



Case Report

Pneumocystis *Jiroveci* Mimicking COVID-19 Pneumonia in a Patient who is Receiving Ipilimumab and Nivolumab Combination Therapy: A Case Report

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Abstract

The novel coronavirus SARS-CoV-2 that first appeared in December 2019 has threatened the world in a matter of months. The preoccupation by the risk of this disease might mislead the clinician and distract him from providing the best care for his patients who are as well exposed to other risks and conditions. We report in this article the case of a metastatic melanoma patient treated with immunotherapy, who presented for fever, respiratory symptoms and a diffuse bilateral lung infiltration with ground glass opacities. He was first suspected of having COVID-19 pneumonia, but then the right diagnosis of *Pneumocystis Jiroveci* pneumonia was made and this needed timely decision making in order not to lose the patient.

Keywords: Cancer, COVID-19, checkpoint inhibitors, computed X-ray tomography; ground glass opacities, pneumocystis

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On the 31st of December 2019, China reported for the first time the outbreak of a novel coronavirus also called SARS-CoV-2 or COVID-19. Since then the disease spread extremely fast to be declared by the World Health Organization as pandemic on the 11th of March 2020.^[1] Chinese researchers were the first to be interested in the implication of this disease on the management of patients with cancer. In fact, hospitals capacities were overwhelmed and many centers made arrangements to be able to accommodate the growing number of COVID-19 patients, multiplying the risk of exposure of cancer patients to the SARS-CoV-2.^[2] Moreover, most of the data available from Chinese trials encourage oncologists to withhold or postpone cancer treat-

ment during the pandemic because outcomes of oncology patients who acquire the COVID-19 is worse than that of the general population.^[3–5] Nevertheless, this fear as well as the preoccupation of the healthcare system with the fight of COVID-19 can have adverse implications on the management of cancer patients.^[6] We believe that this distraction effect affects not only the management but also the clinical judgement of practitioners in front of their patients' symptoms. We hereby report the case of a patient who is actively treated for a metastatic melanoma, who presented to our emergency department with fever and respiratory symptoms that made us think of COVID-19 pneumonia, but who actually had a *Pneumocystis Jiroveci* infection.

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Case Report

This is the case of a 68-year-old man known to have a history of well controlled hypertension and diabetes mellitus during the past 3 years, as well as coronary artery disease and paroxysmal atrial fibrillation. He reports a history of resection of a “nevus” of the dorsal region in a private clinic one year ago that was not pathologically assessed.

In February 2020, an MRI of the brain was performed upon his complain of generalized paresthesia that appeared progressively mainly affecting his distal limbs. It showed multiple diffuse metastatic lesions in the brain parenchyma as well as metastatic localizations in C1 and C2 vertebral bodies.

A PET-CT scan showed multiple metastatic bone lesions and a cutaneous and subcutaneous infiltration at the level of the scar where the “nevus” was resected. A biopsy of this infiltration confirmed the diagnosis of malignant melanoma with negative BRAF mutation.

He was started on oral corticosteroids and underwent a whole brain and cervical spine irradiation at a dose of 2000 cGys in 5 sessions which ended in March 13, with nearly complete neurological recovery.

While he remained on a daily dose of prednisone 40 mg as part of a tapering program because a faster dose reduction was attempted and not tolerated by the patient, a systemic treatment with the combination of Ipilimumab (240 mg) and Nivolumab (80 mg) was prescribed, according to the CheckMate 067 trial.^[7] He was admitted to the same-day ward to receive his first cycle of immunotherapy on the 1st of April 2020. His performance status was 0 at that time and he was completely asymptomatic. He was adequately wearing a surgical face mask, a pair of gloves and following social distancing rules.

At day 3, on the 4th of April, he presented to the emergency department for a sudden generalized weakness and a 38 °C fever before his admission. Blood pressure was normal; the patient had tachycardia with 110 bpm and had a SpO₂ of 89%. He did not complain of cough, but was tachypneic. He denied any recent travel or contact with a confirmed or suspected case of COVID-19.

Oxygen was delivered by nasal canula with a need of 5 L/ min to maintain a SpO₂ of 94%. Laboratory tests showed normal white blood counts ($5,5 \cdot 10^9/L$) with neutrophilia ($4,91 \cdot 10^9/L$) and lymphopenia ($0,34 \cdot 10^9/L$), a markedly elevated CRP (413 mg/L), a procalcitonin at 0.25 mcg/L and an LDH that is twice the upper limit of normal. Chest X-Ray showed nonspecific multifocal ill-defined bilateral infiltrates (Fig. 1). An enhanced high resolution CT (HRCT) scan was subsequently done and showed bilateral diffuse

ground glass opacities (GGO) with a mosaic attenuation, central distribution and peripheral sparing in both lungs. These GGO are also seen with superimposed intralobular and interlobular septal thickening, also known as a “crazy paving” pattern. Some small nodules were also noted in both lung bases, less than 7 mm in dimension. No lymphadenopathy, pleural or pericardial effusion were found (Fig. 2). Differential diagnosis according to the radiologist included *Pneumocystis Jiroveci* pneumonia (PCP), a cytomegalovirus (CMV) pneumonia, diffuse alveolar hemor-

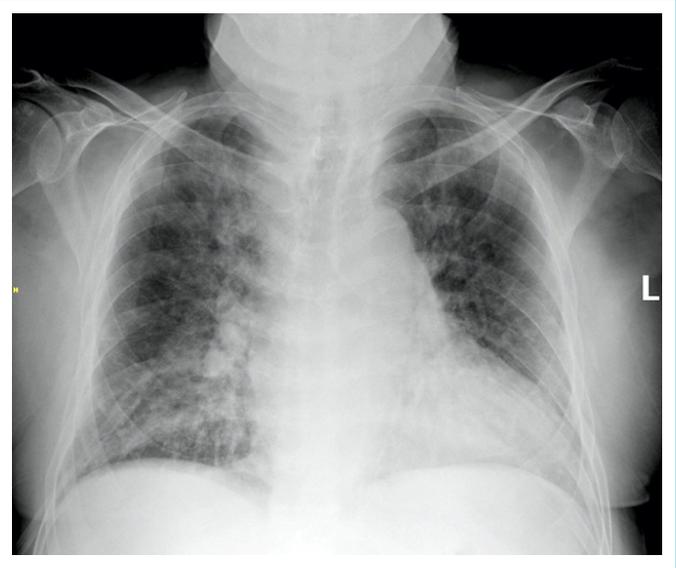


Figure 1. AP chest X-ray done in the emergency department, showing nonspecific multifocal ill-defined bilateral infiltrates.

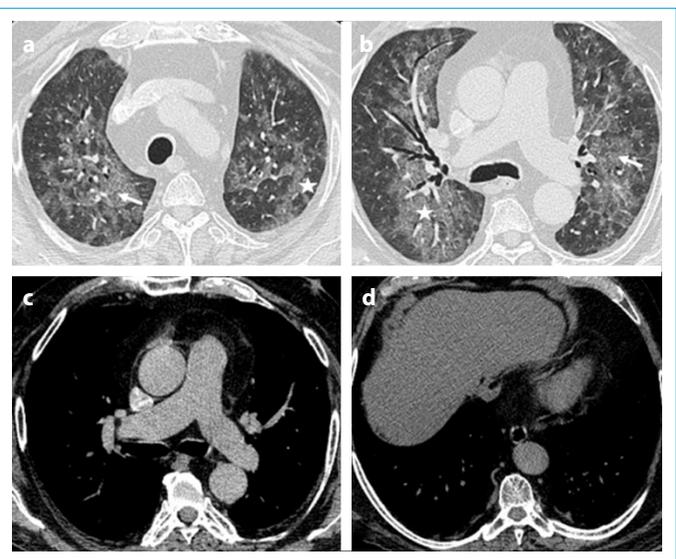


Figure 2. (a, b) Lung window in the HRCT of the chest done at admission showing bilateral diffuse central perihilar ground glass opacities (star) with intra and interlobular septal thickening and a crazy paving pattern (arrow). (c, d) Mediastinal window of the same HRCT showing no lymphadenopathy or pleuro-pericardial effusion.

rhage, and less probably a pneumonitis related to immune-checkpoint inhibitors therapy.

A SARS-CoV-2 RT-PCR was sent on a nasopharyngeal swab and the patient was transferred to the intensive care unit after he was started on levofloxacin 750 mg. He had a rapid clinical deterioration and was intubated few hours later. A bronchoscopy with bronchoalveolar lavage was done and specimens were sent for analysis. Levofloxacin was replaced by meropenem and vancomycin and by one dose of amikacin. In parallel, an anti-COVID-19 treatment was initiated as per the protocol of our institution while awaiting the laboratory results. The following day, while the patient continued to deteriorate with acute respiratory distress syndrome features and lactic acidosis, the SARS-CoV-2 RT-PCR came negative and *Pneumocystis Jiroveci* was microscopically identified in the bronchoalveolar lavage by direct fluorescent antibody staining. A treatment with trimethoprim-sulfamethoxazole was initiated on day 3. The anti-COVID-19 protocol was stopped after the second RT-PCR performed 24 hours later came negative. The patient's situation stabilized starting day 4 and improvement was witnessed afterwards.

An informed consent to publish these data was obtained from the patient's wife who was his legal representative due to his critical situation at the time we decided to report his case.

Discussion

The management of cancer patients during the COVID-19 pandemic is very controversial. Because of the vulnerability of this population, oncologists tend to keep a low threshold for suspicion.^[8] However, this attitude might mislead the clinician towards missing other differential diagnosis.

In front of our patient's presentation we considered the following differential diagnosis:

- A COVID-19 pneumonia

672 confirmed cases of COVID-19 were reported in our country until the 18th of April 2020, out of around five millions habitants, most of them had chronic comorbid conditions. A close contact with a confirmed case or a history of recent travel to another endemic region was not found in all these patients.^[9] Our patient was admitted to the hospital for immunotherapy three days before his present admission and was seeking medical care in the past two months. According to data published by Zhang et al.,^[5] a hospital-associated transmission was found in 28.6% of cancer patients who were diagnosed with COVID-19 in their cohort.

Fever was reported in 87% and fatigue in 41% of laboratory confirmed cases in the largest retrospective national-wide cohort in China.^[10] Both findings were present in our pa-

tient along with respiratory symptoms. As for the patients' laboratory results, an elevated LDH with markedly elevated CRP were consistent with results of patients diagnosed with COVID-19 pneumonia in the literature, as well as the low procalcitonin value that made a bacterial pneumonia less likely.^[11] The patient also had marked lymphopenia, but his white blood cells pattern could also be consistent with neutrophilia resulting from corticosteroids exposure. Moreover, bilateral GGO found on the HRCT scan raised our index of suspicion. Most common features of COVID-19 pneumonia on HRCT are peripheral bilateral multifocal lung GGO, consolidation, crazy paving, reversed halo sign, multifocal organizing pneumonia, traction bronchiectasis and microvascular dilation within the lesions.^[12, 13] Hence, the central perihilar distribution of GGO and the prominent septal thickening in this patient were against this diagnosis. However, a case of a Chinese patient with lung adenocarcinoma who had atypical imaging findings was reported. This patient had a laboratory confirmed COVID-19 infection and his chest CT scan showed diffuse, irregular, small ground-glass opacities with partial consolidation, which is not strongly suggestive of COVID-19.^[14]

One could have thought that the double immunotherapy compromised our patient's immunity and predisposed him to a COVID-19 infection, however this relationship is not yet clear in the literature.^[15] Moreover, the use of corticosteroids in patients with a COVID-19 infection is not advised by many experts^[16] and we thought that if our patient had a COVID-19 pneumonia his rapid clinical deterioration could be linked, at least in part to the prolonged treatment with high dose prednisone.

- A Pneumonia caused by another pathogen

Cancer patients are more vulnerable to any viral, bacterial or fungal infection. This observation is not debatable in patients undergoing chemotherapy especially for those who are at increased risk of neutropenia. The risk of an opportunistic infection in patients treated with immune checkpoint inhibitors is less proved.^[17] However, the major risk factor for this patient is his prolonged exposure to high dose prednisone. In fact, the incidence of PCP in patients on immunosuppressive therapy, including corticosteroids is higher than that in the general population, and most of international guidelines recommend a PCP prophylaxis in patients treated with high dose corticosteroids.^[18, 19] Early empiric coverage of *P. Jiroveci* without laboratory confirmation is not a standard of care. Nonetheless, findings on the chest CT scan of this patient along with his history of corticosteroids exposure should raise the suspicion of a PCP.

- A pneumonitis related to immune checkpoint inhibitors
- A radiographically confirmed pneumonitis related to im-

munotherapy, especially with nivolumab and pembrolizumab usually develops within the range of 2.6 months after starting therapy (range: 0.5–11.5 months)^[20] which was too soon for our patient. In a series of 43 patients who have been treated with an anti-PD1 or anti P-DL1, with or without an anti-CTLA4, the incidence of pneumonitis was 5% and those who were on a combination therapy were more affected. The median duration of exposure to immune checkpoint inhibitors before the diagnosis of pneumonitis is made was 2.8 months, but the earliest case occurred 9 days after exposure, and onset was earlier with combination therapy.^[21] Our patient had only a 4 days exposure history to immunotherapy, but we raised the possibility of an early pneumonitis as a differential diagnosis although we knew that this short-term exposure along with the concomitant treatment with oral corticosteroids makes this diagnosis less likely.

Among the differential diagnosis on HRCT, the most likely in an immunocompromised patient would be a PCP. Even though CT findings such as cysts, consolidation and nodules were lacking, our patient had bilateral diffuse central perihilar GGO associated with mosaic attenuation and interlobular and intra lobular septal thickening which are the main and most frequent findings in PCP.^[22] Pleural and pericardial effusions are rare in PCP.^[22] Moreover, a CMV pneumonia – or any viral induced pneumonia – would be included in the differential diagnosis since it induces diffuses patchy GGO. However, the lack of tree in bud opacities, nodules and consolidation made it less likely.^[23, 24] Diffuse alveolar hemorrhage can show multiple GGO and consolidations with a crazy paving pattern, but the clinical presentation would usually be more severe and frequently includes hemoptysis.^[25] Lastly, a checkpoint-inhibitor pneumonitis presents a wide spectrum of findings such as acute interstitial pneumonia, acute respiratory distress syndrome, a cryptogenic organizing pneumonia and a nonspecific interstitial pneumonia (NSIP).^[20] Neither the imaging finding nor the timing of onset favored this diagnosis in our patient over others.

Conclusion

SARS-CoV-2 is a real threat for healthcare professionals and for cancer patients. Oncologists are challenged during this pandemic to provide the best care for their patients without exposing them to the risk of infection. A biggest challenge for them is to maintain a good clinical sense and not let this outbreak distract their clinical judgement. We should always keep a higher index of suspicion in cancer patients during this pandemic but also be aware that this population remains exposed to the same risks and complications as before the pandemic and has all the rights to get the care for every condition other than a coronavirus disease.

Disclosures

Informed consent: Written informed consent was obtained from the parents of the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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