SciMedCentral

Journal of Clinical Nephrology and Research

Review Article

Complement-Mediated Microangiopathies

Yusuf Ulusoy*, Fahri Sahin, and Guray Saydam

Department of Internal Medicine and Hematology, Ege University Hospital, Turkiye

***Corresponding author**

Yusuf Ulusoy, Department of Internal Medicine and Hematology, Ege University Hospital, 35100 Bornova, Izmir, Turkiye, Tel: 902323903562; Email: ulusoy_yusuf@hotmail.com

Submitted: 01 April 2017

Accepted: 13 June 2017

Published: 15 June 2017

ISSN: 2379-0652

Keywords

- Complement
- Microangiopathies
- Hemolytic uremic syndrome
- Eculizumab

Abstract

Complement system includes about sixty plasma and membrane proteins that form a terminal lytic complex at the end of the cascade through three distinct pathways. It has three major functions; identification of foreign particles, elimination of them and enhancing inflammatory response. These mechanisms are well controlled but abnormal complement activation may pathologically happen as in complement-mediated hemolytic uremic syndrome, C3 glomerulopathies and systemic lupus erythematosus. Host cells are protected from this system by expressing complement regulatory molecules on their surfaces. The absence of these regulators makes cells sensitive to complement dependent lysis. Complement-mediated hemolytic uremic syndrome (HUS) results from a loss of function mutation in the genes complement factor H, CD46 (previously known as MCP) and gain of function mutation in the genes complement factor B, C3. Complement-mediated HUS formerly known as atypical HUS should be treated in a distinct manner from secondary HUS. The major and clinically important outcome is renal damage, however many distinct manifestations may occur during the disease course. Eculizumab, a C5 monoclonal antibody, is the agent that is used in treatment of complement-mediated HUS. Blockage of C5 by eculizumab prevents endothelial cell destruction caused by membrane attack complex which is the terminal product of complement system, and provides more satisfactory results than traditional treatment modalities. Even though this drug is a breakthrough for complement-mediated HUS, its high cost and side effects make clinicians to tend prudent use of it, thus a challenging issue emerges.

ABBREVIATIONS

ADAMTS13: A Disintegrin and Metalloproteinase with a Thrombospondin Type 1 Motif Member 13; C1,3,4,5,7: Complement Factors 1, 3, 4, 5, 7, respectively; CFB: Complement Factor B; CFH: Complement Factor H; CFI: Complement Factor I; DAF: Decay Accelerating Factor; DIC: Disseminated Intravascular Coagulation; HELLP: Hemolysis Elevated Liver Enzymes, Low Platelet Levels; HUS: Hemolytic Uremic Syndrome; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MAC: Membrane Attack Complex; MBL: Mannan-Binding Lectin; MCP: Membrane Cofactor Protein; PNH: Paroxysmal Nocturnal Hemoglobinuria; STEC: Shiga Toxin-Producing Escherichia Coli; THBD: Thrombomodulin; TMA: Thrombotic Microangiopathy; TTP: Thrombotic Trombocytopenic Purpura

INTRODUCTION

Hemolytic uremic syndrome (HUS) is one of the thrombotic microangiopathies which is described by the triad of intravascular red blood cell hemolysis, thrombocytopenia and acute renal injury. Even though what we understand is clear when a clinician talks about atypical hemolytic uremic syndrome, the "atypical" term for a disease with a known cause is no longer recommended, complement-mediated HUS term is more useful and clear. Current classification divides HUS into two categories; primary and secondary HUS. Primary HUS is caused by complement dysregulation, which includes mutations in the complement regulatory genes or antibodies against these regulators. Secondary HUS cases mostly occur after a period of diarrhea caused especially by Shiga toxin-producing Escherichia coli, as well as after an attributed drug exposure or during autoimmune disorders. Complement system is an enzyme cascade and plays role in innate immunity and inflammation. Normal cells express some regulatory proteins which prevent complement damage under physiologic conditions. Abnormalities in complement system are associated with some disorders, such as complement-mediated HUS, C3 glomerulopathies and systemic lupus erythematosus. Complement-mediated HUS is a relatively rare disorder affecting both children and adults. Nearly half of primary HUS cases demonstrate complement dysregulation such as loss of function mutations in the gene of complement factor H, CD46 or gain of function mutations in the gene of C3 and factor B. Antibodies against regulatory proteins may also cause complement-mediated HUS. Each abnormality has some differences on clinical onset and outcomes. Traditionally, the treatment of complement related disorders include plasma therapy and renal replacement but some advanced therapies come into practice to inhibit complement system. In this article we will review complement-mediated HUS in the context of how complement system acts.

COMPLEMENT SYSTEM

The discovery of complement dates back to the late 19th century when some investigators explored the bactericidal effects of plasma and serum [1]. Complement is now known as a maestro of innate immunity and it leads immunological and inflammatory processes, extending its formerly thought missions. Critical features include activation by triggers, enzymatic amplification at multiple steps, and rigid control to prevent self-damage. Complement system comprises nearly sixty plasma proteins and cell surface proteins, about half of them are regulatory proteins and some of them are proteases that are activated also by proteolysis as in the case of digestive system [2]. The complement system is a triggered-enzyme cascade which is initiated by a pathogen or apoptotic stimulus. Contact with a pathogen activates cascade and each precursor zymogen triggers the next zymogen to be cleaved and keep system to proceed.

Upon infections, the pathogens that lack complement regulatory proteins stimulate alternative pathway and a large quantity of complement activation occurs. This activation leads to generation of adaptive immunity and pathogen clearance. Pathogens are attacked by complement pathways to be eliminated by different mechanisms. Complement system includes anaphylatoxins that attract phagocytes to the site of inflammation, and activate leukocytes, endothelial cells and platelets.

Functions of the complement are destruction of microbes, clearance of apoptotic cells and immune complexes, promotion of inflammatory responses [3,4]. It's also known complement plays a role in angiogenesis, mobilization of hematopoietic progenitors, tissue regeneration [5-8]. Complement system works in plasma, tissues and within cells. This activity has to be well regulated into the limits of physiologic functions without excessive activity. Normal human cells express regulatory proteins on their membranes to prevent damaged by complement activity; plasma also contains some proteins to control excess complement activity [9].

During inflammatory responses complement system is activated and orchestrate inflammation, elimination of pathogens and allow adaptive immune system to gain time till it acts. Inadequate or excess complement activation both causes some disorders. Deficiency causes recurrent infections, mostly encapsulated bacterial infections, including Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae type b, and autoimmunity which usually presents with systemic lupus erythematosus. Deficiencies of complement regulatory proteins have been well described. C1 deficiency is associated with autoimmunity; a well described example is systemic lupus erythematosus. C1 inhibitor deficiency causes hereditary angioedema characterized by fatal edematous reaction of mucous membranes. CD59 and DAF deficiency causes paroxysmal nocturnal hemoglobinuria when erythrocytes are lack of these inhibitors. Heterozygous mutations in the genes for factor I, factor H, CD46, as well as autoantibodies to factor H or a gain-of-function mutation in C3 or factor B have been associated with complement-mediated HUS. C3 glomerulopathies, age-related macular degeneration are other examples for complement regulatory system abnormalities [10-13]. As knowledge increases about complement system and related disorders, targeted therapies come into question. In the last decade the aspect has changed markedly with the arrival of new agents to inhibit complement system, and continue to be developed.

COMPLEMENT SYSTEM ACTIVATION PATHWAYS

There are three distinct pathways of complement system to be activated; the classical, the alternative and the lectin pathway, however in reality these pathways are interconnected (Figure 1). The classical pathway includes components of C1 to C4 and can be initiated by the binding of C1q, the recognition subunit of C1, to the constant (Fc) regions of antigen-antibody complex. Immunoglobulin M or IgG both have capability to activate complement [14]. This binding allows interaction with innate and adaptive immunity. Beside the capacity of binding to antibodies, C1q may also recognize pathogenic molecules directly [15-17].

The lectin pathway, also called as mannan-binding lectin (MBL) pathway, is initiated by binding of mannan-binding lectin to carbohydrates on bacteria, viruses or fungi [18]. Ficolin and MBL-associated serine protease-2 (MASP-2) are another multimolecular complexes act as C1q on the classical pathway to activate complement without antigen-antibody interaction [19].

Alternative pathway elements are referred as factors, such as factor B. During physiologic conditions, alternative pathway is active to maintain a low level of complement activation to survey pathogens before they initiate inflammation by a process of spontaneous hydrolysis of C3 [20]. Hydrolysed C3 interacts with other alternative pathway molecules to form C3bBb and then it is stabilized by properdin, at last C3bBbP complex is formed, it is named as C3 convertase complex. C3b, formed by the classical and the lectin pathway, also facilitates this pathway.

All three pathways proceed to form their own C3 convertase. C3 convertase is a serine protease that cleaves C3 to C3a and C3b. This complex further increases the formation of C3b and in turn it augments the complement activity. C3 convertase also acts as a receptor for C5 to cleave it to C5b, but this interaction occurs with low affinity. After an additional C3b molecule binds to C3 convertase, C5 cleavage rate increases [21]. Enzymatic cleavage of C5 to C5a and C5b is the final step of each activation pathway. Upon cleavage, C5b molecule switches into a different conformational position and interacts with C6, C7, C8 and multiple C9 molecules, respectively [22]. The terminal molecule is named as the membrane attack complex (MAC), C5b-9, that creates a lytic pore in the membrane. C5b-7 is lipophilic and provides binding to the cell membrane [23]. C8 penetrates cell membrane; it is homologous to perforin, a cytolytic mediator produced by natural killer and cytotoxic T cells [24]. One to eighteen C9 molecules form a tubular channel to induce calcium flux and pathogen lysis [25,26]. Membrane attack complex regulation has critical importance to prevent self or excessive damage.

The classical and lectin pathway are responsible for degradation of apoptotic cells [27,28]. Apoptotic cells are lack of complement regulatory proteins and cannot escape from elimination by complement system. Additional pathways have been reported by some authors [29].

COMPLEMENT REGULATORS

C4b binding protein is a plasma protein that possesses two different inhibitor activity of complement; first it enzymatically

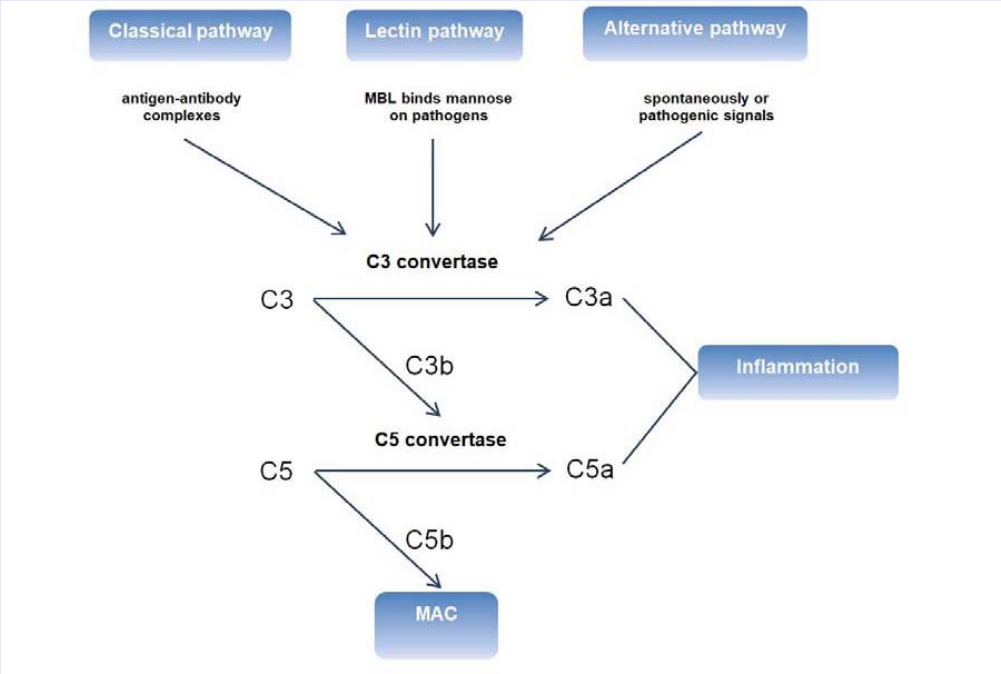

Figure 1 There are three major pathways to activate complement system. The classical pathway starts with binding of C1q to antigen-antibody complexes. After a sequence of enzymatic activity including complement factor 4 (C4) and complement factor 2 (C2), the C3 convertase is formed. The lectin pathway depends on carbohydrates on pathogens to be activated; once it is activated it proceeds to form C3 convertase after an enzymatic activity alike in the classical pathway. The alternative pathway is perpetually active and resembles a low-level C3b activity during physiologic conditions. C3b interacts with the alternative pathway molecules to form C3 convertase, then it further cleaves more C3 and self amplifies this pathway. Before the so-called terminal pathway sets in, C3a and C5a both take a role in inflammation while C3b opsonizes pathogen. MAC, the terminal pathway of these mechanisms, lyses cellular membranes. (MBL: Mannan-Binding Lectin; C3: Complement Factor 3; C5: Complement Factor 5; MAC: Membrane Attack Complex).

splits C4b2a complex, and second it acts as a cofactor of plasma enzyme factor I which is another complement inhibitor.

C1 inhibitor is the only plasma inhibitor for activated C1 and it controls initiation of the classical pathway and the lectin pathway. DAF (CD55) and CD46 are membrane proteins that work together and complete each other. DAF makes C2a to split from C4b2a, CD46 is a cofactor for factor I-mediated cleavage of C4b. Considering DAF is active to inhibit convertase on the membrane, the intercellular space could be the area of new forming convertases, but CD46 is a kind of buffer mechanism to block the fluid-phase convertase activity. This relationship makes them co-workers. Additionally, DAF and CD46 inhibit C3bBb activity.

Complement receptor 1 (CD35) is another membrane-located regulator of C4b2b. CFH presents in the plasma and displace Bb from C3bBb to inhibit C3 convertase activity. Complement system comprises inflammatory mediator such as C3a and C5a and these molecules have some regulations also. Controlling C3 convertase is a key regulation mechanism of complement system, but later stages can also be controlled. S protein binds to a site on the membrane and prevents C5b-7 complex to be settled on the cell. MAC is inhibited by CD59 (MAC inhibitor factor). CD59 is expressed on almost all cell types and blocks C9 to bind C5b-8 complex. Gain of function mutations in the gene of factor B also plays role in complement-mediated HUS [30]. Factor B interacts with C3b in the alternative pathway of complement system; forming C3bBb after cleaved by factor D to Bb and Ba.

COMPLEMENT-MEDIATED HUS

Hemolytic uremic syndrome is defined by microangiopathic hemolytic anemia accompanying by thrombocytopenia and acute kidney injury. While the most common cause of HUS is Shiga toxin-producing Escherichia coli infection, complement dysregulation accounts some of them, especially non STEC-associated cases. Since we have found out more about the pathogenesis of non STEC-associated HUS, the term atypical HUS is displaced by complement-mediated HUS. Thus, HUS is currently divided into two categories; primary causes, which is related either complement gene mutations or antibodies to complement factor H; and secondary causes, which is related with an infection, drug, pregnancy or autoimmune diseases [31]. Quinine, gemcitabine, quetiapine, mitomycin, cyclosporine, tacrolimus, bevacizumab, cocaine are some of the drugs that may cause secondary hemolytic uremic syndrome [32]. Complement dysregulation accounts for about 50% of none STEC-associated HUS [33]. A link between complement system abnormality and hemolytic uremic syndrome was first described in 1981 in an Asian family [34]. To date, many complement system associated mutations have been described. It is believed that complement-mediated HUS is triggered by a means, such as infection or pregnancy if an individual patient has complement system dysregulation. When a pathogen stimulates complement system, defective regulation on host cells causes unremitting complement activity; this in turn perpetuates the cascade to form the end products, such as C3 convertase complex, MAC. Vascular

endothelial cells are damaged by MAC and prothrombotic milieu arises leading to the activation of coagulation cascade. Renal endothelial damage and microvascular thrombosis occurs as a result. Microvascular thrombosis creates shear stress and results in both thrombocytopenia and erythrocyte fragmentation.

GENETIC DEFECTS IN COMPLEMENT-MEDIATED HUS

Nearly a half of patients with complement-mediated HUS have mutation of complement regulatory proteins or autoantibodies against them, but individuals those whom have a family history of complement-mediated HUS have more detectable genetic cause [35]. The molecular defects include inactivating mutations of C3 convertase inhibitors; CFH (25%), CD46 (5 to 10%), CFI (5 to 10%); THBD (5 to 10%) and gain-of-function mutations of activators C3 (5 to 10%), CFB (1%) [33,35]. Compound mutations are found in about 10% of the affected individuals [36-38]. Anti-CFH antibodies have been reported in about 8 to 10% of cases [39,40]. These antibodies disrupt binding of CFH to C3 convertase C3bBb. Anti-CFH antibody are associated with more aggressive clinical features and more frequent relapses when compared with other type complement dysregulated cases [39,41,42]. Possibly the gene region of CFH related proteins 1-5 are mutated in some patients and associated with severe disease in some conditions [43]. Beside this, long term outcomes are affected by which genetic abnormalities the patient have; while 80 to 90% of patients with only CD46 mutation has normal renal functions and no hematologic abnormalities after therapy, patients with mutation of CFH has only 20 to 30% and non-mutation-detected patients have 40% long-time outcomes [41].

More than 100 mutations in CFH have been described, although most of those do not clinically manifested [34,44,45]. Once CFH gene related disorder becomes overt, it has the worst course of all complement-mediated HUS, and proceeds to end stage renal disease in approximately 60% of patients despite best care [42].

CLINICAL PRESENTATION

Complement-mediated HUS is a relatively rare disorder that affects both children and adults. In nearly half of patients the disease may occur spontaneously, on the other hand it is triggered by infection, surgery, pregnancy, inflammation and trauma. The clinical trial is microangiopathic hemolysis, thrombocytopenia and acute kidney injury, but it affects multiple systems. Abdominal pain, diarrhea, nausea, headache, visual disturbances, dyspnea, mental status changes or even seizures and coma may be the presentation. Although the association of diarrhea and STEC-HUS is well known, in up to 24% of patients with complement-mediated HUS describe diarrhea [33]. Hypertension may be present due to glomerular injury caused by microthrombosis. Acute kidney injury may be severe and requires dialysis. Cardiac involvement includes arrhythmias, myocardial injury, pericarditis and heart failure. Some patients present with multiple organ failure due to diffuse microthrombosis and it proceeds to death unless immediately treated. It is reported that unusual presentations may become, such as in a case scenario of hypertension accompanying with proteinuria and mild thrombocytopenia, without overt loss of kidney function and hemolysis.

DIAGNOSIS

Complement-mediated HUS must be distinguished from other TMAs but there is no specific laboratory test for this (Figure 2). Thrombocytopenia, anemia and elevated serum lactate dehydrogenase level suggests a TMA is possible. Further studies, such as haptoglobin, bilirubin, peripheral blood smear, must be done. Schistocytes on peripheral blood smear are essential to define TMA but they may not be seen at early phases of the disease. It is crucial to draw blood for ADAMTS13 activity and inhibitor levels before treatment. Complement dysregulation must be evaluated in patients presenting with microangiopathic hemolytic anemia. Patients with family history require more attention. It is important that the presence of ADAMTS13 deficiency makes TTP more possible and the presence of bloody diarrhea with a positive Shiga toxin test or culture positivity makes STEC-HUS more possible. It must be kept in mind a group of patients presenting with diarrhea have complement-mediated HUS, and not all patients with STEC-HUS give a history diarrhea [42]. Pneumococcal-associated HUS occurs mainly in children, and rarely affects adults [46]. As well as pneumococcal studies have to be done in a patient with TMA. ADAMTS13 activity less than 5%, the diagnosis is TTP. Serum levels of C3, C4, CFH, CFI and genetic mutation analysis may guide to establish diagnosis; however they may be all normal, because serum complement activity poorly correlate with serum levels of them [47]. Not all non-TTP and non-STEC-HUS patients have complement-mediated HUS; DIC, HELLP, anti-phospholipid antibody syndrome, heparin-induced thrombocytopenia, PNH, autoimmune and infectious processes have to be excluded before the diagnosis made. Although TTP is more common in adults and STEC-HUS is more common in children, complement-mediated HUS can present at any age. HUS cases almost always have renal involvement, but TTP causes renal injury in a minor subset of patients [48]. Thus, neither age nor the type of organ involvement can be used as a reliable diagnostic tool.

TREATMENT

The condition is life-threatening and requires immediate approach to avoid organ damage and death. In addition to supportive care such as appropriate fluid and electrolyte replacement; dialysis, plasma exchange or infusion was a mainstay of therapy for a long time before eculizumab era. The rationale of plasma therapy is to maintain normal levels of complement regulatory proteins and to remove antibodies to these regulators. Although there are no evidence, plasma exchange is preferred rather than infusion by most experts, as it avoids the risk of volume overload in the condition of acute kidney injury. Plasma therapy provides hematologic recovery of more than a half of patients [33]. The lesser the time between the disease onset and starting therapy, the more the possibility of kidney function recovery occurs [49]. Plasma therapy should be performed daily until platelet count, serum lactate dehydrogenase and hemoglobin levels are gradually improved, or as long as waiting for test results for complement system. Permanent kidney damage requiring dialysis cannot be avoided in some group of patients despite periodic plasma therapy anyway [50]. Eculizumab is a humanized monoclonal antibody against C5. It prevents the cleavage of C5 to C5a and C5b and

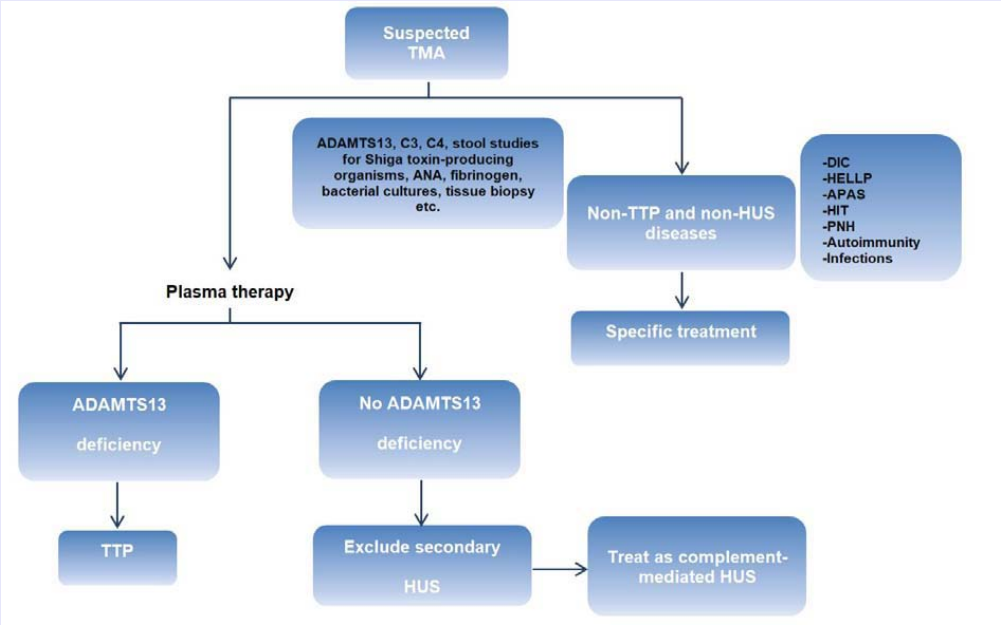

Figure 2 A patient with thrombocytopenia and intravascular hemolysis should be suspected as TMA, although TMA is a pathological definition. After a careful exclusion of non-TTP and non-HUS diseases, patients should be empirically treated with plasma infusion or plasmapheresis if blood is drawn for ADAMTS13 studies. More than %10 of ADAMTS13 activity and no detectable ADAMTS13 inhibitor cautiously exclude TTP. If secondary causes of HUS such as shiga toxin-producing organism infections, suspicious drug exposure cannot be documented, patients are presumed to have complement-mediated HUS, especially if genetic tests indicate complement dysregulation. (ADAMTS13: A Disintegrin and Metalloproteinase with a Thrombospondin Type 1 Motif, Member 13; ANA: Anti-Nuclear Antibody; HUS: Hemolytic Uremic Syndrome; TTP: Thrombotic Thrombocytopenic Purpura; DIC: Disseminated Intravascular Coagulation; HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet Levels; APAS: Anti-Phospholipid Antibody Syndrome; HIT: Heparin-Induced Thrombocytopenia; PNH: Paroxysmal Nocturnal Hemoglobinuria).

the formation of membrane attack complex, thereby reducing endothelial damage and microthrombosis. Observational studies demonstrate its effectiveness especially in patients with severe complement-mediated HUS who are at risk for end-stage renal disease, mortality or recurrence [51]. There are some case series revealing the effectiveness of eculizumab. It is observed that eculizumab decreases dialysis dependence, improves renal functions, maintains normal platelet and serum lactate dehydrogenase levels in patients with complement-mediated HUS [52]. Eculizumab is shown to be safe and effective in pediatric patients according to a prospective phase II trial by Greenbaum et al. [53]. Eculizumab may have some side effects such as infection with encapsulated bacterial organisms. Thus, patients must be vaccinated against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenza type b at least 14 days before initiation of eculizumab therapy. Other serious side effects include hypertension, asymptomatic bacteremia, peritonitis and venous sclerosis at the infusion site [54]. Current approach is life-long treatment with eculizumab, but clinicians make an effort to discontinue this therapy considering side effects and high cost. There are a few case series in the literature searching eculizumab cessation in complement-mediated HUS patients. In a study, 3 of 10 patients relapsed after discontinuation and all of them recovered without any complication after resuming eculizumab [55]. Another study including 17 patients has shown favorable outcomes after cessation of eculizumab therapy, noting that 6 of them have no known complement dysregulation [56]. The largest case serial has been reported by Fakhouri et al. [57]. Virtually all patients in France those whom discontinued eculizumab therapy have been reviewed and monitored closely for relapse. The study indicates that genetic abnormalities do not affect response to eculizumab but are major factors for complement-mediated HUS relapse. All patients have recovered their baseline renal function after prompt resuming of eculizumab. CFH dysregulated patients appear to have the highest probability of relapse, however patients respond well after early initiation of eculizumab. With these limited data obtained from relatively small and single center case studies, the decision to discontinue eculizumab therapy depends on risk assessment for relapse. Genetic abnormality is the major determinant guiding cessation of eculizumab, but additional factors such as age, renal function status, patient preference and adherence, as well as high cost issue, are need to be interpreted.

Complement regulatory proteins CFH, CFI, CFB, and C3 are synthesized in the liver. Thus, liver transplantation has been successfully performed in some patients [58-65]. However, isolated liver transplantation is not recommended in complement-mediated HUS patients with normal functioning kidney due to possible adverse effects of long term immunosuppressive therapy [66]. Renal transplantation may be beneficial for some subgroup of patients. Patients, who failed to respond to plasma therapy and eculizumab, are candidates for renal transplantation. Patients should undergo transplantation with a preventive therapy such as plasma infusion, plasmapheresis or eculizumab. Although CFH and C3 mutated patients have unfavorable outcomes, patients with CD46 mutation may have better outcomes after renal transplantation [43,45,67,68]. CFI mutations do not carry a high

risk of recurrence of complement-mediated HUS; however some studies have conflicting results [47,69,70]. Recurrent disease should be treated with eculizumab since plasma therapy is not beneficial for these patients [71].

DISCUSSION & CONCLUSION

It is important to describe patients with complement-mediated HUS and distinguish them from other TMAs, considering their treatment options and follow-up parameters are different from each other. Unfortunately there is no early marker of complement-mediated HUS, so the diagnosis depends on the clinicians suspect based on the physical exam, available laboratory results and patient history. As we understand the molecular basis of complement-mediated HUS, genetic testing becomes more important. Another compelling issue is what the best treatment is for patients with complement-mediated HUS. Eculizumab has satisfactory results since it has first used to inhibit complement cascade. Nonetheless, the disease has more complicated course and the main concern is whether our patient will be dialysis dependent or not. The question is how long the eculizumab therapy should continue, even though there are some limited data about it, there is no certain answer, until longer term experiences have been obtained.

REFERENCES

1. Mayer MM. Complement: historical perspectives and some current issues. Complement. 1984; 1: 2-26.
2. Kemper C, Pangburn MK, Fishelson Z. Complement nomenclature 2014. Mol Immunol. 2014; 61: 56-58.
3. Walport MJ. Complement. First of two parts. N Engl J Med. 2001; 344: 1058-1066.
4. Walport MJ. Complement. Second of two parts. N Engl J Med. 2001; 344: 1140-1144.
5. Kahr WH. Complement halts angiogenesis gone wild. Blood. 2010; 116: 4393-4394.
6. King KY, Goodell MA. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. Nat Rev Immunol. 2011; 11: 685-692.
7. Lee HM, Wysoczynski M, Liu R, Shin DM, Kucia M, Botto M, et al. Mobilization studies in complement-deficient mice reveal that optimal AMD3100 mobilization of hematopoietic stem cells depends on complement cascade activation by AMD3100-stimulated granulocytes. Leukemia. 2010; 24: 573-582.
8. Mastellos DC, Deangelis RA, Lambris JD. Complement-triggered pathways orchestrate regenerative responses throughout phylogenesis. Semin Immunol. 2013; 25: 29-38.
9. Nicolas S. Merle, Remi Noe, Lise Halbwachs-Mecarelli, Veronique Fremeaux-Bacchi, Lubka T. Roumenina. Complement System Part II: Role in Immunity. Front Immunol. 2015; 6: 257.
10. Fakhouri F, Frémeaux-Bacchi V, Noël LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. Nat Rev Nephrol. 2010; 6: 494-499.
11. Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C. Complement factor H polymorphism and age-related macular degeneration. Science. 2005; 308: 421-424.
12. Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005; 308: 419-421.
13. Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308: 385-389.
14. Kishore U, Ghai R, Greenhough TJ, Shrive AK, Bonifati DM, Gadjeva MG, et al. Structural and functional anatomy of the globular domain of complement protein C1q. Immunol Lett. 2004; 95: 113-128.
15. Roumenina LT, Popov KT, Bureeva SV, Kojouharova M, Gadjeva M, Rabheru S, et al. Interaction of the globular domain of human C1q with Salmonella typhimurium lipopolysaccharide. Biochim Biophys Acta. 2008; 1784: 1271-1276.
16. Albertí S, Marqués G, Hernández-Allés S, Rubires X, Tomás JM. Interaction between complement subcomponent C1q and the Klebsiella pneumoniae porin OmpK36. Infect Immun. 1996; 64: 4719-4725.
17. Gaboriaud C, Frachet P, Thielens NM, Arlaud GJ. The human c1q globular domain: structure and recognition of non-immune self ligands. Front Immunol. 2011; 2: 92.
18. Matsushita M, Endo Y, Taira S, Sato Y, Fujita T, Ichikawa N, et al. A novel human serum lectin with collagen- and fibrinogen-like domains that functions as an opsonin. J Biol Chem. 1996; 271: 2448-2454.
19. Matsushita M, Endo Y, Fujita T. Structural and functional overview of the lectin complement pathway: its molecular basis and physiological implication. Arch Immunol Ther Exp (Warsz). 2013; 61: 273-283.
20. Müller-Eberhard HJ. Molecular organization and function of the complement system. Annu Rev Biochem. 1988; 57: 321-347.
21. Kinoshita T, Takata Y, Kozono H, Takeda J, Hong KS, Inoue K. C5 convertase of the alternative complement pathway: covalent linkage between two C3b molecules within the trimolecular complex enzyme. J Immunol. 1988; 1950: 3895-3901.
22. Hadders MA, Bubeck D, Roversi P, Hakobyan S, Forneris F, Morgan BP, et al. Assembly and regulation of the membrane attack complex based on structures of C5b6 and sC5b9. Cell Rep. 2012; 1: 200-207.
23. Preissner KT, Podack ER, Müller-Eberhard HJ. The membrane attack complex of complement: relation of C7 to the metastable membrane binding site of the intermediate complex C5b-7. J Immunol. 1985; 1950: 445-451.
24. Hadders MA, Beringer DX, Gros P. Structure of C8alpha-MACPF reveals mechanism of membrane attack in complement immune defense. Science. 2007; 317: 1552-1554.
25. Bhakdi S, Tranum-Jensen J. Complement lysis: a hole is a hole. Immunol Today. 1991; 12: 318-320.
26. Cole DS, Morgan BP. Beyond lysis: how complement influences cell fate. Clin Sci. 2003; 1979: 455-466.
27. Nauta AJ, Castellano G, Xu W, Woltman AM, Borrias MC, Daha MR, et al. Opsonization with C1q and mannose-binding lectin targets apoptotic cells to dendritic cells. J Immunol. 2004; 173: 3044-3050.
28. Clarke EV, Weist BM, Walsh CM, Tenner AJ. Complement protein C1q bound to apoptotic cells suppresses human macrophage and dendritic cell-mediated Th17 and Th1 T cell subset proliferation. J Leukoc Biol. 2015; 97: 147-160.
29. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, et al. Generation of C5a in the absence of C3: a new complement activation pathway. Nat Med. 2006; 12: 682-687.
30. Goicoechea de Jorge E, Harris CL, Esparza-Gordillo J, Carreras L, Arranz EA, Garrido CA, et al. Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome. Proc Natl Acad Sci U S A. 2007; 104: 240-245.

31. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6: 60.

32. Zayd L. Al-Nouri, Jessica A. Reese, Deirdra R. Terrell, Sara K. Vesely, James N. George. Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood. 2015; 125: 616-618.

33. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010; 5: 1844-1859.

34. Thompson RA, Winterborn MH. Hypocomplementaemia due to a genetic deficiency of beta 1H globulin. Clin Exp Immunol. 1981; 46: 110-119.

35. Le QM, Roumenina L, Noris M, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome associated with mutations in complement regulator genes. Semin Thromb Hemost. 2010; 36: 641-652.

36. Geerdink LM, Westra D, van Wijk JA, Dorresteijn EM, Lilien MR, Davin JC, et al. Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics. Pediatr Nephrol. 2012; 27: 1283.

37. Kavanagh D, Richards A, Fremeaux-Bacchi V, Noris M, Goodship T, Remuzzi G,et al. Screening for complement system abnormalities in patients with atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol. 2007; 2: 591.

38. Esparza-Gordillo J, Jorge EG, Garrido CA, Carreras L, López-Trascasa M, Sánchez-Corral P, et al. Insights into hemolytic uremic syndrome: segregation of three independent predisposition factors in a large, multiple affected pedigree. Mol Immunol. 2006; 43: 1769.

39. Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, et al. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol. 2010; 21: 2180-2187.

40. Moore I, Strain L, Pappworth I, Kavanagh D, Barlow PN, Herbert AP, et al. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. Blood. 2010; 115: 379-387.

41. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006; 108: 1267.

42. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007; 18: 2392.

43. Bienaime F, Dragon-Durey MA, Regnier CH, Nilsson SC, Kwan WH, Blouin J, et al. Mutations in components of complement influence the outcome of Factor I-associated atypical hemolytic uremic syndrome. Kidney Int. 2010; 77: 339-349.

44. Loirat C, Noris M, Fremeaux-Bacchi V. Complement and the atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2008; 23: 1957-1972.

45. Warwicker P, Goodship TH, Donne RL, Pirson Y, Nicholls A, Ward RM, et al. Genetic studies into inherited and sporadic hemolytic uremic syndrome. Kidney Int. 1998; 53: 836-844.

46. Waters AM1, Kerecuk L, Luk D, Haq MR, Fitzpatrick MM, Gilbert RD, et al. Hemolytic uremic syndrome associated with invasive pneumococcal disease: the United kingdom experience. J Pediatr. 2007; 151: 140-144.

47. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Marie-Agnès Dragon-Durey, Stéphanie Ngo, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults.Clin J Am Soc Nephrol. 2013; 8: 554-562.

48. Cataland SR, Wu HM. Atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: clinically differentiating the thrombotic microangiopathies. Eur J Intern Med. 2013; 24: 486-491.

49. Waters AM, Licht C. aHUS caused by complement dysregulation: new therapies on the horizon. Pediatr Nephrol. 2013; 28: 165.

50. Loirat C, Garnier A, Sellier-Leclerc AL, Kwon T. Plasmatherapy in atypical hemolytic uremic syndrome. Semin Thromb Hemost. 2010; 36: 673-681.

51. Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, Cantrell A. A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). BMJ Open. 2013; 3: e003573.

52. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Eng J Med. 2013; 368: 2169-2181.

53. Greenbaum LA, Fila M, Ardissino G, Al-Akash SI, Evans J, Paul H, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int. 2016; 89: 701-711.

54. Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int. 2015; 87: 1061-1073.

55. Ardissino G, Testa S, Possenti I, Tel F, Paglialonga F, Salardi S, et al. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. Am J Kidney Dis. 2014; 64: 633.

56. Merrill SA, Brittingham ZD, Yuan X, Moliterno AR, Sperati CJ, Brodsky RA, et al. Eculizumab cessation in atypical hemolytic uremic syndrome. Blood. 2017.

57. Fakhouri F, Fila M, Provôt F, Delmas Y, Barbet C, Valérie C, et al. Pathogenic Variants in Complement Genes and Risk of Atypical Hemolytic Uremic Syndrome Relapse after Eculizumab Discontinuation. Clin J Am Soc Nephrol. 2017; 12: 50-59.

58. Albertazzi V, Bonucchi D, De Amicis S, Americo C, Ghiandai G, Cappelli G. A favorable 3-year outcome of kidney transplantation in atypical hemolytic uremic syndrome associated with a factor H mutation: case report. Transplant Proc. 2010; 42: 1352-1354.

59. Remuzzi G, Ruggenenti P, Colledan M, Gridelli B, Bertani A, Bettinaglio P, et al. Hemolytic uremic syndrome: a fatal outcome after kidney and liver transplantation performed to correct factor H gene mutation. Am J Transplant. 2005; 5: 1146-1150.

60. Cheong HI, Lee BS, Kang HG, Hahn H, Suh KS, Ha IS, et al. Attempted treatment of factor H deficiency by liver transplantation. Pediatr Nephrol. 2004; 19: 454-458.

61. Saland JM, Emre SH, Shneider BL, Benchimol C, Ames S, Bromberg JS, et al. Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. Am J Transplant. 2006; 6: 1948-1952.

62. Haller W, Milford DV, Goodship TH, Sharif K, Mirza DF, McKierna PJ. Successful isolated liver transplantation in a child with atypical hemolytic uremic syndrome and a mutation in complement factor H. Am J Transplant. 2010; 10: 2142-2147.

63. Sánchez-Corral P, Melgosa M. Advances in understanding the aetiology of atypical haemolytic uraemic syndrome. Br J Haematol. 2010; 150: 529-542.

64. Saland JM, Shneider BL, Bromberg JS, Shi PA, Ward SC, Magid MS, et al. Successful split liver-kidney transplant for factor H associated hemolytic uremic syndrome. Clin J Am Soc Nephrol. 2009; 4: 201-206.

65. Wilson C, Torpey N, Jaques B, Strain L, Talbot D, Manas D, et al. Successful simultaneous liver-kidney transplant in an adult with atypical hemolytic uremic syndrome associated with a mutation in complement factor H. Am J Kidney Dis. 2011; 58: 109-112.

66. Zuber J, Le Quintrec M, Morris H, Frémeaux-Bacchi V, Loirat C, et al. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. Transplant Rev (Orlando) 2013; 27: 117-125.

67. Noris M, Brioschi S, Caprioli J, Todeschini M, Bresin E, Porrati F, et al. Familial haemolytic uraemic syndrome and an MCP mutation. Lancet. 2003; 362: 1542-1547.

68. Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. Am J Transplant. 2010; 10: 1517-1523.

69. Le Quintrec M, Zuber J, Moulin B, Kamar N, Jablonski M, Lionet A, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. Am J Transplant. 2013; 13: 663-675.

70. Zuber J, Le Quintrec M, Sberro-Soussan R, Loirat C, Frémeaux-Bacchi V, Legendre C. New insights into postrenal transplant hemolytic uremic syndrome. Nat Rev Nephrol. 2011; 7: 23-35.

71. Zuber J, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012; 12: 3337-3354.

Cite this article

Ulusoy Y, Sahin F, Saydam G (2017) Complement-Mediated Microangiopathies. J Clin Nephrol Res 4(3): 1067.