CASE REPORT

Complement activation: an atypical presentation of an atypical syndrome

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SUMMARY

A 42-year-old Hispanic female and long-distance runner was seen for evaluation of fatigue. Her physical examination showed petechiae and ecchymoses in upper extremities, abdominal distension and bilateral ankle oedema. Laboratory workup revealed anaemia, thrombocytopenia, hypoalbuminemia and proteinuria of 1.4 g/24 hours. No schistocytes were found on peripheral blood smear. CT of her abdomen revealed diffuse small lymphadenopathy and hepatomegaly. Bone marrow biopsy demonstrated normal trilineage hematopoiesis with no hemophagocytosis. The patient was started on oral prednisone with no improvement and was subsequently admitted to the hospital for pulsed steroids, intravenous immunoglobulin and rituximab. Her proteinuria became nephrotic range, and a renal biopsy revealed features of thrombotic microangiopathy limited to the glomerular capillaries. ADAMTS13 was low which is >10% of normal, and a diagnosis of atypical haemolytic-uraemic syndrome (aHUS) was made. Eculizumab was started with prompt response. Whole exome sequencing demonstrated mutation in SPTA1, which has been associated with red blood cell membrane diseases but has not been described in patients with aHUS.

BACKGROUND

Atypical haemolytic-uraemic syndrome (aHUS) is a life-threatening disease affecting both paediatric and adult patients with a slight preponderance in younger patients and adult females. Uncontrolled activation of the alternative pathway of the complement system generates excess membrane attack complex causing renal endothelial damage and resultant microangiopathic haemolytic anaemia. Cases like this one are often misdiagnosed not allowing patients to receive adequate therapy on time. aHUS can be triggered by a variety of events in patients with known predisposing genetic abnormalities or acquired inhibitors of the complement regulator proteins. Our patient was found to bear a germline mutation not previously associated with this condition.

CASE PRESENTATION

A 42-year-old previously healthy Hispanic woman was referred to us in November 2014 for evaluation of decreased stamina, diffuse lymphadenopathy and hepatosplenomegaly. She first noticed a sensible decrease in her stamina and physical performance on long-distance running in September

2014. In late October, she sought medical attention and was found to have petechiae and subconjunctival haemorrhages on examination. When she came to see us, her main complaints were ankle swelling, fever, drenching night sweats, abdominal girth and shortness of breath. On physical examination, breath sounds were diminished at the right base, her abdomen was mildly distended, she had grade two bilateral ankle oedema and a few ecchymotic lesions in both upper extremities. Extensive workup revealed anaemia, thrombocytopenia and hypoalbuminemia as summarised in [table 1](#). A CT scan of the abdomen showed diffuse lymphadenopathy, hepatomegaly and findings consistent with hepatic adenoma. Twenty-four-hour urine protein concentration was 1.4 g/dL. Peripheral blood smear showed polychromasia, anisocytosis and ovalocytes, but no schistocytes or fragmented red blood cells; lactate dehydrogenase (LDH) was normal ([table 1](#)). A positron emission tomographic (PET)/CT scan revealed mildly enlarged lymph nodes in the axillary, retroperitoneal and pelvic regions and spleen with standardized uptake values (SUV) ranges from 2.6 to 4.5. A bone marrow biopsy was performed revealing normal trilineage hematopoiesis, no evidence of B or T cell clonality and no hemophagocytosis, ruling out hemophagocytic lymphohistiocytosis (HLH) as aetiology of the patient condition, as well as bone marrow invasion of any haematological malignant disease.

Thinking of a rheumatologic aetiology for this condition given a positive antinuclear antibody (ANA) of 1:80 (speckled pattern) and the patient's clinical presentation having diffuse lymphadenopathy, anaemia, thrombocytopenia and renal dysfunction, rheumatology was consulted. Differential diagnoses at this point included diseases like lupus systemic erythematosus and Evans syndrome. Further laboratory workup revealed elevated ferritin (645 ng/mL), elevated interleukin 2 (IL-2) receptor (2852 pg/mL) and normal C3 (125 mg/dL) and C4 (25 mg/dL) levels but with an elevated C5 (21 mg/dL). With a working diagnosis of macrophage activation syndrome, the patient was started on prednisone at a dose of 1 mg/kg/day.

Her oedema progressed, and cytopenias worsened. The patient was admitted to the hospital by the rheumatology service for high-dose steroids, intravenous immunoglobulin (IVIG) and rituximab.

After receiving 2 weeks of high-dose steroids, IVIG and rituximab, her complement levels started to drop as seen in [figure 1](#), while her anaemia and thrombocytopenia persisted and her proteinuria

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Table 1 First encounter laboratory data

Studies	Results	Normal values
Haemoglobin	9.9 g/dL	12–16 g/dL
Platelets	67 k/ μ L	150–450 k/ μ L
Creatinine	1.1 mg/dL	0.7–1.3 mg/dL
Alkaline phosphatase	196 U/L	36–92 U/L
Albumin	2.9 g/dL	3.5–5.5 g/dL
ESR	82 mm/min	0–20 mm/min
ANA	Positive 1:80 (speckled pattern)	Negative
LDH	150 U/L	(50–160 U/L)
Peripheral blood smear	No schistocytes	Normal

Source: patient clinical history.

ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

increased to nephrotic range (4.2 g/24 hours). No schizocytes were visualised in peripheral blood smears, LDH continued to be negative and haptoglobin was mildly elevated (253 mg/dL) for which a nephrology consult was obtained, and a renal biopsy revealed features of thrombotic microangiopathy limited to the glomerular capillaries (figure 2). ADAMTS13 was 43, low, but more than 10% of normal, ruling out thrombotic thrombocytopenic purpura (TTP) (table 2); as such, a diagnosis of aHUS was established given the clinical features of the patient.

Eculizumab (Soliris® by Alexion pharmaceuticals) was started at an induction dose of 900 mg/week for 1 month, followed by maintenance doses of 1200 mg every other week. Response to eculizumab therapy is shown in figure 3. The patient was maintained on eculizumab and 3 years later continued to have normal blood counts and no clinical or laboratory signs of aHUS.

She is carrying on a normal life and has gone back to running. Whole exome sequencing (WES) was performed finding no mutations relevant to aHUS.

INVESTIGATIONS

- ▶ CT scan of the chest, abdomen and pelvis showed diffuse lymphadenopathy in the three regions as well as hepatomegaly. A 3.6×3.6 cm mass in the left lobe of liver was later identified with MRI abdomen showing being hypointense on T1 and hyperintense on T2 with enhancement of intravenous contrast, compatible with hepatic adenoma.
- ▶ PET/CT scan revealed mildly enlarged lymph nodes in the axillary, retroperitoneal, pelvic regions and spleen with SUV ranges from 2.6 to 4.5.
- ▶ Follow-up CT of the abdomen and pelvis (post-eculizumab), disclosed resolution of the multiple retroperitoneal and pelvis lymphadenopathy and stable hepatic adenoma.

Figure 1 Trend of complement levels after initial presentation.

Figure 2 Electron+light microscopy of renal biopsy. (A) A glomerulus with thickening and duplication of the glomerular basement membrane. A few inflammatory cells are noted in some glomerular capillary lumina. (B) Immunostain for macrophage (CD68) shows that some of these cells are macrophages. (C) T cells (CD3) are not seen in this glomerulus. (D) Electron microscopic study shows marked enlargement of the lamina densa by electron: fluffy material (fm), loss of mesangial matrix (mm) and few inflammatory cells (ic) in the glomerular capillary lumina. Original magnification ×400 for panels A–C and ×3000 for panel D.

- ▶ Bone marrow biopsy was performed revealing normal trilineage hematopoiesis, no evidence of B or T cell clonality and no hemophagocytosis.
- ▶ Renal biopsy revealed features of thrombotic microangiopathy limited to the glomerular capillaries.
- ▶ WES was ordered and came back positive for a heterozygous mutation in c.6968T>A (p.L2323Q) of the SPTA1 gene.
- ▶ HLH genetic panel is negative.
- ▶ aHUS genetic panel is negative
- ▶ Anti-factor H antibody is negative.

DIFFERENTIAL DIAGNOSIS

- ▶ HLH
- ▶ Evans syndrome

Table 2 Thrombotic microangiopathy workup and genetic panels for HLH and aHUS

Studies	Results	Normal values
ADAMTS13	43	63
Antiplatelet antibody IgG/IgM	Negative	Negative
sCD163	922 mg/mL	(387–785 ng/mL)
Factor H auto-antibody I	<22 U/mL	<22 U/mL
aHUS genetic panel (CFH, CD46, CFI, C3, CFB, CFHR1, CFHR3, CFHR4, CFHR5, thrombomodulin, plasminogen and DGKE)	Negative	Negative
HLH Genetic panel (AP3B1, BLOC1S6, ITK, LYST, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXB2P, TNFRSF7, UNC13D, XIAP)	Negative	Negative

Source: patient clinical history.

aHUS, atypical haemolytic–uraemic syndrome; DGKE, encoding diacylglycerol kinase epsilon; HLH, hemophagocytic lymphohistiocytosis.

Figure 3 Hospital course and response to eculizumab.

- ▶ Macrophage activation syndrome
- ▶ Lupus systemic erythematosus
- ▶ TTP
- ▶ Cancer-associated thrombotic microangiopathy
- ▶ Lymphoma

TREATMENT

Eculizumab (Soliris® by Alexion pharmaceuticals) was started at an induction dose of 900 mg/week, followed by maintenance doses of 1200 mg every other week.

OUTCOME AND FOLLOW-UP

Eculizumab (Soliris by Alexion pharmaceuticals) was started at an induction dose of 900 mg/week for 1 month, followed by maintenance doses of 1200 mg every other week. Response to eculizumab therapy is shown in figure 3. The patient was maintained on eculizumab and 2 years later continued to have normal blood counts and no clinical or laboratory signs of aHUS or lymphoproliferative disorder. She is carrying on a normal life and has gone back to running. She underwent arterial embolization of the hepatic adenoma and multiple follow-up CT scans have shown resolution of lymphadenopathy and hepatomegaly.

DISCUSSION

Patients who present with the classical triad of anaemia, thrombocytopenia and acute kidney injury should raise a suspicion for thrombotic microangiopathy (TMA).¹⁻³ Our patient presented with anaemia, thrombocytopenia and mild proteinuria >1 g/24 hours. Despite having anisocytosis, ovalocytes and polychromasia, we failed to find fragmented red blood cells (FRBCs) in the peripheral blood smear (PBS), and her LDH was within normal limits. She was referred to us for evaluation of diffuse lymphadenopathy. Her PET/CT and bone marrow biopsy were non-specific or diagnostic of lymphoproliferative disorder. The patient was referred to rheumatology for evaluation given her clinical and laboratory findings. Elevated IL-2 receptor, ferritin and low NK cell activity—all markers of macrophage activation—were present, and the patient was started on glucocorticoids. This dissuaded us from obtaining a lymph node biopsy to rule out indolent lymphoma. The patient's renal function continued to worsen despite steroid treatment, and she was admitted to the hospital for initiation of high-dose steroids, IVIG and rituximab.⁴

The patient's renal function continued to deteriorate, and her proteinuria reached nephrotic range. At that point, we felt that a kidney biopsy would be

diagnostic and nephrology agreed to pursue it despite her low platelets.

With the pathognomonic finding of TMA by light and electron microscopy and a low ADAMTS13, but more than 10% of normal, we ruled out TTP and established the diagnosis of aHUS, and eculizumab was started with excellent response and tolerance. Although the diagnosis of aHUS can be challenging, in most patients who present with anaemia and thrombocytopenia, a simple PBS may give the diagnostic clue if FRBCs are found. An elevated LDH and a low haptoglobin with the aid of ADAMTS13 would make the final diagnosis.

Our patient had an atypical presentation given the absence of typical laboratory findings and very unspecific clinical signs and symptoms. With the aid of the kidney histological findings and ADAMTS13 level, we were able to differentiate among acute kidney injury in the setting of TTP, cancer-associated TMA and our final diagnosis of aHUS.^{5 6}

This heterogeneous disease has been associated with different triggers like cancer, chemotherapeutic agents, viral infections and even pregnancy. The early use of corticosteroids in our patient interfered with our ability to make a diagnosis of lymphoproliferative disease as a trigger for her uncontrolled complement response.^{7 8}

Eculizumab (Soliris® by Alexion pharmaceuticals) is a monoclonal antibody that targets C5 complement protein in order to block the formation of membrane attack complex (MAC). It was approved by the Food and Drug Administration for the treatment of paroxysmal nocturnal hemoglobinuria and aHUS. After initiation of eculizumab, counts recovered in 7 days with a net decrease in proteinuria values of 95% after the first dose.^{9 10}

Usually, as was stated in the background section, the exaggerated activation of the alternate complement cascade can be explained by genetic mutations (60%) or antibody production against regulatory elements (10%).¹¹ Genetic panels were ordered in our patient as well as acquired antibodies, all with negative results.

In 2015, 11 new pathogenic variants, 12 likely pathogenic variants and 68 variants of unknown significance (17 novel variants) were described to be present in patients with aHUS¹²; using this rationale, a WES was ordered and came back positive for a heterozygous mutation in c.6968T>A (p.L2323Q) of the SPTA1 gene which has been associated with red blood cell fragmentation syndromes such as eliptocytosis 2, spherocytosis 3 and hereditary pyropoikilocytosis. Although mutations in this gene have not been associated with aHUS yet, they certainly raise the possibility of adding to our understanding of the pathogenesis of this disease.¹²⁻¹⁴

Only speculations can be made in the mechanism of developing aHUS due to a disruption of the normal erythrocyte membrane given the presence of SPTA1 gene mutation. The combination of an indolent lymphoma (that was unable to confirm due to the previous treatment with steroid) and the likely presence of an erythrocyte membrane abnormality could act as a trigger to activate the complement cascade leading to the pathognomonic microangiopathy limited to the glomerular capillaries observed in our patient kidney biopsy.

Further investigation will be needed to determine the validity of this hypothesis, but the fact that the patient improved clinically and biochemically told us that the patient diagnosis of aHUS was concluding and the precise treatment was started.

Speculations regarding the pathogenesis of aHUS in the presence of SPTA1 gene mutations alone or in combination with other known triggers can be made. Could patients with these or other mutations be predisposed to developing aHUS in the

presence of known triggers? Further investigations are warranted to better understand the multiple possible associations between predisposing genetic traits and acquired triggers that may lead to uncontrolled complement activation and development of aHUS. We are certain that our patient improved dramatically both clinically and biochemically and has resumed a normal life with our diagnosis and treatment. How long to treat her with eculizumab remains unknown.

Learning points

- ▶ aHUS results from chronic, uncontrolled activation of the alternative pathway of the complement system.
- ▶ The current understanding is that they clinically present with a classical association of findings like anaemia with schistocytes, thrombocytopenia, renal dysfunction and neurological deficit which may or may not be present in all patients.
- ▶ In the presence of a common trigger (physical, biologic or chemical) and insufficient levels of these functional regulators, aHUS may develop.
- ▶ Prior to eculizumab, a terminal complement inhibitor, plasma exchange or transfusion therapy was associated with end-stage renal disease in 65% of cases and a 35% mortality rate. Currently, patients being treated with eculizumab benefit from normalisation of blood counts, proteinuria and kidney function.
- ▶ Further studies will be needed to prove the relation among SPTA1 gene mutation, erythrocyte membrane disease and the mounting of aHUS.

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explanation. HAP: general review of the manuscript, final and continuous editing, medical care of the patient, bibliographic review and data interpretation.

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