Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Immune-related pneumonitis with nivolumab and ipilimumab during the coronavirus disease 2019 (COVID-19) pandemic

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Dear Editor,

The city of São Paulo is the epicentre of the coronavirus disease 2019 (COVID-19) pandemic in South America. Until May 24th, 2020, a total 49,306 confirmed cases and 3550 deaths were attributted to the new severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2) in the city [1]. As such, patients with acute respiratory symptoms with hospitalisation criteria are usually admitted under the presumed diagnosis of COVID-19, until at least one negative reverse transcriptase polymerase chain reaction (RT-PCR) test. However, patients undergoing immune checkpoint inhibitors are at risk for immune-related pneumonitis. This currently poses a diagnostic challenge, as symptoms and computerised tomography (CT) findings often overlap [2–5]. Steroids, the main treatment modality for immune-related adverse events, are cautioned against for COVID-19, potentially causing delay in proper management of a severe condition [6].

We present two cases of patients with metastatic melanoma treated with a standard dose of ipilimumab at 3 mg/kg and nivolumab at 1 mg/kg. The first patient is an 83-year-old man with a melanoma of unknown primary origin metastatic to lymph nodes and the

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brain. The second is a 74-year-old woman with uveal melanoma metastatic to the liver. Both patients developed acute respiratory symptoms after the first dose of therapy, with low-grade fever (37.5–37.6 °C), decreased oxygen saturation (89–92%), dry cough and dyspnoea. Symptoms started after 5 and 16 days from the first cycle of treatment, respectively. Chest CT upon hospital admission showed similar findings in both cases, with non-specific bilateral ground glass opacities (GGOs) and alveolar consolidations (Fig. 1A–B). Angio-CT excluded pulmonary embolism. The RT-PCR test was performed for Sars-Cov-2 from a nasopharyngeal swab of both patients at admission, and the patients were started on supportive treatment. The female patient also received intravenous ceftriaxone, oral azithromycin and hydroxychloroquine. Steroids were withheld due to the higher likelihood of COVID-19, based on epidemiology. Both patients developed worsening of their symptoms within the first 48 h. A repeat chest CT performed two days after admission showed a more severe pattern, still suggestive of COVID-19 infection (Fig. 1C). A second RT-PCR test was collected for both, but intravenous methylprednisolone was initiated only for the male patient at that time, with dramatic clinical and radiologic improvement within 24 h (Fig. 1E). For the female patient, steroids were further withheld until a second negative RT-PCR test was released, four days after admission. A third CT scan was obtained, again with worsening of previous findings (Fig. 1D). At this point, immune-related pneumonitis was finally favoured and she was started on intravenous methylprednisolone. Her symptoms also markedly improved within one day. After three days, a repeat chest CT showed a marked improvement in GGOs and consolidations (Fig. 1F). The patients were discharged from the hospital between two to five days after steroid initiation on an oral prednisone taper, without oxygen support and in a good clinical condition. A third RT-PCR test and serologic testing (IgM and IgG) were obtained at discharge, negative for both patients. A mean delay of 3 days in steroid initiation was attributed to the COVID-19 pandemic.

The current pandemic is imposing a presumed diagnosis of COVID-19 in patients with respiratory symptoms in epidemic regions. However, it is important to consider differential diagnosis. For patients undergoing chemotherapy or immunotherapy, pneumonitis is an adverse event that may be present in up to 10% of patients [3].

Immune-related pneumonitis and COVID-19 infection share similar clinical characteristics, such as dyspnoea, cough, increased respiratory rate and lower oxygen saturation. High-grade fever, which could aid in differential diagnosis, occurs in less than a third of patients with COVID-19, while it is documented in 12% of immune-related pneumonitis [2,3]. Radiologically, immune-related pneumonitis findings can vary significantly, with either organising pneumonia signs (unilateral or bilateral patchy alveolar consolidations) or non-specific interstitial pneumonitis (with reticular markings, traction bronchiectasis and GGOs) [5]. For COVID-19, the main findings were peripheral, bilateral GGOs, with or without alveolar consolidations or thickened

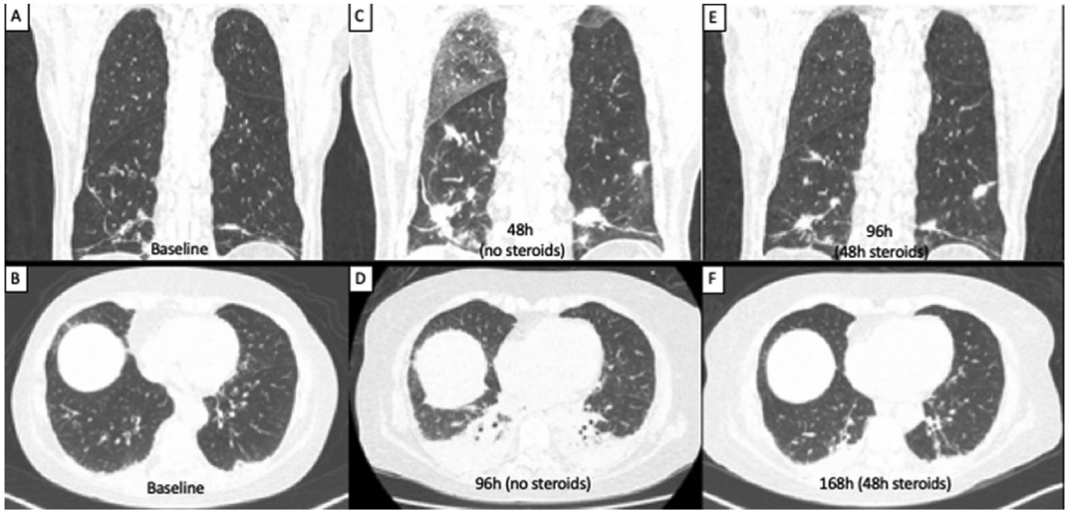

Fig. 1. (A) baseline CT scan of patient 1 upon hospital admission revealing interlobular septum thickening and sparse GGO; (B) Baseline CT scan of patient 2 upon hospital admission revealing few sparse GGO, suspicious for COVID-19; (C) repeat CT scan of patient 1 after 48h of observation while COVID-19 test was pending, showing worsening of disease, with alveolar patchy consolidations and increase in GGOs and septum thickening; (D) repeat CT scan of patient 2 after 96h of supportive treatment, while two COVID-19 tests were negative, showing worsening of GGOs and new alveolar consolidations and interlobular septum thickening; (E) improvement of CT pattern in patient 1 after 48 h of steroids; (F) marked improvement of CT pattern in patient 2 after 48 h of steroids. CT, computed tomography; COVID-19, coronavirus disease 2019; GGOs, ground glass opacities.

intralobular septum, reverse halo sign or other findings of organising pneumonia (seen later in the course of disease) [4].

A positive nasopharynx RT-PCR test confirms the diagnosis of COVID-19 and is the gold standard diagnostic method. The test, however, may present as a false-negative test in 11–29% of cases, warranting a new test if clinical and radiographic features are highly suggestive of the condition [7].

In this report, the mean delay of corticosteroid administration was 3 days, which may have led to a clinical and radiologic deterioration, increased patient exposure to Sars-Cov-2 in the wards reserved for suspected cases and to a longer hospitalisation.

Although routine corticosteroids should be avoided due to the possible impairment in viral clearance, its role in the current pandemic remains unclear [6,8]. It seems unlikely that a short course of steroids (24–48 h) may irreversibly affect both the clinical outcome of an unconfirmed COVID-19 infection or compromise immunotherapy efficacy. Conversely, symptoms may rapidly improve if the pneumonitis is from immune-mediated aetiology, as occurred in our patients within 24 h.

In conclusion, we warrant caution with the utilisation of immune checkpoint inhibitors during the COVID-19 pandemic, particularly when combining two agents. We recommend always considering immune-related pneumonitis among differential diagnosis when respiratory signs and symptoms overlap with treatment timing. Based on our experience, we consider one negative RT-PCR test sufficient to initiate steroids, in the absence of other likely diagnosis, while a second sample is collected and analysed.

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All authors wrote, proofread, participated in the care of the patient and approved the final manuscript.

Consent for publication

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Ethics approval and consent to participate

Not applicable.

Conflict of interest statement

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