Alternative Pathway Complement Dysregulation in Atypical HUS: A Case Communication

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Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. In contrast to typical HUS, which is triggered by Shiga toxin–producing bacteria, aHUS results from genetic or acquired dysregulation of the alternative pathway (AP) of the complement system and has an estimated incidence of 1–2 cases per million per year [1]. Early recognition is critical, as terminal complement inhibition with C5 blockers significantly improves renal and overall outcomes [2,3].

Complement disorders are increasingly recognized as inborn errors of immunity (IEI), and encompass deficiencies of early classical components (e.g., C1q, C2, C4), alternative pathway regulators (e.g., complement factor H [CFH], complement factor I [CFI]), and terminal pathway components (C5–C9), each associated with distinct infectious, autoimmune, or inflammatory phenotypes [4]. Dysregulation of the AP, particularly involving CFH, plays a central role in aHUS pathogenesis.

PATIENT DESCRIPTION

A previously healthy 6-month-old male infant of Arab Bedouin descent, born to first-degree consanguineous parents was admitted to the hospital with a 3-day history of pallor and vomiting. On presentation, blood pressure was elevated at 115/80 mmHg. Laboratory evaluation demonstrated TMA: hemoglobin 6.7 g/dl, platelet count 32 × 10^9/L, and creatinine 2.1 mg/dl. Peripheral smear revealed numerous schistocytes, accompanied by elevated lactate dehydrogenase and undetectable haptoglobin, consistent with microangiopathic hemolysis.

Stool cultures were negative for Shiga toxin-producing *Escherichia coli*. ADAMTS13 activity was normal (> 10%), excluding thrombotic thrombocytopenic purpura. No secondary causes of TMA, including infection, medications, or autoimmune disease, were identified. There was no known family history of renal disease or similar presentations, and no additional cases suggestive of aHUS were identified in the extended family.

Complement testing showed normal C3 and C4 levels and normal total hemolytic activity. Functional assessment of the alternative pathway (AH50) was not available. Given the early age of onset and parental consanguinity, a genetic etiology was suspected.

Targeted aHUS gene-panel sequencing, including CFH, CFI, CD46, C3, CFB, THBD, and DGKE, revealed no pathogenic variants. However, whole-exome sequencing followed by multiplex ligation-dependent probe amplification (MLPA) identified a de novo heterozygous 84-kb duplication within the CFH gene. Parental genetic testing was negative for this duplication, confirming a de novo event. While this finding suggested the mutation occurred early in development, rare germline mosaicism could not be formally excluded. Serum CFH lev-

el was 380 µg/ml (reference range 250–520 µg/ml), suggesting a qualitative rather than quantitative defect.

Despite supportive care, clinical improvement was not observed. Treatment with eculizumab was initiated according to standard pediatric weight-based protocol and later transitioned to ravulizumab. Meningococcal vaccination and antibiotic prophylaxis were administered prior to complement blockade. The patient demonstrated rapid clinical and laboratory improvement, with normalization of hematologic parameters (hemoglobin 11.2 g/dl, platelets 210 × 10^9/L) and renal function (creatinine 0.4 mg/dl), allowing discontinuation of antihypertensive therapy.

COMMENT

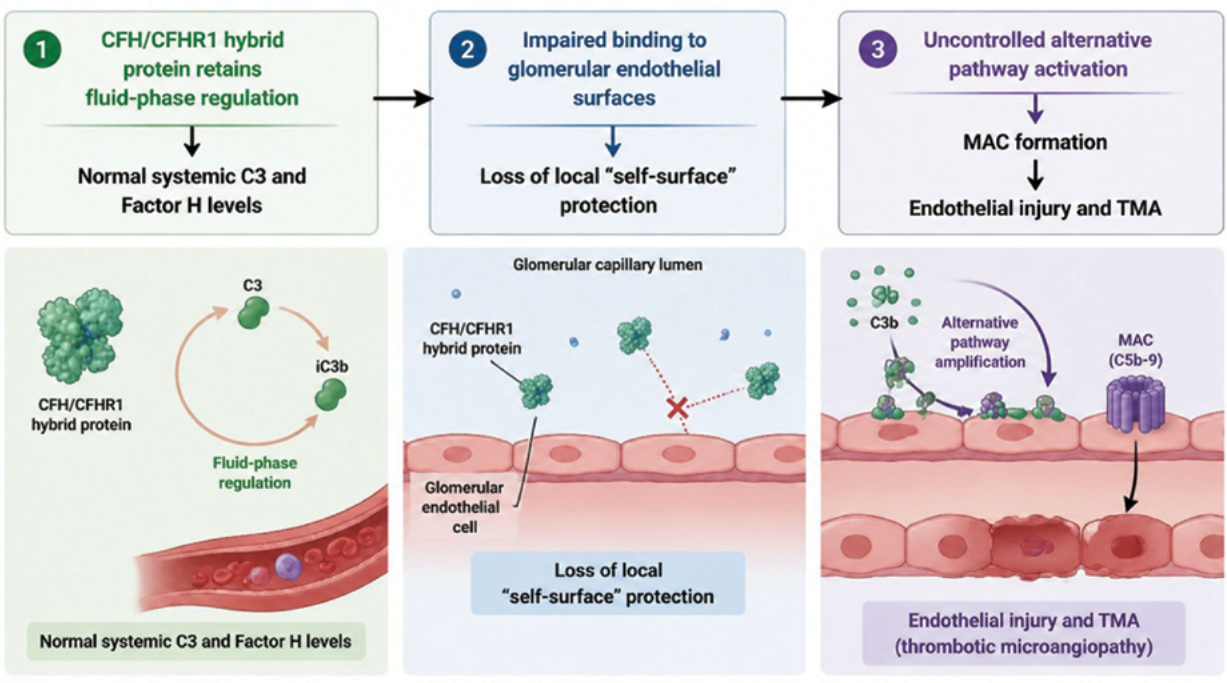
Our case highlights a critical diagnostic pitfall in complement-mediated TMA. Normal complement screening does not exclude a pathogenic defect in the alternative pathway. Routine measurements such as C3 and C4 primarily reflect activation of the classical and lectin pathways and may remain normal in disorders affecting regulatory proteins such as CFH.

The identified structural rearrangement likely results in a *CFH/CFHR1* hybrid gene, a well-described mechanism in aHUS. The hybrid protein maintains effective regulation of C3 in the plasma (the fluid phase), which explains the normal systemic complement levels. However, the loss of the CFH C-terminal recognition domain prevents the protein from binding to host endothelial cells, leading to localized, uncontrolled alternative pathway activation, membrane attack complex (MAC) formation, and renal thrombotic microangiopathy (TMA) [Figure 1] [5]. These hybrid proteins typically disrupt the C-terminal domains of CFH, which are responsible for binding to host cell surfaces, impairing local complement regulation on endothelial cells while preserving fluid-phase regulatory activity. This finding explains the paradox of normal circulating C3 and CFH levels despite severe endothelial injury.

Our case underscores the limitations of standard complement assays and targeted gene panels. Structural variants, such as duplications or hybrid genes, may be missed without comprehensive genomic approaches, including MLPA or copy-number analysis. In patients with high clinical suspicion, particularly those with early onset or consanguinity, extended genetic testing should be pursued even when initial evaluations are unrevealing.

Although functional assays of the alternative pathway (e.g., AH50) may provide additional information, their availability is limited and normal results would not exclude regu-

Figure 1. Proposed pathogenic mechanism of the *CFH/CFHR1* hybrid protein



latory defects at the endothelial surface level. Thus, clinical judgment remains central to early diagnosis.

Therapeutically, prompt initiation of complement inhibition is essential and should not be delayed pending genetic confirmation. C5 blockade with eculizumab or ravulizumab has transformed the prognosis of aHUS, preventing irreversible renal damage and reducing mortality [2,3]. The patient's rapid response further supports the pivotal role of uncontrolled terminal complement activation in disease pathogenesis.

CONCLUSIONS

Atypical HUS should be strongly considered in infants presenting with TMA, even in the presence of normal complement levels. Our case emphasizes that normal complement screening may be misleading and that comprehensive genetic evaluation is often required to establish the diagnosis. Early initiation of complement blockade remains the cornerstone of management and can be lifesaving.

Declaration of AI use

Parts of this manuscript were reviewed and edited for language and style using ChatGPT (OpenAI, GPT-5). In addition, Figure 1 was generated using an AI image creation tool (NoteGPT) based on the authors' conceptual design and mechanical specifications. The authors critically reviewed and verified all text and visual content for accuracy, scientific integrity, and originality.

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References

1. Yan K, Desai K, Gullapalli L, Druyts E, Balijepalli C. Epidemiology of atypical hemolytic uremic syndrome: a systematic literature review. *Clin Epidemiol* 2020; 12: 295-305.
2. Stea ED, D'Ettorre G, Mitrotti A, Gesualdo L. The complement system in the pathogenesis and progression of kidney diseases: What doesn't kill you makes you older. *Eur J Intern Med* 2024; 124: 22-31.
3. West EE, Woodruff T, Fremeaux-Bacchi V, Kemper C. Complement in human disease: approved and up-and-coming therapeutics. *Lancet* 2024; 403 (10424): 392-405.
4. Poli MC, Aksentijevich I, Bousfiha AA, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. *J Hum Immun* 2025; 1 (1): e20250003.
5. Piras R, Valoti E, Alberti M, et al. *CFH* and *CFHR* structural variants in atypical hemolytic uremic syndrome: prevalence, genomic characterization and impact on outcome. *Front Immunol* 2023; 13: 1011580.

Capsule

Oxysterol organization of lung immunity

Although fungal pathogens strongly induce type 2 immunity, these same responses can also impair fungal clearance. Using a mouse model of *Cryptococcus neoformans* infection, **Zheng** et al. found that cholesterol-derived oxysterols produced by lung macrophages position T helper 2 (T_H2) cells within fungal granulomas. The G protein-coupled receptor GPR183 mediated sensing of chemotactic oxysterols by T_H2 cells, suppressed macrophage responsiveness to interferon-γ, and promoted *C. neoformans* persistence. These findings identify lung macrophages as key organizers of pulmonary type 2 immunity through oxysterol-mediated positioning of T_H2 cells.

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Capsule

B cells are essential for the antitumor response

The therapeutic success of anti-programmed cell death protein 1 immunotherapy against glioblastoma is limited, but cytotoxic T lymphocyte-associated protein 4 (CTLA-4) immune checkpoint blockade has shown promise. **Kim** et al. showed that B cells are essential for the antitumor response after CTLA-4 blockade in murine glioblastoma models. Treatment increased T follicular helper cell differentiation in tumor-draining lymph nodes, which stimulated the systemic production of glioblastoma-specific class-switched antibodies by antibody-secreting cells. Tumor-reactive antibodies accumulated within the tumor and tagged cancer cells for phagocytosis by intratumoral macrophages, thus promoting tumor clearance. These findings reveal the essential role of tumor-draining lymph nodes in orchestrating B cell-dependent and antibody-dependent antitumor responses, underscoring the interplay between humoral and cellular immunity in cancer treatment.

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