CORRESPONDENCE

Absence of SARS-CoV-2 RNA in COVID-19-associated intestinal endothelialitis

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Recent reports that SARS-CoV-2 virus particles could be visualized by electron microscopy (EM) in endothelial cells of various organs [1] gave rise to the hypothesis that endothelial injury and micro-thrombosis, which are central elements of coronavirus disease 2019 (COVID-19) pathophysiology [2], might be a consequence of direct endothelial cell infection by SARS-CoV-2. However, these observations have been challenged, as intracellular structures such as the endoplasmatic reticulum (ER) may mimic SARS-CoV-2 particles on EM [3].

In a recent issue of *Intensive Care Medicine*, we published images of the resected colon of a COVID-19 patient presenting with non-occlusive mesenteric ischemia (NOMI). The specimens demonstrated severe endothelialitis and EM showed intracellular structures resembling SARS-CoV-2 [4].

The present discussion regarding potential false positive EM findings with regard to SARS-CoV-2 drove us to re-examine our specimens. For this purpose, we established an in situ hybridization technique (SARS-CoV-2 Hulu-FISH probe, MetaSystems). The technique was confirmed using lung tissue from a deceased COVID-19 patient as a positive control (Fig. 1a). Interestingly, the gut endothelium from our original patient was indeed negative for SARS-CoV-2 RNA (Fig. 1b, c). We therefore believe that the Corona-like structures shown by EM in our patient are “morphological look-alikes” of genuine corona viruses (including coated vesicles, multi-vesicular bodies and cross-sections of the rough ER) [5].

Nevertheless, the development of NOMI in severe COVID-19 [1, 4] together with the histological

Fig. 1 Fluorescent in situ hybridization using RNA-SARS-CoV-2 HuluFISH PLUS probe tagged with Atto565 (MetaSystems Probes, Altlußheim, Germany). Abundant positive signals can be seen in lung specimen of a patient who died from Covid-19 pneumonia (red signals, **a**). In the gut specimens of our patient, vessels including those with severe endothelialitis were completely negative (**b**); only single signals in cells located within interstitium can be seen (**c**) (micrographs by courtesy of Jessica Schmitz, Nephropathology Unit, Institute of Pathology, MHH)

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demonstration of massive intestinal endothelialitis and microvascular thrombosis is of high clinical relevance for intensivists fighting COVID-19. Evidently, some patients with severe COVID-19 develop a systemic vasculitis, the pathogenesis of which is not yet understood but might be triggered by indirect effects rather than direct viral infection.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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