中文題目：以感染為初始表現的非典型溶血性尿毒症候群：病例報告

英文題目：Atypical hemolytic uremic syndrome neglected initially in an infected patient underlined with chronic kidney disease and multiple comorbidities

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare type of thrombotic microangiopathy (TMA). aHUS patients have inherited and/or acquired complement abnormalities, leading to complement function dysregulation in the alternative pathway. Complement factor H (CFH) mutation is the most common cause of aHUS. In most cases, triggering factors (e.g., infection, drug, autoimmune disease, pregnancy, metabolic disorder, etc.) are required for primary aHUS manifestation. aHUS has a poor prognosis. Eculizumab, a humanized monoclonal complement 5 inhibitor, is beneficial in controlling renal disease and thrombocytopenia in aHUS patients. Herein, we present an adult patient with aHUS neglected initially in an infected patient underlined with chronic kidney disease (CKD) and multiple comorbidities.

Case presentation: A 55-year-old man presented to our emergency department with progressive general malaise for 2 weeks. The patient had underlying type 2 diabetes mellitus and CKD. Physical examination revealed cachexia and pale conjunctiva. Laboratory data revealed leukocytosis (white blood cell count: 11500 per μL), anemia (hemoglobin: 8.5 g/dL), thrombocytopenia (platelet count: 67000 per μL), elevated C-reactive protein (255.6 mg/L), and impaired renal function (creatinine: 4.26 mg/dL). Urinalysis exhibited pyuria (WBC: 61.2 per μL) and bacteriuria (157.9 per μL).

Under the impressions of urinary tract infection (UTI) and acute on CKD, hydration and antibiotics were initiated. On the third day of admission, Coca-Cola like urine was noted. Follow-up laboratory data revealed renal function deterioration (creatinine: 5.44 mg/dL) despite an improvement in infection. Hemodialysis was initiated due to progressive renal failure with anuria.

On the thirteenth day, worsening anemia and thrombocytopenia without bleeding symptoms or signs were also noted (hemoglobin 9.4 g/dL to 6.7 g/dL and platelet count 52000 per μL to 13000 per μL in 3 days). Anemia examination revealed elevated lactate dehydrogenase (239 U/L) and direct bilirubin (0.73 mg/dL) levels, as well as decreased haptoglobin concentration (<4.0 mg/dL); blood smear revealed schistocyte presence (2+).

Hemolysis was confirmed and the Coombs test revealed negative results, indicating MAHA. Thrombocytopenia examination excluded disseminated intravascular coagulation. Other laboratory data revealed no evidence of metabolic disorders, viral infection, autoimmune diseases, or cancer. The stool culture demonstrated no evidence of Shiga-toxin producing *Escherichia coli*.

On the nineteenth day, ecchymosis was observed over the patient's abdomen, four limbs and the scrotum. Severe anemia (hemoglobin: 5.5 g/dL) and thrombocytopenia (platelet count: 2000 per μL) were also noted. TTP was suspected on the basis of MAHA, thrombocytopenia and renal failure. Plasma exchange (PE) was initiated pending the ADAMTS-13 result, which revealed a normal range of activity (62.9%) a week later. TTP was excluded, increasing the possibility of aHUS. The gene report revealed two CFH mutations, including exon 23 c.3572C>T/c.3590T>C, which are aHUS pathogenic variants. We subsequently applied for rare disease verification and Eculizumab to National Health Insurance.

Discussion: In clinical practice, prioritizing impressions and attributing other diagnoses to the main one are common, leading to the risk of neglecting other potential etiologies. In this case, we initially focused on infection control, attributed renal failure and thrombocytopenia to infection, and attributed renal anemia. However, progressive anemia and thrombocytopenia were noted after complete infection treatment, suggesting that MAHA had developed; hence, we commenced anemia and thrombocytopenia examinations.

After the patient was diagnosed with aHUS, we found certain aHUS clues upon reviewing his disease progress. Coca-Cola like urine may not be typical in clinical scenarios. Serial urinalysis exhibited worsening microscopic hematuria despite improved pyuria, suggesting that microscopic hematuria might have resulted from microangiopathy (hemoglobinuria) instead of UTI.

In adults, TTP has a higher prevalence than aHUS does, and should be excluded prior to aHUS diagnosis. aHUS diagnosis confirmation is time-consuming. Although PE is a supportive treatment, it may be beneficial for aHUS patients through the replacement of the abnormal complement with a healthy one.

Eculizumab is an effective but expensive treatment for aHUS. Controversies regarding the optimal Eculizumab treatment duration remain. Studies have demonstrated that patients with CFH mutations carry the highest risk of relapse after Eculizumab discontinuation. Resuming Eculizumab helps in renal function recovery and platelet count normalization. The

appropriation of Eculizumab discontinuation should be based on the existence of aHUS pathogenic variants, and patient compliance with close monitoring is essential for the early detection of relapse.

Conclusion: aHUS is a rare type of TMA with exclusive diagnosis. Complement abnormalities in the alternative pathway play a crucial role in pathogenesis and triggering factors are usually necessary for disease manifestation. PE is a supportive treatment, while Eculizumab helps in preventing ESRD. We presented an aHUS case with a clinical presentation of MAHA, thrombocytopenia, and renal failure, who was diagnosed with pathogenic variants in CFH gene.