Editorial

Thrombotic Microangiopathy

Ponlapat Rojnuckarin

Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok

Thrombotic microangiopathy (TMA) is a pathological term describing disseminated platelet-containing thrombi in microcirculation. This pathology manifests clinically as microangiopathic hemolytic anemia (MAHA), i.e. traumatic red blood cell fragmentation and consumptive thrombocytopenia on peripheral blood smear. Therefore, meticulous blood smear examination is absolutely required to make diagnosis. Furthermore, organ dysfunction, mainly brain and kidney, may be the consequences of these micro-vascular obstructions.

TMA is heterogenous in clinical manifestations due to the differences in pathophysiologic mechanisms. Thrombotic thrombocytopenic purpura (TTP) usually presents with MAHA with or without neurological symptoms, e.g. headache, alteration of consciousness or seizure. The majority of TTP have very low or undetectable levels of ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13) or von Willebrand factor-cleaving protease resulting in elevated levels of unusually large von Willebrand factor (vWF) multimer that can agglutinate platelets. This ADAMTS13 deficiency is usually caused by ADAMTS13 auto-antibody in acquired idiopathic TTP and rarely caused by hereditary ADAMTS13 gene mutations in congenital TTP (Upshaw Schulman syndrome). Plasma exchange is the key treatment of TTP by replacing ADAMTS13 enzyme, as well as removing ADAMTS13 auto-antibody and unusually large VWF multimer. Notably, many acquired TTP patients and most congenital TTP patients still have very low ADAMTS13 during remission without any hematologic abnormalities or neurological symptoms. Therefore, ADAMTS13 defect is not the sole mechanism of TTP. Precipitating factors for the TMA episodes are likely to be present, yet remain to be identified. Plasma exchange does not eliminate the root causes of TTP, i.e. autoimmunity or genetic mutations, but it serves as a supportive measure while waiting for the spontaneous remission of an episode. Nevertheless, immune-modulation using pulse steroid[1] and/or antiCD20 antibody[2] has been shown to be beneficial in acquired idiopathic TTP.

The other class of TMA that shows prominent renal failure is called hemolytic uremic syndrome (HUS). The common form of the disease occurs in children after bloody diarrhea from organisms producing shiga toxin or shiga-like toxins (verotoxin). These toxins can damage vascular endothelial cells, activate thrombotic reactions in microvasculature and result in TMA. The treatment of this form of HUS is mainly supportive while waiting for spontaneous recovery. The other uncommon form of HUS does not present with prior diarrhea and, thus, termed atypical HUS (aHUS). Approximately 50-60% of aHUS patients have mutations in complement control proteins, e.g. factor H, factor I, membrane cofactor protein (MCP), thrombomodulin, resulting in excessive complement system activation that damages endothelium.[3] Previously, most aHUS will progress to end-stage renal disease requiring long-term dialysis. Recently, an antibody to complement component C5, eculizumab, has been shown to be very effective in aHUS.[4] However, the drug is extremely expensive and needs prolonged continuous treatment.

Without appropriate treatment, TMAs are rapidly fatal. Therefore, early clinical recognition is critical for patient survival. Although ADAMTS13 activity tests are now available in Thailand, the results of the test usually come out too late for clinical decision making.

In addition, typical TTP responding to plasma exchange may show normal ADAMTS13 activity. Typically, plasma exchange needs to be promptly performed in suspected TTP. Subsequently, ADAMTS13 activity results may be used to confirm the diagnosis. Consequently, clinical manifestations and routine laboratories are crucial.[5] Rapid diagnosis requires a high index of suspicion, careful blood smear examination, elevated serum lactate dehydrogenase (LDH), normal coagulogram and exclusion of other causes of MAHA. The definite diagnosis of aHUS is also problematic. Genetic testing for aHUS is not generally available. The diagnosis is usually based on MAHA on blood smear and renal failure. Low ADATMTS13 activities may be helpful to suggest TTP that usually displays milder renal insufficiency.

In this issue of the journal, Krudpoo et al reviewed clinical manifestations of Thai TTP patients in a single center as the information useful in clinical diagnosis.[6] In this series, the mortality rate was still high (60%), although most patients received plasma exchange. Hospital-acquired infections are the important cause of death. Earlier diagnosis and prevention of infectious complications may be helpful for the treatments of TTP in Thailand.

As TMA is a rare disorder, sample sizes of single center studies are usually too small to yield meaningful results. Multicenter registry studies are required. For example, a report from Oklahoma TTP registry recently showed that the surviving patients had high long term mortality after discharge.[7] A prospective multicenter study in Thailand is strongly encouraged in order to obtain useful information for clinical practice.

References

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