



# Atypical hemolytic uremic syndrome after childbirth: a case report

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**Abstract:** We report a case of atypical hemolytic uremic syndrome (HUS) that occurred after childbirth. A 33-year-old female was admitted to the emergency room, complaining of abdominal pain six days after giving birth to twins. The patient was diagnosed with hemoperitoneum due to hepatic hemangioma rupture and a left lateral hepatectomy was performed. Angioembolization was performed for the accompanying uterine artery bleeding. After that, her kidney function worsened after the 12th day postpartum. Microangiopathic anemia, thrombocytopenia and renal dysfunction were observed. Shiga toxin-producing *Escherichia coli* was negative in the stool. Plasma ADMATS 13 activity was normal. After transfer to the nephrology department with suspected atypical HUS, the patient underwent fresh frozen plasma (FFP) transfusion with three hemodialysis sessions. The patient improved without additional dialysis, but a renal biopsy was performed because of persistent proteinuria. Renal pathologic findings were compatible with thrombotic microangiopathy. A genetic test for atypical HUS revealed variants of uncertain significance in the complement factor H related (CFHR) 4 gene and the presence of CFHR3-CFHR1 copy number gain. The *CFHR3-CFHR1* copy number gain found in this case is a rare causative mutation of atypical HUS. This case suggests that genetic testing of atypical HUS should include analysis of *CFH-CFHR* rearrangements as well as general screening for complement-associated genes.

**Keywords:** Atypical hemolytic uremic syndrome (HUS); *CFHR3-CFHR1*; copy number gain; pregnancy; case report

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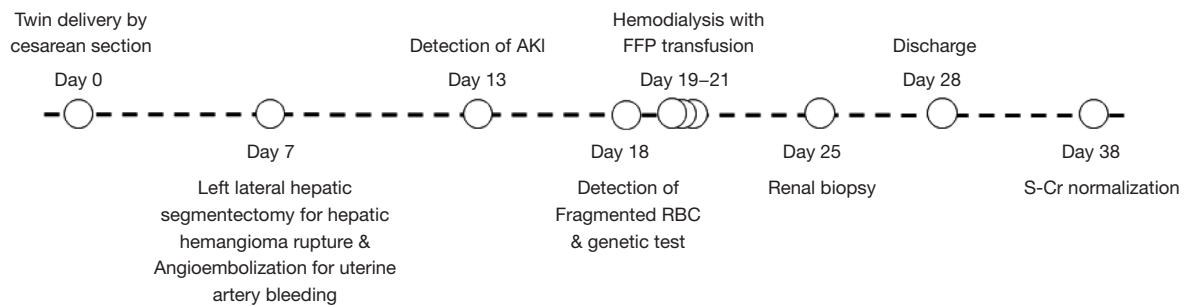
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## Introduction

Hemolytic uremic syndrome (HUS) is a comparatively rare hematological abnormality that accompanies microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (AKI). Atypical HUS is caused by inborn or acquired genetic defects of genes that are associated with regulation of the complement pathway. Atypical HUS is known to be triggered by factors that induce the activation of complement cascades, including

infection, pregnancy, organ transplantation, malignancy, autoimmune disease, and drugs (1). Cases of pregnancy-associated atypical HUS are known to occur during the postpartum period (2). More than half of thrombotic microangiopathies associated with pregnancy have genetic abnormalities in the complement system. Abnormalities of several genes associated with the complement system have been reported (3), and mutations can be diagnosed relatively easily using advanced diagnostic methods, such

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**Figure 1** Timeline of patient's clinical course. AKI, acute kidney injury; RBC, red blood cell; FFP, fresh frozen plasma; s-Cr, serum creatinine.

as new generation sequencing (NGS). Similarly, copy number variation resulting from genomic rearrangement can be diagnosed using techniques like multiplex ligation-dependent probe amplification (MLPA) (4). Here, we report successful treatment of a patient who was diagnosed with postpartum atypical HUS after childbirth by identification of genetic abnormalities in the complement system using NGS and MLPA. This case is an atypical HUS due to the rare copy number variation of the *CFHR* genes, and shows that the genetic test for atypical HUS must be performed for *CFH*-*CFHR* rearrangement. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3789>) (5).

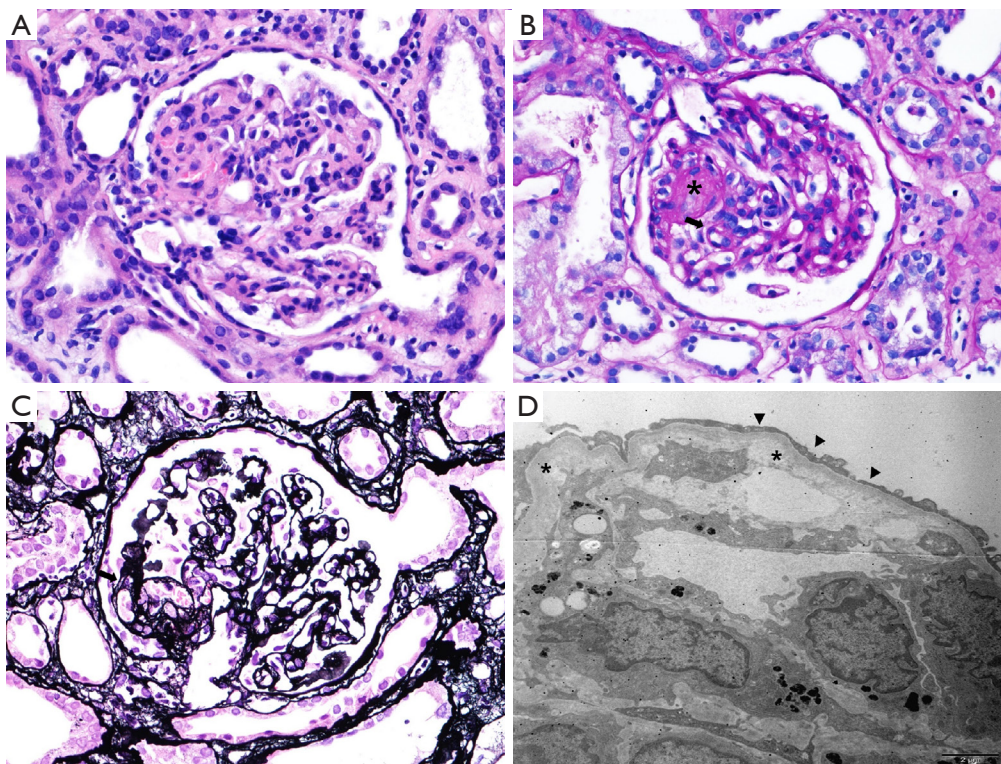
### Case presentation

A 33-year-old woman with renal impairment was referred to our nephrology department. She had delivered twins through Caesarean section 18 days before referral. She denied any underlying disease, medication history or familial history of renal impairment. Six days after delivery, she had received left lateral hepatic segmentectomy and angioembolization of the uterine artery due to hepatic hemangioma rupture and uterine artery bleeding. Her serum creatinine level started to increase approximately 12 days after delivery and continued to increase despite proper management (Figure 1). On the day of referral, her laboratory data were: white blood cell count, 8,800/ $\mu$ L; hemoglobin, 7.7 g/dL; platelet count, 68,000/ $\mu$ L; blood urea nitrogen, 33.2 mg/dL; serum creatinine, 2.46 mg/dL; and lactate dehydrogenase (LDH), 3,958 U/L. Peripheral blood smears were performed for further evaluation of bicytopenia and showed fragmented red blood cells. Together, these results were indicative of thrombotic microangiopathy. The patient had no recent history of

diarrhea and no enterohemorrhagic *Escherichia coli* was detected in her stool. Plasma ADMATS 13 activity was 60%. The lack of accompanying neurological symptoms led us to suspect atypical HUS. Renal biopsy revealed findings consistent with thrombotic microangiopathy (Figure 2).

Hemodialysis was initiated immediately and the patient was administered fresh frozen plasma (FFP). FFP was administered with three sessions of dialysis, after which her laboratory findings began to improve. Platelet counts improved without blood transfusion and serum LDH levels gradually decreased. This trend persisted even after cessation of dialysis and FFP administration. The patient was discharged 10 days after being transferred to the department of nephrology. No signs of renal failure or recurrence of atypical HUS were apparent on her four-month outpatient follow-up, at which her laboratory findings were: serum creatinine level, 0.53 mg/dL; platelet count of 219,000/ $\mu$ L; and serum LDH level, 378 U/L.

Genetic testing was performed concurrently with the treatment regime to identify the cause of the atypical HUS. Sequencing of 17 genes known to be associated with atypical HUS (i.e., *C3*, *C4BPA*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *THBD*, *PLG*, etc.) as well as of *ADAMTS13* and *C5* was performed. Gene sequencing was performed by Illumina Hi-seq 2500 platform, followed by targeted Sanger sequencing for validation of identified genetic variants. Gene dosage tests were performed using MLPA. Genetic profiling revealed a substitutional variant c.1607 T>G {p.[Ile536Arg] or I536R} in *CFHR4*. Additionally, MLPA analysis revealed the presence of a copy number gain in the *CFHR3*-*CFHR1* regions (Figure 3). Genetic testing confirmed a diagnosis of atypical HUS caused by a point mutation and copy number gain in *CFHR*. About 1 year after the onset of the disease, her serum creatinine level was 0.55 mg/dL, and there was



**Figure 2** Renal biopsy. (A) Glomeruli show thickened capillary wall and fragmented red blood cells are trapped in the mesangial matrix (hematoxylin and eosin stain,  $\times 40$ ). (B) The periodic acid Schiff (PAS) stained glomerulus demonstrates segmental mesangiolytic (asterisk) and double contours in capillary basement membrane (arrow) ( $\times 40$ ). (C) Light microscopy image of the kidney biopsy specimen shows double contours of the glomerular basement membrane with Jones methenamine silver stain ( $\times 40$ ). (D) Electron microscopy of the kidney biopsy reveals irregular electron-lucent expansion of the subendothelial zone (asterisk) and diffuse foot process fusion (arrowhead) ( $\times 8,000$ ).

no recurrence or unanticipated outcome during the follow-up period.

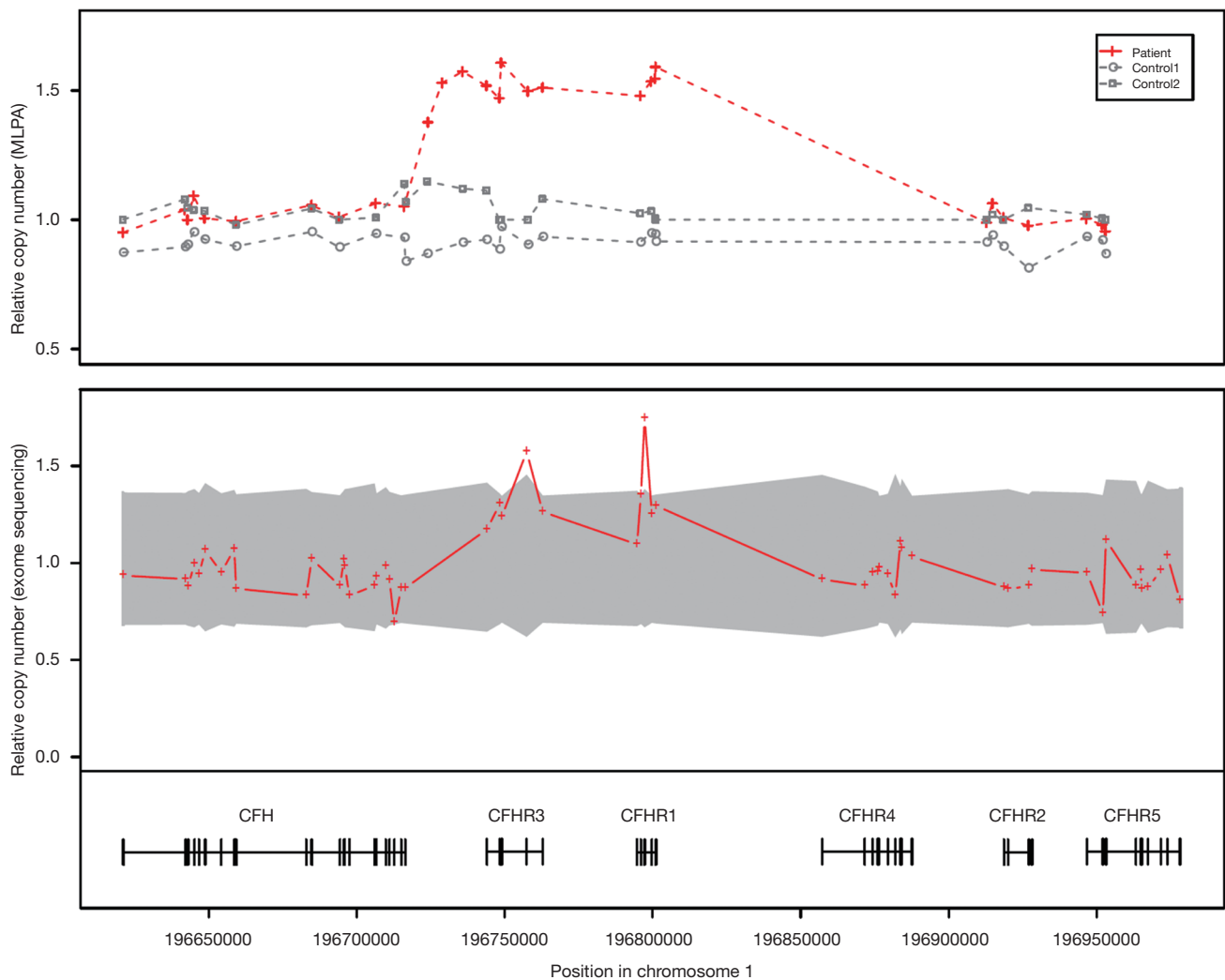
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Discussion

We present a case of pregnancy-associated atypical HUS during the postpartum period in a young woman who has two genetic mutations in the complement cascade. The patient had previously given birth and had no history of diagnosis or treatment with thrombocytopenia or AKI. Fakhouri *et al.* reported that approximately 20% of atypical HUS patients in France are related to pregnancy; ~80% of these were reported during the postpartum period, with the time of onset varying widely from the 3<sup>rd</sup> day postpartum

to the 4<sup>th</sup> month (2). The development of HUS in the current case occurred 12 days postpartum, consistent with previous reports. Initially, development of HUS can be detected through a decrease in platelet counts and AKI. Differentiation from other causes of AKI that may occur during pregnancy, including preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome, and thrombotic thrombocytopenic purpura (TTP), is important (6). Other common causes of AKI, such as volume depletion or acute tubular necrosis, should also be considered. In particular, TTP is very similar to the expression of HUS, which can complicate differential diagnosis. However, even before ADAMTS13 activity test results are confirmed, TTP is more thrombocytopenic and has less severe renal failure than HUS. Furthermore, TTP predominantly occurs in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester of pregnancy (7).

Genomic rearrangement in the *CFH-CFHR* region resulting in copy number gain of *CFHR3* and *CFHR1*



**Figure 3** The relative copy number based on the multiplex ligation-dependent probe amplification (MLPA) study (upper plot). The value 1.0 on Y axis represents two copies or copy neutral. Each “+” represents each probe in MLPA study. The relative copy number based on the exome sequencing copy number analysis (lower plot). Each “+” represents an exon region in exome sequencing study. The grey zone indicates 99% confidence interval of normal controls without copy number alterations.

was discovered in our patient by MLPA analysis. Several previous studies have reported atypical HUS by the *CFHR1/CFH* hybrid gene (4,8,9). Valoti *et al.* reported the generation of *CFHR1/CFH* hybrid gene and an extra copy of *CFHR3* and *CFHR1* in a patient with atypical HUS (4). Although the patient in the current case did not have a *CFHR1/CFH* hybrid gene, her atypical HUS was likely caused by a *CFHR3-CFHR1* copy number gain, which is similar to a variant described by Valoti *et al.* (4). In addition to the copy number gain of *CFHR3-CFHR1*, a variant of uncertain significance was found in the *CFHR4* gene in our

patient. The function of *CFHR4* remains unclear, though it is known to bind to the C3b and to have a complement modulatory activity in the form of a factor H cofactor enhancing activity (10). The I536R mutation in our patients is located in *CFHR4* SCR9, and its role in protein function and disease association is unknown. In addition, except for a deletion of *CFHR1/CFHR4*, no other *CFHR4* mutation has been reported to be associated with atypical HUS.

Our study found a very rare *CFHR3-CFHR1* copy number gain as the cause of atypical HUS. However, our study has some limitations. First, a functional study was



not performed on the discovered mutations. In addition, the mechanism of how CFHR3-CFHR1 copy number gain generated atypical HUS could not be revealed. Second, although no family member with similar symptoms was found, it is a limitation of our study that genetic testing of the family members was not performed because of that.

In summary, we describe a case of atypical HUS that occurred during the postpartum period and was likely caused by a *CFHR3-CFHR1* copy number gain. This case suggests that genetic testing of atypical HUS should include analysis of *CFH-CFHR* rearrangements as well as general screening for complement-associated genes.

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### Footnote

**Reporting Checklist:** The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3789>

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3789>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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