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# Vasculitis in COVID-19: A Literature Review

**Salma Ahmad Almashat***

*Department of Clinical Dermatology, King Abdulaziz University, Jeddah, Saudi Arabia*

## Abstract

Vasculitis has been linked to COVID-19 as a suspected pathological pattern in different cases, however, it is not yet considered a major pathology. This virus has different clinical presentations including; dermatological and other organs involvement which are highly suggestive of the presence of vascular disease. Also, the histopathological examinations reveal ischemic and thrombotic changes. These changes were not associated with DIC or any other thrombotic conditions. The addition of other possible medications that might help in controlling such inflammatory syndrome could be the key to controlling this disease. This literature review highlights some ot the important features for this viral illness and suggests some therapeutic options.

**Keywords:** Vasculitis in COVID-19 • Pathogenesis of COVID-19 • Thrombosis in COVID-19 • Clinical features of COVID-19 • Investigations for COVID-19 • Inflammation in COVID-19 • Management and treatment for COVID-19

## Introduction

COVID-19 is a new viral pandemic which has dramatically driven the medical attention [1]. Until now the pathogenesis and best treatment options are not fully discovered [2]. Also, the rate of mortality and spread of the infection among affected individuals has caused a great urge to understand, prevent and search for a treatment modality [1]. New data suggests that the disease can present differently and it does not necessarily affect the respiratory system [3]. Therefore, SARS2 (Severe acute respiratory syndrome) could be a misnomer for this disease. There are some speculations that the virus could be a direct invader of endothelial cells [4]. These cells form the lining of blood vessels all over the body thus; vasculitis could be a major pathological pattern of this disease [5]. This review highlights some of the clinical parameters that support this idea and suggest the therapeutic options that might control the condition.

## Method

A literature review study using Google scholar and Pubmed search engines. The terms " COVID-19 symptoms, presentation, investigations, histopathological changes, and approach and treatment options" were used to search for data about the condition in May, 2020.

## Dermatological Signs of COVID-19

There are various dermatological changes reported including chilblains [6] urticaria-like lesions, [3] erythematous maculopapular, [7] chickenpox-like or vesicular, [8] livedoreticularis, [7] erythema multiform-like, [6] and petechiae [7]. Such features can present with different forms of vasculitis as well [7].

Kawasaki disease which has mucocutaneous manifestations, and is one of the common causes of vasculitis within the paediatric age group (0-5), [9] is also seen as a presenting feature in children affected with of COVID-19 [10]. The cause of this condition is still unclear; However, Coronavirus is one of the documented infections that can precede Kawasaki disease along with other infections. Also, genetic factors could play a major role [9].

Apparently, the skin is the only organ in the body that can be grossly exposed and examined in live patients, thus, studying the changes occurring in the skin could be very helpful in understanding the internal pathology. Although it is unclear why the skin becomes affected by this virus, there are different speculations [7]. One of them is that the circulating immune-complex induces lymphocytic vasculitis [7]. Another theory is linked to the activation of the keratinocytes by Langerhans cells which become active as a result of the inflammatory process [11]. An additional theory is the possibility that micro thrombi from other organs have resulted in a reduced perfusion of blood to the microvasculature of the skin causing the appearance of livedo-reticularis or as a complication from disseminated intravascular coagulation (DIC) leading to different skin manifestations [12]. It is not yet clear if the virus affects the skin and cause these changes or they are only secondary complications, or it is a combination of both [7]. If vasculitis is considered to be a major pathology with this disease, the reason for the occurrence of different cutaneous manifestations can be generally justified.

In cutaneous vasculitis, some lesions usually occur with deeper skin vessels vasculit which include livedo-reticularis, nodules or ulcer

***Corresponding author:** Salma AhmadAlmashat, Master of Clinical Dermatology, King Abdulaziz University, Jeddah, Saudi Arabia, Tel: +96 (6) 599991123; E-mail: doctor.salma@gmail.com*



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[13]. This might give a hint to the depth of the vascular involvement and the severity of the disease.

There are reports for different skin biopsies taken from COVID-19 positive patients. Patients were not on any new drug treatment when the biopsies were taken. In an erythema multiforme lesion, there is perivascular and interstitial infiltration of lymphocytes, dilated blood vessels in the dermis with neutrophils filling and red-blood-cells were extravasated. Evidence of viral infection is also noted within vesicular lesions [14]. Another erythema multiform-like lesion is reported to appear after clinical improvement from COVID-19 and few days after discharge from the hospital with negative PCR for COVID-19 [14]. In this case, the co-existent pseudo-vesicles and enanthem suggests that the rash is mostly due to viral invasion and not due to drug reaction [14]. Clearly, the virus is inducing an unexplained immunological reaction.

Within an exanthematous rash, a study has revealed two histopathological stages of the rash. Early when first presented, there are only telangiectatic blood vessels. Three days later there were lymphocytic perivascular infiltrate and within the epidermis, Langerhans cells appeared [11]. Also, within the capillary vessels of haemorrhagic exanthema, there are micro thrombi within the dermal vessels [11]. Moreover, a papular erythematous exanthem in the trunk has shown lymphocytic vasculitis and eosinophilic infiltration within the dermis [11]. These variable cellular infiltration and pathological patterns need more detailed descriptiions.

The urticarial skin lesions presented are not typical urticaria as it does not disappear and does not have the typical histopathological features [3]. Similar to urticarial vasculitis clinically [15].

This means that there is an on-going inflammatory process without the presence of viral inclusion bodies within most tested tissues. Necrosis and microthrombi is seen histopathologically, thus, vaso-occlusive events could be greatly associated with the disease. Basically, it has been stated that there is an increased risk of thrombotic events with COVID-19 [16].

## Other Clinical Parameters of COVID 19

The most typical symptoms are fever, sore throat, cough and shortness of breath in a recently exposed person [2]. However, a great number of patients can be asymptomatic [1]. This viral illness does not only present with respiratory symptoms. There has been increasing reports of patients presenting with gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea and vomiting [17]. Haemoptysis and chest pain were also documented [18]. Acute vascular events were frequently documented in different organs with COVID-19 patients [4]. These symptoms can variably present with different forms of vasculitis depending on the vessel affected [9].

The virus can also be found in the stool, and the oro-pharynx and the feco-oral transmission is not yet excluded. In some patient the virus was found in the stool even after clearance of chest infection and remained stool positive for 12 days [17]. Cipriano et al. stress that the gastrointestinal involvement has to be the new focus for physicians to explore [17].

Besides, a prospective cohort study of 333 COVID-19 patients has identified kidney involvement in the form of acute kidney injury or abnormal urine dipstick within 75.4%of patients (65.8% presented with proteinuria, and 41.7% had haematuria) [19]. Retesting patients after recovery reveals normal dipstick and kidney function in a great number. Pei et al. believe that there is an ongoing kidney disease occurring with COVID-19 patients unrelated to a prerenal kidney injury [19]. Kidney involvement is not uncommon with vasculitis, [9] and there is a clear evidence of kidney involvement with a documented haematuria, thus, clearly vasculitis with COVID-19 has to be considered. Unfortunately, patients who had acute-kidney injury had in increased mortality rate by 11% [19].

Lymphopenia is one of the most important diagnostic markers for this virus [20,21] Jiang et al. assume that T-cell subsets count can be a measure for severe disease [20]. The infiltration of lymphocytes around blood vessels of biopsied lesions, [11] might be the reason of lymphopenia due to the depletion of the circulating lymphocytes and redistribution into affected tissue. Also, increased neutrophil/lymphocytes ratio could be an early sign of severe disease [22]. Previously, this ratio was documented to be an important parameter to determine disease severity and activity in different forms of vasculitis including ANCA-vasculitis, [23] Takayasu, [24] adult IgA vasculitis, [25] behcet, [26] cutaneous vasculitis particularly if there is a systemic involvement, [27]. However, this ratio could increase with some infections as well [28].

Also, there could be an increase in fibrinogen, D-dimer levels and ESR [29]. Also, eosinopenia and elevated CRP were significantly acknowledged markers, and it is thought that the combination of these two results can facilitate triaging patients presenting with fever to a suspected COVID-19 patient if presented with high CRP and low eosinophils [21]. It has been suggested that eosinopenia is an essential marker for an unexplained inflammatory syndrome [30]. According to Li et al., the reason for eosinopenia is unclear and it could be related to the viral invasion of bone marrow [21]. However, if the virus invades the bone marrow, pancytopenia might be the outcome and not only lymphopenia and eosinopenia.

Apparently, the virus does not only affect the lungs. Blood vessels, the heart, kidneys, gastrointestinal tract and other organs as well are involved. An autopsy of affected lungs reveals hyaline membrane formation, macrophages and monocytes in alveoli, multinucleated giant cells, lymphocytes, eosinophils and neutrophils [31]. At the level of blood vessels, monocytes and lymphocytic infiltration within blood vessels of alveolar septum which are oedematous and some micro-vessels had Hyaline thrombi. Focal haemorrhage and fibrosis are also observed. More research is needed to understand the role of eosinophils with this disease and if eosinopenia has resulted from the redistribution of eosinophils to the affected tissue. If such theory was proved, different anti-inflammatory therapeutic options can be tried that targets the eosinophilic reactions.

Moreover, an autopsy of the spleen has revealed a reduction in lymphocytes number and cell necrosis [31]. Also, in other parenchymal cells, necrosis is noticed and hyaline thrombus formation in small vessels [31]. Another autopsy shows that most small vessels are congested; there are inclusion bodies within the endothelium which is surrounded by inflammatory cells. There are also apoptotic cells within the lung, heart and intestine [4]. Lymphocytic enothelialitis within the kidneys, heart, intestine and liver

are reported. Myocardial infarction is also present histologically [4]. Clearly, the thrombotic pathology and endothelial inflammation are documented in different scenarios.

Meanwhile, myocarditis is one condition that is repeatedly reported to occur with COVID-19. It could be from the virus invading the myocardium or due to undetected immune reaction [32]. In addition, Magro et al. have reported vascular changes associated with the presence of COVID-19 glycoprotein with the deposition of C5-9 and C4d, and with pauci-inflammatory thrombogenic pattern [33]. These features are an indication of the need to explore the exact pathology of this viral infection and to consider vasculitis as probable clinical sequalae.

## Discussion

Vasculitis is not diagnosed by a single investigation. It is otherwise a combination of clinical, radiological and histopathological findings. There are criteria that support the diagnosis of small vessels vasculitis such as the presence of extravasation of blood and the deposition of fibrin or neutrophils infiltration within the wall support the diagnosis, but these findings alone are not enough and other parameters are important [34]. If the biopsy is taken 24 hours after the appearance of a skin lesion of a suggestive ongoing vasculitis, the neutrophils start to be replaced by lymphocytes and it is ideal to take the biopsy within 48 hours [34]. Theoretically, if COVID-19 causes vasculitis, it could be due to the viral invasion to the endothelium or due to the resultant immune reaction that leads to leukocytoclastic vasculitis. Therefore, for COVID-19 patients, it is also important to know if the antibodies against the virus are not causing autoimmunity against the blood vessel wall. Immunofluorescence of the blood vessel wall is essential to determine this as it can determine different subtypes of vasculitis [34]. In addition, if this virus causes vasculitis, different reported clinical presentations can be eventually explained such as haematuria, haemoptysis, abdominal pain and the thrombo-embolic events.

An intense inflammatory response with very high inflammatory markers has been previously recorded. Also, a study is conducted in China emphasizes that an anti-inflammatory medication has to be added to the treatment regimen in order to prevent severe complications and decrease mortality [35]. Hypercoagulability, cytokines syndrome and vasculitis response is believed to be the possible explanations for patients' deterioration. Interestingly, there is an unusual finding in an autopsy that is not related to cytokine storm, which is the destruction, atrophy and haemorrhagic necrosis of the spleen with reduced lymphocytes count. Similar findings are found in other lymphoid tissue. The presence of inclusion bodies or evidence of viral infiltration is not mentioned with these findings and there is no evidence that the virus directly invade lymphocytes or destroy them [35].

Vasculitis has been suggested to be a clinical syndrome that affects severe COVID-19 disease due to the endothelial damage and evidence of high level of anti-phospholipids which is documented in some patients with thrombosis. The pathological appearance of these patients, such as the infiltration of lymphocytes within the vessels, hyperplasia of small blood vessels with thickening and stenosis also supports the diagnosis of vasculitis. As a differential diagnosis, DIC, antiphospholipid, vasculitis, or autoimmune cross reactivity are all suggested [35]. In addition, not all patients with acro-ischemia due to COVID-19 are found to have developed full DIC picture [36]. The picture presenting in patients with coagulopathy due to this virus is not typical for DIC causing coagulopathy and ischemia [37]. Also, coagulopathic changes are not necessarily preceded by sepsis which commonly precede DIC. This suggests that there is most likely a local thrombus formation within the blood vessels rather than a systemic coagulopathy causing the ischemic features [37].

There are different therapeutic options suggested to control this inflammatory syndrome. Varga et al. suggests that the endothelial inflammation should be controlled with an anti-inflammatory or anti-ischemics, especially with patients who have high risk of cardiovascular event [4].

There are studies which suggest that hydroxychloroquine is improving the clinical appearance of patients with COVID-19. There has not been randomized controlled trial that support this theory; however, different studies have shown that patients taking this medication have a greater clinical picture than the control [35]. This medication has been used to control different autoimmune conditions [35]. Probably, its main efficacy is the modulation of the intense immunological reaction that might be causing the endothelial cell damage.

In addition, it has been observed, in some situation, that the incidence of the disease is less common or at least has an improved clinical appearance. One of them is the reduced incidence and mortality rate within countries giving BCG vaccine to new-borns [38]. The immunomodulatory effect of this vaccine has been greatly explored previously in the literature as it is thought to have a protective value against viruses and atopy [39,40]. Most likely it induces the innate non-specific immune response [40]. Different studies have implied that this vaccine directly induces T regulatory (Treg) cells that is essential in preventing various inflammatory and autoimmune conditions [41]. They are important in controlling the stimulated immunological reaction, preventing the damage which might occur with the inflammatory reaction by managing immune-tolerance to antigens [42]. This suppressive activity is implicated on the activated T cells and other cells to prevent autoimmunity [43]. In addition to that, there is less incidence of the virus within children which could be related to their stronger innate immune response [44]. Probably, this innate immune response could prevent extreme inflammatory reactions or possible autoimmunity seen with some COVID-19 patients.

Regarding biologics, there is evidence that Tocilizumab, an IL-6 inhibitor can be remarkably effective in controlling the disease and it might become included within the treatment protocol for COVID19 patients [35].

Other medications have to be studied as well. One of the interesting medications is Bosentan which is an endothelin-1 receptor blocker and is usually used to treat pulmonary hypertension [45]. Although it is believed that the vasodilatory effect of this medication in patients who has ventilation-perfusion mismatch can worsen ventilation, there has been a case report that contradicts this believe. In this case (published in 2014) a patient had H7N9 influenza virus that leads to ARDS and the patient was eventually ventilated. Antibiotics and an antiviral were started, however his condition continued to deteriorate until he was started on Bosentan to reverse

his pulmonary hypertension. The patient condition had dramatically improved although this medication is not selective for well-ventilated areas within the lungs [45]. The effect of this medication could be explained by another in-vitro study which is conducted on human umbilical vein endothelial cells. This study indicates that with Bosentan, there are significant down regulation of coxsackie-adenovirus receptors. These receptors are responsible for the entrance of coxsackie and adenovirus to the myocadiac cells leading to myocarditis, and without these receptors the virus cannot enter the cell [46]. This also has been proved in a murine study while this medication has greatly reduced the viral load and improved the clinical picture of myocarditis [47]. Kowalczyket al. believe that blocking endothelin-1 receptors has a great potential in controlling sepsis as by blocking these receptors different cytokines would not be released [48]. In addition, there is a case report for a patient who has subcutaneous lupus erythematosus complicated by lower limb vasculitis that has resulted in acute lower limb ischemia. Prednisolone, Iloprost and Alprostadil were all tried but there was no clinical improvement. However, when Bosentan was started, there was a dramatic improvement in lower limb prefusion after 1 week. The patient relapsed after stopping the medication 1 month later, but improved again when it was restarted. 3 months after therapy the leg showed normal perfusion in MRA [49]. Therefore, establishing clinical trials using Bosentan for COVID-19 patients is worthwhile.

In addition, Pentoxifylline is a medication that has an anti-inflammatory property and has been approved to treat different conditions including vasculitis. Therefore, it is worth knowing its efficacy in preventing and treating concurrent vasulopathic problems with this virus [50].

The evidence is highly suggestive of associated vasculitis with this viral illness; however, studies are needed to determine the exact pathogenesis and to select the most appropriate therapy. Most of the cases presented are case reports and case series with a few cohort studies, which means that the real picture for this disease is not yet thoroughly investigated. (Figure 1) summarises some of the reasons of why vasculitis has to be considered with COVID-19 patients. In the meantime, triaging patients would help practitioners estimate the condition and decide for aggressive therapy. Starting high risk patients for a cardiovascular event on an anticoagulant might greatly reduce mortality and complications. It has been stated that the cause of death is mainly due to cytokines storm which leads to ARDS and multiorgan failure, [44] therefore, an urgent focus to break this inflammatory cascade is crucial. Commencing patients on an anti-inflammatory has to be within a window period before the patient significantly deteriorates which is in 1-2 weeks after the beginning of symptoms [35].

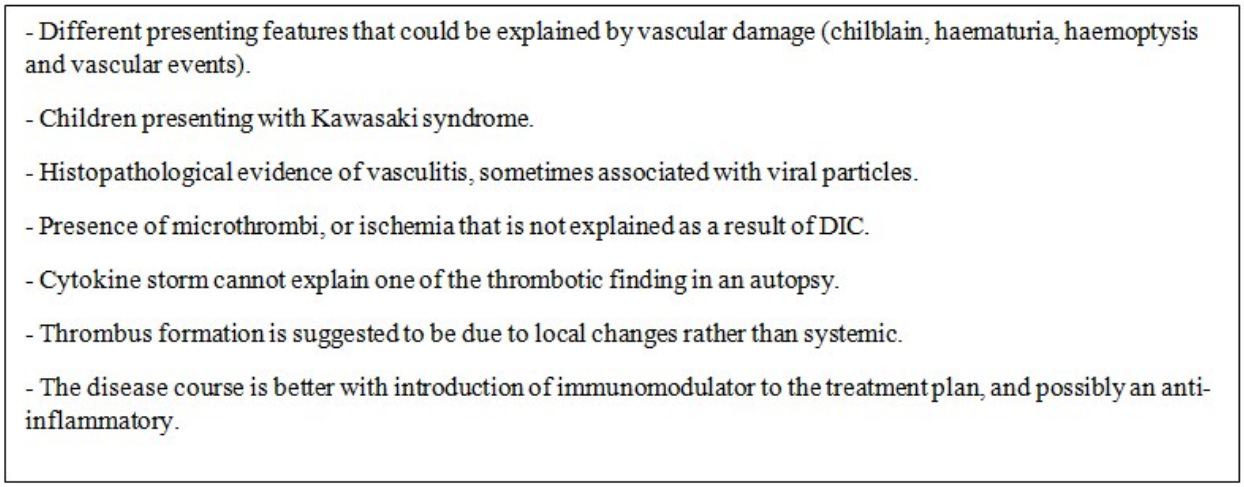


**Figure 1.** Summary of the clues that leads the possibility of ongoing vasculitis with COVID-19.

## Conclusion

If such therapeutic approach became highly effective, social distancing would no longer be required. An effort has to be spent into finding a solution that reverse the severity and prevents complications of the condition rather than waiting for a new specific antiviral or an actual vaccine which might take a long time.

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