Acute peripheral arterial thrombosis in COVID-19. Role of endothelial inflammation

Editor
COVID-19 (SARS-CoV-2 virus) emerged in Wuhan in December 2019 and became pandemic in March 2020. COVID-19 mainly affects the respiratory tract, from mild symptoms to acute respiratory distress syndrome. Due to a global inflammatory response and endothelial damage, COVID-19 may predispose to coagulation disorders that can lead to severe thrombotic events. Angiotensin-converting enzyme 2 receptors constitute the virus gateway expressed in the surface of respiratory tract, intestine, heart and vessels, particularly in the endothelial layer.

We report three patients with no history of peripheral arterial occlusive disease, admitted for severe COVID-19 with acute limb ischemia and femoropopliteal occlusion associated to intra-aortic thrombus. Anatomopathology of resected arterial segments disclosed inflammatory infiltrates and endothelial proliferation throughout the arterial wall.

**Case 1.**
A 63-year-old woman attended for acute right-leg ischemia. Angio-CT showed bilateral pneumonia, near-complete

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thrombosis of distal thoracic/proximal abdominal aorta and total occlusion of right popliteal artery (Fig. 1a, 1b). Angiogram confirmed popliteal and infrapopliteal occlusion, with no patent blood supply to the foot. Above-knee amputation was performed after unsuccessful endovascular treatment with mechanical percutaneous thrombectomy of popliteal artery, thrombolytic therapy and balloon angioplasty. Anatomopathology of arterial segments disclosed occlusive thrombosis with endothelial proliferation in thrombus and all layers of the vessel wall, myofibroblastic proliferation of the intima and collagen deposition in intima and media layers. Inflammatory infiltration of polymorphonuclear cells and macrophages were identified in the intima, with predominance of T-lymphocytes and histiocytes in media and adventitia (CD68, CD3 and CD34 immunostains) (Fig. 1c, 1d). Microabcesses of polymorphonuclear cells, histiocytic aggregates with epithelioid morphology and multinucleated giant cells were observed in the thrombus. SARS-CoV-2 (RT-PCR technique) was not detected in the arterial wall.

Case 2.

A 74-year-old female admitted for pneumonia and critical signs of acute lower limb ischaemia. Angio-CT showed partial thrombosis of thoracic aorta, pre-occlusive thrombosis in common iliac/hypogastric arteries and femoropopliteal occlusion with patent distal anterior tibial artery. Full-dose anticoagulation with low molecular weight heparin (LMWH) was administered. Complete clot resolultion of aortoiliac thrombosis was observed at 3 weeks with persisting femoropopliteal arterial occlusion. Femorotibial bypass with autologous vein was performed for clinical worsening with ischemic ulcers on right foot. Pathological study showed similar findings, with organised occlusive thrombosis and focal endothelial proliferation with T-lymphocytic infiltration.

Case 3.

A 72-year-old woman attended for fever, shortness of breath and signs of arterial ischaemia in left limb. Angio-CT showed extensive bilateral pulmonary, partial thrombosis of aortic lumen and extensive thrombosis of below-knee popliteal artery with patent distal vessels. Full-dose anticoagulation with LMWH was administered with good clinical response. No surgery was required.

Discussion

COVID-19 is responsible for venous and arterial thrombosis. SARS-CoV-2 generates a disbalanced proinflammatory status (cytokine storm) with potential endothelial involvement. All samples showed inflammatory cells such as polymorphonuclears, T-lymphocytes, histiocytes, macrophages and multinucleated giant cells, in the thrombi and all layers of vessels, associated to endothelial proliferation and angiogenesis with a variable degree of collagen deposition and myofibroblastic proliferation. Endothelial damage may lead to vessels thrombosis in peripheral arteries and the aorta, and cause major vascular events such as acute arterial ischemia. This phenomenon suggests that some angiogenic factors promote proliferation of endothelial cells beyond the vessel lumen, surpassing the limits of the usual thrombi recanalisation.

We consider full-dose anticoagulation with LMWH as first-line treatment option, as previously reported. Other anti-inflammatory agents (anti-cytokine drugs, ACE inhibitors or statins) might be used. Open surgery should be favoured over endovascular procedures when medical treatment fails. Any delay in diagnosis and/or treatment may lead to increased morbidity, including limb loss.

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