



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, which first appeared in December 2019, threatened the world within a few months. Being preoccupied with the risk of this disease might mislead the clinicians and prevent them from providing the best care to their patients who are also exposed to other risks and conditions. In this article, we present a metastatic melanoma patient, who presented with fever, respiratory symptoms and a diffuse bilateral lung infiltration with ground-glass opacities treated with immunotherapy. He was first suspected of having COVID-19 pneumonia, but then *Pneumocystis Jiroveci* pneumonia was correctly diagnosed and this had to be decided in a timely manner so as not to lose the patient.

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

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

cancer treatment during the pandemic because the outcomes of oncology patients infected with the COVID-19 are worse than those of the general population.^[3–5] However, this fear as well as the health system's preoccupation with the fight against COVID-19 can have adverse effects on the management of cancer patients.^[6] We believe that this distracting effect not only affects management but also the clinical judgement of practitioners in the face of their patients' symptoms. We hereby report a case actively treated for metastatic melanoma, who presented to our emergency department with fever and respiratory symptoms suggestive of COVID-19 pneumonia, but actually had *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 over the past 3 years, as well as a coronary artery disease and paroxysmal atrial fibrillation. One year ago, he reported a hat resection of a “nevus” in the dorsal region that was not pathologically assessed in a private clinic.

In February 2020, an MRI of the brain was performed upon the complaint of generalized paresthesia that appeared progressively and 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.

The PET-CT scan showed multiple metastatic bone lesions and a cutaneous and subcutaneous infiltration at the scar level where the “nevus” was resected. A biopsy from this infiltration confirmed the diagnosis of malignant melanoma with a negative BRAF mutation. Oral corticosteroids treatment was started and 2000 cGys dose of whole brain and cervical spine was irradiated in 5 sessions that ended in March 13, and almost a complete neurological recovery was achieved.

As a faster dose reduction was attempted and not tolerated by the patient, a daily dose of 40 mg prednisone remained as part of the tapering program, and the patient was prescribed a systemic treatment with the combination of Ipilimumab (240 mg) and Nivolumab (80 mg) according to the CheckMate 067 trial.^[7] He was hospitalized on the same day to receive his first cycle of immunotherapy in April 2020, 1. His performance status was 0 at that time and he was completely asymptomatic. He wore a surgical face mask, a pair of gloves and followed social distance rules. Before his hospitalization, on the 3rd day, he was admitted to the emergency department on April 4, due to a sudden general weakness and a 38 °C fever. Blood pressure was normal; the patient had tachycardia at 110 bpm and a SpO₂ of 89%. He did not complain of cough, but was tachypneic. Not any recent travel or contact with a confirmed or suspected case of COVID-19 was reported. Oxygen was delivered by nasal cannula 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 was 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 performed 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), cytomegalovirus (CMV) pneumonia, diffuse alveolar hemorrhage, and less likely pneumonitis due to immune-checkpoint inhibitors therapy.

SARS-CoV-2 RT-PCR was sent on a nasopharyngeal swab

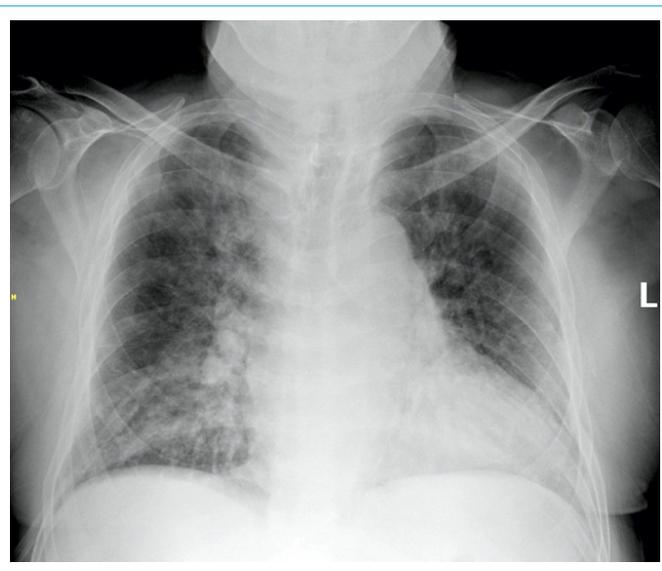


Figure 1. AP chest X-ray taken in the emergency department showing nonspecific multifocal ill-defined bilateral infiltrations.

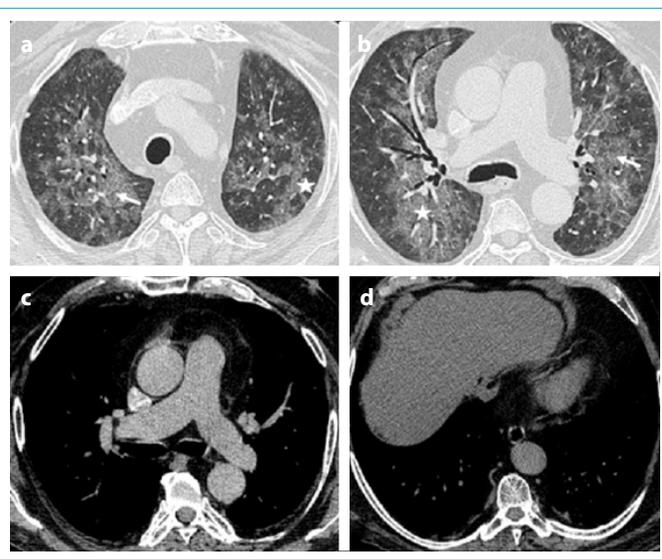


Figure 2. (a, b) The lung window in the HRCT of the chest at the admission showing bilateral diffuse central perihilar ground-glass opacities (star) with intra and interlobular septal thickening and a crazy paving pattern (arrow). (c, d) Mediastinal window of the same HRCT showing no lymphadenopathy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

and the patient was taken to the intensive care unit after being started on levofloxacin 750 mg. The patient had rapid clinical deterioration and was intubated a few hours later. Bronchoscopy with bronchoalveolar lavage was carried out and samples were sent for analysis. Levofloxacin was replaced by meropenem and vancomycin and one dose of amikacin. In parallel with this, 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 appeared negative and *Pneumocystis Jiroveci* was microscopically identified in the bronchoalveolar lavage by direct fluorescent antibody staining. On day 3, a treatment with trimethoprim-sulfamethoxazole was initiated. Anti-COVID-19 protocol was stopped when the second RT-PCR performed 24 hours later turned negative. The patient's condition stabilized from the day 4 and improved afterwards.

An informed consent to publish this data was obtained from the patient's spouse who was the legal representative of him due to his critical condition 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 may mislead the clinician into missing other differential diagnoses.

In face of our patient's condition we considered the following differential diagnosis:

- A COVID-19 pneumonia

In our country, 672 confirmed COVID-19 cases were reported out of around five million inhabitants, until 18 April 2020, most of them had chronic comorbid conditions. All of these patients had no history of close contact with a confirmed case or a recent travel to another endemic area.^[9] Our patient was admitted for immunotherapy three days before his present hospitalization and had been seeking medical assistance for the last two months. According to data published by Zhang et al.,^[5] 28.6% of cancer patients diagnosed with COVID-19 in their cohorts had hospital-related transmission. Fever was reported in 87% and fatigue in 41% of laboratory-confirmed cases in the largest national retrospective cohort in China.^[10] Both findings were present in our patient along with respiratory symptoms. As for the laboratory results of the patient, an elevated LDH with markedly elevated CRP was consistent with the results of patients diagnosed with COVID-19 pneumonia in the liter-

ature, as well as a low procalcitonin value that makes a bacterial pneumonia less likely.^[11] The patient also had marked lymphopenia, but the white blood cell pattern may also be consistent with neutrophilia resulting from corticosteroids exposure. Moreover, the bilateral GGO found in the HRCT scan raised our index of suspicion. The 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 Chinese case with lung adenocarcinoma with 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 that was 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 at least partially related to the prolonged high-dose prednisone therapy.

- A Pneumonia caused by another pathogen

Cancer patients are more vulnerable to any viral, bacterial, or fungal infection. This observation is not controversial in patients receiving chemotherapy especially in those at high risk of neutropenia. The risk of an opportunistic infection is less proven in patients treated with immune checkpoint inhibitors.^[17] However, the main risk factor for this patient was his prolonged exposure to high doses of prednisone. In fact, the incidence of PCP is higher in patients receiving immunosuppressive therapy, including corticosteroids 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 empirical coverage of *P. Jiroveci* without laboratory confirmation is not a standard of care. Nonetheless, the findings on chest CT scan of this patient along with his history of corticosteroid exposure should raise the suspicion of a PCP.

- A pneumonitis related to immune checkpoint inhibitors
A radiographically confirmed pneumonitis associated with immunotherapy, particularly with nivolumab and pembrolizumab, usually develops within 2.6 months after initiation of therapy (range: 0.5–11.5 months)^[20] which was too early

for our patient. In a series of 43 patients treated with an anti-PD1 or anti-P-DL1, with or without an anti-CTLA4, the incidence of pneumonitis was 5% and those who received combination therapy were more affected. The median duration of exposure to immune checkpoint inhibitors prior to 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 a history of only a 4 days of exposure to immunotherapy, but we raised the possibility of an early pneumonitis as a differential diagnosis, although we knew that this short-term exposure made this diagnosis less likely with the concomitant treatment with oral corticosteroids. Among the differential diagnosis on HRCT, a PCP will be the most likely in an immunocompromised patient. 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 intralobular septal thickening, which was 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 – will be included in the differential diagnosis as it induces diffuse patchy GGO. However, the lack of tree in bud opacities, nodules and consolidation made it less probable.^[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] Finally, a checkpoint-inhibitor pneumonitis presents a wide spectrum of findings such as acute interstitial pneumonia, acute respiratory distress syndrome, cryptogenic organizing pneumonia and a nonspecific interstitial pneumonia (NSIP).^[20] Neither imaging finding nor the timing of onset in our patient supported this diagnosis compared to others.

Conclusion

SARS-CoV-2 is a real threat to healthcare professionals and cancer patients. Oncologists are challenging during this pandemic to provide the best care for their patients without exposing them to the risk of infection. The biggest challenge for them is to maintain a good clinical sense and not let this outbreak distract their clinical judgement. We should always maintain a higher index of suspicion towards cancer patients during this pandemic, but also know that this population is exposed to the same risks and complications before the pandemic and is entitled to get care for any condition other than the 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.

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Conflict of Interest: None declared.

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References

1. WHO Timeline - COVID-19 [Internet]. [cited 2020 Apr 17]. Available from: <https://www.who.int/news-room/detail/08-04-2020-who-timeline---covid-19>
2. Wang Z, Wang J, He J. Active and Effective Measures for the Care of Patients With Cancer During the COVID-19 Spread in China. *JAMA Oncol.* 2020 Apr 1.
3. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335–7.
4. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol.* 2020 Mar 25.
5. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020;S0923753420363833.
6. Cortiula F, Pettke A, Bartoletti M, Puglisi F, Helleday T. Managing COVID-19 in the oncology clinic and avoiding the distraction effect. *Ann Oncol Off J Eur Soc Med Oncol.* 2020 Mar 19.
7. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015;373:23–34.
8. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A War on Two Fronts: Cancer Care in the Time of COVID-19. *Ann Intern Med.* 2020 Mar 27.
9. moph [Internet]. [cited 2020 Apr 17]. Available from: <http://www.moph.gov.lb>
10. Liang W-H, Guan W-J, Li C-C, Li Y-M, Liang H-R, Zhao Y, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China. *Eur Respir J.* 2020 Apr 8.
11. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;NEJMoa2002032.
12. Zhou S, Wang Y, Zhu T, Xia L. CT Features of Coronavirus Disease 2019 (COVID-19) Pneumonia in 62 Patients in Wuhan, China. *Am J Roentgenol* 2020;1–8.
13. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020;200843.
14. Qu J, Yang R, Song L, Kamel IR. Atypical lung feature on chest CT in a lung adenocarcinoma cancer patient infected with

- COVID-19. *Ann Oncol Off J Eur Soc Med Oncol* 2020 Mar 9.
15. Kattan J, Kattan C, Assi T. Do checkpoint inhibitors compromise the cancer patients' immunity and increase the vulnerability to COVID-19 infection? *Immunotherapy*. 2020 Apr 14.
 16. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedalscience* 2020;14:1023.
 17. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. Opportunistic infections in patients treated with immunotherapy for cancer. *J Immunother Cancer* 2014;2:19.
 18. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for *Pneumocystis pneumonia* (PCP) in non-HIV immunocompromised patients. *Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group*, editor. *Cochrane Database Syst Rev* [Internet]. 2014 Oct 1 [cited 2020 Apr 17]; Available from: <http://doi.wiley.com/10.1002/14651858.CD005590.pub3>.
 19. Carmona EM, Limper AH. Update on the diagnosis and treatment of *Pneumocystis pneumonia*. *Ther Adv Respir Dis* 2011;5:41–59.
 20. Nishino M, Hatabu H, Hodi FS. Imaging of Cancer Immunotherapy: Current Approaches and Future Directions. *Radiology* 2019;290:9–22.
 21. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol Off J Am Soc Clin Oncol* 2017;35:709–17.
 22. Lu P-X, Deng Y-Y, Liu S-T, Liu Y, Liu Y-X, Wang Y-XJ, et al. Correlation between imaging features of *Pneumocystis Jiroveci* Pneumonitis (PCP), CD(4) (+) T lymphocyte count, and plasma HIV viral load: A study in 50 consecutive AIDS patients. *Quant Imaging Med Surg* 2012;2:124–9.
 23. Franquet T. Imaging of pulmonary viral pneumonia. *Radiology* 2011;260:18–39.
 24. Koo HJ, Lim S, Choe J, Choi S-H, Sung H, Do K-H. Radiographic and CT Features of Viral Pneumonia. *Radio Graphics* 2018;38:719–39.
 25. Park MS. Diffuse alveolar hemorrhage. *Tuberc Respir Dis* 2013;74:151–62.