COVID-19 revolution: a new challenge for the internist

Vasculitis and COVID-19: what do we have to know?

Antonio Tamburello,[1] Laura Castelnovo,[1] Emanuele Bizzi,[2] Francesco Caso[3]

[1]Internal Medicine Operative Unit, ASST Ovest Milanese, Legnano Hospital, Legnano (MI); [2]Internal Medicine Operative Unit, San Pietro Fatebebefratelli Hospital, Rome; [3]Department of Clinical Medicine and Surgery, Federico II University of Naples, Italy

ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, *etc*.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with vasculitis and COVID-19.

Coronavirus infection disease 2019 (COVID-19) can lead to a hyperinflammatory syndrome with multi-organ involvement similar to the vasculitic syndrome.

Correspondence: Antonio Tamburello, Internal Medicine Operative Unit, ASST Ovest Milanese, Legnano Hospital, via Giovanni Paolo II, 20025 Legnano (MI), Italy.
Tel.: +39.0331449178.
E-mail: antonio.tamburello@asst-ovestmi.it

Key words: COVID-19; SARS-CoV-2; SARS-CoV-2 pneumonia; vasculitis.

Contributions: the authors contributed equally.

Conflict of interests: the author declares no potential conflict of interests.

This paper is part of a series of brief articles dealing with COVID-19 and Internal Medicine, coordinated and supervised by Dr. Roberto Nardi and Dr. Ombretta Para.

Received for publication: 5 August 2020.
Accepted for publication: 31 August 2020.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2020; 14:213-215
doi:10.4081/itjm.2020.1403

Further, vasculitic-like manifestations have been reported in several cases, and many COVID-19 findings [fever, fatigue, arthralgia, coagulopathy, leukopenia, lymphopenia, increased serum inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, and ferritin, ground-glass opacities (GGO) of the lung, or mixed GGO and consolidation] resemble aspects characterizing vasculitic syndromes.[1,2] Although the potential pathogenetic link between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vasculitis needs to be still clarified, the angiotensin-converting enzyme 2 (ACE-2), receptor, used by the virus for entering the cells, is also expressed at the level of the endothelium.[2,3] This peculiar way of entry of COVID-19 in human cells induces angiotensin II accumulation, and an angiotensin II excess may contribute to distinctive vascular features, consisting of severe endothelial injury and histologic findings of thrombosis with microangiopathy causing acute lung injury and vessel dysfunction with vasoconstriction, vascular permeability and myocardial remodeling.[4,5] Of note, it has also been described that SARS-CoV-2 can directly infect engineered human blood vessel organoids, which can be inhibited by human recombinant soluble ACE-2.[6] Varga *et al.* evidenced that endothelium inflammation and damage with impaired circulatory function represent key aspects of severe COVID-19.[7] Further, in COVID-19 pneumonia, the in-

filtration of monocytes/macrophages and lymphocytes, associated with alveolar septum vessels congestion and destruction, has been reported.[5,8,9] In addition, the cytokine storm triggered by SARS-CoV-2 has been considered as a key factor of vascular damage and endothelial dysfunction processes.[10] Finally, recent evidence from Di Micco's study group showed that fibrinogen seems to increase early in COVID-19 infection while there seems to be no evidence of an early and significant increase in polymerase chain reaction, partial thromboplastin time, activated partial thromboplastin time (aPTT), and platelets.[11] All the above pieces of evidence have been instrumental in spreading the sense that COVID-19 is associated with disseminated intravascular coagulation and the subsequent consumption coagulopathy, catastrophic antiphospholipid syndrome, and pulmonary embolism, characterized by increased D-dimer levels and fibrin degradation products, and mimicry of vasculitis.[10] In particular, high titer antiphospholipid antibodies, including anticardiolipin immunoglobulin (Ig)A antibodies as well as anti-β2-glycoprotein I IgA and IgG antibodies, have been detected in COVID-19 patients with severe thrombosis.[1] Further, the presence of a lupus anticoagulant may explain prolonged aPTT in COVID-19.[12] Intriguingly, thrombotic manifestations seem to arise as a significant question in severe COVID-19 patients, and upon antigen viral recognition, immune cells, endothelial cells, and platelets have been hypothesized as key factors in the modulation of pro- and anticoagulant pathways of COVID-19.[13-15] Moreover, it has been shown that heparin, besides its anticoagulant effects, also displays an anti-inflammatory action, immunomodulatory properties, and protects glycocalyx from shedding, overall helping to reduce mortality.[16] However, on the other hand, it seems that antithrombotic therapy, both antiplatelet or anticoagulant, does not show a protective effect in severe forms of COVID-19 pneumonia.[17]

From a clinical point of view, heterogenous vasculitic manifestations have been described in COVID-19 patients. These seem to be mainly represented by violaceous macules with '*porcelain-like'* appearance, livedo, purpura, eruptive cherry angioma, and cold urticarial. Acro-ischemia and chilblains can be concomitant. In several cases, other possible cutaneous manifestations, such as exanthema and chickenpox like vesicles, have also been described.[4,18] Recently, our group reported on signs of small blood vessel occlusion, with petechiae, tiny bruises, and transient livedoid eruptions, in two young patients with concomitant COVID-19 pneumonia. In the first case, we described widespread urticaria involving the thigh region and the perimalleolar area with spontaneous resolution in a few days; in the other one, a bilateral leg vasculitic purpura was followed by a fleeting erythematous rash. In both cases, itching was mild, and lesions healed in a few days with steroid therapy.[19] Despite, in contrast to adults with COVID-19, many young patients show milder disease: children seem to manifest an acute vasculitis meeting Kawasaki disease clinical criteria.[20,21] The Italian group of Bergamo recently described a 30-fold increased incidence of Kawasaki-like disease: children diagnosed after the SARS-CoV-2 epidemic were older, had a higher rate of cardiac involvement, and features of macrophage activating syndrome. A similar outbreak of Kawasaki-like disease is expected in all countries involved in the SARS-CoV-2 epidemic.[22,23]

Indeed, in recent years, evidence for a link between viral infections and different vasculitic syndromes is increasing. This is the case of hepatitis C virus-associated mixed cryoglobulinemia and hepatitis B virus-associated polyarteritis nodosa.[24] Viral infections are thought to be the cause of the vasculitis or trigger factors of an immunoinflammatory process of vasculitis, successively sustained by different intrinsic and extrinsic factors.[24] COVID-19 and vasculitis share common elements of the inflammatory mechanisms, and among those, the over-release of proinflammatory molecules also synthesized by endothelial cells. In particular, increased serum IL-6 levels correlate with a severe and multi-organ phenotype of the COVID-19,[1] and in the course of vasculitis, IL-6 plays a key role in the induction and maintenance of inflammation and oxidative stress of the vessel wall.[25,26] Of note, the humanized anti-human IL-6 receptor antibody, tocilizumab, is successfully used for vasculitis treatment[27] and represents a therapeutic strategy for suppressing the COVID-19 cytokine storm.[28] Until today, it remains unclear whether SARS-CoV-2 could act as a triggering factor for the development of an immune-inflammatory dysregulation leading to a vasculitic syndrome; all the actual findings are consistent with the demonstrated close connection between thrombosis and inflammation, processes that mutually reinforce each other but much remains to be understood for better characterizing the vascular involvement in COVID-19. However, despite still limited evidence, shared clinical aspects between COVID-19 and vasculitic syndromes could address further investigations on vascular inflammatory involvement occurring in COVID-19.[28,29]

References

1. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020 [Epub ahead of print, doi: 10.1056/NEJMc2007575].
2. Li C, Xu BH. The viral, epidemiologic, clinical characteristics and potential therapy options for COVID-19: a review. Eur Rev Med Pharmacol Sci 2020;24:4576-84.
3. Ferrario CM, Jessup J, Chappell MC. Effect of an-

giotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.
4. Bouaziz JD, Duong T, Jachiet M, et al. Vascular skin symptoms in COVID-19: a French observational study. J Eur Acad Dermatol Venereol 2020 Apr 27 [Epub ahead of print, doi: 10.1111/jdv.16544].
5. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020 May 21 [Epub ahead of print, doi:10.1056/NEJMoa2015432].
6. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical - grade soluble human ACE2. Cell 2020 [Epub ahead of print, doi: 10.1016/j.cell.2020.04.004].
7. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020 Apr 20 [Epub ahead of print, doi: 10.1016/S0140-6736(20)30937-5].
8. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020 [Epub ahead of print, doi: 10.1016/S2213-2600(20)30076-X].
9. Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Chin J Pathol 2020;49 [Epub ahead of print, doi: 10.3760/cma.j.cn112151-20200312-00193].
10. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020 Apr 30 [Epub ahead of print, doi: 10.1093/cvr/cvaa106].
11. Di Micco P, Russo V, Carannante N, et al. Clotting factors in COVID-19: epidemiological association and prognostic values in different clinical presentations in an Italian cohort. J Clin Med 2020;9:E1371.
12. Bowles L, Platton S, Yartey N, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med 2020 May 5 [Epub ahead of print, doi: 10.1056/NEJMc2013656].
13. Atallah B, Mallah SI, AlMahmeed W. Anticoagulation in COVID-19. Eur Heart J Cardiovasc Pharmacother 2020 [Epub ahead of print, doi: 10.1093/ehjcvp/pvaa036].
14. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020 Apr 9;127:104362.
15. Raucci F, Mansour AA, Casillo GM, et al. Interleukin-17A (IL-17A), a key molecule of innate and adaptive immunity, and its potential involvement in COVID-19-related thrombotic and vascular mechanisms. Autoimmun Rev 2020 May 3:102572 [Epub ahead of print, doi: 10.1016/j.autrev.2020.102572].
16. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus 2020 Apr 8 [Epub ahead of print, doi:10.2450/2020.0083-20].
17. Russo V, Di Maio M, Attena E, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: A multicenter observational study. Pharmacol Res 2020;159:104965.
18. Zhang Y, Cao W, Xiao M, et al. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. Zhonghua Xue Ye Xue Za Zhi 2020;41:E006.
19. Castelnovo L, Capelli F, Tamburello A, et al. Symmetric cutaneous vasculitis in COVID-19 pneumonia. J Eur Acad Dermatol Venereol 2020 May 7 [Epub ahead of print, doi:10.1111/jdv.16589].
20. Scarpa R, Costa L, Del Puente A, Caso F. Role of thymopoiesis and inflamm-aging in COVID-18 phenotype. Pediatr Neonatol 2020 Apr 15 [Epub ahead of print, doi: 10.1016/j.pedneo.2020.04.001].
21. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr 2020 Apr 7 [Epub ahead of print, doi:10.1542/hpeds.2020-0123].
22. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020 May 13 [Epub ahead of print, https://doi.org/10.1016/ S0140-6736(20)31103-X].
23. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 7 [Epub ahead of print, doi: 10.1016/S0140-6736(20)31094-1].
24. Sharlala H, Adebajo A. Virus-induced vasculitis. Curr Rheumatol Rep 2008;10:449-52.
25. Yuan SM. Profiles and predictive values of interleukin-6 in aortic dissection: a review. Braz J Cardiovasc Surg 2019;34:596-604.
26. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317-28.
27. Klopfenstein T, Zayet S, Lohse A, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect 2020 May 6 [Epub ahead of print, doi: 10.1016/j.medmal.2020.05.001].
28. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020;395:1517-20.
29. Caso F, Costa L, Ruscitti P, et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun Rev 2020;19:102524.