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Letter to the Editor

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COVID-19 could worsen cerebral amyloid angiopathy

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To the Editor:

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is associated in 26–56% of cases with neurological symptoms (1, 2). COVID-19 patients may develop neurological sequelae including cognitive deficits (3). A systematic literature review based on 27 studies confirms a risk of cognitive impairment in survivors after the resolution of the first COVID-19 symptoms (4). Another recent study focused on magnetic resonance imaging (MRI) data obtained from hundreds of COVID-19 and control patients before and after the disease (5). It showed a reduction in grey matter thickness and global brain volume in COVID-19 patients in comparison with controls. These radiological observations were associated with a greater cognitive decline in COVID-19 patients between the 2 MRI examinations. The main lesions in the brain of the deceased COVID-19 patients are of vascular (6, 7) and inflammatory types (8). Nevertheless, the contribution of latent neurodegenerative and/or cerebrovascular lesions remains elusive. To our knowledge, the effects of a SARS-CoV2 infection on the course of pathology of Alzheimer disease (AD) and related disorders are still unknown. In AD, the prevalence of cerebral amyloid angiopathy (CAA) may reach 80% (9). Aβ-related angiitis (ABRA) is a particular presentation of CAA and is characterized by transmural granulomatous inflammation of the superficial brain vessels (10). Considering its vascular tropism, whether SARS-CoV2 neuropathology has a synergistic effect on ABRA deserves consideration.

Here, we report the case of an 82-year-old man with a 7-year-long history of CAA who died of an ABRA following a SARS-CoV2 infection. The deceased had a history of atrial fibrillation, arterial hypertension, and prostate adenocarcinoma. Sporadic CAA was diagnosed 7 years before death after a transient ischemic attack which was further attributed to a probable amyloid spell (transient focal neurologic episode) (11). MRI scan showed superficial cortical siderosis and microbleeds. At that time, he had no cognitive impairment and was treated with antiepileptic drugs to prevent new neurologic symptoms.

For 7 years, he had a regular neurological follow-up. MRIs showed overall stability of cortical siderosis and cortical atrophy (Fig. 1A, B). However, 2 and 7 years after the diagnosis, some microbleeds appeared (1 insular on the left and 3 post-central on the right).

One year before death, a neuropsychological examination showed evidence of mild cognitive impairment affecting verbal episodic memory and executive functions. The Mattis Dementia Rating Scale score was 126/144. However, 4 months before death, he was independent in activities of daily living and had a Mini-Mental State score of 28/30.

Two months before death, he was diagnosed with COVID-19 in the context of fatigue and fever. At that time, he had a positive SARS-CoV2 nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR). He had no acute respiratory syndrome but shortly after recovery his neurological condition worsened subacutely with gait and speech disorders. Seven days before death, CT and MRI scans showed multiple subarachnoid hemorrhages associated with multiple punctiform ischemic lesions (Fig. 1C, D). Three days before death a CT scan showed an increase in size and number of the fronto-parieto-temporal subarachnoid hemorrhages with hematic deposits within the ventricular occipital horns. He died 67 days after the positive RT-PCR.

The autopsy was performed 4 days after death. The use of the data and the tissues has been approved by the Lille Coronavirus Network "LICORNE study group" (DC 2020-3980) and declared to *Commission Nationale de l'Informatique et des Libertés* (CNIL) (declaration number MAR21-947).

The SARS-CoV2 RT-PCR (RealStar SARS-Cov2 RT-PCR kit 1.0 from Altona Diagnostics, Hamburg, Germany) was

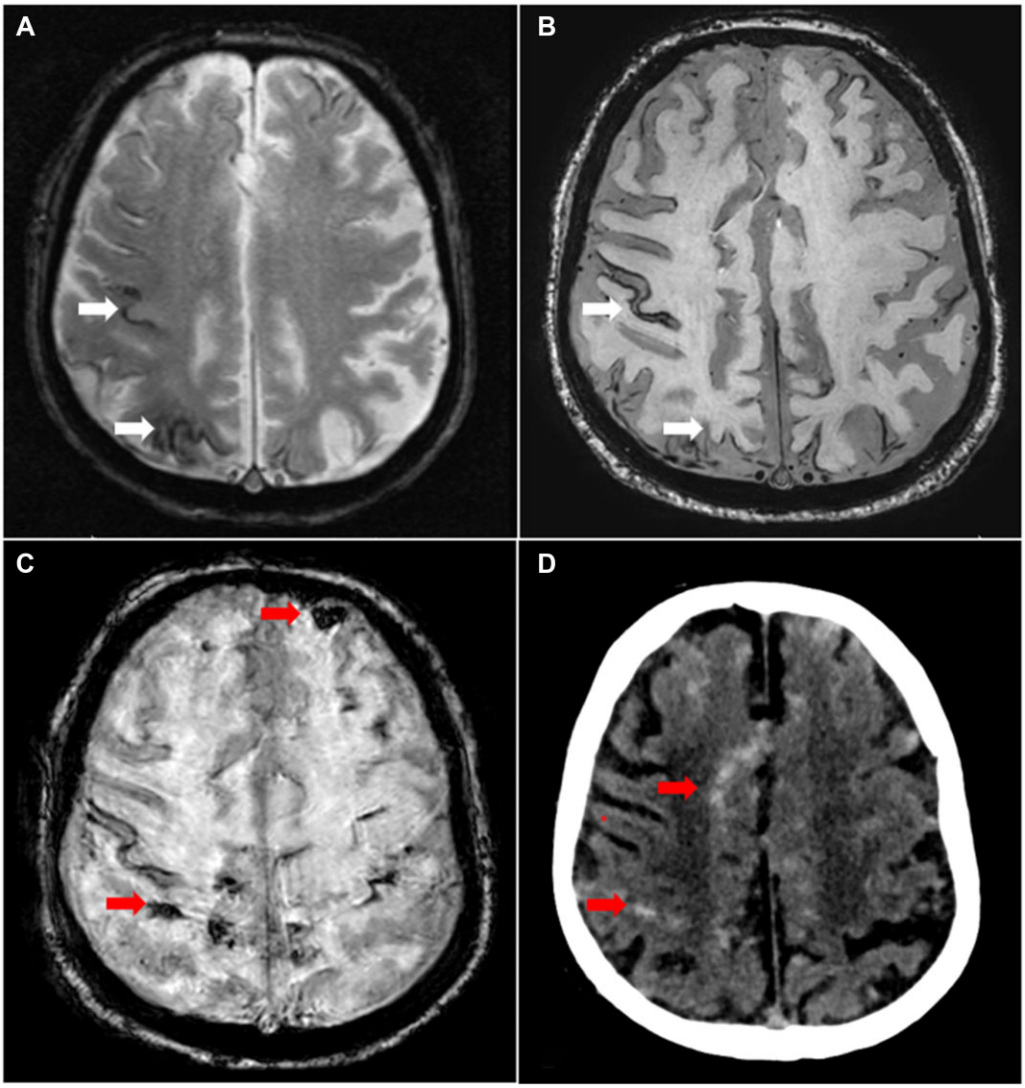

Figure 1. Radiological examination. **(A)** T2 sequence MRI performed after 1 year of follow-up. Cortical siderosis of the right convexity and occipital area (white arrows). **(B)** Overall stability of cortical siderosis (white arrows). **(C)** SWI sequence MRI performed 7 days before death. Frontal and parietal hyposignal corresponding to subarachnoid hemorrhage (red arrows). Artifacts are linked to the patient's movements. **(D)** CT scan with meningeal hyperdensity (red arrow) corresponding to subarachnoid hemorrhage.

performed on fresh samples of stool, heart, liver, trachea, bronchial tubes, lung, kidney, and brain were all negative. Under macroscopic examination, the sulci appeared diffusely hemorrhagic. There was global cortical atrophy that was more predominant in temporal and parietal lobes (Fig. 2A).

Microscopically there was a subarachnoid hemorrhage with multifocal infiltration of the superficial layers in all the cortical samples (Fig. 2B). Strikingly, there was marked granulomatous inflammation of the arachnoid vessels and to a lesser extent of the walls of superficial cortical vessels (demonstrated by immunohistochemistry with anti-CD68 antibody, mouse monoclonal, clone KP1; Dako, Glostrup, Denmark). This was not seen in the deeper vessels (Fig. 2B–F). A majority of T lymphocytes were present in the inflammatory infiltrate (CD5 [mouse monoclonal, clone 4C7; Leica, Wetzlar, Germany], CD2 [mouse monoclonal, clone 271; Leica], CD7 [rabbit monoclonal, clone SP94; Ventana Roche, Oro Valley, CA], CD4 [rabbit monoclonal, clone SP35; Ventana Roche], and CD8 [mouse monoclonal, clone C8/144B; Dako]) with more CD4-positive T lymphocytes than CD8 T lymphocytes. These were mixed with a few B lymphocytes (CD20 antibody, mouse monoclonal, clone L26; Bio SB, Santa Clara, CA). This granulomatous inflammation was associated with CAA of the arachnoidal and superficial cortical vessels that were strongly labeled with the anti-Aβ peptide antibody (mouse monoclonal, clone 6F/3D; Dako) (Fig. 2D, G). There were no macrohemorrhages in the deep cortical layer or in the white matter. There were very sparse microhemorrhages in the nucleus basalis and in the hippocampus and 1 microinfarct in the right anterior temporal lobe (Brodmann area 38 [BA 38]). Regarding parenchymal pathology, we did not find Aβ peptide plaques (Thal phase 0). There was mild Tau pathology affecting the frontal

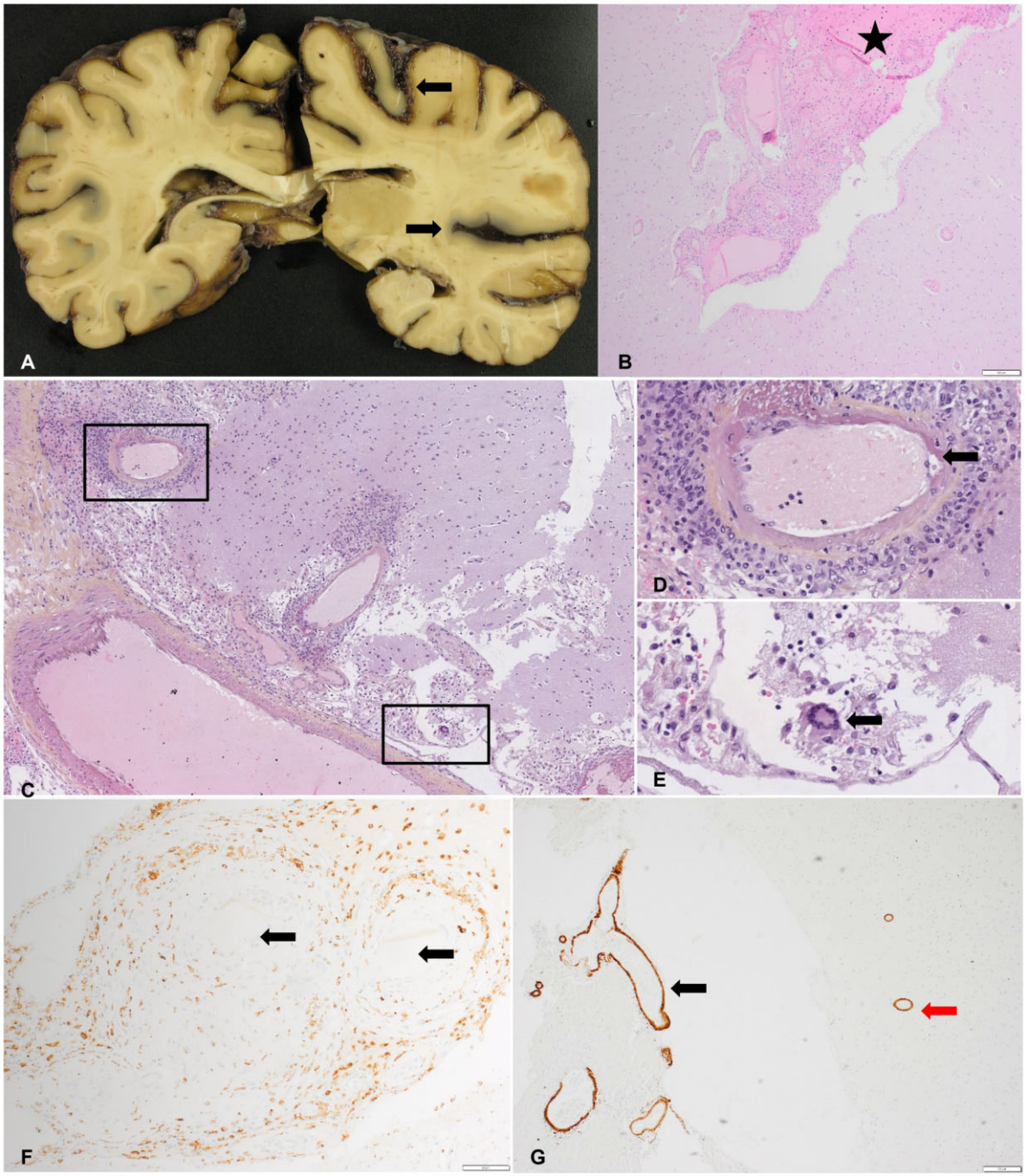

Figure 2. Hemorrhagic and ABRA lesions. **(A)** Hemorrhagic aspect of the sulci (black arrow). **(B)** Subarachnoid hemorrhage (black star) in the gyrus rectus on hematoxylin and eosin (H&E) stain ×40. **(C)** Superficial ABRA involving the arachnoid in the temporal lobe (BA 20-21) with perivascular extension (H&E ×40). **(D)** Higher magnification of upper black box shows macrophages surrounding the wall of a CAA vessel (H&E ×200). **(E)** Higher magnification of lower black box shows a multinucleated giant cell (black arrow) (H&E stain ×200). **(F)** Perivascular macrophages labeled by anti-CD68 antibody in prefrontal area (BA 10) (black arrows: lumen of vessels ×100). **(G)** Arachnoid vessels (black arrow) and superficial cortical vessels (red arrow) in prefrontal areas labeled with the anti-Aβ antibody (×40).

and temporal lobes and hippocampus (Braak stage III) (mouse monoclonal, clone AT8; Thermo Scientific, Waltham, MA). Antibodies targeting TDP-43 (rabbit monoclonal, clone Poly; Proteintech, Rosemont, IL), α-synuclein (mouse monoclonal, clone LB509; Invitrogen, Waltham, MA), p62 (mouse monoclonal, 3/P62 LCK ligand; BD Biosciences, Franklin Lakes, NJ), and Prion Protein (mouse monoclonal, clone 12F10; SPI BIO) were negative on immunohistochemistry.

As far as we know, this is the first description with histological data available of an ABRA following a SARS-CoV2 infection that led to the patient's death. Brain and subarachnoid hemorrhages have already been reported in the MRI in 2 CAA

patients after COVID-19. The first patient was an 88-year-old woman with late-onset AD and the second one was a 38-year-old woman with a duplication of the *APP* gene (12, 13). No pathological confirmation was available since both patients were alive at the time of the publication.

SARS-CoV2 has been detected in the central nervous system (7). Its main receptor is the angiotensin-converting enzyme 2 (ACE2) receptor to which the viral capsular protein named Spike protein can bind. This binding allows the fusion between viral capsule and cytoplasmic membrane, leading to the infection and destruction of the cells by the virus (14). The ACE2 receptor is notably expressed by endothelial cells, smooth muscle cells, and perivascular pericytes. The infection of these cells could cause endothelial dysfunction and thus explain the fact that the COVID-19 brain lesions are mainly of vascular type (6, 7, 15).

Another characteristic of COVID-19 is the dysregulation of immune system with anomalies in pro-inflammatory cytokines production, and innate and adaptive immune system activation and regulation (16). The disease could also trigger autoimmune reactions, for example, due to the uptake by antigen-presenting cells of antigens released from damaged self-tissues in the context of pro-inflammatory secretion (17).

ABRA may be induced by autoimmunity to Aβ depositions (10). Bogner et al (18) showed that ABRA patients had significantly increased immune activation in the brain compared to CAA without ABRA patients and had a decreased Aβ deposits in the brain parenchyma adjacent to affected vessels, in accordance with the hypothesis of an excessive immune response to Aβ deposits in ABRA.

We thus speculate that when our patient became infected, he may have had an infection of the brain vessels leading to vessel lesions and to Aβ deposits' exposure. The immune system might have then reacted against the Aβ deposits and consequently caused the ABRA. This case report brings new clues to the long-lasting effects of SARS-CoV2 on the brain of infected patients, especially on the ones with latent vasculodegenerative lesions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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