

Figure 2 In these pictures, we can observe the HHV8 virus (a, orange arrow) and a macro vesicle containing numerous viral particles with the morphological features of corona virus particles (b, blue arrow). In figure c, instead, we can observe both viruses together.

- Smaller nuclear viral particles (80 nm) consisting of central round black core surrounded by a brighter halo that we interpreted as HHV8 virus (Fig. 2a,c orange arrow).
- Large cytoplasmic vesicles containing spherical particles with crown-like spikes ranging from 80 to 100 nm in diameter that we identify as SARS-CoV-2 (Fig. 2b,c blue arrow).

Considering the well-known influence of the HIV virus on some form of Kaposi sarcoma,² we wonder, if there could be any similar relation between SARS-CoV-2 virus and HHV8. Finding both COVID-19 and HHV8 viruses in a patient's specimen observed under TEM³ led us to speculate the mechanisms of co-infection of these pathogens. It also suggested a significant role of IL-6 in the process, which was already established during the trials using anti-IL-6 drugs in the hyperinflammatory phase of COVID-19 infection.⁴

Moreover, we assume there is an interaction between the SARS-CoV-2 and the Kaposi sarcoma virus, where the first actor contributes to stimulate an hyperinflammatory status leading to proliferation of the HHV8 resulting in recurrence of Kaposi Sarcoma.


Lastly, we suggest the use of TEM to confirm the presence of the virus in skin specimens in laboratory environments, where specific antibodies versus SARS-CoV-2 are not available.

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The patient has given written informed consent to the publication of her case details.

Conflicts of interest

Dr. E. Leoni, Dr. M. Cerati, Dr. G. Finzi, Dr. M. Lombardo and Dr. F. Sessa have nothing to disclose.

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COVID-19 and immune checkpoint inhibitors

Editor,

SARS-CoV-2 confronts physicians with critical questions, including the use of anticancer therapies in the context of a possible COVID-19 infection. Based on a case report of a patient with metastatic melanoma, the course of a COVID-19 infection

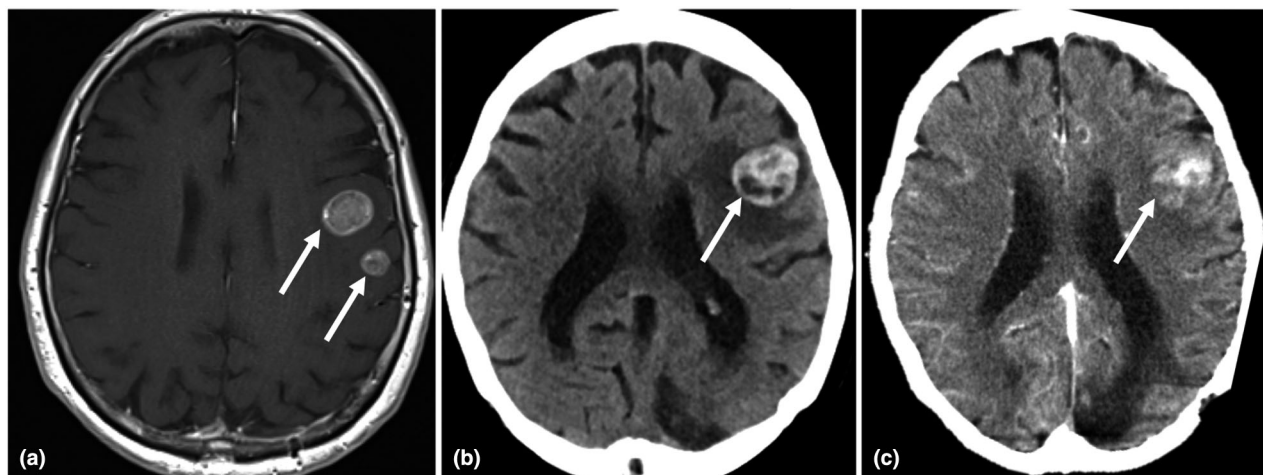


Figure 1 Brain imaging (a) Contrast enhanced MRI of the brain depicting two metastases in the left precentral gyrus (arrow) before therapy (b) CT of the brain with growth of one metastasis (arrow) (c) contrast enhanced CT of the brain after radiotherapy showing residual metastasis (arrow).

under immune checkpoint inhibitor (ICI) therapy will be shown, and recent literature will be discussed.

An 83-year-old woman with a history of melanoma was admitted to the emergency room with a visual field defect and severe headache in 12/2019. A brain MRI showed a tumour in the left occipital lobe and in the precentral gyrus. The patient underwent excision of the symptomatic left occipital tumour. Histology revealed melanoma brain metastasis. Additionally, stereotactic radiation therapy of the metastasis in the precentral gyrus was performed (Fig. 1). Whole-body CT scan showed no signs of extracranial metastasis. ICI therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg was initiated. Seven weeks later, the patient developed dry cough, dyspnoea, diarrhoea and fever. SARS-CoV-2 RNA was detected in nasopharyngeal swabs. The chest X-ray showed severe pulmonary consolidation. In addition, deep vein thrombosis and pulmonary embolism were diagnosed requiring anticoagulant therapy. An acute respiratory distress syndrome required tracheal intubation. Intensive care was required for 2 months before improvement in pulmonary function was achieved. On follow-up chest CT, pulmonary consolidation had significantly decreased (Fig. 2). After 2 months of mechanical ventilation, the patient was successfully weaned and extubated. The patient is recovering adequately. Brain MRI showed tumour regression, without signs of extracranial metastasis in whole-body CT scan.

Cancer patients are at higher risk of infection and severe infection outcomes. However, a large cohort of cancer patients was evaluated for COVID-19 in the United States to identify risk factors for COVID-19 susceptibility in cancer patients.¹ The prevalence of COVID-19 among cancer patients appeared to be lower than in the general population despite numerous potentially risky appointments at the clinic. Immunosuppressive

chemotherapies leave the patients more susceptible to infections like COVID-19. In contrast, ICIs are able to restore cellular immunocompetence.² However, an analysis of 423 COVID-19 cases depicted immunotherapy as an independent risk factor of severe COVID-19 pneumonia.³ Patients receiving ICI may develop symptoms consistent with immune-related adverse events (irAEs), COVID-19 infection or both.⁴ For example, a SARS-CoV-2 infected patient may present with fever, cough and dyspnea (mimicking ir pneumonitis), elevated troponin or heart failure (mimicking ir myocarditis) or/and elevated liver function tests (mimicking ir hepatitis).

The pulmonary changes observed in COVID-19 infection are comparable to those in ir pneumonitis and are caused by hyperactivation of the immune system, resulting in cytokine storm. Hence, patients who are more prone to develop irAEs are more likely to develop a cytokine storm in the case of SARS-CoV-2 infection characterized by a hyperinflammatory reaction with high levels of pro-inflammatory cytokines like interleukin-6 (IL-6).⁵ Clinical trials investigating anti-IL-6 therapy in patients with severe COVID-19 pneumonia yielded conflicting results.^{6–8} The WHO established a living guidance for the clinical management of COVID-19 and strongly recommends corticosteroids for the treatment of patients with severe COVID-19.⁹

Another relevant aspect is the effect of COVID-19 related diagnostic delays in cancer patients. A recent analysis shows a reduction in long-term survival of more than 10% due to a diagnostic delay of 3 months in most cancer types.¹⁰

This case report shows that elderly, frail patients under ICI treatment can survive a critical COVID-19 infection. Patients with an active tumour disease are facing a lethal outcome if diagnostic measures or/and tumour therapy are postponed. Patients under ICI treatment may develop symptoms possibly consistent

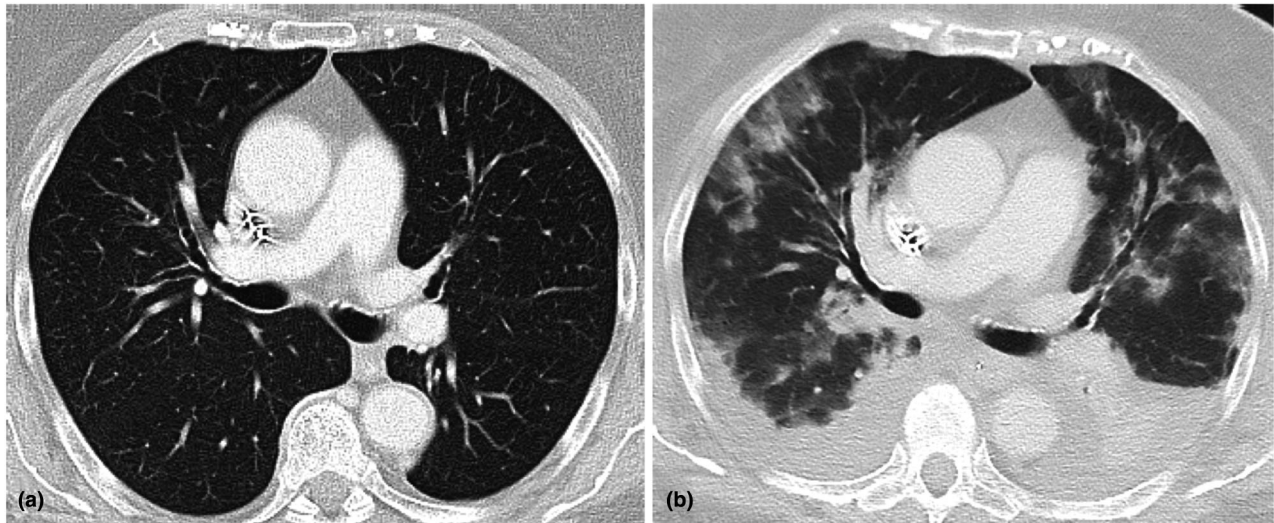


Figure 2 Pulmonary imaging (a) Normal chest CT scan before therapy. (b) Chest CT scan during therapy. Subpleural and peribronchovascular oval and round ground glass opacities, representing COVID-19. Bilateral pleural effusions were an additional finding.

with both irAEs or COVID-19. Several drugs are being investigated in clinical trials to treat critical COVID-19 infections. The WHO strongly recommends corticosteroids for the treatment of patients with severe COVID-19. We would like to point out that we described and discussed a single case. Multicentre retrospective studies are crucial to collect clinical data of as many patients as possible with COVID-19 and cancer to guide clinicians on management.

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