VIA MEDICA

CASE REPORT

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COVID-19 infection during treatment with pembrolizumab in combination with chemotherapy for the treatment of lung adenocarcinoma

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ABSTRACT

The use of pembrolizumab with chemotherapy in first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) is an opportunity for patients to suppress their disease and increase their chances of life extension. COVID-19 (Coronavirus Disease 2019) vaccination is an opportunity for cancer patients to reduce their risk of disease and have a benign disease course. In this report, we present a benign course of SARS-CoV-2 (Severe Acute Respiratory Syndrome *Coronavirus 2*) infection in 68-year-old patient with metastatic lung adenocarcinoma undergoing chemoimmunotherapy who had previously received full COVID-19 vaccination. The control CT scans performed after 3 months of treatment showed partial regression of the tumor mass. On control tomography after 6 months, an intensification of fibro-consolidative changes and ground glass opacities were described. The lesions were characteristic of a history of SARS-CoV-2 infection. The neoplastic lesions described on tomography showed stabilization. After 9 months, long-term stabilization of the disease was achieved. Patients undergoing immunotherapy or chemoimmunotherapy may be at risk of developing severe COVID-19. Therefore, vaccination against SARS-CoV-2 should be strongly recommended in lung cancer patients undergoing immunotherapy.

Key words: non-small cell lung cancer, COVID-19, pembrolizumab, immunotherapy

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Introduction

The use of pembrolizumab with chemotherapy in first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) is an opportunity for patients to suppress their disease and increase their chances of life extension (long survival). COVID-19 (Coronavirus Disease 2019) vaccination is an opportunity for cancer patients to reduce their risk of disease and have a benign disease course. Good treatment tolerance and an infection-free therapeutic regimen increase patients' chances for better therapeutic outcomes. In this report, we present a benign course of SARS-CoV-2 (Severe Acute Respiratory Syndrome *Coronavirus 2*) infection in an elderly patient with metastatic adenocarcinoma of the lung undergoing chemoimmunotherapy who had previously received full COVID-19 vaccination.

Case report

The 68-year-old male patient was admitted to the Pulmonology Clinic because of increasing pain in the thoracic spine and left shoulder that had persisted for several months. Chest radiography showed the lung apex tumor. In addition, the patient complained of weakness, decreased exercise tolerance, and had lost approximately 5 kg in 3 months. The patient had good performance status. He was a cigarette smoker (history of 25 pack-years). He stopped smoking about 2 years ago

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after an inferior wall myocardial infarction. He suffered from ischemic heart disease and circulatory insufficiency. He underwent angioplasty of the circumflex branch (Cx) of the left coronary artery with drug-eluting stent (DES) implantation and with controlled hypertension after inguinal hernia surgery 5 years earlier.

Computer tomography scan showed a 82 × 75 × 58 mm tumor mass over the left hilum, involving the aortic arch, and infiltrating the Th2, Th3 and Th4 vertebral bodies with their arches on the left side. The infiltration of the posterior segments of 3rd and 4th ribs on the left side was also shown. The tumor displaced the esophagus to the right side, and there was a possibility of esophageal infiltration. The patient was referred to the Department of Thoracic Surgery for invasive diagnostics. An attempt to obtain material for histopathological examination during endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) enhanced bronchoscopy was unsuccessful. The material was obtained during open lung biopsy (left video-thoracoscopy). Histopathological examination described adenocarcinoma tissue with expression of (TTF1) and cytokeratin 7 (CK7) in immunohistochemical (IHC) examination. The presence of mutations in the *Epidermal Growth Factor Receptor* (*EGFR*) gene, rearrangements in the *ALK* (*anaplastic lymphoma kinase*) and *ROS1* genes were excluded. Programmed death ligand 1 (PDL1) expression was diagnosed by the IHC method in 5% of tumor cells. To qualify the patient for systemic treatment, a new computed tomography (CT) was performed, whose description did not differ significantly from the previous one (T4N2M1 stage according 8th lung cancer TNM classification).

The patient was examined for eligibility for treatment according to drug program B.6 using pembrolizumab and carboplatin-based chemotherapy with pemetrexed for the first-line treatment of advanced, metastatic, non-small cell lung cancer. The patient met all program criteria. He did not have any exclusion criteria based on the program's provisions. After premedication with vitamin B12 and folic acid, the patient received treatment with the regimen: pembrolizumab 200 mg, pemetrexed 500 mg/m^2, carboplatin area under curve (AUC) 6. Granulocyte growth factors were also administered prophylactically. The patient received palliative irradiation to the thoracic spine.

After 3 courses of treatment, the patient developed grade 3 granulocytopenia, grade 2 anemia, and grade 2 thrombocytopenia. During the treatment of granulocytopenia and anemia, granulocyte growth factor and red blood cell growth factor were used with normalization of blood morphotic parameters. The control CT scans performed after 3 months of treatment showed partial regression of the tumor mass: from 70 × 69 mm to 62 × 47 mm. It still involved the aortic arch, with less pronounced infiltration of bony structures and less infiltration into the spinal canal. The mass adhered to the esophagus and trachea but did not displace them. There was a partial regression of the fibro-epiglottic zones in the uvula and in the lower lobe of the left lung. The lymph node of the aortic-pulmonary window decreased in size from 19 × 16 mm to 16 × 12 mm. Numerous mediastinal lymph nodes were not enlarged in the short axis. The right hilar lymph node decreased from a size of 17 × 12 mm to 15 × 10 mm (Fig. 1).

Treatment was continued with pembrolizumab and pemetrexed for another 3 months with good tolerability. In November 2021, the patient underwent SARS-CoV-2 infection confirmed by an antigen test. For approximately 2–3 days, the patient had fatigue, rhinitis, and moderately elevated temperature (up to 37.4 degrees Celsius). The patient had been vaccinated against COVID-19 with two doses of Moderna vaccine. The last dose was administrated 2 months before the symptoms of infection. ABBOT antigen tests were per-

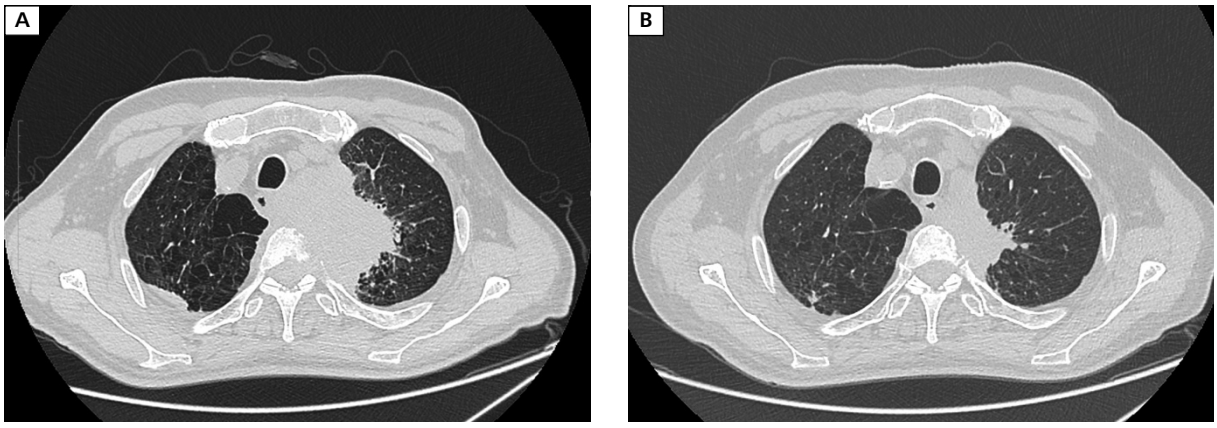

Figure 1. A. 82 × 75 × 58 mm tumor mass over the left hilum described on computer tomography scan before treatment. Infiltration of the thoracic vertebrae is also visible; **B.** Computer tomography of the lung performed after 3 months of treatment showing partial regression of the tumor mass and vertebrae infiltration

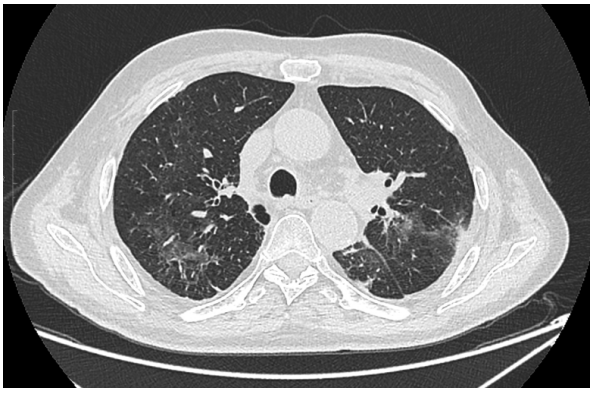

Figure 2. Computer tomography of the lung performed after 6 months of treatment showing an intensification of fibroconsolidative changes and ground glass opacities. The lesions are characteristic of a history of SARS-CoV-2 infection. The neoplastic lesions showed stabilization according to RECIST 1.1

formed each time before admission to the hospital for scheduled treatment. The patient's results were always negative. The patient continued treatment as scheduled.

On control tomography, evaluating the effects of therapy after 6 months, an intensification of fibro-consolidative changes and ground glass opacities were described. The lesions were characteristic of a history of SARS-CoV-2 infection (Fig. 2). The neoplastic lesions described on the tomography showed stabilization according to RECIST 1.1 criteria (*Response Evaluation Criteria in Solid Tumors*). The patient continued treatment with pembrolizumab and pemetrexed, with good tolerance and performance status for another 3 months. After 9 months of treatment, there was further stabilization of the tumor lesions on computed tomography. However, there was a significant regression of the areas of fibro-consolidative changes typical for SARS-CoV-2 infection. The patient still remains in good condition and with good tolerance continues treatment with pembrolizumab with pemetrexed.

Discussion

The benefit of pembrolizumab in combination with chemotherapy in NSCLC patients was demonstrated in the KEYNOTE-189 trial. In this trial, pembrolizumab (anti-PD-1 monoclonal antibody) with chemotherapy was used in the first-line treatment of metastatic non-squamous NSCLC. This placebo-controlled study compared the efficacy of chemoimmunotherapy versus chemotherapy (a regimen containing platinum-based chemotherapy) in previously untreated patients. The median of progression-free survival (PFS) for patients receiving pembrolizumab was 10.3 months and 6 months for patients in the control group. In addition, 12-month survival rate in the pembrolizumab group was 69.2% and 49.4% in the placebo group [1].

Subsequent analyses showed median overall survival (OS) of 22 months for pembrolizumab-treated patients and 10.7 months for placebo-receiving patients. The benefits obtained in the KEYNOTE 189 trial were independent of the status of metastatic lesions in the liver and brain, and the toxicity profile remained at an acceptable level [2].

According to ESMO (the European Society of Medical Oncology) recommendations, COVID-19 vaccines are both safe and effective for people with cancer. Patients with advanced cancer represent a high-risk group for severe COVID-19 and should be vaccinated as a priority. In addition, the patient's environment (family, caregivers, medical staff) should be vaccinated to minimize transmission. There is no evidence to suggest that COVID-19 vaccines significantly affect the efficacy or safety profile of anticancer therapies, including immunotherapy and cytotoxic chemotherapy. Therefore, COVID-19 vaccination in this group of patients should be strongly recommended [3].

It is known that cancer patients are more susceptible to infections and have an increased risk of pulmonary complications and death from SARS-CoV-2 infection than healthy individuals.

These observations were confirmed in a study by Yu et al. [4]. This retrospective study involving 1524 patients showed that patients with cancer were more likely to get SARS-CoV-2 infection [odds ratio (OR) = 2.31; 95% CI: 1.89–3.02] compared with the general population. This risk appears to be increased both in patients with and without active anticancer treatment. Patients with non-small cell lung cancer and aged over 60 years were most at risk of developing COVID-19 [4]. Smoking has also been identified as an independent risk factor for severe cases of COVID-19 [5].

A severe course of COVID-19, described as hyperinflammatory reactions, is associated with massive immune cell activation. The hypothesis that reduced immunity caused by the tumor itself or its treatment may be a protective element against the massive immune response observed in COVID-19 is not entirely true. Chronic inflammation resulting from cancer, older age of the patient, or treatment with immune checkpoint inhibitors (ICIs) may exacerbate the proinflammatory immune response, leading to increased cytokine production from T cells and phagocytes. Chronic inflammation is present in lung cancer due to both the tumor microenvironment and pathological changes present in the lung. For this reason, it is believed that older patients with lung cancer treated with ICIs experience a dysregulation of the immune system, which consequently may lead to severe forms of COVID 19 precisely in this group of patients [6, 7].

Conclusion

The use of pembrolizumab with chemotherapy in first-line treatment of patients with advanced NSCLC

may lead to remission or stabilization of the disease, sometimes lasting several years. Vaccination for COVID-19 is an opportunity for cancer patients to reduce the risk of developing the disease, as well as the benign course of the disease. Good treatment tolerance and an infection-free treatment regimen increases the chance of patients achieving better therapeutic outcomes. The use of pembrolizumab with chemotherapy in patients with advanced non-small cell non-small cell lung cancer can lead to stabilisation of the disease, sometimes lasting for many years. However, it appears that patients undergoing immunotherapy may be at risk of developing severe COVID-19. Therefore, vaccination against SARS-CoV-2 should be strongly recommended in lung cancer patients undergoing immunotherapy.

Conflict of interest

Author declare no conflict of interests.

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