



Multifocal nivolumab immune-related adverse effects during asymptomatic SARS-CoV-2 infection: causality or casuality?

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Dear Editor,

Immune checkpoint inhibitors (ICI) have deeply reshaped the treatment and prognosis of oncological disorders, although they have been associated with the occurrence of immune-related adverse effects (irAE) that may require immunotherapy and treatment discontinuation. The role and the outcomes of SARS-CoV-2 infection, that may trigger autoimmune disorders, in patients receiving ICI treatment are still widely uncertain [1].

We report the case of a patient that developed a severe and refractory irAE during asymptomatic SARS-CoV-2 infection.

A 78-year-old man with a 24-h history of confusion was admitted to the emergency department (ED), where he underwent to brain CT and CT angiography that resulted unremarkable. During his stay in the ED, the patient developed a rapidly progressive respiratory failure and refractory hypotension: nasal swab tested positive for SARS-CoV-2. His medical history was relevant for metastatic melanoma under treatment with PD-1 inhibitor nivolumab (two infusions, the last 2 weeks before admission). He had no history of autoimmune conditions.

He was admitted to the intensive care unit (ICU) where he was intubated and treated with dopamine infusion. SARS-CoV-2 PCR was repeated on broncho-alveolar lavage and tested positive again; however, the patient did not develop any clinical or radiological signs of SARS-CoV-2-associated pneumonia. Infectious disorders were ruled out by negative procalcitonin and C reactive protein; however, blood

chemistry revealed an increase of muscle creatine kinase (2982, r.v. 39–308 ug/L) and troponin (1103, r.v. < 15 U/L). The transthoracic echocardiogram and electrocardiogram were consistent with myocarditis.

During his stay in ICU, the patient worsened, and at the time of neurological evaluation, he was wakeful, unable to interact with the examiner, with severe proximal muscle weakness of arms, legs, and neck extensors. The patient had a complete gaze palsy and a left extensor response; he was completely dependent on mechanical ventilation and dopamine infusion.

Brain MRI revealed small ischemic foci in the right frontal lobe (Fig. 1a, b); the EEG showed a severe diffuse slowing with no epileptiform discharges. CSF analysis resulted unremarkable. Nerve conduction studies were within normal range, but electromyography showed myopathic signs with acute denervation in proximal muscles. Repetitive nerve stimulation was consistent with neuromuscular junction dysfunction.

A nivolumab immune-related adverse effect (irAE) was suspected and a broad panel of autoantibodies was requested including myositis specific and associated antibodies, onconeural and neuronal surface antibodies, anti-acetylcholine receptor (ACh-R), and anti-muscle-specific kinase antibodies. Anti-Ro52, anti-ACh-R, and anti-titin antibodies resulted strongly positive, while a weak positivity for anti-CV2/CRMP5 antibodies was detected; the remaining antibodies tested negative.

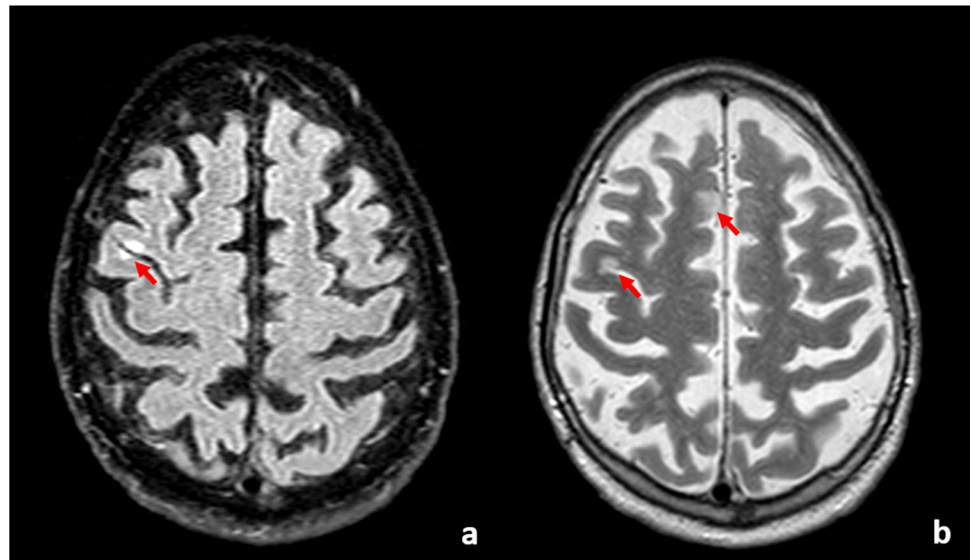
The patient was treated with a course of intravenous methylprednisolone (1000 mg for 5 days, then slowly tapered until a maintenance dose of 100 mg/day). At the end of high dose steroid treatment, the patient started to interact with examiners, CK were within normal range, and the EEG markedly improved; however, he was still unable to wean from ventilation. He was promptly treated with 7 cycles of plasma exchange with no benefit. A trial of intravenous immunoglobulins, eventually followed by

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Fig. 1 Fluid attenuated inversion recovery (FLAIR) (a) and T2 weighted (b) scans showing two small right frontal ischemic lesions (red arrows). Both lesions had restricted diffusion in diffusion weighted scans



a second-line treatment, was planned, but the patient developed a severe bilateral ventilation-associated pneumonia that rapidly worsened resulting in fatal outcome.

Our patient developed a severe, multifocal irAE (myasthenia, myositis, and myocarditis) with multiple antibodies positivity (anti-ACh-R, anti-titin, anti-Ro-52) during asymptomatic SARS-CoV-2 infection. Our patient also presented with acute encephalopathy with evidence of small ischemic lesions that could be secondary to the hypoxic damage related to hypoventilation or to nivolumab toxicity, although the latter hypothesis is less probable given the normal CSF findings, that are atypical for irAE [2].

SARS-CoV-2 infection has been associated with different autoimmune neurological complications [3], which may widely overlap with irAE and which may also respond to immunotherapy. Given the strong association with nivolumab treatment, we diagnosed our patient with irAE rather than an autoimmune complication induced by SARS-CoV-2; however, we cannot exclude that the two conditions may have acted interdependently. Indeed, we hypothesize that SARS-CoV-2 and nivolumab exerted a synergic role in the development of a severe, refractory neurological autoimmunity: SARS-CoV-2 infection has proven to induce an overexpression of PD-1 in CD8+ T cells, even though those T cells are still functional and not exhausted [4], and thus an ideal trigger for autoimmunity. Moreover, the role of concurrent viral infections in patients that develop irAE during ICI treatment has already been demonstrated for Epstein-Barr virus [5], and our case suggests that SARS-CoV-2 could have acted similarly.

To our knowledge, this is the first case of nivolumab irAE associated with concomitant asymptomatic SARS-CoV-2 infection. Physicians should be particularly vigilant for autoimmune complications in patients that are being treated with ICI during SARS-CoV-2 pandemic.

Declarations

Ethical approval None.

Consent to participate Consent was acquired from the patient's closest relative.

Consent for publication Consent was acquired from the patient's closest relative.

Competing interests The authors declare no competing interests.

Informed consent Consent was acquired from the patient's closest relative.

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