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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Immune checkpoint inhibitors in SARS-CoV-2 infected cancer patients: the spark that ignites the fire?

Since December 2019, a novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially reported in Wuhan, China, rapidly spread in other 114 countries worldwide, becoming pandemic [1].

In general, COVID-19 is acute resolved disease but it can also be deadly, mainly in older people and those with underlying medical conditions, such as cardiovascular disease and cancer [2].

Cancer patients are at high risk of developing severe COVID-19 illness, probably due to their immunosuppressive state also favoured by anticancer treatments, including chemotherapy and surgery [3]. To date, limited evidence has been available on the relationship between SARS-CoV-2 infection and treatment with immune checkpoint inhibitors (ICI), such as anti-programmed-cell-death-protein 1 (PD-1) and programmed-cell-death-ligand 1 (PD-L1) monoclonal-antibodies, which have notably improved the survival of lung cancer patients.

Here we report the case of a 53-year-old-man, treated with nivolumab (PD-1 inhibitor) for a metastatic non-small-cell lung cancer, who developed a hyperacute fatal pneumonitis following infection by SARS-CoV-2. The patient, current smoker, lived in Bergamo, the area with currently the highest COVID-19 prevalence in Italy [4]. He had a history of squamous cell carcinoma of the esophagus, treated with surgery and adjuvant chemotherapy nearly 20 years earlier. In August 2016, he underwent right superior bilobectomy for a non-oncogene-addicted, PDL1 negative lung adenocarcinoma. In March 2018, bilateral lung metastases were diagnosed. First-line chemotherapy with carboplatin and pemetrexed was administered with fast disease progression. On June 2018, second-line nivolumab was started, with prolonged stabilization up to a total of 31 administrations (Fig. 1a). Treatment was well tolerated with no major adverse events. Last treatment dose was given on February 25, 2020, with no acute toxicity. On March 7 the patient was admitted to the Emergency Department due to the sudden onset of fever and acute dyspnea. The oxygen saturation at rest in ambient air was 78%, and body temperature was 38 °C. Chest CT-scan showed diffuse bilateral ground-glass opacities suggestive for viral infection (Fig. 1b). Blood tests showed mild leukocytosis (10.5 × 103/μL) with neutrophilia (8.5 × 103/μL) and increased level of C-reactive protein (31.7 mg/dL) and lactate dehydrogenase (616 U/L). SARS-CoV-2 real-time reverse-transcriptase-polymerase-chain-reaction evaluated on the nasal oropharyngeal swab was positive. Despite oxygen supplementation and supportive care, clinical conditions and vital signs rapidly declined until death, which occurred 12 h after symptoms onset (Fig. 1c).

Managing of lung cancer during the SARS-COV 2 pandemic era is very challenging for thoracic oncologists, called to make “the best” for treating their patients coping with novel clinical issues raised by the virus outbreak. In fact, since smoking habit was correlated with higher risk of SARS-COV-2 infection and severe COVID-19 manifestations [5], patients with lung cancer patients could be considered more susceptible for the infection and its complications. In addition, many features considered as risk factor of mortality for COVID-19 are often found in lung cancer, such as older age, COPD and other smoke-related cardiovascular disease [2]. The suspicion of COVID-19 in lung cancer patients is complicated by the inconsistency of infection-related symptoms, such as fever, cough and shortness of breath, which are hardly distinguishable by those observed in case of disease progression, superinfection or treatment-related toxicities. Furthermore, ICI and tyrosine kinases inhibitors could cause interstitial pneumonitis which shares radiological pattern with COVID-19.

In our case a long-responder to nivolumab, developed during the treatment a rapidly fatal interstitial pneumonitis and was found infected by SARS-CoV-2. Interstitial pneumonitis represents the most fatal adverse events related to PD-1/PD-L1 inhibitors and in parallel is the typical manifestation of COVID-19. ICI-related pneumonitis usually occurs during the first 3–6 months of treatment [6]. Acute-distress respiratory syndrome related to COVID-19 typically appears 10–12 days after the onset of initial symptoms [2]. Thus, the distinctive features of our case report, such as the late onset during immunotherapy (after 21 months of nivolumab) and the hyper-acute clinical course with sudden deterioration are uncommon for both ICI-related pneumonitis and COVID-19.

A possible explanation to the “explosive” clinical course observed could be that concomitant PD-1 inhibition and SARS-CoV-2 infection might have negatively synergized and, probably through hyper-activation of CD8 T-cells, may have favoured the excessive immune response called “cytokine-storm”, considered as responsible of the severe acute respiratory distress syndrome in COVID-19 as well as in ICI toxicity [7,8]. The anti-PD(L)1 agents mainly act by restoring the effector function of CD-8+ T-cell, which are also involved in defense against viral infections. Notably, lung pathological findings of a fatal case of COVID-19 revealed over-activation of CD8+ T-cells with high cytotoxicity [9], as observed with ICI-toxicity [6]. Considering the strict overlap between ICI mechanisms and COVID-19 pathogenesis, a negative synergy in lung injury cannot be excluded. Whether the tissue-damage could be stopped by steroid use remains an open question, since glucocorticoids represent the standard treatment of ICI-related pneumonitis while the role in the treatment of COVID-19 is still controversial, due to the potential involvement in delaying virus clearance [10]. Unfortunately, we were unable to collect proofs supporting our hypothesis, such as an histological case-description, the viral genome search in the lung or cytokines dosage, due to the fast clinical deterioration of patient.

While waiting for further evidence on the risk of fatal pneumonitis underlined by our “real –life” case report, a more intensive surveillance may be advisable for patients receiving immunotherapy during SARS-CoV- 2 pandemia. Recent recommendations on lung cancer treatment in COVID-19 era suggest to prolong ICI administration interval in order to

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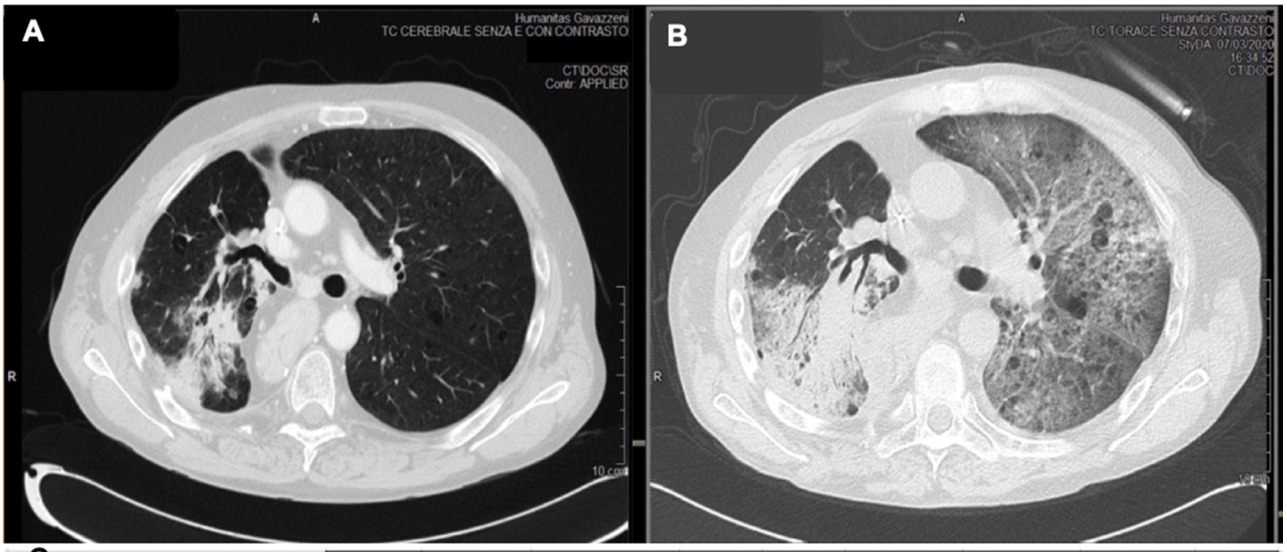

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	Home	Hospital							
Day		March 7th				March 8th			
Time	14:00	15:53	17:00	19:15	21:30	00:58	02:59	05:40	06:26
Fever	Subjective	38°C	38°C	37,7°C	37°C	Not detected	Not detected	Not detected	
Shortness of breath									
Oxygen Saturation (%)		78	56	45	60	70	80	60	
Blood Pressure (mmHg)		120/70	80/40	80/40	83/43	70/45	55/33	30/15	
Heart Rate (beats per minute)		78	85	80	80	110	102	43	
Respiratory Rate (breaths per minute)					17	17	19	7	
Glasgow Coma Scale						3	3	3	
Oxygen Supplementation		Reservoir bag masks							
Drug		Paracetamol	Paracetamol, Sodium Chloride			Piperacillin/ tazobactam	Morphine	Haloperidol	
		CT-Scan	Nasal Swab for SARS-COV-2 RNA test						Death

Fig. 1. The panel A and B show thorax CT scans obtained at the same level and after the injection of intravenous iodine contrast. The image of the panel A shows one of the pulmonary metastases sited in the right upper lobe. CT-scan was performed on January 2020 after 28 administrations of nivolumab. The image of panel B shows bilateral ground-glass opacities indicating an interstitial pneumonia. The lesion of the right upper lobe is not measurable due to the surrounding interstitial involvement. The CT scan was performed on March 7, 2020 after the admission to Emergency Department. The panel C describes clinical course of the patient including vital signs, symptoms, examination and treatment from the day of illness until the death.

reduce the risk of infection [11]. However, making "case by case" decision could be advisable and should be based on accurate evaluation of the balance between the infection complications and the risk of cancer progression, favored by avoidable treatment delay.

Declaration of Competing Interest

None.

Authors contribution

All authors contributed equally to the manuscript.

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