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CASE REPORT

A rare complication of eculizumab treatment for atypical hemolytic uremic syndrome

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disease characterized by uncontrolled activation of the complement system. The introduction of eculizumab, a monoclonal antibody that blocks the complement protein C5, has significantly improved patient prognosis. However, eculizumab treatment is associated with a risk of adverse effects. We report a severe and complex case of aHUS in a 4-year-old boy, triggered by viral infections (influenza A and parvovirus B19) and influenced by genetic predisposition. An unexpected complication – a severe rash following eculizumab administration – necessitated discontinuation of the drug. Given the patient's genetic risk factors, crovalimab was planned as an alternative treatment in case of recurrence. At the one-year follow-up, the patient's kidney function remained stable, indicating a favorable outcome. This case underscores the complexity of aHUS management, the importance of genetic screening, and the need for vigilance in monitoring adverse drug reactions.

KEY WORDS:

atypical hemolytic uremic syndrome, anti-C5 monoclonal antibody, eculizumab, thrombotic microangiopathies.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening form of thrombotic microangiopathy (TMA) characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, in the absence of Shiga toxin-producing *Escherichia coli* (STEC) infection. aHUS is caused by dysregulation and uncontrolled activation of the alternative complement pathway. It is often linked to pathogenic variants affecting complement regulatory proteins. The introduction of eculizumab, a monoclonal antibody that blocks the complement protein C5, has significantly improved patient prognosis. However, despite its efficacy, eculizumab is associated with a risk of adverse effects. We present the case of a 4-year-old boy with a multifactorial presentation of aHUS, preceded by viral infections and complicated by a severe and unexpected cutaneous reaction to eculizumab.

CASE PRESENTATION

A 4-year-old Caucasian boy was referred to the pediatric nephrology department with suspected hemolytic uremic syndrome (HUS). He presented with fever up to 39.6°C, cough, and hematuria. The patient vomited twice and experienced numerous episodes of diarrhea without blood. Symptom onset occurred two days prior to admission. Upon arrival, the patient appeared pale, dehydrated, with small petechiae on the skin and mild edema of the lower extremities. Initially, diuresis was present at 3 mL/kg/hour. Blood tests showed the following results: hemoglobin (Hb) level of 10.4 g/dl, schistocytes present (count 105‰), raised lactate de-

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TABLE 1. Progression of laboratory parameters

Parameters	Normal value	Admission	Day 2	Day 6	Day 9 (2nd day of CVVHDF)	Day 23	Day 34 (severe rash)	Day 43	Day 435
Urea [mmol/l]	2.5–6.0	10.6	17.5	32	7.7	16.4	8.3	14.7	6.5
Creatinine [µmol/l]	13.3–57.0	68	139.3	670	132	233	157	59.1	42.5
eGFR [ml/min/1.73 m^2]		60.6	29.4	6.1	31	17.5	26	69.8	102
Hemoglobin [g/dl]	11.0–14.0	10.4	8.6	7.7	9.0	11.2	9.5	11.8	12.7
Hematocrit (%)	31.0–37.7	27.8	23.1	20	24.3	30.7	28.1	33.8	36.1
Platelet count [10^3/µl]	150–450	8.0	24	15	115	463	132	557	359
LDH [IU/l]	145–345	4565	4831	4548	4353	438	415	375	298
Albumin [g/l]	35–52	35.9	28	25	25.1	40	29.5	50.3	48
AST [U/l]	15–50	282	327	214	139	33	17	84	36.3
CRP [mg/l]	< 10	40	20	< 5	51	31	66	< 5	< 5
Procalcitonin [ng/ml]	< 0.5	23.8	31	25.5	14.6	0.8	26	0.27	
Proteinuria [g/l]	< 0.3	45	52	26		0.8	0.8	1.0	0.1

AST – aspartate aminotransferase, CRP – C-reactive protein, CVVHD – continuous venovenous hemodiafiltration, eGFR – estimated glomerular filtration rate, LDH – lactate dehydrogenase

hydrogenase (LDH) at 4565 IU/l, negative direct Coombs test, thrombocytopenia (platelet count 8.0 × 10^3/µl), and acute kidney injury, as indicated by an elevated serum creatinine of 68 µmol/l and an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m^2. Additional laboratory findings included a pH of 7.43, bicarbonate 13.8 mmol/l, BE –8.4 mmol/l, sodium 133 mmol/l, potassium 4.06 mmol/l, total bilirubin 41 µmol/l, AST 282 U/l, ALT 32 U/l. Table 1 shows the changes in the parameters over the following days. Ultrasound revealed increased echogenicity of the kidneys. Stool tests for Shiga toxin and a PCR gastrointestinal pathogen panel, including STEC, were both negative. The activity of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) was 107%. Complement analysis results were as follows: complement factor C3 0.84 g/l, complement factor C4 0.18 g/l, factor H 196.5 µg/ml (within normal range), anti-factor H antibodies – negative, C5b-9 (membrane attack complex) 163.6 ng/ml (slightly below normal), CH50 47.0 U/ml (within normal range). Levels of membrane cofactor protein (MCP) on the surface of peripheral blood leucocytes were also normal. Initial management included fresh frozen plasma (FFP) therapy, with one unit transfused. The patient was subsequently started on the C5 inhibitor eculizumab. Blood culture was positive for *Staphylococcus warneri*, and antibiotic therapy with ceftriaxone and vancomycin was initiated and continued for 14 days. Moreover, infections with influenza A and parvovirus B19 were diagnosed. Oseltamivir was administered. Due to further deterioration of renal function and a significant reduction in diuresis (anuria since day 4), continuous ambulatory peritoneal dialysis (CAPD) was started. The boy later developed aspiration pneumonia and hypertension (blood pressure 150/90 mm Hg despite receiving three antihypertensive drugs), requiring transfer to the intensive care unit (ICU) for respiratory support and blood pressure management. Vital signs included: heart rate 70 beats/minute, oxygen saturation 95% (on 5 l oxygen *via* face mask), and blood pressure 135/80 mm Hg. Pulmonary examination revealed massive crackles on the left side. The patient was given RBC and albumin transfusions in addition to antibiotic therapy with metronidazole and a continuous infusion of intravenous bumetanide. Multiple antihypertensive agents were required, including amlodipine, metoprolol, doxazosin, clonidine, urapidil, and dihydralazine. Parenteral nutrition was also necessary for 17 days. A significant decrease in ultrafiltration was observed due to a malfunction of the Tenckhoff catheter. Given the inadequacy of CAPD, continuous renal replacement therapy (CRRT) was initiated. The boy was also diagnosed with cholelithiasis. After seven days of CRRT, the Tenckhoff catheter was repositioned, and the patient was switched back to CAPD. Diuresis resumed after 12 days of anuria. Three doses of eculizumab were administered (on the 2nd, 9th, and 23rd days of hospitalization), along with prophylaxis-initially with ciprofloxacin, which was replaced by penicillin after the third dose. The day after the third dose of eculizumab, an itchy, macular rash appeared on the upper and lower extremities. The boy appeared somnolent and weak. Over the next few days, the rash worsened significantly, with the development of papules, vesicles, petechiae, and erosions, as shown in Figures 1 and 2. Numerous lesions covered the extremities and partially the face and trunk. The patient also developed a high fever, generalized edema, effusions into body cavities, and low blood pressure. He became anxious and agitated. Vancomycin and meropenem therapy were resumed. Treatment for the skin lesions included hydrocortisone and oxytetracycline ointments, along with emollients. Additionally, antihistamines such as cetirizine were administered, followed by hydroxyzine. A dermatology and allergology evaluation confirmed the suspicion of a drug-induced

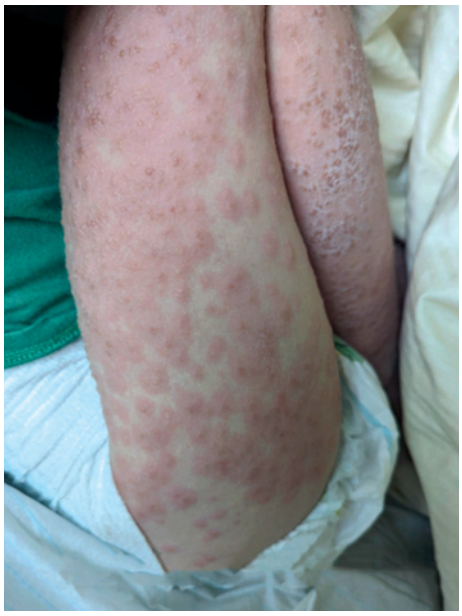

FIGURE 1. Eighth day of skin lesions

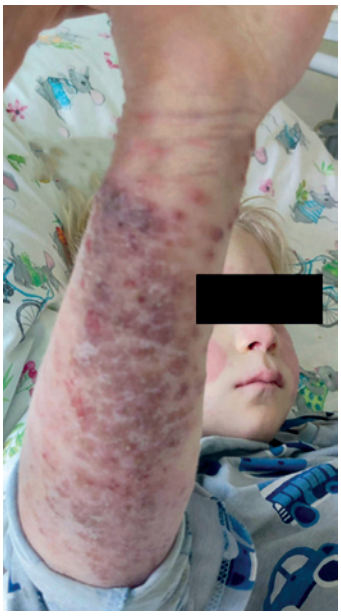

FIGURE 2. Tenth day of skin lesions

rash. After 10 days, gradual improvement was observed, without the appearance of new lesions. The blood culture was negative; PCR tests for HSV-1, HSV-2, and VZV were negative; anti-EBV IgM and IgG tests were also negative. The eosinophil count was mildly elevated (1.1×10^9/l), observed on the 6th day of the rash. Over the following days, the eosinophil count normalized, measuring 0.1×10^9/l by the 11th day of the rash. Given the severe adverse event, a consultation with the national coordination team led to the decision to discontinue eculizumab, and the fourth dose was not administered. Diuresis remained stable, and kidney function improved, leading to the discontinuation of dialysis after 30 days. In the following days, significant clinical and laboratory improvement was observed, allowing for the gradual discontinuation of diuretics and antihypertensive drugs. The patient recovered well and was discharged in good condition after 42 days in the hospital. At discharge, his serum creatinine was 59 µmol/l, eGFR 69.3 ml/min/1.73 m², blood pressure 104/61 mm Hg, and diuresis 3.7 ml/kg/hour. Genetic testing revealed risk factors associated with a less favorable disease course and an increased likelihood of disease recurrence, including TGTGT haplotype variants in the *CFH* gene and GGAAC haplotype variants in the *CD46* (*MCP*) gene. Additionally, the variants rs2301612 and rs2285489 were identified in the *ADAMTS13* gene. These variants are associated with familial thrombotic thrombocytopenic purpura. One-year follow-up revealed stable kidney function (serum creatinine 42.5 µmol/l, eGFR 102 ml/min/1.73 m²), well-controlled hypertension (with ramipril therapy), and no laboratory evidence of hemolysis.

DISCUSSION

This case report describes a complex and severe presentation of HUS in a 4-year-old boy, highlighting the multifactorial nature of the disease and the challenges in its management. The presence of severe thrombocytopenia, microangiopathic hemolytic anemia (as evidenced by schistocytes), and acute kidney injury confirmed the diagnosis of HUS. The patient's clinical presentation was preceded by viral infections, including influenza A and parvovirus B19. These infections may have triggered complement system activation, leading to TMA. The pathogenic role of the influenza virus is also linked to its production of neuraminidase (NA), similarly to *Streptococcus pneumoniae*. Additionally, next-generation sequencing (NGS) revealed risk factors, including the haplotypes *CFH-H3* (CFH tgtgt) and *MCP* ggaac, which have been previously associated with aHUS [1]. Approximately 40–60% of patients with aHUS have identifiable pathogenic variants in complement-related genes. The *CFH-H3* risk haplotype (CFH-tgtgt), which includes rs3753394 in the promoter region and rs800292, rs1061170, rs3753396, and rs1065489 in the coding region, is associated with aHUS [2]. Moreover, the *ADAMTS13* variants rs2301612 and rs2285489, linked to thrombotic thrombocytopenic purpura (TTP), were also identified. Although ADAMTS13 activity was normal, these genetic findings suggest an underlying predisposition to microangiopathic events. Due to the absence of STEC, the diagnosis was classified as aHUS. The patient required treatment with eculizumab, a first-line therapy for aHUS. Eculizumab inhibits the cleavage of C5 into C5a and C5b, thereby preventing the formation of the membrane attack complex (C5b-9). It is also used to treat other rare diseases, including paroxysmal nocturnal hemoglobinuria (PNH), generalized myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD). The introduction of eculizumab in aHUS has significantly improved patient prognosis. However, despite its efficacy, eculizumab is associated with a risk of adverse effects. An unexpected

complication was the occurrence of a severe rash following eculizumab administration, a reaction not commonly reported, which required discontinuation of the drug. The timing of the rash suggests a possible link to eculizumab, as cutaneous adverse drug reactions usually occur within 12–24 hours of exposure [3]. Although other factors, such as concurrent infections or medications, could contribute, blood culture and virological tests were negative. The DRESS syndrome (drug rash with eosinophilia and systemic symptoms) was also considered; however, there was no evidence of lymphadenopathy or hepatic involvement. The diagnostic criteria proposed by the Japanese consensus group – including eosinophilia exceeding 1.5×10^9/l – were not fulfilled [4]. Therefore, it is impossible to determine whether the reported adverse event was specifically related to medication exposure or underlying disease-related morbidity. The median time to onset of eculizumab adverse events is 159 days (range 11–738 days) [5]. Infections appear to be the most common adverse event among patients ≤ 25 years old treated with eculizumab for aHUS [6, 7]. The most commonly reported noninfectious adverse events were nausea and abdominal pain, followed by infusion reactions (fever, chills, skin rashes, itching, flushing, shortness of breath), hypertension, headache, vomiting, back pain, diarrhea, and anemia [6]. Skin and subcutaneous tissue disorders account for 1.99% of adverse events associated with eculizumab [5]. A severe, potentially life-threatening rash following eculizumab treatment is an unexpected complication, not commonly reported in standard side effect profiles. Only a few cases of skin reactions associated with eculizumab have been described. A cutaneous drug reaction was reported as a side effect of eculizumab in a patient treated for antibody-positive neuromyelitis optica [8]. In this case, the rash appeared also after the third infusion, the characteristics of the skin lesions were similar, and discontinuation of eculizumab was also required. Additionally, a life-threatening desquamating rash and hyperammonemia following the administration of eculizumab for PNH were reported [9]. These cases illustrate the need for vigilant monitoring during eculizumab therapy. The genetic predisposition identified in this patient raises concerns regarding the risk of disease recurrence. aHUS is known for its relapsing nature, especially in individuals with complement dysregulation. The identified *CFH* and *CD46* gene variants suggest a higher susceptibility to future episodes, warranting long-term follow-up. In the case of disease relapse, it was planned to administer crovalimab treatment. Crovalimab is used for the treatment of PNH. It was approved for use in the United States in June 2024 and in the European Union in August 2024. Crovalimab is a novel anti-C5 sequential monoclonal antibody recycling technology (SMART), allowing it to bind to C5 multiple times. This enables less frequent dosing and reduces the treatment burden [10]. A one-year follow-up revealed

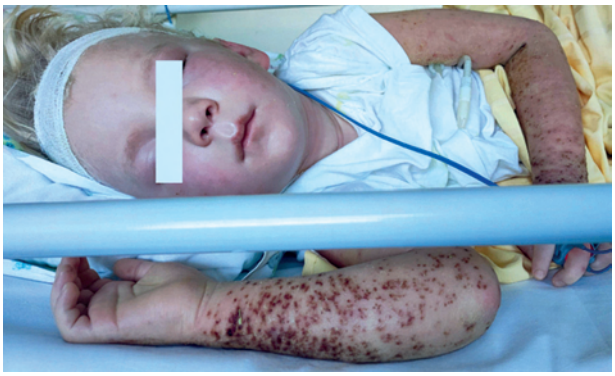

FIGURE 3. Twelfth day of skin lesions

stable kidney function, suggesting a favorable long-term outcome despite the initial severity and treatment challenges. This case underscores the potential for severe complications in aHUS, including infections, hypertension, dialysis, intensive care unit management, and multiple pharmacological interventions, and highlights the complexity of managing aHUS. In particular, the unexpected occurrence of a severe rash, likely related to the administration of eculizumab, posed a major management challenge. Our understanding of drug reactions associated with eculizumab is limited; therefore, it is crucial to report potential life-threatening adverse effects, such as an acute, severe skin rash. In conclusion, the patient's complex medical history, involving atypical triggers, genetic predispositions, and treatment-related complications, offers valuable insights into the diagnosis and management of aHUS.

DISCLOSURES

1. Institutional review board statement: The parents gave their consent to present the case and include photographs in the manuscript.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 2013; 8: 554-562.
2. Pickering MC, de Jorge EG, Martinez-Barricarte R, Recalde S, Garcia-Layana A, Rose KL, et al. Spontaneous hemolytic uremic syndrome triggered by complement factor H lacking surface recognition domains. J Exp Med 2007; 204: 1249-1256.
3. Tempark T, John S, Rerknimitr P, Sataporn pong P, Sukasem C. Drug-induced severe cutaneous adverse reactions: insights into clinical presentation, immunopathogenesis, diagnostic methods, treatment, and pharmacogenomics. Front Pharmacol 2022; 13: 832048.
4. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Clin Aesthet Dermatol 2013; 6: 31-37.

5. Wang XF, Bao LR, Hu TL, Xu RF, Gao WN, Wang JY, et al. Adverse drug events (ADEs) risk signal mining related to eculizumab based on the FARES database. Front Pharmacol 2025; 15: 1440907.
6. Muff-Luett M, Sanderson KR, Engen RM, Zahr RS, Wenderfer SE, Tran CL, et al. Eculizumab exposure in children and young adults: indications, practice patterns, and outcomes – a Pediatric Nephrology Research Consortium study. Pediatr Nephrol 2021; 36: 2349-2360.
7. Nishimura JI, Kawaguchi T, Ito S, Murai H, Shimono A, Matsuda T, et al. Real-world safety profile qof eculizumab in patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, or generalized myasthenia gravis: an integrated analysis of post-marketing surveillance in Japan. Int J Hematol 2023; 118: 419-431.
8. Sharma R, Romo M, Nelson F. Eculizumab-related drug reaction in a patient with neuromyelitis optica. Clin Case Rep 2023; 11: e6835.
9. Knoll BM, Letendre L, Steensma DP. Life-threatening desquamating rash and hyperammonemia following administration of eculizumab for paroxysmal nocturnal hemoglobinuria. Am J Hematol 2008; 83: 881-883.
10. Röth A, Nishimura JI, Nagy Z, Gaàl-Weisinger J, Panse J, Yoon SS, et al. The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria. Blood 2020; 135: 912-920.