Introductory comments about the special series of thrombotic microangiopathy

Nearly 100 years have passed since the first reported case of thrombotic thrombocytopenic purpura (TTP). In 1924, Eli Moschcowitz first described a 16-year-old girl who was brought to the hospital with an abrupt onset of petechiae and pallor; she rapidly progressed to a coma and died shortly thereafter. Her autopsy report showed the presence of disseminated hyaline thrombosis in small arterioles and capillaries (1). Similar cases were sporadically reported as Moschcowitz's disease for many years (2,3). It was suspected that the lack of a plasma factor that stimulates the production of platelets in the marrow that results in thrombocytopenia and a powerful poison that results in occlusive thrombosis in these patients. Only until 1982 when Moake and his colleague observed the presence of circulating usually large von Willebrand factor (ULVWF) in plasma of patients with chronic relapsing TTP, was there a clue that ULVWF may play a role in the pathogenesis of TTP. These ULVWF multimers are only observable in the patient plasma during clinical remission but not in the acute episodes of the disease. Moake and colleagues hypothesized that the lack of plasma enzyme that cleaves or degrades ULVWF multimers may be the cause of TTP (4). Such a hypothesis was later confirmed by Furlan and Lämmle (5,6) and Tsai *et al.* (7). They demonstrated that plasma levels of VWF-cleaving metalloprotease is deficient in patients with acute TTP, but not in those with hemolytic uremic syndrome (HUS), a different disorder resulting in from Shiga toxin-producing *E. coli* infection (8) or complement activation (6,9). Later, immunoglobulin (Ig)G-type autoantibodies were isolated from acute TTP and shown to have inhibitory activity towards plasma VWF-cleaving protease. These IgG autoantibodies reduce or disappear following clinical remission but can reappear if the disease relapses (7). In 2001, the VWF-cleaving metalloprotease was identified (10-12) and cloned (11,13), which belongs to the 13th member of ADAMTS family, named ADAMTS13 (11,13). Rapid progress has been made in past decades regarding laboratory diagnosis, disease mechanism, and therapeutic modalities. This special series of thrombotic microangiopathy aims to highlight some of these progresses from several renowned scientists and clinicians in the field.

The first article by Halkidis and colleagues provides a brief snapshot of the historic journey of TTP research (14). It summarizes the centennial accomplishment of many scientists, clinicians, and entrepreneurs, from the first case reported to the identification of disease mechanism, and to the development of various diagnostic tests and management strategies of TTP. The second article from Sakai and colleagues discusses recent progress of genetics and emerging therapies in hereditary TTP (hTTP) or congenital TTP (cTTP) (15). To date, more than 200 mutations are identified on *ADAMTS13* associated with cTTP, which spans the entire *ADAMTS13* gene or protein (16,17). There appears to be some degree of genotype-phenotype correlation. For instance, patients with mutations in the amino terminal half of ADAMTS13 may develop TTP early in life while those with mutations in the distal domains of ADAMTS13 may develop the disease as adults, often triggered by pregnancy or postpartum infections (18). Plasma infusion (18), or more recently recombinant ADAMTS13 (19-21), is the treatment of choice for cTTP.

The next article by Liu and myself provides a comprehensive overview of the pathogenesis and novel therapeutics in immune-mediated TTP (iTTP) (22). Nearly all iTTP cases are caused by IgG antibodies against ADAMTS13, which are shown to bind the spacer domain of ADAMTS13 resulting in conformational changes in the catalytic domain, leading to its inability to cleave VWF (23,24). These inhibitory antibodies may also form immune complexes with ADAMTS13 that result in an accelerated clearance of ADAMTS13 protein from circulation (25,26). The therapeutic goal in iTTP is to remove autoantibodies against ADAMTS13 by therapeutic plasma exchange (TPE), inhibit platelet-VWF interaction and block thrombus formation by caplacizumab, and suppress acute inflammation and antibody production with the use of corticosteroids and rituximab. Such a triple therapy (e.g., TPE, caplacizumab, and immunosuppressives) has significantly accelerated the disease recovery, shortened the stay in the intensive care units and hospital, and reduced clinical exacerbation/relapse, as well as improved survival rate of iTTP (27).

The course of iTTP can be unpredictable. The next article by Lu provides a narrative review of clinical markers that can be used to predict adverse outcomes of iTTP (28). Among the biomarkers investigated, plasma ADAMTS13 activity, big endothelin-1, soluble thrombomodulin, syndecan-1, histone/deoxyribonucleic acid complexes, cell-free DNA, citrullinated histone 3, S100A8/A9, lactate dehydrogenase, and troponin appear to have a role in predicting the outcomes of iTTP,

including mortality or disease exacerbation or relapse.

TTP must be differentiated from complement-mediated HUS (cHUS). Wu and colleague describe the role of complement activation in pathogenesis and therapeutic targets of cHUS (29). They summarize the role of rare heterozygous loss-of-function mutations in the gene encoding complement factor H, membrane cofactor protein, and factor I or a gain-of-function of in the gene encoding factor *B* or *C3* in causing cHUS. Human monoclonal antibody against complement C5 (e.g., eculizumab) inhibits the formation of membrane attack complex (MAC) and has been shown to be highly efficacious in treating cHUS and reducing the rate of end-stage renal disease and mortality. More recently, the transplant-associated thrombotic microangiopathy (t-TMA) is another type of cHUS, resulting from acquired activation of the complement system. Qi and Han provide a narrative review of t-TMA: its pathogenesis and therapeutics (30). The anti-C5 monoclonal antibody (e.g., eculizumab) is as efficacious in treating t-TMA as it is for cHUS.

Despite progress being made in recent years, the understanding of the pathogenic mechanism of TTP and the treatment options are still limited. Several animal models of TTP including mice, zebrafish, rats, and baboons have been developed to further explore the role of many genetic or environmental factors that trigger TTP. Zheng and I summarize all the animal models of TTP available to date (31). Each has its advantages and potential pitfalls. For instance, *Adamts13*$^{-/-}$ mice do not develop spontaneous TTP unless it is in a specific strain (CAST/Ei) of mice or being challenged with Shigatoxin-2 or recombinant VWF; *adamts13*$^{-/-}$ zebrafish develop mild thrombocytopenia without causing fatality; rats or baboons with acquired antibody-mediated inhibition of ADAMTS13 activity also develop a transient but non-fatal TTP. Nevertheless, these animal models allow us to test potential triggers for TTP and novel therapeutic agents prior to clinical trials.

Overall, this specific series summarizes the most recent literature on thrombotic microangiopathy research, clinical development, and patient management. It provides an incredible resource for the readers who are interested in conducting research on thrombotic microaniopathy and/or taking care of patients with such a medical condition. I hope that the readers will enjoy reading the series.

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X. Long Zheng

X. Long Zheng, MD, PhD
Department of Pathology and Laboratory Medicine, The University of Kansas Medical Center, Kansas City, KS, USA.
(Email: xzheng2@kumc.edu or longzheng01@gmail.com)

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