

Viral hemorrhagic fevers due to endotheliopathy-associated disseminated intravascular microthrombosis and hepatic coagulopathy: pathogenesis based on “two activation theory of the endothelium”

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Abstract

Viral hemorrhagic fevers are rare but the life-threatening hemorrhagic disorder associated with viral sepsis. The demise of the patient occurs due to severe inflammation, multi-organ dysfunction syndrome and hemorrhage associated with poorly-defined coagulopathy. Sepsis of several families of RNA viruses causes endothelial injury that orchestrates inflammation and multi-organ dysfunction including the liver. To address additional clinical and hematological features, a novel pathogenesis based on “two-activation theory of the endothelium” is proposed. Endothelial injury activates endothelial cells that promote various clinical syndromes such as consumptive thrombocytopenia, multi-organ dysfunction and thrombotic microangiopathy. Endotheliopathy initiates two independent molecular events at endothelial cells: 1) release of inflammatory cytokines and 2) activation of the platelet and exocytosis of unusually large von Willebrand factor multimers. The former triggers activation of inflammatory pathway and the latter mediates activation of microthrombotic pathway. In viral sepsis, the activation of inflammatory pathway causes inflammation, but the activation of microthrombotic pathway manifests as disseminated intravascular microthrombosis (DIT). The pathogenesis of viral hemorrhagic fevers is hepatic coagulopathy triggered by acute hepatic necrosis as a result of endotheliopathy-associated DIT, which also could manifest as TTP-like syndrome.

New terminology: Microthrombogenesis; Disseminated intravascular microthrombosis (DIT); Vascular microthrombotic disease (VMTD)

Introduction

Viral hemorrhagic fevers commonly occur in several families of RNA viruses: *Arenaviridae* (e.g., Lassa), *Bunyaviridae* (e.g., Hanta), *Filoviridae* (e.g., Ebola and Marburg) and *Flaviviridae* (e.g., yellow fever and dengue). It is a life-threatening hemorrhagic disorder, but the pathogenesis of hemorrhagic disorder is poorly understood [1].

Clinical features of viral hemorrhagic fevers include inflammatory symptoms such as fever, myalgia, arthralgia, malaise and weakness. Hemorrhagic signs are petechiae, bleeding in internal organs and external bleeding from bodily orifices like the mouth, eyes, or ears. Some patients develop bloody diarrhea. Eventually critically ill patients could progress to more serious conditions including seizures, delirium, shock, renal failure, acute respiratory distress and multi-organ dysfunction.

Thrombocytopenia in viral hemorrhagic fevers (TCIP)

Potential causes of the hemorrhagic disease include: 1) thrombocytopenia related to bone marrow suppression or platelet destruction secondary to endothelial activation from viral sepsis [2,3], 2) disseminated intravascular coagulation (DIC) [1,3-5], and 3) hepatic coagulopathy associated with virus-induced hepatitis/hepatic necrosis [1,6,7]. However, no credible clinical and laboratory data have been documented to explain the underlying coagulopathy.

Although viral hemorrhagic fevers commonly occur with etiology-undetermined thrombocytopenia in critically ill patients (TCIP) [1-

3,6-9], its relationship to bleeding is not clearly determined because thrombocytopenia is typically mild to moderately severe and it alone can't be accountable for the severe hemorrhagic disorder. Thus, thrombocytopenia has not entered as a serious issue in caring of viral hemorrhagic fevers other than platelet transfusion to maintain it at a safe level.

It is well known that the critical illnesses due to pathogens from bacterial, viral, fungal or parasitic sepsis are oftentimes associated with TCIP [10]. This term has been applied to etiology-undetermined thrombocytopenia after exclusion of known causes of acute thrombocytopenia (e.g., heparin-induced, drug or transfusion-associated, DIC-associated, hypersplenism-related, etc.). An interesting finding is TCIP not only occurs in sepsis/septic shock, but also occurs in other critical illnesses (e.g., severe trauma, complications of surgery, pregnancy and transplant, and immunologic and collagen vascular diseases) [10-13]. Recently, significant correlation was noted between the degree of thrombocytopenia and severity of the disease, and TCIP influenced the prognosis and likelihood of recovery [14,15]. Severe thrombocytopenia has been associated with systemic inflammatory

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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 including viral hemorrhagic fevers.

Endotheliopathy and the “two-activation theory of the endothelium”

Viral hemorrhagic fevers are known to cause the injury to endothelial cells (ECs) leading to endotheliopathy and endothelial dysfunction, and endotheliopathy triggers multiple molecular events [18-20]. According to novel thesis of the “two-activation theory of the endothelium” (Figure 1) [6], endotheliopathy promotes the activation of two independent endothelial pathways (*i.e.*, inflammatory and microthrombotic). In short, two important molecular events are: 1) release of inflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor- α , and others) [20-22], and 2) activation of the platelet and exocytosis of unusually large von Willebrand factor multimers (ULVWF) [23-25]. The former triggers inflammation through “activation of inflammatory pathway”, and the latter mediates microthrombogenesis via “activation of microthrombotic pathway” as illustrated in Figure 1. In endotheliopathy, microthrombogenesis is the process in which long elongated ULVWF strings are anchored to ECs to recruit activated platelets, and to assemble and decorate platelet-ULVWF complexes as microthrombi [25-27]. This results in disseminated intravascular microthrombosis (DIT) triggering thrombotic thrombocytopenic purpura (TTP)-like syndrome.

Endotheliopathy-associated DIT is TTP-like syndrome

DIT is the underlying pathological condition leading to vascular microthrombotic disease (VMTD). Systemic VMTD includes two

clinical disorders: thrombotic thrombocytopenic purpura (TTP) and TTP-like syndrome. In TTP, microthrombogenesis occurs in circulation due to hyperactivity of ULVWF in both hereditary and antibody-associated type, but in TTP-like syndrome developing in viral hemorrhagic fevers and other critical illnesses, it occurs at the intravascular surface of ECs. The different pathogenesis and clinical characteristics of TTP and TTP-like syndrome are summarized in Table 1. In the critical illness DIT is made of microthrombi that consist of platelet-ULVWF complexes and is anchored to ECs. DIT as a result of endotheliopathy in viral hemorrhagic fevers can be called endotheliopathy-associated DIT/VMTD.

In viral hemorrhagic fevers, endotheliopathy-associated DIT/VMTD could trigger TTP-like syndrome [6,28-31], which is characterized by consumptive thrombocytopenia, microangiopathic hemolytic anemia (MAHA)/atypical MAHA (aMAHA) (if schistocytes are fewer) and hypoxic organ dysfunction syndromes. Unlike true DIC in which hemostatic (coagulation) disorder occurs following tissue factor (TF) pathway activation, endotheliopathy-associated DIT/VMTD is the microthrombotic disorder occurring as a result of microthrombogenesis. In endotheliopathy-associated DIT/VMTD, TF pathway activation is not involved and thus coagulation factors are not consumed and depleted.

Are viral hemorrhagic fevers due to “DIC”?

The simple answer is no. Viral hemorrhagic fevers have been attributed to “DIC” [3-5,32], mainly utilizing the International Society on Thrombosis and Haemostasis (ISTH) DIC-scoring system and accepting the microthrombosis in the critically ill patient as the marker for hemostatic (coagulation) disorder. This diagnosis hasn’t been based on more reliable coagulation factor assay of FVIII and FV, which are typically depleted in true DIC as seen in acute promyelocytic leukemia [33].

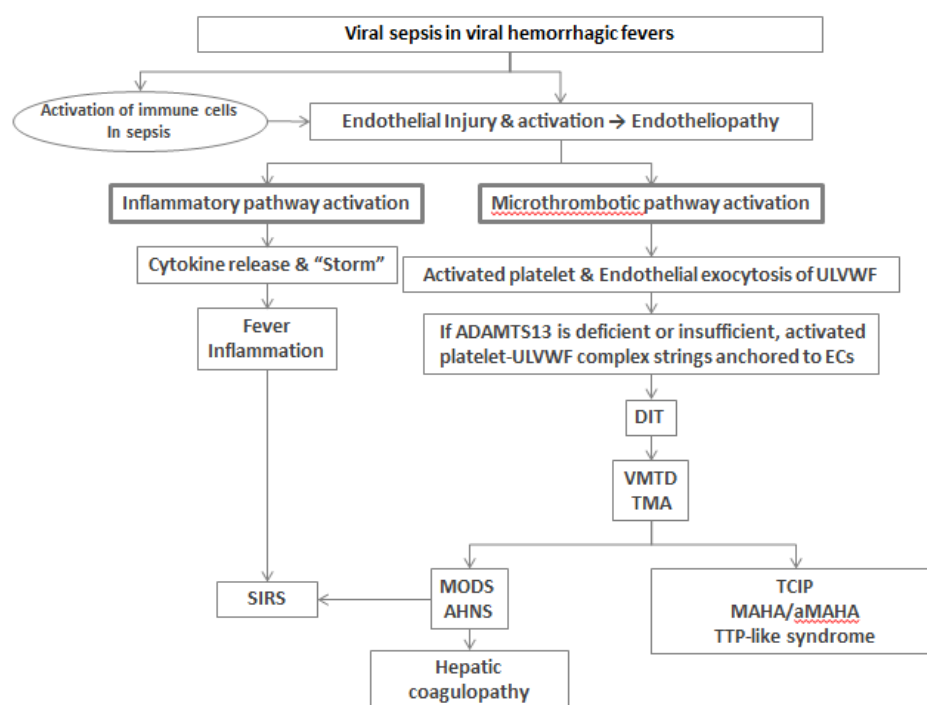


Figure 1. Pathogenesis of endotheliopathy-associated DIT/TTP-like syndrome in viral hemorrhagic fevers.

AHNS, acute hepatic necrosis syndrome; aMAHA/MAHA, atypical microangiopathic hemolytic anemia/microangiopathic hemolytic anemia; ARDS, acute respiratory distress syndrome; DIT, disseminated intravascular microthrombosis; ECs, endothelial cells; MODS: multi-organ dysfunction syndrome; MTA, microthrombotic angiopathy; SIRS, systemic inflammatory response syndrome; TTP, thrombotic thrombocytopenic purpura; VMTD, vascular microthrombotic disease; ULVWF, unusually large von Willebrand factor multimers;

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

	Antibody-associated DIT/VMTD (Acquired TTP)	Endotheliopathy-associated DIT/VMTD (TTP-like syndrome)
Etiology	Anti-ADAMTS13 antibody	ECs injury leading to their dysfunction due to sepsis, surgery, trauma, Shiga toxin, preeclampsia, cancer, drugs, and others
Probable pathogenesis	↓	↓
	Increased destruction of ADAMTS13	Release of eULVWF and anchored to ECs
	↓	↓
	Hyperactive mULVWF→ Aggregate with platelet	Decorated eULVWF with platelets
	↓	↓
	Microthrombosis	Microthrombosis
ADAMTS13 level	Usually <5%	Usually 20-70%
ADAMTS13 antibody	Positive	Negative
Intravascular ULVWF	Increased	Increased
Thrombocytopenia	Present	Present
Anemia	MAHA	MAHA/aMAHA
Schistocytes	Always present at usually >2%	Typically be present with fewer schistocytes
Hypoxic organ dysfunction	Present	Present
Typical examples of involving organs	Brain (CNSD); Kidneys (ARF)	Brain (CNSD); lungs (ARDS); liver (HELLP); kidneys (HUS); bowels (GIHS); liver (AHNS); adrenals (Waterhouse-Friderichsen syndrome) muscle (rhabdomyolysis); skin (purpura fulminans)
Advanced stage of organ involvement	MODS	SIRS; MODS
Coagulopathy	Absent	Absent unless hepatic coagulopathy occurs
Response to TPE	Very good response	Excellent response if treated early
Platelet transfusion	Contraindicated	Contraindicated

DIT, disseminated intravascular microthrombosis; VMTD, vascular microthrombotic disease; TTP, thrombotic thrombocytopenic purpura; SIRS, systemic inflammatory response syndrome; CNSD, central nervous system dysfunction; ARDS, acute respiratory distress syndrome; GIHS, gastrointestinal hemorrhagic syndrome; AHNS, acute fulminant hepatitis/acute hepatic necrosis syndrome; ARF, acute renal failure; HUS, hemolytic uremic syndrome; TPE, therapeutic plasma exchange; mULVWF, megakaryocytic unusually large von Willebrand factor multimers; eULVWF, endothelial ULVWF; TMA, thrombotic microangiopathy; MAHA, microangiopathic hemolytic anemia; aMAHA, atypical MAHA; ECs, endothelial cells

Donald McKay in early1950s coined the term “DIC” [34] for a microthrombotic disorder, which he interpreted as a coagulation disorder. He and his followers have believed intravascular hyaline microthrombi in the luminal arterioles and capillaries in the pathologic tissue examination consist of micro-clots of platelets, coagulation factors and fibrins. In coagulation profile, the supporting evidence is prolonged prothrombin time, prolonged activated partial thromboplastin time, hypofibrinogenemia, and increased fibrin degradation products. In many patients with “DIC”, however, coagulation profile has been 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.

Clinically “DIC” and endotheliopathy-associated DIT/VMTD (*i.e.*, TTP-like syndrome) are the same in their underlying risk factors and presentation. Both “DIC” and TTP-like syndrome almost always occur in critical illnesses (e.g., sepsis/septic shock, trauma, immunologic and collagen-vascular diseases, and complications of surgery, pregnancy and transplant) [35, 36]. In both disorders, the pathology is characterized by arteriolar and capillary hyaline microthrombi with variable fibroblastic proliferation [37, 38]. Hematological features are also the same with consumptive thrombocytopenia and MAHA/aMAHA. Thus “DIC” and endotheliopathy-associated DIT/VMTD must be the same disorder.

Microthrombogenesis and activated TF coagulation pathway

According to the “two-activation theory of the endothelium”, DIT induced by microthrombogenesis is completely different from true DIC occurring as a result of activated TF coagulation pathway.

Their characteristic differences are shown in Table 2. The former is a microthrombotic disorder, but the latter is a hemostatic (coagulation) disorder. Considering the difference between “DIC” and DIT in their currently accepted pathogenic mechanisms, “DIC” must have been understood with a wrong concept. Hence, “DIC” is a misnomer. For more than 60 years, this unfortunate misconception of “DIC” has created confusion in medical science and practice, including diagnostic dilemma and treatment failures until this day [39-41].

It should be emphasized that no single laboratory test or set of tests is sensitive or specific enough to allow a definite diagnosis of “DIC” [39]. In most cases the diagnosis is based on the combination of results of non-specific laboratory test results in the patient with a clinical condition known to be associated with “DIC” [41].

If one understands and accepts the fact that “DIC” is a misnomer but one accepts it as endotheliopathy-associated DIT/VMTD, viral hemorrhagic fevers can be explained perfectly well by the concept of DIT. The next question is how viral hemorrhagic fevers get the hemorrhagic disorder. Another word, What is the correct diagnosis for “DIC” that is associated with abnormal coagulation profile?” In viral hemorrhagic fevers, acute fulminating hepatitis/acute hepatic necrosis, especially multifocal necrosis type, occurs regularly without a good explanation [42-46]. Acute fulminant hepatitis and hepatic necrosis are not due to viral hepatitis, but are due to DIT. The “two-activation theory” supports hepatic coagulopathy could occur due to endotheliopathy-associated DIT/VMTD causing multiple hepatic microinfarctions (AHNS) as noted in Figure 1 [6]. Indeed, hepatic coagulopathy shows exactly the same coagulation profile as seen in “acute DIC”.

True DIC is very rare but occurs perhaps in acute promyelocytic leukemia, presumably due to TF expression from leukemic cells [47].

Table 2. Hematological and clinical characteristics of endotheliopathy-associated DIT/VMTD 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 coagulation pathway
Site of activation	Intravascular surface 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; PT; aPTT; TT	Normal	Prolonged
FDP	Normal	Increased
FVIII activity	Normal or increased	Markedly decreased
Thrombocytopenia	Moderately severe	Mild to very severe
Associated clinical syndromes	TTP-like syndrome AHNS with hepatic coagulopathy 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)

APL, acute promyelocytic leukemia; aPTT, activated partial thromboplastin time; aMAHA/MAHA, microangiopathic hemolytic anemia/MAHA; ATRA, All-trans retinoic acid; DIC disseminated intravascular coagulation; DIT, disseminated intravascular microthrombosis; ULVWF, endothelial unusually large von Willebrand factor multimers; FV, factor V; FVIIa, activated factor VII; FVIII, factor VIII; FDP, fibrin degradation products; MTA, microthromboticangiopathy; PT, prothrombin time; TF, tissue factor; TPE, therapeutic plasma exchange; TT, thrombin time; MODS, multi-organ dysfunction syndrome; rADAMTS13, recombinant ADAMTS13; SIRS, systemic inflammatory response syndrome; VMTD, vascular microthrombotic disease

Table 3. Differential characteristic hematologic features among thrombopathies and coagulopathies (Adapted from Chang JC (6) with permission).

	TTP & TTP-like syndrome (DIT)	TTP-like syndrome (DIT) associated with HC (e.g., Ebola) = acute “DIC” of McKay	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

TTP, thrombotic thrombocytopenic purpura; HC, hepatic coagulopathy; DIT, disseminated intravascular microthrombosis; DIC, disseminated intravascular coagulation; PF, primary fibrinolysis; MAHA, microangiopathic hemolytic anemia; aMAHA, atypical MAHA; FFP, fresh frozen plasma; AFA, anti-fibrinolytic agents; ATRA, all-trans retinoic acid

As illustrated in Table 2, the predominant feature of true DIC is hemorrhage without MAHA/aMAHA and hypoxic organ dysfunction [33,47,48]. This supports that MAHA/aMAHA, MODS and TTP-like syndrome are the manifestations of endotheliopathy-associated DIT.

In differentiating true DIC from hepatic coagulopathy, the most important test is the assay of coagulation factors: especially for depleted FVIII and FV in true DIC, and increased FVIII and markedly decreased liver dependent FVII in hepatic coagulopathy. A suggested guideline for

laboratory tests is presented in Table 3 to aid in differential diagnosis among complicated thrombopathies and coagulopathies [6].

In viral hemorrhagic fevers, TCIP is the earliest indicator suggesting that microthrombogenesis is in progress. If the hemorrhagic disorder occurs, it is not due to true DIC nor is likely due to thrombocytopenia, but most likely is due to hepatic coagulopathy. The “two activation theory” not only explains concomitant inflammation, TCIP and progressive hypoxic organ dysfunction, but also would help to unmask unrecognized syndromes such as impending cytokine “storm”, TTP-like syndrome, MAHA/aMAHA, MODS and SIRS in viral hemorrhagic fevers.

Conclusion

Viral hemorrhagic fevers are not due to “DIC” but are due to endotheliopathy-associated DIT/VMTD, which hematologic manifestation could lead to TTP-like syndrome. The treatments for viral hemorrhagic fevers are fresh frozen plasma for hepatic coagulopathy and therapeutic plasma exchange for TTP-like syndrome if the diagnosis is confirmed [6]. If therapeutic plasma exchange is not available, clinical trials using anti-microthrombotic agents such as recombinant ADAMTS13 and N-acetyl cysteine may be considered. Platelet transfusion and anticoagulation therapy are contraindicated.

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