

Appearances Can Be Deceiving - Viral-like Inclusions in COVID-19 Negative Renal Biopsies by Electron Microscopy

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We have observed morphologically indistinguishable inclusions within podocytes and tubular epithelial cells both in patients negative for coronavirus disease 2019 (COVID-19) as well as in renal biopsies from the pre-COVID-19 era.

We postulated that endogenous mimickers could be present that are morphologically indistinguishable from SARS-CoV-2 virions ultrastructurally.

Viral-like inclusions, consisting both of single vesicles with diameters between 50 and 139 nm, as well as packed groups within larger vesicles, were found in all 15 cases, either in podocytes, tubular epithelium, or vascular endothelial cells ([Figure 1](#)).

A number of potential natural mimickers that can generate intracellular groups of round vesicles mimicking SARS-CoV-2 virions could be listed, the most likely being endocytic vesicles and endosomal compartment components such as microvesicular bodies containing exosomes, among others. Endocytosis leads to the formation of 60–120 nm vesicles, which is within the size range described for SARS-CoV-2 (60–140 nm) ([2](#)). These endocytic vesicles may be coated by different proteins, one of the most common being clathrin ([13](#)). The presence of coating proteins may be responsible for the presence of an electron-dense area surrounding these vesicles, giving the appearance of a viral corona.

Alternatively, the viral-like inclusions could represent microvesicular bodies containing exosomes before their release onto the cell surface.

This again could contribute to increased numbers of cytoplasmic vesicles within podocytes in patients with COVID-19 who are proteinuric, and could lead to the mistaken assumption that these represent virions. Individual exosome sizes vary, but they are generally between 30 and 150 nm ([21](#)), which falls within the size range reported for SARS coronaviruses ([9](#)). The potential for confusion of coronavirus particles with normal cellular components was in fact highlighted in a detailed ultrastructural study by the Centers for Disease Control and Prevention (CDC) of the SARS-CoV responsible for the 2003 SARS outbreak ([9](#))

Recognition of this pitfall of “viral-like particles” actually dates back to the 1970s, when the potential for mistakenly assuming that normal cellular components, such as phagocytic vacuoles, microvesicular bodies, or extracellular breakdown products, could represent viral particles was emphasized after a proliferation of studies claiming to have found ultrastructural viral particles within different types of cancer cells and fluids ([23](#)).