Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 196 (2020) 559–560

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Demystifying pulmonary vascular complications in severe coronavirus disease-19 pneumonia (COVID-19) in the light of clinico-radiologic-pathologic correlation

Coronavirus disease-19 (COVID-19) has spread throughout the world after its emergence in Wuhan, China in December 2019. The disease is caused by a single-stranded RNA virus referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Ever since the outbreak of COVID-19, changes in small segmental or subsegmental pulmonary vessels were reported in 70–89% cases of COVID-19 pneumonia on non-contrast chest computed tomography (CT) in addition to the typical imaging findings of viral pneumonia like ground glass opacities (GGOs), crazy paving pattern and consolidation [1]. The novel imaging finding of small pulmonary vessel changes was variably described as “vessel enlargement or thickening”. This was believed to be a unique feature of COVID-19 pneumonia which had not been described earlier in any infectious disease setting. In the absence of histopathological data, it was speculated to occur due to three possible mechanisms in isolation or in varying combinations namely, cascading effect of proinflammatory cytokines, small pulmonary vessel thrombosis and infection induced secondary pulmonary vasculitis [1]. This intriguing feature of pulmonary vascular enlargement or thickening was thought to be contributory to respiratory failure in COVID-19 pneumonia.

The pulmonary post-mortem findings of diffuse alveolar damage (DAD) in COVID-19 cases fairly corroborate the earlier reported imaging features of GGOs or GGOs mixed with consolidations or acute respiratory distress syndrome (ARDS) in severe COVID-19 pneumonia [2–4].

The evidence emerging from autopsy studies attests to the previously reported imaging observation that small pulmonary vascular changes are a regular feature of severe COVID-19 pneumonia.

Ackermann M et.al reported that COVID-19 pneumonia is associated with three distinctive small pulmonary vascular changes on histopathology namely; [1] severe endothelialitis associated with intracellular viral particles and disrupted cell membranes, [2] widespread small pulmonary vascular thrombosis and, [3] new vessel formation (neoangiogensis). They also compared the autopsy findings in COVID-19 pneumonia with the patients who died of ARDS secondary to influenza (H1N1). A comparative histological analysis of small pulmonary arteries with a diameter of 1 mm to 2 mm showed widespread microthrombosis in patients with COVID-19. Small pulmonary arterial thrombi were 9 times as prevalent in patients with COVID-19 compared to the patients with influenza ($p < 0.001$). Additionally, it was observed that new vessel growth was 2.7 times more in COVID-19 pneumonia compared to the influenza pneumonia. Neoangiogensis occurs secondary to tissue hypoxia which indirectly reflects the greater degree of small pulmonary vessel thrombosis in COVID-19 [2].

In an autopsy study of 12 cases, Wichmann et al. could find the cause of death within the lungs or in the pulmonary vascular system in all the cases. They further observed that apart from major pulmonary vessel thrombosis in 4 cases, microthrombi were regularly found within the small pulmonary arteries [3].

Lax SF et.al in another autopsy study of 11 cases reported that segmental or subsegmental pulmonary arterial thrombosis was seen in all the cases with associated vessel wall inflammation and infraction of affected lung segments. This was found despite the fact that all cases had received thromboprophylaxis and none had a clinical suspicion of venous thrombosis antemortem [4].

The inflammed and thrombosed segmental or subsegmental pulmonary vessels demonstrated on lung autopsies seem to represent the imaging correlate of pulmonary vessel enlargement or thickening on chest CT.

To mitigate the risk of thrombosis in severe COVID-19 infections anticoagulant prophylaxis is recommended. Currently, the optimal approach to anticoagulant thromboprophylaxis in COVID-19 is uncertain. American College of Chest Physicians (ACCP) recommends the preferable use of low-molecular-weight heparin (LMWH) at standard doses (as per existing guidelines) as anticoagulant thromboprophylaxis in acutely ill hospitalized and critically-ill COVID-19 patients [5].

Interim clinical guidance from the anticoagulation forum recommends the use of standard dose of thromboprophylaxis for all non-critically ill hospitalized patients with confirmed or highly suspected COVID-19. However, for critically ill or ICU patients with confirmed or highly suspected COVID-19 increased doses of thromboprophylaxis (e.g., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous three times daily, or low-intensity heparin infusion) are recommended [6].

However, despite the use of standard prophylactic anticoagulation a high incidence of thrombotic complications in patients with COVID-19 infection have been reported by numerous recent studies.

In a scoping review of thrombosis risk in COVID-19, Al-Ani et al. analyzed various studies from different countries and concluded that the cumulative incidence of pulmonary thromboembolism (PTE) in the COVID-19 population is higher despite the use of routine thromboprophylaxis [7].

Klok et al. reported a remarkably high incidence (31%) of thrombotic complications including PTE and arterial thrombosis in ICU patients with COVID-19 infection despite the use of low molecular weight heparin thromboprophylaxis [8].

A French multicentre ICU study of 150 COVID-19 patients, demonstrated a 43% prevalence of thrombosis despite the use of prophylactic or therapeutic anticoagulation [9]. Thomas et.al observed a cumulative incidence of 27% and 4% of venous thromboembolism and arterial thrombosis, respectively in their cohort despite the patients receiving prophylactic heparin [10].

van Dam et al. reported that PE phenotype in patients with COVID-19 is different from PE patients without COVID-19 pneumonia. Profound small pulmonary vessel thrombosis, involvement of the peripheral arteries of the lung as reported by this study supports in-situ

https://doi.org/10.1016/j.thromres.2020.06.043
Received 1 June 2020; Received in revised form 21 June 2020; Accepted 24 June 2020
Available online 27 June 2020

immunothrombosis as a contributory pathophysiological mechanism for increased risk of thrombosis in COVID-19 [11].

Desborough et al. found an imaging-proven thrombosis rate of 15% in severe COVID-19 patients. Among these patients with thrombosis only 5% were not thought to be due to immunothrombosis [12].

In contrast, Tang et.al reported a significantly higher D-dimer and fibrin degradation product levels in the non-survivors of COVID-19 pneumonia compared to survivors suggesting that coagulation abnormalities are associated with poor prognosis. This possibly points to a globally increased coagulation activation and thus argues against immunothrombosis as the sole underlying pathophysiological mechanism of thrombosis in COVID-19 [13].

In light of these rapidly emerging corroborative clinical, radiological and pathological data, suggesting a remarkably high prevalence of thrombotic events in COVID-19 pneumonia with frequent pulmonary vascular involvement, it seems plausible to search for other contributory or additive pathophysiological mechanisms in addition to the coagulation dysfunction to account for the high incidence of thrombotic events in severe COVID-19.

The histological finding of widespread pulmonary microvascular thrombosis suggests that not all PTE in COVID-19 are “embolic” in nature and it is reasonably possible that in-situ pulmonary vascular thrombosis (immunothrombosis) contributes to a significant proportion of PTE cases. This notion is further strengthened by the increasingly reported occurrence of higher PTE events in severe COVID-19 despite the use of guideline-recommended thromboprophylaxis.

This emerging hypothesis that not all pulmonary thrombotic events in COVID-19 are embolic could have major therapeutic implications. Overabundant inflammatory response in patients with severe COVID-19 infection associated with severe endothelialitis possibly increases the likelihood of thromboembolic disease and in turn explains the high frequency of PTE. SARS-CoV-2 recruits angiotensin converting enzyme 2 (ACE2) receptors expressed by the endothelial cells and cause endothelial injury which is indicated by the elevated levels of von Willebrand factor (vWF) and Factor VIII in COVID-19. This raises a pertinent query of whether focusing on anticoagulation alone is the right approach to reduce the thrombotic risk in COVID-19 patients. This approach of “anticoagulation alone” may not address all events of thrombosis and also treating all patients with higher doses of anticoagulants may be counterproductive as it increases bleeding complications.

In-situ immunothrombosis, a consequence of severe endothelialitis accelerated by the severe inflammatory response in the background of a procoagulant environment seems to be a contributory pathophysiological mechanism for the high incidence of thrombotic complications in COVID-19. The vascular endothelium is essential for the maintenance of vascular homoeostasis. COVID-19-endotheliitis could explain the microcirculatory dysfunction in different vascular beds and their resultant clinical consequences in patients with COVID-19. The mounting evidence emanating from imaging, histopathological and clinical data suggesting in-situ immunothrombosis as a contributory pathophysiological mechanism for the high rate of thrombotic complications in COVID-19 pneumonia will open alternative targets of therapy to cut down the risk of thrombosis in COVID-19. Targeting inflammation in conjunction with stabilizing the endothelium and rational anticoagulant management might be a preferable approach to lower the thrombotic risk in severe COVID-19.

References

[1] A.H. Parry, A.H. Wani, Segmental pulmonary vascular changes in COVID-19 pneumonia, American Journal of Roentgenology (2020) May 8:W1-.

[2] M. Ackermann, S.E. Verleden, M. Kuehnel, A. Haverich, T. Welte, F. Laenger, A. Vanstapel, C. Werlein, H. Stark, A. Tzankov, W.W. Li, Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 21 (2020 May).

[3] D. Wichmann, J.P. Sperhake, M. Lütgehetmann, S. Steurer, C. Edler, A. Heinemann, F. Heinrich, H. Mushumba, I. Kniep, A.S. Schröder, C. Burdelski, Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study, Ann. Intern. Med. 6 (2020 May).

[4] S.F. Lax, K. Skok, P. Zechner, H.H. Kessler, N. Kaufmann, C. Koelblinger, K. Vander, U. Bargfrieder, M. Trauner, Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series, Ann. Intern. Med. 14 (2020 May).

[5] L.K. Moores, T. Tritschler, S. Brosnahan, M. Carrier, J.F. Collen, K. Doerschug, A.B. Holley, D. Jimenez, G. LeGal, P. Rali, P. Wells, Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report, Chest. 2 (2020 Jun).

[6] G.D. Barnes, A. Burnett, A. Allen, M. Blumenstein, N.P. Clark, A. Cuker, W.E. Dager, S.B. Deitelzweig, S. Ellsworth, D. Garcia, S. Kaatz, Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum, J. Thromb. Thrombolysis 21 (2020 May) 1.

[7] F. Al-Ani, S. Chehade, A. Lazo-Langner, Thrombosis risk associated with COVID-19 infection. A scoping review, Thrombosis Research (2020 May 27).

[8] F.A. Klok, M.J. Kruip, N.J. Van der Meer, M.S. Arbous, D.A. Gommers, K.M. Kant, F.H. Kaptein, J. van Paassen, M.A. Stals, M.V. Huisman, H. Endeman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 10 (2020 Apr).

[9] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 May 4:1–0.

[10] W. Thomas, J. Varley, A. Johnston, E. Symington, M. Robinson, K. Sheares, A. Lavinio, M. Besser, Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom, Thromb. Res. 191 (2020 Jul 1) 76–77.

[11] L.F. van Dam, L.J. Kroft, L.I. van der Wal, S.C. Cannegieter, J. Eikenboom, E. de Jonge, M.V. Huisman, F.A. Klok, Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: a different phenotype of thrombotic disease? Thromb. Res. 6 (2020 Jun).

[12] M.J. Desborough, A.J. Doyle, A. Griffiths, A. Retter, K.A. Breen, B.J. Hunt, Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom, Thromb. Res. 29 (2020 May).

[13] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. 18 (4) (2020 Apr) 844–847.

Arshed Hussain Parry[a,*], Abdul Haseeb Wani[b], Mudasira Yaseen[c], Mohd Iqbal Dar[d]

[a] *Senior Resident, Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India*

[b] *Consultant, Department of Radiodiagnosis, Government Medical College, Srinagar, Jammu & Kashmir, India*

[c] *Senior Resident, Department of Anesthesiology and Critical Care Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India*

[d] *Senior Resident, Department of Cardiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India*

E-mail address: arshedparry@gmail.com (A.H. Parry).

[*] Corresponding author at: Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir 190011, India.