Atypical Hemolytic Uremic Syndrome During Induction Chemotherapy in Neuroblastoma, a Rare Phenomenon or Common Congenital Predisposition?

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is an infrequently encountered complement-mediated thrombotic microangiopathy (TMA) usually associated with germline variants in genes of the complement system. Clinical findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI) with severe hypertension arise due to aberrant complement protein activation in the circulation and significant endothelial damage. Transplant-associated thrombotic microangiopathy has been increasingly recognized after high dose carboplatin, etoposide, and melphalan-chemotherapy followed by autologous hematopoietic stem cell rescue for treatment of children with neuroblastoma (NB). We report the case of a 13-month-old boy with metastatic neuroblastoma who developed aHUS during the first cycle of induction chemotherapy. Germline testing revealed a Complement factor H *(CFH)* gene mutation, Cys357Arg, which is currently classified as a variant of uncertain significance (VUS), although likely pathogenic based on molecular modeling as well as this patient's clinical presentation. The patient has been successfully managed with complement blockade therapy with no recurrence of disease. We review presentations of neuroblastoma with hypertension, along with AKI and thrombocytopenia, to raise awareness about the potential for aHUS in patients with newly diagnosed NB.

TITLE PAGE

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Abbreviation table:

Abbreviation	Definition
aHUS	Atypical Hemolytic Uremic Syndrome
HSCT	Hematopoietic stem cell transplant
VUS	Variant of Uncertain Significance
AKI	Acute Kidney Injury
TMA	Thrombotic microangiopathy
NB	Neuroblastoma
ED	Emergency Department
CT	Computerized Tomography
MIBG	Iodine-123 meta-iodobenzylguanidine
NB	Neuroblastoma
HUS	Hemolytic Uremic Syndrome
TA-TMA	Transplant Associated Thrombotic microangiopathy
ESRD	End Stage Renal Disease
PLEX	Plasma Exchange
ASCT	Autologous Hematopoietic stem cell transplant

Abstract:

Atypical hemolytic uremic syndrome (aHUS) is an infrequently encountered complement-mediated thrombotic microangiopathy (TMA) usually associated with germline variants in genes of the complement system. Clinical findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI) with severe hypertension arise due to aberrant complement protein activation in the circulation and significant endothelial damage. Transplant-associated thrombotic microangiopathy has been increasingly recognized after high dose carboplatin, etoposide, and melphalan-chemotherapy followed by autologous hematopoietic stem cell rescue for treatment of children with neuroblastoma (NB). We report the case of a 13-month-old boy with metastatic neuroblastoma who developed aHUS during the first cycle of induction chemotherapy. Germline testing revealed a Complement factor H *(CFH)* gene mutation, Cys357Arg, which is currently classified as a variant of uncertain significance (VUS), although likely pathogenic based on molecular modeling as well as this patient's clinical presentation. The patient has been successfully managed with complement blockade therapy with no recurrence of disease. We review presentations of neuroblastoma with hypertension, along with AKI and thrombocytopenia, to raise awareness about the potential for aHUS in patients with newly diagnosed NB.

Introduction:

Neuroblastoma (NB) is classically a catecholamine-secreting tumor that arises from primitive ganglionic cells along the sympathetic chain or adrenal medulla[1]. Some NB tumors spontaneously regress, while others are highly aggressive and progressive despite intensive chemotherapy[1]. The initial presentation of NB can include severe uncontrolled hypertension due to tumor compression of the renal vasculature and parenchyma and/or from excess catecholamine release[1]. When hypertension is associated with hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI), it should raise immediate concern for atypical hemolytic uremic syndrome, a type of thrombotic microangiopathy (TMA) seen in those with a genetic predisposition often triggered by infection, malignancy or chemotherapy leading to abnormal activation of the complement cascade leading to endothelial and end organ damage[2]. Atypical HUS (aHUS) is a potential

complication of autologous hematopoietic stem cell transplantation (HSCT) after treatment with high dose carboplatin, etoposide, and melphalan (CEM) for neuroblastoma, particularly in those with genetic variants in complement genes[2,3]. However, it has not previously been reported following initiation of induction chemotherapy for a patient with high-risk NB.

Case Presentation:

A 13-month-old boy born full term presented to the emergency department (ED) with an enlarging left scalp mass and clinical concern from the pediatrician that the differential diagnosis included non-accidental trauma. On evaluation in the ED, vital signs were temperature of 38°C, heart rate 150 beats per minute, respiratory rate 32 breaths per minute with 100% oxygen saturation on room air, and blood pressure 105/72, which was within normal limits for systolic blood pressure and above the 99th percentile for diastolic blood pressure. His physical exam was pertinent for a 3 cm firm non-indurated and non-tender swelling of the right temporo-parietal scalp, as well as bilateral periorbital edema, ecchymoses of the upper eye lids, and bilateral subconjunctival hemorrhages. Abdominal exam was notable for a 7 cm firm mass in the left upper quadrant extending past the umbilicus. Computerized tomography (CT) of the head demonstrated a 14mm lesion in the right pterion with intracranial soft tissue extension causing mild mass effect on the right frontal operculum, a 5 mm extracranial soft tissue lesion, and a 4 mm right parietal lesion with intracranial extension. CT neck, chest, abdomen, and pelvis revealed a large complex mass arising from the right adrenal gland measuring 7.4 x 7.3 x 8 cm, as well as several areas of increased enhancement within the liver measuring as large as 7.4 x 9.1 cm. Iodine-123 meta-iodobenzylguanidine (MIBG) scan demonstrated increased radiotracer uptake in the large heterogenous right adrenal mass, left hepatic lobe, left iliac wing, left proximal femur head, and right proximal femur and right ischial bones as well as right temporal region and bilateral orbital bone lesions, consistent with the diagnosis of metastatic neuroblastoma. Bilateral bone marrow biopsy demonstrated 5% metastatic neuroblastoma with immunohistochemical stains for synaptophysin highlighting the tumor cells. Our patient had high-risk NB based on age, stage of disease, and tumor molecular finding of *MYCN* amplification, and he was treated as per a high-risk induction regimen[4] starting with 5 days of topotecan and cyclophosphamide. On day 6, labs were notable for a rising creatinine of 0.84 mg/dL from a baseline of 0.40 mg/dL (age-specific normal range <0.5 mg/dL) and decreasing sodium to 128 mEq/L from normal levels, which was thought to be mild chemotherapy-induced AKI and hyponatremia that was managed conservatively with fluid restriction. On day 7, he developed oliguria and severe hypertension above the 99th percentile for age. Isradipine and more intensive antihypertensive management had no effect. Blood work demonstrated unexpected laboratory evidence of hemolysis, including rising lactate dehydrogenase and indirect hyperbilirubinemia, as well as undetectable haptoglobin. A peripheral blood smear was notable for multiple schistocytes per high power field, raising concern for TMA. While ADAMTS13 was pending, in the absence of diarrhea and concurrent *E. coli* infection or suspected trigger for HUS and a PLASMIC score of 3, he was trialed on plasma exchange (PLEX), which did not improve his clinical status, decreasing the likelihood of thrombotic thrombocytopenic purpura. A diagnosis of aHUS, instead of other types of TMA, was supported by: CH50 and sC5b-9 elevated at >60 U/mL (normal range 31 – 60 U/mL) and 307 ng/mL (normal range <244 ng/mL), respectively. A genetic susceptibility aHUS panel revealed a Complement factor H *(CFH)*gene mutation, Cys357Arg, which while classified as a variant of uncertain significance, may be pathogenic due to its effect on protein structure and this patient's clinical course (Figure 1)[5,6]. We performed molecular modeling using the open source software, PyMol, and found that the mutation abolishes a predicted intramolecular disulfide bone, thus causing significant structural change to the protein with likely impact on enzymatic function [5,6]. The patient was started on eculizumab treatment, initially at a dose of 300 mg weekly per the recommendations from the drug manufacturer, after receiving quadrivalent meningococcal conjugate and meningococcal group B vaccines and starting Penicillin VK for meningococcal prophylaxis.

Due to his degree of critical illness with declining respiratory status attributable to intractable fluid overload, the patient was intubated and started on continuous veno-venous hemofiltration (CVVH). CH50 began to downtrend after the second dose of eculizumab, while his clinical status and renal function remained tenuous until the fourth dose of eculizumab treatment, at which point he was extubated and CVVH was

discontinued successfully (Figure 2). By day 30 in his first chemotherapy cycle, his clinical status and correlative laboratory markers, including peripheral schistocytes, creatinine, CH50 and haptoglobin, demonstrated stable improvement (Figure 2) and eculizumab dosing was spaced to every 2 weeks. After a 5-week delay in conventional induction treatment to allow recovery, during which he received bridging chemotherapy with irinotecan/temozolomide, he completed four additional cycles of chemotherapy, including re-challenge of cyclophosphamide and topotecan, which had been the suspected trigger for aHUS. He experienced no exacerbation of his aHUS findings apart from a mild transient increase in his creatinine after his first re-challenge with chemotherapy approximately 30 days after his initial presentation (Figure 2). After achieving a partial response to chemotherapy and undergoing surgical resection of his primary tumor, he underwent tandem autologous stem cell transplant (ASCT), first with a conditioning regimen of thiotepa and cyclophosphamide and second with a CEM conditioning regimen[7]. In recognition of the increased risk of transplant associated TMA (TA-TMA), in particular with CEM conditioning, eculizumab dosing was intensified to weekly during his first ASCT and to twice weekly during his second with frequent monitoring of CH50[8]. During radiotherapy and five cycles of immunotherapy with dinutuximab, GM-CSF and cis-retinoic acid, he received weekly eculizumab and maintained stable aHUS marker labs. Eculizumab was spaced again to biweekly maintenance therapy, and after 4 months in remission, he was changed to ravulizumab, which has been dosed monthly. At 20 months after completion of anti-cancer therapy, he has no evidence of tumor recurrence or reactivation of aHUS.

Discussion:

Approximately 2% of children with neuroblastoma can present with hypertension, flushing, and periods of diaphoresis attributed to increased catecholamine secretion [1]. In one retrospective review of 10 patients with both NB and hypertension, four required more than three antihypertensives, including alpha/beta blockade[9]. The hypertension was reported to resolve spontaneously, reflective of decreasing tumor burden in response to chemotherapy, or after surgical resection of the primary tumor. When hypertension rapidly worsens or is associated with hemolysis, thrombocytopenia, and AKI, as noted in our patient, the findings could be attributed to aHUS, which may be more common than previously appreciated[10].

Thrombotic microangiopathy describes a variety of conditions characterized by microangiopathic hemolytic anemia, thrombocytopenia, and AKI. Thrombotic thrombocytopenic purpura, a TMA, is a condition in which lack of ADAMTS13, either due to autoantibodies or congenital mutations, results in excess amounts of high molecular weight von Willebrand multimers. This leads to intravascular micro-thrombosis, hemolysis and damage to the endothelial surface[11]. This condition, which tends to improve following PLEX therapies, is more often characterized by a severe drop in platelet count and mild rise in creatinine[11]. Hemolytic uremic syndrome (HUS), another TMA, is characterized by similar features and specifically associated with *Escherichia coli* Shiga toxin[2]. Atypical hemolytic uremic syndrome (aHUS), less commonly seen, occurs due to dysregulation of the complement pathway, leading to intravascular hemolysis[2]. Endothelial damage and end organ damage, including significant increase in creatinine, results from uncontrolled complement mediated lysis, stiffening of red blood cell membranes, deposits of complement fragments, and microthrombi[2]. Thrombocytopenia results from both platelet consumption and enhanced platelet aggregation and is typically milder than that seen in TTP[12]. Transplant-associated thrombotic microangiopathy (TA-TMA), an HUS seen in approximately 39% of children and young adults undergoing HSCT [13], is associated with CEM-containing conditioning regimens commonly used as part of consolidation therapy for neuroblastoma, post-transplant infection, and genetic variants in complement regulatory genes and more recently has been defined as a possible secondary HUS that typically resolves with removal of a suspected trigger[3,8,14]. Testing for TA-TMA tends to occur after the first ASCT and includes monitoring of blood pressure, urinalysis, and soluble C5b9. aHUS can be diagnosed with clinical evaluation and common blood tests, including a complete blood count, urinalysis and comprehensive metabolic panel, and early recognition and then treatment of this condition when it is severe can allow significant recovery of kidney function.

Germline aberrations have been implicated in 40-60% of patients with aHUS [15]. Our patient was found to have a heterozygous pathogenic mutation in the *CFH* gene. CFH is a complement inhibitor and is present

as a soluble protein that prevents complement activation when bound to cell surfaces in the human body[16]. When CFH does not function to regulate the complement pathway, uncontrolled activation results, leading to endothelial damage and end organ damage[16]. Mutations in this gene have been associated with multiple conditions, most notable of which is aHUS, with 15% of individuals having deletions or duplications, most of which are inherited in an autosomal dominant pattern[17,18]. Germline variants in other complement associated genes, such as *CFH* , *MCP (CD4), CFI, C2, CFB, CFHR1, CFHR3, CFHR4, CFHR5,* diacylglycerol kinase epsilon *(DGKE)*and thrombomodulin (*THBD),* have also been implicated in 50% to 60% of all aHUS cases [17,19]. Based on an analysis of 2317 patients demonstrating at least one deleterious mutation in a complement-associated gene 54% of the time, germline genetic testing for aHUS is recommended for patients with persistent thrombocytopenia or reported ADAMTS13 levels <50%[19]. However, a congenital predisposition is not typically sufficient for clinical manifestations of aHUS; most patients who become symptomatic experience a trigger, which can include infection, systemic lupus erythematosus, or chemotherapy[19], the latter of which our patient was exposed to in the setting of a catecholamine-secreting malignancy. TA-TMA in patients with high-risk neuroblastoma is not well characterized with incidence ranging from 7% to 30% of patients, particularly in those receiving CEM-containing regimens in preparation for autologous HSCT[20,21]. Our patient developed aHUS following his initial chemotherapeutic regimen, containing cyclophosphamide, prior to any CEM-containing regimen or known trigger for secondary HUS, raising concern for an underlying genetic predisposition to aHUS. While there was a risk of recurrence with re-exposure to cyclophosphamide, we chose to move forward with the chemotherapeutic agent that would best treat his underlying malignancy and continue complement blockade to manage his aHUS.

Eculizumab and ravulizumab are FDA-approved monoclonal antibodies that target terminal complement C5 to try to abrogate aberrant complement activation, which therefore leads to improvement in thrombotic microangiopathy, thrombocytopenia, estimated glomerular filtration rate, and event-free survival, as well as improvement in health-related quality of life [22]. Early recognition of TMA and administration of complement blockade decreases rates of end stage renal disease (ESRD)[23]. Without the addition of complement inhibitors, as few as 25% of patients with TA-TMA achieve disease remission [13]. In fact, patients with TA-TMA have been reported to require higher or more frequent dosing of complement blockade to achieve an adequate clinical response[8], which is why we managed our patient conservatively with more frequent dosing during ASCT. While initiation of complement blockade can be effective in these patients at diagnosis, if discontinued prematurely, aHUS may recur [17,24,25]. In these cases, symptoms may not be as responsive to re-initiation of complement blockade, leading to increased morbidity from long term sequelae of aHUS[17]. For these reasons, as well as the germline*CFH* mutation in our patient, complement blockade has been continued after completion of all anti-cancer therapy. For convenience purposes, the patient was transitioned to ravulizumab, which is re-formulated from eculizumab to extend its terminal elimination half-life to allow a dosing regimen of every 4-8 weeks, depending on patient weight[26]. Ravulizumab was shown to be effective in patients <18 years old with documented aHUS who had demonstrated an appropriate clinical response to eculizumab with stable aHUS lab values[27].

This patient's case led us to reconsider how we evaluate hypertension in children with NB. The clinical findings and congenital predisposition to aHUS prompted an aggressive management strategy with eculizumab that maintained complement inhibition during intensive phases of NB treatment. The findings of aHUS may be more common than currently reported given that hypertension and lab abnormalities are often attributed to tumor and/or chemotherapy effect. Delayed recognition of aHUS can result in ESRD and death [28]. There are testing paradigms for TA-TMA that can be applied to patients with aHUS as described in our report, though there is no consensus regarding genetic predisposition testing for at-risk patients (e.g., prior to ASCT for patients with high-risk NB)[13,20,29-31]. We consider it reasonable to pursue germline testing for aHUS in patients with high-risk NB, particularly when those patients develop hypertension and/or have additional concerning laboratory abnormalities, even if ASCT has not yet commenced. Those with germline predisposition to aHUS may benefit from long-term complement inhibition initiated early in treatment course, though a coordinated effort by treating physicians to catalog and study this population of patients is needed. Understanding individual risk factors for aHUS in each patient will allow providers to better care for those with

NB to minimize toxicity and sequelae of aHUS from through early detection and rapid initiation of therapy.

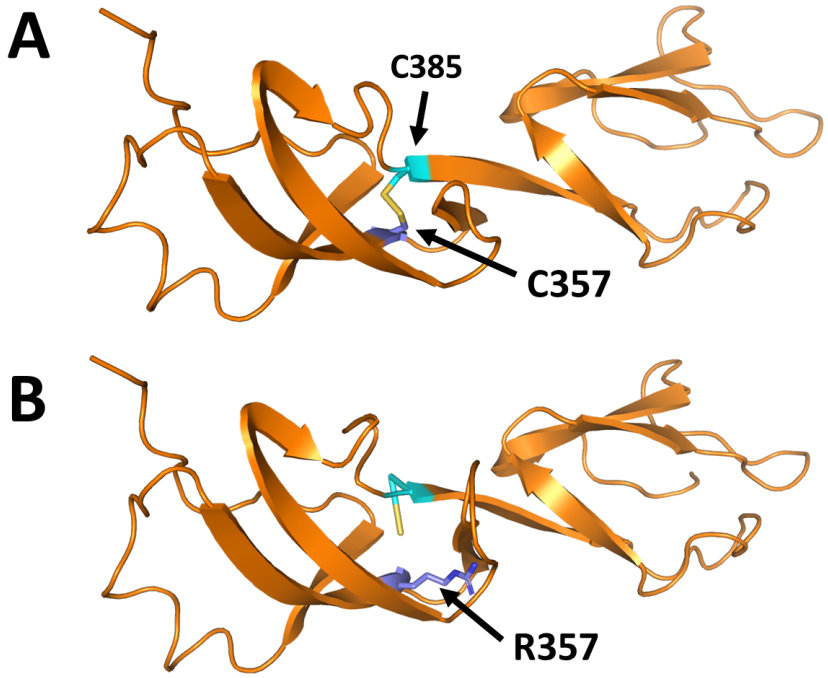
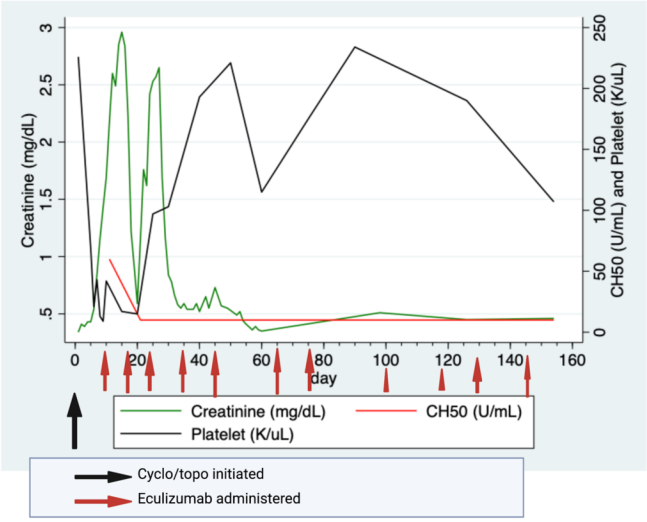


Figure 1. Molecular consequences of Cys357Arg variant of complement factor H gene, *CFH* . Cartoon rendering of a portion of the complement factor H protein structure, extending from amino acid Tyr321 to Ile443, derived from PDB file mmdb_4AYE (). **A**) Location of the disulfide bond between Cys357 and Cys385. B) The Cys357Arg mutation breaks the disulfide bond, potentially destabilizing the molecular structure. Figure generated and mutagenesis performed with PyMOL v2.3.3[6].

Figure 2. Creatinine, platelet, and CH50 trends in a 13-month-old male diagnosed with metastatic neuroblastoma with diagnosis of aHUS following first cycle of chemotherapy with topotecan and cyclophosphamide demonstrating improvement following initiation of therapy with eculizumab.



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