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UNDERSTANDING THE DISEASE

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Understanding organ dysfunction in thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is the epitome of thrombotic microangiopathies (TMA), i.e., rare multisystem diseases characterized by disseminated microvascular thrombosis leading to ischemic damage and dysfunction in multiple organs [1]. The main clinical syndromes presenting as TMA are, beside TTP, the hemolytic uremic syndrome, disseminated intravascular coagulation, pre-eclampsia, the HELLP syndrome, the catastrophic antiphospholipid antibody syndrome, disseminated malignancy, and heparin-induced thrombocytopenia.

The principal laboratory abnormalities of TTP are consumption thrombocytopenia, hemolytic anemia, and the presence of fragmented red cells in blood smears (schistocytes). In spite of severe thrombocytopenia TTP usually presents with signs and symptoms caused by thrombotic occlusions in the microcirculation, only a minority of patients having bleeding manifestations. The mechanism of the disease, originally characterized by a high mortality rate mainly due to cardiac and brain damage, remained unclear until a plasma protease was purified [2, 3] that cleaves specifically von Willebrand factor (VWF), the huge multimeric glycoprotein (present in plasma, platelets, and endothelial cells) that is indispensable in primary hemostasis for adhesion and aggregation of platelets at sites of vascular injury (Fig. 1a). The congenital or acquired deficiency of the metalloprotease [4], identified as the 13th member of the ADAMTS family [5], causes the abnormal presence in plasma of unusually large VWF multimers [6], which aggregate platelets intravascularly and cause their consumption in disseminated thrombi, i.e., the basis of multiple organ dysfunction in TTP (Fig. 1b). Anemia is the consequence of the fragmentation of red cells as they flow in the microcirculation partially occluded by platelet-rich thrombi.

Two main mechanisms cause ADAMTS13 deficiency: mutations in the gene that encodes the protease [7] and the acquired development of anti-ADAMTS13 autoantibodies [8]. Congenital TTP, very rare and representing no more than 5 % of cases, usually develops at birth or during childhood, although it may only become clinically manifest in adulthood, especially during pregnancy [9, 10]. The clinical presentation of congenital TTP is variable, with between-patient differences in terms of clinical severity [11], and acute episodes may be triggered by such conditions as pregnancy and infections.

Acquired TTP accounts for the majority of cases and mainly occurs in adults, sometimes in the absence of obvious triggers but also secondary to other immunomediated diseases, drug intake, and pregnancy [1]. It is often due to anti-ADAMTS13 autoantibodies that inhibit the proteolytic activity of the protease and/or accelerate its plasma clearance [12]. Less typically, the clinical and laboratory signs of acquired TTP develop in patients who

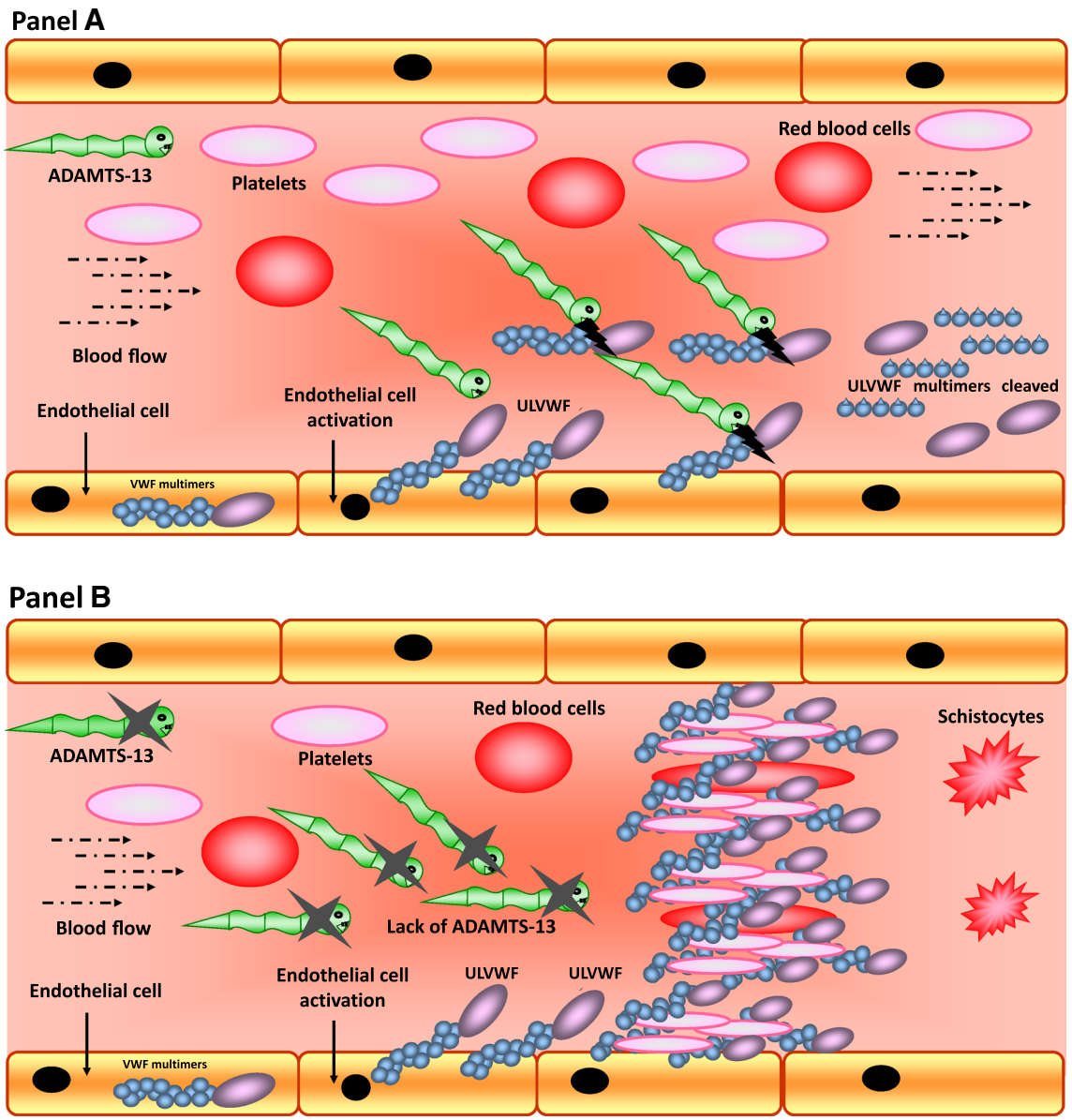

Fig. 1 Role of ADAMTS13 and von Willebrand factor (VWF) in thrombotic thrombocytopenic purpura. **a** Unusually large VWF multimers (ULWF) contained in intact and quiescent endothelial cells of the vessel wall are cleaved by the metalloprotease ADAMTS13 as soon as endothelial cell damage and/or activation releases these multimers in the flowing blood. **b** When ADAMTS13 is deficient or defective in plasma (as in congenital or acquired TTP), uncleaved ULVWF aggregate platelets and thus leads to the formation of platelet-rich thrombi. Widespread aggregation of platelet into disseminated microvascular thrombi leads to consumption thrombocytopenia. Red cells forced by blood flow through occlusive or partially occlusive thrombi are fragmented and cause mechanical hemolytic anemia with the formation of schistocytes

are not ADAMTS13 deficient, in association with such diseases as sepsis, cancer, HIV infection, and bone marrow transplantation [1].

The finding of severe consumption thrombocytopenia and mechanical hemolytic anemia is warranted for a diagnosis of TTP. Signs of hemolytic anemia include, beside schistocytosis, reticulocytosis, and hyperbilirubinemia, low or unmeasurable haptoglobin and negative Coombs test. High serum lactate dehydrogenase (LDH) is a sensitive sign of tissue necrosis due to multiorgan damage. Troponins are often high, owing to frequent cardiac damage. The typical neurological symptoms (coma, stroke, seizures, or focal signs such as motor deficits, diplopia, and aphasia) often fluctuate in presentation and severity, owing to the ongoing formation and dissolution of thrombi in

the cerebral microcirculation. Other symptoms or signs (such as headache, blurred vision, ataxia, or delirium) are less frequent. Symptoms of gastrointestinal and pancreatic ischemia are very prevalent. Even though only a minority of patients have serum creatinine levels higher than 2.0 mg/dL, signs of renal involvement such as microscopic hematuria and proteinuria are frequent, but the need for dialysis is rare. There is no or little laboratory alteration of coagulation and fibrinolysis, even though D-dimer may be moderately raised.

Undetectable or very low plasma levels of ADAMTS13 enzymatic activity (less than 10 %) unequivocally establish a diagnosis of inherited or acquired TTP, even though not all patients, appropriately diagnosed with TTP on the basis of the aforementioned laboratory and clinical findings, present with severe protease deficiency in plasma [1]. Because the results of ADAMTS13 plasma testing may not be available in emergencies, other more widely available laboratory biomarkers, such as platelets lower than 20×10^9/L and creatinine lower than 2.0 mg/dL, may help to predict the cases with severely deficient ADAMTS13 activity [12].

TTP occurs only once (acute sporadic TTP) in approximately two-thirds of the cases. However, in more than one-third of them the disease tends to recur after remission of the acute episode, with a single or several episodes of relapse [1]. The chronic recurrent forms may have a genetic basis or be associated with the persistence of autoantibodies, whereas the forms associated with measurable ADAMTS13 and malignancy, HIV infection, or transplantation usually have a low propensity to recur.

The modern therapy of TTP started in 1991, following a randomized clinical trial that established the greater efficacy of plasma exchange (PEX) over plasma infusion, with a clinical response rate of 78 % in the former compared with 49 % in the latter (corresponding mortality rates, 22 and 37 %) [13]. PEX acts mainly by removing anti-ADAMTS13 autoantibodies, but also replacing the protease.

Plasma therapy should be initiated as soon as the diagnosis of TTP is supported by the aforementioned clinical and laboratory criteria, even if ADAMTS13 results are not yet available [14]. In critically ill patients admitted to hospitals without PEX facilities, daily infusion of large amounts of fresh-frozen plasma (30 mL/kg) should be started promptly. Then patients should be preferably transferred to intensive care units that can optimally manage coma, seizures, ischemic heart disease, and such side effects of PEX as congestive heart failure and catheter-related complications. At least 1.5 plasma volume should be exchanged daily until clinical symptoms and signs disappear, platelets rise to at least 150×10^9/L, LDH and troponins return to normal, and schistocytes are no longer detected, usually 5–10 days after starting PEX.

In congenital TTP prophylactic replacement therapy may consist not only of regularly spaced plasma infusions but also of factor VIII–VWF plasma concentrates containing ADAMTS13 [15]. Despite the fact that the protease has a half-life of 2–3 days, infusions of plasma (15–20 ml/kg) or factor VIII/VWF products every 10 days are usually sufficient to supply enough ADAMTS13 to maintain low but measurable protease plasma levels and thus avoid platelet consumption and mechanical anemia.

In acquired TTP, the more frequent immunopathogenesis should be tackled by adding immunomodulating agents to PEX. Corticosteroids are the first choice in the acute phase (prednisone 1.0–1.5 mg/kg daily), but immunosuppression should also be considered during disease-free intervals in the frame of chronic relapsing TTP. The first choice is rituximab, which blocks the production of anti-ADAMTS13 through the depletion of B lymphocytes. Administered once weekly at a dosage of 375 mg/m^2 for four consecutive weeks, at least two-thirds of patients have a complete response, i.e., the return to normal of ADAMTS13 levels and disappearance of autoantibodies [16]. Other immunosuppressive agents (vincristine, cyclophosphamide, cyclosporine), are usually considered third-line options because of more side effects and less established efficacy. Splenectomy is a last-line option in chronic recurrent forms but at the time of remission, because this surgery carries a high risk of death in severely ill patients with acute TTP. The clinical efficacy of antiplatelet agents and platelet transfusion in acute and chronic TTP is unproven.

New therapeutic agents are being developed for the management of acute TTP: (1) the anti-VWF nanobody caplacizumab, which inhibits the interaction between unusually large VWF and platelet glycoprotein Ib-IX-V, has achieved clinical proof-of-concept in a phase II study in association with PEX [17]; (2) a recombinant preparation of ADAMTS13, not yet available for clinical use.

Concluding remarks

The last 20 years have witnessed spectacular improvements in our knowledge of TTP and development of new diagnostic criteria. The mechanistic role of VWF and its main proteolytic enzyme ADAMTS13 is prominent in the majority of cases, even though forms associated with measurable protease levels may involve other still unknown mechanisms. Triggers are often needed for the occurrence of full-blown TTP, because patients may remain asymptomatic for long periods of time. The clinicians confronted with these patients who are seriously ill owing to widespread organ damage should be cognizant that plasma therapy, mainly PEX, should be instituted promptly in clinically diagnosed cases, even if

ADAMTS13 testing is not available, the protease is present at measurable levels in plasma, and no autoantibody is detected. Immunomodulatory treatments have been attempted in order to prevent relapse, with promising results particularly for rituximab. Given the rarity of TTP, clinical research must be necessarily multicenter and multidisciplinary. For instance, there is a need to confirm preliminary data suggesting that organ damage may be long-lasting, as indicated by a high rate of comorbidities (hypertension, cognitive impairment, major depression) and increased long-term mortality [1].

Conflicts of interest None.

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