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Aortic vulnerability to COVID-19: is the microvasculature of vasa vasorum a key factor? A case report and a review of the literature

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Abstract. – Arterial thromboembolic complications reported in patients with COVID-19 infection suggested that SARS-CoV-2 can trigger atherosclerotic plaque vulnerability. While endothelial cells in healthy subjects protect against thrombus formation, after injury they show prothrombotic activity. In addition, it has been hypothesized that "cytokine storm" might stimulate the production of neo-platelets triggering an abnormal "immunothrombosis" responsible for the hypercoagulable state induced in COVID-19 patients. The aim of this study is to report a case of severe COVID-19 infection characterized by the occurrence of microthrombosis in the vasa vasorum of the aorta.

A 67-year-old male patient, in good health status and without comorbidities, who underwent a severe COVID-19 infection with fatal outcome, showed scattered aortic atherosclerotic plaques, characterized by multiple occlusive micro-thromboses in the vasa vasorum, spread out lymphocytic infiltrates and foci of endotheliitis and endothelial detachment.

This case report confirms the previously described thrombotic involvement of vasa vasorum in COVID-19. The occurrence of the synchronous damage involving both the lumen surface (endothelial dysfunction, endotheliitis and endothelial detachment) and the adventitia (inflammation and occlusive thrombosis of vasa vasorum) could be the key points related to the fatal outcome of the SARS-CoV-2 patients. In our opinion, vasa vasorum thrombosis may thus initiate an atherogenic process that could be characterized by a much more rapid development.

Key Words:
Endotheliitis, COVID-19, SARS-CoV2, Thromboembolic complications, Atherosclerotic plaque.

Introduction

Arterial thromboembolic complications represent a common finding in COVID-19 infected patients[1] who show a disproportionately higher incidence of myocardial infarction and cerebral ischemic stroke[2-5]. Collectively, these data[6] suggest that SARS-CoV-2 could be able to trigger atherosclerotic plaque vulnerability. In spite of our better knowledge on the multiple molecular pathways triggered by COVID-19[7], the linkage between SARS-CoV-2 and the development of a pro-thrombotic phenotype has not been clarified yet.

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All the actions of the hemostatic system are aimed to maintain people distant from both Scylla (bleeding) and Charybdis (thrombosis)[8]. In healthy subjects, the hemostatic system is able to stop bleeding events by both platelets and the coagulation cascade activation. Moreover, the hemostatic system rules a delicate balance between avoiding fibrin formation and deposition within the normal blood vessels. Indeed, fibrinolysis represents a defensive mechanism, being able to remove fibrin from the endothelial cells. Fibrinolysis is in turn well balanced by a fine control of its inducers and inhibitors[9]. Finally, endothelial cells can produce substances, such as nitric oxide, prostacyclin and an ADP deactivation molecule, which maintain platelets distant from their layer thus avoiding their aggregation with consequent involvement in the thrombotic process[10]. Basically, endothelial cells in healthy subjects protect the host from thrombus formation, and they become strongly prothrombotic if a direct injury occurs.

Multiple bits of evidence[11,12] show that, in subjects affected by SARS-CoV-2, endothelium is under attack: lymphocytic endotheliitis and circulating endothelial cells, a typical marker of endothelial injury[13], have been reported following severe COVID-19 infection. Recently, it has been hypothesized that "cytokine storm" caused by SARS-CoV-2 might stimulate megakaryoblasts to produce neo-platelets, triggering an abnormal "immunothrombosis" responsible for the hypercoagulative state typical of COVID-19 infection[14].

Case Report

Here we report a case of a 67-year-old male patient, in good health status and without comorbidities, who underwent a severe COVID-19 infection, with fatal exitus for respiratory failure. Further clinical information is not publicly available because of the sensitive nature of the data; request to access that material from qualified researchers trained in human subject confidentiality protocols may be sent to D'Aloja at Cagliari University through the corresponding author. At autopsy, aorta showed the presence of scattered atherosclerotic plaques. Histology revealed the presence of multiple occlusive micro-thromboses in the vasa vasorum of the aortic wall (Figures 1 and 2). Moreover, lymphocytic infiltrates were observed around the wall of the aortic vasa vasorum (Figure 3). The study of the aortic endothelium in the correspondence of vasa vasorum microthrombi showed foci of endotheliitis (Figure 4) and endothelial detachment (Figures 2, 3 and 4).

Discussion

Our data confirm previous findings on the thrombotic involvement of vasa vasorum in COVID-19 patients[14] and suggest that aortic vasa vasorum thrombosis could represent a key factor which might link the severe forms of SARS-CoV-2 with the transformation of a stable plaque into an unstable lesion[6], with thromboembolic consequences.

All these data taken together support the hypothesis that the influence of SARS-CoV-2 on large vessels such as aorta is more complex than previously thought. The occurrence of virus attack on key targets may be hypothesized:

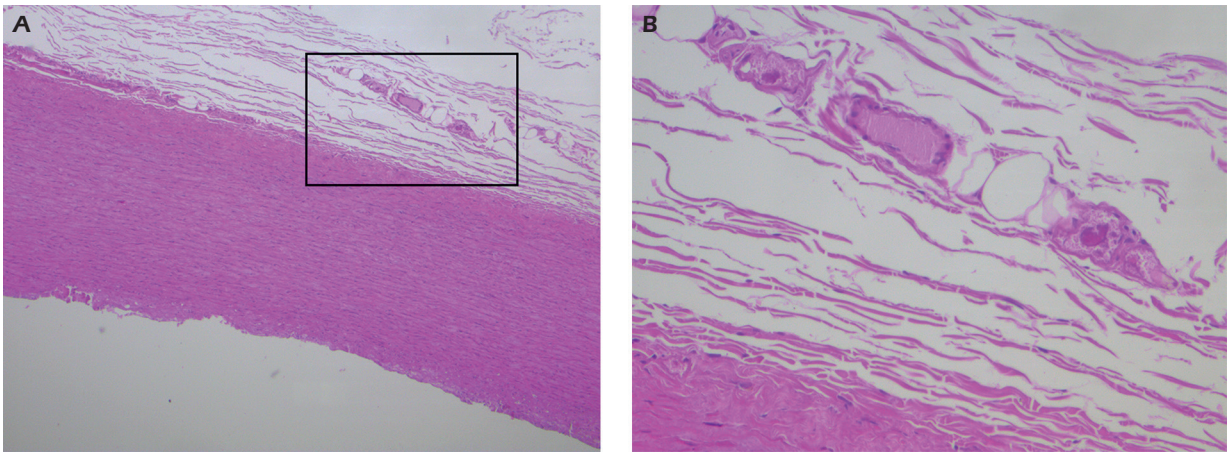

Figure 1. Full thickness of aortic wall at low power view (A original magnification 50×) showing occlusive micro-thromboses in the vasa vasorum at high power field (B original magnification 200×).

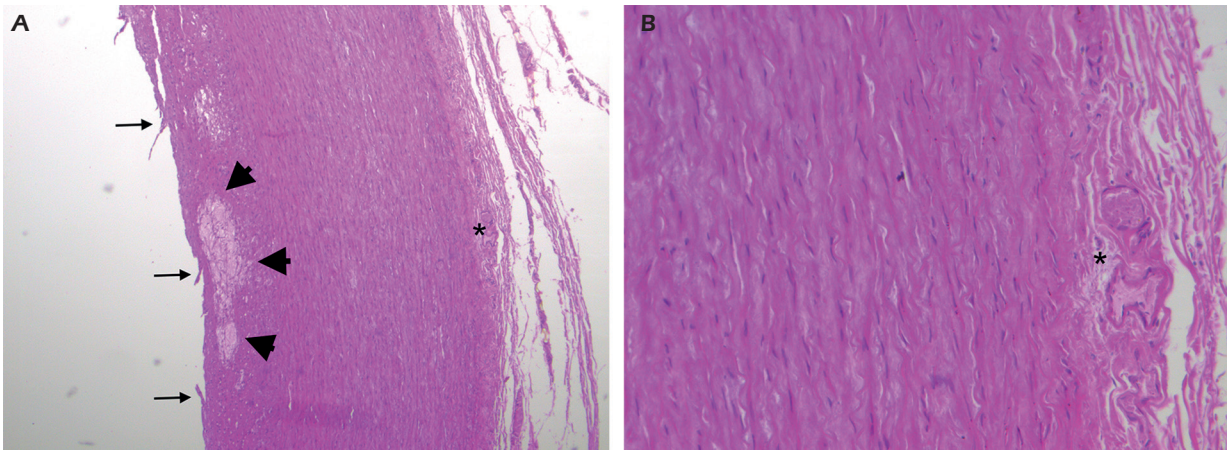

Figure 2. Full thickness of aortic wall at low power view showing endothelial detachment (*arrows*), plaque (*arrowheads*) occlusive micro-thromboses in the vasa vasorum (*)(A original magnification 50×); micro-thromboses of the vasa vasorum at high power filed(B original magnification 200×).

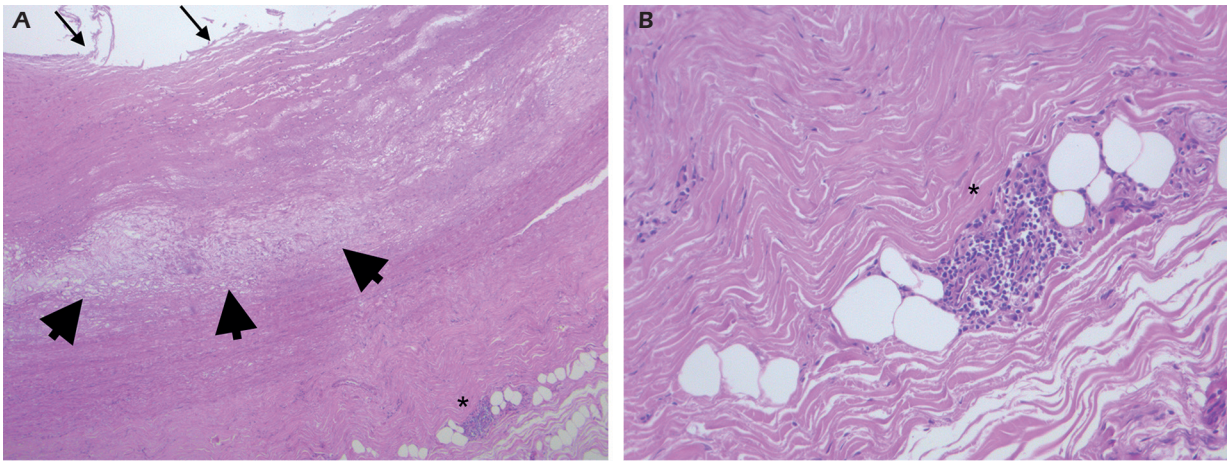

Figure 3. Aortic wall showing endothelial detachment (*arrows*), plaque (*arrowheads*) and lymphocytic infiltrates around vasa vasorum (A original magnification 50×); high power view of the lymphocytic infiltrates detected around vasa vasorum (B original magnification 200×).

at the lumen surface, COVID-19 might cause endothelial dysfunction, endotheliitis and endothelial detachment. However, in the adventitia, vasa vasorum are fired, with inflammation and occlusive thrombosis. This phenomenon may be responsible of the decrease of blood and nutrients that supply the arterial wall thus favoring all the pathological features described above. This statement is supported by an old experimental observation which demonstrated that the occlusion of vasa vasorum leads to the development of vascular lesions[15]. In SARS-CoV-2 patients, vasa vasorum thrombosis may initiate an atherogenic process[16] that could be much more rapid in development.

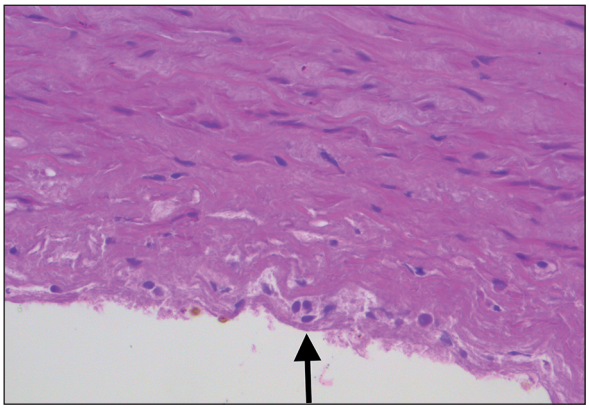

Figure 4. Foci of entotheliitis (*arrow)* in the aortic endothelium seen in correspondence of vasa vasorum microthrombi (original magnification 400×).

Conclusions

The thrombosis of the vasa vasorum should be taken into account in the pathophysiology of the COVID-19 infection as a crucial target of the virus in terms of arterial damage progression. The severe effects of COVID-19 infection in the vascular system could therefore be explained by a progressive multi-level injury, so suggesting that a unique therapeutical target might not be enough to control the effect of these virus attacks. A role of anti-platelet agents along with anticoagulation could be a further anti-thrombotic strategy but new well-planned trials are needed to confirm or not our hypothesis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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