Possible Thrombotic Microangiopathy Occurring in Patient with CNS Localization of SARS-Cov-2

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It is well documented that SARS-CoV-2 can cause damage to endothelial cells in the lungs, the heart, and the kidneys, activating inflammatory and thrombotic pathways [1]. Endothelial cell infection or monocyte activation, upregulation of tissue factors, and the release of microparticles, which activate the thrombotic pathway and cause microangiopathy, might occur for SARS-CoV-2 as for other viruses [2].

In COVID-19 pneumonia, the extensive microvascular damage seems to be related to a macrophage activation syndrome (MAS)-like mechanism [3] which differs from disseminated intravascular coagulopathy (DIC) and induces a coagulopathic cascade with subsequent local microthrombosis and microbleeding in the small pulmonary vessels. A similar immune-mediated microvascular damage could be responsible for CNS manifestations [4].

The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) is a critical step in the pathophysiology of clinical manifestations in patients with COVID-19 [5], as it triggers the formation of a cytokine storm, with marked elevation in the levels of interleukin-1, interleukin-6, and tumor necrosis factor [6]. High levels of these cytokines increase vascular permeability, edema, and widespread inflammation with consequent multiorgan damage [7]. ACE2 receptor is widely expressed on human cells in multiple organs, including blood vessels and the brain [8].

Thrombocytopenia with elevated D-dimer and C-reactive protein in severe COVID-19 and the high prevalence of thrombotic lesions in these patients are consistent with a virus-associated microangiopathic process. Endothelial dysfunction can potentially lead to microvascular and macrovascular complications in the brain, as described so far [9].

MRI signs of brain microvascular injury consists of small SWI hypointensities with a peculiar distribution; in particular corpus callosum is one of the more frequent location.

Extensive and isolated WM microhemorrhages pattern is also reported in critically ill patients, resulting from long term intubation or ECMO [10, 11]. These findings were recently described in a small number of critically ill patients with COVID-19 [12]. Nevertheless, only
a subgroup of our patients required ICU hospitalization.

Similar imaging findings are reported in severe acute respiratory distress syndromes [13], including high altitude cerebral edema (HACE) [14]. Interestingly, in these published cases, microbleeds in the corpus callosum are associated with a restriction on diffusion-weighted sequences, as for cytotoxic edema. The localization of the lesions is very similar to what observed in our series; however, in none of our patient there was associated edema nor focal neither diffuse brain swelling.

Stroke associated with a generalized thrombotic predisposition in COVID-19 is of particular interest. Four out of the eight patients had cardiovascular risk factors for stroke including atrial fibrillation. One patient had pulmonary emboli, but still the presence of microthrombi in the distal portions of the pulmonary vascular tree cannot be excluded. COVID-19 is associated with a prothrombotic state and highly elevated D-dimer levels, and abnormal coagulation parameters have been shown to be associated with poor outcome [15]. In our cohort we observed similar gross coagulation values, but an increased inflammatory response that could be linked with increased microthrombotic events.

Cerebral microbleeds are usually due to extravasation of red blood cells, and in the context of COVID-19 could be due to endothelial dysfunction related to viral binding to the ACE-2 receptors expressed on endothelial cells. Indeed, a recent report described direct viral infection of the endothelial cell and diffuse endothelial inflammation in multiple organ systems [1].

Endothelial injury can occur in the smallest blood vessels and can be considered as “microangiopathy”. Furthermore, activation of the complement related to the viral infection can determine microthrombi formation. We have also to consider that the term “thrombotic” indicates the presence of blood clots. We can speculate that microthrombotic or microangiopatic lesions can occur in other organs besides the lungs, as in the kidneys, the heart, and the brain at the level of the cerebral small vessels, as previously described [16–18].

SWI sequence can detect micro- and macro hemorrhages and delineate cerebral microvasculature and can also reveal low-flow vascular malformations; furthermore, it provides differentiation of calcium from hemorrhage in the brain. Oxyhemoglobin is diamagnetic in nature, whereas deoxyhemoglobin is paramagnetic. The paramagnetic deoxyhemoglobin serves as an intrinsic contrast agent on SWI sequences, and is low in signal. This causes magnetic field inhomogeneity due to two effects: a reduction of T2* and a phase difference between the vessel and its surrounding tissue. This property also forms the basic principle for blood oxygen level dependent functional and venographic imaging. This physical aspect of the SWI sequence can explain why the majority of focal T2 hypointensities are not seen on GE, also supporting the presence not of a true hemorrhage but at least of microthrombosis, that can be located in the vessel wall rather than in the vessel lumen. These findings can be suspicious for endothelial microbleeds (EMBs)/ microthrombi.

A larger prospective study would be necessary to clarify if this pattern of susceptibility imaging abnormalities as observed in this subset of COVID-19 patients with neurological manifestations, may be related to a thrombotic microangiopathy. In this perspective, histopathological correlation could be enlightening.
5.1 Clinical Cases (Figs. 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 5.10)

Fig. 5.1 Axial SWI images show multiple hypointense foci and their spread into lobes: temporal (Panels a, b), frontal, occipital, and temporal in the same patient (Panels c, d)
Fig. 5.2 SWI images show multiple hypointense foci with more diffuse lesions in the splenium and genu of the corpus callosum as the more consistently involved structure (a, b), diffuse punctate hypointensities at the level of internal capsule (Panel c) somehow depicting the perivascular spaces. Panel (d) shows hypointense foci on axial SWI images at thalamic level. SWI images at posterior fossa and the level of basal cisterns demonstrate diffuse hemorrhagic foci predominantly involving the brainstem (Panels e, f).
Fig. 5.3 The comparison between images acquired in the SWI (a, c) and GE sequences (b, d) at the same levels demonstrates the best diagnostic performance of the former in the detection of micro thrombotic/micro hemorrhagic hypointense foci.
**Fig. 5.4** Images acquired in T1 (a), GE and SWI sequences (b, c) at the same level show absence of signal alteration, micro hemorrhagic hypointense foci and linear cortical hemorrhagic images in T1-s compared to the other two sequences.

**Fig. 5.5** Images acquired in GE and SWI sequences (b, c) at the same level show severely hypointense cluster of lesions in the splenium and genu of the corpus callosum, which corresponds to nonsignificant alteration of the signal intensity in the T1 (a) sequence.
Fig. 5.6 The panel describes a type of lesion frequently observed in COVID patients, with typical appearance of left parietal cortico-subcortical ischemic lesion, evident as hyperintensity in T2 (a) and DWI sequences at high values of B (b), with restriction and hypointensity at ADC map (d); also in this area, focal hypointense spots can be observed in the gradient echo sequences, probably indicative of thrombotic / haemorrhagic phenomena (c).
Fig. 5.7  (a–c) Panel shows hypointense foci representing microthrombotic / microhemorrhagic lesions in supratentorial and subtentorial areas, confirming them as better detectable in SWI sequences (d–f) compared to GE conventional imaging (a–c).

Fig. 5.8  Patient presenting at the same time and at different levels the concomitant presence of microhemorrhagic / microthrombotic lesions represented by hypointensity foci (c) and subarachnoid hypointense striae adjacent to sulci, which delineate more extensive and non-focal hemorrhagic areas (a–c).
Fig. 5.9 Patient presenting marked ubiquitous meningeal thickening especially in the fronto-parieto-occipital site, clearly evident in the FLAIR sequences (b, c) and characterized by intense enhancement after gadolinium infusion (a)
Acknowledgments

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Fig. 5.10 Patient presenting diffused meningeal thickening in supratentorial and subtentorial areas, outlined by enhancement in the sequences acquired after contrast medium infusion (b, d), especially in comparison with the image acquired in precontrast T1s (a); a thickening and hyperintensity of the meningeal plane is also well recognizable in the FLAIR sequence (c)
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