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Case Report

Durvalumab-induced organizing pneumonia in extensive-stage small cell lung cancer: A case report and literature review ☆,☆☆

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ABSTRACT

The etoposide-carboplatin and anti-PD-L1 combination has become the standard-of-care for patients with extensive-stage small cell lung cancer (ES-SCLC). This combinational strategy is well tolerated with manageable immune-related adverse effects (irAEs). In this report, we presented a rare immediate irAE after one course of anti-tumor treatment. The patient with ES-SCLC was treated with first-line etoposide-carboplatin chemotherapy and Durvalumab immunotherapy. After one cycle of indicated treatment, the patient developed persistent high-grade fever with extensive consolidation, surrounding by ground glass opacifications. The lesions did not respond to empirical antibiotics and the results for pathogen testing were negative. Histological analysis of biopsy sample yielded organizing pneumonia that was very likely to associate with Durvalumab treatment. The patient was therefore treated with prednisolone that resulted in a rapid radiological improvement. The reporting of this case is imperative for informing acute onset of irAE in patients with ES-SCLC treated with anti-PD-L1 immunotherapy. Differential diagnosis of infection, tumor progression and exacerbation of underlying illness should be considered before the initiation of prednisolone therapy.

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Introduction

Durvalumab is a humanized IgG1 monoclonal antibody that targets tumor cells expressing PD-L1 to provoke anti-tumor immune responses. It is licensed for the treatment of extensive stage small cell lung cancer (ES-SCLC) and stage III unresectable non-small cell lung cancer (NSCLC) following concurrent radiochemotherapy. The CASPIAN trail demonstrated the combination of Durvalumab with etoposide-platinum chemotherapy showed an impressive survival benefits, together with improved quality of life, for patients with ES-SCLC [1]. The adverse effects associated with Durvalumab are usually mild and could be well managed, including pneumonitis, colitis, nephritis, and cardiac, neurological, and endocrine toxicities [2]. Although some of these immune-related adverse effects (irAEs), such as myocarditis and pneumonitis, is relatively rare but could be potentially life-threatening [3,4]. The present case study reported an unusual acute onset of irAE after one course of Durvalumab treatment.

Case presentation

In May 2024, a 53-year-old man (body weight: 86 kg, height: 169 cm) admitted to our institution with complains of cough and hemoptysis. These symptoms have been worsening over the past month before presentation. His medical history was significant for long-term smoking history and hypertension. On physical examination, his vital signs were normal with a saturation of 98% on room air. A 6.1 × 4.2 cm mass with irregular margin, which affected the right main bronchus with mediastinal lymphadenopathy, was identified on chest CT scan (Fig. 1A). The bronchoscopy examination was pursued, which showed occlusion of the right main trachea. Pathological examination of the biopsy sample showed poorly differentiated cancer with a positive expression for TTF-1 (3+), CD56 (2+), INSM1 (1+) and Ki67 (70%) (Fig. 1B). Positron emission tomography (PET)/CT scan yielded evidence of hypermetabolic activity of the right hilar mass (SUVmax = 17.11) with metastasis to mediastinal lymph nodes (SUVmax=18.11). The ^{18}F-FDG uptake was also noticed in the lumbar vertebra (SUVmax = 6.46) (Fig. 1C). The magnetic resonance imaging (MRI) of brain showed no evidence of central nervous system involvement. A diagnosis of ES-SCLC was made 8 days after admission, and the patient was treated with a combination regimen consisting of etoposide-carboplatin (EC) chemotherapy and Durvalumab immunotherapy.

After one cycle of indicated treatment, the patient reported persistent high-grade fever (Tmax = 40.2°C) associated with chills and shortness of breath. Blood tests in a local medical center revealed normal white blood cell count (8.5 × 10^9/L, normal range 4-10 × 10^9/L) and a C-reactive protein (CRP) level of 167.9 mg/L (normal range 0-4 mg/L). Chest CT scan showed a shrinkage of the primary tumor and metastatic lymph nodes (Fig. 1D), however, extensive consolidation, with air bronchograms, surrounded by patchy infiltrates and ground glass opacifications (GGOs) emerged in the right lower lobe. On examination, he was tachypneic and had a body temperature of 39.5°C. The chest auscultation revealed coarse crackles mainly in the right lower lobe. His blood tests showed white blood cell count of 10.62 × 10^9/L (76.1% neutrophils, 16.0% lymphocytes, and 6.9% monocytes), CRP level of 101.5 mg/L, procalcitonin (PCT) level of 0.129 μg/L (normal range 0-0.046 μg/L), and interleukin-6 (IL-6) level of 30.29 ng/L (normal range 0-7 ng/L). A repeated chest CT in our hospital showed progression of the consolidation and patchy GGOs (Fig. 2). The initial diagnosis of community acquired pneumonia was made and antibiotics were commenced, including moxifloxacin 0.4 g/day and ceftazidime 1 g/8h. After one week of indicated treatment, there was no improvement of his symptoms. The patient underwent bronchoscopy with bronchoalveolar lavage (BAL) and the result showed a resolution of the occlusion in the right bronchus. Sample of BAL fluid was sent for pathogen culture, acid-fast bacilli smearing and metagenomic next-generation sequencing (mNGS). The microbiology and molecular testing were all negative for infection. Based on the radiological, laboratory and clinical findings, organizing pneumonia (OP) associated with Durvalumab treatment was considered and confirmed by lung biopsy, which revealed alveolitis with fibrin deposition, foamy macrophages, and Masson bodies, together with polypoid structures in the terminal air spaces and infiltration of chronic inflammatory cells. IHC staining of a neuroendocrine biomarker, CD56, was negative in the biopsy sample (Fig. 3). Therefore, Durvalumab immunotherapy was held, and the patient was initiated on a prednisolone course (0.5mg/kg) that resulted in a rapid clinical improvement in his symptoms. The chest CT scan after 3 weeks of corticosteroid therapy revealed marked reduction in the consolidation and interstitial infiltrates. The patient continued EC chemotherapy and Durvalumab was restarted after gradually tapering the prednisolone to 10 mg per day (Fig. 2).

Discussion

Aberrant expression of PD-L1 on tumor cells contributes to immune evasion of cytotoxic effector T cells, thus, blockade of the PD-1/PD-L1 immune inhibitory signaling is an effective approach to boost anti-tumor immunity. Aside from T cells, PD-1/PD-L1 inhibitors also activate macrophages and dendritic cells. Thus, overwhelmed activation of these immune cells after anti-PD-1/PD-L1 treatment underlies the pathogenesis of irAEs. It is challenging to diagnose drug-induced pneumonitis because various conditions should be firstly excluded, such as infection, tumor progression and exacerbation of underlying illness. We concluded the pneumonitis as Durvalumab involved, since a negative result of pathogen testing, improvement in bronchus occlusion, and no usage of other drugs except for EC chemotherapy plus Durvalumab might also rule out other etiologies for pneumonitis. The consolidation and patchy GGOs resolved soon after starting corticosteroid therapy despite the continuation of EC chemotherapy, suggesting the pneumonitis is very likely to be Durvalumab relevant.

According to a retrospective study assessing the toxicity of Nivolumab and Pembrolizumab in NSCLC, 2 customized anti-PD-1 inhibitors, the most prevalent radiographic finding of pulmonary irAEs is pneumonitis, in which the most com-

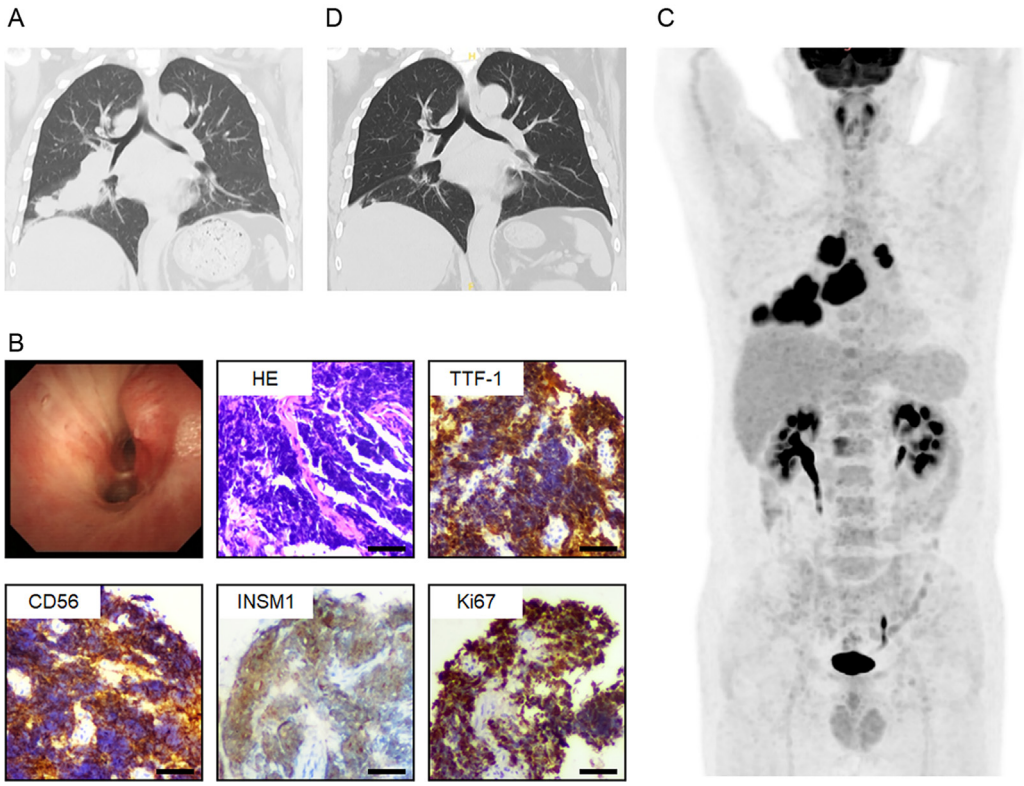

Fig. 1 – Representative radiological and histological images of the patient with ES-SCLC. (A) Chest CT scan in coronal view showed a right lung tumor mass with mediastinal lymphadenopathy upon admission. (B) The bronchoscopy examination showed the neoplasm occluding the right main trachea. Histological examination of the biopsy specimen indicated poorly differentiated tumor cells with a positive expression for TTF-1, CD56, INSM1 and Ki67. Scale bar = 50 μm. (C) PET-CT examination revealed abundant ^{18}F-FDG uptake in the tumor mass, mediastinal lymph nodes and lumbar vertebra. (D) Representative chest CT image showing a dramatic shrinkage of the tumor after one cycle of EC chemotherapy and Durvalumab immunotherapy combination.

mon pattern is OP, followed by nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), and acute interstitial pneumonia (AIP) [5]. The reported median time of onset of PD-1 inhibitors-induced pneumonitis was 2.8 months [6]. Unfortunately, knowledge regarding the pulmonary toxicity of anti-PD-L1 inhibitors in NSCLC is relatively limited. Pneumonitis associated with Durvalumab seemed to be more common in stage III NSCLC patients receiving anti-PD-L1 inhibitors as consolidation treatment after definitive concurrent chemoradiotherapy, with an incidence of 33.9% [7]. Notably, it is difficult to determine whether the pneumonitis is radiation pneumonitis or irAEs pneumonitis. In the phase III randomized AEGEAN trial evaluating the efficacy of perioperative administration of Durvalumab in patients with resectable NSCLC, Durvalumab relevant pneumonitis occurred in 3.7% of patients [8]. As such, chest radiation, together with low-performance status, old age and fibrotic lung disease, have been recognized as risk factors for this entity [9]. Our patient did not have relevant illness however, he is overweight with a body mass index (BMI) of 30.1 kg/m^2. Obesity has been recently considered as a susceptible factor for irAEs, especially in patients with a BMI $\geq$ 30 kg/m^2 yielded a significantly increased risk of developing pneumonitis [10]. In consistent with this notion, our patient developed pneumonitis after administration of the first dose of Durvalumab, which did not respond to empirical antibiotics. A potential mechanism underlying acute onset of pneumonitis may be dysfunctional adipocytes in obese patients produced more adipocytokines, including interleukin-6 and tumor necrosis factor-α, that generates a chronic inflammation state to lower the threshold needed to initiate inflammatory response for Durvalumab-mediated pneumonitis [11]. The diagnosis of OP could be difficult and often delayed due to the nonspecificity of its clinical presentation, and a lack of response to empiric antibiotics interpretation may be the initial hint to this noninfectious pneumonia.

Although pneumonitis in SCLC have been described in clinical trials, the definitive radiological presentations of this irAE remain elusive. In our study, chest CT featuring GGOs and patchy air-space consolidations with a predominantly peripheral distribution pattern supported a presumed diagnosis of OP. The typical manifestations of OP are similar to what we have seen in our patient, such as progressive non-productive cough, shortness of breath, and persistent fever. To the best of our knowledge, this is the first report of acute onset of pneumonitis manifesting OP pattern in ES-SCLC after the first dose of Durvalumab infusion. Intriguingly, the patient was

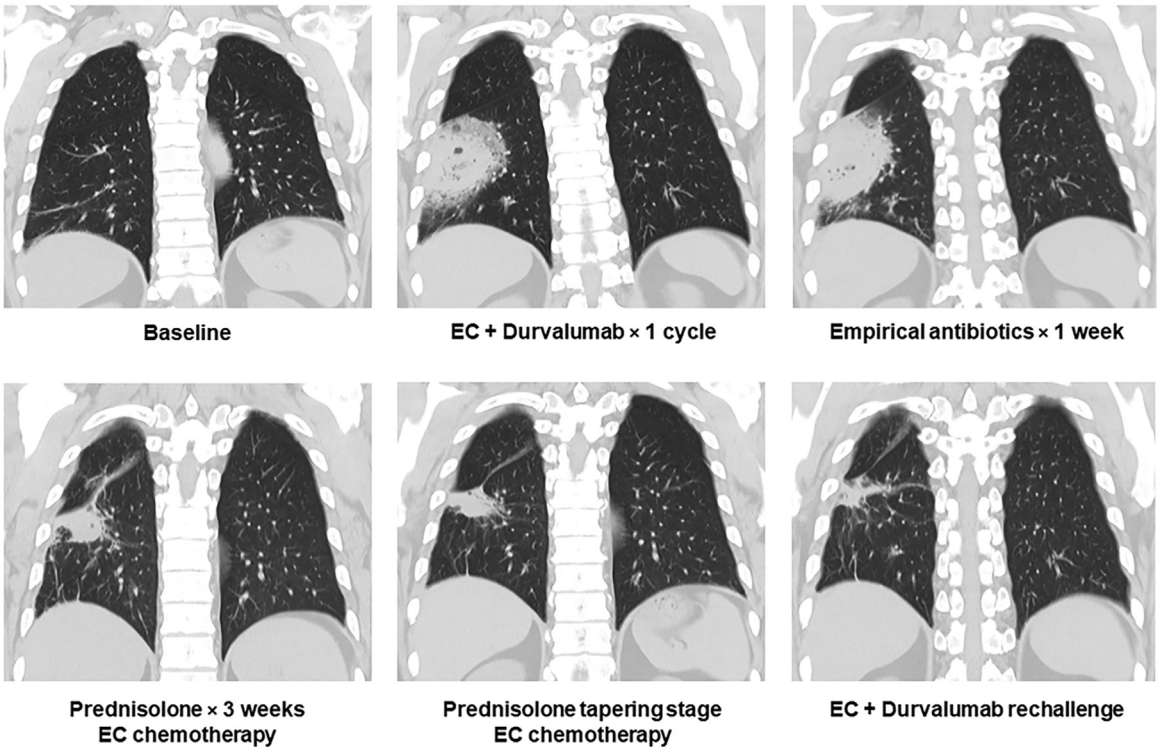

Fig. 2 – Dynamic changes of the consolidation and GGOs after indicated treatment.

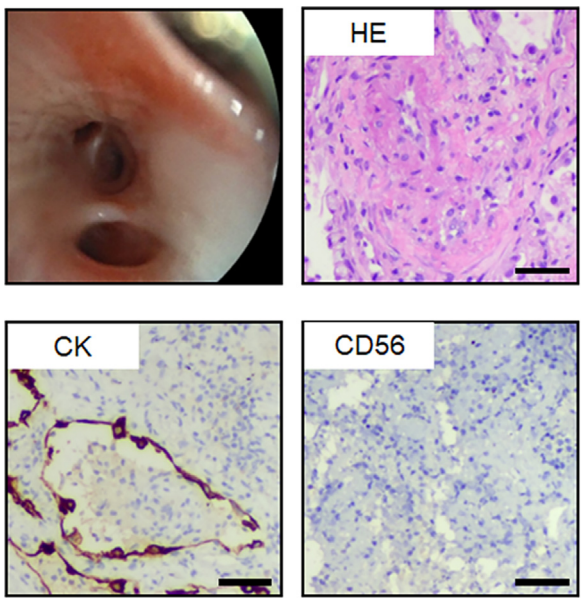

Fig. 3 – Representative images of the repeated bronchoscopy examination and histological analysis of biopsy sample from the consolidation. Scale bar = 50 μm.

responsive to corticosteroids and he restarted Durvalumab therapy after prednisolone tapering. Recurrent pneumonitis during retreatment was not experienced.

Taken together, the awareness of pulmonary irAEs among cancer patients receiving anti-PD-1/PD-L1 inhibitors presenting with new pulmonary findings on chest imaging has become more frequent due to the increased use of immunotherapy. Pathogen testing and repeated biopsy are necessary for the prompt diagnosis and management of this potentially serious adverse event.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from this patient for the publication of any potentially identifiable images or data included in this article. This study was reviewed and approved by the Medical Ethics Committee of Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (2024DZKY-050-01). Written informed consent was obtained from the patient for the publication of this case report.

Patient consent

Informed consent for publication of this case was obtained from the patient.

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