CORRESPONDENCE

Neuropathological Features of Covid-19

TO THE EDITOR: Neurologic symptoms, including headache, altered mental status, and anosmia, occur in many patients with Covid-19.[1-3] We report the neuropathological findings from autopsies of 18 consecutive patients with SARS-CoV-2 infection who died in a single teaching hospital between April 14 and April 29, 2020.

All the patients had nasopharyngeal swab samples that were positive for SARS-CoV-2 on qualitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays. The median age was 62 years (interquartile range, 53 to 75), and 14 patients (78%) were men. The presenting neurologic symptoms were myalgia (in 3 patients), headache (in 2), and decreased taste (in 1). Coexisting conditions included diabetes mellitus (in 12 patients), hypertension (in 11), cardiovascular disease (in 5), hyperlipidemia (in 5), chronic kidney disease (in 4), prior stroke (in 4), dementia (in 4), and treated anaplastic astrocytoma (in 1) (see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

The patients had presented a median of 2 days (interquartile range, 0 to 5) after the onset of the first symptoms of SARS-CoV-2 infection and were hospitalized for a median of 6 days (interquartile range, 2 to 9) before death (Fig. S1A); 11 received mechanical ventilation. According to a retrospective chart review by neurologists, all the patients had a confusional state or decreased arousal from sedation for ventilation. Brain magnetic resonance imaging, electroencephalographic imaging, and cerebrospinal fluid examinations were not performed. Cranial computed tomography without contrast was performed in 3 patients and showed no acute abnormalities; the tumor resection cavity in the patient with a known anaplastic astrocytoma was seen.

Death occurred 0 to 32 days after the onset of symptoms (median, 8 days; mean, 10 days). Autopsies were performed in a uniform manner with sampling of 10 standard brain areas. Specimens were fixed in formalin and stained with hematoxylin and eosin, as described in the Materials and Methods section in the Supplementary Appendix. Gross inspection showed atherosclerosis in 14 brain specimens but no acute stroke, herniation, or olfactory bulb damage. Residual anaplastic astrocytoma was seen in the patient who had received a diagnosis of anaplastic astrocytoma previously (Table 1). Microscopic examination (Fig. S1B) showed acute hypoxic injury in the cerebrum and cerebellum in all the patients, with loss of neurons in the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer, but no thrombi or vasculitis. Rare foci of perivascular lymphocytes were detected in 2 brain specimens, and focal leptomeningeal inflammation was detected in 1 brain specimen. No microscopic abnormalities were observed in the olfactory bulbs or tracts (Fig. S2).

Testing of brain tissue was performed with quantitative RT-PCR (qRT-PCR) for the SARS-CoV-2 nucleocapsid protein (techniques are described in the Materials and Methods section in the Supplementary Appendix). As shown in Table S3, for 2 patients, all 10 sections were tested, and for the remaining 16 patients, 2 sections were tested (1 from the frontal lobe and olfactory nerve and 1 from the medulla). The results were equivocal (defined as a viral load of <5.0 copies per cubic millimeter) in 5 of 10 brain sections from 1 patient and in 4 of 10 sections from another patient (Table S3); the remaining 11 sections obtained from these 2 patients were negative. In 32 sections obtained from the remaining 16 patients, 3 sections from the medulla and 3 sections from the frontal lobes and olfactory nerves were positive (5.0 to 59.4 copies per cubic millimeter); the results were equivocal in 20 sections and negative in 6 sections. The test results in relation to the interval between the onset of symptoms and death were inconsistent (Fig. S1).

Immunohistochemical analysis (as described in the Supplementary Appendix) was performed to detect SARS-CoV-2 in the same tissue blocks analyzed by qRT-PCR (in 52 blocks from 18 pa-

Table 1. Gross Findings and Results of Histologic Analysis to Detect SARS-CoV-2.*

Patient No.	Days from Symptom Onset to Death	Hours from Death to Autopsy	Gross Inspection		Histologic Analysis
			Brain Volume	Observations	
			grams		
1	20	52	1290	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis
2	6	32	1460	Moderate atherosclerosis	Acute hypoxic ischemic damage
3	12	21	1210	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
4	6	36	1150	Moderate-to-severe atherosclerosis, pale substantia nigra and locus coeruleus	Acute hypoxic ischemic damage, moderate arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
5	9	40	1460	No gross abnormalities	Acute hypoxic ischemic damage
6	0	77	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal leptomeningeal chronic inflammation
7	2	54	1300	Moderate atherosclerosis, cortical atrophy	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Alzheimer's disease
8	2	32	1350	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, moderate arteriolosclerosis
9	23	23	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis
10	7	21	1120	Moderate atherosclerosis, anaplastic astrocytoma tumor resection cavity	Acute hypoxic ischemic damage, recurrent or residual anaplastic astrocytoma
11	26	41	1090	No gross abnormalities	Acute hypoxic ischemic damage, Alzheimer's type II astrocytosis
12	6	45	1130	Mild atherosclerosis, pale substantia nigra	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
13	12	61	1300	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis, focal perivascular chronic inflammation, Alzheimer's type II astrocytosis

14	0	102	1650	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis
15	8	20	1530	Moderate atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis, Alzheimer's type II astrocytosis
16	32	31	1150	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
17	7	25	1300	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal perivascular chronic inflammation, pathological features of Alzheimer's disease
18	9	26	1350	Mild atherosclerosis	Acute hypoxic ischemic damage, single microglial nodule, Alzheimer's type II astrocytosis

* The results of immunohistochemical analysis to detect SARS-CoV-2 were negative in all the patients.

tients). There was no staining in the neurons, glia, endothelium, or immune cells. Nonspecific staining in the choroid plexus was observed in 8 sections obtained from 7 patients; however, this signal was present in negative control brains and did not correlate with the qRT-PCR results (Figs. S1 and S3). The tumor blocks obtained from the patient with anaplastic astrocytoma were not tested by qRT-PCR or immunohistochemical analysis to detect SARS-CoV-2.

In conclusion, histopathological examination of brain specimens obtained from 18 patients who died 0 to 32 days after the onset of symptoms of Covid-19 showed only hypoxic changes and did not show encephalitis or other specific brain changes referable to the virus. There was no cytoplasmic viral staining on immunohistochemical analysis. The virus was detected at low levels in 6 brain sections obtained from 5 patients; these levels were not consistently related to the interval from the onset of symptoms to death. Positive tests may have been due to in situ virions or viral RNA from blood.

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