A Differential Diagnosis of Thrombotic Microangiopathy in a 7-Year-Old Girl

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CASE DESCRIPTION

A 7-year-old girl, who had been born naturally at 41 weeks from a second pregnancy (body weight 3690 g, Apgar score 10/10), was admitted to the Department of Nephrology with symptoms including diarrhea, vomiting, weakness, and reluctance to eat or drink. Routine hematology and biochemistry tests showed anemia, thrombocytopenia, hyperbilirubinemia with a predominance of unconjugated bilirubin, hyponatremia, and acute kidney injury with high creatinine and blood urea nitrogen (BUN) concentration. There was significant proteinuria and erythrocyturia on urinalysis (see Table 1). Athrombotic microangiopathy (TMA) was suspected: the differential diagnosis included Shiga-toxin–producing *Escherichia coli*-associated hemolytic uremic syndrome (STEC-HUS), atypical hemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP), and autoimmune hemolytic anemia (AIHA).

Before the onset of symptoms, the patient had stayed with family in the countryside, where she had been in contact with farm animals. In light of this history and the presence of diarrhea, STEC-HUS was suspected and a PCR for Shiga-toxin–producing *Escherichia coli* was requested. To exclude AIHA and TTP, a Coombs test and ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity quantification were also requested. Hemodialysis was initiated on the second day of hospitalization in response to acute renal failure (serum creatinine 7.2 mg/dL [636.5 µmmol/L]; serum BUN 163 mg/dL [58.2 mmol/L]; see Table 1 and Fig. 1). The urine output (calculated as 1.6 mL/kg body mass/hour with a body mass of 25 kg) was considered normal (reference value: >1 mL/kg body mass/hour; >30 mL/h), and there were no symptoms of pulmonary or peripheral edema. After the initial round of dialysis, the creatinine and BUN concentrations decreased to 4.4 mg/dL (389 µmol/L) and 107 mg/dL (38.2 mmol/L), respectively (Table 1 and Fig. 1). In total, 6 hemodialysis procedures were performed, and 6 units of packed red blood cells and 1 unit of platelet concentrate were transfused (for laboratory results, see Table 1 and Fig. 1).

Results of PCR testing for Shiga-toxin produced by *E. coli* were double-negative, which allowed us to exclude STEC infection. Moreover, ADAMTS13 activity was 97% (reference interval: 61% to 131%), and the Coombs test was negative. TTP and AIHA were therefore excluded, and aHUS was diagnosed, thereby qualifying the patient for treatment with eculizumab. The first dose of eculizumab (600 mg) was administered on Day 4 of her hospital stay without complications. Routine laboratory tests showed normalization of the hemoglobin concentration and platelet count, as well as improved renal function (Table 1 and Fig. 1). However, the total complement (CH50) activity was <12.21 U/mL (reference interval: 41.68 to 95.06 U/mL), which is consistent with complete inhibition of the classical complement pathway. On Day 30 of her admission, it was suggested that the patient might be predisposed to complement-dependent aHUS. Subsequent molecular analysis showed that the patient had biallelic variants in the *CD46* and *CFH* genes, which encode the complement regulatory proteins: membrane cofactor protein (MCP) and complement factor H (CFH), respectively.

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QUESTIONS TO CONSIDER	
1.	Which tests are useful in differentiating between aHUS and TTP?
2.	How does the etiology of aHUS differ from that of other types of HUS?
3.	How does eculizumab affect the complement system?
4.	Which laboratory test can be used to monitor a complement system activity during therapy with eculizumab?

Table 1. Laboratory results.

Parameter, units	Result					Reference interval
	Hospital Day					
	1	2 (before dialysis)	2 (after dialysis)	14 (discharge day)	18 (control visit)	
Hemoglobin, g/dL	5.6	11.2	9.2	10.7	12.0	12.0–15.5
Platelets, 10^9/L	39	111	80	227	242	150–400
Total bilirubin, μmol/L	49.59	35.91	—	—	—	2.56–17.10
Indirect bilirubin, μmol/L	35.91	—	—	—	—	0.00–3.42
Sodium, mmol/L	125	129	—	140	144	130–143
Potassium, mmol/L	4.7	4.6	3.7	4.4	5.5	3.5–5.1
Calcium, mmol/L	2.22	2.19	2.12	2.44	2.62	2.19–2.69
Creatinine, mg/dL[b]	8.1	7.2	4.4	1.2	0.9	0.4–0.6
BUN, mg/dL[c]	185	163	107	66.8	38.8	7.0–22.0
Uric acid, mg/dL[d]	16.7	<0.5[a]	—	6.0	5.3	1.8–5.5
D-dimers, μg FEU/L	6872	—	—	—	—	<500
Lactate dehydrogenase, U/L	3425	3152	3152	—	740	120–300
Urinalysis						
Erythrocyturia [FOV][e]	15–18	—	—	0–1	0–1	<7
Proteinuria [g/L]	2.17	—	—	1.17	0.77	0.00–0.15

[a]Uric acid concentration after administration of Rasburicase.
[b]creatinine [μmol/L]*88.4.
[c]BUN mmol/L *0.357.
[d]uric acid μmol/L *0.0168.
[e]Abbreviation: FOV, fields-of-view.

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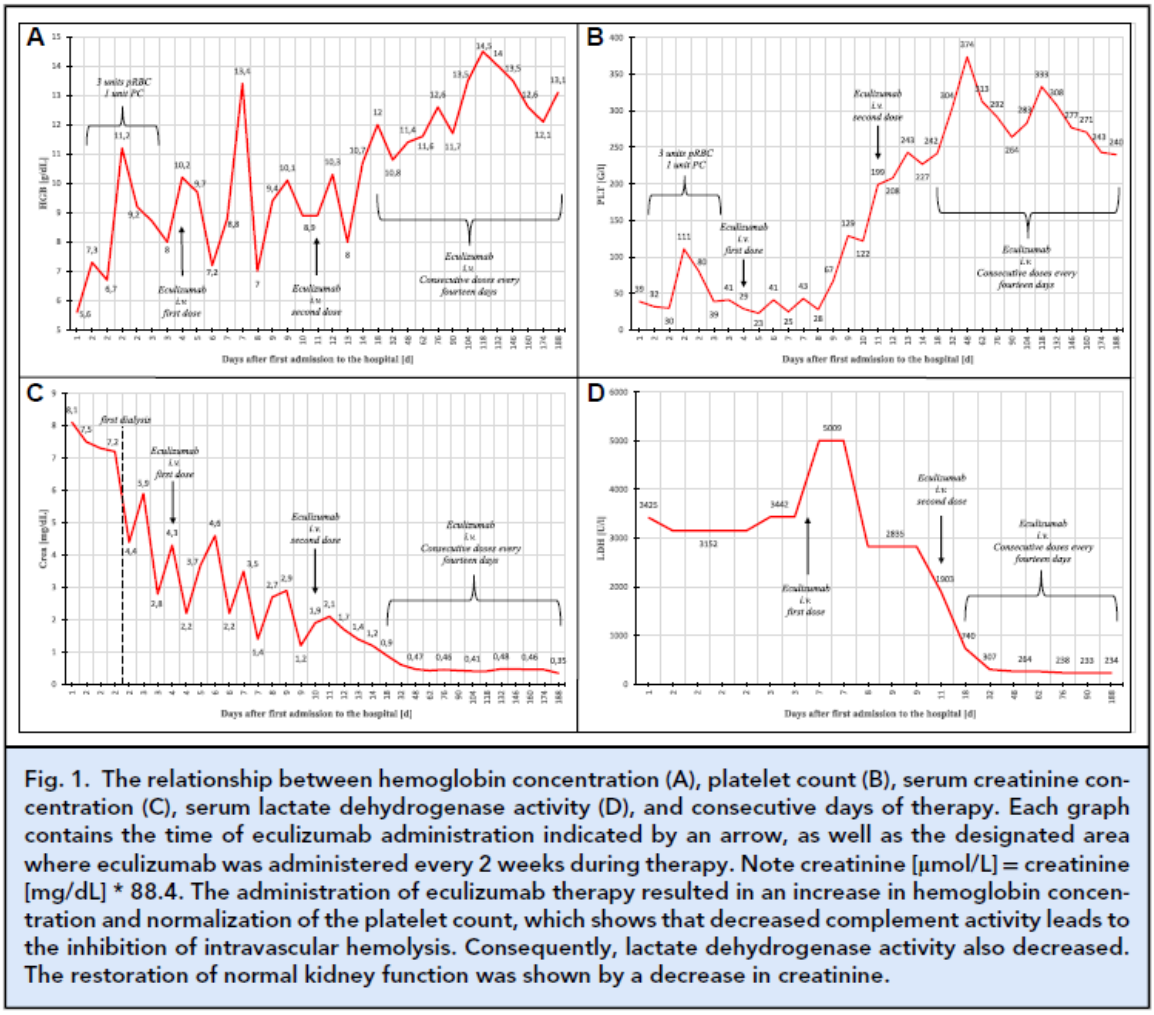

Fig. 1. The relationship between hemoglobin concentration (A), platelet count (B), serum creatinine concentration (C), serum lactate dehydrogenase activity (D), and consecutive days of therapy. Each graph contains the time of eculizumab administration indicated by an arrow, as well as the designated area where eculizumab was administered every 2 weeks during therapy. Note creatinine [µmol/L] = creatinine [mg/dL] * 88.4. The administration of eculizumab therapy resulted in an increase in hemoglobin concentration and normalization of the platelet count, which shows that decreased complement activity leads to the inhibition of intravascular hemolysis. Consequently, lactate dehydrogenase activity also decreased. The restoration of normal kidney function was shown by a decrease in creatinine.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the February 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/2 and follow the link to the Clinical Case Study and Commentaries.

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