Case Report

Fulminant Microangiopathic Hemolytic Anemia Prior Seropositive Antinuclear Antibody: A Difficulty in Diagnosis and Management, Successfully Treated with Methylprednisolone Plus Chemotherapy: A Case Report

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Abstract: *We report a case of thirty-two years old woman came with severe headache for 7 days and alteration of consciousness for 5 days. She had no underlying disease, any medications and fever during this period of illness. Complete blood count showed anemia with thrombocytopenia and the peripheral blood smear and bone marrow study were compatible with microangiopathic hemolytic anemia. Laboratory tests showed BUN 23 mg/dL, creatinine 0.9 mg/dL, direct bilirubin 0.3 mg/dL, indirect bilirubin 2.8 mg/dL. The connective tissue disease study revealed positive ANA1:80 (speckled pattern), negative anti-ds-DNA, negative VDRL. The CT scan of brain showed no any hemorrhage or infarction. The patient gradually recovered and fully gained consciousness after 10 days of treatment with plasma infusion, methyl prednisolone and chemotherapy (endoxan, vincristine). The complete blood count returned to normal after 30 days of therapy. Prednisolone was maintained and tapered off one year later. The serology for ANA was re-tested afterward after 6 months and showed positive ANA >1:320 (nucleolar pattern) which converted to negative after 10 months.*

Key Words : ● *Microangiopathic hemolytic anemia* ● *Antinuclear antibody* ● *Methylprednisolone*

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Thai adult female aged 32 years old, Bangkok

History from cousin, 80% reliability

Chief complant Drowsiness for 5 days

Present Illness 7 days PTA, patient had headache without fever, nausea or vomiting.

Five-day PTA, the headache became more severe along with the conscious level deteriorated to drowsy and was respond to verbal command. She was admitted in local hospital at Singburi where the computerized scan of brain was done and showed no evidence of hemorrhage or infarction. Laboratory tests showed Hb 5.9 g/dL, Hct 16%, WBC 9,200/mm^3, platelet count 60,000/mm^3, ESR 140 mm/h, the direct and indirect Coombs' test were both negative.

One-day PTA, she had vomiting and the consciousness was not improved. She was finally refer to this hospital.

Past history She was healthy and had no any previous illness. She didn't take any medications.

Physical examination T 37°C, PR 100/min RR 22/min, BP 140/80 mmHg

Spontaneous eye opening, not follow command

HEENT	moderately pale, mild jaundice
LN	not palpate
H&L	normal
Abd	no hepatosplenomegaly
Ext	no edema
Skin	no petechiae, no purpura, no ecchymosis
Neuro	E4M5V1
	Pupil 3.0 mm equally react to light, EOM- full
	Fundi borderlined papilledema retinal hemorrhage, left side
	no facial palsy
	Motor at least IV/V, all
	Reflex 1+ all
	BBK plantar flexor response, both sides

Problem 1. Alternation of consciousness
2. Anemia with thrombocytopenia
3. Jaundice without organomegaly

Laboratory test

CBC Hb 5.1 g/dL, Hct 16%, WBC 14,800/mm^3, PMN 68%, L 25%, M 3%, Band 4%, platelet count 19,000/mm^3, NRC 10/100 RBC

Urine exam Yellow/clear, specific gravity 1.018, pH 5, occult blood 3+, protein trace WBC 1-2/HF, RBC 1-2/HF

ESR 45 mm/h

Coagulogram APTT 22.2 s (C=24.3), PT 10.5 s (C=10.8, INR 1.0)

Coombs' test direct - negative
indirect - negative

Electrolyte Na 141 mmol/L K 4.1 mmol/L CL 104 mmol/L HCO_3 27 mmol/L

Blood chemistry Blood glucose 107 mg/dL, BUN 23 mg/dL, creatinine 0.9 mg/dL, LDH 5,973, uric acid 5.9 mg/dL, amylase 50 U/L (30-110)

LFT SGOT 72 U/L, SGPT 28 U/L, alkaline phosphatase 79 U/L, direct bilirubin 0.3 mg/dL, indirect bilirubin 2.8 mg/dL, albumin 4.3 mg/dL

Anti HIV negative

Peripheral blood Microangiopathic hemolytic

anemia blood picture

Bone marrow Productive marrow

CNT dz study VDRL non reactive

ANA positive 1:80 (speckled pattern)

Anti-ds-DNA negative

Anti-SM negative

Anti-nRNP negative

Ultrasound whole abdomen Hepatosplenomegaly with fatty change of the liver, otherwise unremarkable.

Barium enema No evidence of mass lesion or obstruction

Chest X-ray normal

Day 1 Patient was treated with methyl prednisolone 1 g iv OD x 3 days. Hct 16%, WBC 14,800/mm^3 platelet 19,000/mm^3

Patient was transfuse with PRC 2 units and FFP 4 units.

Day 2 Clinically improved, patient could follow command and had verbal response. Hct 28%, WBC 24,200/mm^3, platelet 24,000/mm^3

Patient was transfused with PRC 1 unit and FFP 4 units.

Day 3 No fever, more alert. Hct 29%, WBC 10,700/mm^3 platelet 30,000/mm^3

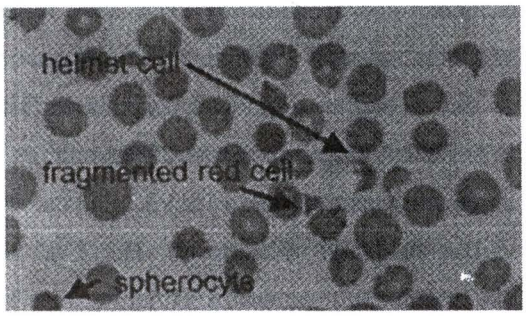
Day 4 Clinically worse, decrease in level of conscious, but can move all extremities. Hct 27%, WBC 9,200/mm^3, platelet 28,000/mm^3

Patient was transfused with FFP 4 units and steroid was continued by using dexamethasone 4 mg iv every 6 hours.

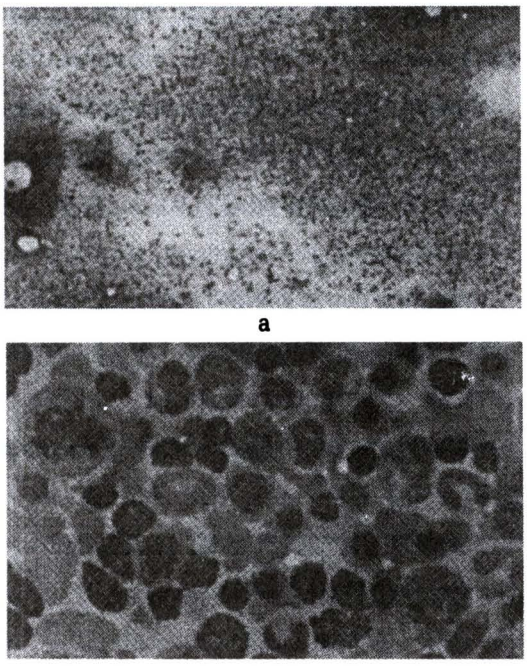
Plan to use plasmapheresis or IVIgG or whole blood exchange and CT brain but couldn't be done because of financial problem.

Day 5 Still drowsiness of conscious. Hct 27%, WBC 12,000/mm^3, platelet 11,000/mm^3

Day 6 No fever, level of consciousness was the same. Hct 26%, WBC 11,700/mm^3, platelet 29,000/mm^3



Picture 1 Peripheral blood smear of the patient showed fragmented RBC, helmet cell, spherocyte.



a

b

Picture 2 Bone marrow finding of the patient. **a.** Productive marrow, adequate stem cell elements. **b.** Erythroid hyperplasia

Patient was treated with endoxan 800 mg IV and vincristine 2 mg IV

Day 7 No fever, level of consciousness was the same, respond to call but didn't talk. Hct 27%, WBC 11,500/mm^3, platelet 35,000/mm^3

Day 8 Improved, more alert, responded to command and spoke slowly. Hct 26%, WBC 8,500/mm^3, platelet 29,000/mm^3

Day 9 No fever, gradually improved. Hct 21%, WBC 8,700/mm^3, platelet 22,000/mm^3

Patient was transfuse with PRC 2 units.

Day 10 Markedly improved. Hct 25%, WBC 8,000/mm^3, platelet 26,000/mm^3

Day 11 Hct 24%, WBC 9,900/mm^3, platelet 41,000/mm^3

Patient was discharged from the hospital with prednisolone (60 mg/d), ranitidine and primalute N.

Day 22 Hct 31%, WBC 23,400 /mm^3, platelet 110,000/mm^3. Prednisolone was tapered.

Day 29 Hct 36%, WBC 11,900/mm^3, platelet 148,000/mm^3

Day 180 Hct 36%, WBC 7,400/mm^3, platelet 300,000/mm^3. ANA positive > 1:320 (nucleolar pattern). Anti-ds-DNA negative

Patient was on prednisolone 5 mg alternate day.

Day 300 Hct 41.3%, WBC 11,600/mm^3, platelet 364,000/mm^3 ANA negative

Discussion

The setting of this patient is adult female without any underlying diseases and medicationpresenting with alternation of consciousness without fever. She also developed acute anemia with clinical evidences of hemolysis (jaundice and elevated unconjugated bilirubin). The blood smear and bone marrow study indicated microangiopathic hemolytic anemia (MAHA). The differential diagnosis of MAHA is in table 1.

In this patient, she had stable vital signs, no fever, and normal coagulogram which suggested that the primary cause should not be infectious in origin. We had screened for malignancy (chest X-ray, ultrasound whole abdomen, barium enema, and pelvic examination) but they did not show any suspicious organs. We had screened for connective tissue disease (non reactive VDRL test, positive ANA 1:80, small amount of proteinuria, MAHA, CNS symptom) which were not evident for systemic lupus

Table 1 Differential diagnosis of microangiopathic hemolytic anemia (MAHA)

Primary
Classic thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Secondary
Carcinomatosis
Pregnancy and pueperium
Tissue transplantation
Renal allograft
Bone marrow allograft
Infection
Connective tissue disease
Drugs and toxin

Table 2 Criteria for diagnose systemic lupus erythematosus (SLE)

Malar rash	
Discoid rash	
Photosensitivity	
Oral ulcer	
Arthritis	
Serositis : pleuritis or pericarditis	
Renal disorder :	persistent proteinuria or >0.5 g/d or >3+ or cellular casts
Neurologic disorder : seizures or psychosis	
Hematologic disorder :	hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia
Immunologic disorder :	positive anti-DNA or anti-Sm or positive anti-phospholipid
Antinuclear antibody	

For the purpose of identifying SLE patients in clinic studies, 4 or more of the criteria are present

erythematosus (SLE). (Table 2) We concerned about thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP-HUS) even though the patient had no fever (pentad for diagnosis: MAHA, thrombocytopenia, CNS symptom, proteinuria, fever). However fever is less frequent in more recent case series. In addition, the present of chills and high, spiking fever should suggest sepsis rather than TTP-HUS. The renal disease in TTP-HUS is usually associated with an urinalysis that is often near normal with only mild proteinuria (usually between 1 and 2 g/d) and few cellsor casts.[2,3] This patient was treated with plasma infusion and steroid (methylprednisolone 1 g/d X 3 day then dexamethasone 16 mg/d) and chemotherapy (endoxan, vincristine) which could some parts cover TTP-HUS and autoimmune/ connective tissue disease. We planned to use plasma exchang but the patient could not afford. She gradually improved after one week of therapy and could discharge from the hospital on day 11. Six months later, the repeated study of serology for ANA was positive >1:320. We agree that this patient had underling possible SLE and had prior TTP.

Some thrombotic microangiopathy similar to TTP can occur in patient with antiphospholipid syndrome which most of them present with venous and arterial thrombosis or frequent abortions.[4] In some case, a TTP-HUS like syndrome occurs in SLE in the absence of antiphospholipid antibodies. Both diseases may have pathogenetical similarity and their clinical features can sometimes not be distinguishable and plasma exchange or plasma therapy is appropriate. TTP and SLE can occur together in children age 6-20 years old.[5] At least 40 cases of TTP in association with SLE in the world literature.[6] Some had successful response to the addition of endoxan to the treatment with plasmapheresis and steroids.[7]

The classification of TTP-HUS syndrome are shown in table 3. The pathogenesis of TTP-HUS may be multifactorial. von Willebrand fac-

Table 3 A classification of clinical syndromes of TTP-HUS

Epidemic childhood HUS
● Following severe diarrhea with enterohemorrhagic Escherichia coli
Adult TTP-HUS syndrome
● Idiopathic
● Drug toxicity
- Cancer chemotherapy
Mitomycin C
Conditioning for bone marrow transplantation
Blemomycin and cisplatin
- Oral contraceptives
- Cyclosporin
- Tacrolimus (FK 506)
- OKT3
- Quinine
- Ticlopidine, Clopidogrel
- Valacyclovir in advanced HIV infection (?)
● Pregnancy or postpartum
● Autoimmune disease
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
● AIDS and early symptomatic HIV infection
● Pnumococcal infection

tor (vWF) is synthesized in endothelial cells and assembled in larger multimers that are present in normal plasma. The larger multimers, called unusually large vWF, are rapidly degraded in the circulation into the normal size range of vWF multimers by a specific vWF -cleaving protease (or cleaving metalloproteinase).[8] Unusually large multimer vWF forms arising from proteolytic digestion accumulate in patients with TTP, being found in the platelet thrombi and serum. These multimers can attach to activated platelets, thereby promoting platelet aggregation. Unusually large multimer vWF accumulation in TTP is associated with absent or markedly diminished cleaving protease activity due to an inherited or acquired deficiency of the protease.[9-12] An inhibitory autoantibody has been found among a high percentage of patients with the acquired forms of this disease.[13] Endothelial injury may be another factor other than cleaving protease deficiency. The platelet activation in HUS may be a secondary response to endothelial injury. The endothelial damage could be directly induced by a drug (as mitomycin C or cyclosporin) or indirectly via neutrophil activation.[14] Vascular endothelial beds of renal and cerebral vessels are commonly involve in TTP while the pulmonary and hepatic microvasculature are usually spared. This pattern was reproduced in one study which evaluated the ability of plasma from adult patients with TTP-HUS to induce apoptosis in microvascular endothelial cells of diverse tissue origin.[15] When incubated with patient plasma, cells of dermal, renal, and cerebral origin were susceptible to apoptotic death in vitro, while those of pulmonary and hepatic origin were not.

Another factor that may underly platelet

aggregation in TTP-HUS is the presence of plasminogen activator type I (PAI -1). Increased levels of PAI-1, the primary inhibitor of the fibrinolytic compounds tissue-type plasminogen activator, has been described in children with postdiarrheal HUS.[16]

Autosomal recessive and dominant forms of familial HUS have been described but comprise fewer than 5 percent of reported cases.[17] Base upon a candidate gene approach, linkage analysis in three families found that the disorder segregated with a genetic locus at chromosome 1q32, the location for the genes encoding the family of complement regulatory proteins.[18] It is unclear how a efficiency in complement regulatory proteins might predispose affected patients to develop HUS. One possible mechanism is that exposure to vascular endothelial cell toxin, such as virus, bacterium or immune complexes, causes a local thrombotic events.[19]

Conclusion

We report a case of TTP prior to develop SLE which was successful treatment with plasma therapy, steroid, endoxan and vincristine.

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บทคัดย่อ: *รายงานผู้ป่วยหญิงอายุ 32 ปีมีอาการปวดศีรษะมาก 7 วันและมีอาการซึมลง 5 วันก่อนมาโรงพยาบาล ผู้ป่วยไม่มีโรคประจำตัว ไม่ได้รับประทานยาเป็นประจำ และไม่มีไข้ในการเจ็บป่วยครั้งนี้ การตรวจ CBC พบมีภาวะโลหิตจางและเกร็ดเลือดต่ำ การตรวจ peripheral blood smear และ bone marrow เข้าได้กับ microangiopathic hemolytic anemia การตรวจทางห้องปฏิบัติการพบ BUN 23 mg/dL, creatinine 0.9 mg/dL, direct bilirubin 0.3 mg/dL, indirect bilirubin 2.8 mg/dL การตรวจทางน้ำเหลืองพบ ANA ให้ผลบวก 1:80 (speckle pattern) ส่วน anti-ds-DNA และ VDRL ให้ผลลบ การตรวจคอมพิวเตอร์สมองไม่พบหลอดเลือดแตกหรือตีบตัน ผู้ป่วยมีอาการดีขึ้นและรู้สึกตัวดีขึ้นหลังจากได้รับการรักษาด้วย plasma infusion, methylprednisolone และยาเคมีบำบัด (endoxan, vincristine) เป็นเวลา 10 วัน CBC กลับเป็นปกติหลังได้รับการรักษาเป็นเวลา 1 เดือน ผู้ป่วยได้รับยา prednisolone อย่างต่อเนื่องและสามารถลดขนาดยาลงจนกระทั่งหยุดยาได้เมื่อรักษาเป็นเวลา 1 ปี การตรวจ ANA ซ้ำในเวลา 6 เดือนต่อมาพบว่าให้ผลบวกมากกว่า 1:320 (nucleolar pattern) ซึ่งต่อมาให้ผลลบหลังจากรักษาได้ 10 เดือน*

Key Words : ● *Microangiopathic hemolytic anemia* ● *Antinuclear antibody* ● *Methylprednisolone*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2543;10:297-304.