Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

"COVID-19 associated divergent thrombotic thrombocytopenic purpura (TTP) syndromes reported so far, five and counting": Classification and possible therapeutic options

ARTICLE INFO

Dear editor,

SARS CoV-2 infection's thrombogenic complications are increasingly recognized as a significant cause of morbidity and mortality in critically ill COVID-19 patients. The so-called "Covid-19 Coagulopathy" is multifactorial in origin; it results from the novel virus triggered severe endotheliitis and a maladaptive hyper-immuno-inflammatory response. This inflammatory onslaught leads to the activation of multiple complement pathways and a complement coagulation cross-talk inducing this hypercoagulable state and its dangerous ramifications that adversely affect the outcome [1,2]. Besides this COVID- 19 coagulopathy, another rare but hazardous thrombotic disorder triggered by this novel virus in some rare, vulnerable patients is the COVID-19 thrombotic microangiopathy (TMA) thrombotic thrombocytopenic purpura (TTP) and the hemolytic uremic syndrome (a HUS). These two syndromes are a constellation of thrombocytopenia, microangiopathic hemolytic anemia, and extensive clot formation in the microvasculature. TTP could be inherited or an acquired disorder, the immune TTP (iTTP) due to the presence of an inhibitor in the latter that leads to a critical decline (<5 %) in the enzyme ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13) activity, resulting in severe thrombotic microangiopathy predominantly involving the central nervous system and kidneys. Normally ADAMTS-13 cleaves the platelet binding, clot promoting highly active and adhesive ultra-large von Willebrand factor (ULVWF) multimers released in response to injury by the damaged endothelium to smaller, lesser active, and inert multimers. This cleavage prevents collagen and platelet binding of these multimers, thus aborting a possible thrombotic microangiopathy. The classic TTP responds to immunosuppressants and, more importantly, plasma exchange which, besides removing these ULVWF multimers and anti-ADAMTS-13 antibodies, restores the depleted ADAMTS-13 levels above the critical threshold. HUS results from inherited or acquired aberrations in the alternate complement system and its regulatory proteins, leading to its perpetual hyperactivation and baneful complications [3].

In this pandemic, a constellation of different syndromes of thrombotic thrombocytopenic purpura (TTP) has been observed so far at two poles of the spectrum. The first is the relatively common, COVID-19-induced TTP-like illness (not true TTP) in critically ill patients, adversely influencing the outcome. It complicates the severe endothelial injury typically seen in severe COVID-19 infection resulting in an overwhelming release of von Willebrand factor (VWF) and the consumption of the VWF cleaving protease ADAM-TS-13. Still, unlike the classic TTP, it is not associated with a critical drop in ADAM-TS-13 activity or the presence of an inhibitor in circulation. It is a unique phenotype of sepsis-like TTP without a dysfunctional VWF-ADAMTS-13 axis, with a relative paucity of platelet binding, clot promoting, adhesive ultra-large VWF multimers hence the inability to trap activated platelets. As a result, thrombocytopenia and hemolytic anemia are typically absent paradoxically; there is a relative thrombocytosis since platelet devouring ultra large hyperactive multimers of vWF are not usually present, without a need for plasma exchange (PEX) [4]. However, some studies have shown conflicting reports regarding the absence or presence of ULVWF in circulation. This discrepancy in reporting could result from methodological or patient-related differences or even low avidity of ADAMTS 13 binding to ULVWF in COVID-19-induced TTP-like illness. From a therapeutic viewpoint, there is accumulating experimental evidence showing a possible role of recombinant ADAMTS-13 (r ADAMTS-13) in aborting the thrombotic process of this TTP- like syndrome along with anticoagulants, with the latter correcting the associated coagulopathy. This therapeutic combination could translate into a favorable clinical outcome since anticoagulants alone can't influence the VWF-ADAMTS-13 axis [5] (Fig. 1A). On the other end of the spectrum are a few more syndromes of classic TTP that could befall COVID-19 patients. The first syndrome is an underlying TTP disorder either due to a genetic defect or an acquired iTTP phenotype which could either relapse or even get unmasked following the COVID-19 hyper inflammatory response.

The second syndrome is a de novo COVID-19 induced iTTP (immune TTP) due to the presence of an ADAMTS-13 inhibiting antibody in circulation; both syndromes require plasma exchange (PEX) and immunosuppressants (Fig. 1B). More than two dozen cases of de novo iTTP have been reported thus far in this pandemic. Their etiology has been directly attributed to SARS CoV-2 infection through a possible novel mechanism or even unmasking of an occult iTTP leading to the appearance of an inhibitor of this protease and a critical drop in ADAM

Abbreviations: TMA, Thrombotic microangiopathy; TTP, Thrombotic thrombocytopenic purpura; HUS, Hemolytic uremic syndrome; iTTP, Immune thrombotic thrombocytopenic purpura; ADAMTS-13, A disintegrin and metalloproteinase with thrombospondin type 1 motif member 13; rADAMTS-13, Recombinant ADAMTS-13; vWF, von Willebrand factor; ULVWF, Ultra-large von Willebrand factor; VITT, Vaccine-induced immune thrombotic thrombocytopenia; VI-iTTP, Vaccine induced immune thrombotic thrombocytopenic purpura; PEX, Plasma exchange.

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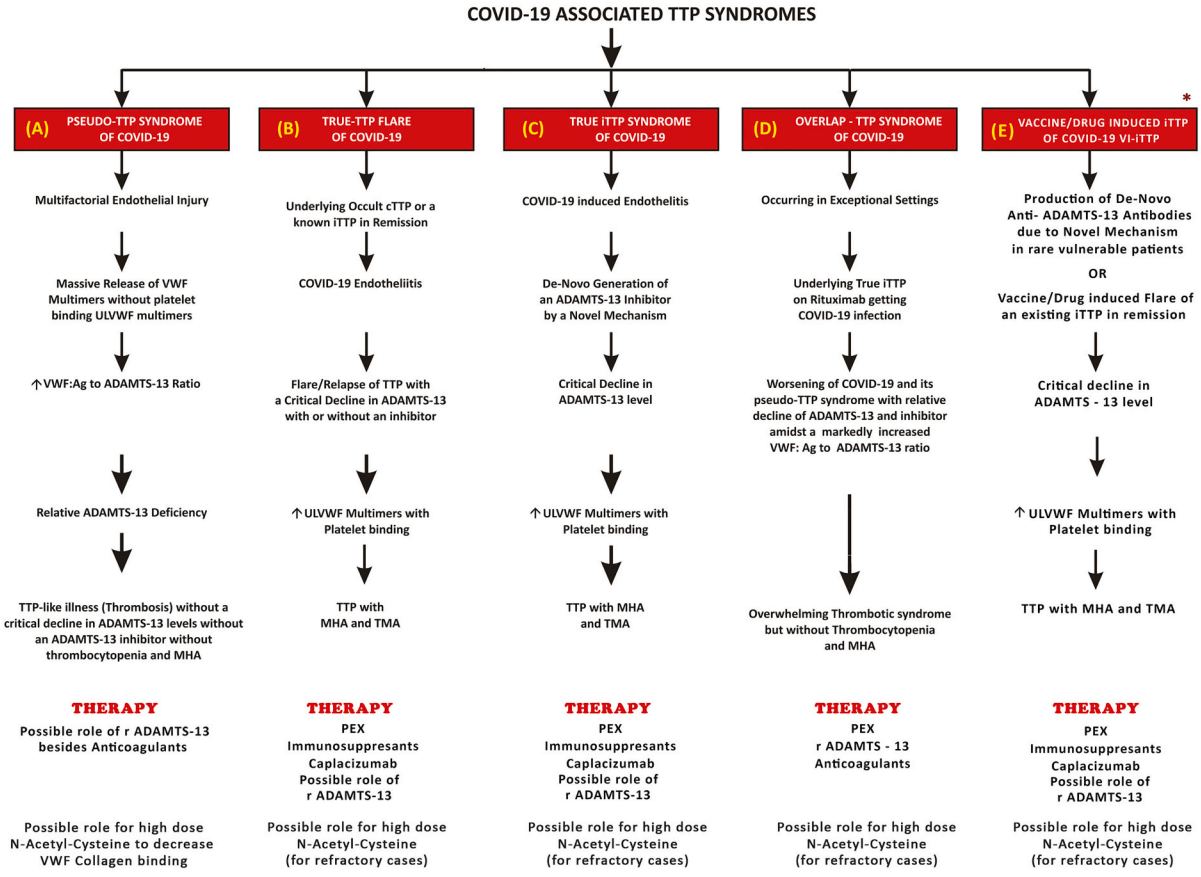

Fig. 1. COVID-19 associated TTP syndromes.

TS-13 activity and a severe TMA. These patients responded to PEX and immunosuppressants [6] (Fig. 1C). Besides these, two more TTP syndromes have surfaced as well. First, a rare and complex overlap TTP syndrome of COVID-19 has been reported recently. In this complex syndrome, the course of an underlying recalcitrant iTTP seems to have been modified by recent exposure to a single dose of anti CD20 monoclonal antibody rituximab (intolerance precluding its further dosing). A superadded COVID-19 infection produced a unique phenotype of TTP with overlapping features of TTP like illness and iTTP [7] (Fig. 1D).

Further augmenting the spectrum is the therapy-related iTTP following exposure to the COVID-19 vaccine leading to either a relapse of a known iTTP in remission or a de novo iTTP due to a novel mechanism (molecular mimicry by the spike antigen and an amplified T cell and B cell response), requiring PEX and immunosuppression [8,9] (Fig. 1E). This vaccine-induced iTTP (VI-iTTP) should not be confused with another recently discovered rare thrombotic syndrome, the vaccine-induced immune thrombotic thrombocytopenia (VITT) following the exposure to ChAdOx1 nCoV-19 (Astra Zeneca) adding yet another entity to the ever-expanding list of thrombotic complications associated with COVID-19. The latter is not a TTP-like syndrome but a HIT (heparin-induced thrombocytopenia) like illness due to vaccine-induced production of antibodies against platelet factor 4 (PF4) polyanion complex without any history of prior exposure to heparin. VITT is characterized by thrombocytopenia and thrombosis at atypical sites: cerebral venous, portal vein, splanchnic vein, and hepatic vein thrombosis with a propensity towards hemorrhagic transformation. It responds to IVIG steroids and non-heparin anticoagulants [10].

It would not be inappropriate to classify the above-mentioned COVID-19-associated TTP phenotypes into different syndromes: a "*pseudo TTP syndrome of COVID-19*,": the virus-induced TTP-like illness, a "*true TTP flare of COVID-19*": the virus-induced relapse of a known TTP in remission, a "*true iTTP syndrome of COVID-19*": a de novo TTP incited by the virus via a novel mechanism, the rare "*overlap TTP syndrome of COVID-19*": as reported by Maharaj et al. [7], and finally the "*vaccine-induced de novo iTTP or an iTTP relapse of COVID-19*." The term pseudo TTP syndrome is justified since the classic laboratory feature of TTP syndrome, namely thrombocytopenia and microangiopathic hemolytic anemia, are absent, leading to an inability to apply the well-known PLASMIC score that has been introduced for a rapid diagnosis of TTP pending the time consuming ADAMTS-13 specific tests or making a diagnosis of TTP in places lacking the facility of ADAMTS-13 related testing [11].

Classifying COVID -19 associated TTP into the syndromes mentioned above would not be redundant, or a futile exercise but can have an immense diagnostic and therapeutic significance based on an insightful clinical and laboratory evaluation in places with such facilities. Pseudo-

TTP syndrome of COVID-19 could be effectively managed with the introduction of anticoagulants and possibly r ADAMTS-13 therapy. True TTP flare of COVID-19 and true iTTP syndrome of COVID 19 could be successfully managed using PEX, immunosuppressants and anti VWF nanobody caplacizumab and possibly rADAMTS-13 as adjuvants. The very rare Overlap TTP syndrome of COVID-19 could benefit from PEX and rADAMTS-13 and anticoagulants and the VI-iTTP by PEX, immunosuppressants, and possibly rADAMTS-13.

Despite a marked reduction in COVID-19 cases globally due to a successful global vaccination policy, this pandemic is still far from over, and critically ill COVID-19 patients continue to be at risk of these TTP syndromes of COVID-19. Therefore, a task force of experts should work on fast-tracking rADAMTS-13 in future trials for these syndromes, especially the more common pseudo-TTP syndrome of COVID-19, targeting hard outcomes in places with the facility of ADAMTS-13 and VWF multimers testing in critically ill COVID-19 patients. However, the optimum dosing and safety can pose a challenge. It is worth a mention that in the pre-COVID-19 era, high doses of the mucolytic drug *N*-acetyl cysteine have been successfully used to attenuate the TMA in some case series of refractory iTTP, driven by its ability to degrade VWF multimers and also blunt their collagen binding. This mechanism of action could be exploited in COVID-19-induced TTP syndromes, especially in the more commonly encountered pseudo-TTP syndrome of COVID-19 since the latter is characterized by a massive release of VWF from the damaged endothelium.

In conclusion, TTP, in the light of COVID-19, seems to be a mixed bag of different syndromes rather than a single entity requiring intense research, understanding, and timely recognition of these syndromes. A germane therapeutic approach could positively influence the outcome (Fig. 1A, B, C, D, and E).

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Credit authorship contribution statement

THM conceptualized wrote and reviewed the, manuscript and created Fig. 1.

Conflict of interest

Nothing to declare.

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