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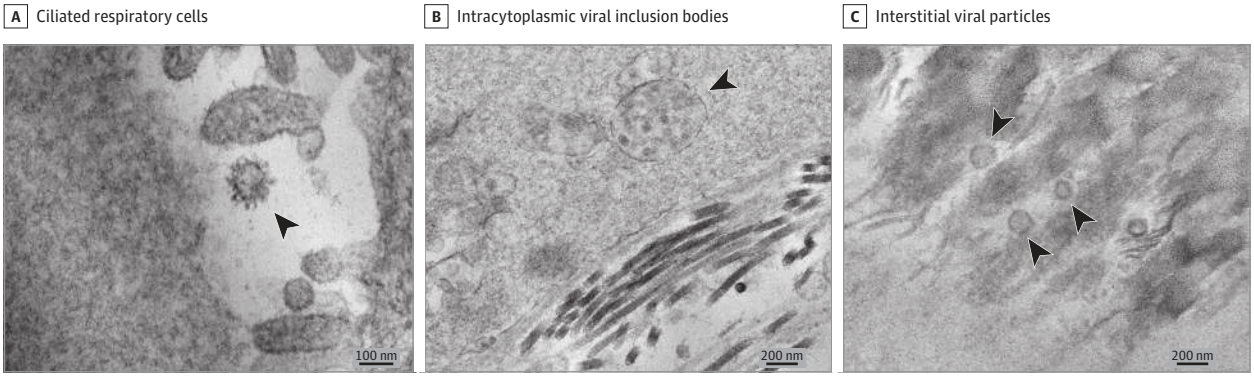
Ultrastructural Evidence of Direct Viral Damage to the Olfactory Complex in Patients Testing Positive for SARS-CoV-2

Neurological manifestations are common in patients with coronavirus disease 2019 (COVID-19), especially in those with severe disease.[1] The mechanisms underlying neuromuscular damage are the objects of substantial scientific research and speculation. We report the clinicopathologic and ultrastructural postmortem findings observed in the olfactory system of 2 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive nasal swabs who underwent minimally invasive autopsy, including nasal endoscopic dissection of the olfactory complex.

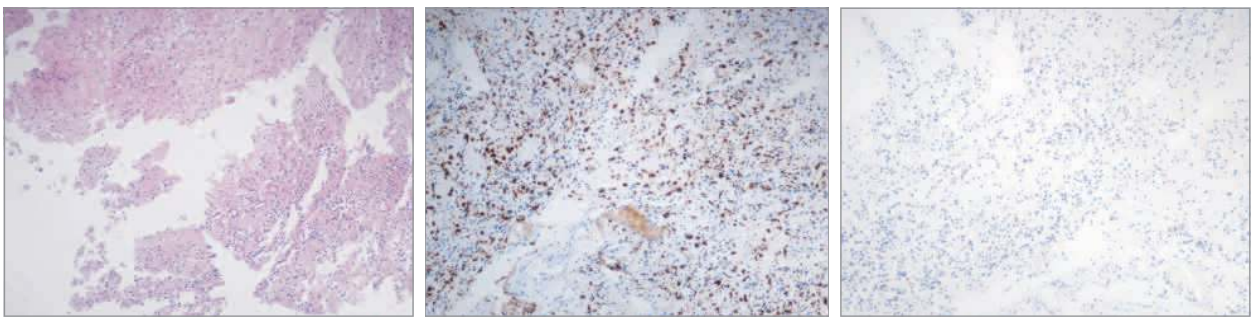
Report of Cases | The first patient had anosmia and died of COVID-19 pneumonia in the intensive care unit; the second patient had ill-defined olfactory dysfunction and died of cardiopulmonary transthyretin amyloidosis. Transmission electron microscopy results revealed the presence of 80-nm to 100-nm viral particles on the cell membrane of ciliated respiratory cells in the olfactory mucosa of patient 2 (**Figure 1**, A). In the olfactory bulb (OB) samples of patient 1, transmission electron microscopy showed intracytoplasmic viral inclusion bodies (Figure 1, B) and interstitial viral particles (Figure 1, C). On light microscopy, the OB sections of patient 1 showed marked CD163-positive/CD68-negative microglial cell infiltration (**Figure 2**) that was associated with sparse CD3-positive lymphocytes, mostly of the CD8-positive cytotoxic subset. In the OB of patient 2, only rare CD163-positive microglial cells and CD3-positive/CD8-positive perivascular lymphocytes were observed. Inflammatory cell infiltration of the nasal and olfactory mucosa was more abundant in the second case, and comprised CD3-positive T lymphocytes of the helper CD4-positive and cytotoxic CD8-positive subsets, CD20-positive B lymphocytes, and CD163-positive macrophages. In the OB of the second patient, there was no ultrastructural evidence of

Figure 1. Ultrastructural Findings



Transmission electron microscopy micrographs showing viral particles (arrowhead) on the cytoplasmic surface (A) in the olfactory epithelium of patient 2, a viral cytoplasmic inclusion body (arrowhead) in the cytoplasm of a cell of the olfactory bulb of patient 1 (B), and viral particles in the interstitial space of the same sample from patient 1 (C).

Figure 2. Light Microscopy and Immunohistochemical Findings From Patient 1



Light micrographs of the olfactory bulb sample of patient 1 showing marked hypercellularity on hematoxylin-eosin (original magnification, ×10) (A), mostly composed of CD163–positive (B)/CD68-negative (C) macrophages on immunohistochemical stains (original magnification, ×20).

viral particles and only rare CD163-positive microglial cells and CD3/CD8-positive perivascular lymphocytes were observed on light microscopy.

Discussion | In the heterogenous spectrum of SARS-CoV-2–associated neurological manifestations,[1] olfactory and gustative dysfunction has been proposed as an early and specific symptom of viral infection and can represent in some patients the only clinical manifestation of COVID-19.[2,3] Whether these and other neurological manifestations are evidence of direct viral damage to the olfactory complex and central nervous system or consequences of a systemic inflammatory response has not yet been supported by in vivo observations. The recent finding of SARS-CoV-2 receptor angiotensin-converting enzyme 2 and *TMPRSS2* transcripts in olfactory horizontal basal cells, microvillar cells, Bowman glands, and olfactory sustentacular cells, but not in olfactory neuron sensors, provided a proof of concept of the susceptibility of the olfactory organ to SARS-CoV-2 infection.[4] We were able to identify SARS-CoV-2 particles in the OB of a patient with severe COVID-19 that were associated with a diffuse infiltration of CD163-positive macrophages and cytotoxic T lymphocytes. The presence of CD163 serves as a marker of macrophage activation induced by the proinflammatory cytokine storm in systemic inflammatory disorders, including Ebola virus infection. A possible role of CD163-positive microglia in virus-mediated inflammation and neuropathogenesis has been previously proposed in patients with HIV and HIV-related encephalitis and various degrees of neurocognitive impairment[5] and might also be a result of SARS-CoV-2–induced hyperinflammation.

Although confirmatory observations on extensive patient series are needed, our findings suggest that passive diffusion and axonal transport through the olfactory complex may be a major route of SARS-CoV-2 entry into the central nervous system, as it was previously shown in animal studies with a human coronavirus strain, human coronavirus OC43.[6] This report supports the clinical hypothesis that the new onset of olfactory dysfunction should either prompt immediate testing for SARS-CoV-2 infection whenever possible or might be considered an additional clinical criterion for self-isolation.

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Published Online: August 13, 2020. doi:10.1001/jamaoto.2020.2366

Conflict of Interest Disclosures: Dr Morbini reported personal fees from MSD and Roche outside the submitted work. No other disclosures were reported.

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Spontaneous Cerebrospinal Fluid Leak in a Transgender Man: Is Testosterone Therapy a Risk Factor?

Report of a Case | A transgender man in his 20s presented with 9 months of right-sided rhinorrhea. He reported spontaneous onset of clear, salty nasal drainage without history of trauma. The patient also reported postural headaches but denied vision loss. He had a history of chronic sinusitis with nasal polyposis and had undergone bilateral endoscopic sinus surgery 6 months prior, but rhinorrhea preceded surgery. The patient's medical history was significant for taking testosterone cypionate intramuscular injections, 200 mg, bimonthly for 6 years. He had undergone previous subcutaneous mastectomy for gender confirmation. The patient denied any history of meningitis. Examination showed brisk right rhinorrhea when leaning forward. Results of β_2 transferrin assay for cerbrospinal fluid (CSF) were positive, and computed tomographic (CT) scans showed a defect in the middle fossa lateral to the right foramen rotundum in a hyperpneumatized sphenoid sinus, with extensive mottling of the skull base bilaterally including ovoid bony defects from arachnoid pits and aberrant granulations (**Figure 1**) consistent with idiopathic intracranial hypertension (IIH).

The patient underwent expanded endonasal surgery by otolaryngology and neurosurgery specialists for CSF leak repair. A lumbar drain was placed. A transpterygoid approach was performed to allow straight-line access to the skull base defect. The vidian nerve was transected for access, whereas the maxillary nerve was preserved. An encephalocele with active CSF leak was identified and reduced with bipolar electrocautery. The bony defect measured 4 mm, with unhealthy and irregular surrounding bone (**Figure 2**). The CSF leak was repaired with inlay collagen dural substitute, septal cartilage inlay graft, and free mucosal onlay graft harvested from the nasal floor. The lumbar drain was removed on postoperative day 2,