Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Checkpoint inhibitor pneumonitis mimicking COVID-19 infection during the COVID-19 pandemic

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Dear Editors

As of May 27, 2020, 5,612,601 people have been diagnosed with COVID-19 and 349,060 deaths have been recorded, with a mortality rate of up to 6.22 % worldwide. Despite the current COVID-19 pandemic, many advanced lung cancer patients continue to receive regular immunotherapy, such as programmed cell death protein 1 (PD-1), programmed cell death protein 1 ligand (PDL-1) checkpoint inhibitors (CIs) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), as salvage therapies [1]. Checkpoint inhibitor pneumonitis (CIP) is the most common fatal immune-related adverse event (irAE) in lung cancer patients receiving Cls and CIP related mortality may more than 20 %. During current COVID-19 pandemic, CIP is hard to distinguish from COVID-19 infection as they share similar clinical and radiographic presentations but different therapy strategies. Therefore, how to distinguish between the two diseases is an urgent issue.

The overall incidence of CIP is 2.79−5.17% [1,2], and PD-1 inhibitors have a higher incidence than PDL-1 inhibitors [3]. The incidence of CIP is also higher in patients receiving a combination of CIs and chemotherapy than in those receiving CI monotherapy [1,3]. The mortality rate of all CI-associated irAEs is 0.45 %, among which CIP is the most common cause of death of irAEs [1] and CIP related mortality may up to 22.7 % [4]. The median interval between the first dose of CIs to the onset of CIP is 2.8 months (9 days to 19.2 months) [1,2] and the median incubation period of COVID-19 infection is 5.1 days, with 97.5 % becoming symptomatic within 11.5 days [5]. The pathology of CIP often reveals different degrees of lymphocyte infiltration (mainly $CD8^+$ T cells), and granuloma, interstitial pneumonitis, organized pneumonitis, diffuse alveolar injury or eosinophilic infiltration may also be present. Few studies have reported the pathology of COVID-19, however an autopsy report showed diffuse alveolar damage and airway inflammation [6]. Edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells in the early stage [7]. With regards to radiographic manifestations, bilateral distribution of ground glass opacities with or without consolidation in posterior and peripheral lungs is the cardinal hallmark of COVID-19. However, in CIP, the radiographic presentations are also ground glass opacities, reticular opacities, consolidations [1–3], including the following patterns: cryptogenic organizing pneumonia, ground glass opacities, interstitial pneumonitis, hypersensitive pneumonitis and pneumonitis not otherwise specified. The lower lobe is the most commonly involved lobe and the most common distribution is mixed and multifocal. The diagnosis of CIP is made after the exclusion of other diseases, and COVID-19 infection needs to be confirmed by RT-PCR, isothermal amplification assay or serology test. The most common symptoms in CIP are dyspnea, followed by cough, fever and 33 % of cases are asymptomatic. In COVID-19 infection, the most common symptom is fever, followed by cough, fatigue, sputum production, and shortness of breath [8]. Early detection and discontinuing CIs if CIP develops is the most reliable management, and steroids are the standard treatment for CIP [1–3]. In contrast, steroids may be harmful for COVID-19 patients and not indicated in current management [9]. Several drugs have been used by the beginning of COVID-19 outbreak and a great number of clinical trials have been launched to investigate the therapeutic effect. Though No U.S. Food and Drug Administration (FDA)-approved drugs for COVID-19 infection as yet, the FDA has authorized the emergency use of remdesivir to treat hospitalized adult and pediatric patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Recently, Beigel et al. reported a global trial of remdesivir therapy for COVID-19 infection and successfully achieved the primary endpoint. The rate ratio for recovery was 1.32 (95 % confidence interval, 1.12–1.55; $P < 0.001$) and the median recovery time was 11 days compared to 15 days in those who received placebo [10].

We summarize the differences between CIP and COVID-19 infection in Table 1 and wish the summary could help clinicians to distinguish CIP from COVID-19 infection in current horrible COVID-19 pandemic.

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Table 1
The differences between checkpoint inhibitor pneumonitis (CIP) and COVID-19 infection.

	Checkpoint inhibitor pneumonitis (CIP)	COVID-19 infection
Incidence	Overall 2.79 − 5.17 % [1,2,3] PD-1 inhibitors/ PDL-1 inhibitors = 4 % / 2 % # The incidence of CIP is higher in those receiving CI and chemotherapy than with CI monotherapy	–
Interval to onset	Median time 2.8months, with a wide range (9 days to 19.2 months)[1,2]	Median incubation period of 5.1 days, with 97.5 % becoming symptomatic within 11.5 days [5].
Pathology finding	Different degrees of lymphocyte infiltration, mainly $CD8^+$ T cells, including granuloma, interstitial pneumonitis, organized pneumonitis, diffuse alveolar injury or eosinophilic infiltration [1]	Diffuse alveolar damage and airway inflammation in an autopsy report [6]. Edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells in the early stage [7]
Mortality	CIP is the most common cause of death in all CI- associated irAEs, and CIP related mortality may up to 22.7 % [1,4]	6.22 % (349,060 deaths /5,612,601 confirmed cases) to May 27, 2020
Chest CT	The basic imaging signs of CIP include ground-glass opacity(GGO), consolidation, interlobular septal thickening, distraction branch expansion, nodules, and reticular shadow [1,2] and some studies divided CIP into five patterns, included cryptogenic organizing pneumonia; ground glass opacities, Interstitial pattern, hypersensitive pneumonitis and pneumonitis not otherwise specified. # Involvement: Lower > middle > upper lungs # Distribution: Mixed and multifocal > peripheral and lower and diffuse	Bilateral distribution of GGO with or without consolidation in posterior and peripheral lungs is the cardinal hallmark of COVID-19 [8]. COVID-19 images included GGOs 14 − 98 %; consolidation 2 − 64 %; GGO and consolidation 19 − 59 %; interlobular septum thickening 1 − 75 %; reticular pattern 1 − 22 %; crazy paving 5 − 36 %; air bronchogram 21 − 80 %; bronchial wall thickening 11 − 23 %; pleural thickening 32 %, subpleural line 20 %, nodules 3 − 13%, reversed halo sign 2 − 3%, pleural effusion or pericardial effusion 1 − 8%; lymphadenopathy 4 − 8%
Diagnosis	The diagnosis of CIP should be made after excluding other interstitial lung diseases and infection [1,2,3].	RT-PCR, isothermal amplification assays, serology tests
Symptoms	Dyspnea, cough 35 %, fever 12 %, chest pain 7 %. asymptomatic 33 % [1,2,3].	Fever 85 − 90 %, cough 65 − 70 %, fatigue 35 − 40 %, sputum production 30 − 35 %, shortness of breath 15 − 20 %, myalgia/arthralgia 10 − 15 %, headaches 10 − 36 %, sore throat 10 − 15 %, chills 10 − 12 % [5,8].
Treatment	Early detection and discontinue CIs. Steroids are the standard treatment for CIP. For grade 2–3 CIP, an equivalent dose of prednisolone of 1–2 mg/kg/ day is recommended. The overall course of steroid treatment is approximately 6–8 weeks [1,2].	No FDA-approved drugs as yet, but in the United States, the FDA has authorized the emergency use of remdesivir to treat hospitalized adult and pediatric patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Steroids may be harmful [9]

immune-related adverse events, irAE; checkpoint inhibitor, CI; checkpoint inhibitor pneumonitis, CIP; ground glass opacities, GGO; Food and Drug Administration, FDA; programmed cell death protein 1, PD-1; programmed cell death protein 1 ligand, PDL-1.

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