Pneumonitis from immune checkpoint inhibitors and COVID-19: current concern in cancer treatment

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ABSTRACT
Pneumonitis is a rare but serious adverse event caused by cancer immunotherapy. The diagnosis between COVID-19-induced pneumonia and immunotherapy-induced pneumonitis may be challenging in the era of COVID-19 outbreak. Some clinical symptoms and radiological findings of pneumonitis can be attributed to the coronavirus infection as well as to an immune-related adverse event. Identifying the exact cause of a pneumonitis in patients on treatment with immunotherapy is crucial to promptly start the most appropriate treatment. The proper management of immune checkpoint inhibitors for the risk of pneumonia must take into account a series of parameters. Accurate attention should be payed to symptoms like cough, fever and dyspnea during immunotherapy.

Pneumonitis is a rare but serious side effect of the immune checkpoint inhibitors (ICIs), involving 2.7% of the patients treated with anti-programmed cell death 1 (PD-1) monotherapy and 6.6% of the patients receiving the combination of anti-PD-1 and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4).[1] Early diagnosis and proper management are required to obtain a complete recovery and avoid an unfavorable outcome.[2] Pneumonitis-related deaths were reported in 0.2%–2.3% of patients enrolled in clinical trials, with a higher incidence in patients with non-small cell lung cancer.[1]

Several clinical presentations and radiological findings have been described. At diagnosis, the majority of patients present cough and dyspnea, while fever occurs in about 12% of the cases.[3] Five main radiological features have been defined: (1) patchy or confluent peripheral consolidation; (2) ground-glass opacities with focal areas of increased attenuation; (3) interstitial with interlobular septal thickening, peribronchovascular infiltration and honeycomb aspect; (4) bronchiolitis-like appearance with centrilobular nodules; and (5) blending of nodular and various subtypes.[3] The pathological examination usually reveals interstitial pneumonitis and organizing pneumonia with granulomas and rare alveolar damage.[4]

The management of ICI-related pneumonitis requires immunosuppressive therapy which should be started as soon as possible.

The diagnosis of an ICI-related pneumonitis can be made after ruling out other causes of similar lung involvement, such as carcinomatous lymphangitis or infections.

This issue is particularly relevant during the current outbreak of COVID-19.[5] Indeed, COVID-19 infection is often associated with bilateral pneumonia, which has been observed in 79.4% of the patients.[6] Lung involvement caused by COVID-19 is usually characterized by multiple peripheral lesions with the following features: ground-glass opacity often associated with reticular pattern, consolidation, microvascular dilatation and vacuolar images, fibrotic and subpleural lines.[7]

COVID-19 pneumonia is associated with fever in 91.7% of patients, cough in 75%, fatigue in 75%, dyspnea in 36.7% of patients and gastrointestinal symptoms in 39.6%.[8] Ocular signs, such as conjunctivitis, have been reported in 31.6% of patients.[9]

Despite some symptoms being more typical of COVID-19 infection (table 1), patients under treatment with ICIs and without certain exposure to COVID-19-positive subjects may present symptoms that can be ascribed to a coronavirus infection as well as to an immune-related toxicity. Especially when the presenting symptoms are only dyspnea and cough, the differential diagnosis between an ICI-adverse event and COVID-19 infection becomes more difficult.

In addition, during treatment with immunotherapy, patients with cancer often take acetaminophen to manage pain or steroids to treat previous immune-related toxicities. Both acetaminophen and steroids can mask a modest fever.

Figure 1 shows the CT scan of a 75-year-old patient with metastatic melanoma under

Table 1 Main clinical features associated with ICI pneumonitis or COVID-19 pneumonia

	ICIs	COVID-19
Fever	✓	✓
Dyspnea	✓	✓
Cough	✓	✓
Conjunctivitis	–	✓
Gastrointestinal manifestations		
Diarrhea	✓*	✓
Belching	–	✓
Nausea	–	✓
Emesis	–	✓

*As a further immune-related adverse event.
ICI, immune checkpoint inhibitor.

Box 1 Checklist with 10 parameters which can be considered for the management of cancer immunotherapy during COVID-19 outbreak

Is the patient over 75 years old?
What is the aim of the treatment?
Does the patient suffer from lung diseases? If yes, are they severe?
Does the patient suffer from other serious diseases, such as diabetes or heart failure?
Is the patient on treatment with ICI monotherapy or with ICI combination?
Has the patient previously had an immune-related pneumonitis?
Does the patient have other immune-related adverse events?
Does the patient live alone? Is the patient able to comply with physical and social distancing?
Does the journey to reach the hospital expose the patient to additional risks?
Is the patient continuing to work exposing himself to additional risks?

anti-PD-1 therapy during the coronavirus pandemic, recently admitted in our hospital. The patient had only mild dyspnea. The imaging findings of the CT scan could be related to both coronavirus pneumonia and immune-toxicity. It was necessary to clarify the cause before administering the most appropriate treatment. To date, we know that additional specimens should be considered to make a definite diagnosis of COVID-19 when the first nasopharyngeal and oropharyngeal swabs are negative.[10] Indeed, the possibility of false negative results with PCR on naso-oropharyngeal samples should be taken into account due to different factors, such as the quality of the specimens or the technical problems of the analysis.[10] Serological tests for COVID-19 are also available and can be helpful in case of negative PCR.[11] The time necessary to obtain the results for the definite diagnosis does not allow to promptly undertake steroids, which are the main-stay of therapy for ICI-related pneumonitis. In fact, the role of steroids for COVID-19 pneumonia is still debated: they were not initially recommended due to possible harms,[12] while it has been recently described a benefit of dexamethasone for the treatment of critically ill patients receiving ventilation or oxygen.[13] The pneumonitis of the above reported patient was attributed to ICI after ruling out the COVID-19 infection.

Identifying the exact cause of a pneumonitis in a patient treated with ICIs could be challenging during the current COVID-19 outbreak. Furthermore, ICI-related pneumonitis can occur at any time, ranging from few

Figure 1 Immune-related pneumonitis with nodular and ground-glass pattern in a patient on treatment with anti-PD-1 agent, resembling a typical pattern of COVID-induced pneumonia.

days after first ICI administration to 19 months,[3] and it is not possible to exclude an immune-related pneumonitis according to the time of onset.

We must also consider that the simultaneous presence of other immune-related adverse events could lead to the hypothesis of pneumonitis most likely due to immuno-therapy; however, it does not rule out a viral etiology.

Several concerns arise on the management of patients under ICI therapy. It is advisable to test for COVID-19 all the patients on ICI treatment at the first onset of fever, cough, dyspnea or other symptoms typical of a viral infec-tion. In this way, it is possible to detect an early lung involvement and promptly start the therapy. On the other hand, when a pneumonitis is found in a patient on treat-ment with ICI, it can be useful to refer him to a 'COVID-19' center to immediately run the test for COVID-19.

Another relevant issue is the possibility that ICI could enhance the 'immunological storm' induced by COVID-19 infection and, consequently, worsen the clin-ical outcome of viral pneumonia. No data are currently available to support this hypothesis. However, the doubt is whether a precautionary delay of ICI administrations can protect our patients when we can reasonably exclude a strong impact on tumor control.

The choice regarding the administration of the immune checkpoints for the risk of pneumonitis must take into account a series of parameters (box 1). In fact, the clinical decision on the management of immuno-therapy should consider the age of the patients (given the increased mortality in the elderly), simultaneous other immune-related adverse events for which a steroid therapy was started, previous immune-related pneumonitis, the comorbidities (including pulmonary disease or other major diseases), the possibility to monitor closely the clin-ical vital signs of a patient, if the patient lives alone, if it is simple for the patient to reach the hospital (considering whether the journey is long and exposes the patient to additional risks), and if the patient is continuing to work actively (in this case if the work exposes him to additional risks).

It may be crucial to carefully evaluate the risk of pneumonitis and the expected clinical benefits especially in patients who are candidates for a combined immunotherapy.

Of course, the general conditions of the patient and the aim of the treatment must be considered in this context.

Until more data are available, accurate attention should be payed to symptoms like cough, fever or dyspnea during ICI treatments. Patients' education and phone or mail counseling should be encouraged. When these symptoms occur, chest CT scan and COVID-19 test should be performed as soon as possible in order to start early the appropriate treatment. Overall, considering the paucity of the data, we had the possibility to provide only a reflection.

The systematic collection of clinical and biological data from oncological patients can help to recognize the pneumonia due to COVID-19 and establish the proper management of immunotherapy and its adverse events during the pandemic.

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