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Case Report

CD46 Deficiency Complicated by Coronary Artery Aneurysm: A Case Report

Nakysa Hooman[1*], Behnoosh Tasharofi[2], Roya Isa Tafreshi[1], Elham Zarei[3], Nafiseh Mortazavi[4], Soudabeh Hosseini[5,6], Parsa Yousefichaijan[7]

1. Department of Pediatrics, Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
2. Department of Genetics, Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences. Tehran, Iran.
3. Department of Radiology, Aliasghar Clinical Research Development Center, School of Medicine, Ali Asghar Children Hospital, Iran University of Medical Sciences, Tehran, Iran.
4. Department of Pathology, Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
5. Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
6. Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran.
7. Department of Pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran.

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Corresponding Author:
Nakysa Hooman, Professor.
Address: Department of Pediatrics, Aliasghar Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
E-mail: hooman.n@iums.ac.ir

ABSTRACT

Background and Aim: Membrane attack complex deficiency accounts for 10-15% of cases of complement dysregulation-associated hemolytic uremic syndrome (HUS).

Case Presentation: We report a case involving a 7-year-old girl who presented with HUS. Assessment of the complement pathway revealed persistently low levels of CD46. Initially, she required kidney replacement therapy, but following partial recovery of renal function, she was able to discontinue therapy for several years. During this period, she was admitted multiple times for pneumonia, hypertensive crises, and relapses of her underlying condition, which were managed accordingly. Whole-exome sequencing revealed a mutation in the membrane cofactor protein (MCP; *CD46*). At the age of 12.5 years, she was readmitted with fever and dyspnea, during which a coronary artery aneurysm was detected via echocardiography. Treatment with intravenous immunoglobulin, corticosteroids, and aspirin was initiated to prevent thrombosis. Unfortunately, she passed away after three years of irregular and inconsistent follow-up. To the best of our knowledge, the occurrence of a coronary artery aneurysm has not been previously reported in association with CD46 deficiency.

Conclusion: In conclusion, the integration of cardiac markers and echocardiography into the routine assessment of patients with cHUS is essential for monitoring potential cardiovascular complications.

Keywords: Coronary aneurysm, Membrane cofactor protein (MCP), Atypical hemolytic uremic syndrome (HUS)

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Introduction

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, along with evidence of thrombotic microangiopathy (TMA) in tissue samples. Complement dysregulation-associated HUS (cHUS) is often associated with recurrences and complications, particularly prior to the advent of C5 inhibitors. Membrane cofactor protein (MCP) is a transmembrane complement regulator extensively expressed on cell surfaces and serves as a cofactor for complement factor I. MCP deficiency is linked to various inflammatory disorders, autophagy, and modulation of T cell activation. Additionally, it is a component of the complosome, an intracellular complement system. Cardiovascular involvement, including heart failure, hypertension, and cardiac ischemia, has been rarely reported in HUS. In this report, we describe coronary artery aneurysm as an unrecognized complication of cHUS.

Case Presentation

Clinical scenario and laboratory tests

We present a girl aged 6 years and 7 months, previously healthy with no significant medical history. She was admitted with fever, nausea, and vomiting. The following day, she developed hematuria, oliguria, and acute kidney injury. Concurrently, she experienced abdominal distension and pain, which were associated with fluid overload. Physical examination revealed a weight of 19 kg, height of 120 cm, and blood pressure of 150/90 mm Hg. The patient exhibited edema, and diffuse fine rales were auscultated bilaterally in the lungs. The parents were distant relatives, and her older sibling was suspected of having celiac disease.

Investigations

Initial laboratory tests revealed the following: white blood cell count of 18900 cells/mcL, hemoglobin level of 8.3 g/dL, platelet count of 35000 cells/mcL, blood urea nitrogen (BUN) of 97 mg/dL, creatinine of 8 mg/dL, uric acid of 10.7 mg/dL, lactate dehydrogenase (LDH) of 3,246 IU, aspartate aminotransferase (AST) of 98 IU, alanine aminotransferase (ALT) of 28 IU, and albumin of 2 g/L. Urinary dipstick results were positive for blood (3+) and protein (4+), with a urine protein-to-creatinine ratio of 12.5 mg/mg.

The results of the complement pathway assessment were as follows: Factor H, 665 mg/L (reference range: 350-950 mg/L); Factor B, 293 mg/dL (reference range: 240-400 mg/dL); Factor I, 22 mg/dL (reference range: 38-58 mg/dL); C3, 100 mg/dL; C4, 23 mg/dL; CH50, 80%; ADAMTS13, 105% (reference range: 50-160%); ADAMTS13 inhibitor, 0.3 U/mL (≤0.4 U/mL); ANA, negative; CD46, 2% (reference range: 500-1500 cells/mm^3); D-dimer, 1600 mg/L; and ferritin, 293 ng/mL (reference range: 30-400 ng/mL). Repeated assessments of the complement pathway on different occasions revealed persistently low levels of CD46, ranging from 3% to 5%.

Imaging results

Chest and lung CT scans suggested cardiomediastinal widening, with peribronchial thickening noted in the bilateral parahilar and right paracardiac regions, as well as subsegmental consolidation in the left retrocardiac region, accompanied by partial obscuration of the diaphragmatic borders (Figure 1).

Kidney biopsy results

Histological examination revealed that most glomeruli exhibited mesangiolysis with endothelial swelling, resulting in occlusion of capillary lumens and a solidified pattern. One arteriole displayed intimal swelling and myointimal proliferation with lamination of its wall. The tubules showed extensive tubular injury and foci of necrosis in their epithelial lining. Immunofluorescence studies demonstrated negative immune reactions. The biopsy confirmed extensive thrombotic microangiopathy (Figure 2).

Genetic study

A comprehensive genetic analysis utilizing whole exome sequencing identified a previously unreported homozygous missense variant within exon 3 of the *CD46* gene (c.374T>G; p.F125C). This variant is located within the complement control protein (CCP) domain, which is both functionally significant and a known mutational hotspot. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the identified genetic alteration was classified as a variant of uncertain significance (VUS) (Figure 3).

Treatment, outcome, and follow-up

Management

The patient underwent continuous ambulatory peritoneal dialysis for 18 months and, due to partial recovery of

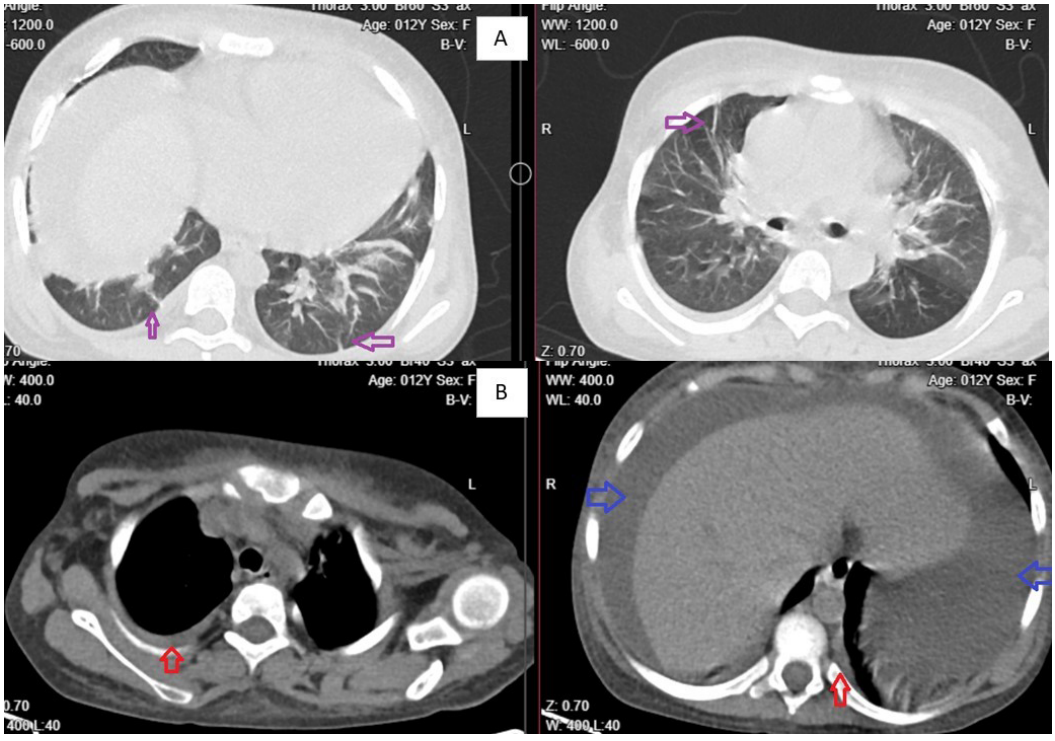

Figure 1. Imaging findings

a) Lung window: A few parenchymal bands suggestive of plate atelectasis are scattered throughout both lungs (indicated by purple arrows); b) Mediastinal window: Minimal pleural effusion is observed bilaterally (indicated by red arrows). In the visible upper abdominal sections, ascites is noted (indicated by blue arrows).

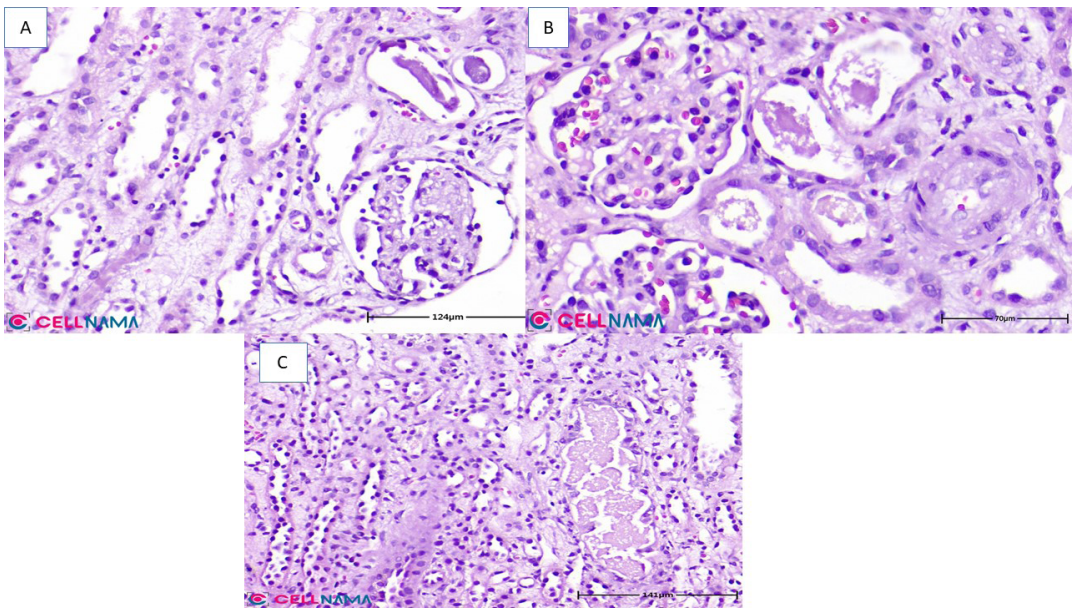

Figure 2. Histopathological findings in kidney biopsy (Hematoxylin and eosin [H&E])

a) Mesangiolysis with endothelial swelling; b) Myointimal proliferation; and c) Tubular injury with foci of necrosis

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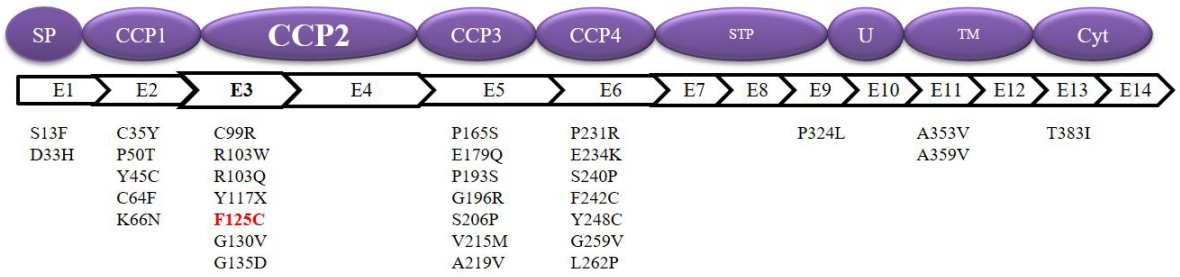

Figure 3. Schematic representation of the *CD46* gene and its protein domains

Abbreviation: CCP: Complement control protein; STP: Serines, threonines, proline-rich region; U: Segment of undefined function; TM: transmembrane domain; CYT: Cytoplasmic tail.

Note: This diagram illustrates that the majority of mutations occur within the four CCP regions of the *CD46* gene. The mutation identified in our patient is highlighted in bold green. The following components are labeled: SP, CCP, STP, U, TM, and CYT.

kidney function, was able to discontinue dialysis for two years. However, she frequently required hospitalization for pneumonia, hypertensive crises, and two episodes of disease relapse, which were managed with 3 sessions of plasmapheresis. At the age of 12 years, she was readmitted with fever and dyspnea. An echocardiogram revealed moderate left ventricular hypertrophy (LVH), with a left ventricular mass index (LVMI) of 176 g/m². Additionally, a giant aneurysmal dilation in the right coronary artery (RCA) was detected, measuring 6.8 mm in width (z-score >8) and 8 mm in length. The left main coronary artery (LMCA) had a diameter of 3.4 mm (z-score: 2.16), and the left anterior descending coronary artery (LAD) was ectatic, with a maximal diameter of 3.4 mm (Figure 4).

Following the identification of the coronary artery aneurysm, the patient received intravenous immunoglobulin (2 g/kg), steroids (500 mg methylprednisolone for three consecutive days), and aspirin (3 mg/kg). Unfortunately, she passed away 3 years later after follow-up (Figure 5). This complication has not been previously reported in the literature.

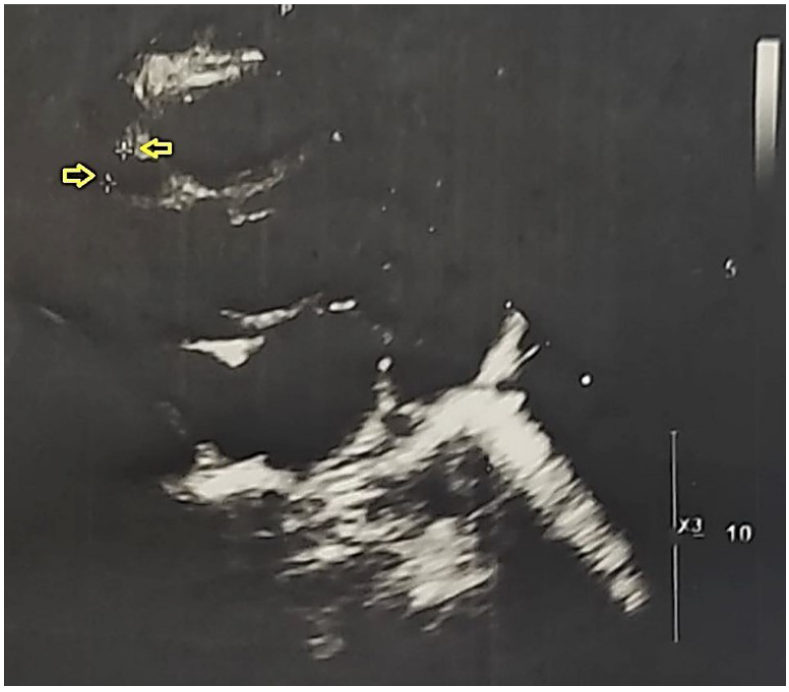

Figure 4. Echocardiographic findings

Note: Echocardiography demonstrates the presence of a coronary aneurysm, indicated by the yellow arrow.

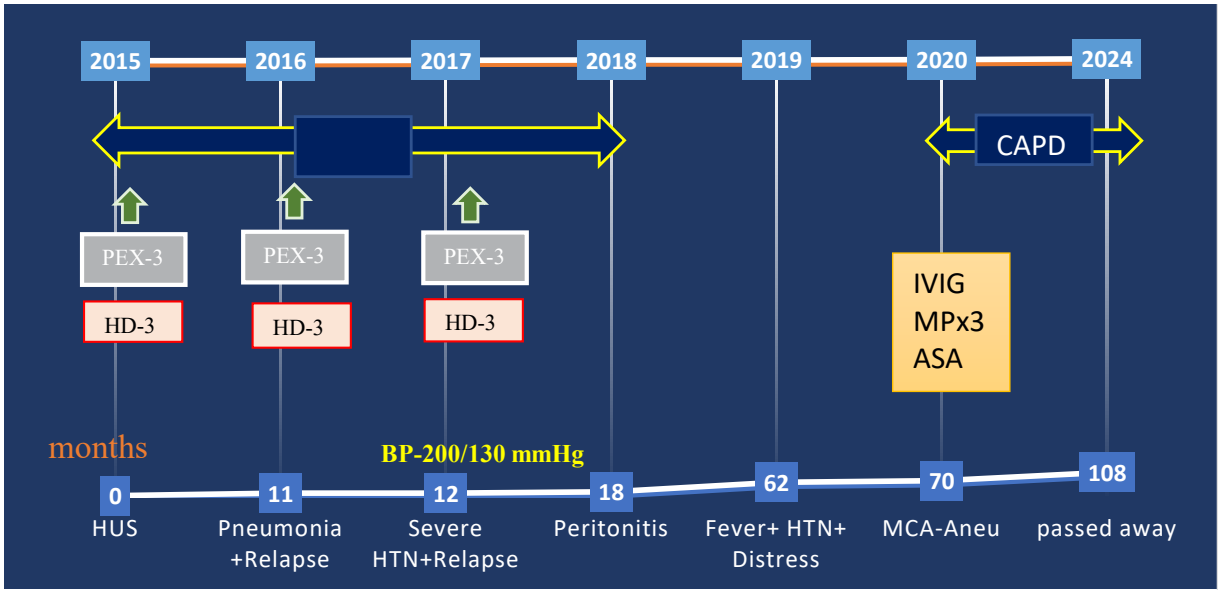

Figure 5. Timeline of management and follow-up events

Abbreviation: CAPD: Continuous ambulatory peritoneal dialysis; PEX: Plasmapheresis; HD: Hemodialysis; IVIG: Intravenous immunoglobulin; ASA: Aspirin; MP: Methylprednisolone; HTN: Hypertension; MCA-Aneu: Main coronary artery aneurysm.

Note: This timeline outlines the management strategies employed and significant events that occurred during follow-up.

Discussion

This case represents the first report of a coronary artery aneurysm in a patient with a mutation in the MCP associated with cHUS, a severe form of thrombotic microangiopathic hemolytic anemia characterized by ischemic organ pathology [1]. The frequency of *CD46* mutations has been reported to be approximately 10% in both sporadic and familial forms of HUS according to a French registry [2]. Cardiovascular morbidity has been documented in 3% to 10% of cHUS cases [3].

MCP is expressed ubiquitously across all cell types except for erythrocytes [4]. Mutations within the CCP domain predispose individuals to atypical HUS. The majority of these mutations are missense mutations with a penetrance of approximately 50%, requiring a second "hit" for phenotypic expression, even when the mutant protein is not present on the cell membrane [4]. Although there is no strong correlation between genotype and phenotype in HUS cases, the mutation identified in our patient was classified as an VUS. The persistently low levels of CD46, recurrent episodes of disease, pneumonia, and hypertensive crises underscore the clinical significance of this genetic finding.

Myocardial infarction has been documented in cases of thrombotic thrombocytopenic purpura due to ADAMTS13 deficiency and mutations in Factor H [5]. Acute cardiac involvement has been reported within the first three days of HUS onset [6]. Elevated troponin levels may indicate cardiac damage in HUS, and both early and late development of dilated cardiomyopathy have been observed in various case reports [7, 8]. Complement system dysfunction, altered levels of complement Factor H, and matrix metalloproteinases-6 have been associated with arterial wall destruction, contributing to the development of coronary artery aneurysms [9].

Experimental models of demonstrating modulation of the complement system have shown promise in addressing cardiovascular disorders [10]. Filip et al. evaluated cardiac function in 50 HUS patients during the acute phase, 3 months later, and 1 year post-diagnosis, finding arterial hypertension and LVH, along with evidence of systolic or diastolic dysfunction and deep vein thrombosis [11]. Andersen et al. reported a rare case of HUS-induced cardiac arrest that was successfully reversed by cardiopulmonary bypass. In that instance, HUS was attributed to *Escherichia coli* subtypes O55:H7 and O121:H19, alongside two novel heterogeneous mutations in C5 (c.1060C>A) and C3 (c.4535G>A) [12].

Shahini et al. studied terminal complement system products in the plasma of 188 heart failure patients, aged 67 years, matched for age and sex, and found that dysregulation of the alternative complement pathway was correlated with the severity of heart failure [13]. CD46 deficiency has been linked to HUS, glomerulonephritis, vasculitis,

Alzheimer disease, and pregnancy-related disorders [4]. The deposition of C5b-9 at the site of arterial aneurysm rupture indicated the role of complement activation in vascular remodeling [10]. However, the occurrence of coronary aneurysms has not been previously mentioned.

In our case, the patient was monitored by echocardiography during each admission, and a coronary aneurysm developed after 7 years. At that time, C5 inhibitors were not available in our country, and management was limited to plasmapheresis, dialysis, and a short course of steroids and cyclosporine. This outcome highlights the inadequacy of these treatments in maintaining cardiovascular integrity.

Conclusion

In conclusion, cardiac markers and echocardiography should be combined into the routine assessment of patients with complement-mediated cHUS to monitor potential cardiovascular complications.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (Code: IR.IUMS.REC.1404.439).

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Authors' contributions

Conceptualization and writing the original draft: Naksa Hooman; Analysis and data interpretation: Behnoosh Tasharofi, Roya Isa Tafreshi, Nafiseh Mortazavi, Elham Zarei, and Soudabeh Hosseini; Resources and data collection: Parsa Yousefichaijan.

Conflict of interest

The authors declared no conflict of interest.

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