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Case Series of the Month

Clinical Characteristics and Outcome for Four SARS-CoV-2-infected Cancer Patients Treated with Immune Checkpoint Inhibitors

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Abstract

Preliminary data suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with higher mortality among cancer patients, particularly in those on systemic therapy. It is unclear whether this applies to patients receiving immune checkpoint inhibitors (ICIs). In this case series, 74 patients from a single institution with genitourinary (GU) cancer on ICI were followed up during a 12-wk period. During this period, 11 patients (15%) developed symptoms consistent with coronavirus disease 2019 (COVID-19) and four (5%) tested positive. Two patients had metastatic urothelial cancer (treated with atezolizumab) and two had metastatic renal cancer (treated with ipilimumab and nivolumab). All had additional risk factors associated with COVID-19 mortality and two received steroids within 1 mo of infection. Two patients developed symptoms requiring hospitalisation. All four are alive 32–45 d after their first symptoms and 28–38 d after testing positive. These patients all had multiple risk factors associated with severe COVID-19. These data suggest that the higher risk of COVID-19 death associated with systemic therapy in cancer may not apply to patients on ICIs. Assessment of COVID-19 severity in these patients can be complicated by the underlying cancer and its treatment.

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1. Case series

1.1. Background

Preliminary data suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) is associated with higher mortality among cancer patients [1]. Potential explanations include the immune suppression caused by the malignancy and the use of systemic anticancer treatments, such as chemotherapy, immunotherapy, and radiotherapy [2]. Current data on COVID-19 mortality among cancer patients group treatment modalities such as immune therapy and targeted therapy (n = 7) together, which is flawed [3]. Therefore, it is currently unknown whether the use of immune checkpoint inhibitors (ICIs) in cancer patients is safe during the COVID-19 pandemic. It is possible that ICIs may enhance the cytokine storm associated with COVID-19 [4]. This issue

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Table 1 – Clinical characteristics and outcomes for patients with COVID-19 infection

	Patient 1	Patient 2	Patient 3	Patient 4
Patient and tumour characteristics				
Age (yr)	52	68	66	72
Gender	Male	Male	Male	Male
ECOG performance status	1	1	1	1
Previous/current smoker	No	Yes	No	Yes
Comorbidities	HTN	HTN	HTN	HTN, diabetes
Tumour type	RCC	RCC	UC	UC
Stage of disease	IV	IV	IV	IV
Sites of metastatic disease	Bone	Lung	Lung	Lymph nodes
Current line of cancer therapy	1st	1st	2nd	2nd
Current cancer treatment	Ipilimumab/ nivolumab	Ipilimumab/ nivolumab	Atezolizumab	Atezolizumab
Duration of current anticancer therapy	3 mo	3 wk	6 mo	4 mo
Time from last ICI administration to COVID-19 diagnosis	8 wk	2 wk	3 wk	3 wk
Treatment-related toxicities requiring steroids[a]	Rash G3	None	Pneumonitis G2	None
Length of steroid treatment	28 d	NA	28 d	NA
Time from last steroid dose to COVID-19 diagnosis	9 d	NA	21 d	NA
COVID-19 symptoms and management				
Clinical symptoms of COVID-19[a]	Fever G2, myalgia G1, dyspnoea G3	Fever G2, cough G1	Cough G1, dyspnoea G2	Cough G1, diarrhoea G1
Time from symptoms to hospital admission	4 d	NA	NA	10 d
COVID-19 management	Hospital admission	Outpatient management, self-isolation	Outpatient management, self-isolation	Hospital admission
Significant laboratory test results	CRP↑↑, ferritin ↑↑	CRP ↑	CRP ↑	Lymphocytes ↓↓
Significant imaging results	Bilateral involvement on chest X-ray	NA	NA	Chest X-ray normal
Inpatient management	O_2, antibiotics	NA	NA	Fluids, antibiotics
COVID-19 outcome/hospitalisation status	Recovered, discharged from hospital	Recovered	Recovered	Recovered, discharged from hospital
Duration of hospitalisation	28 d[b]	NA	NA	2 d
Survival status	Alive	Alive	Alive	Alive
Follow-up since first signs of COVID-19	32 d	34 d	45 d	37 d

ECOG = Eastern Cooperative Oncology Group; HTN = hypertension; RCC = renal cell carcinoma; UC = urothelial carcinoma; NA = not applicable; CRP = C-reactive protein.

[a] Symptoms were graded according to the National Cancer Institute Common Terminology Criteria, version 4.03.

[b] The patient was clinically fit for discharge 11 d after hospitalisation. Prolonged hospitalisation occurred due to management of social problems.

is complicated by the treatment of immune-mediated toxicities with immunosuppressive steroids. For these reasons, guidelines have suggested to proceed with caution or avoid/interrupt treatment [5,6]. Here we describe the clinical characteristics and outcomes of four COVID-19 patients with genitourinary (GU) cancer treated with ICIs.

1.2. Cases

An audit on patients receiving single-agent (PD-1/PD-L1 inhibitor) or combination ICIs (PD-1/CTLA-4) during a 12-wk period from the start of the COVID-19 pandemic was performed for a single institution in London, UK on April 7, 2020. Data for all patients with GU cancer who received at least one cycle of ICI during this period were collected. Patients were either seen as outpatients or via telephone consultation. Patients with positive COVID-19 infection (cobas® SARS-CoV-2 test, Roche Diagnostics) were identified in accordance with UK government policy regarding testing [7]. The work was assessed and approved by the Barts Health research governance group.

A total of 74 patients received ICIs between February 1 and April 27, 2020 and were prospectively followed because of their high risk of COVID-19. All patients received at least one dose of treatment. Owing to the long half-life of ICIs, all patients had received an effective treatment dose. During this period of surveillance, 11 patients (15%) had symptoms (nine with fever, eight with cough, four with dyspnoea, three with myalgia, and two with diarrhoea) indicating possible COVID-19 infection. Six of these patients were not tested but remained in isolation because of suspected COVID-19 (UK policy). One patient tested negative. Four patients (5%) tested positive; these cases are described below (Table 1 and Fig. 1). All four are alive 32–45 d after their first symptoms and 28–38 d after testing positive for COVID-19.

Patient 1 was diagnosed with metastatic clear-cell renal cell carcinoma and received first-line combination therapy with CTLA-4/PD-1 inhibitors. After the second cycle the patient developed a severe rash and was started on corticosteroids 28 d before his first COVID-19 symptoms (FCS). The patient developed rigors, fever, cough, and

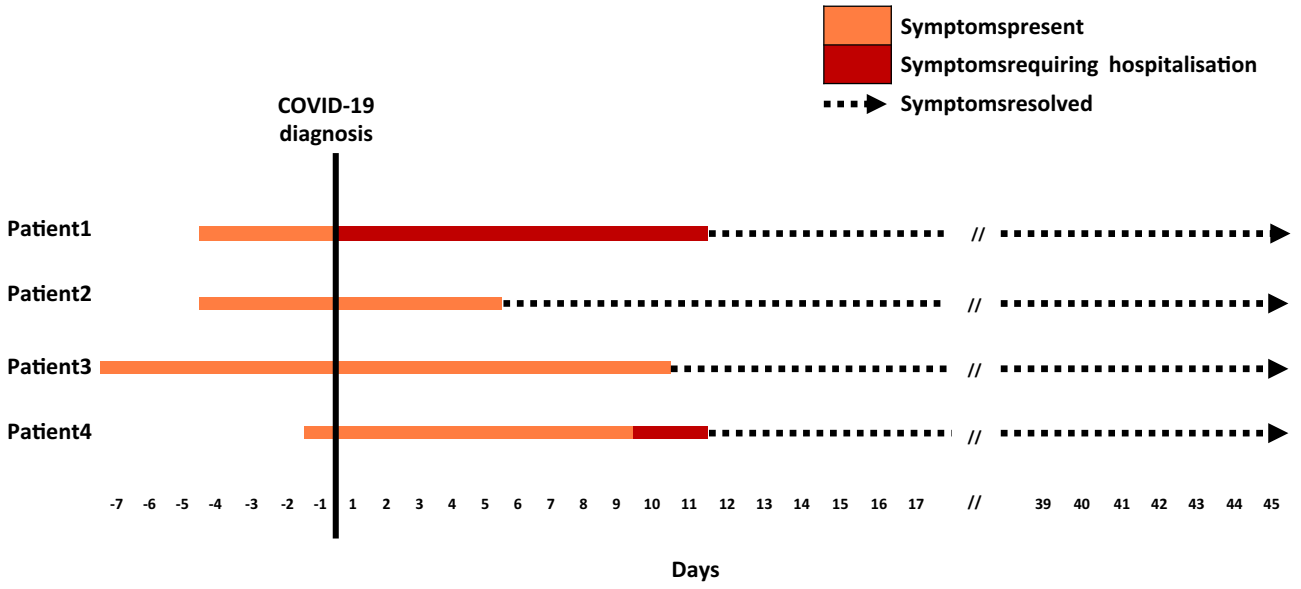

Fig. 1 – Clinical course and outcome for cancer patients receiving immune checkpoint inhibitors who tested positive for COVID-19.

dyspnoea 4 d after stopping steroids. After initial self-isolation, his symptoms worsened and the patient was admitted to hospital. On admission, he had a temperature of 38.8 °C and oxygen saturation (SpO_2) of 60%. Laboratory tests showed elevated C-reactive protein (CRP; 272 mg/l) and ferritin (995 μg/l) levels (Fig. 2). A chest X-ray revealed bilateral lung infiltrates. The patient was diagnosed with COVID-19 pneumonia and started on intravenous co-amoxiclav and clarithromycin and nasal high-flow oxygen therapy. After an initial increase in oxygen requirement (up to 60 l) the patient showed signs of improvement 48 h later and was successfully weaned off oxygen therapy. His CRP level normalised and the patient was clinically fit for discharge from hospital 32 d after FCS. The patient has not yet resumed cancer treatment because of personal reasons but plans to start again in the near future.

Fig. 2 – Symptoms and outcome for patient 1 with COVID-19 during hospitalisation. Evolution of clinical vital signs (temperature), requirement for supplemental O_2, and C-reactive protein (CRP) levels in blood.

Patient 2 was diagnosed with stage IV clear-cell renal cell carcinoma 2 mo before COVID-19 diagnosis and received first-line CTLA-4/PD-1 inhibitors. The patient presented with FCS (temperature of 38.8 °C and a dry cough) 16 d after his first ICI treatment. He tested positive for COVID-19 4 d later. He had no clinical or laboratory signs (CRP 18 mg/l, SpO_2 96% on air) of COVID-19 severity and was managed as an outpatient with self-isolation. The fever and cough resolved 5 d later, and the patient resumed his cancer treatment after completion of his self-isolation period.

Patient 3 received atezolizumab for treatment-refractory urothelial carcinoma for 6 mo before his FCS without evidence of cancer progression. At 7 wk before FCS, he developed immune-related pneumonitis confirmed by chest computed tomography (CT), which was successfully treated with systemic corticosteroids, after which the patient was restarted on atezolizumab. Shortly after, he developed a new cough and dyspnoea on exertion (SpO_2 93%) and tested positive for COVID-19. His blood work-up demonstrated a moderate increase in CRP (29 mg/l) and some persistent fibrotic changes on chest CT. The patient did not require oxygen supplementation and was managed with self-isolation. The dyspnoea and cough resolved within 7 and 10 d, respectively. The patient remained apyrexic throughout and resumed his cancer treatment 36 d after FCS.

Patient 4 received single-agent atezolizumab for treatment-refractory urothelial carcinoma starting 4 mo before FCS. Following recent symptomatic cancer progression, an antibody drug conjugate was added to atezolizumab 1 d before FCS. After contact with an unwell family member, the patient developed a cough and tested positive for COVID-19. Two days later the patient developed diarrhoea, which led to severe dehydration and hospitalisation 10 days after FCS. Laboratory work-up showed acute kidney injury (creatinine 276 mg/dl) with mild CRP elevation (25 mg/dl) and lymphocytopenia (0.6×10^9/l). The patient was started on fluid replacement therapy and intravenous tazobactam/piperacillin. He improved rapidly and was discharged 48 h later. The patient resumed his treatment with atezolizumab 31 d after FCS.

2. Discussion

The incidence and prevalence of COVID-19 are unknown because of the sporadic nature of testing. The incidence among cancer patients is likely to track that in the general population, although the need to attend hospital for health care reasons may put cancer patients at higher risk. This and the overlap between cancer symptoms and COVID-19 may account for the relatively high incidence of symptoms and COVID-19 positivity in our cohort.

Mortality rates among COVID-19-positive cancer patients are high, especially those receiving anticancer treatment 14 d before infection (hazard ratio 4.07, 95% confidence interval 1.08–15.32) [3]. However, risks associated with chemotherapy, targeted therapy, and ICIs are likely to differ. Therefore, combining these therapy modalities in one analysis is flawed.

As demonstrated by our cohort, COVID-19 patients receiving ICI therapy do not necessarily have a severe disease course, despite multiple risk factors (male [$n = 4$], age [$n = 3$], cancer [$n = 4$], and hypertension [$n = 4$]) and they are able to restart immunotherapy. This questions the hypothesis in a recent recommendation that ICIs may be associated with higher COVID-19 morbidity and mortality [5]. Previous data suggest that ICIs do not appear to predispose to other viral pneumonias such as influenza [8] potentially supporting our position, although there are case reports of more frequent herpes simplex virus with ICIs [9].

In our series, two patients had previous immune-mediated toxicities requiring systemic corticosteroids. Despite this, both patients made a full recovery, countering concerns in recent guidelines surrounding steroids [5]. Further data are required.

The clinical pictures associated with COVID-19 and metastatic GU cancers overlap, complicating the diagnosis, as demonstrated by patients in this series who developed fever, cough, dyspnoea, and diarrhoea. Parameters for assessing COVID-19 severity have been identified (elevated CRP and ferritin, lymphopenia, and elevated neutrophil/lymphocyte ratio) that are also commonly abnormal in cancer patients [10]. This requires consideration when diagnosing and assessing COVID-19 severity.

A literature review revealed COVID-19 in one other GU cancer patient receiving ICIs and eight patients receiving ICIs in other cancers [1,3]. These patients also recovered. It is therefore premature to give guidelines suggesting that ICIs are unsafe or that treatment modifications are required during the COVID-19 pandemic [6]. Further data are required.

Conflicts of interest: The authors have nothing to disclose.

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