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Concise Review

The Understanding of Thrombotic Thrombocytopenic Purpura: Dyadic, Triadic, Pentadic, and Other Manifestations

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Thrombotic thrombocytopenic purpura (TTP) was originally described by Moschkowitz in a 16-year-old girl who presented with fever, anemia, central nervous system impairment, renal dysfunction, and respiratory and cardiac failure in 1924 [1]. In this patient, the pathologic finding of hyaline thrombi in the terminal arterioles of the majority organs was considered to be characteristic of the disorder. Over the years, after further clinical observation, the classical triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and fluctuating central nervous system abnormalities was considered to be the gold standard for this diagnosis [2]. In addition, many of these patients present with fever and renal function impairment. Accordingly these additional features included in the triad have born out the concept of pentad for the diagnosis of TTP [3].

It soon became apparent that some cases of TTP might not have all the triadic manifestations. Additional fever and renal function impairment were found not to be specific enough for the diagnosis. Nevertheless, establishing the diagnosis primarily relied on the basis of Coombs negative MAHA, thrombocytopenia, and neurologic abnormalities in the absence of other possible causes of this manifestation [4]. These criteria served clinicians well in confirming the classical TTP, and atypical features, such as pancreatitis, abdominal pain, respiratory dysfunction, and others, have been considered to be exceptional presentations [5–10]. Undoubtedly the adherence to the triad or pentad interfered with the identification of TTP in some cases and also contributed to the delay of the diagnosis in others. Because these criteria were used, the incidence of TTP was perceived to be extremely rare [11]. Until the 1970s, in clinical practice, atypical cases of TTP had often been either missed or delayed in diagnosis when neurological changes were not a predominant presentation.

Because TTP was a fatal disease in most of the patients until mid-1970s, earlier diagnosis was not greatly emphasized since no consistently effective treatment had been available. Still the medical literature demanded these triadic and pentadic manifestations for the purpose of the dissemination of information. Things then changed for the better when plasma exchange [12] and plasma infusion [13], which were found to be highly effective, were employed in clinical practice. Subsequent clinical trials that supported the effectiveness of exchange plasmapheresis with response rate of approximately 70% [14,15] and the recognition of the importance of timely treatment have called the urgent need for making earlier diagnosis to achieve a favorable outcome. This necessity led to propose the dyadic concept, which consists of MAHA and unexplained thrombocytopenia, as the sufficient and essential components in establishing the diagnosis of TTP after exclusion of hemolytic-uremic syndrome and HELLP syndrome [16,17]. The neurologic change, renal failure, or fever was not considered to be the sine qua non for the diagnosis. Using these criteria, more cases of TTP, both classical and secondary, have been recognized in earlier stage of the disease, and timely plasma exchange has resulted in improved clinical outcome [16–18].

As a consultant, the clinical hematologist has begun to identify TTP in increasing numbers when called in for evaluation of unexplained thrombocy-

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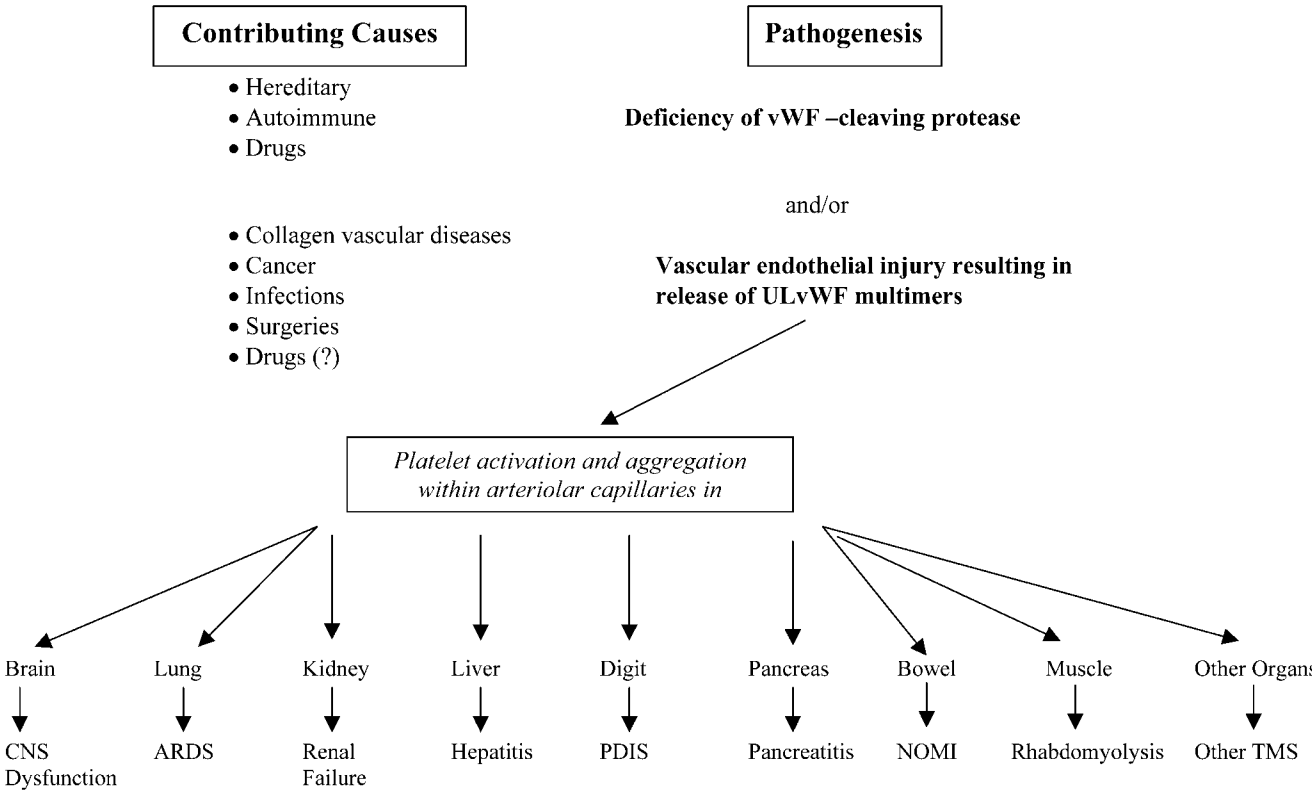

Fig. 1. Proposed pathogenesis and presentation of TTP. TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor; ULvWF, unusually large von Willebrand factor; CNS, central nervous system; ARDS, acute respiratory distress syndrome; PDIS, peripheral digit ischemic syndrome; NOMI, non-occlusive mesenteric ischemia; TMS, thrombotic microangiopathic syndrome. (Modified from J Investig Med 2002;50:201–206 after permission.)

topenia and anemia in various clinical settings. Although TTP has typically been understood in terms of a classical form, meaning idiopathic form, it has become clear that there are secondary cases of TTP that have been caused by or associated with other medical conditions. This secondary TTP has mainly been seen in the following five conditions: 1) collagen vascular diseases, 2) infectious diseases, 3) side effects of certain drugs, 4) neoplastic diseases, and 5) complications of certain surgeries (Table I).

When secondary TTP as well as classical form are diagnosed, atypical presentations that were previously considered to be unexplainable are found to be the manifestation of TTP. These include certain cases of pancreatitis [6], acute respiratory distress syndrome [7,18,19], and peripheral digit ischemic syndrome [16,18]. Additionally certain cases of non-occlusive mesenteric ischemia [19], rhabdomyolysis [20], hepatitis [18], skin and subcutaneous gangrene [21], myocardial ischemia [22], and ophthalmic dysfunction [10] are also found to be the manifestation of TTP. Considering these observations, in addition to triadic, pentadic, and dyadic criteria, the clinician has to understand that TTP can present with other atypical features, of which the recognition is critical in earlier diagnosis and timely management of TTP. These atypical presentations and possible pathogenesis are summarized in Figure 1 [18].

TABLE I. Conditions Associated With Secondary TTP

Collagen vascular diseases	Systemic lupus erythematosus
	Scleroderma
	Polyarteritis nodosa
	Rheumatoid arthritis
Infectious diseases	Bacterial endocarditis
	HIV infection
Drugs	Cyclosporin A
	Ticlopidine
	Clopidogrel
	Tacrolimus
	Quinine
Neoplastic diseases	Breast cancer
	Stomach cancer
	Lung cancer
Surgeries	Cardiovascular surgery
	Intestinal surgery

In retrospect, the fixed idea of the triad in diagnosing TTP has perhaps hampered the understanding of TTP, and the expanded criteria to the pentad further mystified the disease. The proposal of a dyadic concept has opened the opportunity for earlier diag-

nosis and contributed to the saving of many lives but still does not emphasize the large picture of TTP. Now, after careful clinical and laboratory observation in clinical cases, we have sufficient knowledge to explain the pathophysiologic process of TTP [23,24]. TTP is manifested as an ischemic disease of multiple organs in varying degrees, which is caused by disseminated capillary microthrombi due to interaction between activated platelets and the arteriolar endothelial surface [25]. The laboratory findings are consumptive thrombocytopenia and microangiopathic hemolytic anemia. Ischemic dysfunction of various organs may occur in addition to that of the brain and kidney (Fig. 1).

It is high time for us to reeducate ourselves about pathogenesis and clinical presentations of TTP outside the narrow definition confined to the central nervous system and renal dysfunction. We will serve our patients much better if we abandon the concept of triad and pentad in establishing the diagnosis of TTP.

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