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Case Report

Infliximab Treatment in Immune-related Pneumonitis with Respiratory Failure after High-dose Steroids: A Patient with Metastatic Gastric Cancer

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Abstract

Patients treated with immune checkpoint inhibitors sometimes have immune-related adverse events (IRAEs). Immune-related pneumonitis (IRP) is an uncommon but potentially fatal IRAE. We report a 69-year-old man with metastatic gastric cancer who received paclitaxel and nivolumab after failure with oxaliplatin and capecitabine. After his third dose of nivolumab, he had progressive shortness of breath and was diagnosed as having IRP with respiratory failure. He received high-dose methylprednisolone for 2 days, however, the response was not satisfactory. Thus, we added infliximab 5 mg/kg to high-dose methylprednisolone. With the combination of infliximab and high-dose methylprednisolone, the IRP greatly improved. Moreover, he had nearly complete remission of gastric cancer and was progression free for 3 months without any further anticancer treatment.

Keywords: Checkpoint inhibitor, immune-related adverse event, infliximab, programmed cell death-1 inhibitors, pneumonitis, respiratory failure

Introduction

Programmed cell death-1 (PD-1) inhibitors have been used as immune checkpoint inhibitors (ICIs) in treating many types of cancers, including melanoma, lung adenocarcinoma, head-and-neck squamous cell carcinoma, and urothelial cell carcinoma. In advanced gastric adenocarcinoma, PD-1 inhibitors have been shown to be superior to conventional third-line treatment.[1]

With the increasing use of ICIs, the rate of immune-related adverse events (IRAEs) has also increased, including pruritus, diarrhea, and hypothyroidism.[2] Among these adverse events, immune-related pneumonitis (IRP) is one of the most troublesome because it is associated with high rates of mortality and morbidity. The early administration

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of high-dose steroids is suggested for patients with IRP.[3] Patients with steroid-refractory IRP may benefit from adding infliximab.[4-6]

Here, we present a patient with advanced gastric cancer who received a combination of nivolumab and paclitaxel as second-line treatment and had IRP with respiratory failure. The IRP was resolved with a combination of infliximab and high-dose methylprednisolone after failure of high-dose methylprednisolone alone. This is the first reported patient who had severe IRP with respiratory failure who was successfully weaned from a ventilator after the administration of infliximab.

Case Report

A 69-year-old male Taiwanese retired engineer presented with abdominal fullness with vomiting, poor appetite, and body weight loss. He was not taking medication for any chronic diseases, did not drink alcohol or smoke, and had no family history of cancer. Abdominal echo revealed multiple liver tumors. Computed tomography (CT) showed multiple heterogeneous liver tumors, thickness of the gastric antrum, and multiple regional lymphadenopathies. Esophagogastroduodenoscopy showed a huge mucosal lesion, Bormann type III with gastric outlet obstruction, so a biopsy and stent placement were done. The pathology disclosed poorly differentiated adenocarcinoma, and an immunohistochemical study showed CK7 (+), CK20 (−), P40 (−), GATA3 (−), TTF-1 (−), Her-2 (−, score: 0), PD-L1 combined positive score < 1%, and no defect of mismatch repair genes. The initial diagnosis was gastric cancer with liver metastases, T3N3aM1. Before systemic treatment, his performance status was ECOG 0 with normal liver and renal function (total bilirubin: 0.9 mg/dl and creatinine: 0.82 mg/dl) without other underlying chronic diseases.

Oxaliplatin and capecitabine were administered as his frontline treatment, and no obvious severe adverse effects were noted. After four cycles of treatment, vomiting recurred, and follow-up CT [Figure 1] revealed rapidly progressive disease and gastric outlet obstruction due to the tumor growing into the stent. After discussion with the patient and his family, they preferred to add immunotherapy to second-line chemotherapy, so we used paclitaxel 80 mg/m^2 on days 1, 8, and 15 and nivolumab 3 mg/kg on day 1 and 15 in a 28-day cycle as the second-line treatment. On day 29, he came to our hospital for the second courses of day 1 nivolumab and paclitaxel. At that time, he had mild shortness of breath when talking in long sentences without performance restriction. On day 33, his shortness of breath became worse. Moreover, he also had fever with chills and cough without sputum. He had no cluster or travel history. Thus, he came to our emergency department where a physical examination showed fever up to 38.6°C, rapid and shallow respiratory pattern, bilateral rales and wheezing breathing sounds, and desaturation. Chest plain film (chest X-ray [CXR]) [Figure 2] revealed a bilateral, diffuse alveolar pattern. Initial differential diagnoses included pneumonia, cardiogenic pulmonary edema, and IRP. Follow-up cardioechography showed normal wall motion, and electrocardiogram revealed sinus tachycardia without ST-T change.

Broad-spectrum antibiotics were administered, and high-dose methylprednisolone 1 mg/kg was used under the impression of IRP. Due to a poor response to high-dose methylprednisolone, infliximab 5 mg/kg was added, and methylprednisolone was titrated to 2 mg/kg 48 h after the administration of methylprednisolone 1 mg/kg. However, saturation of the patient still deteriorated, and invasive ventilation was applied on day 35. None of the blood cultures and endotracheal tube sputum cultures yielded growth, but broad-spectrum antibiotics were kept due to the heavy anti-inflammation treatment. Bronchoscopy was not performed because of unacceptable oxygenation. Under the combination of high-dose steroids and infliximab, both oxygenation and CXR [Figure 3] improved, and he successfully weaned from invasive ventilation on

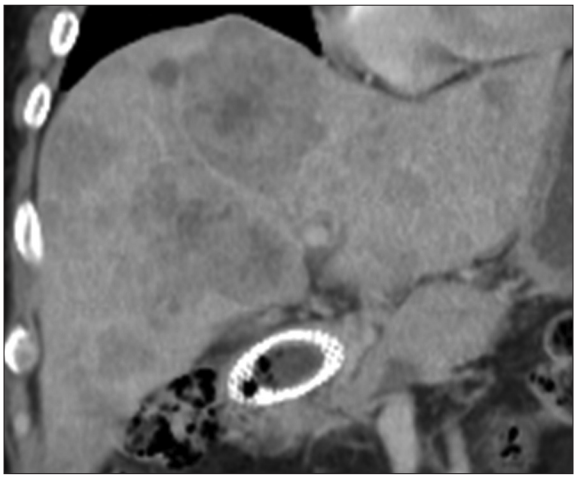

Figure 1: Computed tomography before nivolumab showed heterogeneous liver metastases

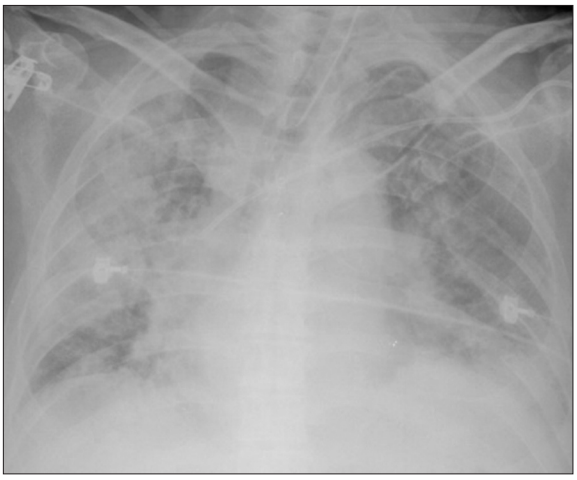

Figure 2: Chest X-ray on day 35 after first nivolumab revealed a bilateral diffuse alveolar pattern and immune-related pneumonitis was diagnosed; invasive ventilation was applied for deteriorating oxygenation

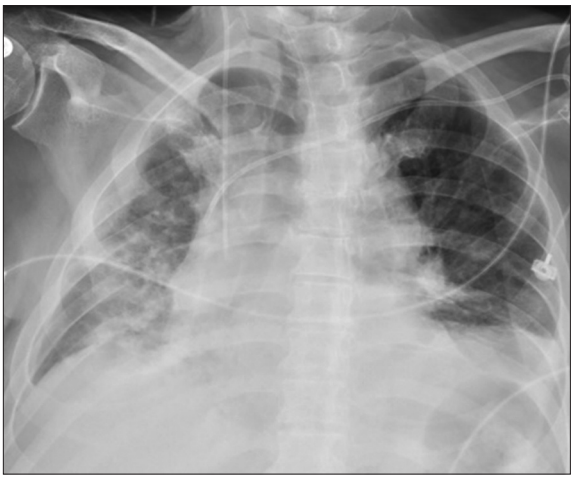

Figure 3: Chest X-ray on day 42 after first nivolumab or 7 days after infliximab showed resolved immune-related pneumonitis. The patient had also been successfully weaned from invasive ventilation

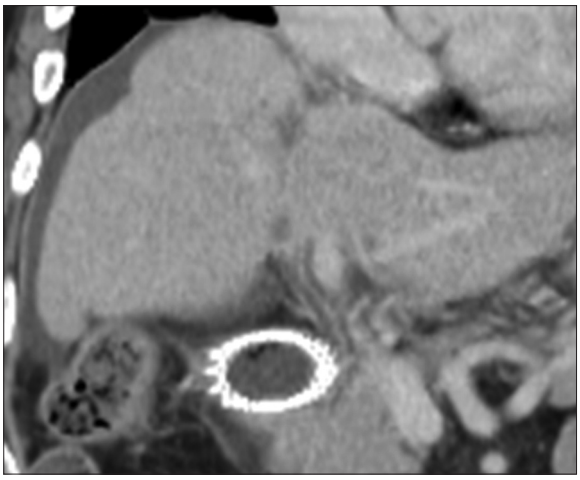

Figure 4: Computed tomography on day 123 after first nivolumab or 90 days after immune-related pneumonitis showed a nearly complete response without any further administration of anticancer treatment

day 40. The steroids were then tapered slowly. On day 64, he was discharged with oral prednisolone 40 mg daily. No further flares of IRP occurred, and he received the last dose of prednisolone on day 106. Moreover, he received no further anticancer treatment. Three months after pneumonitis, follow-up CT [Figure 4] revealed near-complete remission.

Discussion

IRP is an uncommon but potentially fatal adverse effect of ICIs. The overall incidence of IRP caused by PD-1 inhibitors is 2.7%.[7] The early administration of high-dose steroids is the primary goal while treating these patients. The challenges of treating IRP include variable differential diagnoses and poor response to high-dose steroids in some patients.

Physicians should always consider pneumonia as a differential diagnosis and prescribe broad-spectrum antibiotics. In addition to collecting blood and sputum cultures, bronchoscopy is indicated if the patient's condition is good. The onset of lymphangitis in the lungs caused by malignancy is insidious and was not compatible with our patient. Cardiogenic pulmonary edema is an alternative diagnosis, especially in patients treated with paclitaxel or ICIs which may induce cardiotoxicity. Cardioechography was performed to exclude this possibility.

Treatments for IRAEs refractory to high-dose steroids include infliximab 5 mg/kg, mycophenolate mofetil 1 g twice a day, intravascular immunoglobulin for 5 days, or cyclophosphamide.[3] Patients with IRP refractory to high-dose steroids may benefit from the addition of infliximab.[4-6] Given the rapid deterioration in respiration, infliximab should be added within 48 h after steroid administration if the response is not satisfactory. Our patient had rapidly progressive IRP with respiratory failure in 2 days, which rapidly resolved with successful weaning from the ventilator 5 days after the administration of infliximab.

The combination of ramucirumab with paclitaxel is the preferred treatment for patients with advanced gastric adenocarcinoma after frontline treatment.[8] Nivolumab treatment has been shown to result in significant improvements in overall survival in patients with advanced gastric adenocarcinoma after two or more standard treatments.[1] However, the combination of paclitaxel and nivolumab has not been reported in patients with advanced gastric adenocarcinoma. Based on experience from the treatment of lung cancer, a combination of ICIs and chemotherapy may result in a synergic effect.[9] Given the obstruction of gastric outlet in our patient, treatment with a high response rate was warranted. Most importantly, our patient expressed a strong preference for ICI treatment even though he did not have any predictive factors for ICIs such as defect of mismatch repair genes or high PD-L1 combined positive score. Even with the discontinuation of ICI and high-dose steroids, he still had nearly complete remission of his gastric cancer. Whether IRAEs play a role in predictive factor needs further evidence.

It is currently unclear whether the rate of pneumonitis increases in patients with gastric cancer receiving a combination of ICIs and chemotherapy, compared with ICIs alone. In a study where patients with lung cancer were treated with ICIs alone, pneumonitis of any grade occurred in 8% of the patients, and pneumonitis of Grade 3 or worse occurred in 3% of the patients treated with pembrolizumab.[10] In patients with lung cancer treated with a combination of ICIs and chemotherapy, pneumonitis of any grade occurred in 4.4% and pneumonitis of Grade 3 or worse occurred in 2.7%. A combination of ICIs and chemotherapy may not increase the rate of pneumonitis in patients with lung cancer.[9] Further studies may reveal the rate of pneumonitis in patients with gastric cancer treated with a combination of ICIs and chemotherapy.

Research involving human participants and/or animals

After a full description of the study, written informed consent

of participation was obtained from the legal guardians. The study protocol was approved by the Ethics Review Board of the China Medical University Ethics Committee on 2020/7/14 (Approval # CMUH109-REC3-079).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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