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Case Report

Immunodeficiency and hemolytic uremic syndrome: a case report

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ABSTRACT

Background. Ataxia-telangiectasia (A-T) is a rare, autosomal recessive disorder characterized by cerebellar ataxia, oculocutaneous telangiectasia, and immunodeficiency, predisposing affected individuals to recurrent and severe infections. This case report presents a rare example of Shiga toxin-producing *Escherichia coli* (STEC)-associated hemolytic uremic syndrome (HUS) in a 12-year-old boy with a known diagnosis of A-T. To our knowledge, this is the first reported case of STEC-HUS in a patient with A-T.

Case Presentation. The patient presented with vomiting and bloody diarhea Investigations revealed hemolytic anemia, thrombocytopenia, and acute kidney injury. The patient received intravenous immunoglobulin, albumin, and continuous renal replacement therapy and recovered.

Conclusion. This case highlights the increased susceptibility of individuals with A-T to infections and the potential for life-threatening complications, such as HUS. The coexistence of A-T and STEC-HUS presentes unique challenges in diagnosis and management. Early recognition and targeted treatment led to a successful recovery and underscored the importance of close follow-up in immunodeficient patients.

Key words: ataxia telangiectasia, hemolytic uremic syndrome, Shiga toxin, immunodeficiency.

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. While it is often caused by Shiga toxin-producing *Escherichia coli* (STEC), it can also arise from inherited mutations in complement-regulating proteins and endothelial damage disorders. The activation of the complement system leads to vascular wall thickening and the formation of fibrin- and thrombocyte-rich thrombi in the microcirculation, resulting in impaired end-organ function, primarily affecting the kidneys or brain. Schistocyte formation and hemolysis are triggered by increased shear stress in partially obstructed vessels, while thrombocytopenia results from platelet consumption and immune-mediated destruction.[1]

Ataxia telangiectasia (A-T) is an autosomal recessive disorder marked by cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility, and radiation sensitivity.[2] A-T is considered a genome instability syndrome, with a global prevalence of approximately 1 in 40,000 to 1 in 100,000 live births.[3] Patients with A-T commonly present with immunological abnormalities, including deficiencies in immunoglobulins and antibodies, as well as lymphopenia. These immunodeficiencies lead to an increased risk of infections and malignancies, particularly of lymphoid origin, alongside frequent issues

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related to pulmonary function, feeding, swallowing, and nutrition.[4]

Approximately two-thirds of patients with A-T exhibit significant immune system abnormalities, including low levels of immunoglobulins (IgG, IgA, IgM, or IgG subclasses), impaired antibody responses to infections and vaccinations, and T-lymphocyte lymphopenia. All these factors predispose individuals to severe infections and complications.[4,5]

This case presentation aims to highlight the clinical features and complications of HUS associated with STEC infection in a patient with underlying A-T, emphasizing the importance of recognizing and managing infections in this disorder.

Case Report

A 12-year-old male, weighing 28 kg, with a known diagnosis of A-T, presented to an tertiary care center with complaints of vomiting and bloody diarrhea for 3-day history. The patient was receiving monthly intravenous immunoglobulin (IVIG) therapy at a dose of 0.4 g/kg due to IgA and IgG deficiency. Prior to the onset of HUS, the patient's baseline serum creatinine level was 0.5 mg/dL, which was within normal limits.

The patient's vital signs at presentation were as follows: SpO_2 93% on room air (98% with 6 L/min oxygen via mask), heart rate 140 bpm, and blood pressure 140/90 mmHg (95th percentile: 120/80 mmHg). Physical examination revealed crepitant rales, a tense abdomen, pretibial edema, and ascites.

Laboratory tests revealed elevated uric acid and lactate dehydrogenase (LDH) levels and decreased complement 3 (C3; 0.81 g/L) and C4 (0.06 g/L) levels. Haptoglobin was notably low at 0.02 g/L, and peripheral blood smear confirmed microangiopathic hemolytic anemia with the presence of schistocytes. Additionally, the patient exhibited significant proteinuria (3+) with a urinary protein-to-creatinine ratio of 3 mg/mg (normal range: <0.2 mg/mg). Renal ultrasound demonstrated increased parenchymal echogenicity in both kidneys, consistent with grade 1 changes. Shiga toxin was tested in the stool sample, confirming STEC infection, and the patient tested positive for STEC with *stx1* and *stx2* genes detected by reverse transcription polymerase chain reaction. Other exclusion tests, including ADAMTS-13 activity, homocysteine, and vitamin B_{12} levels, were all within normal limits (Table I).

Based on the clinical presentation of hemolysis, acute renal failure, and thrombocytopenia, the patient was diagnosed with HUS secondary to STEC infection (STEC-HUS).

The patient was transferred to our pediatric intensive care unit for further management. Upon admission, the patient's immunoglobulin levels were found to be IgG 5.4 g/L (normal range: 7.41-15.13 g/L) and IgA 0.04 g/L (normal range: 0.57-3.5). He was administered IVIG at a dose of 1 g/kg and intravenous albumin at 1 g/kg, followed by diuretic therapy. Despite initial treatment, the patient showed persistent oliguria (urine output: 0.4 mL/kg/hr), necessitating continuous renal replacement therapy (CRRT). Prior to catheter insertion, erythrocyte suspension and platelet suspension transfusions were provided due to anemia (hemoglobin < 6 g/dL) and active bleeding associated with severe thrombocytopenia (< 30,000 /μL).

After 72 hours of CRRT, the patient's urine output improved to an adequate level, allowing for the discontinuation of dialysis. By the ninth day, the patient was fully enterally fed, remained stable on room air with normal vital signs, and had adequate urine and stool output. He was subsequently transferred to the clinic for continued follow-up related to his A-T. At discharge, laboratory tests revealed a hemoglobin level of 10 g/dL, proteinuria of 0.4 mg/mg, urea of 24 mg/dL, and creatinine of 0.6 mg/dL.

Table I. Laboratory values at admission, peak, and discharge with normal ranges in brackets.

Parameter, normal range	Admission	Peak value	On 9th day of admission
Renal function			
Urea (mg/dL, 11-36)	176	198	64
Creatinine (mg/dL, 0.24-0.41)	2.57	4.06	1.1
GFR (mL/min/1.73m^2, >60)	22	46	
Uric acid (mg/dL, 3.4-7)	6.6	7.5	2.5
Phosphate (mg/dL, 2.9-5.1)	5.5	5.8	4.5
Calcium (mg/dL, 9.4-10.2)	7.8	7.5	8.9
Liver function & inflammation			
AST (U/L, <40)	78	80	38
ALT (U/L, <40)	65	70	24
GGT (U/L, <60)	13	50	15
LDH (U/L, 120-300)	1571	1743	1070
CRP (mg/L, <5)	172	172	8.5
Procalcitonin (μg/L, <0.5)	3.6	3.6	0.5
Albumin (g/dL, 3.5-5.5) lowest	2.35	2.2	3.0
Hematologic parameters			
WBC (x10^3/μL, 4-16)	19.4	19.4	6.6
Neutrophils (x10^3/μL, 1.7-5.3)	15.8	15.8	2.9
Lymphocytes (x10^3/μL, 0.8-7.1)	1.0	0.6	0.9
Hemoglobin (g/dL, 10-12.5)	8.7	5.8	5.9
Platelets (x10^3/μL, 150-400)	39	39	66
Haptoglobin (g/L, 0.3-2)	0.02		
Homocysteine (μmol/L, <12)	8.6		
Vitamin B_{12} (pg/mL, >400)	394		
Immunologic parameters			
Complement 3 (g/L, 0.9-1.8)	0.81		
Complement 4 (g/L, 0.1-0.4)	0.06		
IgA (g/L, 0.57-3.5)	0.04		
IgG (g/L, 7.41-15.13)	5.14		
IgM (g/L, 0.35-2.39)	2.07		
Total IgE (g/L, <200)	2.06		

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, Ig: immunoglobulin, LDH: lactate dehydrogenase, WBC: white blood cells.

During the first week, the patient's clinical condition stabilized. Two weeks later, thrombocytopenia, hypertension, and anemia had resolved, and at the two-month follow-up, no proteinuria was detected. At the two-month follow-up, hemoglobin was 12 g/dL, urinary protein was 0.10 mg/mg creatinine, urea was 22 mg/dL, and creatinine was 0.5 mg/dL, all within normal limits for age and sex, and no proteinuria was detected. The pediatric nephrology outpatient clinic recommended follow-up every 3 months to 1 year to monitor the patient's renal function and overall progress. The patient's clinical and laboratory data for the third month following discharge are unavailable.

Table II. Review of cases involving immunodeficiencies complicated by HUS, including clinical, and treatment data.

Case #	Reference	Age, sex	Underlying immunodeficiency	Hematologic findings	Renal findings	Neurological findings	Other clinical findings	Initial treatment	Ongoing treatment	Outcome
1	Nikolajeva et al. [8]	2 mo, male	ADA deficiency	Red cell fragmentation, thrombocytopenia	AKI with nephritic syndrome, required plasmapheresis and peritoneal dialysis	Lethargy, irritability	Multi-organ failure; Prior pneumonia (no pathogen isolated)	Plasmapheresis, peritoneal dialysis	None	Exitus
2	Nikolajeva et al.[8]	16 mo, female	ADA deficiency	Evolving HUS, mild anti-complement factor H autoantibodies	Persistent proteinuria, treated with hemofiltration and plasma exchange	Seizures, visual loss	Hypertension, CKD, vomiting, lethargy (no pathogen isolated)	Hemofiltration, plasma exchange, PEG-ADA	PEG-ADA, gene therapy, enzyme replacement	Alive
3	Nikolajeva et al.[8]	6 yr, male	ADA deficiency	HUS with red cell fragmentation, schistocytes, low fibrinogen	Failure to improve with eculizumab, remained plasmapheresis-dependent	Lethargy, irritability	Reduced Hb	PEG-ADA, eculizumab, plasma exchange	None	Exitus
4	Nikolajeva et al.[8]	9 mo, male	ADA deficiency	No schistocytes or coagulopathy	Renal failure requiring RRT for 30 days (hemofiltration, peritoneal dialysis)	None	*Streptococcus pneumoniae*-positive, two-week diarrhea and fever	Supportive care, PEG-ADA	Gene therapy with lentiviral vector	Mild residual renal impairment
5	Keller et al.[9]	2.5 mo, male	SCID	Megaloblastic anemia, leukopenia, thrombocytosis	Atypical HUS	Seizures, mild hearing loss, intellectual disability	Eczema, recurrent infections	OHCbl, folate, betaine, IgG, TMP-SMX	OHCbl, MeCbl, folate, methyl folate, betaine, IgG	Alive
6	Sudhakar et al.[10]	8 yr, male	X-linked agammaglobulinemia	No hematologic abnormalities	HUS associated with *Citrobacter freundii*	None	Suspected enteroviral myelitis, recurrent sinopulmonary infections, *Giardia lamblia* gastroenteritis, pneumococcal septic arthritis	Hemodialysis, IV methylprednisolone, IVIG, ceftriaxone	IVIG (400 mg/kg/month), azithromycin prophylaxis, tapering prednisolone	Alive

ADA: adenosine deaminase, AKI: acute kidney injury, aPTT: activated partial thromboplastin time, CKD: chronic kidney disease, CMV: cytomegalovirus, CVID: common variable immunodeficiency, EBV: Epstein-Barr virus, Hb: hemoglobin, HUS: hemolytic uremic syndrome, HSV: herpes simplex virus, IgG: immunoglobulin G, IV: intravenous, IVIG: intravenous immunoglobulin, MeCbl: methylcobalamin, mo: months, OHCbl: hydroxocobalamin, PEG-ADA: PEG-ylated adenosine deaminase, PJP: Pneumocystis jirovecii pneumonia, PT: prothrombin time, RRT: renal replacement therapy, SCID: severe combined immunodeficiency, STEC: Shiga toxin-producing Escherichia coli, TMP-SMX: trimethoprim-sulfamethoxazole, VZV: varicella-zoster virus, yr: years.

Table II. Continued.

Case #	Reference	Age, sex	Underlying immunodeficiency	Hematologic findings	Renal findings	Neurological findings	Other clinical findings	Initial treatment	Ongoing treatment	Outcome
7	Bogdał et al.[11]	15 mo	ADA deficiency	Megaloblastic anemia, thrombocytopenia	Atypical HUS	None	VZV (3 months), HSV (9 months), CMV, PJP (15 months)	Peritoneal dialysis (29 days), 8 cycles plasmapheresis, antihypertensives	None	Exitus
8	Milošević et al.[7]	5 yr	CVID	Microangiopathic hemolytic anemia, thrombocytopenia	Acute renal failure, atypical HUS	None	Generalized lymphadenopathy, hepatosplenomegaly, gallop rhythm, recurrent bacterial respiratory infections	Peritoneal dialysis (3 months), corticosteroids	IVIG (400 mg/kg/ month)	Exitus
9	Akcay et al. (Our case)	12 yr, male	Ataxia-telangiectasia	Megaloblastic anemia, thrombocytopenia, uremia	STEC-HUS, 72 hours dialysis	None	Recurrent sinopulmonary infections	Dialysis (discontinued after urine output improvement)	IVIG (400 mg/kg/ month)	Alive

ADA: adenosine deaminase, AKI: acute kidney injury, aPTT: activated partial thromboplastin time, CKD: chronic kidney disease, CMV: cytomegalovirus, CVID: common variable immunodeficiency, EBV: Epstein-Barr virus, Hb: hemoglobin, HUS: hemolytic uremic syndrome, HSV: herpes simplex virus, IgG: immunoglobulin G, IV: intravenous, IVIG: intravenous immunoglobulin, MeCbl: methylcobalamin, mo: months, OHCbl: hydroxocobalamin, PEG-ADA: PEG-ylated adenosine deaminase, PJP: Pneumocystis jirovecii pneumonia, PT: prothrombin time, RRT: renal replacement therapy, SCID: severe combined immunodeficiency, STEC: Shiga toxin-producing Escherichia coli, TMP-SMX: trimethoprim-sulfamethoxazole, VZV: varicella-zoster virus, yr: years.

Informed consent for the publication of this case report was obtained from the patient's parents.

Discussion

This case exemplifies the complex interplay between STEC and the immune vulnerabilities associated with ataxia telangiectasia (A-T). The patient's immunoglobulin deficiencies and history of recurrent infections significantly heightened the risk of severe complications, including STEC- HUS. Notably, this case represents the first documented instance of STEC-HUS in a patient with A-T, emphasizing the unique challenges faced by this population.

In the context of A-T, the patient's immune dysregulation—particularly the low levels of IgA and IgG—complicated the clinical presentation. As A-T predisposes patients to recurrent infections due to immunodeficiencies, as described by Amirifar et al.[2] and Rothblum-Oviatt et al.[4], this patient's immunocompromised state necessitated regular IVIG therapy to mitigate the risks associated with infections.

Talukder et al.[6] proposed that Shiga toxin plays significant role in celluler damage by activating the ATM/p53-dependent DNA damage signaling pathway. In A-T patients with muations in ataxia-telangiectasia (*ATM*) gene, the ATM pathway is already impaired. The ATM protein is essential for DNA repair and the maintenance of genomic stability, playing a crucial role in the cellular response to stress, such as DNA damage and oxidative stress.

When Shiga toxins are presented, they trigger the formation of reactive oxygen species that activate the ATM/p53 pathway, leading to DNA damage. In healthy individuals, the ATM protein facilitate DNA repair, but in A-T patients, ATM dysfunction impairs this repair process. This dysfunction can lead to increased DNA damage, increased cellular stress, and potentially promoting more severe clinical course of HUS.

When cellular damage combines with Shiga toxins-induced endothelial damage, the clinical course of STEC-HUS may worsen in patients with A-T. This interaction between Shiga toxin exposure and ATM dysfunction may increase microangiopathy, and renal and systemic complications in A-T patients, compared to those with normal ATM function.

Therefore, our case highlights the necessity of close monitoring of A-T patients at risk for infections like STEC, because any cellular and vascular that may develop could lead to critival outcomes. Taking this situation into account, developing management strategies is important to improve patient outcomes and reduce the risk of irreversible organ damage.[6]

Comparative analyses with other immunodeficiency cases complicated by HUS provide valuable insights (Table II).[7-11] Notably, four of these patients succumbed to their conditions following HUS, underscoring the serious importance of complications in immunocompromised patients. For example, Nikolajeva et al.[8] described patients with adenosine deaminase (ADA) deficiency, who developed atypical HUS (aHUS), presenting with acute kidney injury and requiring prolonged CRRT. Similar to our case, advanced therapeutic interventions, such as plasmapheresis and replacement therapy are often required to address both immunological and renal issues with ADA deficiency. Furthermore, Bogdał et al.[11] discussed the bidirectional exacerbation of ADA deficiency and aHUS, further emphasizing the need for individualized management strategies in primary immunodeficiencies.

Likewise, Sudhakar et al.[10] reported HUS in a patient with X-linked agammaglobulinemia (XLA), which involves profound B-cell deficiency. The clinical manifestations of HUS in XLA share similarities with those observed in A-T and ADA deficiencies, emphasizing the broader implications of immune dysregulation

in the pathogenesis of HUS. These comparisons highlight the necessity of integrating immune-modulatory therapies, such as IVIG, alongside renal support for optimal patient outcomes.

Our patient's successful recovery following three days of hemodialysis demonstrates the potential for positive outcomes when early and targeted interventions are employed, despite underlying immunodeficiency. As emphasized by Joseph et al.[1], timely initiation of supportive therapies, including dialysis when indicated, is critical in reducing morbidity and preventing long-term renal sequelae.

One of the limitations of our study is that it is a single case report. Additionally, cobalamin levels were not measured, nor was mutation analysis conducted to investigate a potential defect in the alternative complement system and the patient's clinical and laboratory data for the third month following discharge are unavailable.

In conclusion, this case underscores the importance of recognizing the heightened risks and unique complications associated with primary immunodeficiencies, such as A-T, in patients presenting with infectious diseases. Early detection of clinical signs, along with a multidisciplinary approach, is critical in mitigating severe complications and improving patient outcomes. Further research is needed to better understand the complex interactions between immune dysregulation and infectious diseases in high-risk populations.

Ethical approval

The informed consent form was obtained from the patient.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: NA, DT; data collection: İB; analysis and interpretation of results: NA, DT, İB; draft manuscript preparation: NA, DT, İB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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