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Review Article

A Review of Clinical Manifestation of COVID-19 Due to its Effect on the Vascular System

Abu Bakar Siddik[1,*], Tasnim rahman[2], Sajedur Rahman[3], Mohammad D Hossain[3], Mussammat Afsana Ferdousi[4], Kazi Nusrat Tamanna[5], Md Manjurul Islam Shourav[3], Fahmida Eskander Turin[6], Md Sakibuzzaman[7]

[1]Northern International Medical College and Hospital, Dhanmondi, Dhaka, Bangladesh

[2]Wenzhou medical college, Wenzhou, Zhejiang Province P. R. China

[3]Jalalabad Ragib Rabeya Medical College and Hospital, Sylhet, Bangladesh

[4]Dinajpur medical College, Dinajpur, Bangladesh

[5]Armed Forces Medical College, Dhaka, Bangladesh

[6]Rajshahi Medical College and Hospital, Rajshahi, Bangladesh

[7]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

[*]Corresponding author: Abu Bakar Siddik, Northern International Medical College and Hospital, Dhanmondi, Dhaka, Bangladesh, E-mail: Siddikabubakar889@gmail.com

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Abstract

Coronavirus disease 2019 (COVID-19) appears to raise significant public health concerns worldwide. COVID-19 can affect any organ, including the vascular system. Various clinical manifestations of COVID-19, including dermatological and renal manifestations, are likely to indicate vascular involvement. Vasculitis has been associated with COVID-19 as a potential pathological process in multiple cases but is not considered a primary pathology. The immune system produces a tremendous amount of pro-inflammatory cytokines due to COVID-19 infection. These pro-inflammatory cytokines cause endothelial dysfunction and

thrombosis, which can lead to vasculitis. Further, COVID-19 can directly cause endothelial dysfunction by binding to angiotensin-converting enzyme 2 receptors of vascular endothelium. Ischemic changes and vessel thrombosis, which are common findings in vasculitis, were reported in histopathological examinations. Proper treatment and management of vasculitis associated with COVID-19 are our new concerns. This review article highlights some important clinical manifestations of COVID-19 infection due to its effect on the vascular system. The article also describes risk factors, pathogenesis, diagnosis, and possible treatment of this manifestation.

Keywords: COVID-19; Vasculitis; Endothelial Dysfunction; Thrombosis; Pro-inflammatory Cytokine; Cytokine Storm

1. Introduction

Over the last two decades, newly identified c*oronaviruses*, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), *have emerged and caused deadly infectious disease in humans. In December 2019, coronavirus disease (COVID-19), caused by a novel coronavirus (SARS-CoV-2),* has been reported in China and rapidly spread worldwide. At the end of March 2020, COVID-19 had attained pandemic status [1-5]. According to recent updates, the pandemic has spread across 188 countries/regions, infecting around 33,799,264 individuals and 1,010,381 deaths by October 1, 2020 [6].

SARS-CoV-2 enters through angiotensin-converting enzyme 2 (ACE2) receptors in cell membranes, primarily ciliated respiratory cells in nasal sinuses and bronchial trees, alveolar pneumocytes, kidney tubular cells, small bowel, and colon mucosa. Recent research has affirmed that the virus enters into cells via spike protein of viral capsid. The spike protein binds with ACE2 with the help of cellular serine protease TMPRSS2. This binding plays a crucial role in virus internalization and pathogenesis. However, downregulation and blockage of the ACE2 receptor cause cardiovascular functional impairment [7, 8].

In COVID-19 patients, the early hallmark of organ damage is endothelial dysfunction and increased vascular permeability. The normal function of the endothelium is to prevent thrombosis. Endothelial damage caused by COVID-19 leads to a hypercoagulable state. This endothelial dysfunction and hypercoagulability may lead to vasculitis [9, 10]. Bouaziz et al. [8] reported different vascular lesions in COVID-19 patients, such as livedo, violaceous macules with "porcelain-like" appearance, non-necrotic purpura, eruptive cherry angioma, chilblain appearance with Raynaud's phenomenon, necrotic purpura, and chilblain. The pathogenesis of these lesions is still questionable. But may include vasculitis, vascular thrombosis or neoangiogenesis, and endothelial dysfunction [8].

2. Epidemiology

COVID-19 was first detected in Wuhan, located in the Hubei province of China, in December 2019. SERS-CoV-2 is the seventh virus, which comes from the coronaviridae family, that infects humans. Like SARS-CoV, the bat could be a possible reservoir of SARS-CoV-2, but its intermediate host is still unknown. Although it was initially thought that SARS-CoV-2 only transmits from animals to humans,

it was later confirmed that human-to-human transmission is possible and symptomatic patients most frequently spread COVID-19 [4]. On January 30, 2020, the Public Health Emergency of International Concern categorized COVID-19 as a global health concern [11]. Later, the World Health Organization announced it as a pandemic on March 11. After detecting the first case in Wuhan, COVID-19 has spread to all continents except Antarctica [10]. In the United States (US), the first case of COVID-19 was reported on January 22, 2020 [6]. By the end of March, the patients were confirmed in all 50 US states.

COVID-19 infects both males and females (ratio 1.06: 1) and all ages (0 to 90+). There is evidence of vertical transmission found by testing neonates for COVID-19 [12]. No evidence exists of intrauterine or transplacental transmission to neonates [13]. Research showed that 81% of COVID-19 cases present with mild symptoms, 14% develop severe symptoms, and 5% are critically ill. The severity of COVID-19 increases with age and the case fatality rate is about 14.8% for age around 80 and above. The incubation period of this virus is five days, which is similar to that of SARS-CoV (4.4 days) and MERS-CoV (5.5 to 6.7 days) [14].

3. Risk Factors

About 50% of patients with comorbidities, such as cardiovascular diseases and diabetes, have a significant increase in morbidity and mortality [15]. Moreover, patients with a compromised immune system are vulnerable to COVID-19 infection. Medical comorbidities such as hypertension, diabetes mellitus [9], coronary artery disease, heart failure, hepatitis C virus infection, and end-stage renal disease [16] may increase coronavirus infection-associated risk pre-existing vascular dysfunction. Old age, prediabetes, obesity, smoking, anabolic steroid use, and hematological disorder (anemia and leukemia) are critical risk factors [17].

4. Pathogenesis

SARS-CoV-2 uses it is surface spike glycoprotein to enter into the host cell. ACE2 of the cell membrane is used as a receptor by SARS-CoV-2 for its entry into the host cell. Due to this necessity of ACE2, the severity of COVID-19 is strongly related to the number of ACE2 in each tissue. Because of the high expression of ACE2 in multiple epithelial cell types of the respiratory airway such as alveolar epithelium and lung parenchymal type II cells, this virus has a tropism for the respiratory tract. As a result, the transmission of SARS-CoV-2 can occur through direct or indirect respiratory tract exposure [18, 19]. Upon entry into the human body, SARS-CoV-2 exerts its pathology through multiple mechanisms. Of all pathways that disrupt the renin-angiotensin-aldosterone system (RAAS), viral components that cause direct toxicity to the cellular environment, endothelial cell damage or inflammation, and thrombus formation, dysregulation, or exacerbation of the body's immune response have the most significant contribution. While more research is still required on the significance and association of these pathways in the pathophysiology of COVID-19. After all, several studies have shown that some of these pathways and their results, in specific ACE2-spike induced viral entry and RAAS dysregulation can be regarded as a unique feature of COVID-19 infection.

ACE2-mediated entry is thought to be the primary mechanism of SARS-CoV-2 infection. ACE2 is the functional receptor for both SARS-CoV and SARS-CoV-2. However, the spike protein of SARS-CoV-2 has a higher affinity for the ACE2 receptor than that of SARS-CoV. SARS-CoV-2 has, therefore, an infection rate higher than SARS-CoV. ACE2 receptor is expressed in various cell types, including vascular endothelium and respiratory epithelium. SARS-CoV-2 accesses the host cells initially by membrane fusion through either the plasma membrane or an endosomal membrane. Recognition of ACE2 occurs via the trimeric spike protein of SARS-CoV-2 when it binds to the ACE2 catalytic domain's hydrophobic pocket. Upon proteolytic cleavage by the cellular serine protease TMPRSS2 or other proteases, this spike protein becomes activated. This activation initiates ectodomain shedding of ACE2 and internalization of ACE2 via clathrin-dependent and independent endocytosis pathways, which finally causes the fusion of virus particles with host cells and, ultimately, virus entry. Several studies showed that coronaviruses could use alternative routes for viral entry. For example, several other receptors, including CD209L (L-SIGN), CD209 (DC-SIGN), neuropilin receptors (NRPs), and CD147/Basigin, were reported to facilitate SARS-CoV-2 entry [18-20].

Once inside the host cells, the virus may cause acute respiratory distress syndrome (ARDS). This may be due to an aggressive immune response (i.e., cytokine storm), which ultimately causes vascular damage by induction of apoptosis and pyroptosis, hypercoagulability, and dysfunction. An aggressive immune response further augments endothelial dysfunction. All the factors that facilitate the entry of SARS-CoV-2 are expressed by endothelial cells. Thus, endothelial dysfunction plays as one of the most important denominators for COVID-19-related deaths. Evidence such as elevation of C-reactive protein, ferritin, interleukin-6 (IL-6), IP-10, MCP1, MIP1A, and TNF-α in the blood of COVID-19 patients leads to the conclusion that COVID-19 could primarily disrupt the vascular endothelium [21].

Endothelial dysfunction means loss of the normal endothelial cell function, such as the ability to promote vasodilation, fibrinolysis, and anticoagulation process. A recent study has demonstrated that nearly 72% of non-survivors of COVID-19 infection had evidence of hypercoagulability. Many factors such as inflammation, direct endothelial cell injury, and hypoxia-mediated upregulation of the hypoxia-inducible factor 1 (HIF-1) signaling pathway could contribute to hypercoagulability in COVID-19 patients. Infection-mediated endothelial injury is evidenced by a significantly elevated (529 U/dL compared to a normal level of 100 U/dL) von Willebrand factor (VWF) level in blood. VWF is a circulating adhesive glycoprotein that plays a vital role in regulating angiogenesis and vascular permeability. It is secreted from endothelial cells and platelets. Elevation of VWF is found in vasculitis, inflammation, aging, and diabetes. High levels of VWF may be used as a marker of endothelial dysfunction. The release of VWF leads to platelets activation and aggregation. Upon activation of platelets, it releases VEGF and polyphosphates from dense granules. VEGF causes upregulation and expression of tissue factor, which is the major activator of the coagulation cascade. Polyphosphates accelerate the activation of factor V, inhibition of the anticoagulant activity of tissue factor pathway

inhibitors, promotion of factor XI activation by thrombin, and enhancement of the synthesis of thicker fibrin strands. These thick strands of fibers are resistant to the fibrinolysis process. VWF also acts as a carrier of coagulation factor VIII and plays a vital role in the blood coagulation process. Endothelial inflammation (Endothelialitis) of different vascular beds, including the lungs, kidney, heart, small intestine, and liver, is evidenced by the presence of activated neutrophils and macrophages. Endothelialitis can trigger cytokine release, induce the formation of neutrophil extracellular traps (NETs), fibrin, and microthrombus, inhibit fibrinolysis, and finally activate complement pathways. NETs further damage the vascular endothelial cells and activate both extrinsic and intrinsic coagulation pathways. These factors ultimately lead to microthrombi deposition in the vessels and microvascular dysfunction [20, 22].

Excessive cytokine release is characterized by a significant elevation of pro-inflammatory cytokines and leads to cytokine release syndrome (CRS). Several studies showed that COVID19 patients had increased levels of pro-inflammatory cytokines. Among all, soluble interleukin-2 receptor (IL-2R), IL-6, and tumor necrosis factor-α (TNF-α) are the most significant.

Nevertheless, several studies highlighted that, in COVID-19 patients, IL-6 is much lower than in typical hyper-inflammatory conditions such as ARDS or CRS. This difference should be used to distinguish COVID-19 from those conditions. IL-6 plays a significant role during the early phase of inflammation by activating endothelial cells. Activated endothelial cells possess an increased vascular permeability due to enhanced EC contraction and loosening of inter-endothelial junctions. Upon activation, they also release other pro-inflammatory cytokines/chemokines such as IL-8 and monocyte chemoattractant protein-1 (MCP-1). Research showed that levels of IL-6 seem directly proportional to the severity of COVID-19. Besides IL-6, soluble IL-2R is also found to be correlated with the severity of the disease. T-helper lymphocytes secrete IL-2, which then binds to IL-2R and provides both stimulatory and regulatory immune functions. The pulmonary endothelial cells express IL-2R, and binding of IL-2 induces pulmonary edema. Other pro-inflammatory cytokines, such as IL-6, IL-1β, and TNFα, inhibit the normal antithrombotic and anti-inflammatory functions of endothelial cells [22, 23].

Activation of the complement pathway also leads to endothelial damage, inflammation, and thrombosis. C5a anaphylatoxin causes exaggerated early pro-inflammatory responses. Ii causes activation of neutrophils and macrophages. C3a complement fraction plays a vital role in the process of infection-related lung injury. Studies showed that high serum C3a might predict the development of ARDS. Furthermore, both C3a and C5a increase endothelial permeability [24].

5. Histopathology

Histopathological evidence showed that COVID-19 causes endothelial inflammation with blood clots in the both micro and macrovascular circulation of venous and arterial origin. In vitro studies showed that SARS-CoV-2 directly infects schemed human blood vessel organelles. Increased levels of IL-6, IL-2 receptor and TNF-α could play a role in endothelial dysfunction and extravasation of leukocytes. The

biopsy of lung tissue from a deceased COVID-19 patient revealed vessel injury with cytoplasmic vacuolization and cell detachment in small and medium-sized lung tissue [23]. Other lung tissue analyses exhibited the desquamation of pneumocytes, hyaline membrane formation, bilateral diffuse alveolar damages, and cellular fibromyxoid exudate. In addition to these histological changes, there were notable cytopathic effects such as indications of multinucleated syncytial cells, atypical enlarged pneumocytes, interstitial mononuclear inflammatory infiltrates, and large numbers of lymphocytes in the infected lung tissue [13]. Some tissue biopsies exhibited co-existence of spike glycoprotein with CD4 and CDb5-9 in interalveolar septa and cutaneous microvasculature. The pathological links between complement activations in lung and skin tissues have been discussed [16].

In postmortem histopathology of 26 patients, Su et al. [23] detected virus particles in renal tubular epithelial cells and podocytes. The researchers also reported endothelial swelling with foamy degeneration and segmental fibrin thrombus in glomerular capillary loops, which caused significant injury to the endothelium of renal cells [23]. There is a debate about whether these vascular changes are due to SARS-CoV-2 or pre-existing comorbidities such as hypertension and diabetes [23].

Further histological examinations of patients affected by COVID-19 revealed leukocytoclastic vasculitis or hypersensitivity vasculitis, which was shown as acute necrotizing vasculitis with neutrophilic infiltration, karyorrhexis, and fibrinoid necrosis. Fibrinoid necrosis occurs when antigen-antibody complexes, fibrin, and complement anaphylatoxins get deposited in the blood vessel wall, which suggests a clue for diagnosing immune-mediated vasculitis due to type 3 hypersensitivity. Another disorder reported in COVID-19 patients is platelet aggregation, which results in hypercoagulability and thrombosis [25].

6. Clinical Features

The clinical presentation of COVID-19 ranges from asymptomatic or mild infection to severe pneumonia with ARDS that requires mechanical ventilation in an intensive care unit (ICU). Other severe complications include sepsis, septic shock, multiple organ dysfunction syndromes, and vasculitis [26]. COVID-19 cases can be classified by the severity of clinical manifestations into three types [27]:

1. Mild disease: In 81% of the cases, non-pneumonia and mild pneumonia occur.
2. Severe disease: In 14% of the cases, patients suffer from dyspnea, blood oxygen saturation (SpO2) $\leq$ 93%, respiratory rate $\geq$ 30/min, PaO2/FiO2 ratio < 300, and/or lung infiltrates > 50% within one to two days.
3. Critical disease: In 5% of cases, patients develop septic shock, respiratory failure, multiple organ dysfunction, or failure.

The most common presentation of COVID-19 infections is cough, fever, sore throat, dyspnea digestive symptoms, loss of taste and smell, and some skin manifestations that have been reported by several dermatologists. For example, Castelnovo et al. [28] reported two cases of cutaneous involvement in young patients with moderate to severe pulmonary involvement and comorbidities. One patient had diffuse urticarial lesion over the thigh and perimalleolar region with spontaneous recovery in a couple of days. The initial presentation of the other

patient was vasculitic purpura in the legs that became a fleeting erythematous rash, later diagnosed as ARDS with severe respiratory failure [28].

According to Galván Casas et al., skin lesions associated with COVID-19 are categorized by their clinical manifestations into five classes [29]:

(a) Urticarial lesions

(b) Maculopapular eruptions

(c) Livedo or necrosis

(d) Acral areas of erythema with vesicles or pustules (pseudochilblain)

(e) Other vesicular eruptions

During the pandemic, reports from different countries described COVID-19 patients with chilblain-like lesions (acro-ischemic, perniosis like, and pseudochilblain). Studies also reported patients with chickenpox-like lesions or vesicular, livedo reticularis, erythema multiforme like lesions, and petechiae. These manifestations were present with a different type of vasculitis. The presumptive pathogenesis of such lesions can be immune-complex-induced lymphocytic vasculitis, vessel thrombosis, neoangiogenesis, or immune dysregulations [5, 8].

7. Diagnosis

A reliable diagnosis of COVID-19 includes medical history, symptoms, radiographic changes, and laboratory tests. The gold standard test for direct detection of SARS-CoV-2 is reverse transcription-PCR. Swabs are taken from the nasopharynx or oropharynx. Then viral RNA is extracted from the swab and subsequently amplified by reverse transcription-PCR. Other blood tests that might be abnormal, but are not diagnostic for COVID-19, include fibrinogen, D-dimer, CRP, aPTT, PT, platelet count, lymphocyte count, LDH, INR, factor VIII, pro-inflammatory cytokines (e.g., IL-1 and IL-6), circulating complement protein (e.g., C3, C4, C5b-9 and Bb), and antiphospholipid antibody [16]. Among these hematological parameters, increased fibrinogen and D-dimer level, lymphopenia, and increased lymphocyte/neutrophil ratio have been significantly correlated with the severity of the disease. In COVID-19 patients, activated ECs of severely infected lung recruit lymphocytes from the blood, thus leading to lymphopenia [9]. One of the poor outcomes in SAR-CoV patients was neutrophilia due to complement activation, which is an index for illness severity [16].

The diagnosis of COVID-19 can include a stool examination. The virus was occasionally found in patients' stool. Even after recovering from a chest infection, the stool remained virus-positive for 12 days [9]. Therefore, stool analysis can be used for monitoring COVID-19 related complications. Chest X-ray and CT of the Chest are also performed in severe cases of SARS -CoV-2 patients. In severe cases of hypoxemia in COVID -19, chest X-ray had shown bilateral airspace opacities [16].

8. Treatment

Since the beginning of the pandemic, treatment has been the main focus of public attention. There have been many intellectual debates, fierce search for, and even geopolitical controversy regarding an effective medication. For a new disease caused by a mutation prone virus, treatment choices have been evolving.

The treatment has been varied widely for COVID-19 related vasculitis as well. Immunomodulatory drugs have been on the frontline from the beginning. This

treatment approach primarily targets endothelial dysfunction induced by infection as well as immune dysregulation. Dexamethasone has proven to reduce 28-day mortality in patients requiring respiratory support [14]. Steroids have been historically used in syndromes similar to COVID-19; however, researchers did not find any mortality benefit in milder cases.

Heparin is another widely used medication for COVID-19 patients. Despite its primary role as an anticoagulant, heparin has been known for its anti-inflammatory effect which benefits patients with asthma or ulcerative colitis as well as patients undergoing coronary angio bypass grafting and cataract surgery [11]. Young et al. [30] proposed several mechanisms for this anti-inflammatory effect: First, heparin is a highly acidic polymer and binds to various proteins including C terminal motif of interferon-gamma, and P-selectin; therefore, it can inhibit neutrophil adherence to activated endothelial cell and future release of toxic radicals and proteolytic enzymes. Second, heparin can modulate the effect of TNF alpha and NF-kB. Finally, heparin binds to apoptotic protease activating factor-1, thus inhibiting cytochrome c mediated apoptosis of cells.

Zhang et al. [31] described vasculitis mimicry and thrombosis as a prominent feature of severe COVID-19 patients. They also discussed the role of other immunomodulatory drugs such as Tocilizumab, Baricitinib (JAK inhibitor), Chloroquine, Hydroxychloroquine, along with glucocorticoid [30]. A case report of Kawasaki disease was found in a COVID-19 infected child who was treated with intravenous immunoglobulin and low-dose acetylsalicylic acid [31].

9. Complications

Among COVID-19 patients admitted to the ICU, the incidence rate of thrombotic complications was 31%. In pulmonary CT angiography, 23% of acute pulmonary embolism was related to COVID-19 pneumonia. Acute pulmonary edema has been developed in patients with COVID-19 in which there were occlusion, micro thrombosis, and vasculitis of pulmonary vessels [18]. Studies mentioned renal involvement in the form of acute kidney injury (AKI) [24, 32]. Myocarditis is frequently present in COVID-19 patients [24]. Progressive pulmonary failure, diffuse coagulopathy, and organ dysfunction are linked with high mortality [22].

10. Prognosis

The presence of cutaneous lesions such as chilblain can aid in diagnosing asymptomatic cases and may indicate a good prognosis. However, retiform purpura, acrocyanosis, livedo racemosa, and dry gangrene in critically ill individuals with the systemic hypercoagulable state may predict a worse prognosis. The degree of thromboembolism may significantly be associated with the severity of the disease. Patients who have mild symptoms with low-grade thrombosis can present with temporary livedo reticularis; patients with the severe disease having high-grade thrombosis can present with retiform purpura, livedo racemosa, or limb ischemia [29].

11. Discussion

The COVID-19 pandemic has been spreading across the world at an alarming rate. It causes more morbidity and mortality as compared with SARS and MERS. The rapid spread of this disease led to a halt in our daily life. No effective vaccine or medication has been developed yet. COVID-19 can involve

multiple organs, including the circulatory system. Overall, our analysis of studies supports the strong association of COVID-19 to endothelial dysfunction as well as the subsequent development of vasculitis and skin manifestations. In a retrospective study by Pei et al. [32] in China, among 333 COVID-19 patients, 251 had renal involvement in abnormal urine dipstick test (proteinuria and hematuria) AKI [24, 32]. This type of renal involvement is not uncommon with vasculitis [33], and there is distinct evidence of renal involvement with hematuria, so vasculitis should be considered in COVID-19 patients [24]. Margo et al. [16] demonstrated the activation of alternative and lectin pathways of complement resulting in severe septal capillary injury and deposition of terminal complement complex C5b-9, C4d, and MASP2 in the lungs of their patients. Patients' skin findings with purpuric lesions also showed similar complement-mediated micro thrombotic injury in their study [16]. Studies have also demonstrated that high serum C3a may predict ARDS development [24]. Their inhibitory nature has also shown the role of other pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα on the normal antithrombotic and anti-inflammatory function of endothelial cells. To better manage COVID-19 patients with vasculitis, we need to apprehend further details about the pathogenesis of the virus and its dynamics in the presence of various established risk factors of vasculitis as well as the most appropriate therapy.

12. Conclusion

In order to return to the usual social, economic situation of pre-COVID, the scientific community needs to discover an appropriate and highly effective therapeutic approach. Yet, there is still a lack of evidence for proven causation, identifying risk factors, and definitive management. The focus is now on improving the efficiency of diagnostic tests, developing the vaccine, and spotting the effective drugs. Strong evidence supports the association between COVID-19 and vasculitis. Many approaches have been proposed to manage and treat vasculitis in patients infected with COVID-19. Therefore, clarifying the pathophysiology and treatment of vasculitis in SARS-CoV-2 infection is crucial for accomplishing such goals.

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