Clinical Case Report

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A case report of a child with sepsis induced multiorgan failure and massive complement consumption treated with a short course of Eculizumab

A case of crosstalk between coagulation and complement?

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Abstract

Rationale: This article describes a child with a life-threatening multiorgan failure with disseminated intravascular coagulation (DIC) and massive complement consumption. To our knowledge this therapeutic approach was for the first time effectively applied in a pediatric patient.

Patient concerns: A 14-month-old boy was presented with a severe, rapidly progressing, life-threatening disease because of sudden onset of fever, hemathemesis, hematuria, and bloody diarrhoea alongside fast spreading hematomas and general corporeal edema.

Diagnosis: The most plausible diagnosis in our patient is *Clostridium difficile* sepsis-induced thrombotic microangiopathy alongside with DIC and consumption coagulopathy. The diagnosis was confirmed by positive *C difficile* bacteria strain in coproculture, clinical, and laboratory tests affirming DIC and global complement activation and consumption.

Interventions: The patient was treated with antibiotics (Metronidazole, Vancomycin), plasmapheresis, dialysis, methylprednisolone, mycophenolate mofetil, and Eculizumab.

Outcomes: The child is in fair overall condition in a 2 year follow-up with no complications save chronic renal failure.

Lessons: In rare cases of sepsis with massive complement consumption, a case-sensitive Eculizumab therapy may be at least considered after the resolution of life-threatening multiorgan failure. The application of this drug can be performed only after sepsis induced disease is put under control. A fast withdrawal of Eculizumab after control of massive complement consumption is recommended to prevent triggering of second sepsis reactivation.

Abbreviations: AP = alternative pathway, aPTT = activated partial thromboplastin time, CD46 = membrane cofactor protein 46, CFB = complement factor B, CFH = complement factor H, CFHR5 = complement factor H-related protein 5, CFI = complement factor I, DGKE = diacylglycerol kinase-epsilon, HUS = hemolytic-uremic syndrome, MOF = multiorgan failure, PNH = paroxysmal nocturnal hemoglobinuria, PT = prothrombin time, RBC = red blood cell, THBD = thrombomodulin, TMA = thrombotic microangiopathy, TTP = thrombotic thrombcytopenic purpura.

Keywords: child, disseminated intravascular coagulation, Eculizumab, multiorgan failure, sepsis

Editor: N/A.

The authors of this publication have no competing interests or financial disclosures.

Data and material are available for review on demand.

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:4(e14105)

Received: 16 September 2018 / Received in final form: 12 December 2018 / Accepted: 18 December 2018

http://dx.doi.org/10.1097/MD.0000000000014105

1. Introduction

Clostridium difficile (*C difficile)* colitis is constantly an increasing cause of severe infection disease in children.[1,2] A child with life-threatening multiorgan failure (MOF) caused by *C difficile* is still considered as a challenge for the most plausible treatments.[1,3] Eculizumab, a humanized anti-C5 monoclonal antibody that inhibits terminal pathway activation by blocking the generation of C5b-9 (membrane attack complex) is currently considered as an effective and safe choice for the treatment of patients with uncontrolled complement consumption. Herein, we present a child with MOF and massive complement consumption caused by acute *C difficile* colitis who among other acknowledged treatment also received a short course of Eculizumab.

2. Case presentation

A 14-month-old boy with severe, rapidly progressing, life-threatening disease was admitted in intensive care unit because of sudden onset of fever, hemathemesis, hematuria, and bloody diarrhoea alongside fast spreading hematomas and general

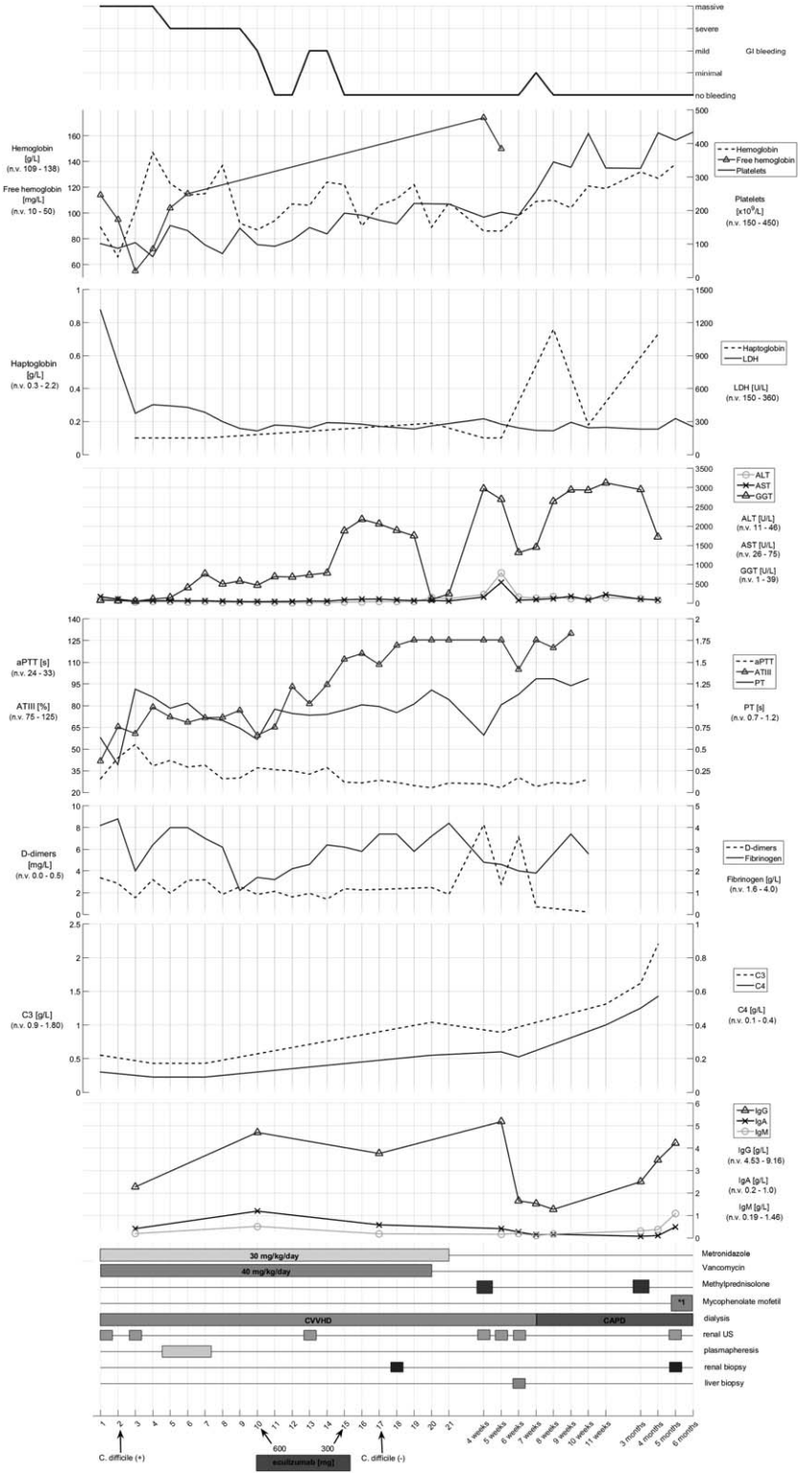

Figure 1. Clinical, laboratory, and treatment time-line of our case.

corporeal edema. A day before onset of the disease the child consumed a small portion of plant soil. Sedation was performed with the goal of life-saving interventions tolerance, blood pressure was maintained via medications and as oliguria/anuria soon progressed a continuous veno-venous hemodialysis was set forth. Anuria was maintained throughout the disease. Previously he was a healthy child with no relevant medical history of similar disease or in family history. No prodromal symptoms were noticed.

Relevant clinical, laboratory, diagnostic, and medication follow-up is shown in Figure 1. The initial presentation of MOF begun with sepsis including gastrointestinal, renal, cardiac,

and liver impairment. Life-threatening anemia and thrombocytopenia required frequent packed RBC and platelet transfusions, avoided as much as possible. Massive bloody diarrhoea was lasting during the first 10 days following by hose outflow. Bleeding edematous gut mucosa was visualized by colonoscopy without signs of intestinal perforation. The child received initially multiple fresh frozen plasma infusions and a short course of plasma exchange with plasma replacement during 4 consecutive days, until stabile vital functions were achieved. Kidney ultrasound showed hyperechogenic kidneys without corticomedullar differentiation. As positive *C difficile* bacteria was isolated in 2 separate coprocultures by 2 independent laboratories, Metronidazole and Vancomycin were administered. Unfortunately, due to technical difficulties we did not achieve positive *C difficile* toxin identification. Shiga toxin was proved negative as well as *E. coli*, Shigella sp., *Streptococcus pneumoniae*, Campylobacter sp., and other bacteria causing HUS. Extensive search for poisonous substances were proved negative alongside with PNH, methylmalonic aciduria and homocystinuria. No fragmentocytes were found in periferal blood. Direct Coombs test was negative.

Coagulation tests revealed normal prothrombin time (PT), elevated activated partial thromboplastin time (aPTT), and increased D-dimers. Fibrinogen was found within normal range. LDH and free hemoglobin were elevated from the beginning of the disease. Antithrombin III values were low and slowly improved during time. All values were tested according to ISTH diagnostic scoring system for DIC guidelines and found negative <5.[4–6] Haptoglobin values were low from the beginning of the disease. C3, factor H levels, and alternative pathway (AP) activity were decreased, without elevation of complement activation markers sC5b9 or C3a. This is probably due to a protein-loss related activity rather than activation and consumption. C1q was severely decreased and with negative anti-C1q, supporting the presence of global complement activation and consumption. Decreased but not deficient ADAMTS13 metalloprotease activity (46%) excluded thrombotic thrombcytopenic purpura (TTP). Liver enzymes (AST, ALT, GGT) were elevated from the beginning of the disease. Vitamin K was supplemented. Immunoglobulins levels (IgG, IgA, and IgM) were found to be lower for the age and in need of occasional substitution even after active disease ceased. Abdominal and brain CT scans were proven negative for gut perforation or brain damage.

From clinical judgment and laboratory findings (normal plasma fibrinogen, elevated D-dimers and free hemoglobin, low haptoglobin and decreased platelets), as well as alternative pathway activation indicating the presence of severe, global complement activation and consumption, we suspected of uncontrollable complement regulator loss and activation process underway the infective *C difficile* disease trigger. Therefore, a secondary thrombotic microangiopathy (TMA) triggered by the infection and by the coagulopathy was assumed. Negative complement activation marker sC5b9 may be explained by plasma sample collection which was taken before ongoing TMA activation.

After administration of Eculizumab in dosage on 10th day of the disease (600 mg) the patient's physical condition soon improved with ceasing of bloody diarrhoea. Second onset of bloody diarrhoea after 5 days also ceased with the second dose of Eculizumab (300 mg). Small amount of bloody diarrhoea was again noticed after 1 month of last Eculizumab administration but treated via symptomatic medications. After administration of Eculizumab, a rapid improvement and normalization of platelets and other hematologic data were noticed alongside with further significant clinical improvement. Haptoglobin level was normalized 6 weeks after the administration of Eculizumab. As patient's clinical state and laboratory values were normalized and with negative support from kidney biopsy, we decided to cease further use of Eculizumab.

As elevation of liver enzymes continued throughout the course of the disease, a liver biopsy was performed showing no tissue pathology. Kidney biopsy was performed 1 week after the start of Eculizumab treatment and showed interstitial nephritis. Therefore, a pulse methylprednisolone therapy (5 days of duration) was administered followed by oral methylprednisolone therapy during following month. As kidney function was not improved, a second kidney biopsy was performed with the same histological features. A second pulse of methylprednisolone was thus performed 2 months after the first one, followed by oral mycofenolate mofetil with no recovery of kidney function afterward. Soon after methylprednisolone/mycofenolate use all liver enzymes fall to normal values after 6 months of its continuous elevation. Other supportive therapy (i.v. immunoglobulins) were also periodically administered. During the genetic workup, the whole coding regions of the genes encoding complement factor H (*CFH*), complement factor H-related protein 5 (*CFHR5*), factor I (*CFI*), membrane cofactor protein (*CD46*), thrombomodulin (*THBD*), factor B (*CFB*), C3 (*C3*), and diacylglycerol kinase-epsilon (*DGKE*) were analyzed by direct DNA sequencing following PCR amplification. The patient was found to be heterozygous for a substitution in exon 2 of the *CFHR5* gene (c.136C>T) causing a proline to serine change at codon 46 of the complement factor H-related protein 5 (p. P46S), interpreted as variant with unknown functional significance. Furthermore, the *CFH* H3 haplotype was identified in the patient, reported as a risk factor of aHUS.

3. Discussion

Since verotoxin test was negative, and the disease showed unusually severe course with MOF, typical HUS could be excluded safely despite obvious triggering of the disease by *C difficile*.[7–10] It is possible that the development of secondary HUS/TTP was related to severe protein loss, but predisposition by the presence of CFH H3 aHUS risk haplotype and/or by the p. P46S CFHR5 mutation should also be considered. Pathogenic factors identified for this case may represent rather a continuum: based on the current pathogenesis model, weak predispositing factors with strong trigger may jointly lead to the development of thrombotic microangiopathy. We consider protein loss (loss of plasma factors and regulators in the GI tract) as the major obstacle in pathogenesis, which may also explain the lack of activation product (sC5b9) elevation. Elevated LDH at the beginning of the disease and free hemoglobin lasting 5 weeks alongside with elevated D-dimers, low platelets, decreased ADAMTS13 activity, consistent and long lasting low level of haptoglobin supports the presence of secondary thrombotic microangiopathy, manifested as MOF and HUS. Genetic analysis does not fully support aHUS either. The boy's mutation was not described previously in patients with aHUS but was observed in 3 patients with MPGN II/DDD (PMID: 16299065) and also in healthy subjects with a relatively low frequency (0.8–1.8%). Based on these data this mutation may or may not have a pathogenic role in the development of aHUS, and was considered as variant with unknown functional significance. Importantly, the possibility of thrombotic microangiopathy triggered by

disseminated intravascular coagulation (DIC)—specific pathology seems plausible explanation.[11]

Therefore, one of the most presumable solutions for the diagnosis in our patient is DIC or consumption coagulopathy which can arise in sepsis-induced thrombotic microangiopathy (TMA), especially in severe cases with reduced ADAMTS13 activity.[12–17] The presence of DIC is supported by aPTT moderate elevation (normalized after 8 days) and reduced antitrombin III (probably due to protein loss) which lasts 12 days to full recovery alongside low platelets count.[4,6] A 7 weeks of elevated plasma D-dimers as well as decreased ADAMTS13 activity are nevertheless consistent with DIC but also with concomittant TMA.[4] Both, ADAMTS13 and aPTT have prognostic significance for DIC evolution indicating increased possibility of renal failure.[4,18,19] Normal level of fibrinogen as well as ISTH score repeatedly negative results are not compatible with DIC (low plasma fibrinogen is often associated with severe forms of DIC.[4–6] However, normal level of fibrinogen observed in severe septic DIC may be due to its substantial overproduction which compensates the rate of actual consumption.[6] We should expect prolonged PT (usually >50%) associated with liver disease, vitamin K deficiency and loss of the coagulation proteins due to massive bleeding.[4] The possible explanation may be the presence of circulating activated clotting factors, such as thrombin and Xa.[6]

After successful treatment of sepsis, symptoms of DIC soon decreased. Eculizumab treatment in sepsis-induced DIC with decreased ADAMTS13 activity was already successfully administered in adult patients.[12,13] The same treatment applies for the secondary TMA.[20] Judging from clinical feature and Eculizumab response, a secondary TMA seems to be probable. It is also supported by long lasting low level of haptoglobin and platelets from the beginning of the disease as well as by minor but steady hemolysis. Fast normalization of LDH is probably partly explained by plasma exchange. Low C3 supports potential concurrent TMA as well. Decreased C3, HF, and AP activity may support complement loss or activation and ongoing TMA; however, these parameters may also be related to infection related consumption. Since, due to a technical difficulties kidney biopsy was performed only 1 week after the start of Eculizumab treatment, it is not possible to draw firm conclusion about the presence or absence of TMA before treatment.

A potential crosstalk between complement and coagulation systems may be involved in our patient as complement is activated in most patients with DIC and active coagulation cascade.[11,12,21–23] Some authors suggested that patients with amplification of the complement and coagulation cascades with clinical progression of the disease may benefit from Eculizumab, preventing the generation of C5a and membrane attack complex impairment.[11,23] Rapid clinical and laboratory response (rise of platelets and C3) after Eculizumab administration best fits such possibility. Infection with *C difficile* supports all aforementioned diagnostic possibilities, (HUS, aHUS, secondary TMA DIC). Unrecognized immune deficiency afore present illness probably contributed to onset of *C difficile* infection-mediated disease since decreased levels of immunoglobulins (IgG, IgA, IgM) IgG) still exist after the cease of active disease.

To our best judgement Eculizumab administration in such clinical cases remains controversial. We are fully aware that if administered sooner than time-optimal without sufficient infection control of triggering MOF, Eculizumab might increase the risk of infection by meningococcus and encapsulated bacteria. By reducing massive complement activation, Eculizumab may temporarily help to prevent tissue damage involved in MOF. We do not recommend Eculizumab administration in all of MOF patients. Instead, a case-sensitive approach in patients with massive complement consumption with short course of Eculizumab may be considered as a temporary solution for complement inhibition. It may look like driving between Scylla and Charybdis but carefully timing Eculizumab administration will temporary reduce devastating complement activation and consumption, minimazing the risk of infection activation. Plausible withdrawal of the drug by its short course of administration may be the proper answer.

To our knowledge, this is the first report of a child treated with Eculizumab in such conditions. Carefully monitoring symptoms and signs of infection with real-time laboratory data and daily evaluation of patient's overall condition may lead physicians to optimal therapy approach. We believe that in similar clinical circumstances apart from *C difficile* triggering infection, the administration of Eculizumab should be at least considered.

4. Declarations

This publication has been approved for publishing in the journal *BMC Pediatrics* by the ethical committee of the University Hospital Centre Zagreb. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Author contributions

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Methodology: Danko Milosevic.
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Supervision: Danko Milosevic.
Validation: Danko Milosevic.
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Writing – review & editing: Daniel Turudic.

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