CCM Interhospital grand round

A Young Lady with Facial Puffiness going into Convulsion

Dr. PANG, Ching Wai
ICU, PMH
18th May, 2010

History

- F/19
- Good past health
- Bilateral lower limb edema and facial puffiness for 1 month
- Mild dyspnoea
- No headache, no impairment of vision
- No haematuria/ dysuria/loin pain
- No Frothy urine
- Absent of rash/ arthralgia

Physical examination

- Blood Pressure: 160-170/90-100 mmHg
- Facial, eyelids puffiness +
- Afebrile
- No rash/ arthralgia/ alopecia
- Clear lung fields
- Soft abdomen, no loin tenderness, no organomegaly
- No papilloedema

- Urine Multistix: RBC +++, Protein +++, hyaline cast +
- RFT: Na=142, K=4, Urea=9.9, Creatinine=84
- Albumin=23, Globulin=25
- Normal LFT
- CBP & clotting profile (pancytopenic)

[redacted]

H

Collect Date :	29/01/05	27/12/08	**29/12/08**	
Collect Time :	12:18	19:31	**14:04**	
Arrive Date :	-----	27/12/08	**29/12/08**	
Arrive Time :	-----	20:22	**15:25**	
Request No. :	H0056524	H0669723	**H0531666**	
Urgency :	Archived	URGENT	--	

					Reference Range	Units
COMPLETE BLOOD COUNT						
WBC	--	3.8	L	--	4.0 - 10.0	x10^9/L
RBC	--	3.31	L	--	3.8 - 4.8	x10^12/L
HGB	--	9.8	L	--	12.0 - 15.0	g/dL
HCT	--	0.276	L	--	0.360-0.460	L/L
MCV	--	83.5		--	80.0 - 98.0	fL
MCH	--	29.5		--	27.0 - 34.0	pg
MCHC	--	35.3		--	33.5 - 36.5	g/dL
RDW	--	13.6		--	11.0 - 15.0	%
PLT	--	146	L	--	150 - 400	x10^9/L
MPV	--	8.0		--	7.0 - 10.0	fL
WBC DIFFERENTIAL						
Neutrophil	--	2.1		--	2.0 - 7.0	x10^9/L
NEU %	--	55.5		--	40.0 - 80.0	%
Lymphocyte	--	1.2		--	1.0 - 3.0	x10^9/L
LYM %	--	32.6		--	20.0 - 40.0	%
Monocyte	--	0.4		--	0.2 - 1.0	x10^9/L
MON %	--	10.4	H	--	2.0 - 10.0	%
Eosinophil	--	0.0	L	--	0.02 - 0.5	x10^9/L
EOS %	--	1.2		--	1.0 - 6.0	%
Basophil	--	0.0	L	--	0.02 - 0.1	x10^9/L
BAS %	--	0.3		--	0 - 2.0	%
ESR, automated	--	--		9	< 31	mm/hr
Remarks	--	N		--		

Footnotes:
N - Final Report. Machine count only.

[redacted]

HOSPITAL AUTHORITY
PRINCESS MARGARET HOSPITAL

INTEGRATED OBSERVATION CHART WITH MEWS

Please sum up the MEWS score above or below the bold line

Observation Frequency Q4H

MEWS (Temp, LOC, SBP, RR) | Date | Time | MEWS (Heart or Pulse Rate)

Temp. (°C) | LOC (U, P, V, A) | Blood Pressure (score SBP only) | Resp. Rate

MEWS Total

SpO_2 % | Oxygen L/min | BW Kg | BO Frequency | Pain Score

Integrated Observation Chart with MEWS

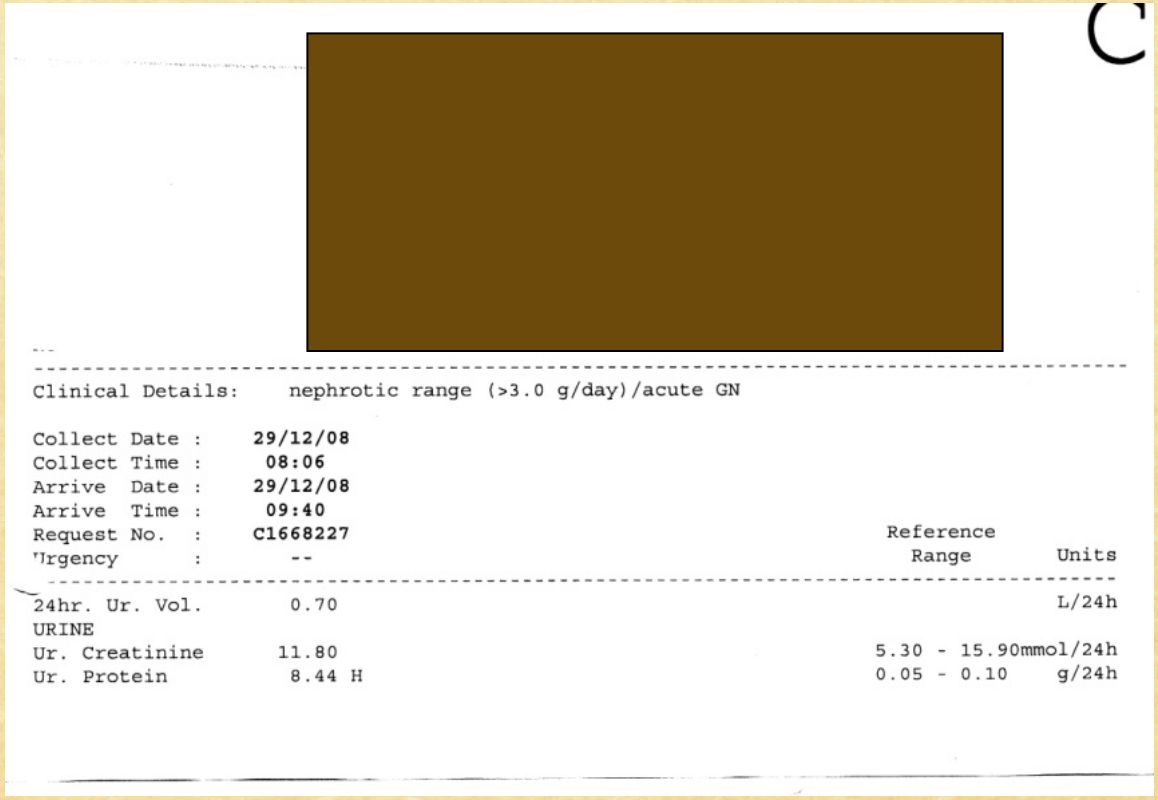
MR 4001 /PM

Rev 8/2008 P.T.O.

- MSU: no growth
- TSH=3.35
- CRP=2.7
- Autoimmune markers (ANA, anti-dsDNA, C3. C4 level) were taken
- USG : Normal kidneys
- 24 hours urine saved
- Discharged home

Progress

- Seen in SOPD
- Heavy proteinuria (8.44gm)
- C3/C4=0.26/0.03 (low)
- ANA=640, Anti-dsDNA >200
- MPO ANCA –ve
- HBsAg/Anti-HCV –ve
- Creatinine Clearance ~ 98 ml/min



Clinical Details: nephrotic range (>3.0 g/day)/acute GN

Collect Date :	29/12/08		
Collect Time :	08:06		
Arrive Date :	29/12/08		
Arrive Time :	09:40		
Request No. :	C1668227	Reference Range	Units
Urgency :	--		
24hr. Ur. Vol.	0.70		L/24h
URINE			
Ur. Creatinine	11.80	5.30 - 15.90	mmol/24h
Ur. Protein	8.44 H	0.05 - 0.10	g/24h

- So…
  - Renal disorder
  - Hamatological disorder
  - Positive ANA
  - Positive Anti-DNA

- Clinical Impression: Lupus Nephritis
- re-admitted x renal biopsy

Re-admitted on 21/1/2009

- USG done by XRD:

US Findings:
Both kidneys are normal in size. Right kidney is 11.6 cm and left kidney 11.2 cm in length. Mild increase in renal cortical echogenicity is suggestive of renal parenchymal disease. No focal lesion, renal stone or hydronephrosis is seen. Bladder appears normal.

Good arterial flow and venous flow are noted in both kidneys. Resistive indices of intra-renal arterial blood flow are normal. Bilateral renal veins are patent with no definite thrombus seen in their lumens. Small amount of ascitic fluid and minimal perinephric fluid over both kidneys are present.

IMPRESSION :
Renal parenchymal disease.
No evidence of renal vein thrombosis.
Small ascites and minimal perinephric fluid.

Renal function…

Collect Date :	27/12/08	27/12/08	19/01/09	19/01/09	**21/01/09**
Collect Time :	19:31	19:31	09:32	09:32	**11:34**
Arrive Date :	27/12/08	27/12/08	19/01/09	19/01/09	**21/01/09**
Arrive Time :	19:49	19:50	11:57	11:37	**14:36**
Request No. :	C9296986	C9296990	C0829533	C0832971	**C0833853**
Urgency :	URGENT	URGENT	--	--	--
Sodium	--	142	--	139	139
Potassium	--	4.0	--	5.3 H	5.2 H
Urea	--	9.9 H	--	18.9 H	21.1 H
Creatinine	--	84 H	--	217 H	211 H
Total Protein	--	48 L	--	46 L	46 L
Albumin	--	23 L	--	21 L	21 L
Globulin	--	25	--	25	25
Total Bilirubin	--	13	--	12	18
ALP	--	45	--	31 L	39 L
ALT	--	18	--	21	26
LDH	--	--	--	--	680 H

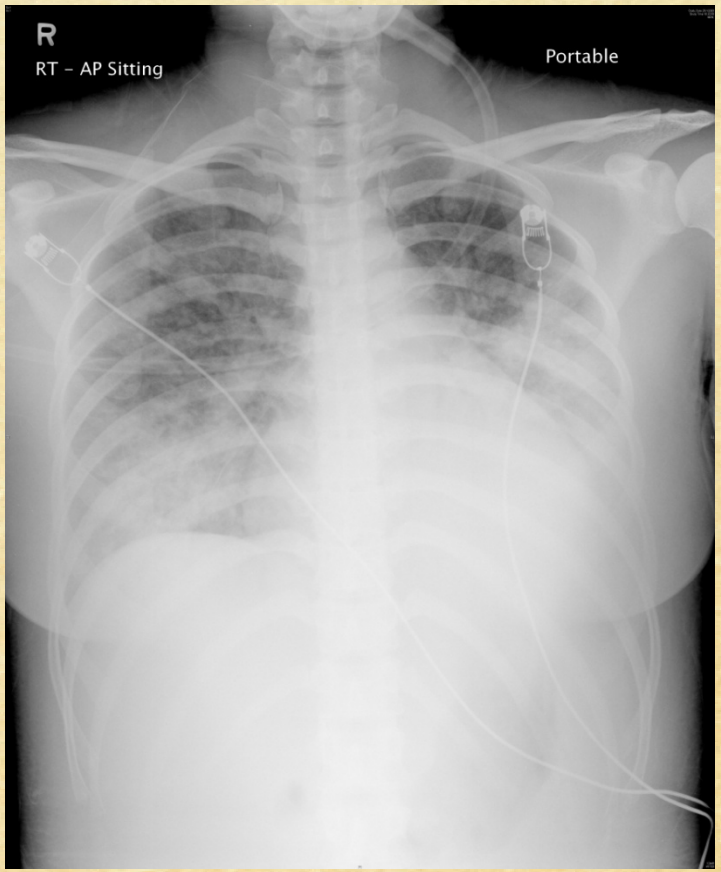
- Just before renal biopsy…

COMPLETE BLOOD COUNT					
WBC	3.8 L	--	6.2	8.7	
RBC	3.31 L	--	1.96 L	1.77 L	
HGB	9.8 L	--	5.5 L	5.2 L	
HCT	0.276 L	--	0.163 L	0.146 L	
MCV	83.5	--	82.9	82.6	
MCH	29.5	--	28.2	29.5	
MCHC	35.3	--	34.0	35.8	
RDW	13.6	--	18.0 H	19.1 H	
PLT	146 L	--	68 L	56 L	
MPV	8.0	--	10.3 H	12.6 H	
WBC DIFFERENTIAL					
Neutrophil	2.1	--	3.3	7.1 H	
NEU %	55.5	--	53.0	80.8 H	
Lymphocyte	1.2	--	2.1	1.2	
LYM %	32.6	--	34.3	14.0 L	
Monocyte	0.4	--	0.8	0.4	
MON %	10.4 H	--	12.1 H	4.5	
Eosinophil	0.0 L	--	0.0	0.1	
EOS %	1.2	--	0.7 L	0.6 L	
Basophil	0.0 L	--	0.0 L	0.0 L	
BAS %	0.3	--	0.0	0.0	
RBC MORPHOLOGY					
Anisocytosis	--	--	--	moderate	
Polychromasia	--	--	--	moderate	
Poikilocytosis	--	--	--	mild	
Schistocytes	--	--	--	some	
Reticulocyte	--	--	--	183.0 H	
RET %	--	--	--	10.4 H	
ESR, automated	--	9	--	--	

- Clotting profile was normal

- Renal biopsy was cancelled
- Subsequent blood tests: Lupus anti-coagulant/ Anti-cardiolipin Ab / Coomb's test –ve/ Haptoglobin <0.06/ ↑ LDH/ Normal clotting
- Specific treatment had been started by the nephrologists
- What is that treatment?

- Developed increased SOB
- Sputum was not purulent
- All along afebrile
- Echocardiogram:
  - Pericardial effusion 1.2cm
  - No cardiac tamponade
- Oliguric
- Fluid overload +++
- Persistent pancytopenia
- Developed haemoptysis
- Required RRT soon afterward



- What is the diagnosis?

- Coomb's test –ve/ Haptoglobin <0.06/ ↑ LDH/ Normal clotting

Collect Date :	27/12/08	27/12/08	19/01/09	19/01/09	21/01/09
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Potassium	--	4.0	--	5.3 H	5.2 H
Urea	--	9.9 H	--	18.9 H	21.1 H
Creatinine	--	84 H	--	217 H	211 H
Total Protein	--	48 L	--	46 L	46 L
Albumin	--	23 L	--	21 L	21 L
Globulin	--	25	--	25	25
Total Bilirubin	--	13	--	12	18
ALP	--	45	--	31 L	39 L
ALT	--	18	--	21	26
LDH	--	--	--	--	680 H

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WBC	3.8 L	--	6.2	8.7
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MCH	29.5	--	28.2	29.5
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RDW	13.6	--	18.0 H	19.1 H
PLT	146 L	--	68 L	56 L
MPV	8.0	--	10.3 H	12.6 H
WBC DIFFERENTIAL				
Neutrophil	2.1	--	3.3	7.1 H
NEU %	55.5	--	53.0	80.8 H
Lymphocyte	1.2	--	2.1	1.2
LYM %	32.6	--	34.3	14.0 L
Monocyte	0.4	--	0.8	0.4
MON %	10.4 H	--	12.1 H	4.5
Eosinophil	0.0 L	--	0.0	0.1
EOS %	1.2	--	0.7 L	0.6 L
Basophil	0.0 L	--	0.0 L	0.0 L
BAS %	0.3	--	0.0	0.0
RBC MORPHOLOGY				
Anisocytosis	--	--	--	moderate
Polychromasia	--	--	--	moderate
Poikilocytosis	--	--	--	mild
Schistocytes	--	--	--	some
Reticulocyte	--	--	--	183.0 H
RET %	--	--	--	10.4 H
ESR, automated	--	9	--	--

And…

- Developed first episode of GTC while she was on her way to ICU
- 3 more episodes of GTC in ICU
- CT brain after convulsion: NAD, no cerebral edema.
- HRCT x haemoptysis: diffuse ground-glass opacities and left lower lobe collapse-consolidation. Pleural effusion. No evidence of pulmonary hemorrhage

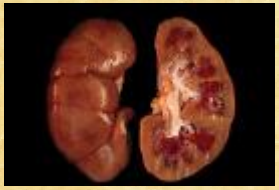
Working diagnosis

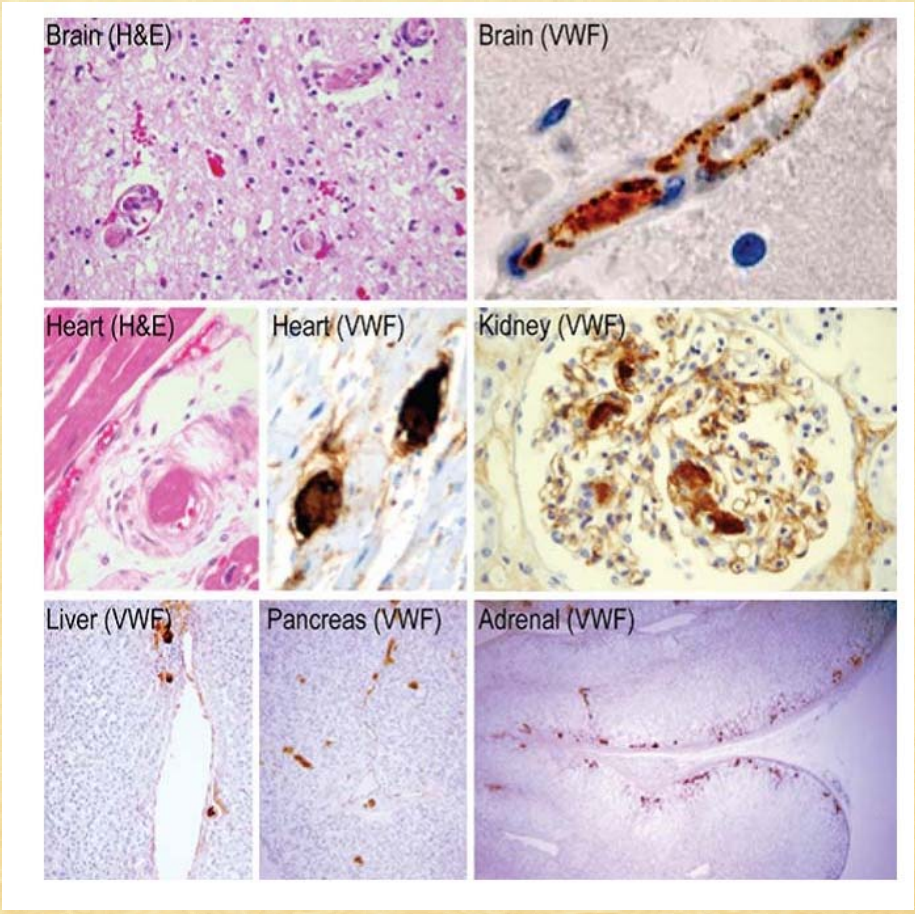
- SLE with multi-systems involvement
- Concomitant Thrombotic thrombocytopenic purpura (TTP)
- Packed cell transfusion to correct the anemia
- daily plasma exchange was started by nephrologist on 23/1/2009
- Added with Myfortic (Prodrug of MMF) initially (proliferative lupus nephritis), later stopped

Thrombotic thrombocytopenic purpura

TTP

- A disorder with characteristic von Willebrand factor (VWF) & platelet-rich microthrombi affecting the arterioles and capillaries of multiple organs.
- Uncommon
  - incidence of idiopathic TTP-HUS — 4.5 cases/million per year (Oklahoma TTP-HUS Registry)
- First described in 1924 by Moschowitz (American clinician and pathologist, 1879-1964)




Brain (H&E)
Brain (VWF)
Heart (H&E)
Heart (VWF)
Kidney (VWF)
Liver (VWF)
Pancreas (VWF)
Adrenal (VWF)

Causes and associated conditions

- Majority of case are idiopathic without an identifiable cause
- Some of them are congenital
- Some are associated with various connective tissue disease (e.g. SLE)
- Toxin–induced (e.g. Shiga toxin): through endothelial injury
- Drug induced (immune-mediated vs. dose dependent)
- Cancer and chemotherapy
- Disseminated malignancy
- Allogeneic hematopoietic cell transplantation
- Pregnancy and oral contraceptives
- Immunosuppressive agents
- HIV infection

Table 1
Drugs associated with thrombocytopenic purpura or hemolytic uremic syndrome

Chemotherapy agents [85,87,149,150]	Mitomycin c, ARA-C, bleomycin, cisplatin, Daunorobucin
Hormonal agents [109,110]	Tamoxifen, oral contraceptives
Antibiotics [108,152]	Penicillin, rifampin, sulfonamides
Toxins [76,79,159]	*Escherichia coli*, bee sting
Immunosuppressive agents [125,154]	Cyclosporin, tacrolimus
Others [151,157,158]	Arsenic, iodine, cocaine, quinine

- If untreated, typically follows a progressive course
  - irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death

Closely related to Hemolytic uremic syndrome (HUS)

TTP and HUS

- share same presenting features
  - thrombocytopenia
  - microangiopathic hemolytic anemia
- TTP:
  - More neurologic symptoms and minimal renal impairment.
  - Adult
- HUS:
  - acute renal failure is dominant with minimal neurologic abnormalities.
  - Children, follow diarrhea caused by E.coli O157:H7

- In many cases it is impossible to differentiate them
- ?2 ends of a disease spectrum
- Both severe neurologic abnormalities and acute renal failure → TTP-HUS
- As in our case

TTP-HUS, The Pentad

- In the era before effective treatment is available, there is a characteristic set of clinical and laboratory findings (The pentad) of the condition:

1. Microangiopathic hemolytic anemia
2. Thrombocytopenia
3. Acute renal insufficiency
4. Neurologic abnormalities, usually fluctuating
5. Fever

- It is now rare to have the full blown disease with effective treatments available

- Only 2 features are required before initiating treatment, namely PLASMA EXCHANGE

The 2 major diagnostic criteria…

1. Thrombocytopenia
   - maybe extreme

2. Microangiopathic hemolytic anemia

Peripheral-Blood Smear Showing Abnormalities Characteristic of Thrombotic Thrombocytopenic Purpura

George J. N Engl J Med 2006;354:1927-1935

The NEW ENGLAND JOURNAL of MEDICINE

Microangiopathic hemolytic anemia (MAHA)

- defined as non-immune hemolysis (i.e., negative direct antiglobulin test) with prominent red cell fragmentation (schistocytes) observed on the peripheral blood smear
- Typical findings of hemolysis:
  - ✓ Increased serum indirect bilirubin concentration
  - ✓ Reduced haptoglobin
  - ✓ Extremely high lactate dehydrogenase (LDH)

Schistocytosis

- Usually < 0.5% of red cell population (mean: 0.05%)
- In TTP-HUS, it could be ranged from 1 to 18%
- Schistocyte count >1 % strongly suggestive of TTP-HUS

Clinical Details: acute renal failure

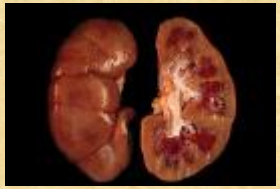
Collect Date :	27/12/08	29/12/08	19/01/09	21/01/09	**22/01/09**		
Collect Time :	19:31	14:04	09:32	11:34	**07:05**		
Arrive Date :	27/12/08	29/12/08	19/01/09	21/01/09	**22/01/09**		
Arrive Time :	20:22	15:25	11:32	14:02	**08:13**		
Request No. :	H0669723	H0531666	H0041256	H0043362	**H0642106**	Reference Range	Units
Urgency :	URGENT	--	--	--	**URGENT**		
COMPLETE BLOOD COUNT							
WBC	3.8 L	--	6.2	8.7	5.6	4.0 - 10.0	x10^9/L
RBC	3.31 L	--	1.96 L	1.77 L	2.14 L	3.8 - 4.8	x10^12/L
HGB	9.8 L	--	5.5 L	5.2 L	6.6 L	12.0 - 15.0	g/dL
HCT	0.276 L	--	0.163 L	0.146 L	0.181 L	0.360-0.460	L/L
MCV	83.5	--	82.9	82.6	84.8	81.0 - 98.0	fL
MCH	29.5	--	28.2	29.5	30.8	27.0 - 34.0	pg
MCHC	35.3	--	34.0	35.8	36.3	31.5 - 36.5	g/dL
RDW	13.6	--	18.0 H	19.1 H	14.9	11.0 - 15.0	%
PLT	146 L	--	68 L	56 L	43 L	150 - 400	x10^9/L
MPV	8.0	--	10.3 H	12.6 H	10.1 H	7.0 - 10.0	fL
WBC DIFFERENTIAL							
Neutrophil	2.1	--	3.3	7.1 H	3.4	2.0 - 7.0	x10^9/L
NEU %	55.5	--	53.0	80.8 H	60.8	40.0 - 80.0	%
Lymphocyte	1.2	--	2.1	1.2	1.6	1.0 - 3.0	x10^9/L
LYM %	32.6	--	34.3	14.0 L	27.8	20.0 - 40.0	%
Monocyte	0.4	--	0.8	0.4	0.6	0.2 - 1.0	x10^9/L
MON %	10.4 H	--	12.1 H	4.5	10.8 H	2.0 - 10.0	%
Eosinophil	0.0 L	--	0.0	0.1	0.0 L	0.02 - 0.5	x10^9/L
EOS %	1.2	--	0.7 L	0.6 L	0.1 L	1.0 - 6.0	%
Basophil	0.0 L	--	0.0 L	0.0 L	0.0 L	0.02 - 0.1	x10^9/L
BAS %	0.3	--	0.0	0.0	0.5	0 - 2.0	%
RBC MORPHOLOGY							
Anisocytosis	--	--	--	moderate	--		
Polychromasia	--	--	--	moderate	--		
Poikilocytosis	--	--	--	mild	--		
Schistocytes	--	--	--	some			
Reticulocyte	--	--	--	183.0 H	--	50.0 - 100.0	x10^9/l
RET %	--	--	--	10.4 H	--	0.5 - 2.5	%
ESR, automated	--	9	--	--	--	< 31	mm/hr

Start Plasma exchange if there is no other clinically apparent etiology

In our case, PE was started on 23/1/2009

Acute renal insufficiency

- due to a renal thrombotic microangiopathy
- Near normal urinalysis with only mild proteinuria (usually between 1 to 2 g/day) and few cells or casts
- anuria, may required dialysis
- Our case



Neurologic symptoms

- present in the majority of patients with TTP-HUS
- subtle changes, such as confusion or severe headache.
- Focal abnormalities (e.g., transient ischemic attack, stroke)
- grand mal seizures and coma
  - Our case had 4 episodes of GTC on 27/1/2009

- CT or MRI :Often show features consistent with reversible posterior leukoencephalopathy syndrome (PRES)

Fever

- Less frequent
- High fever and rigor should suggest the diagnosis of sepsis and DIC rather than TTP-HUS

Laboratory findings in TTP-HUS

Complete blood count
Anemia (microangiopathic hemolytic anemia)
Thrombocytopenia (especially severe in TTP)
Increased reticulocyte percentage
White blood cell count normal to increased
White blood cell differential normal with no immature granulocytes
Peripheral blood smear
Polychromatophilic red cells (ie, reticulocytosis)
Fragmented red cells (schistocytes, helmet cells)
Nucleated red cells may be present, but are not numerous*
Coagulation and Immunohematologic studies
Normal PT
Normal aPTT
Fibrinogen concentration normal•
Fibrin degradation products not increased•
Direct Coombs' test negative
Other laboratory studies
Markedly increased serum lactate dehydrogenase (LDH)
Increased serum indirect bilirubin
Markedly reduced or absent serum haptoglobin
Increased serum creatinine (especially in HUS)

Although all of the findings listed here may be present, the diagnosis of TTP-HUS should be suspected in any patient with otherwise unexplained microangiopathic hemolytic anemia and thrombocytopenia.

TTP: Thrombotic thrombocytopenic purpura; HUS: Hemolytic uremic syndrome; PT: prothrombin time; aPTT: activated partial thromboplastin time.

* The presence of many nucleated red cells suggests inflitrative disease of the marrow, such as occult metastatic cancer.

• Disseminated intravascular coagulation is not typically present, but may be seen when there is diffuse tissue ischemia.

TTP-Pathogenesis

- Microthrombi rich in vWf and platelet in affected organs (e.g. in the glomeruli and arterioles)
- In contrast to fibrin-rich thrombi in DIC

ADAMTS13(A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 repeats)

- Von Willebrand factor (VWf), which is important in clot formation, is synthesized in endothelial cells and assembled in larger multimers that are present in normal plasma

Diagram showing ADAMTS13's function to cleave large multimers of vWF from NEJM

Moake J. N Engl J Med 2002;347:589-600

- Normally the larger multimers, called unusually large von Willebrand factor (ULvWf), are rapidly degraded in the circulation into the normal size range of vWf multimers.

- The congenital and idiopathic form are associated with a deficiency of this specific von Willebrand factor-cleaving protease (ADAMTS13)
  - deficiency of the enzyme is usually severe (<5% activity)
- Causing excessive platelet aggregation → thrombus formation

Proposed Relation among the Absence of ADAMTS 13 Activity in Vivo, Excessive Adhesion and Aggregation of Platelets, and Thrombotic Thrombocytopenic Purpura

Diagram showing ADAMTS13's function to cleave large multimers of vWF from NEJM

Moake J. N Engl J Med 2002;347:589-600

From ASHWebmaster, youtube

ADAMTS13-antibodies

- Ig G auto antibodies (inhibitory and un-inhibitory) to the ADAMTS13 has been found at varying titers among a high percentage of patients with idiopathic TTP
- suggests autoimmune nature of the condition
- Also believed to be the underlying mechanism concerning Immune-mediated drug-induced TTP

- Is ADAMTS13 deficiency invariably give rise to TTP-HUS?

ADAMTS13 deficiency

- most commonly present in patients with classical TTP features
- Severe deficiency had been seen in congenital or iatrogenic TTP
- In classical HUS, level of this enzyme is usually relatively normal

However…

ADAMTS13 deficiency

- There are individuals who has absent ADAMTS13 activity with no manifestations of TTP-HUS

- similarly low levels have been found in some, but not all, children and adults with severe sepsis and associated disseminated intravascular coagulation or ischemic organ failure

Less severe ADAMTS13 deficency

- Disseminated intravascular coagulation
- Idiopathic thrombocytopenic purpura
- Hematopoietic cell transplantation and cyclosporine
- Cancer chemotherapy
- Infection, severe sepsis
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Heparin induced thrombocytopenia
- Leukemia, other neoplasm's
- Acute inflammatory states
- Cirrhosis
- Uremia
- Postoperative period
- Normal subjects
- The newborn

And…

- In animal models, an additional ("second hit") inflammatory or prothrombotic stimulus(e.g. Shiga toxin) was required in order to initiate a clinical syndrome resembling TTP.

- ADAMTS13 levels appear to decrease during the last two trimesters of pregnancy→? Related to the fact of increased frequency of TTP-HUS during pregnancy, especially at the time of delivery.

- So, is it useful to check its level?

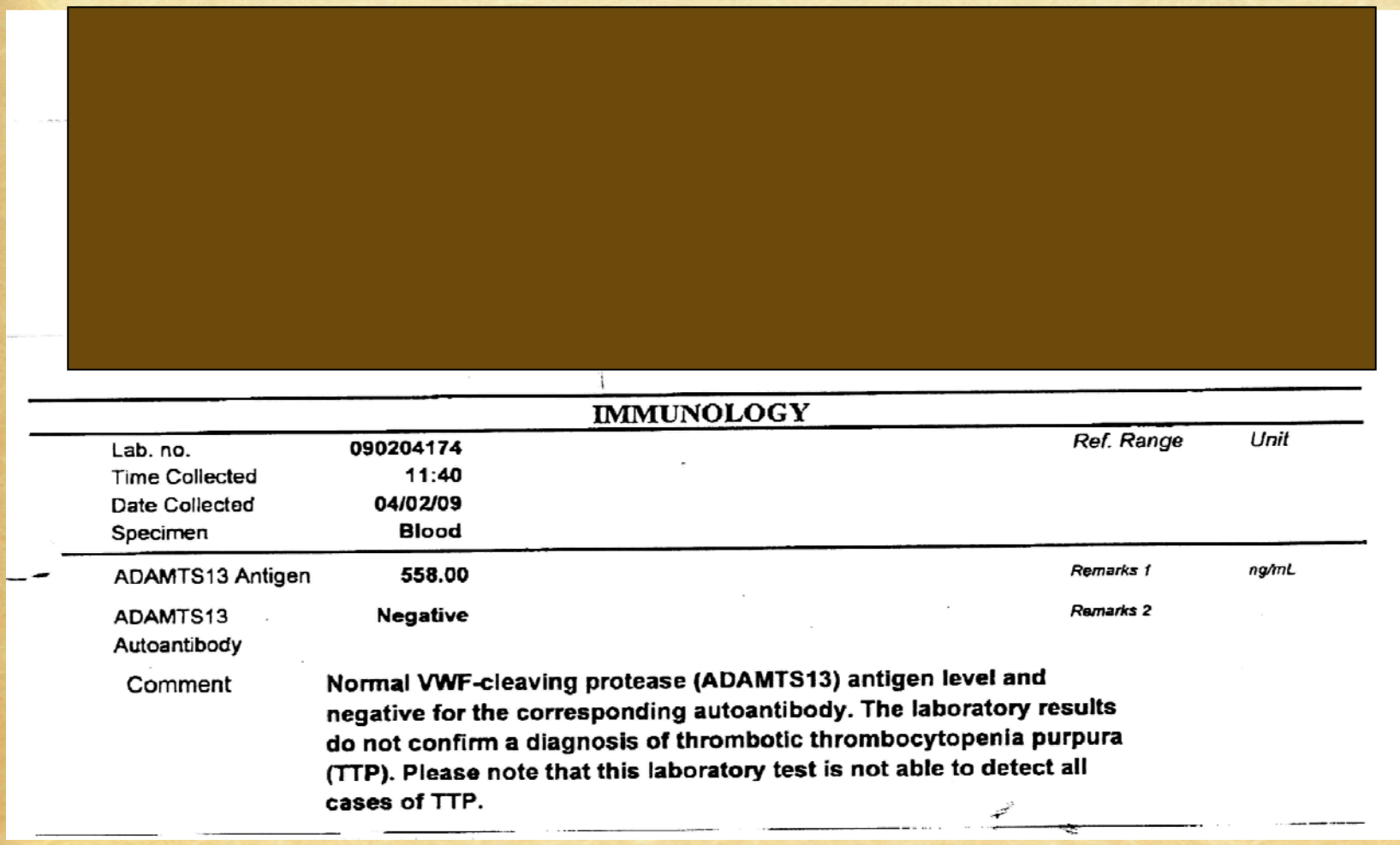
ADAMTS13 Assay – level, antibody

- Should not be used for confirming the diagnosis before treatment is initiated.
- Since Delays in initiating treatment is FATAL
- Important for understanding the pathogenesis of the congenital and acquired causes of TTP-HUS

ADAMTS13 assay… is useful!

- severe reduction (<5% of normal act.) of ADAMTS13 levels is highly specific for TTP in the correct clinical setting
- Very useful to monitor treatment response and relapse in those who has a very low level of ADAMTS13 in the beginning

- In our case, the enzyme and its antibody level were check after 10 sessions of plasma exchange…
- Limited value in our case



IMMUNOLOGY

		Ref. Range	Unit
Lab. no.	090204174		
Time Collected	11:40		
Date Collected	04/02/09		
Specimen	Blood		
ADAMTS13 Antigen	558.00	Remarks 1	ng/mL
ADAMTS13 Autoantibody	Negative	Remarks 2	

Comment: **Normal VWF-cleaving protease (ADAMTS13) antigen level and negative for the corresponding autoantibody. The laboratory results do not confirm a diagnosis of thrombotic thrombocytopenia purpura (TTP). Please note that this laboratory test is not able to detect all cases of TTP.**

TTP-HUS- presence of other Pathogenesis

- Some of patients suffering from TTP-HUS do not have ADAMTS13 deficiency
- Other pathogenesis include

✓ Endothelial injury

✓ Increased platelet aggregation

✓ Genetic factors

Endothelial injury

- could be directly induced by a drug or indirectly via neutrophil or platelet activation
- Believed to be the underlying mechanism of TTP-HUS caused by Shiga toxin, or dose-dependent drug toxicity
- Could also be a "second hit" for those who are asymptomatic and yet have a low ADAMTS13 level

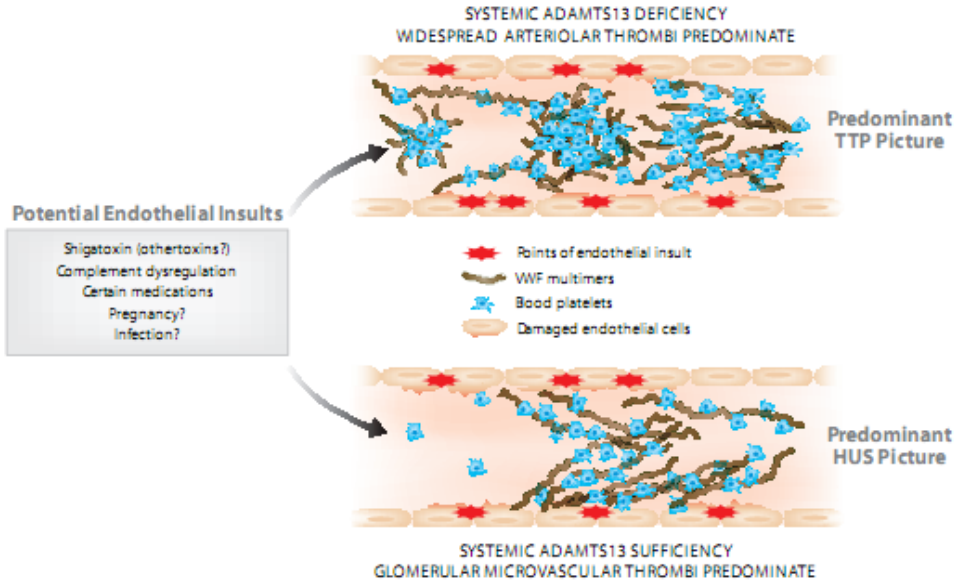


Figure 1. Hypothetical model for shared pathophysiology between HUS and TTP. In this proposed model, the inciting event for both HUS and TTP is a similar endothelial insult brought about by any of a variety of sources (or combination of sources) that results in widespread endothelial activation, inflammation, and damage, including the release of VWF and other contents of the Weibel-Palade bodies. The subsequent events may be determined in part by the level of systemic ADAMTS13 activity. In the case of systemic ADAMTS13 *deficiency* (top), ADAMTS13 is not available to process the newly released VWF, resulting in the widespread formation of VWF and platelet thrombi throughout the arteriolar circulation and the clinical picture of TTP. Conversely, in the case of systemic ADAMTS13 *sufficiency* (bottom), TTP is avoided by ADAMTS13-mediated release of platelet/VWF thrombi throughout the arteriolar circulation. For reasons that are not understood, circulating ADAMTS13 is not able to cleave efficiently VWF that is released in the glomerular microcapillary circulation, resulting in thrombus formation, increased inflammation, glomerular damage, and the clinical picture of HUS. Potential reasons for the inability of ADAMTS13 to cleave VWF in the glomerular circulation may include unfavorable shear stress not permissive for the proper unfolding of VWF (decreasing access of ADAMTS13 to the sessile bond within the folded VWF A2 domain) and the local presence of molecules that may interfere with ADAMTS13 activity or with its interaction with VWF.

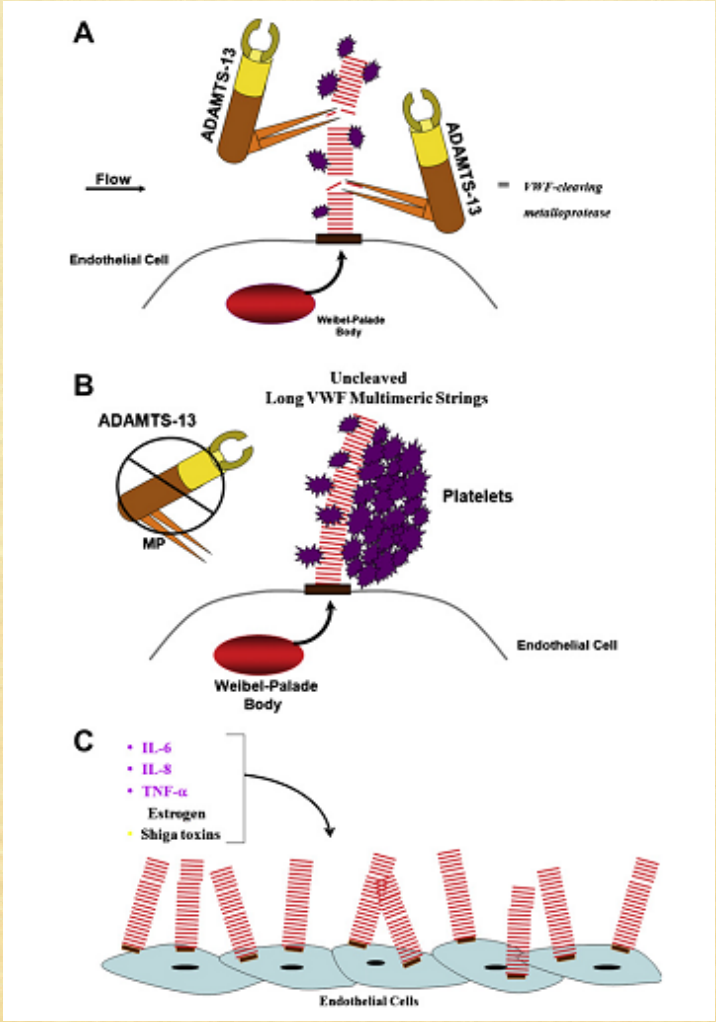
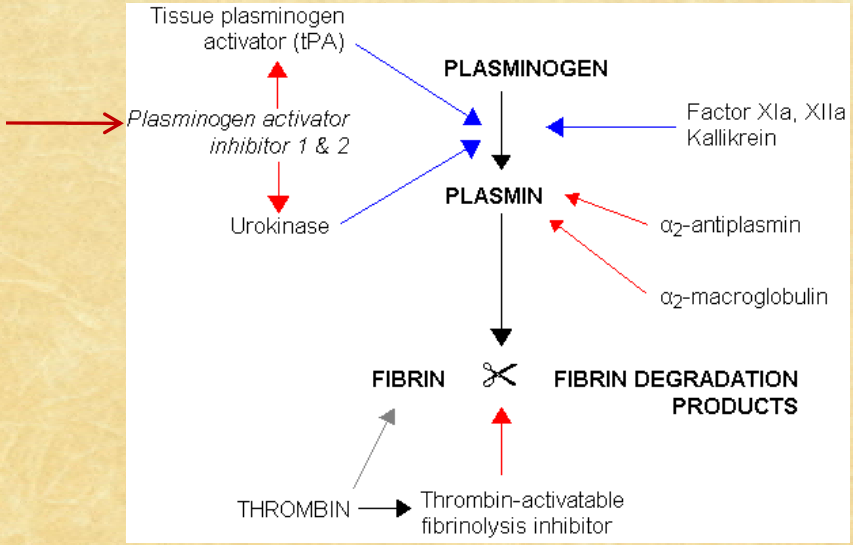


Fig. 1. (A) In normal individuals, ADAMTS-13 enzyme molecules from the plasma attach to, and then cleave, long "sticky" VWF multimeric string like structures secreted from stimulated endothelial cells at an exposed 1605-6 peptide bond in VWF monomeric subunits. (B) Absent or severely reduced activity of ADAMTS-13 in patients with TTP prevents the timely cleavage of the long VWF multimeric strings secreted by stimulated endothelial cells. Platelets adhere and aggregate onto the uncleaved long VWF strings. Severe congenital deficiency of ADAMTS-13 activity caused by gene mutations, or profound inhibition of ADAMTS-13 activity caused by acquired autoantibodies, result in a propensity for TTP. (C) TTP episodes are especially likely to occur in the absence (or severe reduction) of ADAMTS-13 if there is increased concurrent endothelial cell secretion of long VWF strings (eg, in the presence of inflammatory cytokines, estrogen, or certain bacterial toxins).

Increased platelet aggregation

- Increased levels of plasminogen-activator inhibitor type 1 (PAI-1) {the primary inhibitor of the fibrinolytic compounds tissue-type plasminogen activator and urokinase} have been described in children with post diarrheal HUS



Genetic factors

- Predisposing effect of factor V leiden towards thrombotic microangiopathy
- Autosomal recessive and autosomal dominant forms of familial HUS

TTP-HUS -etiology

- Idiopathic
- Toxin –induced (e.g. Shiga toxin): ?through endothelial injury
- Drug induced (immune-mediated vs. dose dependent)
- Cancer and chemotherapy
- Disseminated malignancy
- Allogeneic hematopoietic cell transplantation
- Pregnancy and oral contraceptives
- Immunosuppressive agents
- HIV infection

Table 1. Clinical Categories of the Acquired Thrombotic Thrombocytopenic Purpura (TTP) Syndromes.*

Category	Cause or Associated Conditions	Risk Factors	Clinical Features†	Treatment	Clinical Course
Idiopathic TTP	Severe deficiency of ADAMTS 13 activity is present in many but not all patients. Relapses may be triggered by pregnancy and inflammatory conditions (e.g., infection, surgery, and pancreatitis).	Black race, female sex, obesity	One third with no neurologic abnormalities; fever uncommon; acute renal failure rare	Plasma exchange is required, and immunosuppressive treatment is appropriate.	Eighty percent of patients recover. In patients with a severe deficiency of ADAMTS 13 activity, the relapse rate is 50%.
Pregnancy	In addition to being pregnant, patients may have a severe deficiency of ADAMTS 13 activity.	Near-term or postpartum period	May be indistinguishable from severe preeclampsia, eclampsia, and the HELLP syndrome	Plasma exchange is required, and immunosuppressive treatment may be appropriate.	Relapse may occur, but most subsequent pregnancies are unaffected.
Autoimmune disorders	Acute flares of systemic lupus erythematosus, antiphospholipid antibody syndrome, or scleroderma may be indistinguishable from TTP. Patients may have a severe deficiency of ADAMTS 13 activity.	Predominantly female sex; young adulthood and middle-age	Severe manifestations of the primary autoimmune disorders, usually including renal failure	Immunosuppressive treatment is required, and plasma exchange may be appropriate.	The course is chronic, and the mortality rate is high.
Prodrome of bloody diarrhea	Patients have hemorrhagic enterocolitis caused by Shiga toxin–producing bacteria, typically *Escherichia coli* O157:H7.	Female sex in adults and white race in both children and adults	"Typical" HUS in children; in adults, renal failure and severe neurologic abnormalities common	Children are treated with supportive care. Plasma exchange may be appropriate for adults. Immunosuppressive treatment is unnecessary.	Death or end-stage renal disease occurs in 12% of children. Mortality rate in adults is 45%. Relapse may not occur.
Acute, immune-mediated drug toxicity	Quinine is the most common cause. Quinine-induced TTP is caused by quinine-dependent antibodies to multiple tissues. Ticlopidine, clopidogrel, and other drugs have been implicated.	With quinine, older age, white race, and female sex	With quinine, sudden onset of systemic symptoms with acute renal failure; possible fever, diarrhea, liver adverse effects, and neutropenia	Plasma exchange may be appropriate. Immunosuppressive treatment is unnecessary.	With quinine, mortality rate is 15% and chronic renal failure is common. Relapse occurs only with reexposure to the drug.
Cumulative, dose-dependent drug toxicity	Cancer chemotherapy with mitomycin, gemcitabine, and possibly other agents has been implicated, as have immunosuppressive agents (e.g., cyclosporine and tacrolimus).	Drug dose and duration	Insidious onset and a progressive course after etiologic agent is discontinued; renal failure common	The benefit of plasma exchange or any other treatment, other than stopping the drug, is uncertain.	Mortality is high because of the underlying condition. Chronic renal failure is common.
Hematopoietic stem-cell transplantation	Allogeneic transplantation may be a precursor of TTP-like syndromes. The incidence is variable because diagnostic criteria are uncertain.	High-risk procedures (e.g., unrelated donor, HLA mismatch, active disease); presence of acute graft-versus-host disease; sepsis	Thrombotic microangiopathy usually limited to the kidney	The benefit of plasma exchange is unlikely.	Mortality is high because there are multiple complications.

* HELLP denotes hemolysis, elevated liver enzymes, and low platelets, and HUS hemolytic–uremic syndrome.
† The clinical features are in addition to thrombocytopenia and microangiopathic hemolytic anemia.

Differential Diagnosis

- Systemic vasculitis or other connective tissue disease: typically have other systemic symptoms.(e.g. malar rash, arthralgia)
  - SLE with multi-organs involvement
- Catastrophic Antiphospholipid syndrome: prolonged aPTT. Antiphospholipid Ab
  - Anti-cardiolipin Ab Normal, Lupus anticoagulant -ve
- Scleroderma renal crisis: previous history of limited/ systemic sclerosis

- Malignant hypertension: History and clinical signs
- Pre-eclampsia
- HELLP syndrome
- DIC: ?high fever, septic foci.
  - Consumption of components of the coagulation cascade→ ↓ fibrinogen,factor V, VIII. ↑ PT & aPTT
- Disseminated malignancy: mucin-producing adenocarcinoma, failed to respond to plasma exchange

Table VI. The variation in presenting features and management of TMA in pregnancy.

Diagnosis	Classic TTP	Post-partum HUS	HELLP	Pre-eclampsia/eclampsia
Time of onset	Usually < 24 weeks	Post partum	Usually > 34 weeks	Usually > 34 weeks gestation
Histopathology of lesions	Widespread platelet thrombi	Thrombi in renal glomeruli only	Hepatocyte necrosis & fibrin deposition in periportal sinusoids	Glomerular endothelial hypertrophy and occlusion of placental vessels
Haemolysis	+++	++	++	+
Thrombocytopenia	+++	++	++	++
Coagulopathy	–	–	+/–	+/–
CNS symptoms	+++	+/–	+/–	+/–
Liver disease	+/–	+/–	+++	+/–
Renal disease	+/–	+++	+	+
Hypertension	Rare	+/–	+/–	+++
Effect on fetus	Placental infarct can lead to IUGR and mortality	None, if maternal disease is controlled	Associated with placental ischaemia and increased neonatal mortality	IUGR, occasional mortality
Effect of delivery on disease	None	None	Recovery, but may worsen transiently	Recovery, but may worsen transiently
Management	Early plasma exchange is imperative	Supportive ± plasma exchange	Supportive, consider plasma exchange if persists	Supportive ± plasma exchange

Treatment

Idiopathic TTP-HUS is a MEDICAL EMERGENCY

that is almost always fatal if left untreated

Plasma exchange

- Is the only therapy demonstrated to be effective in RCT
- reverses the platelet consumption responsible for the thrombus formation and symptoms that are characteristic of this disorders
- Reduced the mortality of patients with idiopathic TTP from >90% to ~25%
- Should be initiated even if there is some uncertainty about the diagnosis of TTP-HUS

Plasma exchange

- Removal of the patient's plasma depletes the circulating level of autoantibody to ADAMTS13 when present, and also depletes the circulating Unusually Large von Willebrand factor (ULVWf) multimers
- Replacement of the patient's plasma via infusion of normal plasma supplies the missing protease (ADAMTS13).

Plasma exchange

- may be beneficial even when the ADAMTS13 activity is not severe reduced
- There are TWO EXCEPTIONS to the general recommendation of plasma exchange in TTP-HUS:

1. Post diarrheal HUS in children: usually resolves spontaneously, following supportive therapy alone
2. TTP-HUS caused by Cancer chemotherapy or transplantation:
   - result of dose-dependent drug toxicity
   - systemic infections
   - or acute graft-versus-host disease

   only sporadic and anecdotal reports that suggest efficacy of plasma exchange

Plasma exchange

- Large volumes of plasma are needed for the treatment of a patient with TTP, estimated to be approximately 115 units per treatment course in a 60 kg patient
- risk of transfusion-related complications (e.g., infection, volume overload, allergic reaction).
- Catheter-related complication

Plasma exchange- Fresh Frozen Plasma

- Large volumes of fresh frozen plasma (FFP) (approximately four units per liter of plasma removed) from many different donors are required during plasma exchange, increasing the risk of anaphylactoid reactions
- “pretreat” with adrenaline/ steroid

Plasma exchange -

Cryoprecipitate-poor plasma

- The volume of replacement may be lesser than FFP because of its “effectiveness”. since VWF is largely removed in the cryoprecipitate.
- However 2 small randomized, controlled trials found no difference in efficacy between whole plasma and cryoprecipitate-poor plasma
- deficiencies of fibrinogen and factor VIII

Plasma Exchange - how often?

- initially performed daily until the platelet count has normalized and hemolysis largely ceased, as evidenced by a return of the serum lactate dehydrogenase (LDH) concentration to normal, or nearly normal, levels
- Most centers use 1 x plasma volume exchange, 1.5 plasma volume for resistant case
  - Estimated plasma volume: 0.07x BW (kg) x (1-Hct)

- Whether stop right away, or tapers it gradually is still not clear .
- The British recommend stopping the PE on the 2nd day of normalization of platelet count (British Society for Hematology, 2006)

Plasma exchange-complication

- Largely were related to the use of a central venous catheter

Resistant Disease

- 10 to 20 percent of patients will have a transient, incomplete, or no response to plasma exchange therapy
- Usually those who have moderate deficiencies of ADAMTS13 only (i.e. >10 percent activity) without demonstrable anti-ADAMTS13 antibodies

Our Case

[redacted] H

Clinical Details: acute renal failure

Collect Date :	27/12/08	29/12/08	19/01/09	21/01/09	**22/01/09**		
Collect Time :	19:31	14:04	09:32	11:34	**07:05**		
Arrive Date :	27/12/08	29/12/08	19/01/09	21/01/09	**22/01/09**		
Arrive Time :	20:22	15:25	11:32	14:02	**08:13**		
Request No. :	H0669723	H0531666	H0041256	H0043362	**H0642106**	Reference	
Urgency :	URGENT	--	--	--	**URGENT**	Range	Units
COMPLETE BLOOD COUNT							
WBC	3.8 L	--	6.2	8.7	5.6	4.0 - 10.0	x10^9/L
RBC	3.31 L	--	1.96 L	1.77 L	2.14 L	3.8 - 4.8	x10^12/L
HGB	9.8 L	--	5.5 L	5.2 L	6.6 L	12.0 - 15.0	g/dL
HCT	0.276 L	--	0.163 L	0.146 L	0.181 L	0.360-0.460	L/L
MCV	83.5	--	82.9	82.6	84.8	81.0 - 98.0	fL
MCH	29.5	--	28.2	29.5	30.8	27.0 - 34.0	pg
MCHC	35.3	--	34.0	35.8	36.3	31.5 - 36.5	g/dL
RDW	13.6	--	18.0 H	19.1 H	14.9	11.0 - 15.0	%
PLT	146 L	--	68 L	56 L	43 L	150 - 400	x10^9/L
MPV	8.0	--	10.3 H	12.6 H	10.1 H	7.0 - 10.0	fL
WBC DIFFERENTIAL							
Neutrophil	2.1	--	3.3	7.1 H	3.4	2.0 - 7.0	x10^9/L
NEU %	55.5	--	53.0	80.8 H	60.8	40.0 - 80.0	%
Lymphocyte	1.2	--	2.1	1.2	1.6	1.0 - 3.0	x10^9/L
LYM %	32.6	--	34.3	14.0 L	27.8	20.0 - 40.0	%
Monocyte	0.4	--	0.8	0.4	0.6	0.2 - 1.0	x10^9/L
MON %	10.4 H	--	12.1 H	4.5	10.8 H	2.0 - 10.0	%
Eosinophil	0.0 L	--	0.0	0.1	0.0 L	0.02 - 0.5	x10^9/L
EOS %	1.2	--	0.7 L	0.6 L	0.1 L	1.0 - 6.0	%
Basophil	0.0 L	--	0.0 L	0.0 L	0.0 L	0.02 - 0.1	x10^9/L
BAS %	0.3	--	0.0	0.0	0.5	0 - 2.0	%
RBC MORPHOLOGY							
Anisocytosis	--	--	--	moderate	--		
Polychromasia	--	--	--	moderate	--		
Poikilocytosis	--	--	--	mild	--		
Schistocytes	--	--	--	some	--		
Reticulocyte	--	--	--	183.0 H	--	50.0 - 100.0	x10^9/l
RET %	--	--	--	10.4 H	--	0.5 - 2.5	%
ESR, automated	--	9	--	--	--	< 31	mm/hr

[redacted]

[redacted] H

Clinical Details: acute renal failure & ? APO
Post HD and PE

Collect Date :	12/02/09	13/02/09	14/02/09	14/02/09	**16/02/09**		
Collect Time :	13:34	13:06	10:30	13:47	**11:17**		
Arrive Date :	12/02/09	13/02/09	14/02/09	14/02/09	**16/02/09**		
Arrive Time :	14:56	15:06	11:02	14:40	**12:28**		
Request No. :	H0074504	H0075100	H0076216	H0606079	**H0081360**	Reference	
Urgency :	--	URGENT	URGENT	URGENT	--	Range	Units
COMPLETE BLOOD COUNT							
WBC	7.3	5.9	3.9 L	4.5	3.1 L	4.0 - 10.0	x10^9/L
RBC	3.30 L	2.97 L	2.58 L	2.43 L	2.45 L	3.8 - 4.8	x10^12/L
HGB	9.1 L	8.5 L	7.4 L	7.2 L	7.2 L	12.0 - 15.0	g/dL
HCT	0.268 L	0.243 L	0.211 L	0.205 L	0.201 L	0.360-0.460	L/L
MCV	81.3	81.8	81.8	84.1	82.1	81.0 - 98.0	fL
MCH	27.5	28.4	28.7	29.8	29.4	27.0 - 34.0	pg
MCHC	33.8	34.8	35.1	35.4	35.8	31.5 - 36.5	g/dL
RDW	19.5 H	19.3 H	18.9 H	20.9 H	18.3 H	11.0 - 15.0	%
PLT	50 L	48 L	47 L	46 L	30 L	150 - 400	x10^9/L
MPV	7.7	8.9	6.8 L	9.6	9.4	7.0 - 10.0	fL
WBC DIFFERENTIAL							
Neutrophil	6.3	4.8	2.3	3.0	2.1	2.0 - 7.0	x10^9/L
NEU %	86.4 H	80.9 H	58.0	67.8	65.5	40.0 - 80.0	%
Lymphocyte	0.4 L	0.6 L	0.9 L	0.8 L	0.6 L	1.0 - 3.0	x10^9/L
LYM %	6.0 L	9.6 L	23.1	18.3 L	18.7 L	20.0 - 40.0	%
Monocyte	0.5	0.5	0.7	0.6	0.5	0.2 - 1.0	x10^9/L
MON %	7.1	8.7	17.3 H	12.8 H	15.4 H	2.0 - 10.0	%
Eosinophil	0.0	0.0	0.0	0.0 L	0.0 L	0.02 - 0.5	x10^9/L
EOS %	0.5 L	0.5 L	1.1	0.7 L	0.5 L	1.0 - 6.0	%
Basophil	0.0 L	0.0	0.0	0.0 L	0.0 L	0.02 - 0.1	x10^9/L
BAS %	0.0	0.4	0.6	0.4	0.0	0 - 2.0	%
RBC MORPHOLOGY							
Polychromasia	mild	mild	--	--	--		
Schistocytes	some	some	some	--	some		
Reticulocyte	120.0 H	110.0 H	--	--	--	50.0 - 100.0	x10^9/l
RET %	3.6 H	3.7 H	--	--	--	0.5 - 2.5	%
Remarks	Y	Y	Y	N	Y		

[redacted]

Anti-dsDNA: ↓ from >200 to 20

What do we do then…?

- Revise the working diagnosis
- If diagnosis is certain,
  - Increase the plasma exchange to twice daily
  - another reasonable option for those with poorly responsive or resistant disease is the addition of other modalities (e.g.glucocorticoids, rituximab)

Glucocorticoids

- A useful adjunct in patients with idiopathic TTP-HUS
- An empirical regimen, adapted from the management of patients with systemic lupus erythematosus who have severe flares of activity, is the use of very high pulse doses of methylprednisolone, such as 1000 mg/day for three days.
- ? maintenance steriod

- unclear benefits in patients with TTP-HUS and HIV infection because of the high potential for side effects and accelerated immunosuppression

Our case

- Pulse steriod given, followed by maintenance systemic steriod
- Started even before plasma exchange
- So… ineffective

Rituximab

- As salvage therapy

1. Patients with a more severe course and with more neurologic abnormalities
2. do not respond to plasma exchange,
3. develop worsening disease in spite of continuing plasma exchange plus Glucocorticoids,
4. relapsing disease

Rituximab

- A monoclonal anti-CD 20 antibody
- Binds to and clears B lymphocytes responsible for antibody production by
  - Complement-dependent cytotoxicity
  - Antibody-dependent cellular cytotoxicity
  - Apoptosis
- Useful in both acute refractory and chronic relapsing TTP

Rituximab

- Decision to add the medicine is guided by clinical, ADAMTS13 activity and antibody level
- Intravenous infusion of 375mg/m^2 for 4 weeks time, weekly dose
- Administered immediately following PE

Rituximab

- Associated with rapid normalization of clinical features and routine laboratory parameters within a median of 11 days of initiation of therapy
- Superior safety record and no infectious complication

The STAR Study: plasma exchange plus Glucocorticoids with or without Rituximab

- A multi-institutional randomized phase III clinical trial
- Start recruiting patients during 2009, will assess the efficacy of rituximab administered early in the course of patients with TTP to determine if it is beneficial in diminishing the requirement for plasma exchange and/or decreasing the frequency of exacerbations and relapses

Our case

- Self paid

Princess Margaret Hospital

Invoice for Sale of Medication 自購藥物發票

Patient Type: Public (IP)

Ticket No.: 取藥編號 | Invoice Date: 發票日期 [redacted] | Invoice No.: 發票編號 [redacted] | (Standalone Invoice Printing)

Drug Code 藥物編號	Description 藥物名稱	Quantity 數量	Amount(HKS) 金額(港幣)
ONC # RITU02	RITUXIMAB INJECTION 10MG/ML 50ML	1 VIAL	13,750.0
		Total	$ 13,750.0

Processed by: [redacted]

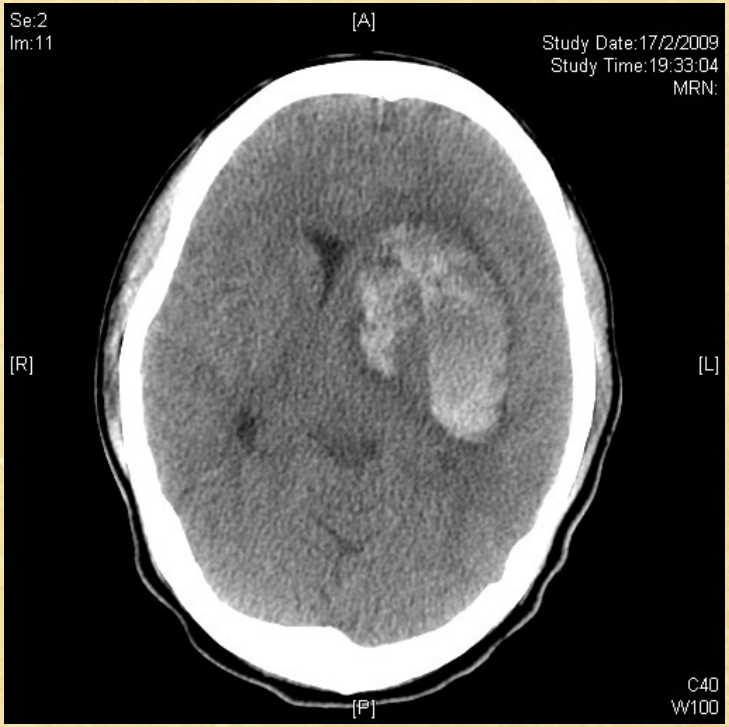
Accounts Office

Amount paid HK$

- 2 weekly doses had been given
- Just before the 3rd dose, she developed vomiting and drop of conscious state

Sad ending…

- 3rd dose of rituximab was withheld
- Neurosurgeon: conservative treatment
- "NAR" discussed
- Patient succumbed on 23/2/2009



Other agents

- Vincristine-?interference with vWF-platelet binding
- IVIg
- No significant benefit
- not an alternative to continuing plasma exchange

- Cyclosporine-targets T cells, itself can induce TTP-HUS
- Splenectomy
- ? as last resort in cases who fail the rituximab treatment

Platelet transfusion

- Production of new or expanding microvascular thrombi
- May lead to new or worsening neurologic symptoms, acute renal failure
- Contraindicated in TTP unless there is life-threatening hemorrhage. (guideline, British Journal of hematology, 2003)

After plasma exchange

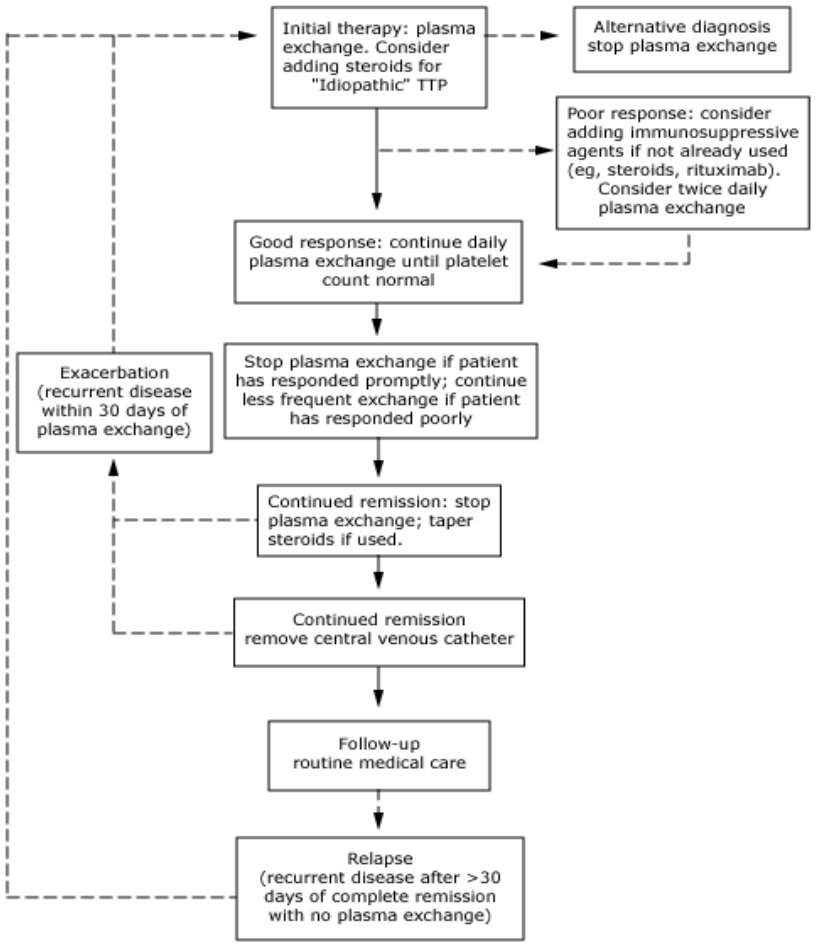
- After discontinuation of plasma exchange, patients should be frequently monitored with complete blood counts and serum lactate dehydrogenase (LDH) concentrations

- Relapses, defined as recurrent TTP-HUS after at least 30 days of no treatment and no evidence of TTP-HUS, are common in patients with severe ADAMTS13 deficiency who respond to the initial course of therapy.
- Relapses usually occur within the first year, but occasionally are seen as late as 10 years

Maintenance therapy

- no known effective maintenance therapy for the prevention of relapses in idiopathic TTP

Management of patients with TTP-HUS



Solid arrows represent an ideal course; broken arrows represent common variations.

Reproduced (revised) with permission from George, JN. How I treat patients with TTP-HUS. Blood 2000; 96:1223. Copyright © 2000 American Society of Hematology.

- In summary

SLE + TTP, as in our case…

- Response to therapy appeared to be poorer and mortality higher
- ?related to the multi-organs involvement of SLE and the presence of 2 potentially life-threatening conditions
- Prior use of corticosteriods and immunosuppressive in SLE may have slowed the tempo of development of TTP by partially suppressing the immune mechanism that could trigger TTP

Thank you

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