

A Perspective of Immunologists in Thrombotic Microangiopathies

Sabry Abd-Allah Shoeib MD, PhD¹, Alaa Efat Abdel-Hamid MD¹, Emad Mohammad El-Shibeni MD¹
and Amira Abdel-Monem Noureldeen M.B.B.CH².

¹Department of Internal Medicine, Faculty of Medicine, Menoufia University, Egypt.

²Resident Doctor of Internal Medicine, 10th of Ramadan hospital, HIO, Egypt.

amiranoureddin@hotmail.com

Abstract: Objectives: Aim of this work To understand the immunological bases of Thrombotic microangiopathy syndromes and their implications in diagnosis and therapy. **Data Sources:** Medline databases (PubMed, Medscape, [Science Direct](#)) and all materials available in the Internet from 2009 to 2017. **Article Selection:** The article studied, if the articles did not fulfill the inclusion criteria they were excluded. **Data Extraction:** If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, adequate information and defined assessment measures. **Data Synthesis:** Short reviews were made on thrombotic microangiopathy Syndromes. **Findings:** In total 63 potentially relevant publications were included, 37 were about immuno-pathogenesis of thrombotic microangiopathy. 26 were about immune –based diagnosis and therapy of thrombotic microangiopathy. **Conclusion:** The immune system plays an important role in the pathogenesis of thrombotic Microangiopathies, either through aberrant complement activation, or through autoantibodies formation. In thrombotic thrombocytopenic purpura, Complement can be activated through anti-ADAMTS13 antibodies immune complexes, or infected or damaged cells. New ADAMTS13 autoantibody testing has prognostic values and also differentiates acquired TTP from rare cases of hereditary TTP. Plasma exchange replenish ADAMTS-13 and remove the ultra-large Von Willebrand Factor and ADAMTS-13 autoantibodies. Adjunctive immunosuppressive therapy as humanized anti-CD20 monoclonal antibody (Rituximab) with plasma exchange produced good response in patients with refractory or relapsing acquired TTP, also Adjuvant treatment with intravenous immunoglobulin (IVIG) potentiate remission. In Shiga-toxin-induced HUS, it is thought that complement is activated via p-selectin, The atypical Hemolytic Uremic Syndrome results from aberrant complement alternative pathway activation secondary to mutation in *CFH*, *CFI*, *CD46*, *THBD*, *CFB* and *C3* genes or anti-FH antibodies. A recent study has confirmed C3 reduction in severe cases of shigatoxin E.coli-HUS, also Low levels of C4 have also been observed. Eculizumab (anti-C5) is recommended for cases of aHUS. [Sabry Abd-Allah Shoeib, Alaa Efat Abdel-Hamid, Emad Mohammad El-Shibeni and Amira Abdel-Monem Noureldeen. **A Perspective of Immunologists in Thrombotic Microangiopathies.** *Stem Cell* 2017;8(4):50-53]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). <http://www.sciencepub.net/stem>. 9. doi:[10.7537/marsscj080417.09](https://doi.org/10.7537/marsscj080417.09).

Key words: thrombotic Microangiopathy, acquired TTP, HUS, complement activation, ADAMTS13 autoantibodies.

1. Introduction

Thrombotic microangiopathies syndromes (TMAs) consists of group of diseases sharing common histopathologic and clinical findings. The differential diagnoses are generally broad, while the workup is complex and may be confusing. Pathologically microvascular thrombosis, consumptive thrombocytopenia and microangiopathic haemolytic anaemia (MAHA), lead to end-organ damage and infarction. Patients may present with acute renal failure and/or cerebral dysfunction, although other organ involvement can also occur (1).

TMA is a life-threatening disease that was associated with a high mortality rates, of more than 90% before treatment with plasmapheresis. Nowadays, survival rates have significantly improved, but sporadic non-Shiga-toxin-induced HUS still has a mortality rate of up to 50% in some patients. The outbreak of diarrhea-associated HUS due to E. coli

O104: H4 in Germany in 2011 have demonstrated the severity of this disease. Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are the two most important conditions which have distinct pathophysiologies and treatment pathways. TMAs can also occur associated with cancer, infection, transplantation, drug use, autoimmune disease, and pre-eclampsia and hemolysis, elevated liver enzymes and low platelet count syndrome in pregnancy (2).

2. Materials and Methods

Search Strategy: We reviewed papers on the immunological bases of TMA from Medline databases which are (Pub Med, Medscape, Science Direct) and also materials available in the Internet. We used / Thrombotic Microangiopathies / Thrombotic thrombocytopenic purpura / Acquired TTP /atypical hemolytic uremic syndrome /complement activation /

ADAMTS13 autoantibodies / HIV associated TMA / Pregnancy associated TMA /cancer associated TMA/ Eculizumab as searching terms.

Article Selection: All the reviews were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

-Published in English language.

-Focused on and discussed the immunological bases of Thrombotic microangiopathy syndromes and their implications in diseases and therapy.

Data Synthesis: A structured systematic review was performed illustrated with diagrams.

3. Results:

The initial search presented 260 articles, papers and journals about the title of the article with the key words mentioned; extraction was made, including assessment of quality and validity of papers. 63 published articles met the inclusion criteria. Studies concerning with complement dysregulation, autoantibodies formation in TMA syndromes was collected; arranged in topics through the article.

4. Discussion

Thrombotic microangiopathies syndromes (TMAs) consists of group of diseases sharing common histopathologic and clinical findings. The differential diagnoses are generally broad, while the workup is complex and may be confusing. In recent years, The ADAMTS-13 deficiency and defective complement regulation became the two major causes of thrombotic microangiopathies. Now classification of thrombotic TMA is pathogenetically rather than clinically. This pathogenesis-based disease classification requires new diagnostic approaches and provides a framework for therapeutic plans (3).

Immunopathogenesis Of Tma: (Searching For Clues)

The immune system plays an important role in the pathogenesis of TMA, through either aberrant complement activation, or through auto-antibodies formation. Thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome and typical shiga toxin-induced hemolytic uremic syndrome are all diseases of aberrant complement activation. Acquired TTP is an autoimmune disease due to formation of ADAMTS 13 autoantibodies, also quinine-induced TMA is due to formation of antibodies. Diagnostic evaluation and treatment of TMA syndromes should be initiated concurrently. Clinical diagnosis is often unreliable, and testing takes some time, so empirical treatment should be started in patients presenting with MAHA, thrombocytopenia and renal and/or neurological dysfunction. it is recommended to start 'urgent and empirical' therapeutic plasma exchange

(TPE) with fresh frozen plasma or solvent-treated plasma, in children presented with shiga toxin-induced HUS (4).

Thrombotic thrombocytopenic purpura

In thrombotic thrombocytopenic purpura, activation of complement has an important pathogenic mechanism. Complement can be activated directly in several ways, including anti-ADAMTS13 antibodies immune complexes, or infected or damaged cells. Anti-ADAMTS13 IgG antibodies particularly subtypes 1 and 3 may directly activate the classical complement pathway, while IgG2 activates the alternative pathway better. Inflammatory cytokines have an important role in TTP as IL-10 stimulates anti-ADAMTS13 IgG production, leading to antibody-mediated complement activation, also IL-6 stimulates the inflammatory response associated with microvascular thrombosis in TTP (5).

In acquired TTP, anti-ADAMTS13 autoantibodies may alter enzyme function either through direct neutralizing effect, by inhibition of ADAMTS13 activity, or through opsonization process and phagocytosis. Measurement of ADAMTS13 activity is the most commonly used laboratory test in the workup of suspected TTP. New tests for ADAMTS13 autoantibodies provide prognostic information related to response to TPE and risk of relapse, and also differentiates acquired TTP from hereditary TTP. Anti-ADAMTS13 IgG, as detected by ELISA, were found in a majority of patients with severe ADAMTS13 deficiency (6).

Treatment of acquired TTP with plasma exchange remove auto-antibodies and ULWVF and replenish ADAMTS13 activity. Immunosuppressive therapy (e.g., Glucocorticosteroids and Rituximab) inhibits autoantibody formation. Although the survival rate among patients with acquired TTP exceeds 80%, patients remain at risk for microthrombotic complications until remission is achieved. Rapid-onset therapy designed to prevent further micro-thrombus formation by targeting the binding of platelets to ultralarge von Willebrand factor multimers is a potential approach to the treatment of acquired TTP. Caplacizumab, an anti-von Willebrand factor humanized single-variable-domain immunoglobulin (Nanobody, Ablynx), targets the A1 domain of von Willebrand factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor, so used for treating acquired TTP (7).

Hemolytic Uremic Syndrome

In shiga-toxin mediated HUS, complement activation happens through different mechanisms. First, purified Stx-2 selectively bind complement factor H and also activate complement. Secondly, lipopolysaccharide (LPS) activates complement, and binds to the membrane adhesion molecule P-selectin

in platelets in HUS patients, which bind C3b and trigger the alternative pathway (8).

The atypical Hemolytic Uremic Syndrome is a rare syndrome, that leads to end stage renal disease in approximately 60% of patients. The hallmark of the aHUS is mutations in complement alternative pathway genes through mutations in *CFH*, *CFI*, *CD46*, *THBD*, *CFB* and *C3* genes that result in hyper-activation of the alternative complement pathway, leading to endothelial damage and platelet aggregation. Anti-CFH antibody bind to the C-terminal domain of CFH and impair CFH-mediated cell surface protection (9).

A recent study has confirmed C3 reduction in severe cases of Stx-HUS. Low levels of C4 indicates activation of the classical and/or lectin pathways that leads to C4 consumption, Normal plasma C3 and low C4 suggests activation of the alternative pathway of complement during the acute phase of typical haemolytic uraemic syndrome; however, Normal C3, C4, CFH, and CFI plasma levels do not exclude the diagnosis of complement dependent-HUS (9).

Plasma exchange therapy is the first line for the management of aHUS, That aims to eliminate abnormal complement regulatory proteins and anti-CFH antibodies, and replenish normal complement regulatory proteins. A humanized monoclonal antibody Eculizumab, binds to C5 complement protein, and suppresses C5 cleavage to C5a and C5b and thereby prevents the production of the membrane attack complement complex (MAC), recommended in the early stages of treatment of aHUS in pediatrics and also may be considered for treating extra-renal organ injury in patients with aHUS. Decreased platelet counts usually resolve after 1 to 2 weeks of eculizumab therapy Eculizumab. In anti-CFH antibody-positive patients, plasma exchange combined with immunosuppressants or steroids have given better outcomes with reduced antibody titers (9).

Other TMA Syndromes

In most cases, pregnancy is only a precipitating factor for thrombotic microangiopathy. Treatment of TMA occurring during pregnancy should be tailored to the underlying pathogenic mechanism: through restoration of ADAMST13 serum activity in TTP with plasma exchanges and B cell-depleting therapy, or through inhibition of complement alternative pathway activation in aHUS using antiC5 blocking antibody Eculizumab (10). Multiple components of the complement cascade have the capacity to alter the phospholipid composition of the outer membranes of cells. Complement C3a induces platelet activation and aggregation. negatively charged phospholipids, whereas abundant Cell activation will also release granular contents, which generally enhance pro-coagulant responses, and release of microparticles will

provide extra surfaces for clot formation.thrombin accelerates activation of both complement pathways. klarrikrein and factor XIIa cleaves complement components (11).

Although many drugs have been reported to be associated with TMA, only quinine-associated TMA has been supported by documentation of drug-dependent antibodies. Also Quetiapine and gemcitabine have been reported with acute episodes of TMA. Drug-dependent antibody bind to antigens on multiple cells epitopes. Quinine-dependent antibodies may mediate TMA, in part, by activation of endothelial cellshistory of drug intake potentalte diagnosis. and management is usually supportive. In patients cancer, (metastatic or not) TMA may be caused by commonly used chemotherapy agents, either through dose-dependent toxicity or an acute immune-mediated reaction, most of them induce HUS. Sunitinib-induced thrombotic microangiopathy is reported in patients with renal cell carcinoma and other malignancies. Plasma exchange has no known benefit for patients with cancer-induced TMA (12).

TMA is the most common microvascular injury associated with HIV infection. The endothelial damage is caused by viral invasion or indirectly by the action of cytokines/HIV-associated proteins on endothelial cells. Complete deficiency of ADAMTS13 due to development of IgG autoantibodies have been reported. Raised inflammatory cytokines such as tumor necrosis factor- α and interleukin-1, and enhanced apoptosis of microvascular endothelial cells in these patients have been found. plasma exchange is essential for treatment however corticosteroids should be individualized, monoclonal antibodies and splenectomy is recommended in refractory cases (13).

Corresponding Author:

Name: Amira Abdel-Monem Noureldeen M. B., B. Ch.

Address: 66, sector-7, 10th of Ramadan city, El-sharquia governorate, Egypt.

E-mail: amiranoureddin@hotmail.com

References

1. Go RS, Winters JL, Leung N, Murray DL, Willrich MA, Abraham RS et al., Thrombotic Microangiopathy Care Pathway: A Consensus Statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. mayo c p; 2016:05.015.
2. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman K D, Kremer Hovinga J, et al., Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and

- related thrombotic microangiopathies. *jth*.2017;15, 2: 312–322.
3. Tsai H M. Autoimmune thrombotic microangiopathy: advances in pathogenesis, diagnosis, and management. *Semin Thromb Hemost*. 2012; 38(5):469-82.
 4. Varela C J, and Tomlinson S. Complement: An overview for clinician. *Hematol Oncol Clin North Am*. 2015; 29(3): 409–427.
 5. Westwood JP, Langley K, Heelas E, Machin S J, Scully M, Complement and cytokine response in acute Thrombotic Thrombocytopenic Purpura.: *British Journal of Haematology*. 2014;164(6): 858–866.
 6. Kristi J. Smock. The Role of ADAMTS13. Testing in the Work up of Suspected Thrombotic Thrombocytopenic Purpura.2016; available at: <http://www.aacc.org/publications/cln/articles/2016/april/the-role-of-adamts13-testing-in-the-work-up-of-suspected-thrombotic-thrombocytopenic-purpura>.
 7. Peyvandi F, Scully M, Kremer Hovinga J A, Cataland S, Cataland S, Knöbl P, et al. Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med*. 2016;374:511-52.
 8. Ferraris JR, Ferraris V, Acquier AB, Sorroche PB, Saez MS, Ginaca A et al. Activation of the alternative pathway of complement during the acute phase of typical haemolytic uraemic syndrome. *Clin Exp Immunol*. 2015;181(1):118-25.
 9. Kato H, Nangaku, M., Hataya, H. et al. “Clinical guides for atypical hemolytic uremic syndrome in Japan” (2016): *Clin Exp Nephrol* 20: 536–543.
 10. Fakhouri F, Vercel C and Frémeaux-Bacchi V. Obstetric Nephrology: AKI and Thrombotic Microangiopathies in Pregnancy. *CJASN*. 2012; 7 (12):2100-2106.
 11. Kurisawa S and Stearns-Kurosawa JD, Complement, thrombotic microangiopathy and disseminated intravascular coagulation. *J Intensive Care*. 2014; 2(1): 65.
 12. Noronha V, Punatar S, Joshi A, Desphande RV, Prabhash K. “Sunitinib-induced thrombotic microangiopathy”(2016); *J Can Res Ther*; (12):6-11.
 13. Dineshkumar T , Dhanapriya J, Jaganathan P, Sakthirajan R , Gopalakrishnan N , Balasubramanian T, et al., Thrombotic microangiopathy as an initial manifestation in HIV patients *Indian. J Crit Care Med*. 2016; 20(6): 374–376.

6/6/2017