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Atypical hemolytic uremic syndrome after myomectomy: A case report

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy due to inability to regulate the complement cascade, resulting in thrombocytopenia, intravascular hemolysis, and end-organ damage. Over 70% of cases are associated with mutations in complement or complement regulatory proteins, and some two-thirds have recognized complement-activating conditions triggering an aHUS event. We describe a case of aHUS after abdominal myomectomy in a 42-year-old woman that was managed with plasma exchange and eculizumab (an anti-C5 monoclonal antibody). The diagnosis was confirmed by biopsy of normal-appearing deltoid skin that demonstrated microvascular C5b-9 deposition, diagnostic of systemic complement pathway activation. Although extremely uncommon following gynecologic surgery, aHUS should be considered in the setting of postoperative oliguric acute kidney injury, as prompt diagnosis is necessary to prevent significant morbidity and mortality.

1. Introduction

Thrombotic microangiopathy (TMA) comprises a spectrum of disorders marked by widespread microvascular thrombosis leading to hemolytic anemia and end-organ damage [1]. Atypical hemolytic uremic syndrome (aHUS) is a rare form of TMA characterized by uncontrolled activation of the alternate complement pathway leading to endothelial cell dysfunction, platelet activation, and deposition of microthrombi, leading to hemolytic anemia and renal impairment [2,3]. aHUS may be due to inherited abnormalities of proteins involved in the complement pathway, which are identifiable in 70% of cases, and may be triggered by complement-amplifying conditions such as pregnancy, infection, malignant hypertension, medications, and surgery, recognized in about two-thirds of cases [4–7].

Eculizumab and its long-acting counterpart, ravulizumab, are humanized monoclonal IgG antibodies that bind to complement protein C5, and are the only FDA-approved treatments for aHUS [8,9]. Prompt diagnosis and treatment are key to reducing the high degree of morbidity and mortality associated with aHUS. We describe a case of TMA with anuric acute kidney following abdominal myomectomy with a large amount of intra-operative blood loss that was ultimately diagnosed as aHUS and successfully treated with eculizumab.

2. Case presentation

A 42-year-old woman, gravida 1 para 1001, with symptomatic uterine fibroids was admitted to hospital for surgical management. She had had one prior Cesarean section but was healthy. Magnetic resonance imaging (MRI) revealed a large fibroid uterus with a total volume of 1830 mL (Fig. 1). Her preoperative hemoglobin (Hb) level was 11.2 g/dL, and the remainder of her laboratory data did not show any abnormalities in renal or hepatic function.

The patient underwent abdominal myomectomy via Pfannensteil incision, where at least ten intramural and subserosal fibroids were removed, weighing a total of 979 g, ranging in size from 1.4 cm to 14.0 cm. Estimated blood loss was 1700 mL, and 709 mL of intraoperative blood salvage was given back to the patient. Her course was complicated by oliguria intraoperatively, which progressed to anuria at five hours after surgery despite fluid resuscitation. She remained hemodynamically stable and had an appropriate abdominal exam. Laboratory values

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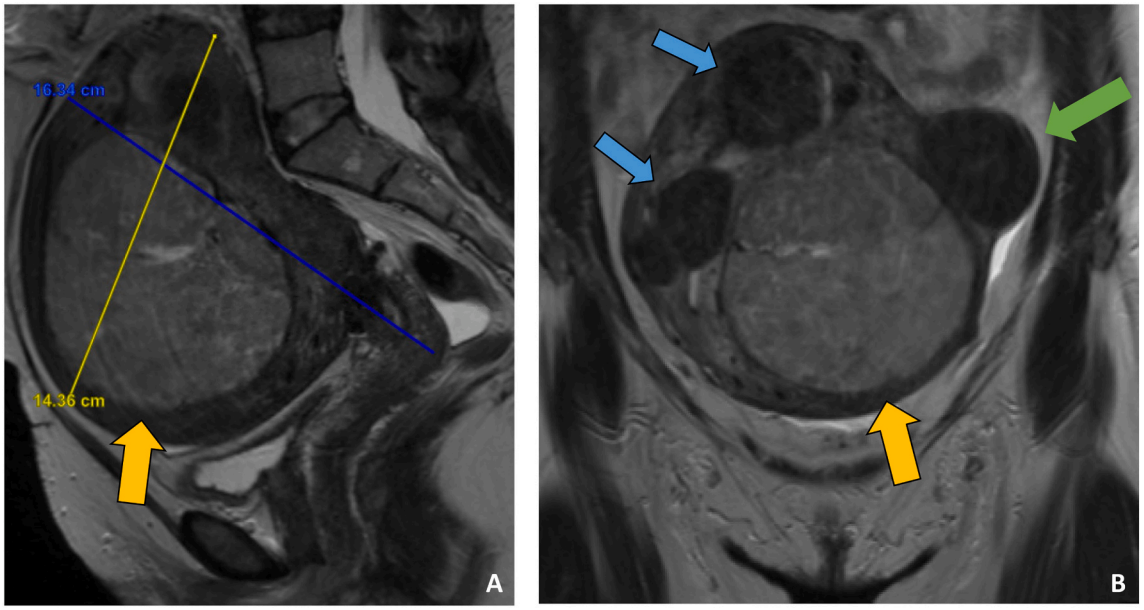

Fig. 1. Preoperative MRI findings four months prior to myomectomy. (A) T2-weighted sagittal MRI with markedly enlarged fibroid uterus and dominant 10.6 cm heterogeneously enhancing intramural left body leiomyoma (*yellow arrow*) (B) T2-weighted coronal MRI with dominant intramural fibroid (*yellow arrow)* and multiple other subserosal (*green arrow*) and intramural/submucosal fibroids (*blue arrows*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

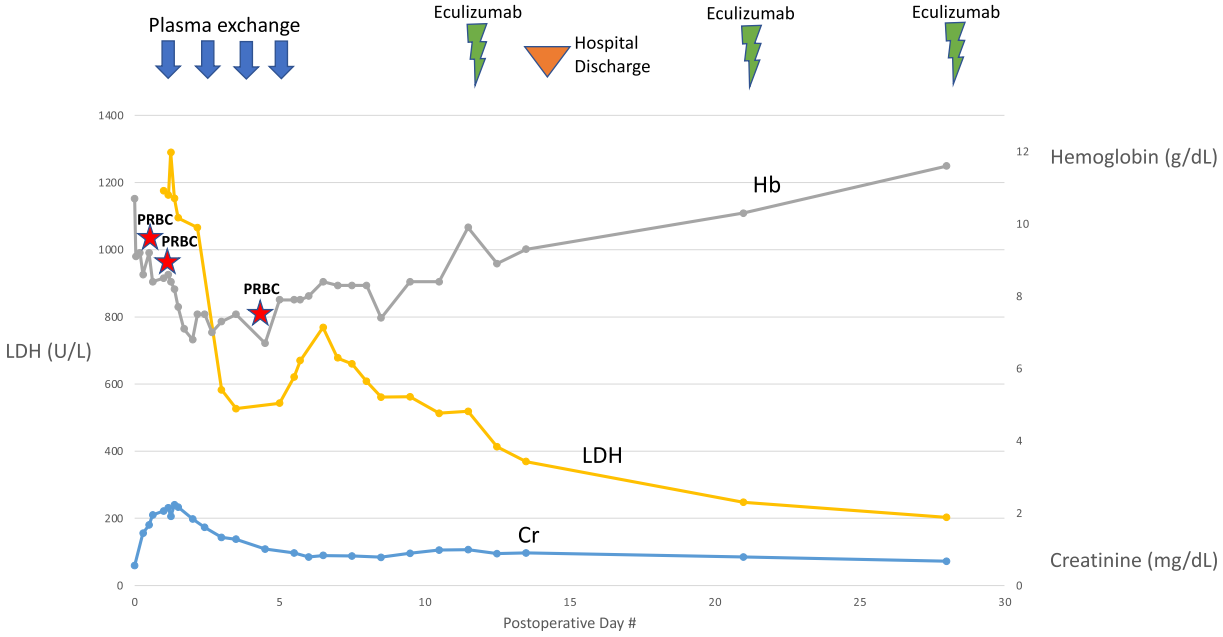

Fig. 2. Clinical course of the patient's case. LDH: lactate dehydrogenase, Hb: hemoglobin; Cr: creatinine, PRBC: 1 unit of packed red blood cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

revealed an expected Hb level of 8.6 g/dL, but with significant thrombocytopenia (platelets 86 $\times$ 10^3/μL) and acute kidney injury (AKI) with creatinine 1.45 mg/dL (Fig. 2).

On postoperative day 1, she was transfused two units of packed red blood cells given concern for acute blood loss anemia. Although urine output improved, her Hb did not show an expected rise and she continued to have worsening thrombocytopenia, to 53 $\times$ 10^3/μL, and renal dysfunction, with creatinine 1.95 mg/dL. Computed tomography angiography (CTA) showed no evidence of ongoing bleeding, and renal ultrasound did not demonstrate an obstructive etiology for her AKI. Further laboratory tests showed haptoglobin of <6 mg/dL, lactate dehydrogenase (LDH) 1290 U/L, reticulocyte count 3.46%, and blood smear with thrombocytopenia and many schistocytes (average 7 per high-power field) (Table 1). Her overall picture was concerning for evolving TMA, such as disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), or thrombotic thrombocytopenic purpura (TTP).

On postoperative day 2, the patient began daily plasma exchange due to intermediate risk for TTP, after which her creatinine and urine output improved (Fig. 2). She remained clinically stable with normal PT, aPTT and fibrinogen and no signs of bleeding, lowering concern for DIC. Platelet levels nadired to 29 $\times$ 10^3/μL and began to increase on

Table 1
Laboratory data for markers of hemolysis and complement levels.

Postoperative Day	1	2	6	10	14	28
Fibrinogen, activity (180–400 mg/dL)	166	434	191	444	479	
Haptoglobin (40–240 mg/dL)	<6	<6	32	88	179	195
Lactate Dehydrogenase LDH (118–230 U/L)	1176	1290	543	562	369	203
Reticulocyte count (%)	3.25	3.46	4.88	10.03	6.93	
ADAMTS13 Activity (%)		62				
ADAMTS13 Inhibitor (BU)		<0.4				
Complement, C3 (90–180 mg/dL)		88				
Complement, C4 (12–36 mg/dL)		22.7				
Complement Activity, Total (38.7–89.9 U/mL)		53.8				<12.5

postoperative day 5. At this time, laboratory results showed ADAMSTS13 activity of 62% with no inhibitor, making the diagnosis of aHUS more likely (Table 1).

By postoperative day 6, platelet levels improved to 90 × 10^3/μL and creatinine normalized to 0.73 mg/dL; however, her hemolysis markers, including LDH and haptoglobin, continued to worsen, concerning for ongoing hemolysis. A punch biopsy of normal-appearing deltoid skin was obtained by dermatology to assess for evidence of tissue complement deposition to help guide further management. Histology revealed eleven positive staining blood vessels for C5b-9 in the dermis and subcutaneous tissues, supporting the diagnosis of aHUS (Fig. 3). Genetic testing did not reveal any complement mutations. Eculizumab 900 mg was initiated intravenously on postoperative day 12, and she was discharged home on postoperative day 14 with stable hemoglobin, resolved thrombocytopenia, improving hemolysis markers, and a return to baseline renal function. The patient was doing well on 1200 mg biweekly maintenance eculizumab infusions for at least six months.

3. Discussion

We report a case of aHUS manifesting immediately after abdominal myomectomy with clinical and laboratory improvement following early plasma exchange; the patient ultimately continued recovery with eculizumab. TMA was suspected due to classic laboratory findings of thrombocytopenia, anuric AKI, and hemolytic anemia with peripheral schistocytes. As there were no signs of ongoing bleeding, and fibrinogen and bleeding time remained stable, DIC was determined to be less likely. She was initially treated with plasma exchange within 24 h of TMA diagnosis but this was eventually discontinued as normal ADAMST13 activity and absent inhibitor essentially ruled out TTP as an etiology. Atypical complement-mediated HUS was suspected as the likely cause of her TMA given no diarrheal illness suspicious for Shiga toxin-producing *Escherichia coli* (STEC) HUS and multiple reports in the literature of surgical stress leading to complement activation as a precipitating factor in aHUS, including myomectomy [6,10–13].

A coagulopathy following uterine myomectomy was first recognized as a potential complication as early as 1961 [14]. Many case reports describe DIC following myomectomy, with risk factors including marked degenerative change and/or massive size [15,16]. Both DIC and aHUS involve activation of the coagulation pathway and thrombocytopenia. However, hyperfibrinolysis is typical for DIC, while significant complement-mediated endothelial cell injury with resultant microvascular thrombosis and hemolytic anemia without hyperfibrinolysis is seen in aHUS [1]. Of interest is the fact that the uterine fibroids in this case showed marked degenerative changes (Fig. 4). It is very possible that there are certain common pathophysiologic events that underlie the development of both DIC and atypical HUS following myomectomy. For example, the release of large quantities of tissue factor from degenerating uterine myomas could trigger the clotting pathway, a critical stimulus for alternative complement pathway activation. After ruling out other causes, her findings and clinical picture were most consistent with surgical stress as the likely inciting factor for aHUS.

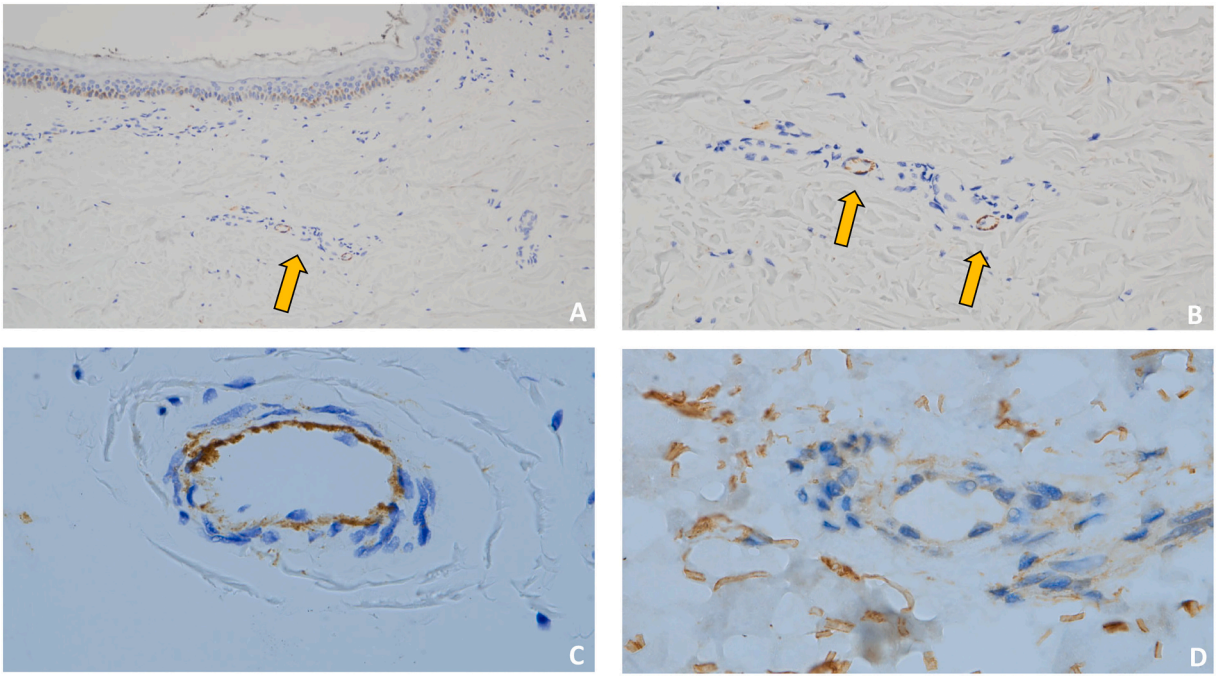

Fig. 3. Microvascular deposits of C5b-9 in a normal deltoid skin biopsy using a diaminobenzidine (DAB) technique. (A) A characteristic finding in aHUS is one of microvascular deposits of C5b-9 within the superficial microvasculature. In this image, there are two positive staining microvessels for C5b-9 within the superficial dermis (*yellow arrow*). (B) A higher magnification (400×) of the same two microvessels (*yellow arrows*). (C) Microvascular staining is observed throughout the depths of the biopsy including the deeper dermis. There is endothelial and subendothelial granular immunoreactivity for C5b-9 within an arteriole (100×). (D) No significant microvascular immunoreactivity to Cd4 staining, an expected finding in aHUS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

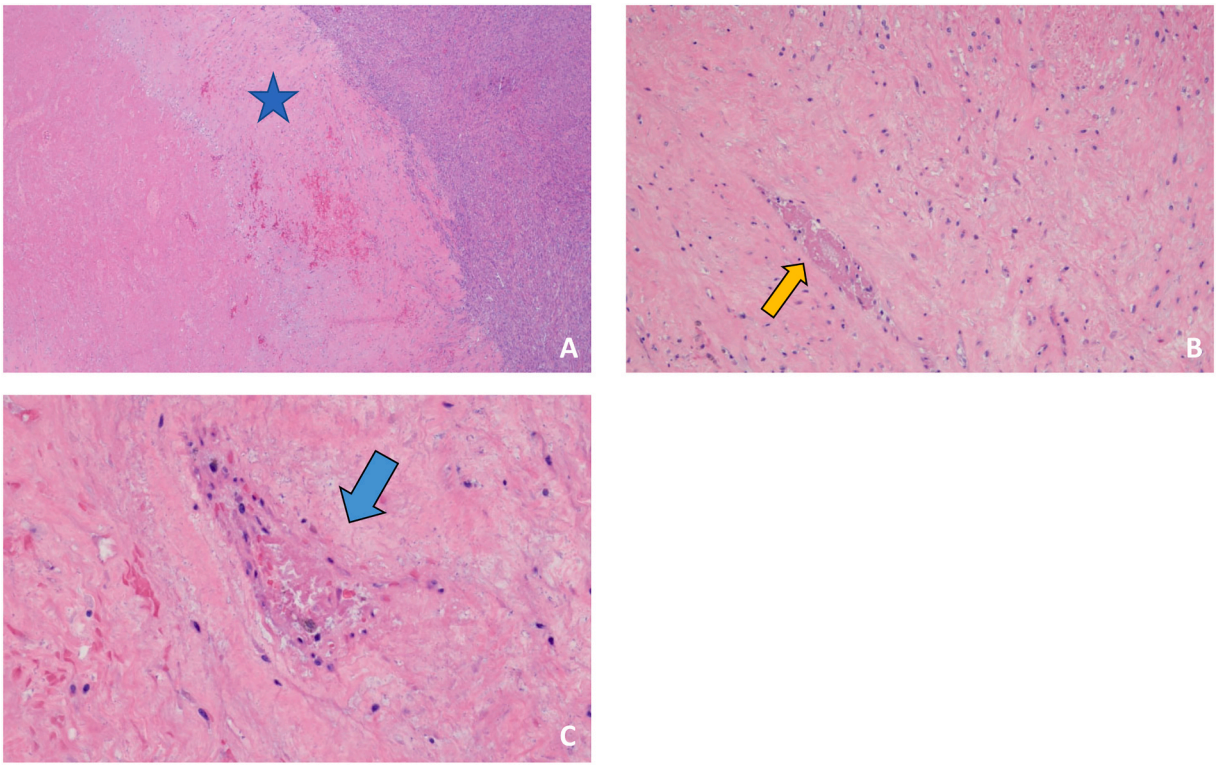

Fig. 4. Histologic images from myomectomy specimen. (A) Zone of infarction within the preserved viable leiomyoma *(star)*. (B) Thrombosed blood vessel within the zone of infarcted myoma (*yellow arrow*). (C) A severely damaged blood vessel within the zone of infarction exhibiting endothelial necrosis and thrombosis (*blue arrow*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

While two reports have described the development of aHUS following myomectomy [12,13], our case demonstrates very quick recognition of complement-mediated TMA with initial improvement following plasma exchange, as fresh frozen plasma (FFP) contains commonly deficient complement factors in aHUS [17]. Plasma exchange was effective for the acute management of this patient; however, the underlying cause of complement dysfunction still needed to be addressed to prevent ongoing renal damage. Eculizumab is a monoclonal, humanized anti-C5 antibody that prevents cleavage of C5 into C5a and C5b, which prevents activation of the alternate complement pathway and formation of C5b-9, the membrane attack complex (MAC) [8]. Since its approval for treatment of aHUS in 2011, eculizumab has been demonstrated to be an organ-sparing, life-saving treatment, and early intervention is associated with better outcomes [8,18]. The patient was planned to have at least six months of therapy, based upon her clinical response and absence of recognized complement mutations [19].

Atypical HUS is a clinical diagnosis by exclusion of other etiologies of TMA, and there is no direct diagnostic study. Testing for autoantibodies to complement proteins or genetic testing for inherited causes of aHUS may be revealing, but the results of these tests often take weeks to be returned, as they did for our patient [5]. Kidney biopsy is invasive, cannot be performed in patients with significant thrombocytopenia, does not identify the type of TMA and does not direct treatment decisions. A more practical approach for confirming the diagnosis of aHUS is a biopsy of normal skin procured from the deltoid area, chosen to reduce false positive results from sun-exposed skin. The quantitative extent of microvascular C5b-9 deposition is key in ruling in or out a diagnosis of systemic complement pathway activation [15,20]. Extensive C5b-9 microvascular deposits were appreciated from the patient's normal deltoid skin biopsy, supporting the diagnosis of aHUS (Fig. 3).

Our case describes the development of aHUS following gynecologic surgery. While two cases of aHUS have been reported after laparoscopic myomectomy complicated by postoperative intraabdominal bleeding [12,13], our patient had a larger volume of intraoperative blood loss and showed early signs of TMA with oliguria during her surgery. Her AKI continued postoperatively, and she was found to have progressive thrombocytopenia and laboratory signs of hemolysis. Early identification of TMA likely contributed to the initial improvement of her platelet count and renal function after initiation of plasma exchange, potentially avoiding the need for hemodialysis. Once DIC and TTP were effectively ruled out, she was initiated on eculizumab with further favorable response.

This patient is the first to our knowledge to have extensive complement deposition confirmed on tissue biopsy to support the diagnosis of surgery-induced aHUS. While extremely rare, TMA should be suspected in patients after myomectomy and other major gynecologic surgery with AKI and laboratory abnormalities demonstrating hemolysis, as early diagnosis and treatment can prevent irreversible renal injury and death.

Contributors

Kelsey Musselman contributed to data collection and analysis, and drafted the manuscript.

Jeffrey Laurence contributed to data analysis and editing of the manuscript.

Cynthia Magro contributed to histopathological analysis and editing of the manuscript.

Pasha Rahbari contributed to patient management, data analysis, and editing of the manuscript.

Thomas Di Vitantonio contributed to data analysis and editing of the manuscript.

Yelena Havryliuk contributed to patient management, data analysis and editing of the manuscript.

All authors approved the final article to be submitted.

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Patient consent

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

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

Dr. Jeffrey Laurence has a research grant from Alexion, the manufacturer of eculizumab. The other authors report no conflict of interest.

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