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Case report

MULTIFACTORIAL ETIOLOGY OF ATIPICAL HEMOLYTIC UREMIC SYNDROME - CASE REPORT

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Abstract: **Introduction:** Hemolytic uremic syndromes are characterized by the simultaneous occurrence of hemolytic anemia, microangiopathy, thrombocytopenia, and acute renal insufficiency. In terms of the clinical prodrome, they can be classified as typical, which is more common and occurs in 90% of cases, often preceded by diarrheal syndrome induced by enterohemorrhagic Escherichia coli. Alternatively, there is an atypical and rarer form associated with pneumococcal infection, dysregulation of the alternative complement pathway, and cases involving the use of cyclosporine. Hemolytic anemia is confirmed in laboratory analyses (presence of fragmented red blood cells, decreased hemoglobin, undetectable haptoglobin values, and elevated LDH values), along with thrombocytopenia and an increase in nitrogenous substances (urea and creatinine).

Case report: The report details the case of an 18-month-old girl who experienced acute renal insufficiency subsequent to a respiratory infection. Ten days preceding admission, the patient exhibited nasal discharge, and during the seven days leading up to hospitalization, she presented with fever. Furthermore, two days prior to admission, the onset of persistent vomiting and abdominal pain occurred. Suspected of bowel intussusception, the patient underwent a surgical assessment where acute surgical pathology was ruled out. The absence of urination, coupled with heightened urea and creatinine levels, prompted consideration of hemolytic-uremic syndrome, later confirmed as atypical during hospitalization. This was grounded in the clinical presentation, devoid of diarrhea syndrome but marked by nasal discharge over the preceding ten days. The administration of fresh frozen plasma yielded no improvement, and there were decreased values of the C3 complement component, H factor, and reduced ADAMTS13 activity. The lack of verotoxins from enterohemorrhagic Escherichia coli further supported the diagnosis of atypical hemolytic-uremic syndrome. After the first dose of eculizumab, a terminal complement C5 component inhibitor, the girl recovered renal function and established diuresis.

Conclusion: The prompt diagnosis of atypical hemolytic-uremic syndrome is challenging due to nonspecific symptoms like nasal discharge, vomiting, fatigue, and abdominal pain. Laboratory analyses, lacking specific criteria, make it difficult to conclusively identify aHUS at the disease's onset. In Serbia, pneumococcal immunization is recommended as a preventive measure, administered through a conjugated vaccine in three doses starting from the second month of life. Rapid and accurate differentiation between typical and atypical HUS is crucial for effective treatment and prognosis. Typical HUS requires hemodialysis and plasmapheresis, whereas atypical HUS is managed with plasmapheresis, immunosuppressive therapy, and eculizumab. Administering eculizumab heightens the risk of meningococcal infection by inhibiting the C5 complement component. Therefore, it is crucial not to disregard the importance of meningococcal immunization.

Keywords: atypical hemolytic uremic syndrome, pneumococcus, renal failure, complement system, eculizumab.

INTRODUCTION

Atypical Hemolytic Uremic Syndrome (aHUS) represents a complex and rare disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Unlike its more common counterpart, aHUS is associated with diverse etiologies, including dysregulation of the alternative complement pathway, pneumococcal infections, and drug-induced cases, necessitating a comprehensive understanding for accurate diagnosis and targeted therapeutic interventions (1).

Among all aHUS cases, 40% are induced by an invasive strain of pneumococcus that secretes neuraminidase, an enzyme breaking down neuraminic acid coating renal endothelium, red blood cells, platelets, and hepatocytes. This results in the exposure of the Thomsen-Friedenreich (TF) antigen, subsequently triggering the activation of the immune system and coagulation cascades. Other forms of atypical HUS result from dysregulations in the alternative complement pathway activation, specifically mutations in genes encoding complement regulatory factors H (CFH) and I (CFI), which inactivate the C3b complement component (2).

The rarest form of atypical HUS involves a mutation in the gene responsible for synthesizing the liver protease ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13). This protease acts enzymatically on von Willebrand factor (vWF), cleaving it into smaller peptides. In the absence or reduced activity of ADAMTS13, von Willebrand factor circulates as a large polypeptide, facilitating platelet adhesion and contributing to the formation of microthrombi in circulation (3, 4). This case report shows the simultaneous occurrence of pneumococcal infection, reduced activity of the ADAMTS13 protease, and activation of the alternative complement pathway.

CASE REPORT

An 18-month-old girl, conscious but visibly unwell, arrived at the surgical ward presenting with fever, tachypnea, lethargy, and widespread edema. The primary concerns leading to admission were persistent vomiting and abdominal pain, raising suspicion of an acute surgical condition. Symptom onset occurred ten days prior, marked by escalated nasal discharge and, over the preceding seven days, the patient exhibited ongoing fever along with a notable episode of vomiting greenish contents observed the day before admission.

Despite the implementation of intravenous rehydration protocols, the patient's condition showed no improvement, and alongside continuous vomiting, anuria was diagnosed. Acute surgical pathology was effectively ruled out. Biochemical analyses revealed elevated urea levels at 21.8 mmol/L, creatinine at 261 µmol/L, thrombocytopenia at 81.4 x 10^9, and anemia with hemoglobin at 81.7 g/L and Red Blood Cell count at 3.06 x 10^{12}/L. This constellation of findings raised suspicion of hemolytic-uremic syndrome. With diuretic stimulation proving ineffective and anuria persisting, a dual-lumen catheter was inserted into the right femoral vein, initiating venovenous hemodialysis. Simultaneously, a fifteen-day regimen of fresh frozen plasma infusions was initiated. Unfortunately, during this period, a satisfactory diuretic response was not achieved, as it did not exceed 50 ml in 24 hours.

During the course of hospitalization, a series of examinations were undertaken to further assess the patient's condition:

Biochemical Analysis: Glucose: 4.36 mmol/L,- Total CO2: 16, Potassium (K): 4.9 mmol/L, Sodium (Na): 131 mmol/L, Chloride (C): 94 mmol/L, Calcium (Ca): 1.94 mmol/L, Magnesium (Mg): 0.82 mmol/L, Phosphorus (P): 2.23 mmol/L.

Liver Function Tests: AST: 330 U/L, ALT: 392 U/L, GGT: 7 IU/L, LDH: 8735 IU/L, Total Bilirubin: 9.7 µmol/L, Direct Bilirubin: 4.22 µmol/L, Total Proteins: 43, Albumin: 27 g/L.

Coagulation Tests: PT (Prothrombin Time): 13.4 s; 75%, aPTT (Activated Partial Thromboplastin Time): 23.2%, TT (Thrombin Time): 20.5 s, Fibrinogen: 4.4 g/l, D-dimers: 4040 ng/mL, AT III (Antithrombin III): 73%.

Immunology Panel: IgA: 0.589 g/L**,** IgM: 1.02 g/L**,** IgG: 6.65 g/L**,** Haptoglobin: 0.177 g/L**,** ANA (Antinuclear Antibodies) screen: 0.2**,** IgM anti-dsDNA: 2.8 IU/mL**,** IgG: 4.5 IU/mL**,** Anti-MPO: 1.3 U/mL**,**Anti-PR3 (Proteinase 3) antibodies: 2.4 U/mL.

Imaging and Cultures:

• Abdominal ultrasound and chest X-ray showed normal findings.

• Hemoculture indicated a negative result for coagulase-negative Staphylococcus.

• Urine culture was sterile.

• Nasal swab revealed Streptococcus pneumoniae, while the throat swab was sterile.

• Immunochromatographic stool testing did not detect the presence of Shiga toxins type 1 (STX1) and type 2 (STX2) from enterohemorrhagic Escherichia coli.

• The activity of ADAMTS13 metalloprotease was measured at 20%, falling below the reference range of 67-150%.

Complement and Coagulation Factors:

• Total complement activity, classical pathway (Hemolytic test): 40 CH50/mL (reference range 48-103 CH50/mL)

• Total complement activity, alternative pathway (WIELISA Alt): 71% (reference range 70-125%)

• Complement C3: 0.8 g/L (reference range 0.9–1.8 g/L)

• Complement C4: 0.15 g/L (reference range 0.15-0.55 g/L)

• Factor H antigen: 194 mg/L (reference range 250-880 mg/L)

• Complement Factor I antigen: 95% (reference range 70-130%)

• Complement Factor B antigen: 184% (reference range 70-130%)

• Anti-Factor H IgG autoantibody: 26 AU/mL (reference range < 110 AU/mL)

• C1q antigen: 33 mg/L (reference range 60-180 mg/L)

• Anti-C1q IgG autoantibodies: 15 U/mL (reference range < 52 U/mL)

• SC5b-9 (terminal complement complex): 255 ng/mL (reference range 110-252 ng/mL)

Tables 1 and 2 show the values of urea, creatinine, LDH, blood pressure, urine output, Red Blood Cells, hemoglobin, haptoglobin, and platelets at different stages of the disease, including the onset, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab.

Based on the patient's history (marked by the absence of diarrhea), clinical manifestations (persistent hemolysis despite fresh frozen plasma administration, and absence of diuresis), and laboratory findings (lack of verotoxin, decreased levels of C3 complement component and CFH, reduced ADAMTS13 activity, and isolation of Streptococcus pneumoniae in nasal swab), a diagnosis of atypical hemolytic-uremic syndrome (aHUS) was established. Consequently, treatment with eculizumab, a terminal complement C5 component inhibitor, was initiated. Notably, diuresis was restored, and renal function improved by the fifth day of eculizumab administration.

The patient received two doses of eculizumab during hospitalization, spaced three weeks apart, and continued the regimen post-discharge. Presently, having received 50 doses, the patient exhibits normal laboratory parameters and maintains good overall health. Furthermore, immediate meningococcal immunization was administered post-eculizumab treatment due to the heightened risk of meningococcal infection.

We obtained verbal and signed consent of the patient´s parents to publish the case report.

All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments.

DISCUSSION

In examining the case of the afflicted young girl, we can discern that atypical Hemolytic Uremic Syndrome (aHUS) manifested as a result of pneumococcal infection, with the activation of both the classical complement pathway and the alternative complement pathway (4). This activation is linked to reduced activity of serum factor H regulatory protein and hepatic ADAMTS13 protease. The invasive pneumococcus, equipped with its neuraminidase enzyme, cleaves neuraminic acid from renal endothelium, hepatocytes, erythrocytes, and platelets, leading to the subsequent exposure of the Thomsen-Friedenreich (TF) antigen. IgM TF antigen antibodies trigger the classical complement pathway by activating the C1 component, leading to the cleavage of complement component C4 into C4a and C4b. The C4b fragment then cleaves the C2 component (yielding C2a, C2b), resulting in the formation of C3 convertase (C4b2a). The C3 convertase of the classical pathway facilitates the cleavage of the C3 complement component into C3a and C3b. The C3b fragment subsequently binds to C3 convertase (C4b2a), initiating the assembly of C5 convertase

Table 1. *The values of urea, creatinine, LDH, blood pressure, as well as urine output, at the onset of the disease, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab*

	Urea	Creatinine	LDH	Blood pressure	Urine output
Disease onset	21.8 mmol/L	261 umol/L	8735 IJ/L	130/80 mmHg	50 mL/24
After hemodialysis and plasma exchange	24 mmol/L	247 umol/L	6543 IJ/L	120/75 mmHg	70 mL/24
After eculizumab	8.6 mmol/L	43 umol/L	631 IJ/L	100/60 mmHg	500 mL/24

Table 2. *The values of Red Blood Cells (RBC), hemoglobin (HGB). haptoglobin and platelets at the onset of the disease, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab*

	RBC	HGB	Haptoglobin	Platelets
Disease onset	$3.06x10^{12}$/L	70 g/L	0.02 g/L	$20x10^{9}$/L
After hemodialysis and plasma exchange	$3x10^{12}$/L	80 g/L	0.05 g/L	$100x10^{9}$/L
After eculizumab	$3.6x10^{12}$/L	107 g/L	1.3 g/L	$385x10^{9}$/L

for the classical complement pathway (C4b2a3b). The C5 convertase facilitates the breakdown of the C5 complement component into C5a and C5b, ultimately enabling the creation of the C5b-9 complex, which detrimentally affects endothelial cell membranes. Consequently, a cascade of thrombocytopenia, hemolysis, and acute renal insufficiency unfolds, indicated by reduced haptoglobin levels, elevated total bilirubin, and increased lactate dehydrogenase (2, 5, 6).

The alternative pathway of the complement system activation is continually active due to the spontaneous hydrolysis of the complement component C3. The C3b fragment binds to Bb, with factor B having undergone protease-mediated breakdown into the Bb fragment. This resultant C3bBb complex serves as the "C3 convertase of the alternative complement pathway," catalyzing the breakdown of fresh C3 complement components (C3a, C3b). Binding of the C3b fragment to C3bBb gives rise to the generation of C5 convertase of the alternative complement pathway (C3bBb3b). The subsequent breakdown of the C5 complement component results in the formation of the C5b-9 complex, also known as the membrane attack complex, which leads to the disruption of glomerular cell membranes. The alternative complement pathway, which is constantly active at a low rate, is rigorously governed by regulatory proteins—C1 inhibitor, C4-binding protein, complement factor H (CFH), and complement factor I (CFI)—all of which effectively inhibit its unwarranted activation (7, 8).

CFH is the most significant protein for regulating the activity of the alternative pathway of the complement system. This plasma protein has two binding sites for the C3b fragment of complement component C3 and, under normal physiological conditions, acts as a guardian, protecting the host from harm triggered by the alternative pathway activation. A deficiency or impairment in CFH function leads to intensified C3b fragment activity, increased complement system activation (resulting in C3a, C5a, C5b-9 production), endothelial cell damage, and the formation of blood clots within microvasculature (9).

Finally, the diminished activity of the hepatic proteolytic enzyme ADAMTS13, crucial for breaking down von Willebrand factor on the endothelial surface, culminates in heightened microthrombosis in circulation. This occurs because von Willebrand factor, being a substantial molecular entity, circulates and acts as a nexus for platelet adherence, consequently fostering the formation of microthrombi (10).

In any scenario, plasmapheresis stands out as the frontline treatment for both typical and atypical HUS when initiated at the disease onset. This approach effectively eliminates dysregulated, non-functional proteins that regulate both the classical and alternative pathways of the complement system. If, even after five consecutive daily plasma exchanges, hemolysis persists or renal function does not show improvement, it signifies uncontrolled aHUS—this is the case even if the platelet count returns to normal levels (2, 11, 12).

The presence of uncontrolled aHUS signals the need for treatment with a complement C5 component blocker, such as eculizumab, recommended for lifelong therapy. It is important to note that platelet transfusion is contraindicated due to the potential exacerbation of blood clot formation in the microvasculature of various organs (5).

CONCLUSION

While pneumococcal immunization may offer a preventive avenue for aHUS, the scarcity of this condition directs our primary attention to the treatment and complication prevention in affected children, particularly chronic kidney issues. The lifelong administration of eculizumab in cases like the one presented poses both practical and financial challenges, where hospital visits require physical and psychological effort, and the treatment itself is costly and sometimes difficult to obtain. These cases emphasize the crucial role pediatricians have in ongoing complication prevention and management. Furthermore, the disease's etiology highlights the susceptibility of pediatric patients to acute infections, posing a significant risk due to complement system disruptions. Notably, the use of eculizumab increases the vulnerability to meningococcal infections, underscoring the need for vigilant monitoring and preventive measures in this patient population.

Abbreviations

ADAMTS13 - a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
aHUS - Atypical Hemolytic Uremic Syndrome
CFH - complement regulatory factor H
CFI - complement regulatory factor I
HUS - Hemolytic Uremic Syndrome
TF antigen - Thomsen-Friedenreich antigen
vWF - von Willebrand factor

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Sažetak

MULTIFAKTORSKA ETIOLOGIJA ATIPIČNOG HEMOLITIČKO UREMIJSKOG SINDROMA - PRIKAZ SLUČAJA

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Uvod: Hemolitičko uremijski sindromi karakterišu se istovremenom pojavom hemolitičke anemije-,mikroangiopatije, trombocitopenije i akutne bubrežne insuficijencije. U odnosu na klinički prodrom mogu biti: tipični, koji je češći i javlja se u 90% obolelih kada mu prethodi dijarealni sindrom (izazvan enterohemoragičnom Escherichia coli) i atipični ređi oblik vezan za pneumokoknu infekciju, poremećaj aktivacije komplementa alternativnim putem i kod upotrebe ciklosporina. U laboratorijskim analizama potvrđuje se hemolizna anemija (nalaz fragmentisanih eritrocita, sniženje hemoglobina, nemerljive vrednosti haptoglobina i povišene vrednosti LDH), trombocitopenija i porast azotnih materija (uree i kreatinina).

Prikaz slučaja: U radu je prikazan slučaj obolele devojčice uzrasta 18 meseci kod koje je nakon respiratorne infekcije došlo do razvoja akutne bubrežne insuficijencije. Deset dana pre toga devojčica je imala sekreciju iz nosa, a poslednjih sedam dana pre hospitalizacije imala je temperaturu. Takođe, dva dana pre prijema, počelo je povraćanje sa bolovima u stomaku koji nisu prestajali. Nakon konsultacije hirurga, a zbog sumnje na invaginaciju creva, isključeno je akutno hirurško oboljenje, a kako dete nije mokrilo, uz povišene vrednosti uree i kreatinina, posumnjalo se na hemolitičko uremijski sindrom koji je u daljem toku hospitalizacije i dokazan kao atipičan i to na osnovu kliničke slike u kojoj nije bilo dijarejalnog sindroma, ali je dete imalo sekreciju iz nosa unazad deset dana. Takođe, na primenu sveže smrznute plazme nije došlo do poboljšanja, a tu su i snižene vrednosti C3 komponente komplementa, H faktora i snižena aktivnost ADAMTS13, kao i odsustvo verotoksina enterohemoragične E. koli što sve govori u prilog postavljanja dijagnoze aHUS-a. Nakon prve doze ekulizumaba – terminalnog inhibitora komplementa C5 komponente, devojčica je oporavila bubrežnu funkciju i uspostavila diurezu.

Zaključak: Rano dijagnostikovanje aHUS-a je izuzetno teško jer kliničkom slikom dominiraju nespecifični simptomi kao što su sekrecija iz nosa, povraćanje, malaksalost i bolovi u stomaku. Takođe, ni u laboratorijskim analizama nema specifičnog kriterijuma koji bi nagovestio aHUS na samom početku bolesti. Kao meru prevencije možemo savetovati imunizaciju protiv pneumokoka koja se u našoj zemlji obavlja konjugovanom vakcinom u tri doze, počev od drugog meseca života. Takođe je neophodno precizno i brzo razlikovanje tipičnog od atipičnog HUS-a jer od toga zavisi lečenje i prognoza bolesti, jer se tipični HUS leči hemodijalizom i plazmaferezom, dok se atipični leči plazmaferezom, imunosupresivnom terapijom i ekulizumabom. Ne sme se zaboraviti na imunizaciju protiv meningokoka kada se primenjuje ekulizumab, zbog njegovog inhibitornog dejstva na C5 komponentu komplementa, što povećava rizik od meningokokne infekcije.

Ključne reči: atipični hemolitičko uremijski sindrom, pneumokok, bubrežna insuficijencija, sistem komplemenata, ekulizumab.

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