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Case Report

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Acute Systemic Capillary Leak Syndrome Mimicking Atypical Hemolytic Uremic Syndrome

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ABSTRACT

We present the case of a 42-year-old male admitted with a constellation of acute, rapidly progressive symptoms including profound anasarca, severe abdominal pain, oliguric acute kidney injury, and an initial laboratory picture suggestive of thrombotic microangiopathy (TMA) with severe thrombocytopenia and microangiopathic hemolytic anemia. Despite aggressive supportive care and empirical plasma exchange for presumed atypical hemolytic uremic syndrome (aHUS), the patient's condition continued to deteriorate with refractory hypovolemic shock despite massive fluid resuscitation. The absence of expected complement pathway abnormalities and a rapidly fluctuating hematocrit with apparent "vanishing" intravascular clots prompted a deeper diagnostic dive, ultimately revealing an exceedingly rare, acute presentation of systemic capillary leak syndrome (SCLS) unmasked by a preceding viral prodrome. This case highlights the critical importance of considering rare differential diagnoses in the context of diagnostic ambiguity, even when a more common, albeit severe, condition appears to fit the initial clinical picture.

Introduction

Thrombotic microangiopathies (TMAs) encompass a group of life-threatening disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. Atypical hemolytic uremic syndrome (aHUS), a complement-mediated TMA, is a particularly severe form requiring prompt diagnosis and targeted therapy. Systemic Capillary Leak Syndrome (SCLS), or Clarkson's disease, is an extremely rare and potentially fatal disorder characterized by recurrent episodes of reversible plasma extravasation from the intravascular to the interstitial space, leading to hypovolemic shock, hypoalbuminemia, and hemoconcentration. Its acute presentation can mimic various severe conditions, posing a significant diagnostic challenge. We report an extraordinary case where SCLS acutely presented with features highly suggestive of a TMA, leading to an initial misdiagnosis and highlighting the subtle yet critical differentiating factors.

Case Presentation

A 42-year-old male, previously healthy, presented to the Emergency Department with a 24-hour history of rapidly worsening diffuse abdominal pain, nausea, vomiting, and profound weakness. He reported a mild, self-limiting "flu-like" illness a week prior.

On admission, vital signs were significant for hypotension (BP 80/40 mmHg) and tachycardia (HR 120 bpm). Physical examination revealed generalized pitting edema, particularly prominent in the lower extremities and face, and marked abdominal distension with diffuse tenderness.

Initial laboratory investigations were striking

- Complete Blood Count: Hemoglobin 16.5 g/dL (initially high due to hemoconcentration), Platelets 28 x 10^9/L, WBC 18.0 x 10^9/L.
- Renal Function: Creatinine 3.8 mg/dL (baseline 0.9 mg/dL), Urea 110 mg/dL.
- Liver Function: Mildly elevated AST/ALT.
- Coagulation Profile: Normal PT/aPTT, Fibrinogen 450 mg/dL.
- Lactate Dehydrogenase (LDH): 1200 U/L .
- Haptoglobin: Undetectable.

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- Peripheral Blood Smear: Numerous schistocytes (4-5 per HPF), consistent with microangiopathic hemolytic anemia.
- Urinalysis: Proteinuria, microscopic hematuria, granular casts.

Based on the triad of microangiopathic hemolytic anemia, severe thrombocytopenia, and acute kidney injury, a presumptive diagnosis of TMA, most likely aHUS given the severity and multi-organ involvement, was made. Plasma exchange (PLEX) was initiated empirically, and samples were sent for ADAMTS13 activity (later returned >60%, ruling out TTP) and complement pathway analysis.

Over the next 48 hours, despite aggressive PLEX and massive intravenous fluid resuscitation (over 10 liters in 24 hours), the patient remained profoundly hypotensive, requiring escalating doses of vasopressors. His anasarca worsened dramatically, with his weight increasing by 15 kg. Despite ongoing fluid administration, central venous pressure remained paradoxically low (2-4 mmHg).

A perplexing finding emerged during serial blood draws: his hemoglobin, initially high, began to rapidly fluctuate from 16.5 g/dL down to 8.0 g/dL, then back up to 14.0 g/dL over a matter of hours, seemingly independent of transfusions. This rapid "dilution" and "re-concentration" phenomenon, along with persistent hypovolemic shock despite massive fluid input and low CVP, raised suspicion for massive extravasation. Furthermore, despite the initial peripheral smear showing schistocytes, subsequent smears showed a decreasing number of fragmented red cells, and platelet counts, while still low, did not consistently respond to PLEX. The initial "clot-like" appearance of the patient's blood in the vials seemed to vanish as fluid was administered.

A careful re-evaluation of the entire clinical picture was undertaken. The profound, rapidly fluctuating anasarca, refractory hypovolemic shock with low CVP despite massive fluid, and the transient nature of the MAHA features pointed away from a classical TMA. Crucially, repeated albumin levels consistently showed severe hypoalbuminemia (1.5 g/dL), disproportionate to renal losses.

Given these atypical features, the possibility of SCLS was considered. Serum protein electrophoresis (SPEP) was performed, revealing a transient monoclonal gammopathy of undetermined significance (MGUS) of the IgG-kappa type, a known association with SCLS. Serum IgE and tryptase levels were within normal limits, as were other markers for anaphylaxis or sepsis.

The patient was immediately transitioned from aggressive fluid resuscitation and PLEX to cautious, targeted albumin infusions (25% albumin) combined with diuretics to mobilize the extravasated fluid once the "leak" phase subsided. Intravenous immunoglobulin (IVIg) was initiated as a therapeutic trial for SCLS.

Within 12-24 hours of initiating IVIg and targeted albumin, the patient's condition began to stabilize. Vasopressor requirements decreased, urine output improved, and the anasarca started to resolve. His hemoglobin and hematocrit stabilized, and the thrombocytopenia gradually improved without further PLEX. The renal function also slowly recovered.

Discussion

This case represents an extraordinary diagnostic challenge where a rare disorder, SCLS, precisely mimicked the acute presentation of a life-threatening TMA. The initial constellation of severe thrombocytopenia, MAHA, and AKI strongly suggested aHUS, leading to appropriate empirical treatment with PLEX. However, several atypical features ultimately guided the diagnostic pivot:

- **Refractory Hypovolemic Shock with Low CVP Despite Massive Fluid Resuscitation:** hallmark of SCLS [1,2].
- **Rapidly Fluctuating Hemoglobin and Hematocrit:** the "vanishing clot" phenomenon, highly characteristic of SCLS [2,3].
- **Profound Hypoalbuminemia:** disproportionate to renal losses [4].
- **Transient Nature of MAHA Features:** initial schistocytes and thrombocytopenia resolving without consistent response to PLEX [2,5].
- **Absence of Complement Abnormalities and Normal ADAMTS13:** confirmed lack of TMA mechanisms [1].

The association of SCLS with monoclonal gammopathy, present in this patient, provides a potential underlying immunological trigger [2,3]. The patient's preceding viral prodrome might have served as the "unmasking" event, consistent with previous reports of virus-triggered SCLS episodes, including SARS-CoV-2 and influenza [6-9].

This case underscores the critical importance of a dynamic diagnostic approach and the willingness to reconsider initial diagnoses, even when they seem plausible. Early recognition of SCLS is crucial, as management differs radically from TMAs: aggressive fluid resuscitation can worsen outcomes, while albumin infusions and IVIg are the cornerstones of therapy [2,3].

Pathogenesis

The pathogenesis of acute SCLS remains incompletely defined. Current evidence supports vascular endothelial hyperpermeability (VEH) as the primary driver [4,1,10]. Histopathological evaluations of peripheral microvasculature consistently fail to reveal vasculitis or complement deposition [2,4].

Instead, circulating humoral factors appear central

- Transient elevations of cytokines (CXCL10, CCL2, IL-6) during flares [2].
- Increases in VEGF and angiopoietin-2 with distinct temporal kinetics [2,10].
- Acute-phase sera from SCLS patients disrupting endothelial junctions in vitro, with VE-cadherin redistribution and actin stress fiber formation [10].

Ablooglu demonstrated that endothelial cells from SCLS patients show intrinsic hypersensitivity to inflammatory mediators, explaining the exaggerated vascular response to common infectious triggers [10].

Conclusion

This case highlights a unique and challenging presentation of acute SCLS mimicking aHUS. The "vanishing clot" phenomenon, profound anasarca, and refractory hypovolemic shock with low CVP were critical differentiating features that, upon careful re-evaluation, led to the correct diagnosis. This report emphasizes the need for a broad differential diagnosis in acute multi-organ failure and the pivotal role of meticulous clinical observation. Lifelong IVIg prophylaxis is increasingly recognized as essential to reduce recurrence and mortality [3].

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