Integrative Pulmonary Medicine

A Case of Interstitial Cystitis Associated with the Anti-Programmed-Death-Receptor-1 Inhibitor: Pembrolizumab

Dong XQ, Yu BY*, Gui D, Shao C and Lin ZH

Department of Respiratory Diseases, Ningbo Medical Center Li Huili Hospital, Zhejiang 315000, China

*Correspondence: Bi-Yun Yu, Ningbo Medical Center Li Huili Hospital, Zhejiang 315000, China, E-mail: mouzi2011@163.com

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Abstract

Patients treated with antiprogrammed-death-receptor-1 inhibitor (PD-1) often experience immune-related adverse events (irAEs). Therefore, a case of non-bacterial interstitial cystitis in advanced NSCLC patient associated with Pembrolizumab before the start of ninth cycle is reported. With the use of immunosuppressive steroids, the symptoms disappeared immediately and tapered gradually. The symptoms appeared again when the immunotherapy restarted.

Keywords: Immune checkpoint inhibitors, Immune-related adverse events, Interstitial cystitis

Introduction

Immune Checkpoint Inhibitors (ICIs), such as Programmed cell Death-1 (PD-1), have showed significant anti-tumor effects. They have been increasingly used as first or further lines of treatment of patients with advanced None-Small-Cell Lung Cancer (NSCLC) [1]. It has significantly showed that Pembrolizumab, as one of the PD-1 antibodies, together with pemetrexed and a platinum-based drug have longer overall survival and progression-free survival than that of chemotherapy alone [2]. While the anti-PD-1 antibody Pembrolizumab is reported to be associated with a range of immune-related adverse events (irAEs). The most common ones are diarrhea, fatigue, and pyrexia. However, according to our knowledge, the adverse effect of Pembrolizumab on the urinary bladder has not been reported. Herein we reported a case of interstitial cystitis in NSCLC patient after Pembrolizumab therapy, which was considered to be an irAE.

Case Report

A 61-year-old male patient presented in our medical department with 10 days of headache in June 2018, and a cranial Computed Tomography (CT) revealed lesions in right temporal parietal lobe. It was confirmed that he had an unremarkable medical history except gastric perforation about 40 years ago and he had no specific family history. Then a chest CT showed right hilar mass and bronchoscope revealed external pressure stenosis in right main bronchial. Through the Cytokeratin (CK) 7-positive, CK20-positive, and Thyroid Transcription Factor-1 (TTF-1)-negative reflected by the intracranial surgery pathology using immunochemistry, it was confirmed metastatic adenocarcinoma of lung origin. The EGFR, ALK and ROS-1 mutation were not found according to the high-throughput sequencing technology while TP53 was positive and TMB (Tumor Mutation Burden) was high, about 23.2558 mutations/mb. According to the Union for International Cancer Control staging 8th edition, the patient was staged as T1cN1M1a, stage IVA (brain metastasis).

Seeking the best therapy, the patient received six-cycle of intravenous pemetrexed combined with carboplatin chemotherapy and two-cycle pemetrexed monotherapy. During this period, 200mg Pembrolizumab immunotherapy as recommended were administered...
before each chemotherapy cycle. Before the start of the 9th courses of immunotherapy, the patient sent to our department complained about pain on urination, frequent urination, and macroscopic hematuria. Urinalysis showed Red Blood Cells (RBCs) of 15.5/HPF, White Blood Cells (WBCs) of 646.4/HPF while no bacteria was detected, and urine culture was negative. Urine cytology found neutrophil infiltration and no cancer cells. The CT urography detected bilateral ureter and bladder wall thickening with abnormal enhancement, bilateral ureter dilatation, and perhaps glandular cystitis (Figure 1), and abdominal ultrasonography showed thickness of bladder wall, cystitis glandularis probably (Figure 2). Piperacillin/tazobactam was administered for about 2 weeks, with no effect on symptom. It was suspected that the symptoms were related to the immunotherapy, Pembrolizumab. So 40mg (0.5-1mg/kg/day) methylprednisolone as recommend were performed, the pain and department complained were alleviated immediately after 3 days. The symptoms were reappeared as the steroid decreased to 16mg, and disappeared when increasing dose to 28mg. So we decreased the dose gradually (4mg per 10 days) to avoid relapse. During the cystitis, the patient stopped the chemotherapy and go for a radiotherapy. After the radiotherapy and with low dose of oral steroid, the patient was asymptomatic. So we gave the 9th cycle of immunotherapy, frequent urination and acute urinary pain repeated again. Therefore, we stopped the immunotherapy. The follow-up visits of patients were conducted.

Discussion

Immunotherapy agents in advanced NSCLC can result in improved quality of life and survival. Pembrolizumab is a humanized monoclonal antibody against PD-1. It has antitumor activities by restoring an effective endogenous anti-tumor T-cell response [3]. Anti-PD-1 agents were known to induce various immune-related adverse effects in lung, skin and gastrointestinal tract. The most common ones are diarrhea, fatigue, and pyrexia in the pembrolizumab group [1]. Recently, a systematic review including 5,744 NSCLC patients from 23 studies treated with anti-PD-1 or anti-PD-L1 reported a global incidence of irAEs of 64% (14% grade ≥3) with anti-PD-1 and 66% (21% grade ≥3) with anti-PD-L1 agents respectively [4]. In general, adverse events occurred early, mostly in the first three months, but in some cases, the onset of AE's may be extended to one year after the immunotherapy initiation. In our case, the patient developed symptoms when the sixth month of treatment started, which was corresponded with the present research. Survival benefits in elder patients (≥65 years) treated with anti-PD-(L)1 seems are similar with younger in a FDA analysis, and patients enrolled over 75 presented lower incidence of grade 3-5 AE's than patients ≤65 [5]. In a retrospective cohort of 46 NSCLC patients with autoimmune disease reserved ICIs, the overall ir-AE's were 26% (11% grade 3-4), are similar to the people without autoimmune disease [6].

Therefore, as ICIs became a new therapy for more patients, an increasing number of patients are exposed to these drugs with a chance of developing toxicities. As clinician's experience in recognition and management was limited, it was extremely important to make the
distinction that immunotherapy has a completely different underlying mechanism compared to chemotherapy. Most irAEs remain moderate, but in few cases (about 10%), they will become serious, and grade 3-4 toxicities may threaten life [7]. Different guidelines have been published recently for the immunotherapy toxicity management, including early recognition and timely discontinued immunotherapy in severe cases [7,8]. The main treatment for irAEs is steroids, sometimes Tumor Necrosis Factor alpha (TNFα) antagonists or tacrolimus. According to the recommendation, systemic steroids 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day in severe events (grade 3-4) [9]. With careful and slow tapering (more than 6 weeks), the recurrence of irAEs can be avoided. In our case, when the methylprednisolone was reduced to 16 mg per day in the sixth week, the pain on urination and macroscopic hematuria relapsed, so we increased the dose to 28 mg/day and lasted for 1 week and then decreased more slowly. Up to now, there was no clear data to decide the time of retreatment with ICIs after onset of an irAEs. Recently the study has showed that half of NSCLC patients who retreated after irAEs have the experience of recurrence. 24% developed the same, 26% had a new toxicity and there was 5% related mortality, but the initial grade and time of retreatment did not influence risk [10].

Although mechanism of immune-related adverse events was not fully understood, the irAEs have been found to show a clear correlation with the therapeutic efficacy [11-13]. A research enrolled 270 patients who received ICIs showed that the median OS (not reached versus 8.21 months), PFS (5.2 versus 1.97 months), and ORR (212.9% versus 5.7%) were significantly better for patients with irAEs compared with patients with no irAEs [12]. The article also demonstrated that higher rate of irAEs is not correlated with higher treatment exposure, and there was no significant difference between earlier irAEs and better outcomes.

We hereby reported the first case of interstitial cystitis induced by pembrolizumab, which required steroid administration. During the clinical practice except for the typical rash, diarrhea, and fatigue, other systemic symptoms should also be concerned with the possibility of immune-related diseases. Furthermore, pembrolizumab-induced interstitial cystitis needs to be appropriately diagnosed and treated to ensure that maximize survival benefit from immunotherapy.

References

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