제 229회 대한결핵 및 호흡기학회 심포지엄 증례보고

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YUMC

구 O 일 M/25 (7586590)

- C.C : Fever, cough (4days), hemoptysis (2days)

- P.I : 상기 25세 남환은 4일 전부터 고열, 기침 가래 발생하여 타병원 입원 하였으며 2일 전부터 객혈 및 급성신부전 악화하여 고용량 스테로이드 치료 시작하였으나 호전 없어 응급실 경유 본원 전원함.

Past history

- Medical history
  - HTN / DM (-/-), Old pul TBc (-)
  - No history of drug use or recent travel (-/-)
- Social history
  - Occupation : university student
  - Smoking : Never smoker
- Familiy history - none

Review of systems

- Cough / hemoptysis (+ / +)
- Dyspnea / DOE (+ / +)
- Fever / Chill (+ / -)
- General weakness / Easy fatigue (- / +)
- Poor oral intake / Wt loss (- / -)
- Arthritis /Skin rashes (-/-) Lymphadenopathy (-)
- Abdomen pain/ Nausea/ Vomitting/ Diarrhea (-/-/-/-)
- Dysuria/ Urgency (-/-)

Physical examination

- Vital sign > BP 188 / 89 mmHg PR 116 /min
  BT 38 ºC RR 26 /min

✓ G/A> Acute ill-looking, alert, oriented

✓ HEENT> not anemic, anicteric
  PI(-) PTH(-/-)
  LNE(-/-) V/E(-/-) carotid bruit(-/-)

✓ Chest> symmetric expansion without retraction
  RHB without murmur
  mild crackles over both lower lobes

✓ Abdomen> Soft abdomen/ No tenderness

Laboratory findings (1)

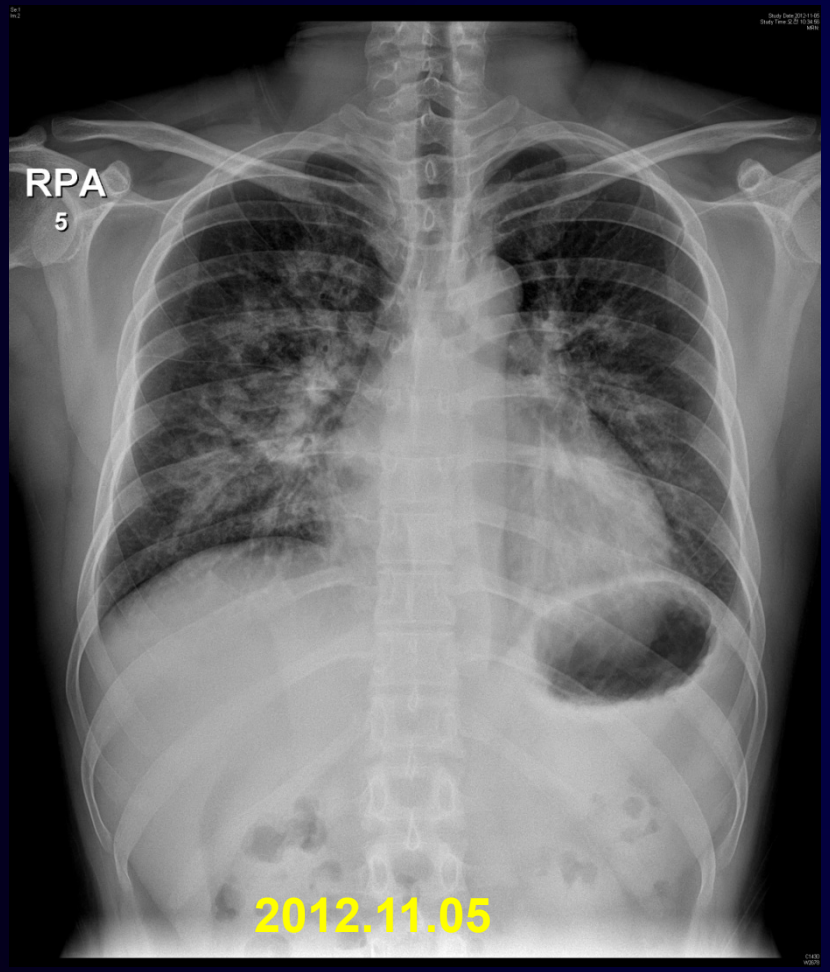
- CBC : 15500 (70.3%) / 14.4 / 134K
- PT(INR) / aPTT : 1.04 / 28.1
- BUN / Cr : 32.2 / 2.6 mg/dL (FeNa 7.6%)
- Urinalysis: Blood 1+ Protein 2+ Glucose-
  RBC 3~5 /HPF WBC 1~3 /HPF
- Total protein / Albumin : 5.9 / 3.3 g/dL
- AST / ALT : 16 / 13 IU/L
- ABGA - PH/$PaCO_2$/PaO_2/HCO_3/SaO2:
  7.49/31/57/23.6/92%
- CK/CK-MB/TnT/NT-proBNP: 59/1.87/0.052/ >35,000

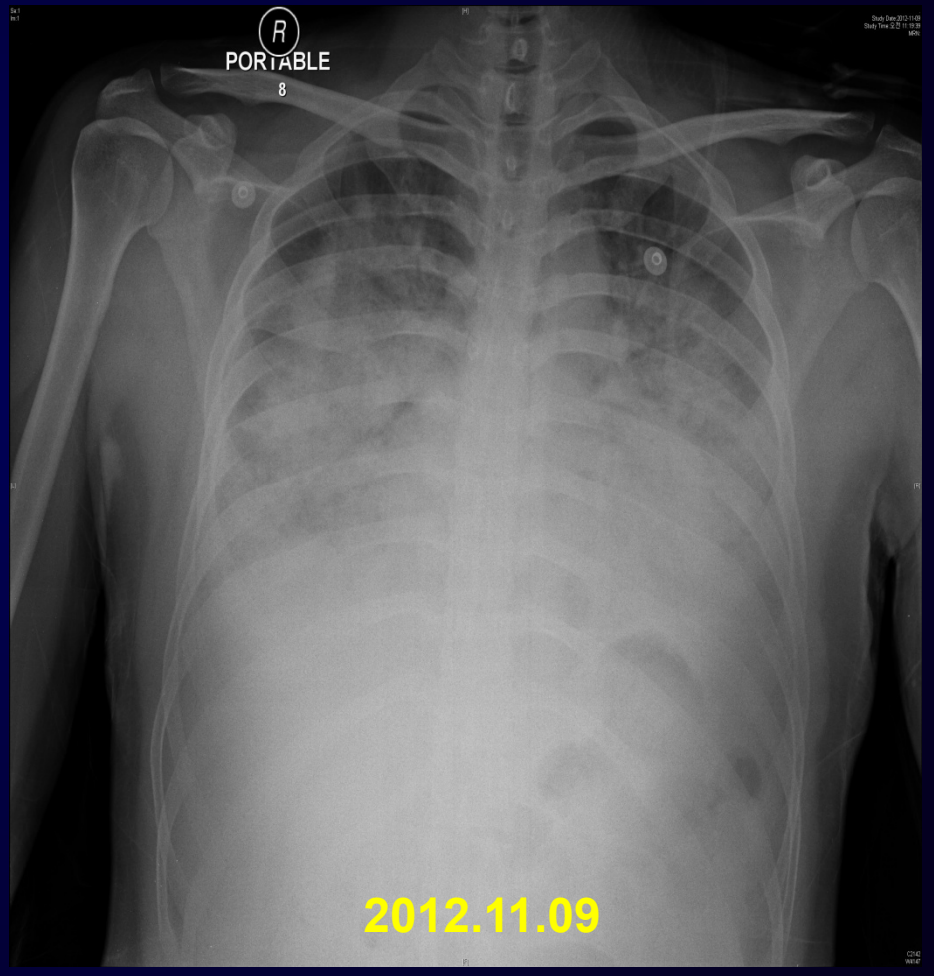
Laboratory findings (2)

- R.tsutsugamushi Ab/ leptospira Ab/ Hantaan Ab (-/-/-)
- CMV Quantitative PCR<250 copies/mL
- Autoimmune marker
  - P-ANCA /C-ANCA /anti-ds DNA Ab /ANA /anti-GBM Ab (-)
  - Anti-Cardiolipin antibody/anti-CCP/ Anti-Scl 70/anti SS-a/b (-)
- C3 130 mg/dl, C4 38 mg/dl (normal range)
- Anti-HIV I/II Ag (-) HBsAg/Anti-HCV (-/-)
- CEA: 28.4U/mL CA 125: 72 U/mL
- CYFRA 21-1: 6.01 U/mL β2-microglobulin: 4.45 mg/L

4412339 68/M

Initial chest images





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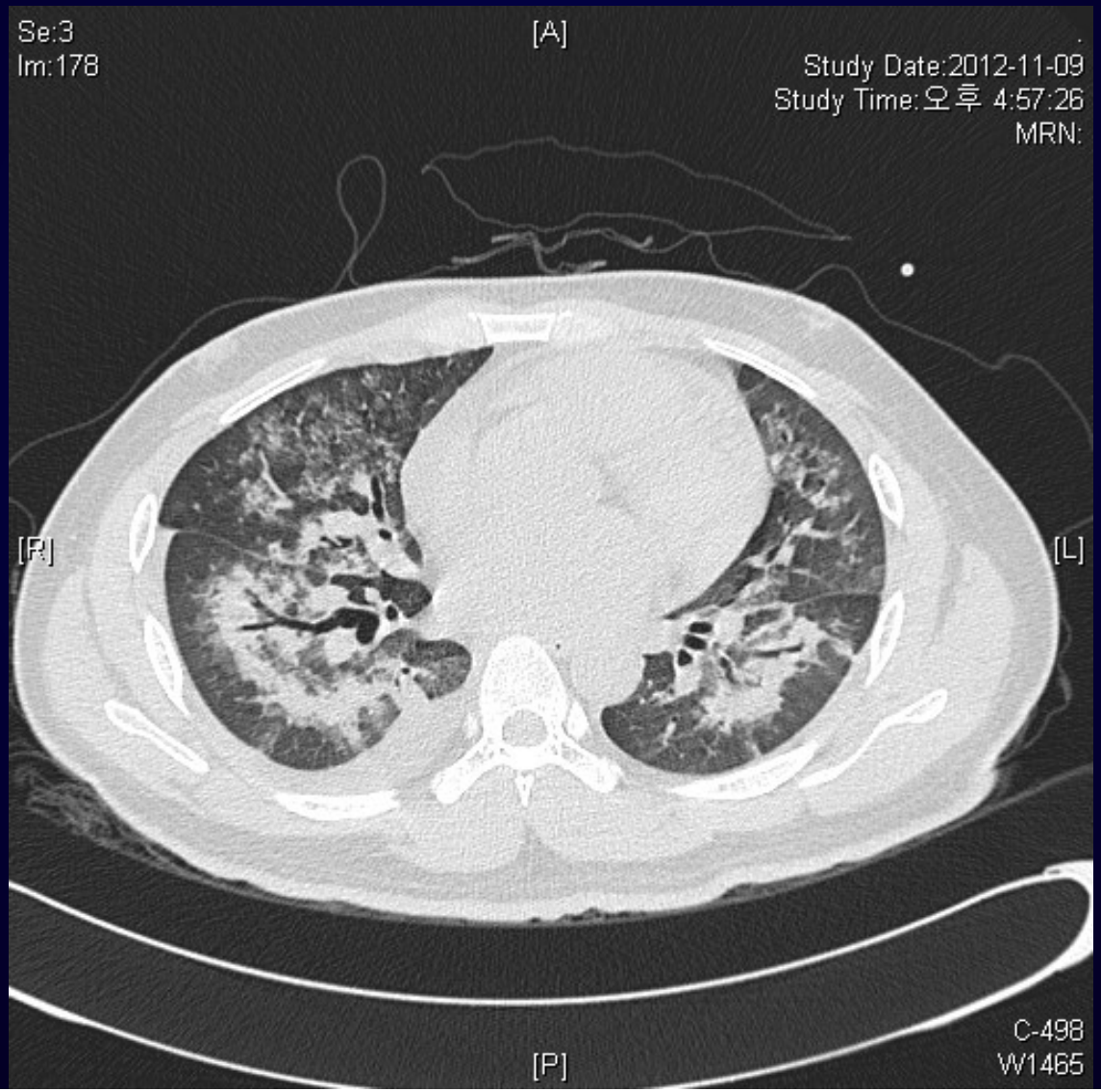
Chest CT



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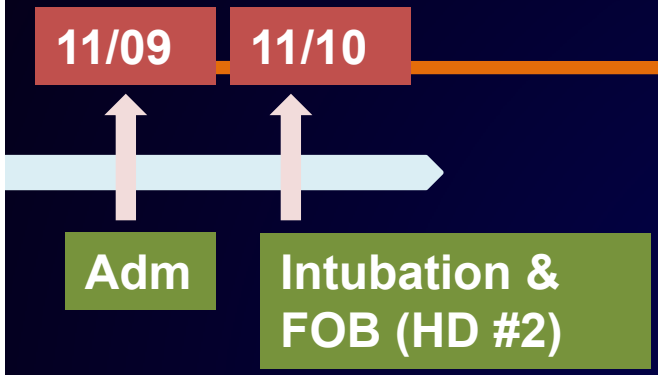
Echocardiography

1. Severe global hypokinesia of LV with relatively preserved basal posterior wall
2. Normal sized cardiac chambers with reduced LV systolic function (EF : 35%)
3. Mild concentric LVH with echogenic myocardium
4. Summation of E/A wave d/t tachycardia (E/E' : 10)
5. Minimal pericardial effusion

Impression

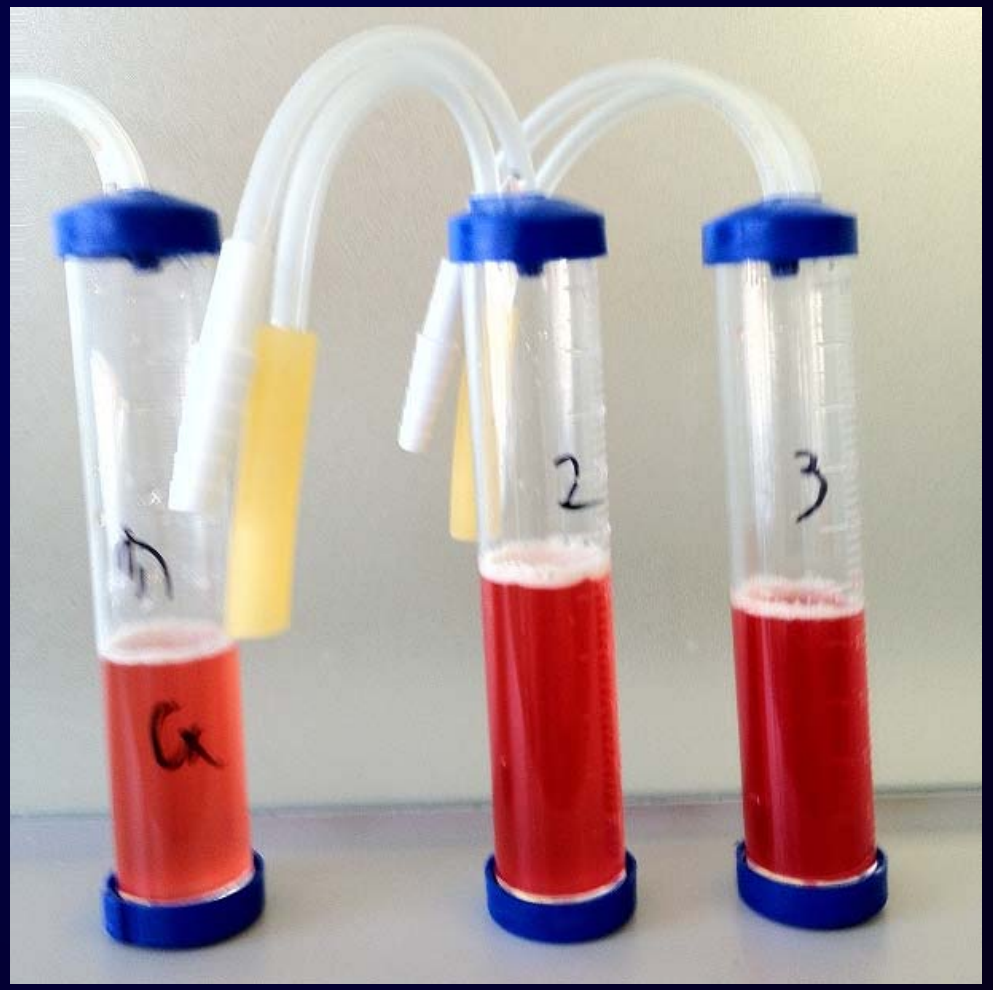
- R/O Vasculitis related alveolar hemorrhage
- R/O Connective tissue disease related glomerulonephritis
- R/O myopericarditis
- R/O stress induced cardiomyopathy

Bronchoscopy



No endobronchial lesion.

Serial bronchoalveolar lavage aliquots
→Progressive increase in bloody return



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BAL fluid analysis

Bronchoalveolar lavage	Routine Body Fluid Ex.	Color		Bloody
		Turbidity		Cloudy
		RBC		12850
		WBC		42
		Polymorphonucle		34
		Mononuclear cell		65
		Eosinophils		1
		Basophils		0
		Other		0
		SG		1.006
		pH		7.2
	Amylase			52

Bronchoalveolar lavage	RSV virus culture		Negative for 3 days
	Adenovirus culture		Negative for 3 days
	Influenza A culture		Negative for 3 days
	Parainfluenza 1 culture		Negative for 3 days
	Parainfluenza 2 culture		Negative for 3 days
	Parainfluenza 3 culture		Negative for 3 days

Bronchial Washing	CMV Quantitative PCR		<250
Sputum	Legionella pneumophila PCR		Negative
Bronchoalveolar lavage	Pneumocystis jiroveci PCR		Negative

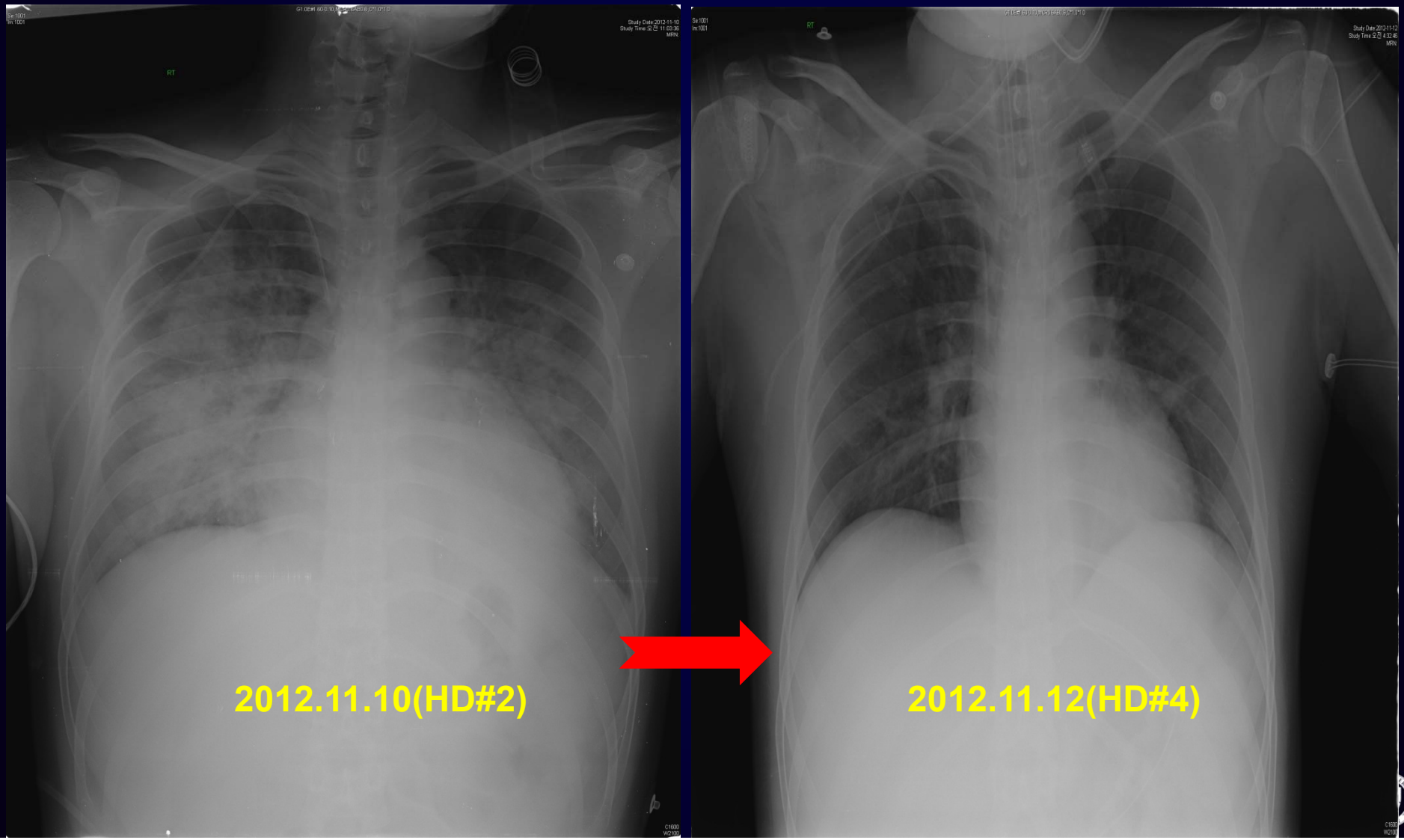
Bronchoalveolar lavage	BAL fluid quantitative culture	<1,000 CFU/ml Bacteria and Fungi

Bronchial Washing	Mycobacterium culture(액체배지법)	MGIT | No growth for 6 weeks
	Mycobacterium culture(고체배지법)	No growth for 8 weeks
	AFB fluorescent smear	Negative
	Mycobacterium tuberculosis complex PCR	Negative

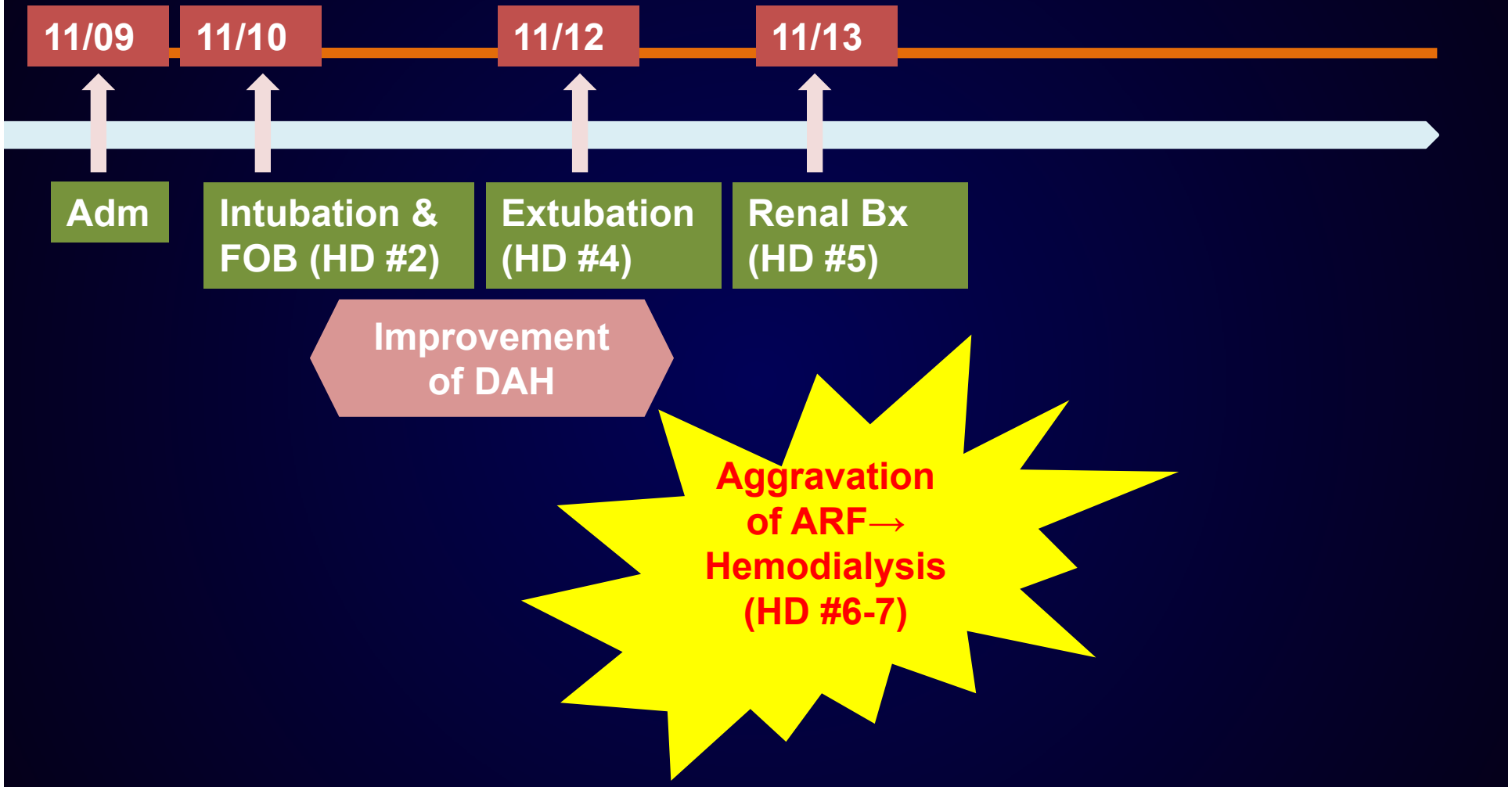
Cytology:
Negative for malignancy
D-PAS (-) GMS (-)

CD4/CD8 =46.1/38.4=1.2

CXR after steroid Tx

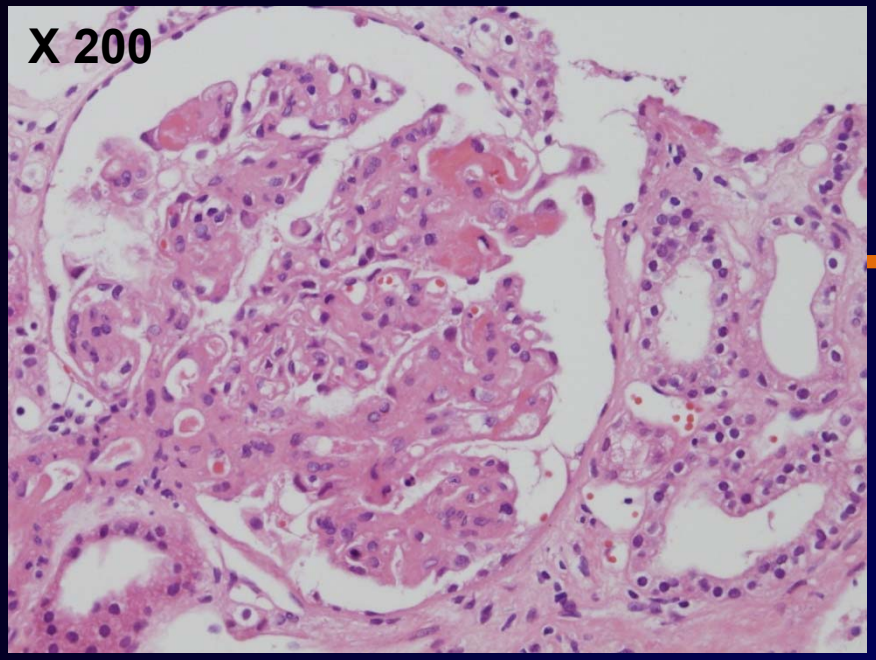


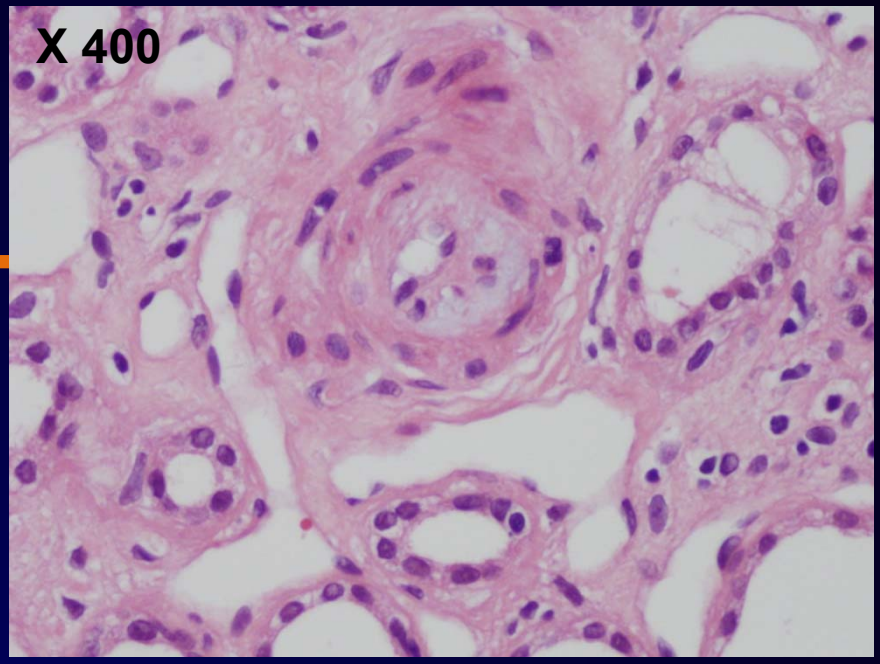
Renal biopsy

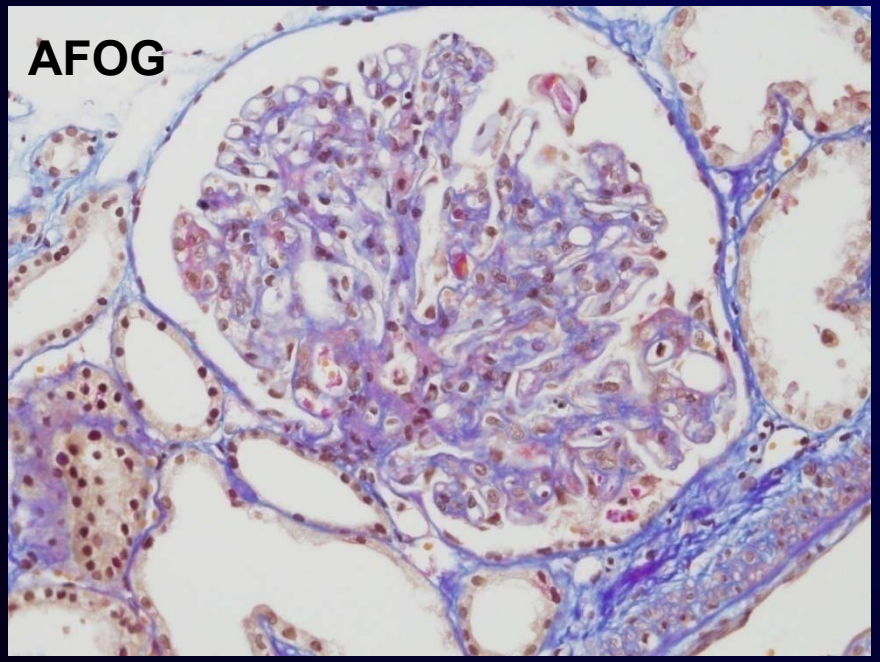


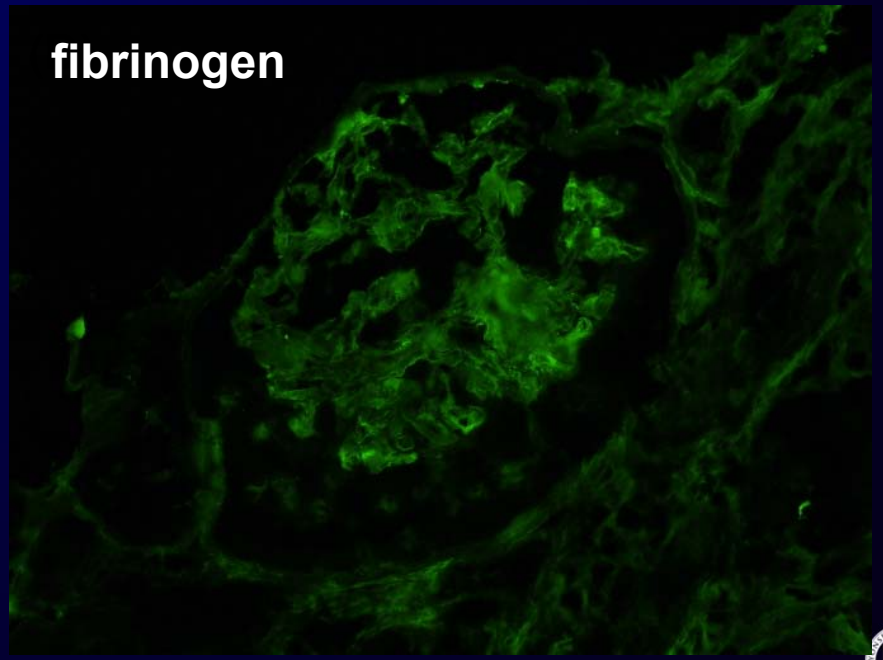
Antibiotics: Tazocin+cravit (~HD#6) → Meropenem+Cravit(~HD #23)

Steroid MP 125mg #2----------1000mg #4---125mg #2---------- tapering









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Pathologic finding

- Thrombotic microangiopathy, involving glomeruli and small arteries

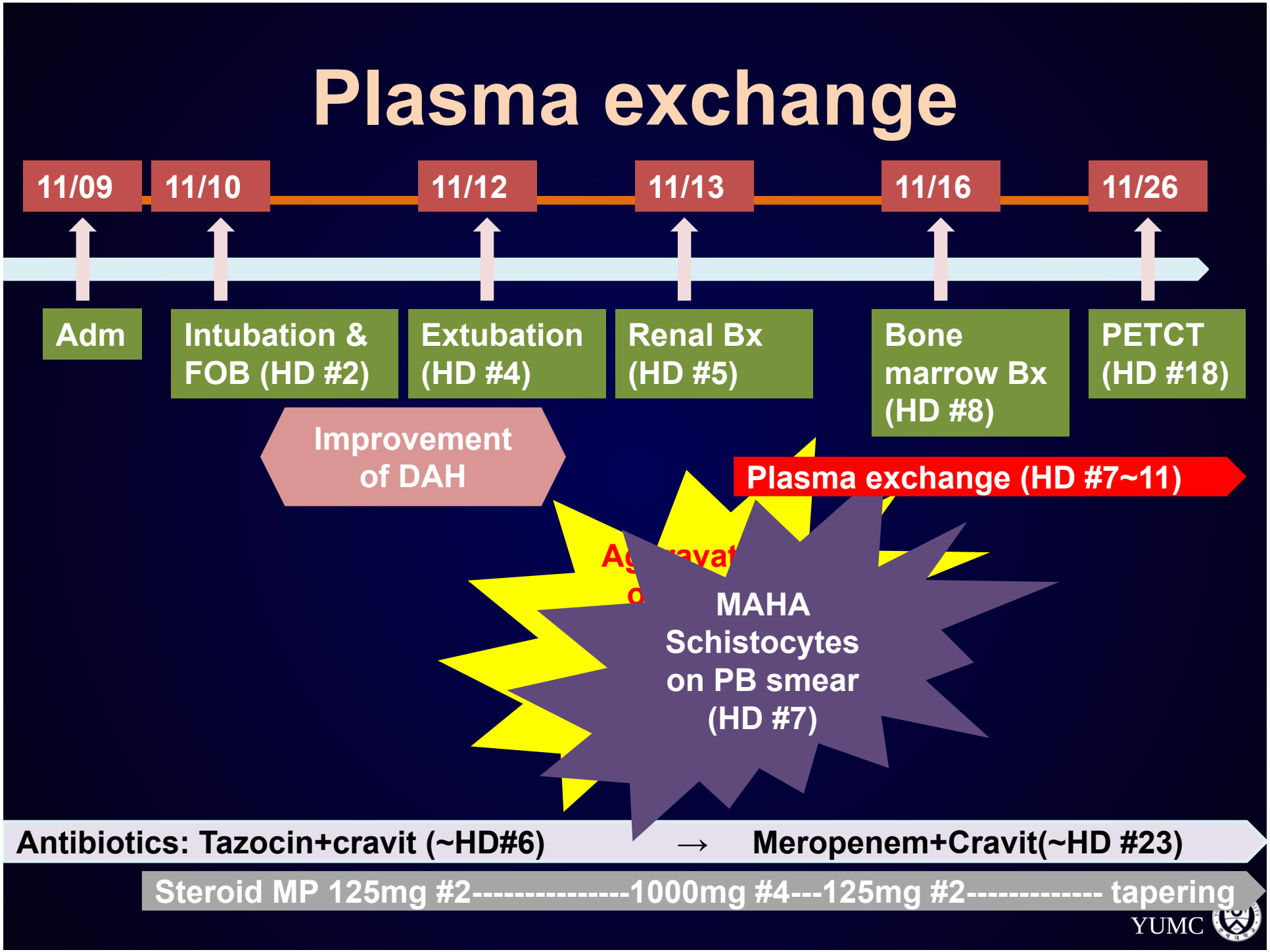
Final diagnosis

Atypical hemolytic uremic syndrome
presenting as
alveolar hemorrahge and myocarditis

Additional information

- RT-PCR of nasopharyngeal swab: Rhinovirus (+)
- Stool test
  - EHEC (Enterohaemorrhagic *Escherichia coli)* toxin (+)
  - Stool culture :No growth for E.coli O157, O26, O111
- Indirect and direct Coombs test (-)
- von Willebrand factor (vWF) antigen level:193 %
- von Willebrand factor (vWF) activity:171.9%
- Platelet multi-function test (ADP, Epinephrine):normal
- vWF multimer study: normal
- Complement Factor H, Factor I, Factor B, membrane co actor protein and ADAMTS-13 :Not performed by lack of utility.

Plasma exchange



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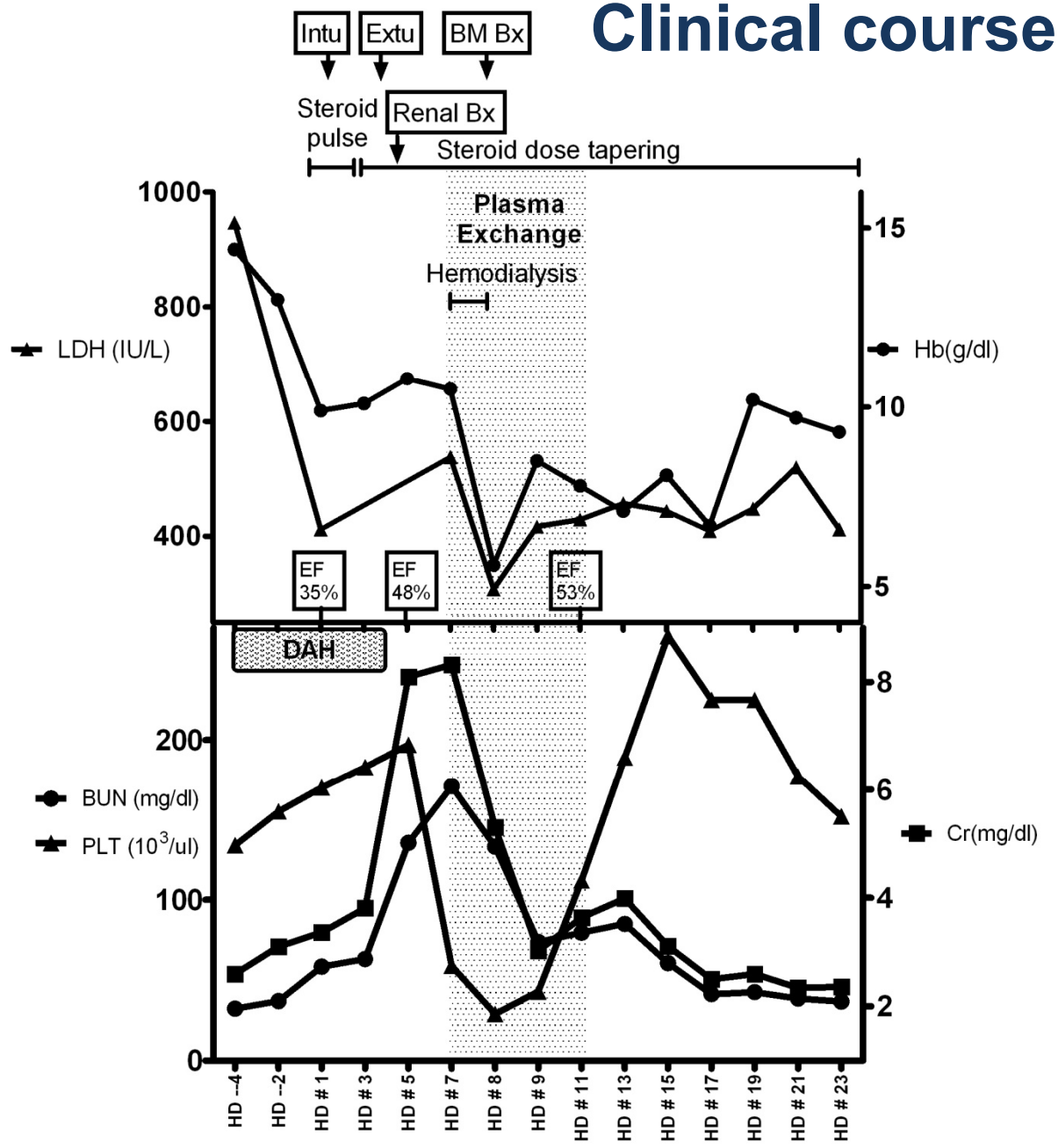
Clinical course



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Treatment plan

- Plasma exchange- Consecutive 5days
- Steroid maintenance
  - Tapered out over a period of 2month
- CRF management in Nephrology
  - BP control
    - ❖ACE inhibitor, CCB, BB
- Echocardiography follow up
  - TTE(2013.2): EF 65% LV wall thickness ↓

REVIEW

Hemolytic uremic syndrome

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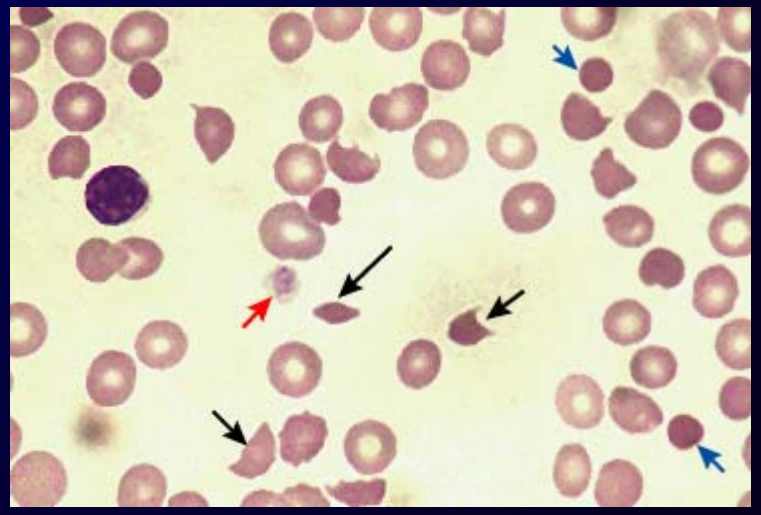
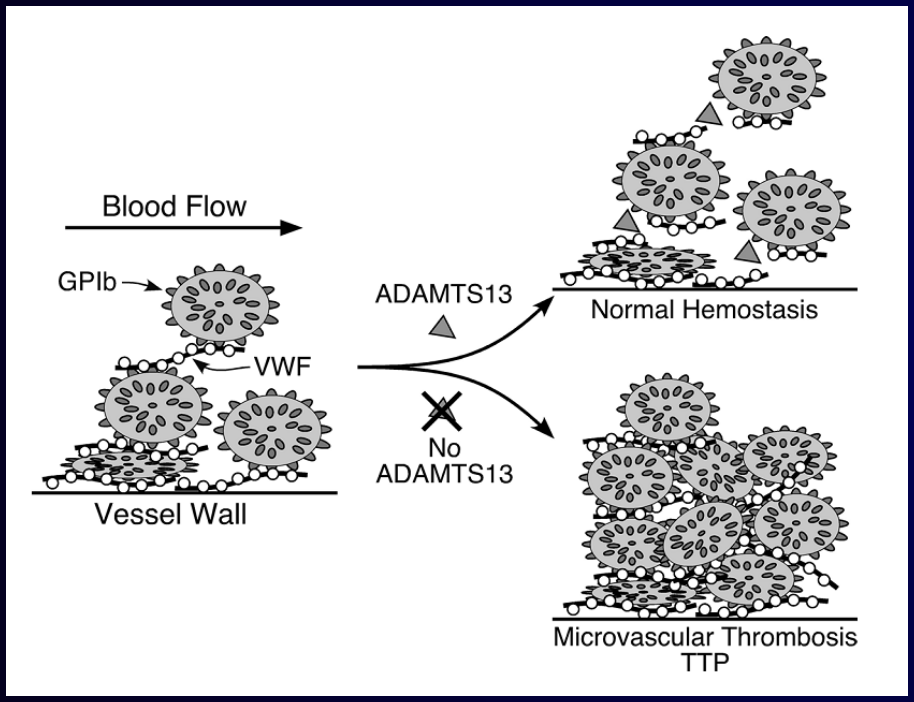
Hemolytic uremic syndrome

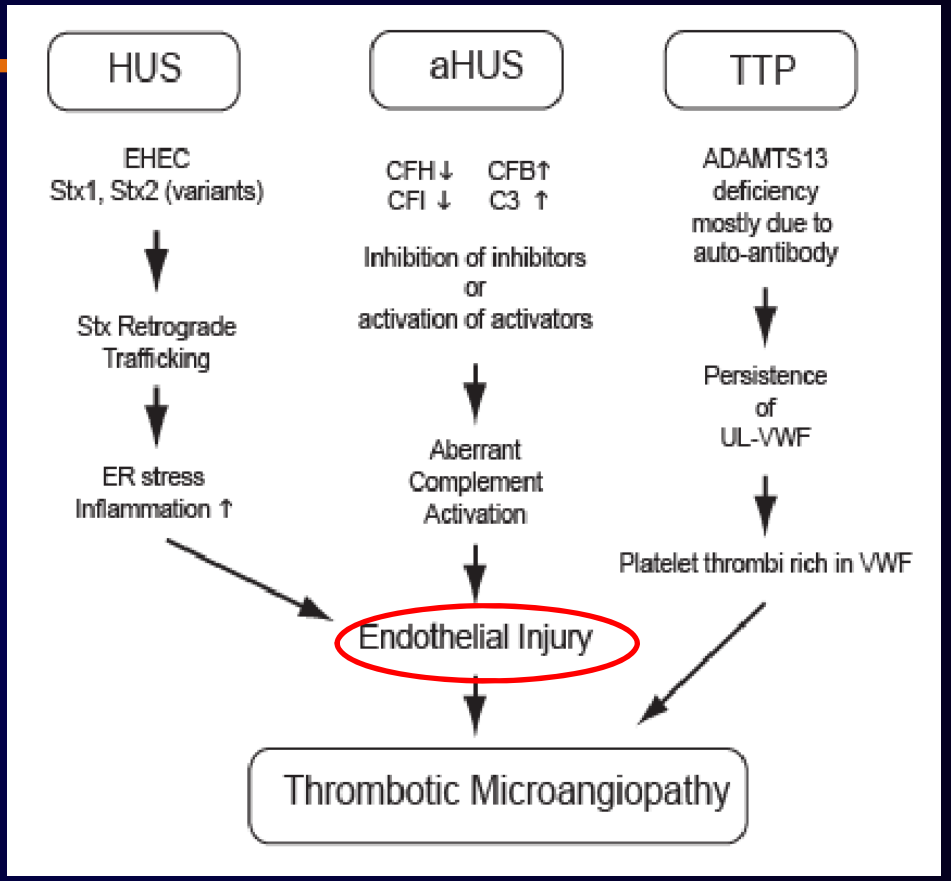
- ✓Triad
  - – Mechanical intravascular hemolytic anemia with schistocytosis(microangiopathic hemolytic anemia)
  - – Thrombocytopenia
  - – Acute renal failure(ARF)



Thrombotic microangiopathy

TTP





Affecting arteriole and capillary walls with endothelial cell swelling and detachment (Subendothelial accumulation of protein and cell debris→ thrombi obstructing lumina)

No activation of the coagulation cascade

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Classification

Table 1. *Causes of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura*

Infectious
- Infection with Shiga-like toxin producing *Escherichia coli* (*STEC*)
- Infection with neuraminidase producing *Streptococcus pneumoniae*
- Human immunodeficiency virus (HIV)

Complement dysregulation
- Genetic abnormalities in complement (regulating) proteins
- Acquired defects (autoantibodies against CFH)

ADAMTS13 deficiency
- Genetic abnormalities
- Autoantibodies against ADAMTS13

Clinically associated with
- *Systemic diseases*: SLE, antiphospholipid syndrome, defective cobalamin metabolism
- *Medication*: ticlopedin, mitomycin, bleomycin, cysplatin, quinine, tacrolimus, cyclosporin, rifampicin, clopidopogrel
- *Malignancies*: chemotherapy
- *Viruses*: cytomegalovirus, parvovirus
- *Transplantation*: calcineurin inhibitors, rejection
- *Pregnancy*: oral contraceptives, pre-eclampsia, HELLP syndrome
- *Glomerulopathies*: MPGN type II
- *Bone marrow transplantation*: radiation, medication, graft vs host disease

Typical HUS

90 % of childhood HUS

50%

Atypical HUS

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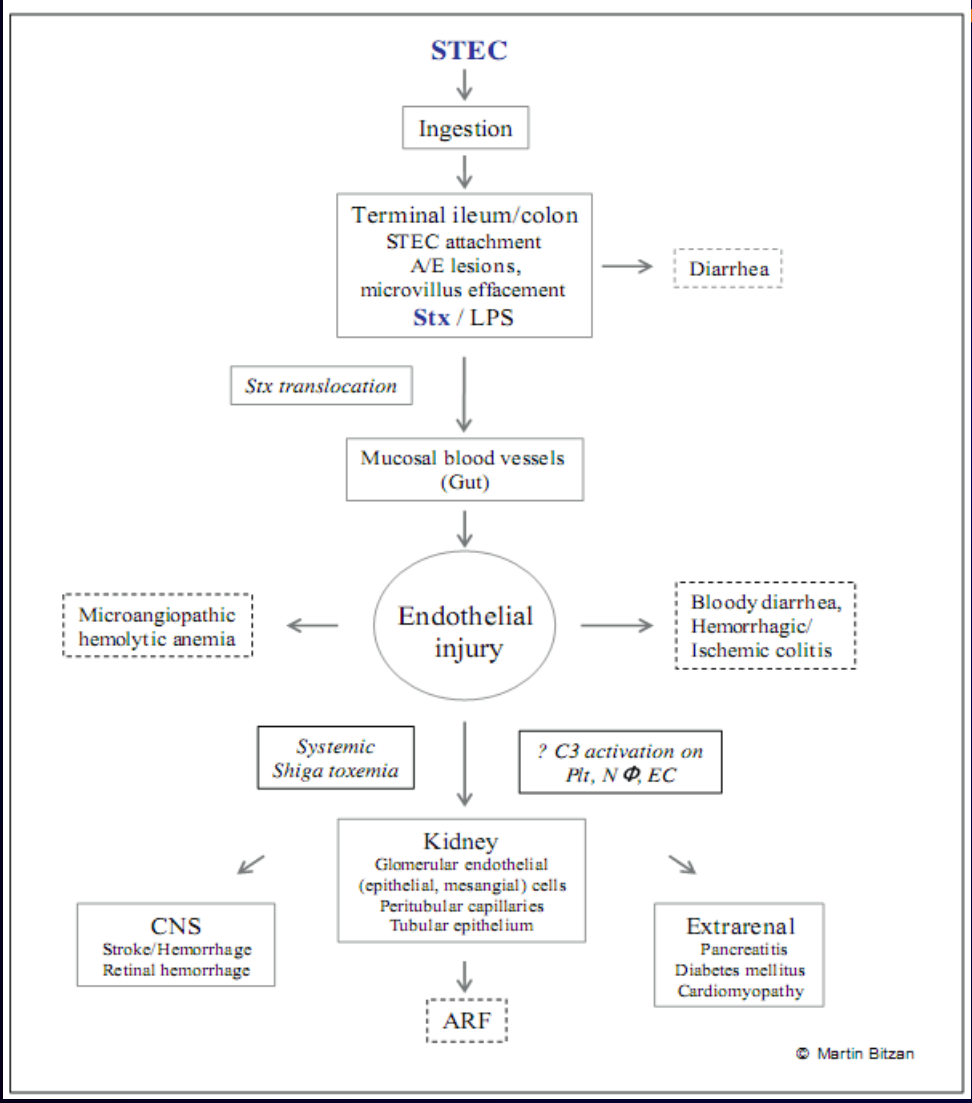
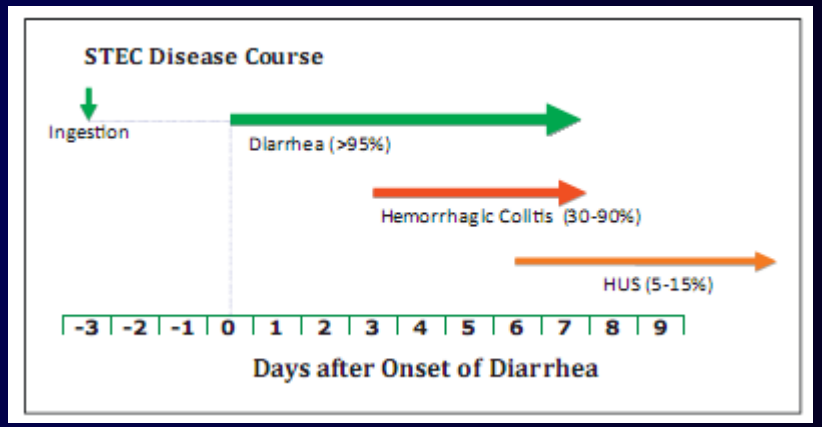
Shiga toxin-mediated HUS





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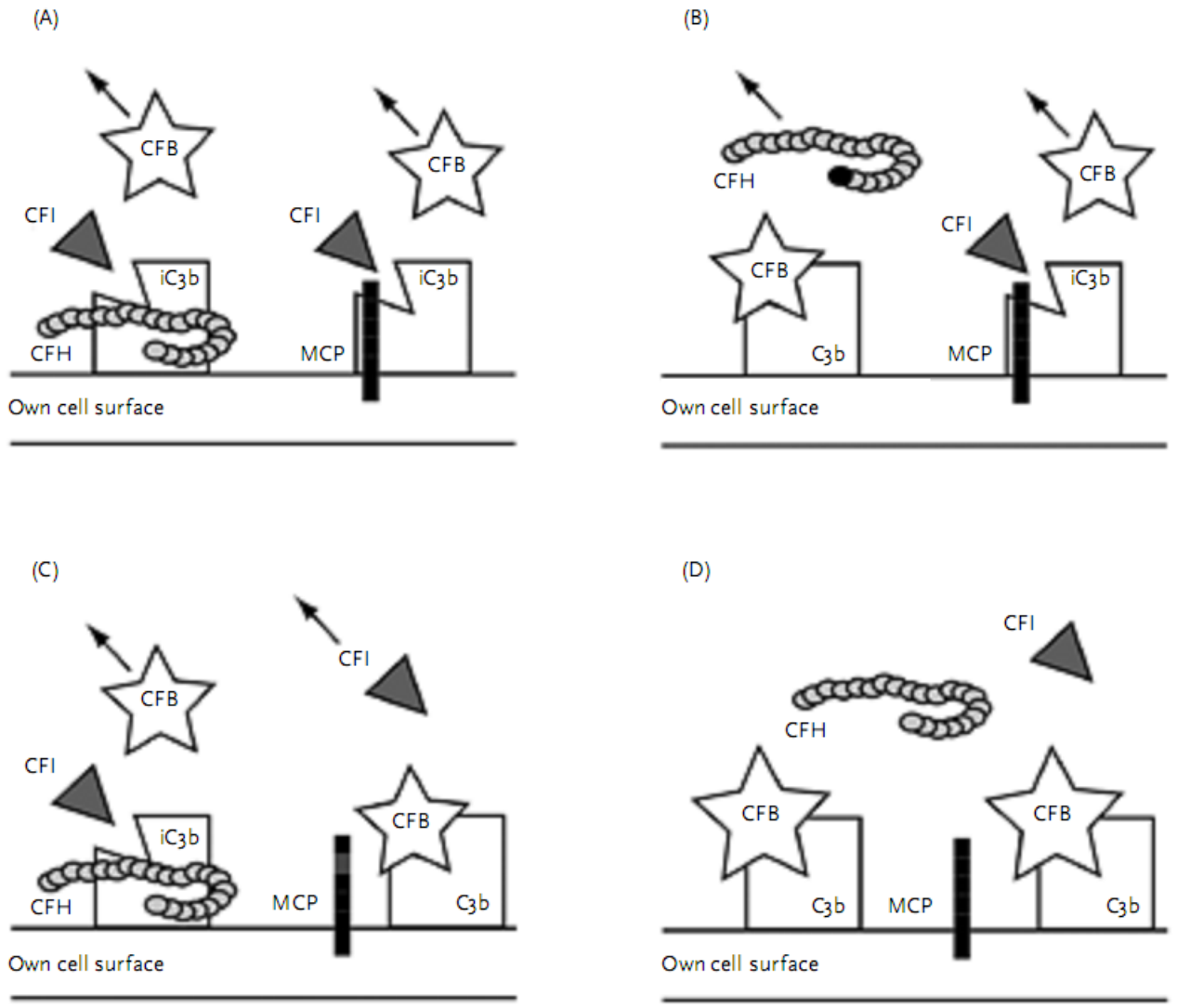
Atypical HUS

Figure 2. *Schematic model for the mechanism of alternative complement pathway regulation at host cell surfaces*



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Investigations for atypical HUS

	Investigations
STEC infection[1]	Stool or rectal swab: culture for STEC (MacConkey for *E. coli* 0157:H7); PCR for *Stx* genes and other virulence characteristics; ELISA and/or Vero cell tissue culture assay for Stx Serum: anti-LPS antibodies against prevalent serotypes
Pneumococcal infection[2]	Bacterial culture from (usually) sterile body fluids, DAT (Coombs test), (respiratory) viral testing
Disorders of complement regulation	C3, C4 (plasma/serum) Factor H, Factor I, Factor B (plasma/serum) Anti-factor H autoantibodies MCP surface expression on leucocytes (polynuclear or mononuclear leucocytes by FACS analysis) Gene mutation analysis in factor H, factor I, MCP, C3, factor B ± THBD
ADAMTS13 deficiency (inherited or acquired)	Plasma ADAMTS13 activity or dosage (ELISA) ± inhibitor
Cobalamin metabolism:methyl malonic aciduria	Plasma/urine amino-acid chromatography (hyperhomocysteinemia, hypomethioninemia; homocystinuria); urine organic acid chromatography (methyl-malonic aciduria) Mutation analysis in *MMACHC* gene
HIV	Serology, viral load (PCR)
Pregnancy, HELLP syndrome	Pregancy test, liver enzymes. Investigate as in lines 3 and 4
Miscellaneous	Antinuclear antibody, lupus anticoagulant, anti-phospholipid antibodies

Difference in disease outcome and risk of post-transplant recurrence according to complement abnormality

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Treatment-1

- ✓ Supportive treatment
  - – Refer to a specialized center (critical care)
  - – Multivisceral involvement may occur
    - ARF/Oliguria/volume overload/ HTN
    - Cardio-respiratory failure, Neurologic deterioration
  - – pRBC transfusion when Hb<8mg/L
  - – Platelet transfusion are contraindicated (TMA process worsened)

Treatment-2

✓Plasma Exchange

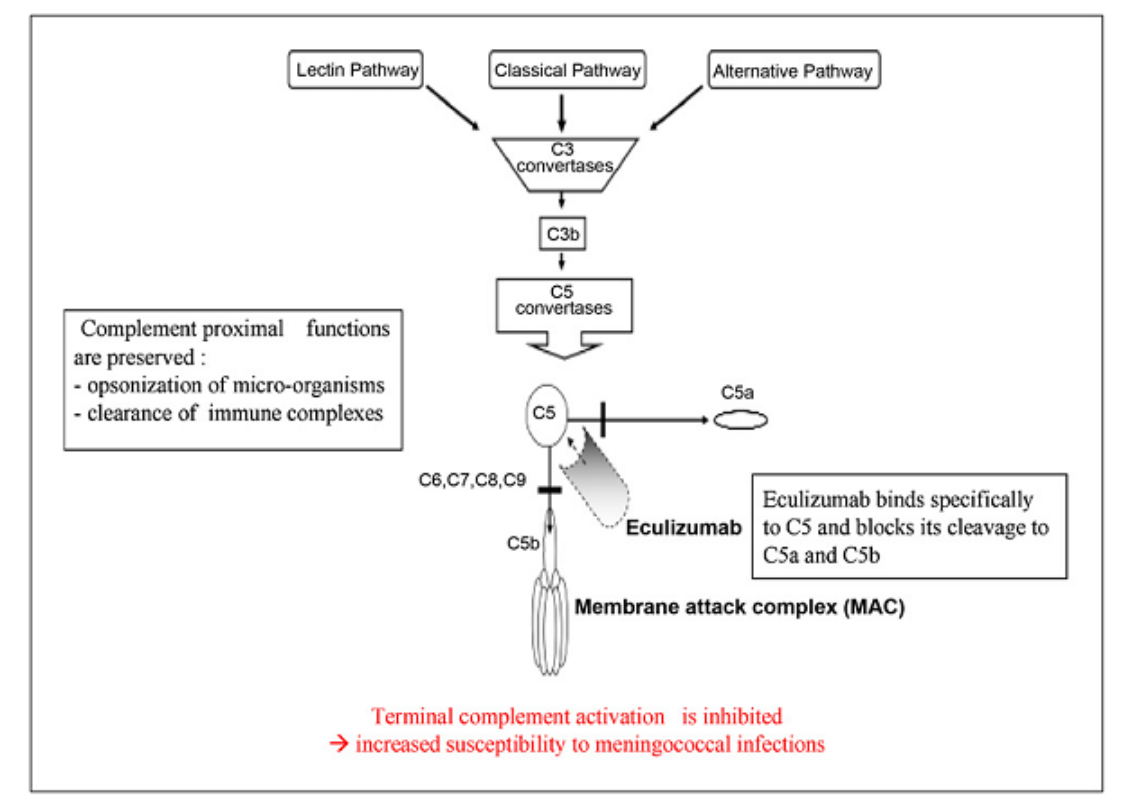
- TTP-HUS is a clinical diagnosis.
- Laboratory and genetic studies are found in only 40% of patients and take several months.

→Timely manner to urgent plasam exchange!

- 1.5 plasma volume (60-75ml/kg) with FFP
- Until all TMA criteria are under control
- Platelet>150K, renal function improving (Cr ↓)
- If lack of improvement of renal function/ contined hemolysis after 3-5 PE/주 →Daily PE or Eculizumab

Treatment-3

✓Complement blockers Eculizumab



Expectation

1) Prevent progression to ESRD in aHUS patients

2) Successful kidney transplant to aHUS patients on dialysis

✓Combined liver-kidney transplantation

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Alveolar hemorrhage and HUS

Clin Exp Nephrol (2011) 15:948–952
DOI 10.1007/s10157-011-0516-z

CASE REPORT

Respiratic

Pandemic H1N1 influenza A viral infection complicated by atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage

Pulm
Typic

Harin Rhee · Sang Heon Song · Yong Jae Lee · Hyun Ju Choi · Jin Hee Ahn · Eun Young Seong · Soo Bong Lee · Ihm Soo Kwak

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Impaired immune system
+
combined etiology with an infectious trigger
(Influenza or cytomegalovirus etc)

Alveolar hemorrhage in aHUS
-Uncommon,Poor prognosis
-PLT normal range, no evidence of hemolysis
→Alveolar wall necrosis in the absence of fibrin thrombus deposition
→Microvascular damage, loss of capillary intergrity
Good response to Steroid treatment

Summary

- Hemolytic uremic syndrome should be considered as a uncommon cause of alveolar hemorrhage and myocarditis.
- Thrombocytopenia & MAHA without apparent etiology →Suspect the diagnosis of HUS/TTP and consider to initiate plasma exchange.
- Atypical HUS is a multigenetic and multifactorial disease→ Several investigations are recommended.
- Plamsa exchange is the first choice of treatment.

  New therapeutic options (Eculizumab etc) are emerging.