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Case Report

Reactivation of COVID-19 in a neurosurgical patient with early neuropsychiatric presentation. Does seroconversion mean immunity?

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ABSTRACT

Background: In the aftermath of COVID-19 outbreak, there is a strong need to find strategies to monitor SARS-CoV-2 transmission. While the application of screening techniques plays a major role to this end, there is evidence challenging the real significance of seroconversion. We reported a case of COVID-19 reactivation associated with a neurosurgical operation with early neuropsychiatric involvement presumably promoted by olfactory and gustatory impairment in the first infection.

Case Descriptio: A 57-year-old man was referred for a 2-month history of progressive development of imbalance, dizziness, and vomiting. Magnetic resonance imaging showed two bilateral hemispheric cerebellar lesions. In line with our triage protocol, the patient underwent a nasopharyngeal swab for RNA of SARS-CoV-2 detection, which resulted positive. Of note, the patient had reported in the previous month hyposmia and hypogeusia. After a period of 14 days, three new swabs were performed with negative results, leading the way to surgery. In the early post-operative period, the patient manifested acute onset of psychotic symptoms with hyperactive delirium, followed by fever and acute respiratory failure. A chest computed tomography revealed a specific pattern of ground-glass opacities in the lower lobes bilaterally, suggesting a viral pneumonia. Serological tests demonstrated the seroconversion and a new nasopharyngeal swab confirmed SARS-CoV-2 infection.

Conclusion: Our report highlights the importance of comprehensive screening assessments in sensitive cases highly susceptible to COVID-19 recurrence.

Keywords: COVID-19, Neuropsychiatric presentation, Neurosurgery, Reactivation, SARS-CoV-2, Seroconversion

INTRODUCTION

In the aftermath of COVID-19 outbreak, there is a strong need to find strategies to monitor SARS-CoV-2 transmission. While the application of screening techniques plays a major role to this end, there is evidence challenging the real significance of seroconversion.[12]

We report a case of COVID-19 reactivation in a seroconverted patient following a neurosurgical intervention and manifesting early neuropsychiatric symptoms. The possible underlying mechanisms are further discussed.

CASE PRESENTATION

This 57-year-old man was referred for a 2-month history of progressive development of imbalance, dizziness, and vomiting. On examination, he presented with wide-based gait, uncoordinated limb movements, and nystagmus on extreme gaze. Radiological investigations disclosed two bilateral hemispheric cerebellar lesions, suggestive of metastases [Figure 1]. On April 2020, he was then admitted to the C. Besta Neurological Institute (Milan, Italy), which was appointed as reference center for the treatment of neuro-oncological patients from other departments in Lombardy during the COVID-19 emergency period. In line with our triage protocol, the patient performed a nasopharyngeal swab for viral RNA of SARS-CoV-2 detection with reverse transcription-polymerase chain reaction (RT-PCR) by Allplex™ 2019-nCoV Assay (Seegene Inc., Seoul, Korea) for amplification of RdRP, N and E genes. The test was positive and SARS-CoV-2 infection was confirmed. The patient had a history of family exposure (the two daughters tested positive) and reported in the previous month only hyposmia and hypogeusia without rhinorrhea or nasal obstruction, which had resolved at the time of admission. Blood tests at admission revealed no significant abnormalities. A chest computed tomography (CT) reported a left pulmonary lesion suggestive of tumor in the absence of inflammatory changes [Figure 2]. According to our classification of urgency in category A+, meaning patients with intracranial tumors with mass effect or with progressive neurological deficit, without deterioration of consciousness, for which treatment is deferred for up to 10 days, two swabs were resampled after 7 days and both were still positive.[5] Considering the neurological and radiological stability, it was established to perform three new swabs after a period of 7 days with negative results, leading the way to surgery. The two cerebellar lesions were then surgically removed with a pathological result of pulmonary adenocarcinoma metastases. In the early post-operative period, the patient manifested acute onset of psychotic symptoms with hyperactive delirium. He was admitted to the intensive care unit, and antipsychotic therapy was administered with quetiapine (up to 1 g/day); chlorpromazine and sedation with propofol and dexmedetomidine until control of the neuropsychiatric picture were obtained. Four days after surgery, the patient suddenly developed fever (up to 38.5°C) and acute respiratory failure. Another chest CT scan disclosed a radiological pattern of ground-glass opacities in the lower lobes bilaterally, suggesting a viral pneumonia [Figure 2]. Laboratory findings revealed an increased inflammatory response with higher white blood cell counts (15.94 × 10^9/L), higher neutrophil counts (14.54 × 10^9/L), lower lymphocyte counts (0.79 × 10^9/L), lower platelet count (66 × 10^9/L), increased D-dimer (1.77 mg/L), and C-reactive protein (229.8 mg/L) levels. Serological tests were performed using LIAISON® SARS-CoV-2 S1/S2 IgG kit (Diasorin S.p.A, Saluggia, Italy), an indirect chemiluminescent immunoassay serology test for detecting IgG antibodies against S1/S2 antigens. An antibody level of 133 kAU/L was found (positive: >15.0 kAU/L). The RT-PCR on a nasopharyngeal swab was negative. Under the strong radiological and laboratory suspicion of pneumonia

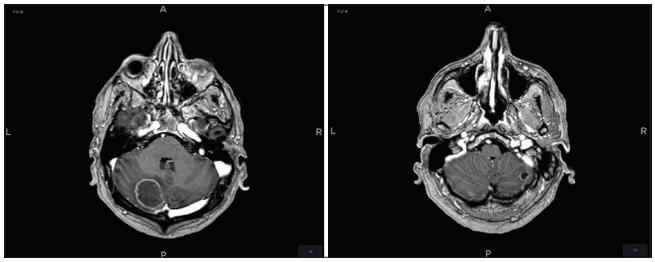

Figure 1: Axial post-contrast pre-operative magnetic resonance T1-weighted imaging showing two bilateral hemispheric cerebellar lesions, suggestive of metastases.

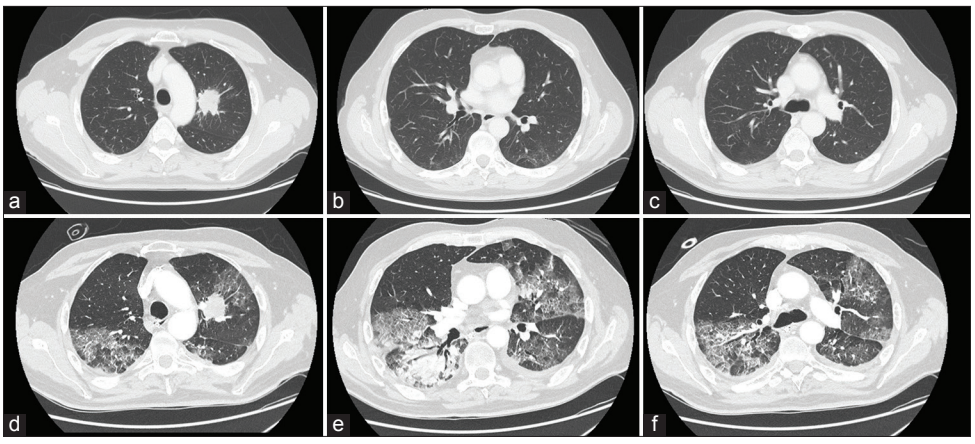

Figure 2: (a-c) Chest computed tomography (CT) scans showing a left pulmonary lesion suggestive of tumor in the absence of inflammatory changes at admission; (d-f) chest CT scans showing ground-glass opacities in the lower lobes bilaterally at the onset of fever and acute respiratory failure.

from COVID-19, a new RT-PCR was performed after 72 h which confirmed SARS-CoV-2 infection. Oxygen therapy with alternating cycles of high-flow nasal cannula and low-flow venturi mask was administered until full recovery.

DISCUSSION

Recent studies have suggested that SARS-CoV-2 can spread in the brain through the olfactory nerve and bulb and reach a latency state by eluding the immune response.[3,9-11] In our case, the hyposmia developed at the first infection, and the neuropsychiatric signs unfolded during early post-operative reactivation of the virus seem to corroborate this hypothesis.

It has been documented that up to one-third of patients with COVID-19 develop neuropsychiatric symptoms, including delirium, and these manifestations tend to occur early in the disease (mean period: 1–2 days). However, these patients may be associated with a more severe evolution of the disease.[7] It has been hypothesized that neuropsychiatric symptoms may have a multifactorial origin through direct factors such as invasion of the central nervous system by the virus through the olfactory bulb or indirectly through the immune response with the influence of medical therapy, the psychological impact of the disease, social isolation, and age.[3,11] Studies on transgenic mice supported the hypothesis that the virus can spread probably using transneuronal/transsynaptic routes employing axonal transport in the brain after entering through the olfactory nerve and bulb.[8] Recently, Politi *et al*. have described in magnetic resonance imaging in FLAIR sequences bilateral cortical hyperintensity of the olfactory bulbs and of the right gyrus rectus in a 25-year-old woman with COVID-19 demonstrating severe anosmia, dysgeusia, and mild dry cough without fever or other symptoms.[9] Our patient reported olfactory and gustatory disturbances as the unique symptoms of the first infection. Indeed, it has been estimated that about 5% of patients may have hypogeusia and hyposmia in SARS-CoV-2 infection.[7] These signs may be the result of inflammatory injury of the olfactory epithelium due to the particular tropism of the virus for the nasal mucosa expressing proteins required for host cell entry, ACE2, and TRMPSS2.[4] Moreover, findings suggest that neurons and glial cells can also express ACE2 protein that can make them vulnerable to viral invasion.[2] A recent letter to the editor by Roe further hypothesized that SARS-CoV-2, similarly to several other viruses, can reach a latency state in the central nervous system by eluding the immune response and reactivate when a stress weakens the immune defense system.[10]

In accordance with these observations, we hypothesize that olfactory and gustatory dysfunction in the first infection may have been the predisposing cause of neuropsychiatric involvement in early post-operative reactivation of the virus. Thereafter, the spread of the virus provoked pneumonia with characteristic chest CT findings of ground-glass opacities in the lower lobes bilaterally.

Ai *et al*. recommend that a chest CT scan with typical features may be useful in early detection of suspected COVID-19 cases, despite an initial negative RT-PCR test.[1] Based on this evidence and strong clinical and laboratory findings, we repeated the swab which resulted positive, confirming the reactivation of the viral infection.

Another study by Ye *et al*. reported 5 patients with reactivation of 55 patients (9%) after discharge. All 5 patients had typical chest CT findings with clinical features similar to the other non-recurrent patients. Their reactivation time range was 4–17 days. The authors assumed that immunosuppressive therapies may be the main factor causing reactivation.[13] According to these data, our patient presented a recurrence of infection, intended as a RT-PCR positive, after 15 days from the three negative swabs and was taking corticosteroid therapy for cerebellar metastases. In addition, surgery and general anesthesia would have then played a pivotal role in triggering COVID-19 reactivation by inhibiting the immune system.

Hoang *et al*. in a recent letter to the editor discuss possible scenarios of the recurrence of a positive RT-PCR after discharge with a negative test, considering false negatives, reactivation, and reinfection.[6] The false negatives may be attributable not only to the diagnostic accuracy of the test kit but also to the sampling procedure. Comparing the Allplex™ 2019-nCoV assay (Seegene Inc., Seoul, Korea) RT-PCR kit used by us with the FDA approved kit (CDC, Atlanta, USA), the manufacturer declared a 100% positive percent agreement (95% CI: 92.75% ~ 100.00%) and a 93.07% negative percent agreement (95% CI: 85.76% ~ 96.93%).

Serological tests on our patient, performed in parallel with pneumonia and post-operative positive RT-PCR, demonstrated seroconversion with high levels of IgG (133 kAU/L). These neutralizing antibodies could be the product of the first infection, since recent publications indicate a mean time of seroconversion between 9 and 14 days after the onset of the disease, and we place the reactivation of the infection in the immediate post-operative period when neuropsychiatric symptoms occurred [Figure 3].[14]

In this view, we can infer that the antibodies, presumably produced by the first infection, were not protective against the virus, raising the suspect that under particular stress conditions weakening the immune defense system, seroconverted patients may still be at risk of reactivation and spread of the virus.

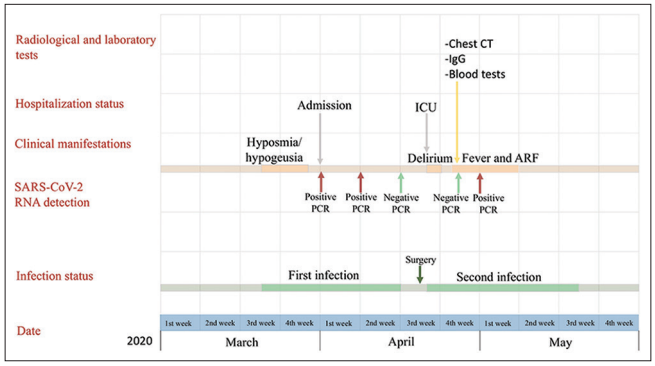

Figure 3: Timeline of clinical symptomatology and diagnostic investigations, from March 2020 to May 2020. ARF: Acute respiratory failure, CT: Computed tomography, ICU: Intensive care unit, PCR: Polymerase chain reaction.

In agreement with Hoang *et al*., we believe that the problem of SARS-CoV-2 reactivation is of crucial importance in the global public health emergency management, warranting further thorough investigation of its underlying mechanisms and prevalence.[6]

CONCLUSION

We reported a case of COVID-19 reactivation associated with a neurosurgical operation with early neuropsychiatric involvement presumably promoted by olfactory and gustatory impairment in the first infection. Our report highlights the importance of comprehensive screening assessments in sensitive cases highly susceptible to COVID-19 recurrence.

Acknowledgments

Ethical compliance statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Patient signed informed consent regarding publishing his data and photographs.

Data availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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