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COVID-19 lung disease is a pulmonary vasculopathy

We read with interest the review by Bailey and Copley titled – *CT features of acute COVID-19 and long-term follow-up* – published in the January 2024 issue of *Clinical Radiology*.[1]

Introduction

The authors discuss the role of computed tomography (CT) in understanding the pathology of COVID-19 in view of histological findings. This is a refreshing approach, as much of the radiology literature has focused solely on diagnostic features without reference to histology. We write to draw together important points made by the authors regarding the underlying pathophysiology of COVID-19 as determined by imaging, and to offer additional perspectives.

Although the review discusses the many vascular characteristics of lung disease in acute COVID-19, the approach taken is in line with a conventional view that the disease is a respiratory pneumonia, which may or may not be complicated by vasculocentric pathology. We propose that the radiological and histological vasculopathic features are so dominant that the disease is more accurately considered primarily as a small-vessel pulmonary vasculopathy, rather than an inflammatory disease of the airways, which may be only secondarily complicated by vascular phenomena. This model of pathogenesis is evidenced by the dominant macroscopic vascular distribution and characteristic vascular phenomena visible radiologically and by correlation with histological microangiopathic processes.

Vascular distribution and characteristics

The lung damage caused by COVID-19 characteristically results in bilateral and symmetrical pattern of ground glass opacities or consolidation, which is predominantly peripheral and posterior in distribution.[2,3] This pattern correlates with the typical distribution of vascular pathological processes in other lung diseases.[4]

The distinct vasculocentric phenomena visible in COVID-19 lung disease also indicate underlying vasculopathic processes. The term 'pulmonary emboli' is used throughout the review. In light of the autopsy features of immunothrombosis and microangiopathic endothelial damage – entities that drive the disease in COVID-19[5–7] – the term 'pulmonary emboli' is misleading. It implies the thrombi have arrived from outside the lungs, as in the majority of cases of conventional deep-vein-thrombosis-driven emboli, rather than by thrombosis forming *in situ* within the lungs themselves. As correctly highlighted by the review, the microthrombotic *in situ* processes of immunothrombosis represent a different pathophysiological mechanism from conventional thromboembolic disease. Aligning with this, the study of CT pulmonary angiography (CTPA) findings in acute COVID-19 by van Dam *et al.* demonstrated a more distal distribution of macroscopic thrombi compared with non-COVID-19 patients.[8] Also, dual energy CT (DECT) studies proved perfusion defects to be unrelated to the presence or absence of macroscopic filling defects.[7] Indeed, pulmonary microvascular obstruction with perfusion defects, with thromboinflammatory processes, without macroscopic thromboembolism, was described as early as April 2020.[9] Optical Coherence tomography also shows microscopic distal pulmonary arterial thrombosis regardless of the presence or absence of macrothrombotic clots visible on conventional CTPA.[10] Lastly, there is no classic relationship with deep vein thrombosis.[11] From these findings, the visible lung damage evidently represents intrinsic vasculopathic processes, regardless of the presence or absence of macroscopic filling defects on CTPA, and the development from microthrombosis to macrothrombosis depends on the development and stage of the *in situ* procoagulant microangiopathy.

The review mentions *reverse halo* as a sign of organizing pneumonia in the context of COVID-19 lung disease. It is important to recognize that this sign can result from pulmonary infarction.[12,13] It should be emphasized that organizing pneumonia itself also arises from pulmonary infarction in any context.[14,15]

As COVID-19 lung disease develops, the vascular phenomenon of aberrant angiogenesis is identified by

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hierarchical phase-contrast tomography as a primary life-limiting pathology. This angiogenesis generates intrapulmonary arteriovenous shunting by the bronchial circulation with the formation of 'Sperrarterien' (specialized, spiral-like intrapulmonary arteriovenous anastomoses recruited by hypoxia and flow irregularities).[16]

Airways

As well as acknowledging the dominant vascular entities, it is also important to recognize the lack of airways inflammation. The lung disease of COVID-19 is devoid of airways inflammation to the point that its presence should be considered inconsistent with the diagnosis.[17] Comparisons of the CT features of COVID-19 versus those of influenza report significant differences in the appearance of the airways. In COVID-19 there is a distinct lack of bronchial wall thickening and tree-in-bud opacification of the airways.[18]

The review refers to the non-specific nature of ground glass opacities resulting from alveoli partially collapsing or partially filling with fluid. However, the filling of the alveoli should neither be assumed to be due to fluid filling nor the result of a pathological process which primarily affects the airways. It is important to acknowledge that ground glass opacities are found in non-airway-centric pathologies, such as *in situ* pulmonary vascular congestion due to microthrombotic phenomena, as well as pulmonary oedema and pulmonary hemorrhage.[2,9] Importantly, hierarchical phase-contrast tomography demonstrates well-preserved alveolar structure, but with alveolar obstruction due to the presence of thrombi.[19]

The current review uses the terms *pneumonia* and *pneumonitis* interchangeably, favoring *pneumonitis* toward the end. The term *pneumonia*, which has been used widely in the COVID-19 literature, means nothing more or less than *lung disease*, so it is too general and can mistakenly imply inflammation originating within the airways. The term *pneumonitis* seems an improvement because it implies an inflammatory process, but it does not implicate the vascular compartment, or refer to pulmonary vascular phenomena. The available evidence frames the vascular structures as the primary site of systemic disease in COVID-19. The review supports important evidence for such a primary vascular focus without addressing the pathogenesis necessary for accurate image interpretation. Terminology, which refers to the primary vascular pathology, as demonstrated by various imaging modalities, such as *pulmonary vasculopathy,* or *pulmonary thrombotic microangiopathy*, is required to more accurately describe the lung disease of COVID-19.[7,20]

Correlation of radiology and histology

The primacy of the vascular pathogenesis visible radiologically becomes even more apparent in light of histological features.

The review mentions the 'vascular enlargement sign', specifically referring to enlargement of distal subpleural arteries, and the 'vascular tree-in-bud' sign, a distinct feature of COVID-19 lung disease.[9,20–22] As the authors state, these phenomena are thought to relate to the histological entity of microvascular thrombosis – or immunothrombosis (inflammatory-mediated *in situ* clotting).[20] Indeed, the histological literature highlights that thrombosis at the capillary level is a dominant histological feature and is identified as a universal finding on autopsy.[23]

As stated in the review, the visible findings of COVID-19 on CT correlate with histological diffuse alveolar damage (DAD) and acute respiratory distress syndrome (ARDS). However, it is important to acknowledge that neither DAD nor ARDS are considered typical in the setting of acute COVID-19 and relate to fibrin deposition and immunothrombosis.[6,24,25] Also, the histological finding of DAD does not necessarily implicate airway pathology as a primary event. By definition, DAD is manifested by injury to *both* the alveolar lining *and* endothelial cells resulting from reduced oxygen tension of any cause.[26] This definition encompasses vasculocentric pathology with endothelial damage as a primary insult explaining the radiological features of COVID-19, instead of being secondary to an airway insult. Importantly, endothelial damage is widely considered the central process to the underlying pathogenesis of COVID-19, both in the lungs and elsewhere in the body, and both in the acute and post-acute phases.[5,27–31] The initial pulmonary symptoms can be explained by a prothrombotic syndrome with endotheliitis at the level of the alveolar capillaries.[5,27,32] If microthrombus formation is not stopped by timely treatment, the vasculopathy will develop into arterial and venous macrothrombosis.[32] This explains the high percentage of patients with arterial pulmonary thrombi visible on imaging in late stage COVID-19 disease in combination with low percentages of deep vein thrombosis in the same patient population.[11,32]

The direct correlation of imaging and histology shows microvascular alterations to be key pathophysiological drivers.[33,34] Notably, microvascular damage and thrombosis are found on autopsy even in areas that were radiologically normal on pre-mortem CT, thus implicating vascular changes leading to DAD.[34]

Furthermore, the distribution of SARS-CoV-2 infection in the lungs, as described histologically with topological correlation, shows that the upper lobes are typically not infected.[35] Conversely, the lower lobes, which are highly damaged, contain high viral loads.[35] This distribution of infection is both aligned with the vascular distribution in other pulmonary pathologies[4], and contrary to the pattern seen in pulmonary pathologies caused by inhaled pathogens.[36]

Long COVID

In consideration of post-acute COVID-19 it is important to highlight persistent vasculocentric imaging phenomena in people with the respiratory symptoms of long COVID. In this context, Xenon MRI studies demonstrate failure of gas transfer, implicating thrombosis of the alveolar capillaries in distinction from airway disease.[37–40] Dual energy CT

(DECT) studies of patients previously hospitalized with COVID-19 demonstrate a persistent microangiopathy. At 6 months, 7.5% had persistent macroscopic clots on the CTPA element of the DECT, and 87% of patients had persistent perfusion defects in the lungs on the iodine map. Some patients with perfusion defects had no residual lung damage visible with CT.[41] Importantly, in the setting of respiratory symptoms of long COVID, the benefits of perfusion-based imaging has been highlighted, regardless of the severity of the acute-phase disease.[42] It is also important to view these persistent vasculopathic phenomena visible radiologically in light of findings of persistent endothelial damage[30,31] and persistent fibrinaloid microscopic thrombi in the context of long COVID patients.[43,44] All features converge on a persistent microangiopathic pathology.

Variants

The review does not mention the time period in which the image examples were obtained. It is important to acknowledge that the morphological features of COVID-19 lung disease visible radiologically have changed over time. This change is dependent on viral variants with a distinction reported between Omicron compared to pre-Omicron variants – Omicron causing less vasculopathic phenomena compared with patients infected with the Delta variant, and Omicron, causing more bronchocentric and less severe disease.[45,46] Importantly, these distinctions are independent of vaccination status.[45] Such morphological differences also align with data demonstrating Omicron to be a less hypercoagulopathic variant.[47] This explains why vascular damage to the lungs in the context of acute COVID-19 is now a rarity, in our current experience only occurring in immunocompromised patients.

Intravascular delivery concept

Drawing together the observations highlighted in the review, we propose that the combined radiological and histological distribution of vasculocentric lung damage implicate primary vasculopathic processes. We conclude that these processes were driven by direct viral entry into the pulmonary vasculature via an intravascular route from the upper respiratory tract (the nasal and oral cavities) in the pre-Omicron SARS-CoV-2 variants.[48–50] Although both epithelial cells and endothelial cells were infected by pre-Omicron variants, it was the consequence of endothelial cell interaction (either infection or cell surface interaction) and subsequent damage, which were responsible for the lung disease.[5,28] Thus, we propose that the intravascular distribution of the virus accounts for the vascular distribution and characteristics visible radiologically and evidenced histologically.

Finally, on the basis of a more complete understanding of the vasculopathic phenomena evidenced radiologically and histologically, we consider the terms *pulmonary embolism*, *pneumonia* and *vascular complications* as fundamentally misleading and unhelpful in the description of the lung disease of acute COVID-19. In preference, the more accurate terminology for *primary pulmonary vasculopathy* or *pulmonary thrombotic microangiopathy* should be used in recognition of the endothelial damage and *in situ* inflammatory-mediated thrombosis at the core of the disease.

We thank the authors for their contribution and submit this response in the hope of offering a conceptual advance regarding the pathogenesis of COVID-19 lung disease.

Author contribution

GLJ – Contributed substantially by drafting, critically revising, adding important intellectual content and editing the correspondence.

RA – Contributed substantially by critically revising and adding important intellectual content.

MO – Contributed substantially by critically revising and adding important intellectual content.

All authors approve wording of the submission, agree to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Graham Lloyd-Jones reports a relationship with FDI World Dental Federation that includes: travel reimbursement. Graham Lloyd-Jones reports a relationship with Radiology Masterclass that includes: board membership. Graham Lloyd-Jones is an advisory board member for Long COVID support (patient led charity). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Bailey S, Copley SJ. CT features of acute COVID-19 and long-term follow-up. *Clin Radiol* 2024;**79**:1–9.
2. Shi H, Han X, Jiang N, *et al*. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;**20**:425. 343.
3. Haseli S, Khalili N, Bakhshayeshkaram M, *et al*. Lobar distribution of COVID-19 pneumonia based on chest computed tomography findings; A retrospective study. *Arch Acad Emerg Med* 2020;**8**:e55.
4. Nemec SF, Bankier AA, Eisnberg RL. Lower lobe-predominant diseases of the lung. *Am Roentgenol* 2013;**200**:712–28.
5. Ackermann M, Verleden S, Kuehnel M, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Eng J Med* 2020;**383**:120–8.
6. Nicolai L, Leunig A, Brambs S, *et al*. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. *Circ* 2020;**142**:1176–89.
7. Ridge CA, Desai S, Jeyin N, *et al*. Dual-energy CT pulmonary angiography quantifies vasculopathy in severe COVID-19 pneumonia. *Radiol Cardiothorac Imaging* 2020;**2**.
8. Van Dam LF, Kroft LJM, van der Wal LI, *et al*. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary

embolism: a different phenotype of thrombotic disease? *Thromb Res* 2020;**193**:86e9.
9. Oudkerk M, Büller HR, Kuijpers D, *et al*. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19. *Radiol* 2020;**297**:E216–22.
10. Hajjar LA, Ancona MB, Filho RK, *et al*. Microvascular lung vessels obstructive thromboinflammatory syndrome in patients with COVID-19: insights from lung intravascular optical coherence tomography. *Front Med* 2023;**10**.
11. Li M, Xiao L, Cai J, *et al*. Absence of a causal link between COVID-19 and deep vein thrombosis: insights from a bi-directional Mendelian randomisation study. *J Glob Health* 2024;**14**:05001.
12. Godoy MCB, Viswanathan C, Marchiori E, *et al*. The reversed halo sign: update and differential diagnosis. *Br J Radio* 2012;**85**:1226–35.
13. Schueremans T, Versavel M, Dubbeldam A. The reversed halo sign in pulmonary infarction due to acute pulmonary embolism. *J Belg Soc Radiol* 2023;**107**:71.
14. Baque-Juston M, Pellegrin A, Leroy S, *et al*. Organizing pneumonia: what is it? A conceptual approach and pictorial review. *Diagn Interv Imaging* 2014;**95**:771–7.
15. Akyıl FT, Ağca M, Mısırlıoğlu A, *et al*. Organizing pneumonia as a histopathological term. *Turk Thorac J* 2017;**18**:82–7.
16. Ackermann M, Tafforeau P, Wagner W, *et al*. The bronchial circulation in COVID-19 pneumonia. *Am J Respir Crit Med* 2021;**205**:121–5.
17. Ufuk and SAVAŞ. Chest CT features of the novel coronavirus disease (COVID-19). *Turk J Med Sci* 2020;**50**:664–78.
18. Shuai W, Chen X, Shan Y, *et al*. Clinical characteristics and CT findings in 148 non-COVID-19 influenza-like illness cases: a retrospective control study. *Front Public Health* 2021;**9**.
19. Walsh CL, Tafforeau P, Wagner WL, *et al*. Imaging intact human organs with local resolution of cellular structures using hierarchical phase-contrast tomography. *Nat Methods* 2021;**18**:1532–41.
20. Patel BV, Arachchillage D, Ridge CA, *et al*. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Care Med* 2020;**202**:690–9.
21. Lang M, Som A, Carey D, *et al*. Pulmonary vascular manifestations of COVID-19 pneumonia. *Radiol Cardiothorac Imaging* 2020;**2**.
22. Eddy RL, Sin DD. Computed tomography vascular tree-in-bud: a novel prognostic imaging biomarker in COVID-19? *Am J Respir Crit Care Med* 2020;**202**:642–4.
23. Carsana L, Sonzogni A, Nasr A, *et al*. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;**20**:1135–40.
24. Copin MC, Parmentier E, Duburcq T, *et al*. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. *Intensive Care Med* 2020;**46**:1124–6.
25. Gatinoni L, Coppola S, Cressoni M, *et al*. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;**201**:1299–300.
26. Katzenstein AL, Bloor CM, Leibow AA. Iffuse alveolar damage–the role of oxygen, shock, and related factors. A review. *Am J Pathol* 1976;**85**:209–28.
27. Huertas A, Montani D, Savale L, *et al*. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19). *Eur Respir J* 2020;**56**.
28. Varga Z, Flammer A, Steiger P, *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;**395**.
29. Zhang J, Tecson KM, McCullough PA. Endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. *Rev Cardiovasc Med* 2020;**21**:315–9.
30. Fogarty H, Ward S, Townsend L, *et al*. Sustained VWF-ADAMTS-13 axis imbalance and endotheliopathy in long COVID syndrome is related to immune dysfunction. *J Thromb Haemost* 2022;**20**:2429–38.
31. Turner S, Naidoo CA, Usher T, *et al*. Increased levels of inflammatory and endothelial biomarkers in blood of long COVID patients point to thrombotic endothelialitis. *Semin Thromb Hemost* 2024;**50**:288–94.
32. Oudkerk M, Kuijpers D, Oudkerk SF, *et al*. The vascular nature of COVID-19. *Br J Radiol* 2020;**93**.
33. Henkel M, Weikert T, Marston K, *et al*. Lethal COVID-19: radiologicepathologic correlation of the lungs. *Radiol Cardiothorac Imaging* 2020;**2**:e200406.
34. Kianzad A, Meijboom LJ, Nossent EJ, *et al*. COVID-19: histopathological correlates of imaging patterns on chest computed tomography. *Respirology* 2021;**26**:869e77.
35. Deinhardt-Emmer S, Wittschieber D, Sanft J, *et al*. Early postmortem mapping of SARS-CoV-2 RNA in patients with COVID-19 and the correlation with tissue damage. *Elife* 2021;**10**.
36. Nemec SF, Bankier AA, Eisenberg RL. Upper lobe—predominant diseases of the lung. *Am J Roentgenol* 2013;**200**:222–37.
37. Saunders LC, Guilhem CJ, Chan H-F, *et al*. Longitudinal lung function assessment of patients hospitalized with COVID-19 using 1H and 129Xe Lung MRI. *Chest* 2023;**164**:700–16.
38. Li H, Zhao X, Wang Y, *et al*. Damaged lung gas exchange function of discharged COVID-19 patients detected by hyperpolarized 129Xe MRI. *Sci Adv* 2021;**7**.
39. Grist JT, Chen M, Collier GJ, *et al*. Hyperpolarized 129Xe MRI abnormalities in dyspneic participants 3 months after COVID-19 pneumonia: preliminary results. *Radiol* 2021;**301**.
40. Matheson AM, McIntosh MJ, Kooner HK, *et al*. Persistent 129Xe MRI pulmonary and CT vascular abnormalities in symptomatic individuals with post-acute COVID-19 syndrome. *Radiol* 2022;**305**.
41. Mohamed I, Broucker VD, Duhamel A, *et al*. Pulmonary circulation abnormalities in post-acute COVID-19 syndrome: dual-energy CT angiographic findings in 79 patients. *Eur Radiol* 2023;**33**:4700–12.
42. Dhawan RT, Gopalan D, Howard L, *et al*. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. *Lancet Respir Med* 2020;**9**:107–16.
43. Turner S, Khan MA, Putrino D, *et al*. Long COVID: pathophysiological factors and abnormalities of coagulation. *Trends Endocrinol Metab* 2023;**3496**:321–44.
44. Nunes JM, Kruger A, Proal A, *et al*. The occurrence of hyperactivated platelets and fibrinaloid microclots in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Pharmaceuticals* 2022;**15**:931.
45. Tsakok MT, Watson RA, Saujani SJ, *et al*. Reduction in chest CT severity and improved hospital outcomes in SARS-CoV-2 Omicron compared with Delta variant infection. *Radiol* 2022;**305**.
46. Ito N, Kitahara Y, Miwata K, *et al*. Comparison of COVID-19 pneumonia during the SARS-CoV-2 Omicron wave and the previous non-Omicron wave in a single facility. *Respir Investig* 2022;**60**:772–8.
47. Grobbelaar LM, Kruger A, Venter, *et al*. Relative hypercoagulopathy of the SARS-CoV-2 beta and Delta variants when compared to the less severe Omicron variants is related to TEG parameters, the extent of fibrin amyloid microclots, and the severity of clinical illness. *Semin Thromb Hemost* 2022;**48**:858–68.
48. Lloyd-Jones G, Oudkerk M. COVID-19: angiotensin II in development of lung immunothrombosis and vasculitis mimics. *Lancet Rheumatol* 2021;**3**:325–6.
49. Lloyd-Jones G, Molayem S, Pontes CC, *et al*. The COVID-19 pathway: a proposed oral-vascular-pulmonary route of SARS-CoV-2 infection and the importance of oral healthcare measures. *J Oral Med Dent Res* 2021;**2**:1–25.
50. Lloyd-Jones G, Pontes CC, Molayem S, *et al*. The oral-vascular-pulmonary infection route: a pathogenic mechanism linking oral health status to acute and post-acute COVID-19. *Curr Oral Health Rep* 2023;**10**:163–74.

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