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Case Report

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Recurrence of Checkpoint Inhibitor Pneumonia More than Three Years after Discontinuation of an Immune Checkpoint Inhibitor

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Abstract

Many immune-related Adverse Events (irAEs) resolve after discontinuation of Immune Checkpoint Inhibitors (ICIs) and treatment with immunosuppression, most commonly corticosteroids. However, some irAEs can recur or persist after discontinuation of ICIs. We herein report a case of Checkpoint Inhibitor Pneumonitis (CIP) with repeated remissions and recurrences for more than three years after discontinuation of immunotherapy in a patient with renal cell carcinoma. This report highlights the finding that despite the absence of ICI re-challenge, CIP can persist for years after cessation of immunotherapy. Further research is needed to identify the risk factors for chronic steroid-dependent CIP and to develop appropriate management strategies.

Keywords: Checkpoint inhibitor pneumonitis; Steroid-dependent; Immune-checkpoint inhibitors; Nivolumab; Recurrence.

Introduction

Nivolumab, a monoclonal anti-PD-1 (programmed death 1) antibody, interferes with PD-ligand 1-mediated signaling and restores the immune system's anti-tumor defenses. In Japan, nivolumab was approved for the treatment of Renal Cell Carcinoma (RCC) after several agents such as sunitinib, axitinib, sorafenib and everolimus, and has been widely used as a third-line or later treatment [1]. Immune-Checkpoint Inhibitors (ICIs) can cause various immune-related Adverse Events (irAEs), including Interstitial Lung Disease (ILD) called as Checkpoint Inhibitor Pneumonitis (CIP). Although most irAEs are generally reversible with immunosuppressive treatments, several retrospective studies have reported refractory CIP [2,3]. Here, we experienced a case of steroid-dependent CIP that relapsed multiple times over three years after discontinuation of nivolumab.

Case report

A 66-year-old woman who had never smoked and had postoperative recurrent RCC with retroperitoneal local recurrence, multiple abdominal lymph nodes, and bone metastases was treated sequentially with sunitinib for approximately 3 months, everolimus for 2 weeks, and axitinib for 1 month. However, her disease progressed. In November 2018, she started receiving nivolumab 200 mg every 3 to 4 weeks and achieved a complete response. She complained of a cough and shortness of breath after receiving 13 doses of nivolumab in August 2019 and was admitted to

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our hospital. Her oxygen saturation on room air was 96%. Fine crackles were audible in both lung fields without fever or signs of arthritis or skin lesions. Laboratory tests showed a white blood cell count of 8,100 /μL, C-Reactive Protein (CRP) level of 22.0 mg/dL (normal range: <0.3 mg/dL), Lactate Dehydrogenase (LDH) level of 195 IU/L (normal range: 110-224 IU/L), Sp-D level of 229 ng/mL (normal range: <110 ng/mL) and KL-6 level of 131 U/mL (normal range: <500 U/mL). Anti-aminoacyl-tRNA synthetase (ARS) antibody, anti-nuclear antibody, proteinase 3(PR-3) - and Myeloperoxidase (MPO) antineutrophil cytoplasmic antibodies were negative. Chest X-ray showed reticular opacities in the bilateral lower lung fields (Figure 1A), and Computed Tomography (CT) of the chest revealed the presence of multiple consolidations with bronchiectasis and surrounding Ground-Glass Opacities (GGOs) in both lungs (Figure 2A). These findings are consistent with a Cryptogenic Organizing Pneumonia (COP)-like pattern in the radiographic patterns of ILD. Her sputum and bronchial lavage fluid (left B9) showed no bacteriological findings. Pathological findings of a transbronchial lung biopsy specimen (left B9) revealed organizing pneumonia leading to a diagnosis of CIP with CTCAE Grade 2. Nivolumab was discontinued and she received steroid pulse therapy (methylprednisolone 1000 mg for 3 days), followed by prednisolone (PSL) 40 mg/day (1 mg/kg/day). Radiographic findings improved significantly six days after the initiation of steroid therapy (Figure 1B), and the steroid dose was gradually reduced over 15 weeks. Five days after achieving complete remission of CIP and completing the PSL taper, she complained of chest pain and fever. Influenza antigen test was negative and laboratory tests showed a white blood cell count of 9,600 /μL (neutrophils: 81.9%, eosinophils: 2.7%, lymphocytes: 9.1%), CRP level 25.8 mg/dL, LDH level 190 IU/L, Sp-D level 144 ng/mL, KL-6 level 113 U/mL procalcitonin level 0.11 ng/mL (normal range: <0.11 ng/mL), and βD glucan level 7.6 pg/mL (normal range: <20 pg/mL). She was diagnosed with pneumonitis again and treated with antibiotic therapy (tazobactam/piperacillin hydrate), but her condition did not improve. She was diagnosed with a recurrence of CIP (Figure 1C, 2B) and was readministered PSL 40 mg/day after steroid pulse therapy, which resulted in a remarkable improvement. Ten days after PSL was tapered down to 5.0 mg/day more slowly in April 2020, she complained of chest discomfort and experienced a second recurrence of CIP (Figure 1D, 2C). PSL was increased to 30 mg/day and then tapered to 10 mg/day over 6 months. In April 2021, a CT scan demonstrated GGOs in the right upper and middle lobes (Figure 2D), suggesting asymptomatic CIP, which resolved without requiring an increase in the steroid dose. After tapering the PSL dose to 7.5 mg/day in November 2022, the patient experienced a recurrence of CIP, resulting in dyspnea in January 2023. (Figure 1E), and the PSL dose was increased back to 10 mg/day. Since then, there have been no further recurrences of CIP while the patient has been receiving a PSL dose of 10 mg/day (Figure 1F).

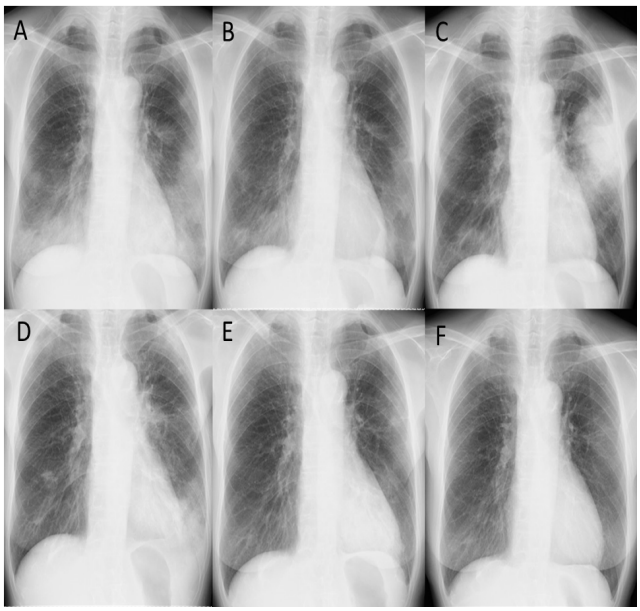

Figure 1: A. Chest X-ray at the time of initial pneumonitis shows reticular opacities in the bilateral lower lung fields. **B.** Chest X-ray six days after starting corticosteroid therapy showed improvement of the reticular opacities. **C.** Chest X-ray at first recurrence of pneumonia demonstrated new dense infiltrates in the left lung. **D.** Chest X-ray at second recurrence of pneumonia revealed reticular opacities in the bilateral lower lung fields with left predominance. **E.** Chest X-ray at the last recurrent pneumonitis showed new reticular opacities in the left middle lung field. **F.** Chest X-ray showed no recurrence of pneumonia with continued prednisolone 10 mg/day.

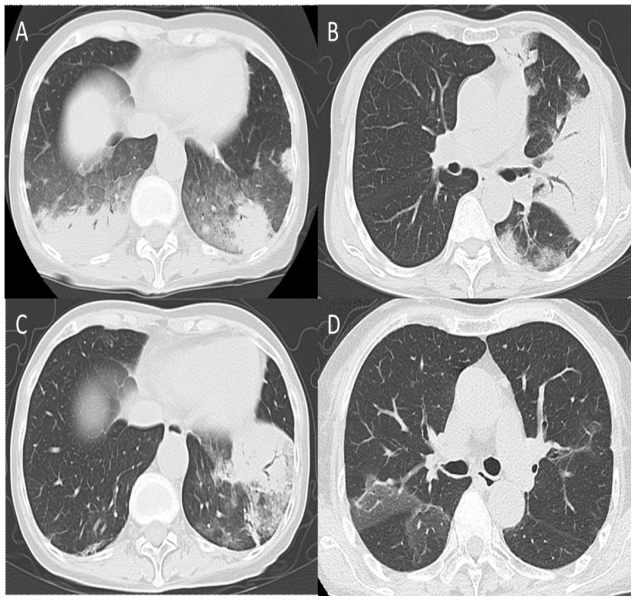

Figure 2: A. CT scan of the chest at initial pneumonitis demonstrated multifocal consolidations and surrounding ground-glass opacities in both lungs, with lower and peripheral distribution, representing a cryptogenic organizing pneumonia pattern based on the radiographic appearance. **B.** CT scan at first recurrence of pneumonia demonstrated new consolidation with air bronchogram in the left upper lobe. **C.** CT scan at second recurrence of pneumonia showed new consolidation in the left lower lobe. **D.** A CT scan showed new ground-glass opacities in the right upper and middle lobes, but the patient remained asymptomatic on prednisolone 10 mg/day.

Discussion

Nivolumab is known to occupy PD-1 on T cells for several hundred days after the last dose [4], and the immunological activation induced by PD-1 blockade would be expected to persist long-term even after removal of nivolumab. In this case, complete remission of RCC was sustained long after discontinuation of nivolumab, during which time CIP recurred multiple times. This may be related to the sustained immunostimulatory effects of ICI and the association between ICI efficacy and irAEs [5].

Several reports have shown that CIP does not respond to corticosteroid treatment or persists long after immunotherapy is discontinued [2,3]. Naidoo J et al. demonstrated that 14% of CIP persisted beyond 12 weeks after the cessation of ICI and became chronic despite adequate immunosuppression [6]. In our case, the exact reason for multiple unprovoked recurrences of CIP is unknown. After discontinuation of nivolumab, RCC has not recurred and no new drugs have been administered, such as other anticancer drug treatments that could cause drug-induced lung injury. Whenever pneumonitis recurred, we did not perform a histological examination using bronchoscopy or measure viral antigens and various autoantibodies to proactively investigate other causes of recurrent pneumonitis, such as infections or collagen diseases. However, each time the patient experienced a recurrence of pneumonia, they complained of symptoms similar to those of the initial pneumonia, rather than symptoms of upper respiratory infection such as a sore throat, or symptoms of collagen vascular disease such as joint and muscle pain. The patient had undergone several therapies before receiving nivolumab, including everolimus, which has a higher incidence of drug-induced interstitial lung disease compared to nivolumab. However, the initial pneumonitis occurred after 10 months of receiving nivolumab, and we do not believe it was caused by other RCC drugs administered prior to nivolumab, such as axitinib or everolimus. We suspected that the effect of prior therapies could be one of the possible mechanisms for the repeated recurrences in this patient. However, recent reports have shown that prior therapy does not increase the incidence of nivolumab-induced irAEs in RCC patients [1,7].

A Guideline for the treatment of irAEs states that corticosteroids should be tapered over the course of at least 4-6 weeks [8]. Tao H. et al. conducted a cohort study of CIP recurrence in lung cancer patients, and showed that the duration of PSL equivalent dose ≥15 mg/day in patients with CIP recurrence was significantly shorter than in patients without recurrence [9]. They recommend administration of a PSL-equivalent dose ≥15 mg/day at least 4 weeks to prevent recurrence of CIP. In addition, it is known that ILD with a radiographic COP-like pattern often recurs when corticosteroid doses are tapered or discontinued, and corticosteroid should be tapered more slowly in recurrent cases. In our case, duration of PSL ≥15 mg/day in initial CIP, first and second CIP recurrence was 9.2, 9.2, and 17.7 weeks, respectively, which are considered sufficient corticosteroid doses and durations.

Most irAEs resolve with a corticosteroid taper of 4-8 weeks, but refractory cases may require immunosuppressive therapy other than corticosteroids. There is no consensus on the treatment of steroid-refractory CIP, which is defined as no improvement of respiratory symptoms within 72 hours of appropriate corticosteroid therapy. In practice, the following drug options are used: infliximab, mycophenolate mofetil, tocilizumab, and Intravenous Immunoglobulin (IVIG) [2,3,10]. In our case, PSL 10 mg/day was administered long-term after a second recurrence of CIP, which occurred while on PSL 5 mg/day. Given the side effects of long-term corticosteroid therapy, PSL was reduced to 7.5 mg/day, resulting in a relapse. Chronic steroid-dependent CIP may require the addition of a second immunosuppressive agent for steroid weaning, as well as for steroid-refractory/resistant CIP.

We present a case of chronic steroid-dependent CIP with multiple recurrences over three years after discontinuation of ICI. Careful observation is required when tapering corticosteroid doses, even long after discontinuation of ICI. Further research is needed on the risk factors for chronic steroid-dependent CIP and the development of appropriate management strategies.

Declarations

Conflicts of interest: The authors have no conflicts of interest.

Ethics statement: Written informed consent was obtained from the patient for publication of this case report.

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