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COVID-19 vasculitis and novel vasculitis mimics

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Lancet Rheumatol 2021; 3: e224–33

Published Online January 7, 2021 https://doi.org/10.1016/S2665-9913(20)30420-3

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COVID-19 has been occasionally linked to histologically confirmed cutaneous vasculitis and a Kawasaki-like vasculitis, with these entities generally having minimal or no lung involvement and a good prognosis. Unlike these vasculitis types, patients with severe COVID-19 pneumonia can develop cutaneous vasculitis-like lesions and systemic arterial and venous thromboemboli, including cryptogenic strokes and other vasculopathy features. Proposed underlying mechanisms for these severe manifestations have encompassed immune dysregulation, including an anti-phospholipid syndrome-like state, complement activation, viral dissemination with direct systemic endothelial infection, viral RNAaemia with immunothrombosis, clotting pathway activation mediated by hypoxaemia, and immobility. In this Viewpoint, we highlight how imaging and post-mortem findings from patients with COVID-19 indicate a novel thrombosis in the pulmonary venous territory distal to the alveolar capillary bed, a territory that normally acts as a clot filtration system, which might represent an unappreciated nidus for systemic microembolism. Additionally, we suggest that this mechanism represents a novel vasculitis mimic related to COVID-19 that might lead to cryptogenic strokes across multivessel territories, acute kidney injury with haematuria, a skin vasculitis mimic, intestinal ischaemia, and other organ ischaemic manifestations. This finding is supported by pathological reports of extensive pulmonary venular thrombosis and peripheral organ thrombosis with pauci-immune cellular infiltrates. Therefore, severe COVID-19 pneumonia with extensive pulmonary intravascular coagulopathy might help to explain the numerous systemic complications of COVID-19, in which the demonstration of direct organ infection has not adequately explained the pathology.

Introduction

Mortality in the ongoing COVID-19 pandemic has been strongly linked to diffuse alveolar damage and associated immunothrombosis in the pulmonary capillary network and adjacent vessels.[1,2] This pulmonary vascular pathology has been conceptualised in relation to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of pneumocytes and endothelial cells, with dysfunction of pulmonary vasculature and systemic endothelial tissue, as well as associated aberrant cytokine responses, contributing to mortality.[3] We have previously highlighted how SARS-CoV-2 alveolar-centric inflammation triggers pulmonary immunothrombosis (termed pulmonary intravascular coagulopathy [PIC]), in which immunothombosis predominates over endothelitis as the central driver of severe COVID-19, and we suggested that this represents a distinct entity from disseminated intravascular coagulation (DIC).[4] The PIC pathology, leading to hypoxaemia and pulmonary artery hypertension in some patients rather than systemic viral infection including myocarditis, offers a simple model to explain COVID-19 mortality in patients with cardiovascular risk factors.[4,5]

Clinically, vascular dysfunction related to COVID-19 manifests beyond the lung in different ways, including deep venous thrombosis, pulmonary embolism, large arterial thrombosis, and multiorgan venous and arterial thromboses, and these manifestations have been attributed to factors such as hypoxaemia, viral sepsis, immobility, and occasionally vasculitis.[6] In some cases, DIC (which represents a vasculitis mimic) might occur with fulminant COVID-19 lung disease and is also characterised by diffuse thrombosis and haemorrhaging.[7] When DIC and large vessel thrombosis are excluded, it is clear that patients with severe COVID-19 pneumonia can also have severe skin vasculitis-like changes, suspected cerebral vasculitis, and multiorgan failure whereby viral endothelitis, direct viral infection, or vasculitis are suspected.[8,9]

In this Viewpoint, we consider the literature pertaining to these different types of extrapulmonary vascular lesions in COVID-19, with a focus on vasculitis and vasculitis mimics. We describe the basis for the different patterns of genuine vasculitis associated with COVID-19, including isolated cutaneous vasculitis, Kawasaki disease and Kawasaki-like disease, and COVID-19 vasculitis mimics. We highlight a novel potential mechanism for vasculitis mimics in the context of SARS-CoV-2 infection involving immunothrombosis in the pulmonary venule circulation and secondary systemic embolisation as an unappreciated mechanism underlying organ thromboembolism and vasculitis mimics.

Skin vasculitis in COVID-19

Skin lesions with features of vasculitis have been reported in COVID-19 cases ranging from mild or asymptomatic to fulminant disease,[10] with reported changes exhibiting a predilection for the dorsal surfaces of the toes, including rounded, well circumscribed erythematous to violaceous plaques or nodules, diffuse digital erythema, and chilblain-like lesions.[11,12] However, the skin lesions in children and younger people typically occur in the absence of COVID-19 pneumonia (figure 1). In these patients, such COVID-19 skin lesions exhibit vasculitic changes with perivascular cuffing and inflammatory lymphocytic infiltration, which might lead to luminal thrombosis.[13,14] Consistent with predominant vasculitic disease, one study reported asymptomatic, funduscopic changes typical of retinal vasculitis in a child with chilblains.[15]

The predominant cutaneous findings in adults with severe or critical COVID-19 pneumonia are distinct from the vasculitic changes seen in infected but otherwise

healthy young people, and these cutaneous manifestations were the first major pointers to the potential relevance of vasculitis mimics in COVID-19. Necrotic skin lesions were reported in 6% of patients with cutaneous pathology associated with COVID-19 and were associated with older age, increased disease severity, and a 10% higher risk of mortality.[10] In another study of five patients with severe COVID-19 respiratory failure, skin lesions (seen in three patients) were characterised by a pauci-immune thrombogenic vasculopathy with terminal complement component activation in the vessel walls, and occasional SARS-CoV-2 spike protein deposition.[16] Some of these reported cases exhibited extensive thrombosis that was disproportionally severe compared with the magnitude of inflammation, suggesting that complement activation was secondary to thrombosis or embolism.[16] As such, the disease process is likely to be a vasculitis mimic. This theory is supported by the observation that complement activation coincides with ischaemic–reperfusion injury in mice.[17] Another case report of a patient with COVID-19 and retiform purpura, a vasculitis mimic, clearly showed extensive cutaneous vascular thrombosis, an absence of inflammatory cells, and expression of terminal complement components in the vessel walls, further supporting complement pathway activation secondary to ischaemia.[18]

What is crucially different between the cases of severe COVID-19 pneumonia and COVID-19-associated cutaneous vasculitis in otherwise healthy patients is an absence of a type I interferon (IFN) response, which has been reported in some studies of critically ill patients (figure 1).[19] A proposed theory explaining these dichotomous cutaneous patterns involves a robust type I IFN response that mimics human monogenic diseases, collectively termed interferonopathies, with excessive type I IFN production and chilblains without clinically significant pneumonia at one end of the spectrum, and low type I IFN responses with severe COVID-19 pneumonia at the other end of the spectrum (figure 1).[20] According to this theory, an initial failure to mount a robust type I IFN response to the virus is followed by an overproduction of innate immune cytokines (produced in an effort to contain the infection) that drive severe PIC.[21] This theory is further supported by immunogenetics studies in patients with severe COVID-19, in which defects in type I IFN signalling have been shown.[22] However, there is contradictory literature on this point, with some studies reporting high type I IFN gene signatures in patients with severe COVID-19; these discrepancies have not yet been resolved.[23,24]

Other recognised vasculitis mimics, especially DIC, merit consideration in patients with severe COVID-19; however, in general, normal fibrinogen and D-dimer concentrations differentiate DIC from other vascular pathologies related to COVID-19, in which these components are typically elevated.[4] In a retrospective study that included seven critically ill patients with COVID-19 and acro-ischemia presentations (including finger or toe cyanosis, blistering, and gangrene), the pathophysiology of the cutaneous lesions was acknowledged as being unclear, with immune dysregulation, vasculitis, vessel thrombosis, neoangiogenesis, or a hypercoagulable state suggested as possible mechanisms.[25] However, four of these patients were diagnosed with definite DIC.

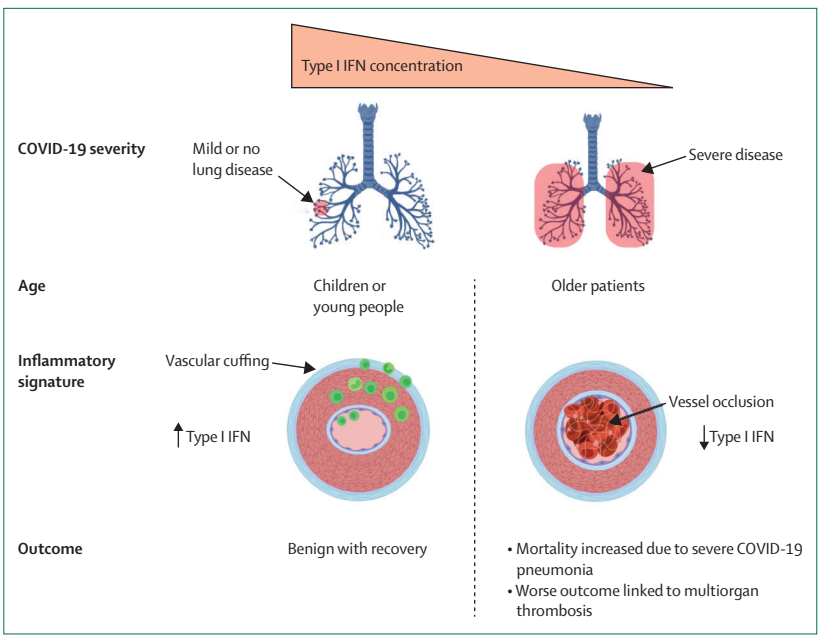

Figure 1: **Patterns of disease leading to vasculitis and vasculitis mimics**
Two distinct mechanisms underscore the cutaneous disease seen in COVID-19. For mild disease in younger patients, a transient vasculitis limited to the skin might occur in the context of robust immune responses to COVID-19, including vigorous type I IFN responses and mild lung disease. The basis for Kawasaki-related vasculitis, in general or in COVID-19, is poorly defined; however, it typically occurs in individuals with minimal or no lung infection. For severe COVID-19 pneumonia with respiratory failure, cutaneous vasculitis is linked to small vessel thromboembolic disease. This pattern could be partly due to thrombosis of small and large vessels in situ due to severe illness, hypoxaemia, and RNAaemia in some severe cases. The pattern might also be linked to diffuse embolism from the pulmonary venular, left heart, and arterial emboli dislodgement from thrombi. Cutaneous disease in patients with severe COVID-19 might be linked to type I IFN disablement and elevations in multiple proinflammatory cytokines. IFN=interferon.

Kawasaki-like disease spectrum and vasculitis in COVID-19

Analogous to the cutaneous vasculitis seen in younger patients with COVID-19, coronary artery vasculitis or a Kawasaki-like disease has been reported in predominantly younger patients with SARS-CoV-2 infection.[26] Kawasaki-like disease typically occurs as part of a severe hyperinflammatory state, termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome (MIS, or MIS-C) in the USA, with the latter terminology now being adopted.[27] This syndrome is rarely associated with the coronary artery aneurysms typical of Kawasaki disease, which occur in less than 10% of cases.[28,29] Older children and even young adults might be affected, and abdominal pain and diarrhoea of unclear cause might occur.[30] There has been some evidence of direct cardiac endothelial infection or endotheliitis from in-vitro studies in which endothelial organoid cultures

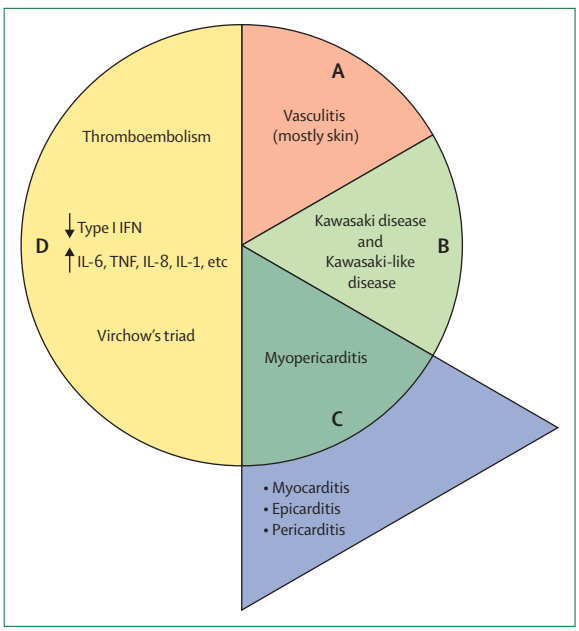

Figure 2: **Types of vasculitis disease**
A) Uncommon and mild cutaneous vasculitis is linked to robust immune responses, typically occurs in otherwise healthy patients, and involves skin only, with a predilection for the toes. This cutaneous vasculitis occurs in the context of robust type I IFN production and intact anti-SARS-CoV-2 immunity. B) Kawasaki disease can occur in patients with non-severe infection, presenting with classically described coronary aneurysms but with a pattern of skin involvement distinct to that in isolated mild cutaneous vasculitis. Kawasaki-like disease, seen in older children and young adults with non-severe infection, is associated with prominent cardiac muscle involvement and absence of aneurysms. C) Predominant myocarditis might occur as part of the Kawasaki phenotype and be the dominant clinical picture, and cases with cardiac inflammation might occur without any detectable aneurysm formation (blue panel). D) The vasculitis mimics seen in severe COVID-19 pneumonia, associated with cardiac disease, are likely to be linked to multifaceted mechanisms consequent to severe pulmonary territory immunothrombosis, hypoxaemia, pulmonary hypertension, pulmonary venular territory embolism, arterial thromboembolism, and systemic venous thromboembolism. Decreased type I IFN responses and subsequent activation of proinflammatory cytokines (IL-1, IL-6, IL-8, TNF, etc) and chemokines result in immunothrombosis. IFN=interferon. IL=interleukin. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. TNF=tumour necrosis factor.

were infected with SARS-CoV-2.[31] However, Kawasaki-like disease typically occurs in patients without discernible COVID-19 pneumonia or active infection, suggesting that direct viral infection is unlikely to be a factor.[30]

It is noteworthy that before the COVID-19 pandemic, fulminant Kawasaki disease was well recognised in the context of an acute severe myocarditis, without discernible coronary vasculitis and aneurysm development.[32] Outside the setting of severe pneumonia, adults with COVID-19 might also present with severe myopericarditis identified by MRI.[33] Interestingly, some cardiac autopsy studies in cases of severe COVID-19 pneumonia have reported prominent lymphocytic infiltration in the epicardial tissue; however, to date, there have been no direct data that link pericardial and epicardial inflammation and coronary artery aneurysms, even though both territories are obviously contiguous.[34] The fact that coronary artery aneurysms are uncommon in COVID-19-related Kawasaki-like disease, yet myocarditis is very common,[29] points to the possibility of convergent mechanisms of Kawasaki-like disease around myocardial inflammation. Nevertheless, the mechanisms are unclear, and a link to either vasculitis or cardiac viral myocyte infection remains unproven (figure 2).

Severe COVID-19 pneumonia with PIC is associated with elevated concentrations of cardiac enzymes, which probably represent extreme biophysical and hypoxaemic cardiac stress and systemic immunothrombosis and thromboembolism (figure 2).[29] Accordingly, a post-mortem study of 39 patients with severe COVID-19 pneumonia showed no evidence of myocarditis or vasculitis, but noted the presence in cardiac tissue of occasional immune cells containing viral nucleic acid.[34] It can be surmised that across the entire spectrum of COVID-19, there are very few cases with demonstrable coronary vasculitis and that, when it does occur, it is in the setting of mild lung infection with a Kawasaki-like disease phenotype.

Apart from such patterns of cutaneous and cardiac vasculitis, there is little evidence for primary vasculitis in other organs. One exception was the presence of severe large vessel cranial vasculitis identified by MRI in a patient with severe COVID-19 pneumonia;[35] however, the MRI changes reported would also be consistent with concomitant giant cell arteritis.[36]

Systemic arterial and venous thromboembolism in severe COVID-19

Critically ill patients with COVID-19 might exhibit generalised thrombotic states, including gangrene and digital necrosis related to peri-mortem DIC;[37,38] however, systemic arterial and venous thromboses are also well described in this patient group. Commonly recognised systemic venous thrombotic states in COVID-19 pneumonia are deep vein thrombosis and extensive pulmonary thromboembolism.[39,40] This venous-centred thrombosis seems to be very common in patients with severe COVID-19 who are on ventilators in intensive care.[41]

Systemic large arterial thrombosis is a recognised cause of stroke in patients with COVID-19.[6] Small artery thromboses have also been reported in patients with COVID-19, although small distal thromboses could have seeded from a proximal thrombus.[42] In addition to both large and small arterial thromboses, valvular thrombosis related to infection with coronavirus family viruses (termed marantic endocarditis) and left ventricular cavity thrombosis have been reported in both the previous severe acute respiratory syndrome (SARS) epidemics and the current COVID-19 pandemic.[43,44] Collectively, arterial tree thrombosis could serve as a source of systemic arterial tree embolism, which embolises distally and then mimics vasculitis; however, overall, this might represent a relatively uncommon vasculitis mimic (figure 3).

The underlying mechanisms of systemic thrombosis in patients with severe COVID-19 are incompletely defined,

and factors including direct viral endothelitis, complement-mediated vascular injury, and autoimmunity have been proposed. In some cases, pathology is ascribed to anti-phospholipid syndrome, but relevant autoantibodies might arise transiently in the context of severe infection, rather than being indicative of authentic or primary antiphospholipid syndrome, which is a persistent condition that has not yet been convincingly shown to arise after pneumonic and tissue damage resolution.[45] Severe hypoxaemia is associated with predominantly venous thrombus formation.[46] We have previously pointed out that positive pressure ventilation used in severely ill patients with COVID-19 might force viral RNA into the systemic arterial and venous trees, driving immunothrombosis. As such, it is noteworthy that viral RNAaemia is more common in patients on ventilation than in patients not on ventilation.[4,47] Systemic venous thrombosis in patients with severe COVID-19 and cardiac pathology attests to such a potential mechanism,[44] as does prostatic venous plexus thrombosis reported in post-mortem samples.[48] When the existing recognised vasculitides and systemic thrombosis are taken into account, we believe that a novel vasculitis mimic that afflicts the systemic arterial tree might underscore much of the systemic vascular pathology in COVID-19 (table 1).

Pulmonary venular thrombosis: setting the scene for a vasculitis mimic

We would like to propose a unifying hypothesis that could better explain the common occurrence of ischaemic lesions in the brain, peripheral organs, and skin in patients with severe COVID-19 pneumonia. We propose that this vasculitis mimic emanates from PIC with small thrombosed pulmonary veins that lie beyond the lung capillary filtration network and, therefore, represent a potential source of systemic emboli with direct access to the CNS, solid organs, skin, and other organs.

Both small-sized and medium-sized pulmonary arteriole and venule thromboses are well reported in COVID-19 without discernible vessel infection.[49] Fox and colleagues[50] reported images showing pulmonary venule thrombosis in post-mortem samples from patients who died of COVID-19 pneumonia. Immune cell infiltration of thin-walled pulmonary venous circulation in conjunction with adjacent inflammation outside of the vascular tree in the lung parenchyma, as well as hypercoagulability within the blood compartment, means that so-called Virchow's triad is readily fulfilled in the pulmonary venous circulation. Another study reported diffuse small vessel microthrombosis without specific reference to the pulmonary venous territory vessels.[51] Pulmonary capillary thrombosis has also been described in influenza, but skin and neurological stroke complications were rarely reported.[52,53] Overall, these differences between influenza and COVID-19 might reflect the increased magnitude of small vessel immunothrombosis in COVID-19.[54]

Outside of COVID-19, pulmonary vein or tributary thrombosis is a rare entity linked to different causes, including direct invasion by lung cancer; infection in immunocompromised patients; previous surgery, including lung transplantation; atrial fibrillation; or, occasionally, an idiopathic entity. This thrombosis manifests with multiple systemic embolic phenomena with organ ischaemia or chest pain, pulmonary haemorrhaging, and pulmonary infarction due to pulmonary backpressure, all of which are features that are well recognised in patients with severe COVID-19.[55] To the best of our knowledge, viral pneumonia has not been linked previously to pulmonary vein drainage territory thrombosis; however, thromboembolic pathology has been occasionally noted in animals following bacterial pneumonia.[56]

Importantly, CT pulmonary angiography studies in patients with severe COVID-19 pneumonia often show dilated, tortuous vessels in the subpleural lung region. This pattern of pathology is known to occur in pulmonary venous hypertension and in pulmonary veno-occlusive disease,[57] whereby the changes probably represent dilatation of pulmonary venules related to obstruction. These patterns of vascular dilatation were evident in up to 80% of patients with severe COVID-19 pneumonia and were typically juxtaposed to regions of ground glass opacity, thus supporting the link between alveolitis and PIC with occlusion of the draining venous territory. Another study showed vascular enlargement, including subpleural vascular enlargement in 72 (71%) of 101 patients with COVID-19 pneumonia, and the authors noted that

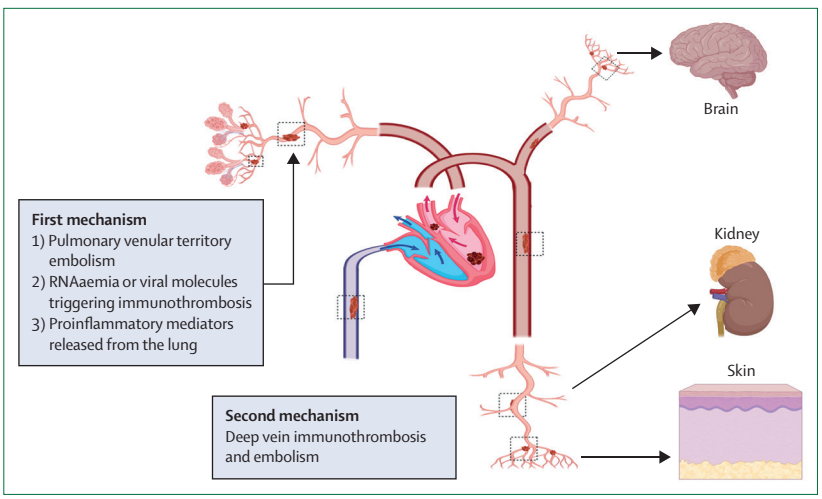

Figure 3: **Sources of thromboembolic material for vasculitis mimics in COVID-19**
SARS-CoV-2 infection might lead to a vasculitis mimic by two major mechanisms. First, local pulmonary intravascular coagulopathy might lead to embolisation originating in the pulmonary venous vasculature location, given that it is a well established site of thrombosis in COVID-19 and readily fulfils Virchow's triad outside of pulmonary venular walls, inflammation within pulmonary venule walls, change in flow due to decreased capillary drainage, and probable changes within the vessel lumen due to clotting cascade factors and immunothrombotic SARS-CoV-2 viral RNA. Given that the pulmonary vein system has thinner walls than the pulmonary arterial system, the vein system could also favour the effect of exogenous alveolar inflammation spread to this territory with extensive venular immunothrombosis. Second, a systemic hypercoagulopathy might exist due to dissemination of viral RNA that triggers immunothrombosis outside of the pulmonary circulation in the arterial and venous trees. Such a scenario might lead to embolisation originating from the heart or the arterial tree itself. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

	Systemic venous thrombosis	Pulmonary vein tributary thrombosis
Site	Typically large veins (eg, lower limbs)	Multiple small veins in the lung
Emboli	More likely to be large	Multiple and small
Risk factors	Age, stasis, obesity, obstruction, and swelling	Age and immunothrombosis
Therapy	Anticoagulants	Corticosteroids, possibly cytokine blockers, possibly anticoagulants
Composition	Rich in fibrin	Neutrophils, platelets, fibrin
Speed of resolution	Slow	Rapid due to multiple small clots including inflammatory cells
Diagnosis	Doppler ultrasonography	Post-mortem

Table 1: **Basic clinical, histological, and therapeutic characteristics of thrombotic events in systemic and pulmonary veins in patients with severe COVID-19**

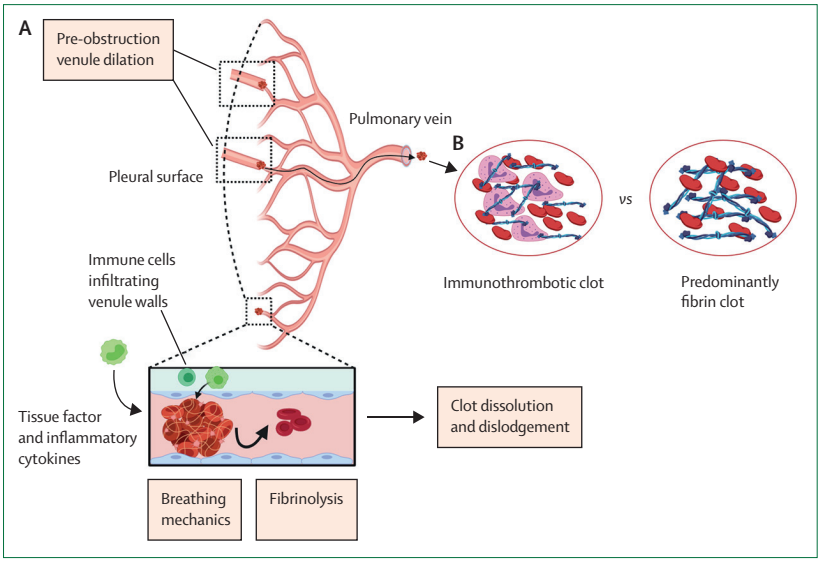

Figure 4: **Basis for pulmonary venule microthrombosis with embolism**
A) Pulmonary venule thrombosis occurs due to severe and proven SARS-CoV-2 centric alveolitis. Inflammatory mediators and inflammatory cells outside of the thin-walled pulmonary venular circulation; immune cell infiltration of venular walls; activated immune cells within venules; and release of procoagulation tissue factor and other procoagulants, and proinflammatory mediators trigger venular thrombosis. Activation of the fibrinolytic pathway, as evidenced by increased D-dimers and respiratory distress, lung tissue movement, and potential impact of barotrauma in ventilated patients with severe COVID-19 all contribute to the proposed systemic emboli derived from the pulmonary vein territory. Systemic microemboli that originate beyond the pulmonary capillary filtration network access the circulation. Pulmonary venule thrombosis is evident histologically, and CT scanning of the chest frequently shows pre-obstruction vascular dilatation. B) The main difference between an immunothrombotic clot and a classical clot is that the classical type is predominately composed of fibrin and platelets, rather than immune cells.
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

such lesions were distinct from vascular changes related to carcinomatosis.[58]

Pulmonary venous circulation microembolism as a vasculitis mimic in COVID-19

To the best of our knowledge, the possibility that cutaneous lesions in severe COVID-19 pneumonia might be due to embolisation originating from the pulmonary post-capillary venous network has not been considered (figures 3, 4). The model that we propose not only relates to a viral alveolitis with extensive pulmonary immunovascular thrombosis, or PIC, as reported,[4,21] but also encompasses systemic arterial circulation embolisation (figure 4). The extensive deep vein thrombosis and pulmonary embolism occurring in the large veins on the right side of the heart can be readily imaged, and the fibrin-based clot composition is fairly well understood.[41] By contrast, left-sided pulmonary circulation venular thrombosis is relatively hidden to imaging.

Emerging studies have shown that clot composition in PIC is different to that in deep vein thrombosis, involving small clots with abundant NETosed neutrophils, platelets, and some fibrin.[44,53] Autopsy specimens from patients with severe COVID-19 had platelet and neutrophil immunothrombotic clots, not just in the lungs but also in other organs including the heart and kidneys, which suggest direct embolisation.[59] Nevertheless, other mechanisms might have been operational and further evaluation of the arteriolar territories is necessary.

Brain involvement in COVID-19: vasculitis mimics rather than viral infection?

Organs that require a large percentage of cardiac output, including the brain and kidneys, are expected to suffer more from the damaging effects of systemic embolisation.[60] Given that the focus of this Viewpoint is novel vascular immunopathology in COVID-19, the role of direct infection of the CNS by SARS-CoV-2 is not discussed; however, evidence for and against CNS infection is summarised in the panel. What is the evidence that neurological disease related to COVID-19 in humans represents a vasculitis mimic? In one study, patients who died of COVID-19 pneumonia had an increased degree of disorders of consciousness and hypoxic encephalopathy compared with patients who recovered, although individuals with the most severe COVID-19 also had the highest number of comorbidities.[71] In the same study, 40 (82%) of the 49 patients who died, but only 44 (38%) of 117 patients who recovered, had microscopic haematuria, a well recognised complication of systemic embolism with microscopic infarction.[71] A second study from Wuhan (China) reported that among the 88 patients most severely affected by COVID-19, occurrence of neurologic manifestations was higher compared with patients with non-serious infection, including ischemic strokes in 5% (n=4); 15% (n=13) had impaired consciousness; and 19% (n=17) had unexplained skeletal muscle injury.[72] The retrograde theory of viral migration into the CNS was put forward by Mao and colleagues,[72] but haematuria was not reported nor was there any description of skin symptoms in the same study.

In a French study of 13 patients with confirmed COVID-19 pneumonia without obvious stroke who underwent brain MRI for unexplained encephalopathic features, two individuals had small ischaemic-type lesions and all 11 patients who had perfusion imaging had bilateral frontotemporal hypoperfusion defects—both non-specific findings.[73] In this study, electroencephalogram and cerebral spinal fluid reports for SARS-CoV-2 were generally

normal or negative, and the authors thus concluded that encephalopathy related to critical illness, a cytokine-mediated pathology, or the effects of medication withdrawal were potential causative factors independent of SARS-CoV-2 infection.

An investigation of two US cohorts, comprising over 3400 patients, reported that 31 (1·6%) of 1916 patients with COVID-19 had acute ischaemic strokes (odds ratio 7·6, 95% CI 2·3–25·2), compared with 3 (0·2%) of 1486 patients with previous influenza pneumonia, indicating a tropism of SARS-CoV-2 and cerebrovascular disease.[74] In a quarter (n=8) of the patients with COVID-19 and stroke, stroke was a presenting feature; however, more importantly, this was cryptogenic or its cause was not defined, and multiple vascular territories occurred in over half (n=17) of these stroke cases.[74] Reports that cryptogenic strokes are more common in patients with COVID-19 than in those with severe influenza pneumonia also supports the concept that poorly defined viral differences and virus–host interactions underscore an increased propensity for vascular injury with severe SARS-CoV-2 infection.[72,75]

A small autopsy study comparing COVID-19 pneumonia with influenza pneumonia showed a much greater burden of pulmonary capillary thrombosis in COVID-19 pneumonia, suggesting presence of pulmonary venular immunothrombosis in COVID-19.[74] The consequence of these vascular changes would favour thrombosis of the pulmonary vein drainage territory, consistent with the increased stroke rate observed with severe COVID-19. During the height of the COVID-19 pandemic in New York (NY, USA), almost 1% of patients hospitalised with COVID-19 had unexplained or cryptogenic strokes, which was significantly more common than this type of stroke in patients without COVID-19 or in patients with ischemic stroke treated at the same hospital over the same months in 2019.[76] In turn, this occurrence was correlated with high D-dimer concentration, which is known to be linked to the diffuse PIC characteristic of COVID-19 pneumonia and reflects fibrinolysis.[76]

Unifocal and multifocal lesions with features of CNS vasculitis have been reported in patients with severe COVID-19; however, histological studies substantiating the nature of the pathology are needed.[77] The co-occurrence of diffuse cutaneous lesions and extensive ischaemic lesions in the deep brain on MRI, without any discernible vascular source, have been proposed to suggest a cerebral vasculitis centred on the endothelium.[78] However, pathological reports favouring thromboembolism over vasculitis are emerging. A neuropathological examination of brain tissue from 20 patients who died of COVID-19 showed infarcts in six patients, with most of these described as "small and patchy peripheral and deep parenchymal ischaemic infarcts," with no histological evidence of vasculitis reported.[79] To summarise, the inconsistent demonstration of viral RNA in the brains of patients with COVID-19-related neurological disease along with severe immunothrombosis of the pulmonary venular territory suggests an unappreciated mechanism for CNS disease in the context of severe lung infections, particularly COVID-19.[80]

***Panel*: Evidence and views around putative coronavirus infections of the CNS**

Evidence for:

- Anosmia development as an initial symptom in COVID-19 has raised the issue of direct neuroinvasion and infection.[61]
- The commonly reported neurological manifestations of severe COVID-19 have been conceptualised in relation to direct viral infection.[62]
- Circumstantial evidence for SARS-CoV-2 encephalitis, including imaging findings and positive cerebral spinal fluid PCR results, have been occasionally reported.[63]

Evidence against:

- SARS-CoV-2 RNA is absent from the circulation in many cases of severe COVID-19.
- Cerebral spinal fluid PCR result for SARS-CoV-2 is often negative in cases of COVID-19 with brain involvement.[64]
- Severe brain involvement is most often linked to severe lung involvement, suggesting that CNS disease is often a complication of pulmonary involvement rather than a primary condition.[65]

Evidence from murine models:

- Direct brain infection in mice has been shown. Before SARS-CoV-2, it was already well established that murine coronaviruses induced severe CNS infection with encephalitis, although not via spike protein–ACE2 receptor engagement but via spike protein–CEACAM-1 (BGP-1) receptor engagement.[66]
- For optimal lung infection with human coronavirus family members SARS, MERS, and SARS-CoV-2 in mice, transgenic expression of relevant human receptors is required. Transgenic human ACE receptor expression in mice was associated with diffuse active viral brain infection but minimal CNS inflammatory infiltration at the time of histological evaluation.[67]
- Transgenic expression of a human DPP-4 receptor gene conferred lethality to MERS viral infection in mice, with active viral infection of the CNS, especially of the brain stem and thalamus; infection of human neuronal cell lines could also be shown. In this model, active viral infection and perivascular lymphocytic cuffing were reported, but kidney infection was not evident and damage at this site was thought to reflect hypoxia.[68]
- Replication of SARS-CoV-2 in human ACE transgenic mice has been reported for the lung and kidney, but virus replication was not detectable in the brain. Despite the scarcity of robust experimental evidence for direct SARS-CoV-2 infection, some human coronaviruses, most notably human coronavirus OC43, is both neuroinvasive and neurotropic in mice setting, especially via olfactory nerve entry.[69,70]

ACE=angiotensin-converting enzyme. DPP=dipeptidyl peptidase. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome.

Potential vasculitic involvement of other organs in COVID-19

Besides brain involvement, studies have reported severe small arteriolar and venular thromboses in multiple organs in patients with severe COVID-19, including the kidneys, spleen, and liver, which were attributed to a polyangiitis in one study.[81] Multiple regions of infarction in the spleen, lymphoid tissue, and kidneys also point towards arterial bed thrombosis, as previously reported in the SARS epidemic, although severe ischaemia per say might have been responsible.[82] Given the high degree of

	Features	Comments	Mechanisms and outcomes
Primary vasculitis	Might occur in patients with mild COVID-19; more common in childhood and young patients than in older patients	Examples include isolated cutaneous vasculitis and Kawasaki-like disease	Good prognosis; not linked to severe lung infection or RNAaemia
Related to disseminated intravascular coagulation	Critical COVID-19 pneumonia in patients with severe lung disease	A pre-terminal event	Bad prognosis
Systemic arterial thrombosis	Uncommon but seen in cardiac chambers, valves, and occasionally large vessels in patients with severe COVID-19	Might contribute to strokes and other organ ischaemia; probably under-recognised	Immunothrombotic viral RNA possibly a key driver
Systemic venous thrombosis	Not only deep vein thrombosis and pulmonary embolism but also extensive venous thrombosis	Common in patients with critical illness in many settings	Possibly immunothrombotic viral RNA; known deep vein thrombosis risk factors
Novel vasculitis mimic	Embolisation from pulmonary venous tree to systemic arterial tree	A proposed unrecognised vasculitis mimic	Further research needed to distinguish from above factors linked to arterial tree thrombosis

Table 2: **Causes of extrapulmonary vascular disease in patients with COVID-19 that might be independent of direct systemic viral endotheliitis**

perfusion of the kidneys, another study reporting haematuria in up to half of patients with severe COVID-19 also supports a shared pathology with the CNS,[83] as does the pauci-immune thrombotic type of cutaneous vasculitis described in critically ill patients.[84]

With respect to gut involvement, critical gut ischaemia was reported in 2·5% of patients with COVID-19, compared with no cases in individuals with influenza.[85,86] Studies have also reported liver and adrenal infarction in a few cases, indicating compromised arterial blood supply.[87] The source of embolisation in the pulmonary venular territory leading to a vasculitis mimic would be expected to involve arterial tree divisions only and is distinct from systemic venous thrombosis as a cause of tissue damage, which has been reported in organs such as the heart (table 2).[88]

Immunology considerations in COVID-19 mimics of vasculitis

The microscopic vascular thrombosis in the lungs and peripheral tissues of patients with severe COVID-19 has shown evidence for the deposition of alternative and mannose-binding lectin complement pathway proteins adjacent to thrombosis, suggesting local complement activation.[84] The same study indicated limited co-localisation of the SARS-CoV-2 spike protein and complement pathway components.[84] The diffuse organ damage in patients with severe COVID-19 has also been likened to microangiopathic haemolytic anaemias, such as thrombotic thrombocytopenic purpura and haemolytic uremic syndrome, in which complement activation has a role.[89] Nevertheless, the reported changes with thromboses in medium and large vessels, the absence of anaemia and schistocytes, and often normal platelet counts argue against complement-mediated injury as a common vascular pathology scenario in COVID-19.[90]

In mouse models of SARS and Middle East respiratory syndrome, a role for complement in the pathology has been shown; however, there is no reported experimental evidence for such a scenario with regard to extrapulmonary tissue involvement.[91,92] The absence of SARS-CoV-2 RNA in the blood of patients with COVID-19 in many settings also challenges this model.[93] Unlike bacteraemia and associated septicaemia, with vascular immunothrombosis acting as a containment strategy, the mechanisms underlying viral sepsis and immunothrombosis is less well studied, although intravenous injection of adenovirus in mice has been shown to activate complement and innate immunity.[94] Furthermore, cell damage and necrosis can cause macrophages to release tissue factor, one of the principal activators of the blood coagulation cascade.[94] Overall, tissue damage, cell injury, and necrosis are pervasive activators of the complement cascade, even in the context of tissue injury without infection; therefore, the presence of complement pathway proteins does not necessarily imply a vasculitis scenario.[95] Evidence for simultaneous innate immune activation, complement activation, and coagulation cascade activation has emerged in COVID-19, and neutrophil extracellular traps, neutrophil-derived tissue factor activity, and soluble C5b-9 have been detected in the serum of some patients, suggesting that integration of these pathways contributes to pulmonary and systemic circulation thrombosis.[96] Because of the multitude of activators of the complement cascade, and a direct role for viral infection of the systemic vascular tree has not been shown, other explanations for vasculitis related to COVID-19 are needed.

Future directions and conclusions

We have highlighted the distinct patterns of vasculitis, predominantly related to cutaneous and coronary arteries, that might occur in patients with COVID-19 in association with mild or absent lung infection. We point out how immunothrombosis of the pulmonary venular territory could be an unrecognised lung-centric source for embolism and how this thrombosis is especially relevant to diseases of organs with large cardiac output, including the brain and kidneys (table 2).

The extent to which escape of SARS-CoV-2 virions from the lung and intravascular immunothromboses, due to innate immune activation or direct endothelial cell infection, takes place is unclear. However, it is worth noting that SARS-CoV-2 RNAaemia is largely restricted to the most severely ill patients with COVID-19 and is not

Search strategy and selection criteria

We searched PubMed using the search terms "COVID-19", "SARS-CoV-2", and "vasculitis", "vasculitis-like", "endotheliitis", "vasculitic changes", and "Kawasaki disease". We also searched for "D-dimer", "fibrinogen", "creatine kinase", "CK", and "troponin", and reviewed publications that reported data on these parameters. We also searched for articles on immunothrombosis and embolisation. We limited our search to articles that were published in English between Dec 22, 2019, and Oct 20, 2020.

universal even in that setting, pointing towards other mechanisms of thromboembolic disease that might originate in the lungs.[97] Viral infection in other settings might predispose patients to thromboembolism in several ways, with infections such as dengue virus and Ebola virus doing so by direct intravascular infection and coagulation cascade activation, which have distinctive haemorrhagic phenotypes.[97] Future studies are needed to establish to what extent thrombosis in situ, as a result of dissemination of viral RNA, might take place in organs distant from the lungs, triggering thrombotic pathology independently to pulmonary venular territory embolism.

The immunothrombosis that is evident on pathological assessment of small pulmonary vein tributaries in patients with COVID-19 is beyond the capabilities of sophisticated modern imaging.[2] However, the reported pattern of lesions identified by imaging and pathology in antegrade territories (eg, brain and skin) and retrograde territories (eg, subpleural vessel dilation and tortuosity) supports the idea that the pulmonary venous vasculature network is a potential source of embolisation. Further research, which potentially includes left heart catheterisation, access to the pulmonary vein, and the imaging and sampling of blood content from this region, could greatly increase the understanding of this pathological process. This large pulmonary vascular territory is hidden to current imaging techniques and could also be an important player in encephalopathy induced by lung sepsis,[98] which pre-dates the COVID-19 pandemic. Likewise, pathological studies specifically looking at large branch pulmonary veins are needed. Such immunothromboses could result in clot reorganisation and vessel wall remodelling, both of which are well reported from post-mortem tissue from the SARS epidemic.[99] These consequences could lead to long-term pulmonary veno-occlusive disease, terminology that was originally coined in relation to pulmonary hypertension following viral pneumonia, whereby the link between infection and pulmonary veno-occlusive disease is still considered to be strong.[100] The extent to which small calibre pulmonary venules contribute to such a vasculitis mimic in patients with COVID-19 awaits full definition, but might be an overlooked mechanism of multiple extrapulmonary pathologies, including acute and chronic neurological sequelae.

Contributors

DM and JFMM developed the initial concepts for this Viewpoint. All authors contributed to first draft writing, the literature review, critical revision, and editing. All authors have participated sufficiently in this work, take public responsibility for the content, and have made substantial contributions to this research.

Declaration of interests

AVR reports consultancy fees or speaker fees from Eli Lilly, Novartis, Union Chimique Belge, Sobi, Roche, Pfizer, and Abbvie, outside of the submitted work. All other authors declare no competing interests.

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