LETTER TO THE EDITOR

# Ultrastructural evidence for anagen hair follicle infection with SARS-CoV-2 in early-onset COVID-19 effluvium

*Dear Editor,*

Hair loss is the most frequent manifestation of post-COVID syndrome, affecting up to 48% of COVID-19 patients, especially those with more severe and longer term acute disease. Most of the patients who report post-COVID hair loss present it as an early-onset effluvium (<30 days from the acute phase), which is more precocious than expected for the ordinary post-febrile acute telogen effluvium.[1,2]

Despite an overall good prognosis, early-onset COVID-19 effluvium can be severe, and it is characterized by some telogen but frequent anagen dystrophic hairs at the trichogram and an absence of histological inflammation, leading to the hypothesis that COVID-19 can promote some direct disturbance in the hair physiology.[3,4]

In synergy with the host transmembrane serine protease 2 (TMPRSS2), human angiotensin-converting enzyme type 2 (ACE-2) has been identified as a functional receptor for SARS-CoV-2 on the surface of the cell membranes, where ACE-2 binds to the viral spike glycoprotein for its cellular entry. As keratinocytes from hair follicles' outer sheath strongly express ACE-2 and TMPRSS2,[5] we investigated the presence of SARS-CoV-2 in the cytoplasm from the hair follicle of a patient with COVID-19 and early-onset effluvium.

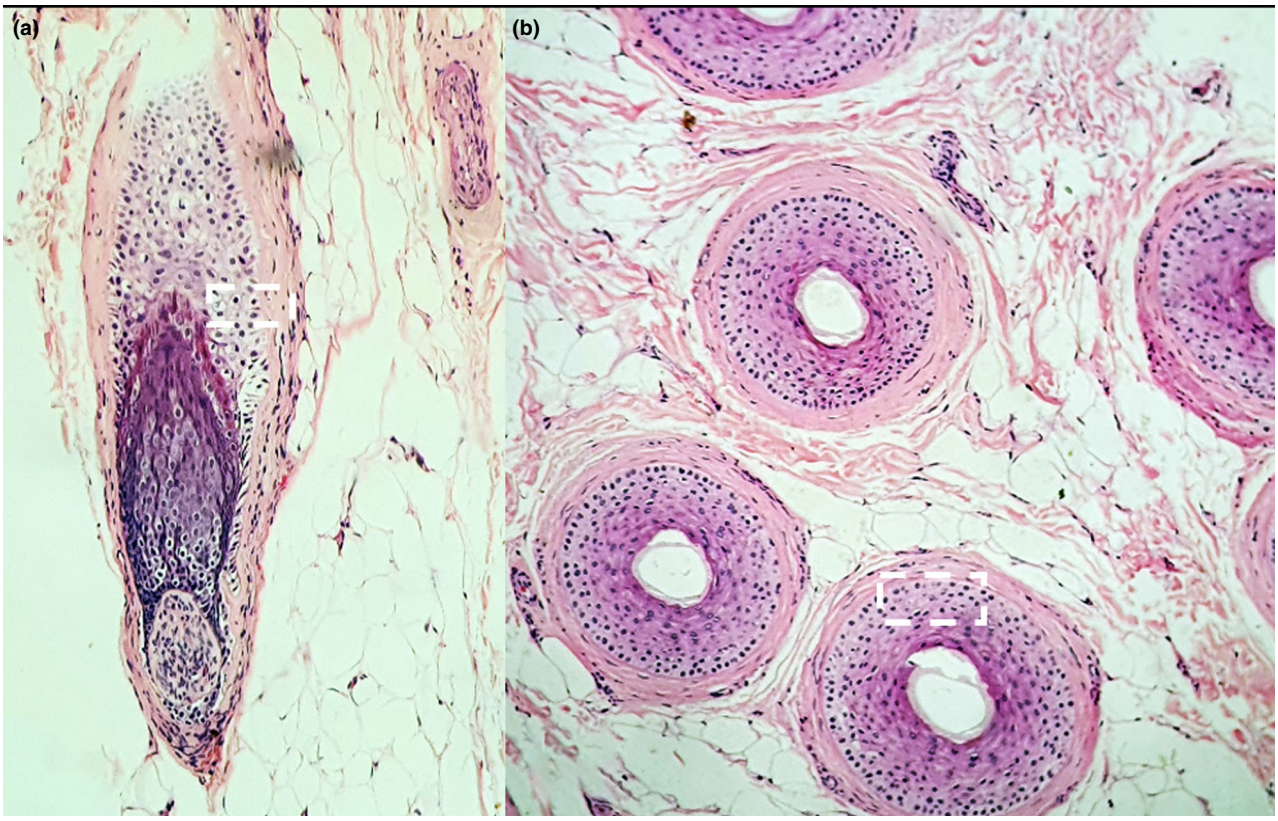


**Figure 1** Early-onset COVID-19 effluvium. Longitudinal (a) and transversal (b) histological sampling at suprabulbar region showing anagen follicles and an absence of inflammatory infiltrate (H&E, 100×). The dotted rectangles evidence the regions explored in the transmission microscopy analysis.

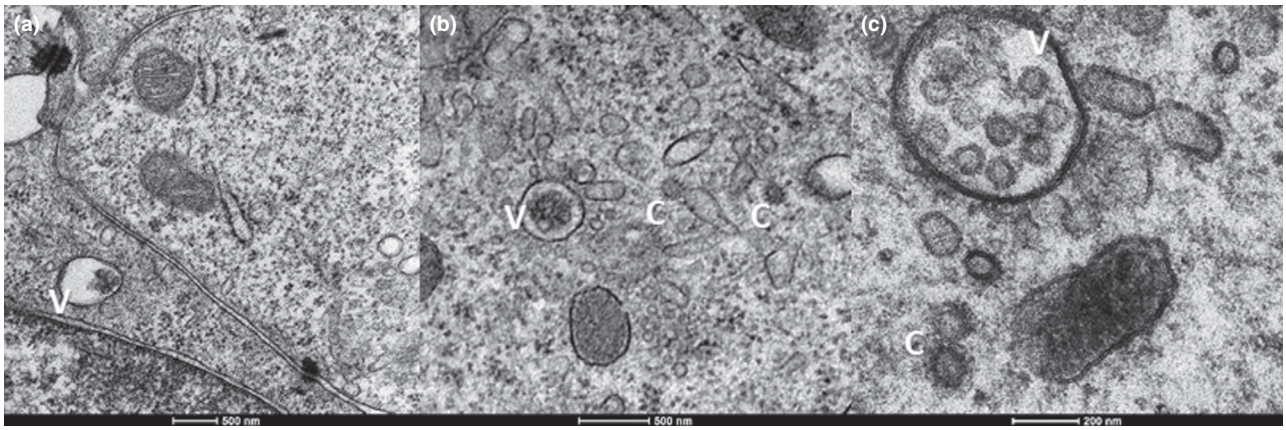


**Figure 2** Early-onset COVID-19 effluvium. Transmission electron microscopy from the outer root sheath from an anagen follicle showing large cytoplasmic vesicles (V) with clusters of spherical particles within and some adjacent free crown-like viral particles (C) with nucleocapsids inside.

A 25-year-old woman was admitted to our hospital with a 7-day history of cough, fever, dyspnoea and a positive PCR test for the COVID-19 antigen, requiring non-invasive oxygen therapy, systemic corticosteroids and antipyretic drugs. She referred to current intense hair shedding and presented a positive pull test with anagen hairs.

A scalp biopsy revealed anagen hairs and the absence of inflammation in the infundibulum, isthmus and suprabulbar areas (Fig. 1). Electron microscopy of the suprabulbar outer root sheath from an anagen follicle (Fig. 2) demonstrated cytoplasmic vesicles (V) with several viral structures within, surrounded by some crown-like viral particles (C). Desmosomes and the morphology of the overall cytoplasmic organelles were unremarkable.

SARS-CoV-2 was identified in most of the patient's human tissues, which substantiates the myriad clinical manifestations both in the acute disease and in post-COVID syndrome. Several skin manifestations and changes in the course of previous dermatoses have been reported and were attributed mostly to epithelial and endothelial infections, as well as to immune dysregulation following COVID-19.[6,7] The intracellular replication of SARS-CoV-2, a positive-sense single-stranded RNA virus, can be characterized by clusters of spherical viral particles of 60–100 nm within large vesicles from the Golgi complex. Some crown-like viral particles with nucleocapsids within can be seen dispersed in the cytoplasm.[8]

The hair cycle is highly sensitive to systemic alterations, such as in body nutrition, inflammation, drugs, endocrine and metabolic changes, which substantiates the different pathways that can lead to hair shedding following systemic diseases, including COVID-19.[2] As keratin is highly immunogenic, hair follicles have evolved in mammalians as a compartment with low immune reactivity and low antigen presentation. This immune privilege can protect the SARS-CoV-2 infected cells from immune response, although it does not hinder viral proliferation.[9] Besides, SARS-CoV-2 reprogrammes the host's cellular metabolism and limits their autophagic machinery in order to propagate viral replication.[10] Despite there are currently no previous ultrastructural studies in other types of effluvium, we hypothesized that the accumulation of damaged mitochondria in the infected follicular cells can lead to the release of reactive oxygen species in the cytoplasm and explain the intracellular alterations that can elicit precocious hair loss.

The high rate of dystrophic anagen hair in the trichogram, the early onset of hair shedding (<30 days), and the intense SARS-CoV-2 replication in the suprabulbar outer root sheath distinguish the early-onset post-COVID-19 effluvium from the post-infectious telogen effluvium usually seen after severe infections.

## Acknowledgements
The patient in this study has given written informed consent to publication of their data.

## Conflict of interest
None.

## Funding sources
None.

## IRB status
This study was approved by the FMB-Unesp IRB (number 4.688.358).

## Data availability statement
All of the data that support the findings of this study are available on request from the corresponding author.

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DOI: 10.1111/jdv.18342