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Thrombocytopenia in critically ill patients due to vascular microthrombotic disease: pathogenesis based on "two activation theory of the endothelium"

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Abstract

The pathogenesis of thrombocytopenia in critically ill patients (TCIP) has not been established yet. Based on "two-activation theory of the endothelium", TCIP is a manifestation of platelet activation and consumption in association with endotheliopathy. Endotheliopathy occurs in many critical illnesses. An injury to vascular endothelial cells (ECs) from pathogen or insult leads to endothelial dysfunction, which initiates the activation of two distinctly independent molecular pathways (*i.e.,* inflammatory and microthrombotic). The activation of inflammatory pathway occurs due to the release of inflammatory cytokines from injured ECs. Inflammatory cytokines mediate inflammation. The activation of microthrombotic pathway is induced by the activation of platelets and endothelial exocytosis of unusually large von Willebrand factor multimers (ULVWF). Activated platelets are recruited by exocytosed ULVWF, which are anchored to ECs, and together assemble microthrombi consisting of platelet-ULVWF complexes. This microthrombogenesis leads to consumptive thrombocytopenia (*i.e.,* TCIP) and disseminated intravascular microthrombosis (DIT). DIT triggers vascular microthrombotic disease (VMTD), which manifestations include hypoxic multi-organ dysfunction syndrome, and thrombotic microangiopathy (TMA). The combined syndrome due to the activation of both inflammatory pathway and microthrombotiic pathway is called systemic inflammatory response syndrome (SIRS). Also, the true nature of "DIC" is endotheliopathy-associated DIT/VMTD (*i.e.,* TTP-like syndrome).

Abbreviations

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, rADAMTS13: recombinant ADAMTS13, AH/AHNS: acute hepatitis/acute hepatic necrosis syndrome, ARDS: acute respiratory distress syndrome, ARF: acute renal failure, CABG: coronary artery bypass graft, C-APLAS: catastrophic anti-phospholipid antibody syndrome, CNS: central nervous system, CNSD: central nervous system dysfunction, DSS: dengue shock syndrome, DIC: disseminated intravascular coagulation, DIT: disseminated intravascular thrombosis, ECs: endothelial cells, GE: gastroenteritis, HC: hepatic coagulopathy, HCP: hantavirus pulmonary syndrome, HCPS: hantavirus cardio-pulmonary syndrome, HELLPs: hemolysis: elevated liver enzymes: and low platelet count syndrome, HFRS: hemorrhagic fever with renal syndrome, HUS: hemolytic-uremic syndrome, LDH: lactate dehydrogenase, MAHA: microangiopathic hemolytic anemia, aMAHA: atypical microangiopathic hemolytic anemia, MERS-CoV: middle east respiratory syndrome-coronavirus, MODS: multi-organ dysfunction syndrome, MOF: multi-organ failure, MRSA: methicillin-resistant staphylococcus aureus, NOMI: non-occlusive mesenteric ischemia, RMSF: Rocky mountain spotted fever, SARS-CoV: severe acute respiratory syndrome-coronavirus, SIRS: systemic inflammatory response syndrome, SFTS: severe fever with thrombocytopenia syndrome, TAMOF: thrombocytopenia-associated multiple organ failure, TCIP: thrombocytopenia in critically ill patients, TMA: thrombotic microangiopathy, TTP: thrombotic thrombocytopenic purpura, ULVWF: unusually large von Willebrand factor multimers, VMTD: vascular microthrombotic disease

Introduction

In the critically ill patient, thrombocytopenia is a very common hematological condition that occurs due to several different pathogenic mechanisms, and manifests with a broad clinical spectrum from benign presentation to life-threatening emergency. Mild to moderate thrombocytopenia plays a minor role in short-term clinical course, but the patient outcome related to the thrombocytopenia depends more upon the underlying pathologic disease.

Even after careful exclusion of the known etiology of thrombocytopenia, the cause of thrombocytopenia cannot be clearly determined in more than half of critically ill patients. This etiology-unidentified thrombocytopenia, encountered in critical illnesses (e.g., sepsis/septic shock, severe trauma, and complications of pregnancy, transplant and surgery), has been designated as "thrombocytopenia in critically ill patients" (TCIP) [1]. TCIP is now suspected to be an unfavorable indicator influencing the prognosis of the patient [2-4].

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TCIP in the critical care setting

The known mechanisms producing thrombocytopenia in critically ill patients include: 1) decreased production of the platelet due to transient bone marrow suppression or myelodysplasia (e.g., infection-associated), 2) increased destruction due to immune or non-immune response (e.g., drug or transfusion-induced), 3) increased utilization (e.g., disseminated intravascular coagulation - DIC), 4) increased consumption (e.g., heparin-induced thrombocytopenia, and thrombotic thrombocytopenic purpura - TTP), and 5) sequestration secondary to hypersplenism [5,6]. To date, TCIP is the term to use after the exclusion of known mechanisms.

The example of critical illnesses and conditions associated with TICP is listed in Table 1. Thrombocytopenia is typically recognized after admission to the critical care unit for conditions such as sepsis, severe physical injury, acute respiratory distress syndrome (ARDS), and central nervous system dysfunction. In severe infection due to pathogen causing bacterial sepsis, viral pneumonia (e.g., Middle East respiratory distress syndrome due to coronavirus), and viral hemorrhagic fevers (e.g., Ebola, hantavirus, and dengue), TCIP occurs in advancing stage of the illness.

TCIP is mild to moderately severe usually with the platelet count not less than 20,000/μL. Hemorrhagic tendency has been uncommon unless it occurs with severe thrombocytopenia, DIC or hepatic coagulopathy. Thus, to some clinicians TCIP is considered to be not a serious issue in the management of critically ill patients.

The degree of thrombocytopenia has been correlated with the severity of clinical course. Increasing thrombocytopenia was associated with higher mortality and longer length of hospital stay, and the increase of the platelet count was an early sign of clinical improvement [2-4,6-10]. Severe thrombocytopenia commonly has occurred in association with progressive multi-organ dysfunction syndrome (MODS) [4,11,12] and systemic inflammatory response syndrome (SIRS) [13,14]. These observations support TCIP is an important participant in the pathogenesis of the critical illness.

Endothelium and critical illnesses

The endothelium is a delicate biological structure that lines the entire circulatory system. It maintains the integrity of the blood supply by protecting the human body from the invasion of pathogen and insult. It also guards the circulatory system against unneeded intravascular coagulation by preventing the intrusion of tissue factor (TF) at the basement membrane of ECs [15]. ECs do not express *in vivo* TF. In sepsis and other critical illnesses, the membrane barrier of ECs is not disrupted. Thus, TF does not enter into circulation from extravascular compartment, and intravascular coagulation (*i.e.,* DIC) cannot be initiated. However, injured ECs become activated, and endothelial dysfunction leads to endotheliopathy triggering several molecular responses [16-22].

Endotheliopathy is associated with inflammation [23], platelet activation [24] and exocytosis of unusually large von Willebrand factor multimers (ULVWF) [25-27]. It is also associated with thrombocytopenia (*i.e.,* TCIP) and disseminated intravascular microthrombosis (DIT) [28,29]. Other clinical syndromes associated with critical illnesses include SIRS [13,14], ARDS [19,22], MODS [4,6,11,12,14], "DIC" [30-32], thrombotic thrombocytopenic purpura (TTP)-like syndrome [33-39], hepatic coagulopathy, and others [36,40].

Current hypothesis for the pathogenesis of vascular microthrombosis, especially in sepsis, is based on the intricate interaction between inflammation and coagulation system. The release of endothelial cytokines would trigger TF-mediated activation of coagulation leading to disseminated intravascular micro blood clots, inducing to vascular microthrombosis (*i.e.,* "DIC") [30,41,42].

Table 1. Examples of thrombocytopenia (TCIP)-associated conditions seen in critical care.

	Causes	Involved organs	Associated syndromes
Infectious agent			
Virus	Ebola	Lungs; liver; multi-organs	ARDS; hepatic necrosis; MODS
	H1N1 influenza	Brain; lungs; multi-organs	Encephalopathy; ARDS; MODS
	MERS-CoV	Lungs; multi-organs	ARDS; MODS
	SARS-CoV	Lungs; multi-organs	ARDS; MODS
	Hantavirus	Heart; lung; kidneys	HCPS; HPS; HFRS
	Dengue	Adrenals; multi-organs	DSS; MODS
	SFTS virus	Multi-organs	SFTS; MODS
Bacteria	Neisseria meningitides	Adrenals	Waterhouse-Friderichsen syndrome
	E.Coli O157:H7	Bowels; kidneys	Hemolytic-uremic syndromes; GE
	MRSA	Multi-organs	MODS; SIRS
	Klebsiella pneumonia	Lungs; multi-organs	ARDS; MODS; SIRS
	Various bacterial sepsis	Lungs; multi-organs	ARDS; MODS; SIRS; TAMOF; C-APLAS
Rickettsia	Rickettsia rickettsii	Skin; multi-organs	RMSF; MODS
Fungus	Candida albicans	Multi-organs	MODS; SIRS
Parasite	Plasmodium falciparum	Brain; multi-organs	Cerebral malaria; MODS; ARDS; SIRS
	Plasmodium vivax	Lungs; multi-organs	ARDS
Trauma			
Lungs/chest trauma	Motorcycle accident	Lungs; multi-organs	ARDS; MODS; SIRS
CNS trauma	Head injury	Brain; lungs; multi-organs	Encephalopathy; ARDS; MODS; SIRS
Surgery			
Cardiac surgery	CABG; open heart surgery	Lungs; heart; multi-organs	ARDS; myocardial ischemia; MODS
Vascular surgery	Aortic aneurysm surgery	Lungs; multi-organs	ARDS; MODS
Bowel surgery	Mesenteric inflammation	Mesentery; multi-organs	NOMI; MODS
Pregnancy			
Preeclampsia	Toxin (?); infection (?)	Lungs; uterus; multi-organs	ARDS; HELLPs; Abruptio placenta; MODS
Transplant			
Liver transplant	Infection (?)	Lungs; multi-organs	ARDS; MODS
Kidney transplant	Infection (?)	Lungs; multi-organs	ARDS: MODS

Contrary to this concept, microthrombogenesis plays a key role in the pathogenesis of TTP and TTP-like syndrome. In endotheliopathy, the platelet is activated and excessive amounts of ULVWF are released from ECs [24-27,40]. The result is the formation of microthrombi made of platelet-ULVWF complexes, which also lead to vascular microthrombosis [26,27,34,36,40].

To annotate inflammation and circulatory disorder in the critical illness, a novel hypothesis of "two-activation theory of the endothelium" is proposed [36,40].

Two-activation theory of the endothelium

Endotheliopathy initiates two significant molecular events: 1) release of inflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor-α, and others) [16-22], and 2) activation of the platelet and exocytosis of ULVWF [24-27]. The former triggers inflammation, which is called "activation of inflammatory pathway", and the latter initiates microthrombogenesis, which is expressed as "activation of microthrombotic pathway". These two independent responses are the essence of "two-activation theory of the endothelium" as illustrated in Figure 1. The manifestation of activated inflammatory pathway is inflammation with symptoms such as fever, myalgia, arthralgia, and malaise, and that of activated microthrombotic pathway is consumptive thrombocytopenia, hypoxemia, multi-organ dysfunction and multiple clinical syndromes as presented in Figure 1 and Table 1.

The activation of inflammatory pathway occurs due to release of cytokines in both sepsis and non-septic critical illnesses. Unlike in non-septic illnesses, sepsis also promotes inflammation through another loop of activated circulating immune cell pathway (e.g., macrophages, monocytes, neutrophils, and lymphocytes). This pathway also interacts with activated ECs as shown in Figure 1 [43,44]. This additional cytokine expression accentuates the inflammatory pathway that could result in "cytokine storm". This mechanism explains why severer inflammation occurs in sepsis, which might lead to SIRS [11,13,14,45].

On the other hand, the activation of microthrombotic pathway is initiated by activated platelets and excessively exocytosed ULVWF that are anchored to ECs as long elongated strings [46,47]. If protease ADAMTS13, which cleaves ULVWF to smaller molecular weight VWF, is under expressed [36,48], activated platelets under shear stress of blood flow are recruited to the uncleaved ULVWF strings. This microthrombogenesis generates intravascular microthrombi consisting of platelet-ULVWF complexes at ECs [46,47]. This process sets off DIT and could lead to multiple clinical syndromes.

Endotheliopathy-associated vascular microthrombotic disease

DIT is the underlying pathology provoking vascular microthrombotic disease (VMTD) [36,40], which triggers hypoxic multi-organ dysfunction and thrombotic microangiopathy (TMA). Three kinds of disseminated VMTD are known to exist: 1) antibody-associated VMTD (*i.e.,* acquired TTP), 2) gene mutation-associated VMTD (*i.e.,* hereditary TTP), and 3) endotheliopathy-associated VMTD (TTP-like syndrome). Endotheliopathy-associated DIT/VMTD is the underlying pathologic condition producing TTP-like syndrome. It is characterized by TCIP, microangiopathic hemolytic anemia (MAHA)/atypical MAHA (if fewer schistocytes are present)with/without MODS.

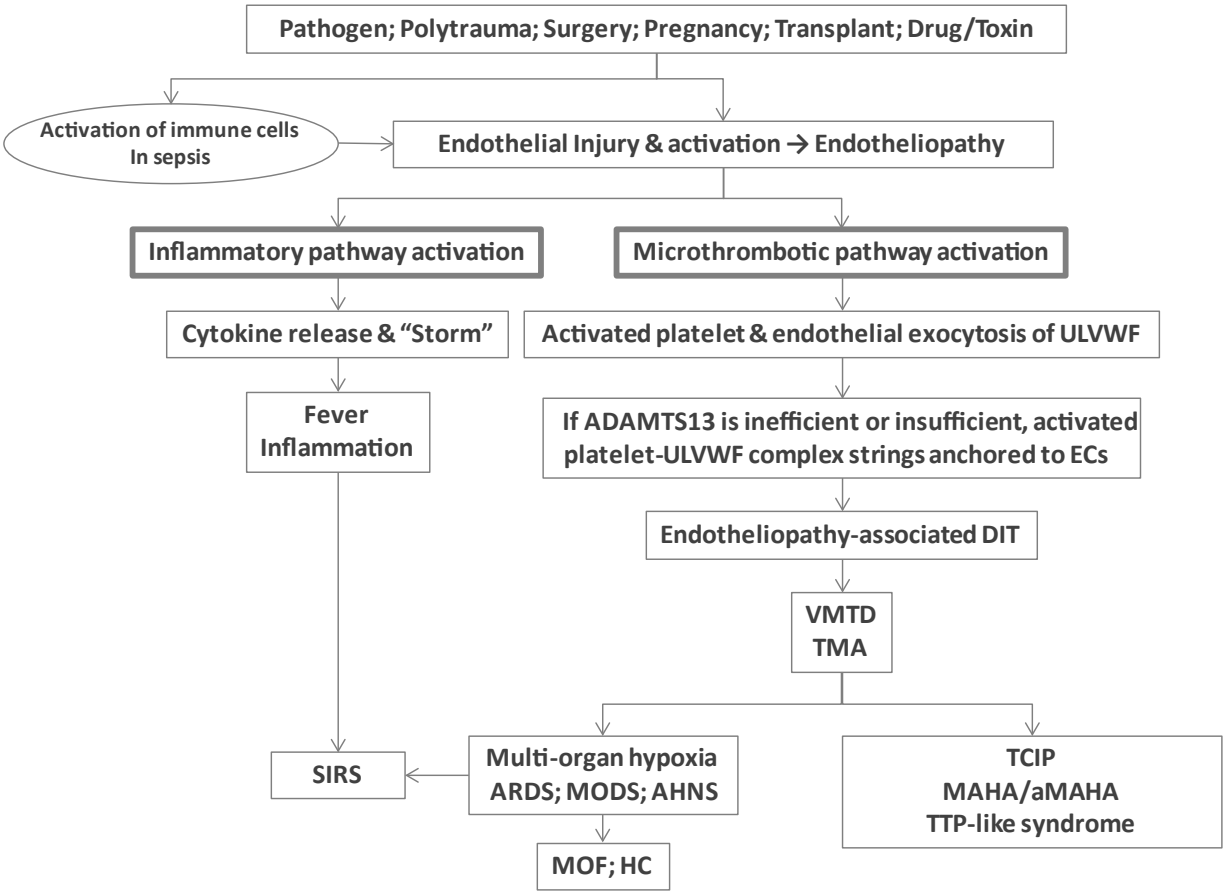

Figure 1. Pathogenesis of TCIP and related syndromes in critically ill patients

Perhaps the dissimilar clinical features (e.g., central nervous system dysfunction in TTP and ARDS in TTP-like syndrome) are related to microthrombogenesis occurring at different sites, resulting in different clinical syndromes due to divergent localization of intravascular microthrombi, even among the TTP-like syndromes (Table 2). TTP seems to be the result of microvascular microthrombosis, but TTP-like syndrome is the result of vascular microthrombosis. In the former, microthrombogenesis occurs in the circulation and formed microthrombi become lodged in microvasculatures [49], predominantly in the brain and kidneys. But in the latter, it occurs at ECs-anchored long elongated ULVWF strings [46,47] in smaller and larger vasculatures, commonly involving the lungs (*i.e.,* ARDS), kidneys (*i.e.,* acute renal failure, hemolytic-uremic syndrome), liver (*i.e.,* acute hepatic necrosis syndrome), intestines (*i.e.,* gastroenteritis), pancreas (*i.e.,* acute pancreatitis), muscles (*i.e.,* rhabdomyolysis), heart (*i.e.,* acute myocardial ischemia), skin (i.e., purpura fulminans), and others.

"DIC" *vs.* DIT

According to the "two-activation theory", DIT induced by microthrombogenesis is completely different from true DIC occurring as a result of activated TF coagulation pathway. DIT is a microthrombotic disorder, but true DIC is a coagulation disorder. Additionally, the current concept of pathologic coagulation (*i.e.,* "DIC") through TF pathway in the critical illness cannot be correct because *in vivo* sufficient TF is not available in the ECs. The characteristic difference between DIT and true DIC is shown in Table 3.

Donald McKay in early 1950s coined the term "DIC" [50] for a coagulation disorder that is caused by abnormally activated intravascular thrombotic state. He and his associates believed intravascular microthrombi in the luminal arterioles and capillaries in the pathologic tissue examination were micro blood clots made of platelets, coagulation factors and fibrins. His followers also supported the diagnosis of "DIC" with the laboratory result of prolonged prothrombin time and activated partial thromboplastin time, hypofibrinogenemia, and increased fibrin degradation products. The most of the coagulopathy associated with thrombocytopenia in the critical illnesses has been ascribed to "DIC" [51-53].

It should be emphasized that since no single laboratory test or set of tests is sensitive or specific enough to allow a definite diagnosis of

Table 2. Genesis and characteristics of DIT/VMTD in TTP and TTP-like syndrome.

	ADAMTS13 gene mutation-associated VMTD (Hereditary TTP) ADAMTS13 antibody-associated VMTD (Acquired TTP)	**Endotheliopathy-associated VMTD (TTP-like syndrome)**
Primary event	Hereditary ADAMTS13 gene mutation Acquired ADAMTS13 antibody formation	Sepsis/septic shock due to pathogens (e.g., viruses; bacteria; fungi; rickettsia; parasites) Polytrauma (e.g., chest/lungs; bones; skull/brain injury) Pregnancy complications (e.g., preeclampsia; abruptio placenta; amniotic fluid embolism) Cancer (e.g., stomach; breast; lung) Transplant (e.g., liver; kidney; bone marrow) Drug and chemical (e.g., cyclosporine; mytomycin C; Shiga toxin; ricin)
	↓	↓
Secondary event	Excessive circulating ULVWF & platelet aggregation	Endothelial injury & platelet activation→ ECs activation & endotheliopathy
	↓	↓
	Microthrombogenesis leading to platelet-ULVWF complexes	Cytokine release and cytokine storm → Inflammation → SIRS Endothelial exocytosis of ULVWF & anchored to ECs as a long elongated strings→ DIT
	↓	↓
Tertiary event	Microthrombi lodged in arteriolar capillary lumens	Vascular microthrombogenesis leading to platelet-ULVWF complexes anchored to ECs
	↓	↓
	VMTD	VMTD
	↓	↓
Final event	TMA (microthrombotic microangiopathy)	TMA (microthrombotic angiopathy)
	↓	↓
	TTP	TTP-like syndrome
Hematologic features		
Platelet	Consumptive thrombocytopenia	Consumptive thrombocytopenia
Red blood cell	MAHA	MAHA/aMAHA
Clinical syndromes		
Inflammation/fever	Fever may be present (?)	Very common
Cytokine storm	Absent	Often present in sepsis/septic shock
SIRS	Absent	Often present in sepsis/septic shock
CNSD	Very common	Common
ARDS	Absent	Very common
GE	Uncommon	Common
AH/AHNS	Uncommon	Common
ARF/HUS	Very common	Common
Hepatic coagulopathy	Not reported	Common
DIC*(see text)	Doesn't occur	Doesn't occur
Laboratory features		
ADAMTS13 activity	Markedly decreased (<5% of normal)	Mild to moderately decreased (20-70% of normal)
ADAMTS13 antibody	Positive in acquired TTP	Negative
LDH	Increased	Increased
Haptoglobin	Markedly decreased	Markedly decreased
Schistocytosis	++ to ++++	None to +++
Therapeutic response to		
TPE	Very good response	Excellent and fast response if treated in early stage
Platelet transfusion	Contraindicated	Contraindicated
rADAMTS13	Unknown at this time; expected to be effective in hereditary TTP	Unknown at this time; expected to be very effective

Table 3. Hematological and Clinical Characteristics of endotheliopathy-associated DIT and true DIC.

	Endotheliopathy-associated DIT (including "DIC" of McKay)	True DIC
Examples	TTP-like syndrome	DIC associated with APL
Nature of the disorder	Microthrombosis made of platelet-ULVWF complexes	Coagulation activated by TF-FVIIa complexes
Mechanism of the genesis	Intravascular microthrombogenesis	Intravascular coagulation
Inciting events	Sepsis, complications of surgery, pregnancy, cancer, and transplant, and drugs/toxins leading to endotheliopathy	APL and drugs (?) leading to TF expression
Hematological manifestations	TTP-like syndrome	Hemorrhagic disorder of APL
Pathogenesis		
Mechanism	Activation of microthrombotic pathway	Activation of TF-FVIIa complex pathway
Site of activation	Intravascular membrane of the endothelium	In circulation of the Intravascular space
Pathology	Endothelial activation/dysfunction → endotheliopathy	TF expression → coagulation and factor consumption
Result of pathogenesis	Formation of platelet-ULVWF microthrombi	Depletion of fibrinogen, FVIII, FV
Essence of pathology	Arteriolar and capillary luminal hyaline microthrombi	Incoagulable blood/unstable blood clots
Effect on the involved organs	Vascular microthrombosis leading to organ hypoxia	Hemorrhage leading to organ damage
Coagulation tests		
Fibrinogen	Normal	Decreased
PT; aPTT; TT	Prolonged	Prolonged
FDP	Normal	Increased
FVIII activity	Normal or markedly increased	Markedly decreased
Thrombocytopenia	Moderately severe	Mild to very severe
Associated clinical syndromes	TTP-like syndrome TMA MODS SIRS	Hemorrhagic disorder
Associated hematologic features		
Schistocytes	0 - +++	0 - + (?)
MAHA/aMAHA	Often present	Absent
Consumptive thrombocytopenia	Always present	Present (?)
Hepatic coagulopathy	May occur	Unusual
Incidence in clinical practice	Very common	Extremely rare
Therapy		
Platelet transfusion	Contraindicated	May be needed for APL
Treatment	TPE; rADAMTS13 (expected to be very effective)	Treat underlying pathology (e.g., ATRA in APL)

"DIC" [54]. In most cases the diagnosis is based on the combination of results of non-specific abnormal coagulation profile in the patient with clinical conditions known to be associated with "DIC" [55].

In clinical medicine, "DIC" mainly has been diagnosed on clinical pretense and is accepted based on the scoring system of the International Society on Thrombosis and Haemostasis (ISTH). Because of the misconception of "DIC", DIT in the critically ill patient has been diagnosed as "DIC". "DIC" diagnosis has not been based on more reliable coagulation factor assay of FVIII and FV, which are typically depleted in true DIC [40,56-59] as seen in acute promyelocytic leukemia. In many patients with "DIC", the coagulation profile is perfectly normal and hemorrhagic tendency does not occur. Puzzled but conveniently, the concept of "chronic/compensated/ covert" was introduced. This description, however, cannot explain inexplicably extensive microthrombi in the absence of depleted coagulation factors.

"DIC" and endotheliopathy-associated DIT/VMTD (*i.e.,* TTP-like syndrome) are exactly the same in their underlying risk factors and presentation. Both almost always occur in critical illnesses (e.g. sepsis/ septic shock, trauma, immunologic and collagen-vascular diseases, and complications of surgery, pregnancy and transplant) [38,60,61]. Pathologically both are characterized by arteriolar and capillary hyaline microthrombi with variable fibroblastic proliferation [49,62]. Hematologically they also present with TCIP and MAHA/aMAHA. Therefore, "DIC" and DIT are exactly the same disorder.

"DIC" perplexity explained

Considering the different pathogenic mechanisms between DIC and DIT, "DIC" must have been started with a incorrect concept. Hence, "DIC" is a misnomer. For more than 60 years, this unfortunate misconception on "DIC" has created confusion in medical science and practice, including diagnostic dilemma [54,55] and treatment failures to date [63].

If one accepts the fact that "DIC" is a misnomer and its euonym must be endotheliopathy-associated DIT, "DIC" can be explained perfectly well by the concept of DIT. The only remaining question is how "DIC" sometimes is associated with hemorrhagic disorder. Another word, "What is the correct diagnosis for acute "DIC" that is associated with abnormal coagulation profile?" The hemorrhagic disorder in "DIC" can be explained by hepatic vascular microthrombosis. Endotheliopathy-associated DIT/VMTD can trigger acute hepatic necrosis syndrome leading to hepatic coagulopathy [40]. Indeed, hepatic coagulopathy shows exactly the same coagulation profile as seen in "acute DIC".

True DIC is very rare but perhaps occurs in acute promyelocytic leukemia, presumably due to TF expression from leukemic cells [64]. The predominant feature of true DIC is hemorrhagic disorder without MAHA/aMAHA, hypoxic organ dysfunction and MODS [56-58]. In differentiating true DIC from hepatic coagulopathy, the appropriate test is the assay of coagulation factors, especially FVIII and FV, which are depleted in true DIC. More importantly, in hepatic coagulopathy, FVIII is normal or increased although it is markedly decreased in true DIC [40,58,59]. Also, a markedly decreased liver dependent FVII occurs in hepatic coagulopathy. A suggested guideline for laboratory tests is presented in Table 4 to aid the differential diagnosis among complicated thrombopathies and coagulopathies [36].

Conclusion

In the critically ill patient, TCIP is the earliest sign suggestive of microthrombogenesis in progress. In addition to inflammation,

Table 4. Differential characteristic hematologic features among thrombopathies and coagulopathies (Adapted and modified from Chang JC (36) with permission).

	TTP & TTP-like syndrome (DIT)	TTP-like syndrome (DIT) associated with HC (e.g., Ebola) = acute "DIC"	DIC (e.g., acute promyelocytic leukemia)	PF (e.g., amyloidosis)
Thrombocytopenia	Always present	Always present	Always present	Not present
MAHA/aMAHA	Almost always present	Usually present	Very unlikely to be present	Not present
Fibrinogen	Normal	Decreased	Always decreased	Always decreased
Factor VIII	Normal	Normal or increased	Markedly decreased	Decreased
Factor V	Normal	Decreased	Decreased	Decreased (?)
Factor X	Normal	Decreased	Usually normal	Normal
Factor VII	Normal	Markedly decreased	Normal	Normal
Factor IX	Normal	Decreased	Normal	Normal
FDP	Normal	Positive	Positive	Strongly positive
Thrombin time	Normal	Prolonged	Prolonged	Prolonged
Thrombosis form	Microthrombi	Microthrombi	Friable macrothrombi (?) or not formed	Absent
Bleeding: Character	Rare, mild petechiae	May cause serious bleeding	Common, serious bleeding	Slow & persistent bleeding
Treatment	Usually no need of treatment	Controllable with FFP	Abrogated with ATRA & chemotherapy	Treatable with AFA
Platelet transfusion	Contraindicated	Contraindicated	May be used with ATRA	Not needed

endotheliopathy-associated DIT/VMTD may lead to MODS, TMA, TTP-like syndrome and SIRS. "DIC" presents with the same clinical, pathologic and hematologic features as TTP-like syndrome. "DIC" should be correctly renamed as TTP-like syndrome.

Author disclosures

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