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Molecular Pathogenesis of Ebola Viral Hemorrhagic Disease: An Update

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ABSTRACT

Ebola viral hemorrhagic disease is rare, but is a serious thrombo-hemorrhagic disorder that can occur in Ebola viral sepsis. The demise of the patient occurs due to severe inflammation, multi-organ dysfunction syndrome and hemorrhage associated with a poorly defined coagulopathy. However, recent studies in COVID-19 pandemic have confirmed that viral sepsis including Ebola virus causes endothelial injury via complement activation that promotes inflammation and microthrombogenesis forming microthrombosis that leads to endotheliopathy-associated vascular microthrombotic disease (EA-VMTD). It commonly develops in the liver of Ebola infection (i.e., acute hepatic necrosis) and in the lungs of COVID-19 infection (i.e., acute respiratory distress syndrome). To address clinical and hematological features, a novel pathogenesis based on "two-activation theory of the endothelium" was proposed. Viral sepsis causes microthrombosis via ultra large on Willebrand factor (ULVWF) path of hemostasis in vivo following endothelial release of ULVWF/FVIII and recruitment of platelets. Endothelial injury promotes release of biomolecules from endothelial cells, which provokes various clinical syndromes including severe inflammation, consumptive thrombocytopenia, microangiopathic hemolytic anemia, and multiorgan dysfunction syndrome. In Ebola viral sepsis, activation of inflammatory pathway causes severe inflammation, but activation of microthrombotic pathway produces disseminated VMTD. The pathogenesis of Ebola viral disease is further complicated by hepatic coagulopathy initiated by acute hepatic necrosis, which results in "microthrombo-hemorrhagic syndrome" (erroneously called "disseminated intravascular coagulation" in the past) associated with thrombotic thrombocytopenic purpura (TTP)-like syndrome. The correct diagnostic term for the viral thrombo-hemorrhagic syndrome is "EA-VMTD with hepatic coagulopathy".

Keywords: Viral hemorrhagic disease; disseminated intravascular coagulation (true DIC); false disseminated intravascular coagulation ("DIC"); endotheliopathy; thrombocytopenia; multi-organ dysfunction syndrome (MODS); thrombotic thrombocytopenic purpura (TTP); TTP-like syndrome; microthrombogenesis; vascular microthrombotic disease (VMTD).

1. INTRODUCTION

In Ebola viral sepsis, Ebola viral hemorrhagic illness is a life-threatening hemorrhagic disorder. Ebola virus has been discovered in a number of African countries. In 1976, near the Ebola River in the Democratic Republic of Congo, Ebola was first found. Since then, outbreaks have appeared sporadically in Africa according to the Centers for Disease Control and Prevention (CDC) and spread to other countries of the world [1].

Clinical features of Ebola viral hemorrhagic disease have included inflammatory symptoms such as fever, myalgia, arthralgia, malaise, weakness and gastrointestinal symptoms. Hemorrhagic signs were petechiae, bleeding in internal organs and from bodily orifices like the mouth, eyes, or ears. Some patients developed bloody diarrhea. Many critically ill patients progressed to more serious conditions, including central nervous system dysfunction such as seizure, delirium, shock, acute pancreatitis, rhabdomyolysis, and multi-organ dysfunction. However, its pathogenesis for hemorrhagic disease has been unknown until recently [2,3].

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2. THROMBOCYTOPENIA IN CRITICALLY ILL PATIENTS

Proposed pathologic mechanism of Ebola hemorrhagic disease was included 1) thrombocytopenia related to bone marrow suppression from viral sepsis [4], 2) disseminated intravascular coagulation (DIC) [5,6], and 3) hepatic coagulopathy associated with virus-induced hepatitis/hepatic necrosis [2,3]. However, no credible clinical and laboratory data have been documented to explain the underlying coagulopathy.

Although Ebola hemorrhagic disease occurred with thrombocytopenia [7-10], its relationship to bleeding disorder has not been clearly correlated because thrombocytopenia was typically mild to moderately severe, and it alone could not produce such a severe Ebola viral hemorrhagic disease. Thus, thrombocytopenia had not been considered as a serious issue in caring of Ebola infection and hemorrhagic fever, but platelet transfusion had been utilized to maintain it at a safe level.

Just like Ebola viral infection, other sepsis of bacteria, viruses, fungi and parasites has often been associated with thrombocytopenia in critically ill patients (TCIP) [11-15]. Therefore, this term has been applied to etiology-undetermined thrombocytopenia in critical illnesses after exclusion of known causes of acute thrombocytopenia (e.g., heparin-induced, drug or transfusion-associated, DIC-associated, hypersplenism-related). An interesting finding was TCIP had occurred not only in sepsis/septic shock, but also developed in other critical illnesses (e.g., severe trauma, complications of surgery, pregnancy and transplant, and immunologic and collagen vascular diseases).

In the past, significant correlation was noted between the degree of thrombocytopenia and severity of the critical illness as well as prognosis and the likelihood of recovery [12,13]. Further, severer thrombocytopenia has been associated with systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS) [16,17]. These observations support TCIP is an important participant in the pathogenesis of the critical illness and serious physical injury.

3. ENDOTHELIOPATHY AND “TWO-ACTIVATION THEORY OF THE ENDOTHELIUM”

Other viral hemorrhagic diseases, including Ebola, had been suspected and has been confirmed to be caused by the injury of endothelial cells (ECs), leading to endotheliopathy and molecular endothelial dysfunction [18-27]. This author proposed that sepsis triggered molecular events via complement activation that promoted two independent pathways provoked by endotheliopathy: 1) inflammatory and 2) microthrombotic to produce two clinical phenotypes of inflammation and vascular microthrombotic disease (VMTD) [22,24-27]. Based on these molecular events, a hypothesis of “two-activation theory of the endothelium” was proposed (Fig. 1) [15]. In short, two important molecular events from endotheliopathy are: 1) release of inflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor-α, interferons and others) [28,29] which cause inflammation, and 2) activation of the platelet [30] and exocytosis of unusually large von Willebrand factor multimers (ULVWF) [31-33] that initiates intravascular hemostasis. In COVID-19 pandemic, this theory has been proven to be correct based on molecular changes in septic COVID-19 patients [27].

In endotheliopathy, the former triggers inflammation through “activation of inflammatory pathway”, and the latter mediates microthrombogenesis via “activation of microthrombotic pathway” as illustrated in Fig. 1. However, in traumatic vascular injury, hemostasis in vivo extends into ECs and subendothelial tissue (SET), in which ECs release ULVWF and SET release tissue factor (TF). This author has theorized that ULVWF multimers recruit platelets and activate ULVWF sub-path of hemostasis in vivo to promote microthrombogenesis that leads to microthrombi strings and TF activates TF sub-path to promote fibrinogenesis that leads to fibrin clots. The products of microthrombi and fibrin clots from activated two sub-paths become unified together and form macrothrombus via the unifying mechanism. From this hemostatic concept, the “two-path unifying theory” of hemostasis has been identified as displayed in Fig. 2 [24-26]. In the endothelial damage, microthrombogenesis begins with long elongated ULVWF strings, which become anchored to the membrane of ECs [33-35] and recruit platelets to assemble “platelet-ULVWF complexes” to form microthrombi strings without TF-FVIIa complex- activated coagulation cascade [24-26]. This mechanism results in disseminated

intravascular microthrombosis provoking thrombotic thrombocytopenic purpura (TTP)-like syndrome. This clinical condition is now defined as vascular microthrombotic disease (VMTD).

4. ENDOTHELIOPATHY AND TTP-LIKE SYNDROME

Recently, it was well documented that endotheliopathy produces TTP-like syndrome with the diagnostic triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and MODS (Fig.1). Further, TTP-like syndrome is found to be characterized by arterial endotheliopathy [36,37]. Disseminated microthrombosis in capillaries and arterioles is the underlying pathological condition leading to VMTD. However, disseminated VMTD includes two different clinical disorders: 1) TTP and 2) TTP-like syndrome as noted in Table 1. In TTP, microthrombogenesis occurs in circulation, probably without significant endotheliopathy, but due to hyperactivity of ULVWF within blood stream, which is the hallmark in both hereditary and antibody-associated VMTD. The former is called gene mutation-associated VMTD (GA-VMTD), and the latter is antibody-associated VMTD (AA-VMTD) [38]. On the other hand, the TTP-like syndrome developing in viral hemorrhagic disease is microthrombotic disease at the intravascular surface of injured ECs within the microvasculature. This VMTD occurring endotheliopathy is caused by microthrombi strings that are composed of platelet-ULVWF complexes at the endothelial membrane. Therefore, this condition can be termed endotheliopathy-associated VMTD (EA-VMTD) [38].

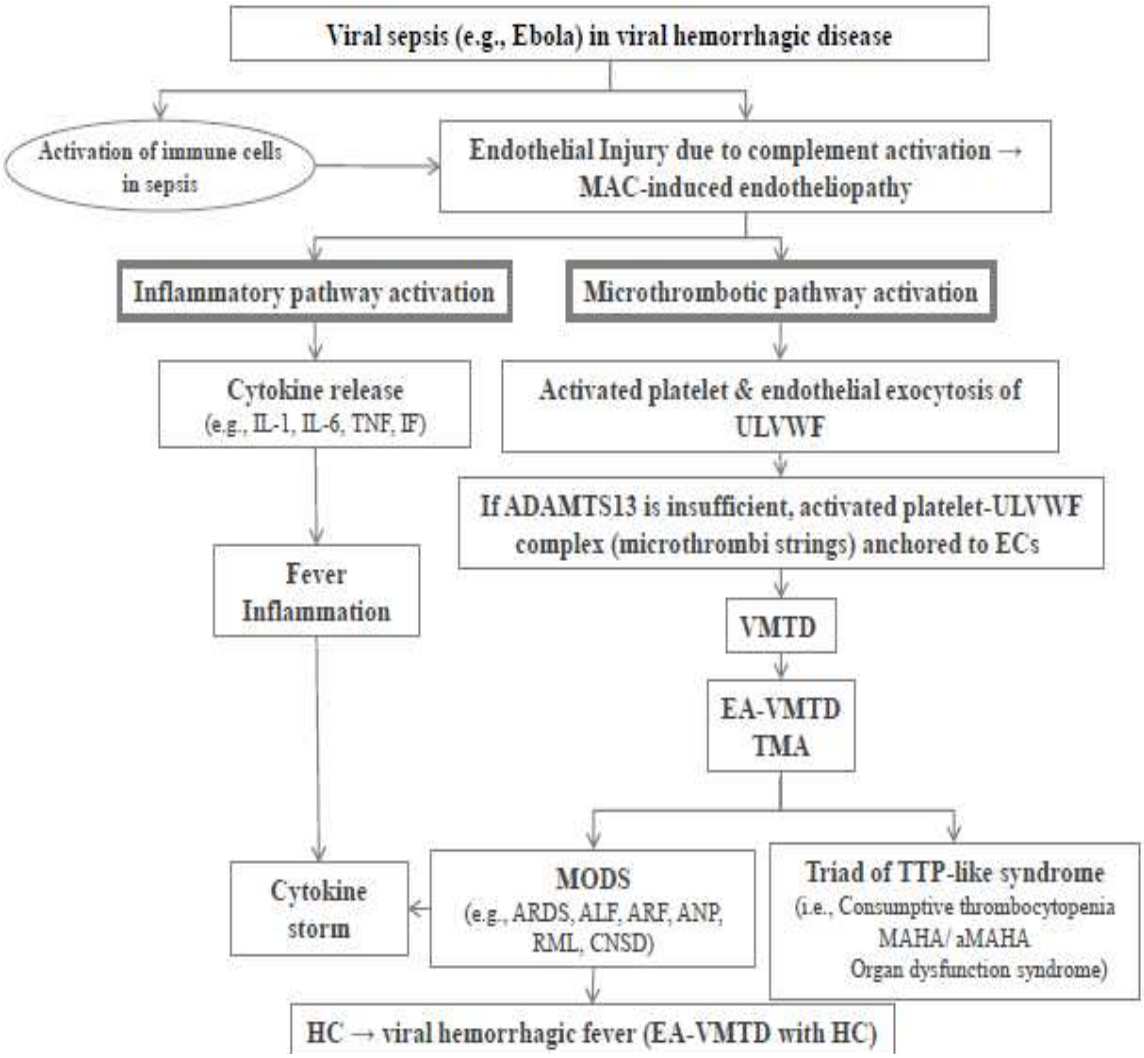

Fig. 1. Molecular pathogenesis of TTP-like syndrome in Ebola viral hemorrhagic disease based on "two-activation theory of the endothelium"

The terminal complement complex (i.e., MAC) triggered by innate immune response due to pathogen such as Ebola virus kills the virus, but also promotes endotheliopathy on the host ECs, leading to activation of two endothelial pathways; one is the inflammatory pathway initiated by various cytokines such as IL-1, IL6, TNF and IF leading to inflammatory syndrome, and the other is microthrombotic pathway provoking exocytosis of ULVWF and FVIII which recruit platelets. Endotheliopathy is characterized by molecular pathogenesis of these cytokines and hemostatic factors. The former causes inflammation and sometimes serious cytokine storm. The latter initiates microthrombogenesis via ULVWF path of hemostasis, which produces disseminated VMTD and orchestrates consumptive thrombocytopenia, microthrombosis, and TTP-like syndrome and MODS. The organ phenotype syndrome in MODS as shown in the Figure. For example, in sepsis complement activation is the initial critical event provoking endotheliopathy. Often, Ebola-induced VMTD affects the liver and leads to hepatic microvascular necrosis, which is consistent with ALF and FHF. This condition leads to hepatic coagulopathy in EA-VMTD causing Ebola viral hemorrhagic fever.
Abbreviations: ARF, acute renal failure; aMAHA/MAHA, atypical microangiopathic hemolytic anemia/microangiopathic hemolytic anemia; ALF, acute liver failure; ANP, acute necrotizing pancreatitis; ARDS, acute respiratory distress syndrome; CNSD, central nervous system dysfunction syndrome; ECs, endothelial cells; FHF, fulminating hepatic failure; HC, hepatic coagulopathy; IL, interleukin; IF, interferon; MAC, membrane attack complex; MODS: multi-organ dysfunction syndrome; RML, rhabdomyolysis; TMA, thrombotic microangiopathy; TNF, tumor necrosis factor; TTP, thrombotic thrombocytopenic purpura; VMTD, vascular microthrombotic disease; ULVWF, ultra large von Willebrand factor; EA-VMTD, endotheliopathy-associated VMTD

In viral hemorrhagic disease, EA-VMTD could provoke TTP-like syndrome [39-42], which is characterized by consumptive thrombocytopenia, MAHA, or atypical MAHA (aMAHA) if schistocytes are fewer in number, and hypoxic MODS. Unlike contemporary dogmatic concept of “DIC”, in which an abnormal hemostatic (coagulation) disorder supposedly occurs in the septic patient following tissue factor (TF) pathway activation [43], EA-VMTD also may occur in the septic patient as a pathological microthrombotic disorder resulting from microthrombogenesis [26,44]. According to “two-path unifying theory of hemostasis” depicted in Fig. 2, TF pathway is not involved in microthrombogenesis, and coagulation factors are not depleted in the EA-VMTD [45], which mechanism was elaborated in my previous publications [24,26].

5. WHAT IS TRUE IDENTITY OF EBOLA VIRAL HEMORRHAGIC DISEASE

ADAMTS13 deficiency is known to occur in liver cirrhosis with overexpression of ULVWF/VWF antigen and increased FVIII activity [46-48]. ADAMTS13 is synthesized primarily in the liver, which was demonstrated by in situ hybridization and immunohistochemistry [49]. Human ADAMTS13 mRNA and protein are localized exclusively to hepatic stellate cells that reside in the interstitial space between hepatocytes and the ECs [50]. Since the liver is already more vulnerable to septic damage than other organs due to the tropism of Ebola virus (i.e., EA-VMTD), underexpressed ADAMTS13, especially in liver cirrhosis, could more likely lead to Ebola viral hemorrhagic disease resulting from hepatic damage. Indeed, acute liver necrosis has been well documented in Ebola hemorrhagic disease [51,52]. Further, liver cirrhosis with overexpressed FVIII and ULVWF can become an easy target producing EA-VMTD. Both ADAMTS13 deficiency due to decreased synthesis and additional hepatic damage due to microthrombosis would be a serious combination promoting hepatic coagulopathy provoking microthrombotic-hemorrhagic syndrome. This syndrome is entirely consistent with old conceptual term of acute/uncompensated/overt “DIC” [26].

Previously, all the viral hemorrhagic diseases have been attributed to false concept of DIC (“DIC”), which was presumed to be activated by TF-FVIIa complexes [22] leading to disseminated “fibrin clots”. Instead, EA-VMTD is the correct concept for “DIC” which is caused by “disseminated microthrombosis” made of the platelet-ULVWF complexes produced from the activated ULVWF path of hemostasis. Theerefore, “DIC”cannot explain how “disseminated fibrin clots” made of fibrin meshes following TF-activated fibrinogenesis is the same to VMTD [43]. The major dilemma is how “DIC” of intravascular coagulation is different from endotheliopathy? In clinical medicine, “DIC” in majority cases had been diagnosed on clinical pretense and typically affirmed its diagnosis based on the elaborative scoring system of the International Society on Thrombosis and Haemostasis (ISTH). Because of this misconception of “DIC”, the microthrombosis occurring in endotheliopathy of the critically ill patient (e.g., sepsis) had been interpreted as “fibrin clots”.

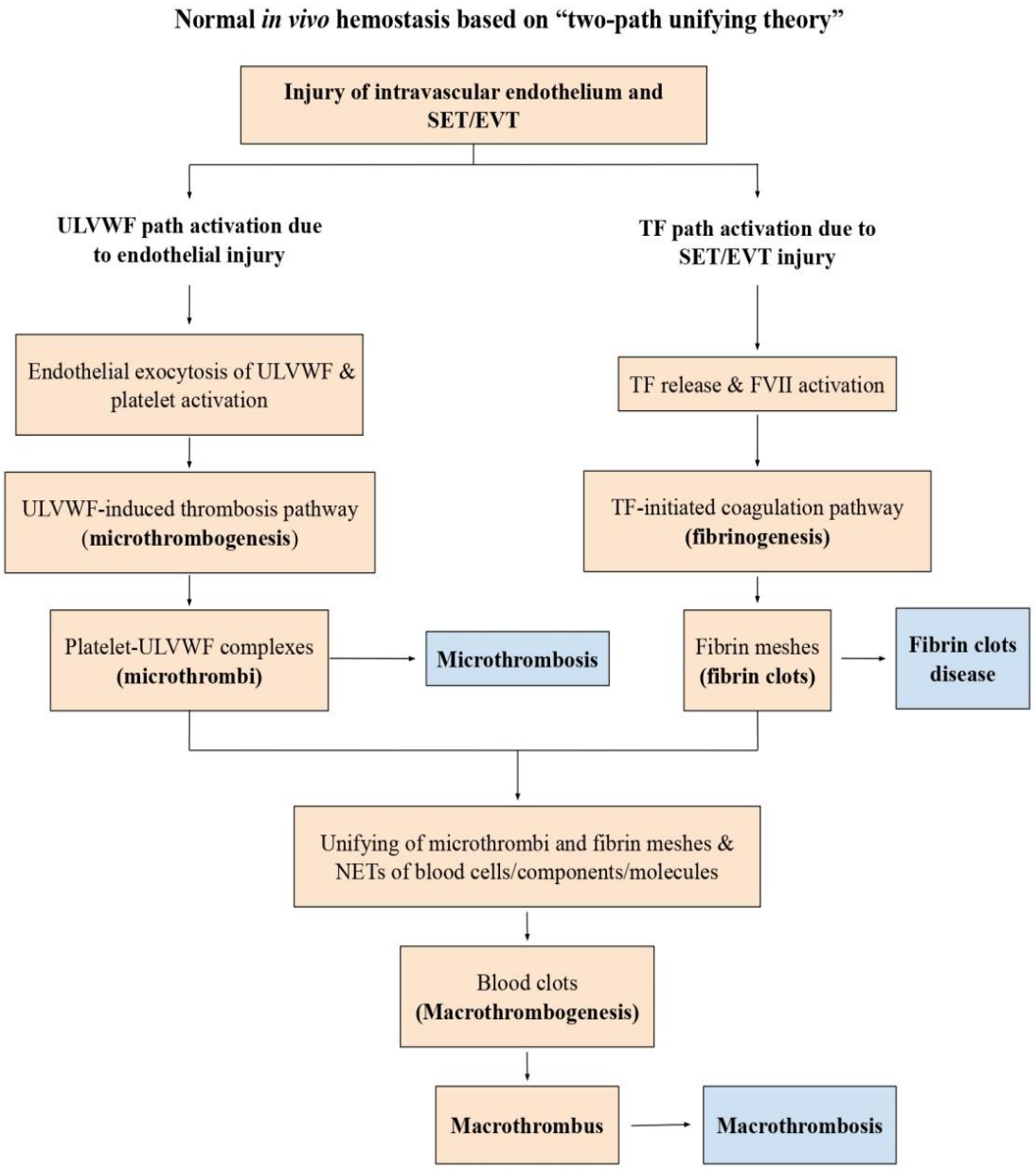

Fig. 2. Novel "two-path unifying theory" of hemostasis and 3 paths of thrombogenesis

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Following a vascular injury, in vivo hemostatic system activates two independent sub-hemostatic paths: microthrombotic (ULVWF path) and fibrinogenetic (TF path). Both are initiated by the damage of ECs and SET/EVT due to external bodily injury and intravascular injury. In ULVWF path from ECs damage, ULVWF multimers are released and recruit platelets, and produce microthrombi strings via microthrombogenesis, but in TF path from SET/EVT damage, released TF activates FVII. The TF-FVIIa complexes produce fibrin meshes/fibrin clots via the mechanism of extrinsic coagulation cascade. The final path of in vivo hemostasis is macrothrombogenesis, in which microthrombi strings and fibrin meshes become unified together with incorporation of NETs, including red blood cells, neutrophils, DNAs and histones. This unifying event "macrothrombogenesis" promotes the hemostatic plug and provides the wound healing in an external bodily injury, and produces macrothrombus in intravascular injury.

Abbreviations: EA-VMTD, endotheliopathy-associated vascular microthrombotic disease: ECs, endothelial cells; EVT, extravascular tissue; NETs, neutrophil extracellular traps; SET, subendothelial tissue; TF, tissue factor; ULVWF, ultra large von Willebrand factor multimers

Table 1. Acquired vascular microthrombotic disease (VMTD): Pathogenic and clinical characteristics of TTP and TTP-like syndrome

	Acquired autoimmune TTP (i.e., Antibody-associated VMTD [AA-VMTD])	**TTP-like syndrome (i.e., Endotheliopathy-associated VMTD [EA-VMTD])**
Etiology	Positive anti-ADAMTS13 antibody	ECs injury leading to dysfunction due to pathogen, surgery, polytrauma, Shiga toxin, preeclampsia, abruptio placenta, cancer, drugs, venom, and others
Probable pathogenesis	↓ Decreased activity of ADAMTS13 ↓ Hyperactive ULVWF → Aggregate with platelets ↓ Formation of platelet-ULVWF complexes ↓ Disseminated microthrombosis (VMTD)	↓ Release of ULVWF/FIII and anchored to ECs ↓ ULVWF attract platelets ↓ Formation of platelet-ULVWF complexes ↓ Disseminated microthrombosis (VMTD)
ADAMTS13 level	Usually <5% of normal	Usually 20-70%
ADAMTS13 antibody	Positive	Sometimes positive
Intravascular ULVWF/FVIII	Not determined yet	Aways present
Thrombocytopenia	Always present	Always present
MAHA with schistocytes	Organ dysfunction syndrome/MODS	Organ dysfunction syndrome/MODS
Typical hypoxic organ dysfunction	CNSD; ARF	CNSD; ARDS; HELLP syndrome; FHF/ALF; ARF/HUS; RML
Inflammation	May be present (?)	ANP; Waterhouse-Friderichsen syndrome; Purpura fulminans
Response to TPE	Excellent good response	Almost always present
Platelet transfusion	Contraindicated	Excellent response Contraindicated

Abbreviations: ALF, acute liver failure; AHNS, ANP, acute necrotizing pancreatitis; ARF, acute renal failure; CNSD, central nervous system dysfunction; ECs, endothelial cells; FHF, fulminant hepatic failure; HELLP, hemolysis, elevated liver enzyme, and low platelet; HUS, hemolytic-uremic syndrome; MAHA, microangiopathic hemolytic anemia; MODS, multiorgan dysfunction syndrome; RML, rhabdomyolysis; TPE, therapeutic plasma exchange; ULVWF, ultra large von Willebrand factor; VMTD, vascular microthrombotic disease; AA-VMTD, antibody-associated VMTD; EA-VMTD, endothedliopathy-associated VMTD

Table 2. Hematological and Clinical Characteristics of EA-VMTD (TTP-like syndrome), "DIC" and true DIC

	TTP-like syndrome	"DIC" (False DIC)	True DIC
Examples	EA-VMTD	"DIC" (EA-VMTD) without HC (chronic DIC) "DIC" (EA-VMTD with HC (acute DIC")	Fibrin clot disease
Inciting events	Sepsis; polytrauma; complications of surgery/pregnancy/transplant; drug/toxin/venom	Sepsis; polytrauma; complications of surgery/pregnancy/transplant; drug/toxin/venom	APL
Hematological manifestations	TTP-like syndrome	TTP-like syndrome without HC (chronic) TTP-like syndrome with HC (acute)	Hemorrhagic disease of APL
Pathogenesis Mechanism	Microthrombogenesis due to ECs damage	Microthrombogenesis due to ECs damage (chronic) Microthrombogenesis due to ECs damage with HC (acute)	Fibrinogenesis due to activated TF
Hemostatic factors	ULVWF and platelets	ULVWF and platelets (chronic) FII, FV, FVII, FIX, FX (acute)	TF-FVIIa complex, FX, FV, FII, FI
Thrombosis/clot forms	Microthrombi strings	Microthrombi strings (chronic and acute)	Fibrin clots Fibrin clot disease
Thrombosis form	Microthrombi strings	Microthrombi strings + fibrin clots	Hemorrhage leading to organ damage
Inflammation	Commonly present	Commonly present	May be present
Coagulation tests			
Fibrinogen;	Normal/increased	Normal/increased (chronic), but decreased (acute)	Decreased
PT; aPTT	Normal	Normal (chronic), but prolonged (acute)	Prolonged
ULVWF/VWF antigen	Increased	Increased (chronic), but variable (acute)	Normal (?)
FVIII activity	Increased	Increased (chronic), but variable (acute)	Normal (?)
D-dimer	Negative	Negative (chronic), but positive	Increased (?)
FSPs	Negative	Positive (acute)	Positive
Thrombocytopenia	Always present due to endotheliopathy	Always present due to endotheliopathy	Present due to APL
ADAMTS13	Mild to moderately diminished	Mild to moderately diminished	Expected to be normal
Treatments	TPE, FFP, IVIG, rituximab, anti-complement Potential therapy: rADAMTS13, NAC	TPE, FFP, IVIG, rituximab (?), anticomplement (?) Potential therapy: rADAMTS13, NAC	ATRA Chemotherapy

Abbreviations: *APL, acute promyelocytic leukemia; ATRA, all-trans-retinoic-acid; DIC, disseminated intravascular coagulation; "DIC", false DIC; ECs, endothelial cells; FFP, fresh frozen plasma; FSPs, fibrin split product; HC, hepartic coagulopathy; IVIG, intravenous immunoglobulins; NAC, N-acetyl cysteine; PT, prothrombin time; aPTT, activated partial thromboplastin time; TF, tissue factor; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; ULVWF, ultra large von Willebrand factor; VWF, von Willebrand factor; VMTD, vascular microthrombotic disease; EA-VMTD, endotheliopathy-associated VMTD*

The dogmatic misinterpretation of DIC was the result of our shortcomings on the comprehension of in vivo hemostatic mechanism and omission of reliable coagulation test results such as overexpressed ULVWF/VWF antigen, increased FVIII activity and "consumptive" thrombocytopenia. FVIII and FV are typically depleted in true DIC as seen in acute promyelocytic leukemia (APL) [53]. In retrospect, like EA-VMTD, "DIC" also has occurred in critically ill patients such as sepsis and pregnancy complication. Now, it is obvious the conceptual "DIC" and microthrombosis must be identical, which means "DIC" is not due to activated TF-FVII extrinsic pathway, but is the result of activated microthrombogenesis in endotheliopathy. In another word, the old concept of DIC is false because it is EA-VMTD. Certainly, Ebola viral hemorrhagic disease is consistent with EA-VMTD coexisting with hepatic coagulopathy.

Donald McKay in early1950s coined the term "DIC" [54] for a coagulation disorder that was caused by abnormally activated intravascular thrombotic state. He and his followers believed intravascular microthrombi in the luminal arterioles and capillaries found in the pathologic tissue examination were made of micro-fibrin clots of platelets, coagulation factors and fibrin. In coagulation test profile, the supporting evidence was prolonged prothrombin and activated partial thromboplastin time, hypofibrinogenemia, and increased fibrin degradation products. Later years, in many patients with the diagnosis of "DIC", the coagulation profile was found to be normal, and hemorrhagic tendency did not occur. Without a persuasive explanation, the conceptual term of "chronic/compensated/covert" DIC was introduced in contrast to "acute/uncompensated/overt" DIC. This definition, however, cannot explain the inexplicably extensive microthrombi (i.e., EA-VMTD) in the absence of depleted coagulation factors.

Chronic "DIC" and EA-VMTD (i.e., TTP-like syndrome) are exactly the same in their underlying risk factors, clinical features and pathologic findings as well as hematologic phenotypes. 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) [55,56]. Pathologically both are characterized by arteriolar and capillary hyaline microthrombi with variable fibroblastic proliferation [57,58]. Both also are characterized by hematologic triad of consumptive thrombocytopenia, and MAHA and MODS. Thus, "DIC" and EA-VMTD are exactly the same disorder but with two different names.

6. EA-VMTD AND True DIC

According to the "two-activation theory of the endothelium" and "two-path unifying theory" of hemostasis in vivo, EA-VMTD promoted by microthrombogenesis in endotheliopathy is different from "true" DIC of disseminated "fibrin clots" occurring in APL via fibrinogenesis of activated TF coagulation pathway. The characteristic differences amongst EA-VMTD, false DIC and true DIC are summarized in Table 2. EA-VMTD is a pathological microthrombotic disorder due to microthrombogenesis; thus, false

DIC does not exist but is a "conceptual" disease. However, true DIC is only seen in APL because it results in disseminated "fibrin clots" from aberrant hemostasis (coagulation) via fibrinogenesis in the absence of vascular injury. Hence, "DIC" of septic coagulopathy is a misnomer. More than 60 years, this unfortunate misconception of "DIC" has created confusion in medical science and practice, including diagnostic dilemma and treatment failures to date.

If one understands and accepts the fact that "DIC" is a misnomer and redefined as EA-VMTD, Ebola hemorrhagic disease can be explained perfectly well by the concept of EA-VMTD with hepatic coagulopathy. In Ebola, fulminant hepatic failure/acute liver failure/acute liver necrosis, especially multifocal necrosis type, has occurred mysteriously [52,59-63]. Now, microthrombo-hemorrhagic syndrome can be interpreted as one of many endotheliopathic syndromes. EA-VMTD with hepatic coagulopathy is characterized by decreased synthesis of FII, FV, FVII, FIX and FX, and overexpressed ULVWF/VWF antigen and increased activity of FVIII. Fibrinogen is increased in early stage of EA-VMTD (i.e., covert "DIC") and is markedly decreased in late stage of EA-VMTD with hepatic coagulopathy (i.e., overt "DIC"). ADAMTS13 activity is expected to be mild to moderately decreased [26, 27].

Table 3. Differential characteristic hematologic features among microthrombopathies and coagulopathies

	TTP-like syndrome (EA-VMTD) equal to covert "DIC"	**TTP-like syndrome (EA-VMTD) associated with HC (e.g., Ebola) equal to overt "DIC"**	**Fibrin clot disease (e.g., acute promyelocytic leukemia) equal to true DIC**	**PF (e.g., amyloidosis)**
Laboratory findings				
Thrombocytopenia	Always present	Always present	Always present	Not present
MAHA/aMAHA	Almost always present	Always present	Not present	Not present
Fibrinogen	Elevated in early stage	Markedly decreased	Decreased	Decreased
ULVWF/VWF antigen	Increased	Increased	Normal (?) to be confirmed	Normal (?) to be confirmed
FVIII	Increased	Increased	Decreased (?) to be confirmed	Normal (?) to be confirmed
FV	Normal	Decreased	Decreased	Normal
FX	Normal	Decreased	Normal (?) to be confirmed	Normal
FVII	Normal	Markedly decreased	Normal (?) to be confirmed	Normal
FDPs	Normal	Increased (due to liver damage)	Increased	Strongly positive
D-dimer	Normal	Increased (due to liver damage)	Increased	Increased (?) to be confirmed
ADAMTS13	Decreased	Markedly decreased (?)	Normal	Normal
Pathology				
Thrombosis form	Microthrombi	Microthrombi	Fibrin clots	Very unlikely to be present Absent
Bleeding character	Petechiae	Serious hemorrhage	Serious bleeding	Slow and persistent bleeding

Abbreviations: DIC, disseminated intravascular coagulation; "DIC", false DIC; EA-VMTD, endotheliopathy-associated vascular microthrombotic disease; FDPs, fibrin degradation products; HC, hepatic coagulopathy; PF, primary fibrinolysis; TTP, thrombotic thrombocytopenic purpura; ULVWF, ultra large von Willebrand factor; VWF, von Willebrand factor

True DIC occurs only in APL, which is presumably due to TF expression from leukemic cells without vascular injury [64,65]. As noted in Table 2, the predominant feature of true DIC is a hemorrhagic disorder without MAHA or hypoxic organ dysfunction [26,44,53]. In differentiating true DIC from EA-VMTD with hepatic coagulopathy, the most important test is the determination of coagulation factors. Thrombocytopenia, increased ULVWF/VWF and FVIII and decreased ADAMTS13 are considered to be the diagnostic markers for endotheliopathy. Also, a coagulation profile showing markedly decreased liver dependent factors fibrinogen and FVII supports underlying hepatic necrosis leading to hepatic coagulopathy. A suggested guideline for laboratory tests is presented in Table 3 to aid the differential diagnosis among complicated microthrombopathies and coagulopathies [3].

In Ebola hemorrhagic disease, thrombocytopenia is due to consumption of platelets in the process of forming microthrombi and is an early indicator suggesting that microthrombogenesis is in progress. If hemorrhagic disorder occurs, it is neither due to DIC nor due to thrombocytopenia alone, but most likely is due to underling hepatic coagulopathy occurring in association with EA-VMTD. In Ebola hemorrhagic disease, the “two-activation theory” of hemostasis not only explains the concomitant inflammation and microthrombosis, but also would unmask unidentified coexisting syndromes such as cytokine “storm”, TTP-like syndrome, consumptive thrombocytopenia, MAHA, and organ dysfunction syndrome, including MODS.

7. CONCLUSION

Reviewed is the molecular pathogenesis of Ebola viral hemorrhagic disease. Ebola viral sepsis promotes disseminated intravascular microthrombosis provoked by the endotheliopathy resulting from complement activation. Subsequent complication of acute hepatic necrosis would also lead to hemorrhagic diathesis. The hematologic phenotype is TTP-like syndrome and hepatic phenotype is hemorrhagic syndrome. Therefore, Ebola hemorrhagic disease is a microthrombo-hemorrhagic syndrome. The diagnosis of EA-VMTD associated with hepatic coagulopathy can be confirmed by elevated endothelial markers and decreased clotting factors, and further can be supported by insufficient ADAMTS13.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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