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Viral Induced Coagulopathy: A Formidable Foe or a Benevolent Friend

Ravindranath Thyyar M*

Department of Pediatrics, Columbia University Irving Medical Center, USA

***Corresponding author:** Thyyar M Ravindranath, Department of Pediatrics, Columbia University Irving Medical Center, Vagelos College of Physicians and Surgeons, 630 West 168th Street, New York, New York-10032, USA, Tel: 845-598-6870; Email: tr2148@gmail.com

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Abstract

Viral Induced Coagulopathy (VIC) as a clinical presentation is seen in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Viral Hemorrhagic fevers (VHF). SARS-COV-2 is predominantly a thrombus generating disease whereas bleeding is observed in VHF. Although diagnosis may not be complicated, management may pose considerable challenges.

Keywords: Virus; Coagulopathy; SARS-COV-2; Viral Hemorrhagic Fever; Thrombosis

Abbreviations: VIC: Viral Induced Coagulopathy; VHF: Viral Hemorrhagic Fevers; SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; DIC: Disseminated Intravascular Coagulation; VWF: Von Willebrand Factor; ACE2: Angiotensin Converting Enzyme 2; CAC: Corona Virus Associated Coagulopathy; NAAT: Nucleic Acid Amplification Test; PT: Prothrombin Time; PAI-1: Plasminogen Activator Inhibitor-1; TAFI: Thrombin Activatable Fibrinolysis Inhibitor; UFH: Un-Fractionated Heparin; LMWH: Low Molecular Weight Heparin; TLR-4: Toll-Like Receptor-4.

Introduction

VIC is not an uncommon condition that clinicians face in their practice. Viral coagulation disorders may present as a subtle clinical laboratory abnormality, overt bleeding characterized by Disseminated Intravascular Coagulation (DIC) with microvascular thrombosis leading to multiple organ dysfunction. Mortality from COVID was reported to be nearly 7 million worldwide [1]. Case fatality rates for viral hemorrhagic fevers (VHFs) were reported to be as high as 80%-90% in developing countries [2]. Annual death rate is estimated at 60,000 out of 100 million infected individuals [3]. Although VHF's may be confined to some endemic areas of the world, the recent globalization and change in weather pattern have encouraged the spread of these infections to different parts of the world [4].

SARS-CoV-2 is a single-stranded enveloped RNA virus and, in comparison, VHFs belonging to the Arena, Buyna, Filo, and Flavi virus families also contain an enveloped single-stranded RNA. These include Ebola, Marburg, Lassa, South American hemorrhagic, and Yellow, Crimean-Congo hemorrhagic, and Rift Valley fevers. Dengue, which belongs to Flavi virus family, can also cause coagulation disorder [5].

Epidemiology

Whereas corona viruses are spread by the air-borne route, VHFs require a carrier for transmission. Examples of tick-borne transmission include Buyna virus and Crimean-Congo hemorrhagic fever. Flavi virus Dengue, on the other hand, is spread by the mosquito *Aedes aegypti*. Close contact with infected blood, stool, body fluids, and fomites can transmit Arena and Filo viruses from person-person [6].

Pathophysiology

Understanding the mechanism involved in thrombo-coagulation leads to a better understanding of available management options. SARS-CoV-2 induces thrombotic complication whereas VHFs result in hemorrhagic manifestations. Coagulation defect is preceded by thrombotic stage, suggesting that VIC clinically presents with one or the other defect depending on when a patient is evaluated by a clinician.

In COVID-19, the coagulation and associated inflammation is generated by elevated factor VIII and Von Willebrand Factor (VWF) resulting from damaged endothelium and fibrinogen. In addition, the endothelium loses its ability to prevent clot formation with decreased Angiotensin Converting Enzyme 2 (ACE2) as well as nitric oxide generation, and thrombomodulin release [7].

VHFs infect immune cells and promote the systemic spread of the virus. Infected macrophages release cytokines, enhance innate immune response, and promote vascular permeability [8]. The resulting inflammation from proinflammatory cytokines is complicated by coagulation defect from viral infection.

The responses that lead to further deterioration in VIC can be characterized as cellular responses which include activated immune cells, endothelial cells, platelets; procoagulation status, and involvement of vasculature. In corona virus associated coagulopathy (CAC), activation of innate immune cells results in the generation of proinflammatory cytokines, leading to a cytokine storm. Impaired adaptive immunity and activation of innate immunity are observed in VHFs. Disruption of endothelial cells in VIC results in thrombus formation and bleeding disorder. Although platelet counts are within normal in COVID-19, platelet aggregation is promoted due to increase in VWF. In contrast, platelet dysfunction along with low platelet number results in bleeding and plasma loss is found in VHFs [9]. Consumptive coagulopathy in Ebola results from secretion of proinflammatory cytokines due to the release of phosphatidylcholine from the viral surface which, in turn, generates thrombin resulting in the consumption of coagulation factors [10]. Although vascular involvement leading to its disruption is seen in COVID-19, it is not common in VHFs with the exception of dengue fever where activated T cells facilitate injury to the vasculature.

Clinical Evaluation

COVID-19 clinical presentations include, asymptomatic or pre-symptomatic infection, that is, individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but have no symptoms consistent with COVID-19.

Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation level (SpO2) ≥94% as measured by pulse oximetry in room air at sea level.

Severe Illness: Individuals who have SpO2 <94% in room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50% on imaging.

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction [11].

VHFs are more difficult to diagnose. One must consider the risk factors associated with VHFs such as travel to endemic areas or to a region that was experiencing an outbreak, close contact with a person that travelled to a region that was experiencing an outbreak of VHFs, history of contact with bats, live stocks, and tics in regions with VHFs outbreak [12]. VHFs present with non-specific features such as fever, headache, and malaise. Other symptoms include retro-orbital, abdominal and joint pain, vomiting and diarrhea. Bleeding gum and epistaxis can also be seen. On physical examination one may notice jaundice, conjunctival injection, facial flushing, petechial rash, cervical lymphadenopathy, conjunctivitis in Lassa fever [13].

Laboratory Evaluation

In COVID-19 white blood cell count is minimally elevated, elevated neutrophil to lymphocyte ratio is observed, with minimal decrease in hematocrit, hemoglobin, and red blood cell count. Increased D-dimer is noticed with normal Prothrombin Time (PT) and Activated Thromboplastin Time (aPTT). The platelet count is normal and low platelet count portends poor prognosis. Increased biomarkers such as IL-6, procalcitonin, ferritin, and troponin-1 indicate poor prognosis. Risk factors for thrombosis include elevated D-dimer, fibrinogen, factor VIII, and the detection of antiphospholipid antibody.

VHFs show a decrease in white blood cell count, decreased neutrophil to lymphocyte ratio,

thrombocytopenia, and elevated hematocrit. A decrease in fibrinogen with prolonged PT and aPTT may occur. DIC occurs in Ebola hemorrhagic fever. Protein C and S are low with normal Antithrombin (AT) activity. Fibrinolysis is affected minimally with increased tissue-Plasminogen Activator (t-PA) and Plasminogen Activator Inhibitor-1 (PAI-1), and decreased Thrombin Activatable Fibrinolysis Inhibitor (TAFI) [14].

Treatment

COVID-19 thrombosis: moderate to severe symptoms include high risk for thrombosis based on age, diabetes etc. Patients are subjected to D-dimer, PT, platelet count, and fibrinogen level. Except for PT, if the counts are abnormal then Un-Fractionated Heparin (UFH) is used with close monitoring for bleeding in an in-patient setting. If the tests are normal, then the treatment is similar to the treatment for patients who are not in the high-risk group, namely, with Low Molecular Weight Heparin (LMWH) [Enoxaparin] [15].

VICs: Suppression of inflammation may be effective using dexamethasone and tocilizumab for VHF induced coagulopathy, although studies are needed to support their use [16,17]. Substitution of coagulation factors and plasma administration may be unsafe. Toll-Like Receptor-4 (TLR-4) antagonist Eritoran has been suggested to reduce leukocyte endothelial activation. Early treatment with immune enhancing drugs such as Interleukin-7 (IL-7), Interleukin-15 (IL-15), Granulocyte-macrophage colony-stimulating factor (GMCF), type I Interferon may restore adaptive immune response leading to resolution of the infection [18]. Statins, with their anti-inflammatory property, may be useful. Tissue Factor Pathway Inhibitor is another novel therapy that may be useful to treat bleeding disorder in VHFs [19]. Combining statins and angiotensin receptor blockers, both known to have endothelial stabilizing effect, was proposed to treat the vascular leak associated with Ebola Virus infection [20]. DIC results in the release of heme from hemoglobin, which potentiates inflammation. Binding of heme with hemopexin and haptoglobin may protect from DIC in VHFs [21].

Conclusion

Activation of the coagulation cascade during viral infection is a protective mechanism found to limit the spread of the infection. However, extreme clotting can lead to DIC and subsequent hemorrhage, such as during Ebola hemorrhagic fever and Dengue hemorrhagic fever. Therefore, when coagulation is well balanced by anticoagulation and inflammatory response is under control, then VIC is a benevolent friend. Otherwise, it may become a formidable foe with increased morbidity and mortality.

Contributor

Thyyar M Ravindranath, MD. Conceived, planned, and executed the short communication.

Conflict of Interest Statement

None

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References

1. Health Pharma & Medtech (2023) Number of coronavirus (COVID-19) cases, recoveries, and deaths worldwide as of May 2, 2023.

2. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM, et al. (2015) Ebola and Marburg haemorrhagic fever. J Clin Virol 64: 111-119.

3. Zapata JC, Cox D, Salvato MS (2014) The role of platelets in the pathogenesis of viral hemorrhagic fevers. PLoS Negl Trop Dis 8(06): e2858.

4. Mangat R, Louie T (2020) Viral Hemorrhagic Fevers. StatPearls Publishing, Treasure Island, USA.

5. Marty AM, Jahrling PB, Geisbert TW (2006) Viral hemorrhagic fevers. Clin Lab Med 26(2): 345-386.

6. Bopp NE, Kaiser JA, Strother AE, Barrett ADT, Beasley DWC, et al. (2020) Baseline mapping of severe fever with thrombocytopenia syndrome virology, epidemiology and vaccine research and development. NPJ Vaccines 5(1): 111.

7. Iba T, Connors JM, Levy JH (2020) The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 69(12): 1181-1189.

8. Sun Y, Jin C, Zhan F, Wang X, Liang M, et al. (2012) Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. J Infect Dis 206(07): 1085-1094.

9. Putri HI, Tunjungputri RN, De Groot PG, Ven AJVD, Mast QD, et al. (2018) Thrombocytopenia and platelet dysfunction in acute tropical infectious diseases. Semin Thromb Hemost 44(7): 683-690.

10. Kennedy JR (2020) Phosphatidylserine's role in Ebola's inflammatory cytokine storm and hemorrhagic

consumptive coagulopathy and the therapeutic potential of annexin V. Med Hypotheses 135: 109462.

11. COVID-19 Treatment Guidelines (2023) Clinical Spectrum of SARS-CoV-2 Infection.

12. Centers for Disease Control and Prevention (2019) Assessing Viral Hemorrhagic Fever Risk in a Returning Traveler.

13. Racsa LD, Kraft CS, Olinger GG, Hensley LE (2016) Viral Hemorrhagic Fever Diagnostics. Clin Infect Dis 62(2): 214-219.

14. Iba T, Levy HL, Levi M (2022) Viral-Induced Inflammatory Coagulation Disorders: Preparing for Another Epidemic. Thromb Haemost 122(1): 8-19.

15. Sharma S, Mishra A, Ashraf Z (2022) COVID-19 Induced Coagulopathy (CIC): Thrombotic Manifestations of Viral Infection. Thrombosis Hemostasis Open 6(1): 70-79.

16. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, et al. (2021) Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384(8): 693-704.

17. Salama C, Han J, Yau L, Reiss WG, Kramer B, et al002E (2021) Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 384(1): 20-30.

18. McElroy AK, Erickson BR, Flietstra TD, Rollin PE, Nichol ST, et al. (2014) Ebola hemorrhagic Fever: novel biomarker correlates of clinical outcome. J Infect Dis 210(4): 558-566.

19. Geisbert TW, Hensley LE, Jahrling PB, Larsen T, Geisbert JB, et al. (2003) Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. Lancet 362(9400): 1953-1958.

20. Fedson DS, Jacobson JR, Rordam OM, Opal SM (2015) Treating the Host Response to Ebola Virus Disease with Generic Statins and Angiotensin Receptor Blockers. mBio 6(3): e00716.

21. Larsen R, Gozzelino R, Jeney V, Tokaji L, Bozza FA, et al. (2010) A central role for free heme in the pathogenesis of severe sepsis. Sci Transl Med 2(51): 51-71.