

Aggressive Disease and Rare Sequelae in a Unique Case of Atypical Hemolytic Uremic Syndrome Secondary to Adult Onset Still's Disease

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy (TMA) which generally presents as a triad of thrombocytopenia, hemolytic anemia and renal failure. We present the case of a 69-year-old woman with ongoing fevers, arthralgias, diffuse rash and pharyngitis for 3 months. Investigation revealed an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin; however, autoimmune and infectious studies were unremarkable, raising the suspicion for adult onset Still's disease (AOSD). Before our patient therapy could be initiated, she presented to our emergency room (ER) with a grand mal seizure and persistence of her initial triad of fevers, arthralgias and rash. Evaluation revealed non-immune hemolytic anemia, thrombocytopenia, and abnormal renal function consistent with TMA and the patient was subsequently started on plasmapheresis, hemodialysis and corticosteroid therapy. ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-13 activity was 38%, ruling out thrombotic thrombocytopenic purpura (TTP). A kidney biopsy demonstrated glomerular changes of TMA and a diagnosis of secondary aHUS triggered by AOSD was established. The patient was treated with eculizumab and high dose steroids with improvement in her laboratory values, eventually becoming hemodialysis-independent. This case highlights the clinical urgency in the prompt recognition of AOSD, a potent inflammatory disorder, which when co-existing with a complement-dysregulatory defect, can significantly augment TMA disease severity.

Keywords: Thrombotic microangiopathy; Adult onset Still's disease; Atypical hemolytic uremic syndrome; Thrombotic thrombocytopenic purpura

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Introduction

Thrombotic microangiopathy (TMA) is a pathologic formation of platelet-containing microthrombi primarily affecting the microcirculation, resulting in the triad of non-immune hemolytic anemia, thrombocytopenia and organ dysfunction. TMA can often involve several disease processes including disseminated intravascular coagulation (DIC), malignant hypertension, scleroderma renal crisis, antiphospholipid antibody syndrome and various drug toxicities. The most common disease processes are hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [1]. HUS most commonly affects children and is characterized by the classic triad mentioned above with prominent renal dysfunction. It is often preceded by an infectious agent which causes widespread inflammation following endothelial damage. There is, however, another entity known as atypical hemolytic uremic syndrome (aHUS) which follows a similar course but its pathogenesis as well as its treatment modality is distinct from HUS.

aHUS is a rare complement-mediated TMA which occurs in both children and adults. Approximately 10% of all cases of HUS are found to be atypical [2] and it is estimated to occur in two individuals per million [3]. The current consensus regarding the mechanism behind aHUS is that it is due to impaired regulation of the body's alternate complement pathway (ACP) [3]. Ongoing research has identified gene mutations in the complement-regulatory proteins, including complement factor H (CFH), complement factor I (CFI), complement factor 3 (C3), complement factor B (CFB), CD46 and the thrombomodulin gene (THBD) [4]. The proposed disease mechanism consists of a triggering event such as an infection, autoimmune disease, pregnancy or drug vasculotoxicity, resulting in activation of the ACP which is inherently dysregulated, subsequently causing diffuse microthrombi, fragmentation hemolysis, consumptive thrombocytopenia and organ ischemia [4, 5]. Of the known triggers leading to aHUS, we present a case of aHUS secondary to adult onset Still's disease (AOSD). Based upon our review of the literature, there have been 21 cases reporting an association between AOSD and TMA but only one case illustrates a possible link between AOSD and aHUS [6]. The objective of this case report is to recognize an unusual presentation of aHUS triggered by AOSD with several severe features suggestive of a CFH mutation.

Case Report

The patient is a 69-year-old Caucasian woman with a past medical history of hypertension, hypothyroidism and stage IA ductal carcinoma in remission status-post surgical resection and radiation. She presented to our facility with ongoing fevers, severe fatigue, arthralgias affecting bilateral hips and knees, a diffuse erythematous rash on her chest and upper extremities, impaired vision, episodic pharyngitis and an abnormal chest X-ray revealing diffuse airspace disease. Pertinent lab findings on initial presentation included hemoglobin (Hgb) 8.2 g/dL, platelets 329 k/mcL and white blood cell (WBC) 11.1 k/mcL. She was also found to have elevated inflammatory markers including erythrocyte sedimentation rate (ESR) 102 mm/h, C-reactive protein (CRP) 15 mg/dL, ferritin 1,608 ng/mL and a negative antinuclear antibody titer (ANA) and rheumatoid factor (RF). Systemic lupus erythematosus (SLE), Sjogren syndrome, dermatomyositis, sarcoidosis, rheumatoid arthritis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, Lyme disease, and Still's disease were all considered as possible etiologies. Given the non-specific nature of her symptoms and the laboratory values noted above, further rheumatological investigation was pursued including anti-double-stranded DNA, anti-smith antibodies, anti-Ro, anti-La, anti-cyclic citrullinated peptide (CCP), ANCA panel, enzyme-linked immunosorbent assay (ELISA) and Western blot analysis for Lyme, creatinine kinase, anti-histidine-tRNA ligase (Jo-1) and anti-topoisomerase (scl-70). These were all found to be unremarkable. Given her skin rash, pulmonary findings, and elevated inflammatory markers in the context of a negative infectious and autoimmune evaluation, the possibility of AOSD was considered. Her symptoms improved with a short course of glucocorticoids and she was advised to visit her primary care physician (PCP) as an outpatient for further evaluation. However, the patient was brought to our emergency department approximately 1 month later after suffering a witnessed grand mal seizure, worsening bilateral vision loss, ischemia of her toes and high-grade fevers. Computed tomography (CT) head at that time was unremarkable and she was started on levetiracetam. Initial laboratory values were remarkable for an elevated blood urea nitrogen (BUN) 73 mg/dL, creatinine 4.64 mg/dL (baseline approximately 0.68 mg/dL), WBC 23.51 k/mcL, Hgb 7.5 g/dL and platelets 71 k/mcL. C3 complement level was 71 mg/dL (reference range: 85 - 193 mg/dL). She was also found to be in new-onset atrial fibrillation with rapid ventricular response which improved and reverted back to normal sinus rhythm with diltiazem hydrochloride. However, a transthoracic echocardiogram at that time revealed new left ventricular systolic dysfunction with an ejection fraction of 30-35%, decreased from 60% approximately 1 year prior. The patient was admitted directly to the medical intensive care unit with multi-organ failure and a tenuous clinical status. The differential diagnosis was felt to include such etiologies as infection, possible paraneoplastic process given her history of breast cancer and a potential rheumatological and/or hematological disorder. The patient was started on dexamethasone 4 mg intravenously daily. Further investigation revealed non-immune intravascular hemolysis with an

elevated lactate dehydrogenase (LDH) of 969 U/L and a haptoglobin of less than 10 mg/dL. A DIC panel was unremarkable with minimally elevated fibrin degradation products (FDPs) and normal fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time (PT). A peripheral smear review revealed 5 - 8 schistocytes per high-power field. An infectious disease evaluation including Shiga toxin and enterohemorrhagic *E. coli* (EHEC) studies were also negative. Given her neurological symptoms, acute renal injury, microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, the overall picture was felt to be consistent with TMA. The patient underwent emergent hemodialysis and plasma-exchange. Following these interventions, the patient's mental status improved to near baseline, although there was minimal improvement of her basic laboratory values. Subsequently, her ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-13 activity returned at 38%, and the most likely diagnosis was felt to be secondary to aHUS. She received a total of 3 days of plasma-exchange during her stay which resulted in transient laboratory improvement. However, she remained anuric with worsening creatinine and thus was continued on hemodialysis. She underwent a kidney biopsy as well as a skin biopsy given her persistent rash. Skin biopsy eventually revealed acanthosis and hyperkeratosis felt to be consistent with Still's disease and the renal biopsy detected glomerular changes of acute and chronic TMA. Eculizumab induction therapy was initiated at 900 mg to be administered weekly for four doses and then transitioned to the maintenance regimen thereafter. She was also started on 60 mg of prednisone daily with a taper for presumed AOSD. Following these interventions, her Hgb and platelet counts improved, and her creatinine returned to near-baseline with improvements in her urine output, allowing discontinuation of dialysis. A repeat echocardiogram revealed improvement of her ejection fraction. Unfortunately, there was no beneficial therapeutic effect on either her vision or digital ischemia, and she ultimately required amputation.

Discussion

AOSD is a potent systemic inflammatory disorder of unknown etiology and pathophysiology. It is characterized by the triad of fevers, arthralgias and rash, but it may also include pericarditis, pharyngitis, lymphadenopathy, seizures and rarely, hemolytic phenomena including TMA [7, 8]. Various triggers have been proposed such as infection or genetic mechanisms, but a specific pathogenesis has yet to be established [7]. To date, AOSD remains a diagnosis of exclusion. The diagnosis is predicated on the inclusion of certain clinical and laboratory findings but, more importantly, it requires the exclusion of other potential diagnoses with similar manifestations.

As mentioned above, aHUS is a rare form of TMA, occurring in two individuals per million [3]. The current understanding of the disease process is that in approximately 70% of cases, there is an initial triggering event, often infectious or inflammatory in nature, which activates the ACP in a patient who has impaired complement-control mechanisms, most commonly due to genetically mutated regulatory proteins [2]. In our

patient, after excluding other potential triggers (infection, systemic autoimmune disease/vasculitis and drug reactions) and identifying the presence of four major Yamaguchi diagnostic criteria (fever spike, arthralgias, typical rash and leukocytosis), and one minor criteria (absence of RF and ANSs) [9], the prevailing opinion was that the most likely co-existing disorder serving as the trigger was Still's disease. Interestingly, this adult patient manifested features of severe disease with advanced involvement of multiple organ systems (cardiac, peripheral vascular, renal, and ocular). Regarding the pertinent investigations, the patient's stress test was negative for ischemia, suggesting microvascular obstruction as the cause of diffuse myocardial ischemia. This cardiac complication has been well-described in aHUS myocardial biopsy data and is attributed to microangiopathic injury of the coronary vasculature. It has been known to occur in 3-10% of patients with aHUS [10]. Of the known aHUS mutations, hereditary CFH defects are typically associated with aggressive disease activity and have been strongly implicated in aHUS-related cardiac complications. Noris and Remuzzi [10] investigated 273 patients with aHUS and of these, seven developed acute cardiomyopathies, with five of seven being found to harbor CFH mutations.

In addition, our patient developed gangrene of the right distal second and third phalanges requiring debridement and ultimately amputation. Severe peripheral defects of the arterioles supplying the distal phalanges have been documented in previous case reports of aHUS [11-13]. Isolated decreases of circulating C3 can occur with CFH mutations, although this profile is not specific for CFH mutations. The described patients above as well as our patient had decreased C3 levels with normal C4 levels.

With reference to the patient's ocular manifestations, her visual loss temporally coincided with her initial and subsequent TMA flares, suggesting a causal relationship. A formal ophthalmological examination revealed dense retinal vascular occlusions. Multiple aHUS case reports have documented visual deficits related to occlusive retinopathy [14-16] and, as is the case with cardiac and peripheral vascular involvement, CFH mutations appear to be frequently incriminated. The formation of microthrombi in retinal and choroidal vessels resulting in ischemic injury is suspected to be responsible for the vision changes found in this subset of patients [15]. Carvalho et al [16] described a patient with a Purtscher-like retinopathy, a rare, downstream vaso-occlusive vasculopathy, in a patient with aHUS harboring a CFH mutation. Fourteen days after initiation of systemic eculizumab therapy, the patient experienced complete resolution of her previous visual deficits. Thus, in a patient with aHUS who develops visual abnormalities, prompt ophthalmological testing and consideration of early treatment with eculizumab should be an important consideration.

Based upon an extensive review of the literature, we were able to identify 21 cases reporting a strong association between AOSD and TMA, but only one case illustrated a possible link between AOSD and clearly-defined aHUS [7].

Although the precise pathophysiological association between AOSD and TMA has yet to be defined, AOSD is known to result in profound systemic inflammation, and thus, undoubtedly, has the potential to generate robust activation of the alternate complement cascade. While AOSD is, for the most

part, a diagnosis of exclusion, physicians should not allow the lack of a recognized disease association or definitive diagnosis to result in a critical delay in treating a very serious disease, which in severe cases, may result in significant morbidity and/or mortality. Our patient had ongoing symptoms for 3 months without a clear diagnosis before presenting to our institution. She ultimately suffered from refractory/irreversible organ injury (visual loss/digital necrosis) despite our best efforts to secure the correct diagnosis and implement appropriate therapy in a timely fashion. Our review of the literature revealed that advanced TMA developed in a substantial percentage of similar cases while AOSD and the associated secondary-aHUS remained in an investigatory phase, thus conveying the urgency of prompt diagnosis and therapeutic intervention in this clinical scenario.

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None to declare.

Conflict of Interest

The other authors have no disclosures to make. Institutional IRB approval was obtained prior to commencement of the study.

Informed Consent

Consent was obtained from patient.

Author Contributions

AK and AY contributed to the conceptualization; AK wrote the original draft; AK, SP, JM and RK contributed to writing the review and editing; AK and RK were involved in the final revision.

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