CASE CONFERENCE

20120213
Speaker: R2 游姿寧
Supervisor: F2 陳欣伶

Patient data

- Age: 36 y/o
- Gender: female
- Date of arriving ER: 2011/08/XX, 20: 44
- Chief complaint: 病患來診為蒼白/貧血
- Consciousness: E4M6V5
- Vital signs: T/P/R 36.8/111/24, BP 126/86, SpO_2 100%
- Triage II
- R2 許

History

- 最近 dyspnea and vomiting, abdominal pain
  - Fever up to 38°C today
  - Mild rhinorrhea, no cough
  - Leg rash for 3 days, not itching, not painful
  - No nausea/vomiting, no abdominal pain
  - No bloody or tarry stool
  - Mens 量中等

Past history

- Denied any systemic disorder
- Allergy: denied
- Denied pregnancy

Physical examination

- Consciousness: clear
- HEENT: pale, conjunctiva: icteric
- Chest: clear BS; RHB
- Abdomen: epigastric tenderness and guarding
- Extremity: mild cold, multiple petechiae, no tenderness, no pitting edema

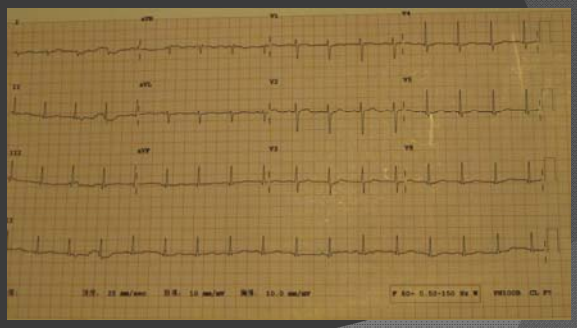
Impression

- Thrombocytopenia and anemia
  - r/o thrombocytopenic purpura
  - r/o ITP

Initial orders (21:16)

- CBC/DC/Plt
- Panel I, lipase
- PT/aPTT
- N/S 500 ml IV st, then 100 ml/hr
- U/A, EIA
- ECG
- 備/輸 Plt 12U
- Bedside echo

ECG



Laboratory data

CBC/DC/Plt		BCS		U/A	
WBC	6.6	Glu	96	RBC	0-1
RBC	2.54	GOT	54	WBC	3-5
Hb	7.4	BUN	16	Epi	1-2
Hct	22.0	Cre	0.9	Crystal	-
MCV	86.6	Na	139	Bac	+
MCH	29.1	K	3.5	Pre EIA	negative
MCHC	33.6	lipase	58		
RDW	18.2				
Plt	10	PT/aPTT			
Seg	64%	PT	10.5		
Lym	24%	INR	0.99		
Mono	7%	aPTT	37.9		
Band	4%				
Meta	1%				

ER course and orders

- 22:00, mild fever (37.5°C)
  - Tinten 1# PO st
- 22: 53
  - check D-dimer, Fibrinogen, FDP
  - 加備 pRBC 4U
- 23: 50, headache
  - Cataflam 1# PO st
- Day 2, 00: 45, still headache
  - Bain ½ Amp IV st

Laboratory data

Item	Data	Reference
Fibrinogen	538 mg/dL	200-500
FDP	10-40 μg/ml	0-10
D-dimer	3418.4 ng/ml	0-500

ER course, Day 2 (1)

- 01:30
  - Hb, Plt after BT 2 hours
  - Consult hematologist cm
  - 輸 pRBC 2U
  - Reticulocyte count
  - T/D-bil
  - RBC morphology
  - DC bedside echo
  - 轉 EC

Item	Data	Reference
Reticulocyte	8.6%	0.5-1.5%
T-Bil	1.7 mg/dL	0.2-1.3
D-Bil	0.6 mg/dL	0-0.4
Hb	7.6 m/dL	11-16
Plt	24 x1000/μl	140-450

- Reticulocyte index (RI)
  = 8.6% x (22/45) / 2
  = 2.1% (>2%: adequate marrow response)

RBC morphology

- Anisocytosis: positive
- Poikilocytosis: positive
- Size Finding: normocytic
- Chromic finding: normochromic
  - Polychromic: marked
- Shape finding:
  - Spherocytes: slight
  - Fragmented cells (=schistocyte): moderate
- Inclusion bodies: no finding
- Other: normal

ER course, Day 2 (2)

- 05:30, progress note
  - 仍 headache, pale looking
  - Family表示headache for 1 week
  - 這幾天只有吃止痛藥
  - 以前有醫師告知有免疫問題, 沒追蹤
  - Check DAT, LDH, urine routine, arrange brain CT to R/O complicated ICH

Brain CT

Urine routine					
Item	Data	Ref	Item	Data	Ref
Color	yellow		RBC	0-1	0-2
Clarity	1+	-	WBC	16-30	0-5
Sp. gr.	1.026	1.00-1.02	Epi	8-15	0-5
pH	6.5	5.5-8.0	Cast	Not found	Not found
OB	2+	negative	Crystal	Not found	Not found
protein	100 (2+)	negative	Bacteria	+	
glucose	negative	negative	Others	Not found	Not found
ketone	negative	negative	Preg. EIA	negative	negative
bilirubin	negative	negative			
urobilinogen	1.0	0.1-1.0			
Nitrite	negative	negative			
WBC esterase	+	negative			

Item	Data	Reference
LDH	752 U/L	135-225
DAT	negative	
IAT	negative	

ER course, Day 2

- 08:00, persistent epigastric pain
  - Arrange PES
- 08:30
  - Bedside echo: CBD dilatation, 1 cm
  - Check C3, C4, ANA, anti-dsDNA, anti-SSA (suggested by AIR Dr.) to R/O autoimmune disease
  - Arrange abdominal echo
- 12: 30
  - Nexium 1Amp IV QD&st
  - Cefmetazole 1g IV Q8H&st
- 14:20
  - Solu-medrol 40 mg IV Q8H&st
- 18: 34, admission to AIR

Item	Data	Reference
C3	89.7 mg/dL	79-152
C4	12.6 mg/dL	16-38

PES

- Stomach
  - Gastritis, superficial, antrum
  - Ulcers, antrum
- Duodenum
  - Duodenitis, bulb

Abdominal echo

- Liver: no cirrhotic change and space-occupying lesions
- IHD: Double-gun sign was noted in the right IHDs
- MBD: dilatation of MBD (1.2cm)
- GB, PV system: negative
- Pancreas: air masking
- Spleen: enlarged
- Diagnosis:
  - Biliary tract:
    - Dilatation of main bile duct
    - Intrahepatic duct stone, right IHD
  - Spleen:
    - Splenomegaly

Summary of admission note

- APN history and left side weakness 10 years ago
- Treated in NTUH, and “immune problem’ was told
- Did not go back for follow-up
- 2 weeks ago, diarrhea for 1 week
- 6 days ago, petechia/bruise over four limbs, intermittent headache and fever
  - Went to LMD, took some anti-pyretics
- Dizziness, poor appetite, palpitation, dyspnea, upper abd dull pain
  - LMD: anemia and thrombocytopenia were found

Tetative diagnosis

- Evans syndrome, suspect systemic lupus erythematosus
- Suspected occult infection, biliary tract infection
- Gastric ulcer

EVANS SYNDROME

Evans syndrome

- In USA:
  - 1/80000
  - Mostly adults; no gender predilection
  - A chronic, relapsing, sometimes fatal course (7%)
- Autoantibody attack RBC and platelet
- Autoimmune hemolytic anemia and idiopathic thrombocytopenic via apoptosis
- Dx: positive DAT and absent any known underlying etiology
- Tx: steroid; IVIG: cyclosporine, azathiprine, cyclophosphamide, vincristine…

Clinical course

- Day 2, day of admission
  - Keep Nexium, Cefmetazole, Solumedrol
  - Add Vit K 1Amp QW2, 5
  - 輸 pRBC 2U
- Day 3
  - Hb: 9.3, Plt: 7
  - 輸 plt 12U
  - ANA: negative, anti-dsDNA: negative, RA: 21.5 (H)

Clinical course

- Day 4
  - Mild headache, nausea, dyspnea
  - Plt: 9
  - 輸 plt 12U
  - Vomiting then conscious disturbance, agitation at 20: 33
    - Vital signs: HR 60-70, BT: no fever, SBP 120-130
    - Consciousness: E3M5V2
    - Lab data: WBC 14800, GOP/GPT 145/153, T/D-bil: 2.8/0.7, BUN/Cre: 18/1.2, Na/K/iCa 142/3.3/4.13, P/Mg 3.04/1.7, Ammonia 39
    - Brain CT: no ICH
  - Sepsis was suspected
  - Give Dormicum for times, change antibiotics to Ceftriaxone and Metronidazole
  - Sedation by Dormicum (0.5 ml/hr)

Clinical course

- Day 5
  - Plt 13
  - Consult Infection man:
    - susp. CNS infection
    - suggest Vancomycin, Ceftriaxone, Ampicillin
  - Consult Neuro Dr.:
    - susp. CNS infection or lupus brain
    - suggest antibiotic treatment, follow-up EEG, do CSF study if Plt >100000

Clinical course

- Day 5
  - Bradycardia was noted, and CPCR was performed since 12:18
  - ABG: pH 7.099, pCO_2 28.8, HCO_3 9.0, SO_2 99.8%
  - WBC 9.9, Hb 6.9, LDH 2177, CK 396, BUN/Cre 26/1.6, Lactate 171.1
  - Then ROSC (when?) with low BP, dilated pupil without light reflex
  - Bradycardia again at 12:40
  - Expired at 13:52

On Day 7

Item	Data	Reference
Anti-cardiolipin IgG	negative	
Anti-dsDNA	negative	
Anti-ENA Sm.	negative	
Anti-ENA SSA.	Positive (169.0)	

Final diagnosis

- Systemic lupus erythematosus

DISCUSSION

Hemolytic anemia
SLE

HEMOLYTIC ANEMIA

Hemolytic anemia

- Congenital/inherited
- Acquired

Symptoms/signs of hemolytic anemia

General	lung	heart	abdomen	GU
weakness	SOB	tachycardia	Abdominal pain (particularly from GB	Darkened urine
fatigue	DOE	palpitation	Splenic enlargement	
dizziness	Chest pain	New or accentuated cardiac murmur		
pallor				
jaundice				

Basic tests and findings in the evaluation of hemolytic anemia

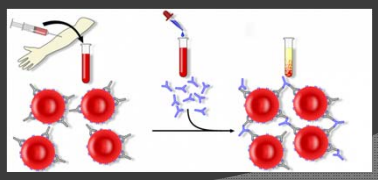
Purpose	Test	Finding
Confirm anemia/blood loss	Hemoglobin (Hb)	decreased
	Hematocrit	decreased
Confirm compensatory RBC production	Reticulocyte count	increased
Confirm hemolysis	Peripheral smear	Schistocytes: intravascular hemolysis
		Spherocytes: extravascular hemolysis
Confirm hemolysis	Lactate dehydrogenase (LDH)	Increased, released by RBCs
	Potassium	Increased, released by RBCs
Confirm hemolysis	haptoglobin	Decreased: intravascular hemolysis
	Free hemoglobin	Increased: intravascular hemolysis
	hemoglobinuria	present
Confirm hemoglobin breakdown	Total bilirubin	increased
	Indirect bilirubin	Increased (hepatic conjugation of bilirubin overwhelmed)
	Urinary urobilinogen	increased

Common etiology of acquired hemolytic anemia

- Immune-mediated acquired hemolytic anemia
  - Autoimmune hemolytic anemia (AIHA)
  - Alloimmune hemolytic anemia
  - Drug-induced hemolytic anemia
- Microangiopathic syndromes
  - Thrombotic thrombocytopenic purpura
  - Hemolytic-uremic syndrome
- Macrovascular hemolysis
- Others
  - Infection
  - Envenomation
  - Chemical exposure
  - Trauma-induced hemolysis

Autoimmune hemolytic anemia (AIHA)

- A auto-antibody against their won RBCs
- Primary or secondary
- Direct antigen test (DAT):
  - i.e. direct Coombs test
  - A screen method



http://www.pathologystudent.com/?p=1003

Categories of AIHA

Warm antibody AIHA: autoantibodies adhere most strongly to RBCs at 37°C	70%-80% of AIHA cases
	50% primary (idiopathic) disease
	50% secondary disease: lymphoproliferative, autoimmune disease, postinfection (transient)
	Usually IgG autoantibody against Rh(D) antigen
	Hemolysis usually extravascular
	Steroid responsive: 70%-80%
Cold antibody AIHA: Autoantibodies adhere most strongly to RBCs at 0-4°C	Cold agglutinin disease: IgM autoantibody against I Ag
	Primary disease: older females
	Secondary disease: lymphoproliferative disorders, postinfection (transient)
	Raynaud phenomenon, livedo reticularis, vascular occlusion
	Attacks precipitated by cold exposure
	Rarely intravascular hemolysis
	Not steroid responsive
	Paroxysmal cold hemoglobinuria: IgG autoantibody against P Ag
	Primary: rare, in adults
	Secondary disease: usually in children after upper respiratory infection
	Intravascular hemolysis during cold weather
	Usually not steroid responsive
Mixed type antibody AIHA: Autoantibodies have variable temp.-dependent RBC adherence	Primary disease: more common in older females
	Secondary disease: lymphoproliferative and autoimmune diseases
	Usually chronic course with severe exacerbations
	Usually steroid responsive

Alloimmune hemolytic anemia

- In Rh(D)- mother with a Rh(D)+ fetus
  - Stimulate alloantibody when: amniocentesis, chorionic villus sampling, delivery, or abortion (threatened or otherwise) or during external cephalic version
  - Admit anti-D IgG or soon after delivery
  - Intrauterine and intravascular fetal transfusion, plasma exchange, IVIG
  - Complication: hydrops fetalis
- After RBC transfusion
  - Stimulate alloantibody
  - In subsequent transfusion: fever, chest and flank pain, tachypnea, tachycardia, hypotension, hemoglobinuria, oliguria
  - May have delayed alloantibody-mediated hemolysis: 3-7 days after transfusion

Drug-induced hemolytic anemia

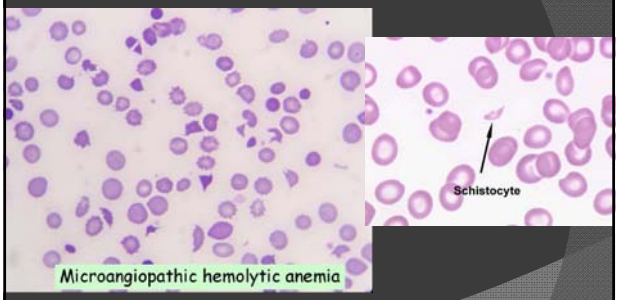
- >100 medications would cause hemolytic anemia
- ED Dr should know the patient's current medication list, drugs used within the prior 1 to 2 weeks
- Steroid can be used in severe cases
- RBC transfusion will aggravate hemolysis!

THANKS

Most often cited drugs inducing autoantibody formation	
Catechin (antidiarrheal)	Methyldopa (antihypertensive)
Cefotetan (antibiotic)	Nomifensine (antidepressant)
Ceftriaxone (antibiotic)	Oxaliplatin (C/T agent)
Cephalothin (antibiotic)	Penicillin G (antibiotic)
Diclofenac (NSAID)	Phenacetin (NSAID)
Fludarabine (C/T agent)	Quinidine (antiarrhythmic)
Interferon (C/T agent)	Rifampin (antibiotic)
Levodopa (antiparkinsonian)	Tolmetin (NSAID)
Mefenamic acid (NSAID)	

Microangiopathic syndromes

- i.e. microangiopathic hemolytic anemia
- Platelet aggregate in microvascular circulation via vWF
- Cause RBC fragmented in arterioles and capillaries
- Including:
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic-uremic syndrome



Thrombotic thrombocytopenic purpura (TTP)

- Classic pentad:
  - CNS abnormalities
  - Renal pathology
  - Fever
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
- Diagnostic criteria
  - Microangiopathic or microvascular hemolytic anemia
  - Thrombocytopenia
  - No other explanation

TTP: epidemiology

- High risk
  - Women
  - Patients age 30 to 50 years old
  - Blacks
  - Hispanics

TTP: pathophysiology

- Decreased ADAMTS-13 activity (<10% of normal)
  → vWF multimers accumulation in microcirculation
  → microthrombus formation
- Increased in
  - Pregnancy: second or early in the third trimester
  - HIV infection, sep. in AIDS progression
  - Influenza vaccination
  - Infection
  - Inflammation: acute pancreatitis
  - Medication use: ciprofloxacin, ofloxacin, levofloxacin, quinine, sirolimus, clopidogrel….within 2 to 12 weeks of starting using

TTP: S/S

End-organ damage
seizure
stroke
Other focal neurologic deficits
coma
Acute renal injury
Acute renal failure
Fetal mortality

TTP: treatment

- Goal: normal platelet count
- Daily plasmapheresis (plasma exchange): 40 ml/kg, up to 1.0-1.5 times a patient's plasma volume
- FFP infusion
- Factor VIII concentrate infusion
- For difficult-to-treat TTP: RBC transfusion, anticonvulsants, antihypertensives, hemodialysis
- Platelet transfusions should be avoided!!

Hemolytic-uremic syndrome

- Typical
  - Occurs in children
  - 1 week after infectious diarrhea (bloody stool, no fever)
  - Shiga toxin-producing E. coli, O157:H7
  - Shigella, Yersinia, Campylobacter, Salmonella
  - Renal involvement
  - Better outcome
- Atypical
  - Older children and adults
  - Extrarenal involvement
  - Streptococcus pneumonia, EBV, BM transplantation, administration of immunosuppresant or C/T agent

HUS: pathophysiology

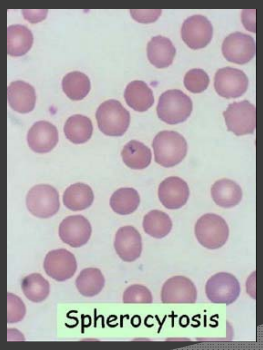
- Shiga toxin enter the circulation
  → bind surfaces of glomerular and renal tubular epithelial and endothelial cells, lining cerebral and colonic epithelial and endothelial, pancreas
- Shiga toxin is mimic to CD36 on endothelial cells and platelet
- Antibiotic attack CD36, cause plate aggregation
- 2 to 14 days after diarrhea

HUS: treatment

- Supportive
- Parenteral opioid analgesia
- RBC or platelet transfusion
- HD or PD for renal failure
- Infection with E. coli O157:H7 should not be treated with antimotility drugs

Macrovascular hemolysis

- Prosthetic heart valve
  - Paravalvular leakage
  - Intracardiac patch repair, aortofemoral bypass, severe AV disease, VAD, ECMO, CP bypass…
  - S/S: florid congestive heart failure, endocarditis
- Lab: schistocytes on PB smear
- Tx: iron, folate, β-block, blood transfusion



SYSTEMIC LUPUS ERYTHEMATOUS

Classification criteria and other clinical manifestations of SLE		
Organ system	Am.Coll.Rheum.Criteria	Other features
Constitutional (84%)		Fever, malaise, anorexia, weight loss
Cutaneous (81%)	1. Malar rash 2. Discoid rash 3. Photosensitivity 4. Oral/nasopharyngeal ulcers	Alopecia, vasculitis, subacute cutaneous lupus, panniculitis, urticaria
Musculoskeletal (85-95%)	5. Nonerosive arthritis	Arthralgias and myalgias, AVN of bone
Cardiopulmonary (33%)	6. Serositis: pleuritis, PE, pericarditis, pericardial effusion	Pneumonitis, myocarditis, CAD
Renal (77%)	7. Proteinuria (>500 mg/dL or 3+), or urinary cellular casts	
Neurologic (54%)	8. Seizure or psychosis	
GI (~30%)		Serositis, vasculitis, abd. Pain, hepatitis, pancreatitis
Hematologic	9. Hemolytic anemia (DAT+), leukopenia, lymphopenia, thrombocytopenia	
Other		Sicca syndrome, Raynaud's
Serologies	10. ANA + 11. anti-dsDNA, anti-Sm, or antiphospholipid +	Complement decreased, ESR increased, CRP increased, anti-Ro, anti-RNP, RF, anti-CCP

CNS lupus

Major manifestations of CNS lupus
Cognitive dysfunction (not thinking clearly, memory deficits)
Headaches
Seizure
Altered mental alertness (e.g. stupor or coma)
Aseptic meningitis
Stroke
Peripheral neuropathy (e.g. numbness, tingling, burning of the hands and feet)
Movement disorders
Myelitis (disruption of the spinal cord)
Visual alternations
Autonomic neuropathy (e.g. flushing reaction or mottled skin)

CNS lupus: pathophysiology

- Disrupted blood supply in the brain
  - Autoimmune vasculitis, clots, emboli, hyperviscosity, antineuronal Ab
- Several cytokines: IL-1, IL-6, INF-γ
- Abnormal hormone producing in HPA axis
- Infection, medication, hypertension, e imbalances, uremia, thyroid disease, strokes, SDH…