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EDITORIAL

COVID-19 pneumonia and immune-related pneumonitis: critical issues on differential diagnosis, potential interactions, and management

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ABSTRACT

Introduction: The COVID-19 pandemic occurred amid the cancer immunotherapy revolution. Immune checkpoint inhibitors (ICIs) have become the standard of care for several solid cancers and are associated with peculiar toxicities, including pneumonitis which has similar features to COVID-19 pneumonia.

Areas covered: We summarize the main hallmarks of lung injury induced by ICIs and severe acute respiratory syndrome coronavirus 2 and discuss the critical aspects for differential diagnosis and management. Symptoms and radiological findings are often similar; conversely, treatments are quite different. Furthermore, we focus on potential interactions generating hypotheses that need confirmatory studies.

Expert opinion: All cancer patients treated with immunotherapy should receive screening for SARS-CoV-2. This would improve the diagnosis and management of pneumonia and guide therapeutic choices. Furthermore, clinicians could estimate the risk/benefit of continuing ICI treatment in COVID-19 positive patients. Temporary withdrawal of the immunotherapy treatment pending resolution of viral infection may be a reasonable option in long-responders patients.

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1. Introduction

The new coronavirus disease (COVID 19 – Corona Virus Disease 2019) has spread worldwide and has killed thousands of people in a few months, leading the World Health Organization (WHO) to declare the pandemic. The virus affects the respiratory tract and reaches the lungs causing potentially fatal pneumonia. Mortality is higher in frail population: elderly, people with chronic illness such as respiratory and cardiovascular diseases, and cancer patients.

Association between cancer and COVID-19 is still unclear. Liang W et al. reported that the patients with cancer had a higher risk of COVID-19 [1]. It could be possibly due to immunosuppression caused by malignancy and anticancer treatments [2]. Another possible explanation lies in cigarette smoking, which is the leading cause of chronic obstructive pulmonary disease and the main risk factor of cancer. Indeed, smokers seem to have a greater susceptibility to develop Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), because tobacco smoking increases the expression of Angiotensin-Converting Enzyme 2 (ACE 2) in the small airway mucosa. ACE2 is a key regulator of cardiovascular and renal function. It has been shown to be the cellular receptor through which SARS-COV-2 enters the alveolar epithelia and causes lung infection [3,4].

The COVID-19 outbreak occurred amid the cancer immunotherapy revolution. Immune Checkpoint Inhibitors (ICIs) have become the standard of care for several solid cancers. These new therapeutic approaches, especially anti-PD1 and anti-PD-L1 antibodies, are associated with peculiar toxicities that can cause pneumonitis with similar features to those of coronavirus [5,6].

Therefore, the right recognition of pneumonia in cancer patients has become an imperative of global relevance. Here, we summarize the main hallmarks of lung injury induced by coronavirus and ICIs and focus on potential interactions. Furthermore, we discuss the critical aspects of differential diagnosis and management.

2. COVID-19 pneumonia

COVID-19 is mainly a respiratory disease. The causative agent is a coronavirus (SARS-CoV-2) with a great infectivity among humans. It can be transmitted via respiratory droplets or close contact [7]. Most infected patients have flu-like symptoms, but when the virus causes pneumonia, they generally have cough, fever, and shortness of breath. Concomitant gastrointestinal symptoms (diarrhea and nausea) are present in 5–10% of cases [8,9]. Asymptomatic and paucisymptomatic patients should be managed with isolation, strict surveillance, and possibly treatment aimed at alleviating symptoms (e.g. acetaminophen and non-steroidal anti-inflammatory drugs). Instead, patients affected by significant pneumonia need hospitalization. The cases with severe illness can develop acute

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Table 1. Hallmarks of COVID-19 pneumonia and immune-related pneumonitis.

	COVID-19 Pneumonia	Immune-related pneumonitis
Causative agent	Severe Acute Respiratory Syndrome Coronavirus 2	Immune checkpoints inhibitors (anti-PD-1/PD-L1 and anti-CTLA4 antibodies)
Clinical features	Cough, fever Dyspnea (in severe cases)	Cough, Dyspnea Fever is less common
Radiological findings	Ground-Glass Opacities Multiple and bilateral mottling with peripheral distribution, Reticular pattern and vascular thickening	Ground-Glass Opacities Cryptogenic organizing pneumonia-like Interstitial pneumonia pattern Hypersensitivity pneumonitis Pneumonitis not otherwise specified
Histopathology	Edema, proteinaceous exudate, vascular congestion, inflammatory clusters with multinucleated giant cells, interstitial fibrosis	Diffuse alveolar damage Sarcoid-like granulomatous reaction interstitial fibrosis
Mild-event Treatment	Isolation, surveillance Symptomatic treatment No steroids	Symptomatic treatment Oral steroids
Serious-event Treatment	Oxygen support Anti-inflammatory drugs and steroids Monoclonal antibodies, Immunoglobulins, Antimalarials drugs, Antiviral agents Mechanical ventilation, intensive care for ARDS	High-dose i.v. corticosteroids Immunosuppressive agents Oxygen support Intensive Care for ARDS

respiratory distress syndrome requiring ICU (Intensive Care Unit) admission and mechanical ventilation. In the symptomatic cases, blood counts often show lymphopenia and higher neutrophil lymphocyte ratio (NLR), and the patients tend to have also other laboratory abnormalities such as higher levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GT), and α-hydroxybutyric dehydrogenase (α-HBDH). Secondary infections rarely occur and should be suspected in the presence of high levels of procalcitonin, which are otherwise normal. Higher plasma levels of IL2, IL6, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα were found in ICU patients compared to NON-ICU patients [8,9]. Indeed, increasing evidence suggests that patients with severe COVID-19 might have a cytokine storm syndrome [10].

The typical radiological finding is ground-glass opacities (GGO) on chest Computed Tomography (CT) scans. Unilateral and multifocal process occurs in pre-clinical setting. Disease radiological progression manifests in symptomatic patients with multiple and bilateral mottling (GGO or mixed consolidations). COVID-19 pneumonia usually presents with peripheral distribution and is often associated with reticular pattern and vascular thickening. Pleural effusion and lymphadenopathies could be observed but are more common in NON-COVID pneumonia [11–13].

Tian S et al. reported histopathology data of COVID-19 pneumonia deriving from the accidental cases of two patients who underwent lobectomies for lung cancer. These patients retrospectively found to have had the infection at the time of surgery. Pathologic findings were edema, proteinaceous exudate, vascular congestion, inflammatory clusters with multinucleated giant cells, interstitial fibroblastic proliferation, and reactive hyperplasia of pneumocytes. Since patients had no symptoms at the time of surgery, the authors conclude that these features could represent an earlier phase of COVID-19 pneumonia [14]. Instead, in the advanced stages of the disease, the main pathological findings are diffuse alveolar damage with lymphocytic infiltrate, small thrombotic vessels, and foci of alveolar hemorrhage [15,16].

There is no specific treatment for COVID-19. Vaccines, biologic and antiviral drugs are under study as potential therapies. Treatment remains mainly based on a symptomatic approach, providing supportive therapies. Patients with mild symptoms are managed with isolation, surveillance, and symptomatic therapy. Patients needing hospitalization are currently treated with oxygen support, fluids, empirical antibiotics, anti-inflammatory drugs, monoclonal antibodies, immunoglobulins, and antiviral agents such as remdesevir, lopinavir, and ritonavir. Severe cases receive steroids, while their use is not recommended in the early stages of the disease. Limited clinical trials suggest that Tocilizumab (anti-IL-6-receptor monoclonal antibody, approved for rheumatoid arthritis) or Chloroquine (antimalarial drug) may be used, but further studies are needed [17–19]. Patients who develop acute respiratory distress syndrome (ARDS), the leading cause of mortality, require mechanical ventilation and intensive care [20–22].

3. Immune-related pneumonitis

Immune checkpoint inhibitors are monoclonal antibodies that enhance the immune response against cancer by binding to inhibitory proteins expressed on lymphocytes or tumor cells. The main immunotherapeutic agents target downregulators receptors, including cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed death-ligand 1 (PD-L1), and anti-programmed cell death protein 1 (PD-1 or CD279). The blockade of these checkpoints inhibits the T-cell inactivation and therefore promotes the cytotoxic activity against cancer cells.

Hyperstimulation of the immune system can cause inflammatory events known as immune-related adverse events (irAEs). Among these, immune-related pneumonitis represents a clinically relevant and potentially life-threatening adverse event. Compared with chemotherapy, ICIs are associated with an increased risk of pneumonitis. Its incidence is higher in patients receiving anti-PD-1/PD-L1 therapy compared with anti-CTLA4 antibodies and increases with combination immunotherapy versus monotherapy (up to 10% versus 3%) [23,24].

The timing of onset and clinical manifestations are variable, often not specific, especially in patients with lung cancer or lung metastases. The most common symptoms are dyspnea and cough; fever and chest pain are less common. Asymptomatic events are often incidental radiological

findings. ARDS was described as rare complication. Patients may have various and nonspecific laboratory abnormalities depending on status of disease and concomitant IrAEs. Secondary infections are possible, and most of them are caused by opportunistic organisms [25,26].

CT scan should be performed in all cases of clinical suspicion. Radiological features are not pathognomonic and could be stratified into five distinct phenotypes: cryptogenic organizing pneumonia-like, ground-glass opacities, interstitial pneumonia pattern, hypersensitivity pneumonitis, and pneumonitis not otherwise specified. Among these, the most frequently reported pattern is that with ground-glass or consolidative opacities in peripheral or peribronchial distribution [27,28].

Data about histopathologic features are lacking, but diffuse alveolar damage, sarcoid-like granulomatous reaction of the lung, and interstitial fibrosis are the main findings of the few cases reported in the literature [25–29].

According to CTCAE (Common Terminology Criteria for Adverse Events), grade 1–2 pneumonitis should be treated with symptomatic medications and oral steroids. In serious events (grade 3 to 4), the patient should be hospitalized and management consist of treatment with high-dose i.v. corticosteroids and permanent discontinuation of immunotherapy. Immunosuppressive agents such as infliximab, mycophenolate mofetil, or Cyclophosphamide, should be used for steroids-refractory events [24].

4. Potential interactions between SARS-CoV-2 and ICIs

Although SARS-CoV-2 appears to be related to the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), it has peculiar virology and different epidemiological and clinical features [30,31]. The accumulated knowledge of the two previous diseases allowed us to deduce the pathophysiology of the novel pathogen. However, the mechanism of the immune response has not been completely understood yet.

Current data suggest that the immuno-pathology of COVID-19 pneumonia may be the result of a cytokine storm. Coronavirus is primarily countered by immune cells including mast cells located in the submucosa of the respiratory tract. When the virus reaches damages the epithelial cells and reaches the alveoli, it attracts neutrophils, macrophages, mast cells, and T helper lymphocytes resulting in a exceeding production of inflammatory cytokines. While cytotoxic T cells are activated for killing infected cells, B cells produce specific antibodies for neutralizing the virus [32,33].

Pro-inflammatory cytokines such as IL-6 and IL-1 are likely to be the key mediators of lung inflammation in COVID-19 and their suppression may have a therapeutic effect. The anti-inflammatory cytokines including IL-37 and IL-38 have the ability to inhibit immune response and inflammation mediated by IL-6 and IL-1 family members. Thus, they represent a potential new therapeutic cytokine-strategy in viral infections including COVID-19 [34,35]

Expression of leukocytes and inflammatory cytokines was analyzed in a cohort of 452 patients with laboratory-confirmed COVID-19. The patients tended to have high NLR values, lymphopenia (especially T cells), and elevated levels of inflammatory cytokines such as TNF-α, IL-1, and IL-6. These alterations were more evident in severe cases [36]. In addition, it has been reported that SARS-Co-V-2 can directly infect, damage and kill T-cells and macrophages [32,36,37]. Indeed, immune cells may express ACE2, the same receptor through which coronavirus binds its main target cells, the type 2 alveolar cells [38,39].

In summary, the activation of innate immunity and the production of pro-inflammatory cytokines activate cytolytic effect on alveolar cells and impairs the adoptive immunity. The viral effect direct on macrophages and T-cells might contribute to the dysregulation of the immune response [32,36,37,40].

Similarly, immune dysregulation is the basis of the immunotherapy toxicities. Increasing levels of cytokines and infiltration of T-cell on normal tissues are described as two possible mechanisms underlying the immune-related adverse events [41,42]. High levels of inflammatory cytokines have been associated with prediction and severity of toxicity in patients receiving anti-PD-1–based immunotherapy [43]. Additionally, cytokine release syndrome (CRS) has been described as a rare complication [44]. So, the cytokine storm is a possible event occurring during ICI treatment and may mediate the onset of serious immune-related adverse events.

Although the pathogenesis of immune-related pneumonitis is little understood, pathological studies indicate that inflammation and lymphocytic infiltration both in the alveoli and in the interstitium are the main causative processes [6]. The mechanism may differ between anti-CTLA-4 and anti-PD-1 therapies, but in both cases, the lung damage would be mediated by the impairment of the immune cells, especially the T-lymphocytes [45].

Based on available data, both COVID-19 pneumonia and immune-related pneumonitis appear to be the result of an aberrant inflammation and impaired lymphocyte functions. In addition, SARS-CoV-2 can directly infect immune cells targeted by ICIs. These evidences suggest a potential mutual and dangerous interaction.

5. Expert opinion

Differential diagnosis between COVID-19 pneumonia and immune-related pneumonitis is challenging. It is based on clinical and radiological features, which are often similar and confusing. Fever, cough, and dyspnea are the most common symptoms. In the COVID-19 pneumonia respiratory distress generally has a late onset compared to fever and cough. Conversely, in the immune-related pneumonitis, dyspnea and cough often appear together, and fever is less common. However, in cancer patients, the symptomatic triad can coexist in both etiologies.

Likewise, radiological findings may not be helpful, especially in the presence of ground-glass opacities on CT scan. Swabs, respiratory samples, and serological tests should ascertain the diagnosis of SARS-Cov-2 infection [46,47], but cannot exclude concomitant immune-related pneumonitis in patients receiving immunotherapy.

In this context, several scenarios open up: immune-related pneumonitis in COVID-19 positive patients; COVID-19

pneumonia in patients receiving immunotherapy; concomitant COVID-19 pneumonia and immune-related pneumonitis. In all these cases, the etiologic diagnosis could be very difficult. It is a critical trouble for clinical practice since therapeutic strategies are quite different. In particular, high doses of steroids are the treatment of choice for the immune-related adverse events and should be used early in patients with pneumonitis. Conversely, corticosteroids have a controversial role in COVID-19. They have been associated with an increased risk for mortality in patients with influenza and impaired clearance of SARS-CoV and MERS-CoV. Therefore, their use is not recommended in the treatment of COVID-19 except in severe cases or ARDS [48,49]. Consequently, therapeutic decisions in the presence of dubious lung injury could be harmful. Furthermore, it is unclear whether drug-induced immunosuppression during serious immune-related pneumonitis (high doses of steroids and immunosuppressive agents) could favor or worsen SARS-CoV-2 infection.

Cancer often requires timely and undelayable treatments. However, with the advent of immunotherapy, a subset of patients have durable benefit and long-term survival. A case of rapid fatal evolution of COVID-19 in an advanced lung cancer patient with a long time response to nivolumab (anti-PD-1 antibody) has been recently reported [50]. Generalizations and hasty evaluations should be avoided but this report increases the focus on possible interactions between coronavirus and ICIs. Little data are available, however sufficient to generate hypotheses: viral infection could interfere with the effectiveness of immune checkpoint inhibitors and promote the onset of toxicity; immunotherapy could increase the risk and severity of COVID-19; Immune-related toxicities in COVID patients could be more serious than in NON-COVID patients. These are all open questions that need confirmatory studies. In the meantime, we need firm recommendations for cancer patients treated with immune checkpoint inhibitors in the COVID-19 era.

In our opinion, all cancer patients treated with immunotherapy should receive screening for SARS-CoV-2. This would improve the diagnosis and management of pneumonia and guide therapeutic choices. Furthermore, clinicians could estimate the risk/benefit of continuing ICI treatment in COVID-19 positive patients. Temporary withdrawal of the immunotherapy treatment pending resolution of viral infection may be a reasonable option in long-responders patients.

Authors' contributions

DS conceived the idea for this paper and coordinated the writing process. MR wrote the original draft and table. MR, FC, DS developed further drafts. FP, AN, ED, AC, BV, and GT critically evaluated and made substantial edits to the manuscript. All authors approved the final version for submissions.

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