ADJUNCTIVE

Steroids: methylprednisolone

Low dose aspirin after platelets > 150,000

Supportive: RBC transfusions, as needed

Platelet transfusions - contraindicated

Folate

Hepatitis vaccine

REFRACTORY TTP: TREATMENT GUIDELINES

Definition: slow or incomplete response to PE
platelets < 150,000 or ↑ LDH > 7 days PE

Recommendation: use replacement fluids without vWF (ck) ; ↑ number of PE

Vincristine; ? Cyclophosphamide or cyclosporine

Severe: splenectomy

PATHOPHYSIOLOGY OF TTP

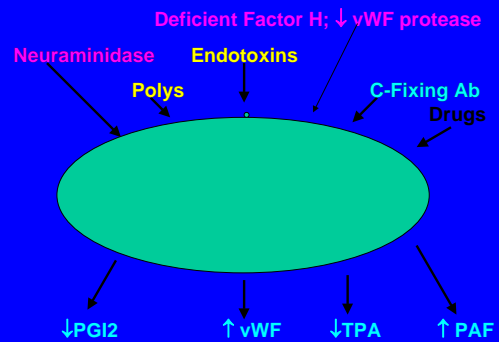
Deficiency in vWF cleaving protease enzyme

ADAMTS 13, due to genetic mutations or autoimmune inhibitors

Accordingly, ultralarge von Willebrand factor multimers (ULvWF) are not cleaved; circulate; form a nidus for thrombi and → shear force, leading to MAHA, ↓ platelets

ROLE OF VASCULAR ENDOTHELIUM: HUS

and TTP : PATHOPHYSIOLOGY



SUMMARY AND CONCLUSIONS

TTP and HUS are forms of TMA

TTP Guidelines available for diagnosis and management

Recent evidence reveals deficient-absent *ADAMTS 13*, a vWF protease cleaving enzyme

Ultra large vWF multimers, therefore, responsible for a cascade of events → widespread microvascular thrombi

Enzyme, and antibody tests against protease not available

D+ HUS (Stx)

Results from exogenous contamination - typically gram negative organisms (E coli 0157:H7 most prominent) - prodrome: colitis

Target organ: renal endothelium

Treatment: supportive Rx; heparin used in post-partum HUS

Acute mortality @ 5% - long term, significant residual - in pediatrics

D- results from 1) pneumococcal infection
2) genetic: defect in Factor H

demonstrated in some (H-HUS); test not available; no specific treatment

Prognosis: unfavorable