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Case Report

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Clinical course of COVID-19 infection in elderly patient with melanoma on nivolumab

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Abstract

Outbreak of the new type coronavirus infection, known as coronavirus infection 2019 (COVID-19), has begun in December 2019, in Wuhan, China. As of today, 3 April 2020, 972,640 people affected and 50,325 people died from Severe Acute Respiratory Syndrome-Coronavirus 2. There is not any standard treatment for coronavirus infection 2019; however, there are promising data for hydroxychloroquine and some anti-retroviral drugs. Programmed death-1 (PD-1)/programmed death ligand-1 (PDL-1) pathway is an important target for the cancer immunotherapy. However, there is a robust pre-clinical and clinical data regarding inhibitor effect of this pathway on the acute or chronic viral infections. Thus, blockade of this pathway may lead to an anti-viral effect and decrease viral load. Here, we report the clinical course of coronavirus infection 2019 infection of a patient in whom older aged, having multiple co-morbidities, and taking nivolumab for metastatic malignant melanoma. In contrast to her older age, comorbidities, and cancer diagnosis, she was in a good condition, and there was also no pneumonia finding. We think that this good clinical course of coronavirus infection 2019 infection may be related to blockade of PD-1/PDL-1 pathway with nivolumab. It is impossible to say that blockade of PD-1/PDL-1pathway is a treatment option for COVID-19; however, we want to share our experience.

Keywords

COVID-19, SARS-CoV2, immunotherapy

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Introduction

After the first reporting of novel coronavirus, known as Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2), outbreak in Wuhan, China in December 2019, World Health Organization (WHO) declared SARS-CoV2 as a pandemic on 11 March.[1] As of today, 3 April 2020, 972,640 people were affected and 50,325 people died from SARS-CoV2.[2]

Older aged people, patients with multiple co-morbidities and immune-suppressed individuals are the frequently and severely affected populations from SARS-CoV2.[3] Cancer patients are the particular population having these conditions. According to Surveillance, Epidemiology, and End Results program (SEER) database, the median age for cancer diagnosis is 66 years.[4] Additionally, cancer treatment causes an immune-suppressive situation. Because of these reasons, cancer patients are one of the most disadvantaged groups for SARS-CoV2.

Approximately 80% of all affected people showed mild respiratory system infection symptoms; however,

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5% of them had critical disease. Cancer patients are more candidate for severe disease when comparing with non-cancer patients (39% vs 8%, $p = 0.0003$).[5] The cancer patients receiving active cancer treatment were also more susceptible to the severe disease (75% vs 43%, respectively).[5] While overall case-fatality rate (CFR) was 2.3%, it was 5.6% in the cancer patients.[3,5]

Case report

A 75-year-old female metastatic malignant melanoma patient was admitted to our emergency department with fever (38.5°C) and severe fatigue on 16 March 2020. She also had multiple co-morbidities of hypertension, diabetes mellitus type 2 (T2DM), atrial fibrillation (AF), coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD).

She had been diagnosed with pathological T4aN2a and B-RAF wild-type cutaneous malignant melanoma on her left foot in 2015 that totally excised. There was no distant metastasis at that time. After surgery, the patient was followed without adjuvant treatment. Four years later, in 2019, lung metastasis was observed, and nivolumab was started on 7 March 2019. A computer tomography (CT) scan revealed partial response (PR) in the third month of the treatment, and treatment was continued with nivolumab. In December 2019, in the ninth month of the treatment, positron emission tomography/CT (PET/CT) scan revealed metabolic complete response (CR) for the lung metastasis, and nivolumab was continued again. Laboratory findings before the first and last dose of nivolumab are shown in Table 1.

Twenty-seventh cycle of nivolumab was administered to the patient on 12 March 2020, and she described diarrhea on the second day of the last administration of nivolumab. On admission of emergency department, she had also mild dyspnea, and her

Table 1. Laboratory results.

Variables	Normal range for adults	Before the 1st cycle of nivolumab	Before the last dose of nivolumab
Hematocrit (%)	35–47	40	39.7
Hemoglobin (g/dl)	11.7–16.1	12.2	13
White-cell count (per 10^9/l)	4.5–11	8.89	9.67
Differential count (%)			
Neutrophils	40–70	56.7	62.7
Lymphocytes	20–45	33.7	25.4
Monocytes	3–9	7.8	9.9
Eosinophils	0–6	1.7	1.7
Basophils	0–1	0.1	0.3
Platelet count (per 10^9/l)	150–400	374	373
Red-cell count (per 10^{12}/l)	3.8–5.2	4.3	4.34
Mean corpuscular volume (fl)	81–102	93	91.5
Sodium (mmol/l)	136–146	141	144
Potassium (mmol/l)	3.5–5.1	5,4	3.7
Chloride (mmol/l)	101–109	106	107
Glucose (mg/dl)	74–100	158	172
Albumin (g/dl)	3.5–5.2	3.6	3.1
Total protein (g/dl)	6.6–8.3	6.6	6.1
Phosphorus (mg/dl)	2.5–4.5	4.39	2.69
Calcium (mg/dl)	8.8–10.6	9.6	8.8
Uric acid (mg/dl)	2.6–6	6.8	8.06
Urea nitrogen (mg/dl)	8–23	26	15.9
Creatinin	0.51–0.95	0.75	0.99
Alanin aminotransferase (U/l)	0–35	7	10
Aspartate aminotransferase (U/l)	0–35	12	19
Alkaline phosphatase (U/l)	130	30–120	97
Gamma glutamyl transferase (U/l)	0–38	11	11
Bilirubin, total (mg/dl)	0.3–1.2	0.28	0.39
Bilirubin, direct (mg/dl)	0–0.2	0.04	0.05
Lactate dehydrogenase (U/l)	0–247	139	185

oxygen saturation was 84% by pulse-oximeter. Due to high level of d-dimer and hypoxia, a pulmonary CT angiography scan was performed. It revealed only bilateral pleural thickness similar to before findings on her PET/CT scan images, and there was no pulmonary thromboembolism. After sampling blood, sputum, and urine cultures, empirical piperacillin–tazobactam was started due to high fever. Laboratory findings on the admission day of emergency department is shown in Table 2.

On 17 March 2020, the patient was hospitalized in the medical oncology unit. She still had fever, and abundant *Candida albicans* (*C. albicans*) was observed in her sputum culture. On the same day, intravenous (IV) fluconazole was started due to the presence of *C. albicans* on sputum culture and continued fever.

One day later, on 18 March 2020, a patient was diagnosed with COVID-19 in the emergency department of our hospital, and all of the patients admitted to the emergency department at the same time with this patient were screened for COVID-19. Our patient was one of these patients. Thus, she was transferred to COVID-19 clinic to be quarantined, and COVID-19 test was performed immediately. She had hypoxia, and she was taking 5 l/min oxygen support via nasal cannula. While waiting for the test result, oseltamivir 75 mg BID and clarithromycin 500 mg BID were started due to community-acquired pneumonia. Empirical metronidazole 500 mg TID was added for diarrhea. Urine and blood cultures were negative. Laboratory findings on the transfer day to COVID-19 clinic is shown in Table 2.

The first result of her COVID-19 real time polymerase chain reaction (real time-PCR) test was negative on 18 March 2020. However, on 20 March 2020, the

Table 2. Laboratory results.

Variables	Normal range for adults	On admission of emergency department	On the day transfer to COVID-19 clinic
Hematocrit (%)	35–47	38.3	34.3
Hemoglobin (g/dl)	11.7–16.1	12.4	11
White-cell count (per 10^9/l)	4.5–11	11.86	7.49
Differential count (%)			
Neutrophils	40–70	82.6	75
Lymphocytes	20–45	9.4	14.6
Monocytes	3–9	7.3	7.5
Eosinophils	0–6	0.4	2.5
Basophils	0–1	0.3	0.4
Platelet count (per 10^9/l)	150–400	293	245
Red-cell count (per 10^{12}/l)	3.8–5.2	3.99	3.51
Mean corpuscular volume (fl)	81–102	96	97.7
Sodium (mmol/l)	136–146	139	145
Potassium (mmol/l)	3.5–5.1	2.7	3.1
Chloride (mmol/l)	101–109	102	110
Glucose (mg/dl)	74–100	163	158
Albumin (g/dl)	3.5–5.2	2.9	2.5
Total protein (g/dl)	6.6–8.3	5.8	5.1
Phosphorus (mg/dl)	2.5–4.5		2.7
Calcium (mg/dl)	8.8–10.6	8.3	7.8
Uric acid (mg/dl)	2.6–6	8.4	5.3
Urea nitrogen (mg/dl)	8–23	12	9
Creatinin	0.51–0.95	1	1.16
Alanin aminotransferase (U/l)	0–35	7	7
Aspartate aminotransferase (U/l)	0–35	12	20
Alkaline phosphatase (U/l)	130	78	55
Gamma glutamyl transferase (U/l)	0–38	10	8
Bilirubin, total (mg/dl)	0.3–1.2	0.36	0.21
Bilirubin, direct (mg/dl)	0–0.2	0.05	0.06
Lactate dehydrogenase (U/l)	0–247	169	157
C-reactive protein (mg/l)	0–5	92	59
Procalcitonin (ng/ml)	0–0.05	0.11	0.12
D-dimer (ng/ml)	0–243	872	

second real time-PCR result became positive, and hydroxychloroquine 200 mg BID was started. Additionally, clarithromycin 500 mg was stopped, and azithromycin was started for COVID-19.

On 22 March 2020, on the second day of the hydroxychloroquine treatment, hypoglycemia was observed, and blood glucose level was 31 mg/dl. The patient had been taking oral anti-diabetics, and all of these oral anti-diabetics were stopped due to hypoglycemia. There was no additional risk factor for the hypoglycemia. In fact, it was considered side effect of hydroxychloroquine. However, there was no another option, and hydroxychloroquine was continued.

The oxygen requirement of the patient decreased step by step, and finally on the third day of the COVID-19 treatment, oxygen saturation level of the patient was 95% while breathing room-air. Diarrhea was also resolved.

As of 23 March 2020, on the fifth day of the COVID-19 treatment, while she was taking oseltamivir, hydroxychloroquine, azithromycin, and piperacillin-tazobactam, a chest CT scan revealed only bilateral minimal pleural effusion which was not accepted associated with SARS-CoV2 pneumonia, and there were also no characteristic findings of the COVID-19. Pleural effusion on the chest CT scan is shown in Figure 1. On the fifth day of the treatment, COVID-19 treatment was stopped due to resolving her clinical findings. Laboratory findings on the first, third, and the fifth day of COVID-19 treatment are shown in Table 3.

On 28 March 2020, on the fifth day after stopping COVID-19-specific treatment, the patient had mild hypoxia. Her oxygen saturation was 96% with 2 l/min oxygen support via nasal cannula. She was also in a good clinical condition. A pulmonary CT scan performed revealed mild ground glass opacity (GGO) areas in the lung parenchyma. GGO in the lung parenchyma is shown in Figure 2. Hydroxychloroquine 200 mg BID and favipravir 600 mg BID were started for COVID-19 pneumonia.

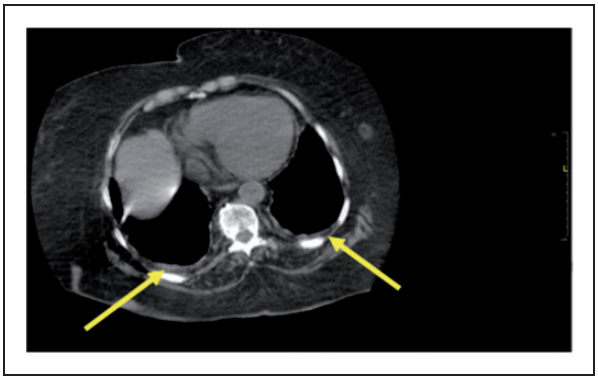


Figure 1. Pulmonary CT image on the first day of COVID-19 diagnosis (yellow arrows indicate 'minimal pleural effusion').

On 1 April 2020, on the fifth day of the favipravir and hydroxychloroquine, her oxygen requirement decreased, and she was still in a good clinical condition despite her multiple co-morbidities and older age. COVID-19 treatment was stopped and the patient was discharged. However, she passed away due to her chronic cardiac problems 10 days after being discharged from hospital.

Discussion

Cancer is an important risk factor for severe SARS-CoV2 infection; furthermore, additional co-morbidities increase the severe disease and mortality rate of the COVID-19. Overall, CFR was 2.3%; however, it was 8% for the aged group 70–79. CFR was also 10.5, 7.3, 6.3, 6, and 5.6% for cardiovascular disease, diabetes, COPD, hypertension, and cancer, respectively.[5] Our patient had all of these co-morbidities, and she had importantly increased risk for severe disease in contrast to her current clinical situation.

Programmed death-1 (PD-1)/programmed death ligand-1 (PDL-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)/B7 interactions play an important role in the inhibition of T lymphocytes. Immune checkpoint inhibitors (ICIs) (e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab, ipilimumab) are used in the cancer treatment by blockade this interaction between T lymphocytes and cancer cells.[6]

Despite their activating effect on T-cell functions against cancer cells, furthermore, there are a lot of pre-clinical data for the effect of the ICIs on acute or chronic viral infections.[7] Additionally, there are also a lot of clinical trials regarding effectiveness of the ICIs on the virus-associated cancers. Tremelimumab is an ICI that inhibits CTLA-4 receptor. In a trial about effect of tremelimumab on hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC), a significant decrease in the HCV viral load and elevation of HCV-specific interferon-gamma level had been reported after tremelimumab.[8]

T-cell exhaustion is a crucial phenomenon in the human immunodeficiency (HIV) virus infections, and PD-1 plays an important role in this exhaustion. Blockade of PD-1/PDL-1 interaction leads to restoration of $CD8^+$ T-cell functions, and improved $CD8^+$ T-cell functions increase the cytokine synthesis and decrease viral load.[9] Besides chronic viral infections, high level of PD-1 expression is observed on the early stage of acute viral infections. Ahn et al.[10] showed a transient increase on PD-1 receptors during early stage

Table 3. Laboratory results.

Variables	Normal range for adults	On the 1st day of COVID-19 treatment	On the 3rd day of COVID-19 treatment	On the 5th day of COVID-19 treatment
Hematocrit (%)	35–47	34.3	33.6	28.7
Hemoglobin (g/dl)	11.7–16.1	10.9	10.9	8.8
White-cell count (per 10^9/l)	4.5–11	3.45	3.85	3.12
Differential count (%)				
Neutrophils	40–70	65.4	42.4	47.8
Lymphocytes	20–45	20.9	42.3	36.9
Monocytes	3–9	12.5	11.7	9.6
Eosinophils	0–6	0.6	3.1	5.1
Basophils	0–1	0.6	0.5	0.6
Platelet count (per 10^9/l)	150–400	273	310	272
Red-cell count (per 10^{12}/l)	3.8–5.2	3.51	3.49	2.91
Mean corpuscular volume (fl)	81–102	97.7	96.3	98.6
Sodium (mmol/l)	136–146	144	144	145
Potassium (mmol/l)	3.5–5.1	3.2	2.8	3
Chloride (mmol/l)	101–109	107	107	113
Glucose (mg/dl)	74–100	73	35	123
Albumin (g/dl)	3.5–5.2	2.5	2.3	1.8
Total protein (g/dl)	6.6–8.3	5	4.6	3.6
Phosphorus (mg/dl)	2.5–4.5	3.5	3.6	2.1
Calcium (mg/dl)	8.8–10.6	7.9	7.7	6.1
Uric acid (mg/dl)	2.6–6	3.6	3.7	2.9
Urea nitrogen (mg/dl)	8–23	6	8	5
Creatinin	0.51–0.95	1.13	1.25	0.89
Alanin aminotransferase (U/l)	0–35	8	10	6
Aspartate aminotransferase (U/l)	0–35	20	28	10
Alkaline phosphatase (U/l)	130	56	55	37
Gamma glutamyl transferase (U/l)	0–38	11	11	11
Bilirubin, total (mg/dl)	0.3–1.2	0.26	0.31	0.28
Bilirubin, direct (mg/dl)	0–0.2	0.05	0.06	0.06
Lactate dehydrogenase (U/l)	0–247	247	187	128
C-reactive protein (mg/l)	0–5		17.8	15.5
Procalcitonin (ng/ml)	0–0.05		0.13	0.06
Neutrophil/lymphocyte ratio		3.1	1	1.3

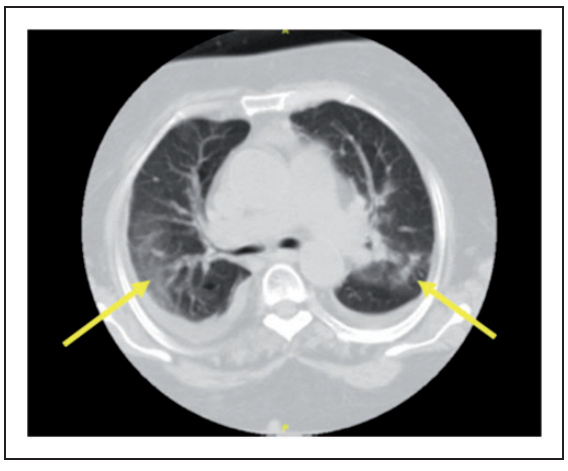


Figure 2. Pulmonary CT image on the 10th day of COVID-19 diagnosis (yellow arrows indicate 'GGO').

of acute viral infections, and they also reported that PD-1/PDL-1 pathway inhibited transforming of naïve $CD8^+$ T cells to effector $CD8^+$ T cells. In addition, virus-infected dendritic cells express high PDL-1 molecules on their surface, and it causes inhibition of the T cells in the acute viral infections.[11] In fact, blockade of PD-1/PDL-1 pathway was considered an important target in the viral infections. According to pre-clinical data, blockade of PD-1/PDL-1 interaction increased the number of effector $CD8^+$ T cells, granzyme synthesis from CD^+8 T cells, and finally decreased viral load in mice.[10]

In 2012, Erickson et al.[12] showed high expression of PD-1 and PDL-1 in the lower respiratory system during acute viral infections. They also claimed that it caused poor CD^+8 T-cell functions and recurrent viral infections in the lower respiratory system of humans.

Our patient was in a very good condition even she had multiple co-morbidities and older age. There was also no clear evidence for SARS-CoV2 pneumonia on her chest CT scan. Before COVID-19 diagnosis, she had been administered 27 cycle nivolumab, and the last dose administered before six days of the COVID-19 infection. PD-1 inhibition in our patient can be a reason for a mild disease instead of severe clinic findings of COVID-19. In addition, hydroxychloroquine, azithromycin, and piperacillin–tazobactam improved mild clinical findings of our patient. Hydroxychloroquine decreases insulin resistance; thus, hypoglycemia is an important side effect among patients taking hydroxychloroquine.[13] We continued to hydroxychloroquine treatment despite its side effect due to no another option for the treatment of COVID-19. At the same time, with positive test results for COVID-19 of our patient, a study was published which showed the efficacy of hydroxychloroquine plus azithromycin for the patients with COVID-19.[14] We started the hydroxychloroquine plus azithromycin based on this study. However, on 30 March 2020, a new publication claimed that there was no evidence for SARS-Cov2 clearance with hydroxychloroquine plus azithromycin.[15] It is obviously seen that we need randomized clinical trials in terms of the effect of hydroxychloroquine plus azithromycin.

In conclusion, there is not enough data about the course of COVID-19 infection in patients under immunotherapy and we would like to share this case. It is not possible to make a recommendation with the available data regarding the uses of immunotherapy and obviously further studies are needed. Therefore, we think it is important to share experiences.

Declaration of Conflicting Interests

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