

Successful management of Epstein-Barr virus-associated severe checkpoint inhibitor-related pneumonitis: A case report

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Abstract. A novel current treatment, immunotherapy, is normally effective for pulmonary lymphoepithelial carcinoma (pLELC). However, it is frequently accompanied by responses such as immune checkpoint inhibitor-associated pneumonitis (CIP), a rare immune adverse reaction that may be fatal in severe cases. pLELC is known to be linked to Epstein-Barr virus (EBV), while associations between EBV and CIP in clinical settings have rarely been reported. A 57-year-old male patient with pLELC presented at our hospital with cough, expectoration, fever and dyspnea following his third course of immunotherapy at another hospital. Diagnosis of grade 4 CIP was confirmed. Simultaneously, a rapid increase in the EBV titer and response of CIP to corticosteroids were observed. The corticosteroids and antiviral drugs were then increased. In spite of his severe condition, the patient recovered within eight days. After discontinuing antiviral drugs, chest computed tomography indicated rapid lesion progression and significantly increased bilateral multiple metastases. To

our knowledge, the present study was the first to report a case of CIP caused by EBV during immune checkpoint inhibitor treatment. It indicates that EBV may be associated with CIP development. As immunotherapy has off-target effects, clinicians should remain aware of combined corticosteroids and antivirals in similar cases.

Introduction

Lymphoepithelial carcinoma of the lung (pLELC) is a rare lung cancer subtype caused by malignant hyperplasia of the lymphoid tissue, now categorized as squamous carcinoma according to the 2020 World Health Organization's Classification of Lung Tumors (1). The pathogenesis of pLELC remains elusive, though Epstein-Barr virus (EBV) is thought to be the primary etiology (2). Although not all pLELC patients test positive for EBV, EBV infection is specific to Asian pLELC populations (3). Current pLELC treatment regimens are consistent with those for squamous lung cancer. However, due to persistent EBV infection, pLELC tumors always involve a strong infiltration of lymphocytes in the tumor microenvironment and high expression of programmed cell death ligand 1 (PD-L1) in tumor tissue, providing a rationale for immunotherapy. Pang *et al* (4) found that patients who receive chemoimmunotherapy (the current first-line treatment for advanced pLELC) gain significantly more survival benefits compared with those receiving chemotherapy.

While immunotherapy provides new options, immune-related adverse events (irAEs) have been widely reported. Among these, immune checkpoint inhibitor-associated pneumonitis (CIP) is rare but potentially fatal (5). CIP is the development of dyspnea and/or other respiratory symptoms and the presence of new infiltrative shadows on chest images, excluding clinical contexts such as lung infection or tumor progression. In clinical practice, the incidence of CIP is as high as 13-19%, and, when occurring during grades 3-4, is frequently life-threatening (6,7). Corticosteroids are the standard of care. While the pathogenesis of CIP remains elusive, possible mechanisms include increased T-cell function and autoimmunity due to elevated antibodies and inflammatory factors (7). Among the links between CIP and viruses, a possible potential association with cytomegalovirus (CMV) has also been reported (8).

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Abbreviations: pLELC, pulmonary lymphoepithelial carcinoma; EBV, Epstein-Barr virus; PD-L1, programmed cell death ligand 1; irAEs, immune-related adverse events; CIP, checkpoint inhibitor-associated pneumonitis; CMV, cytomegalovirus; CT, computed tomography; IT, induced type; TCR, T-cell receptor

Key words: checkpoint inhibitor-related pneumonitis, Epstein-Barr virus, pulmonary lymphoepithelial carcinoma, immune-related adverse events, lung cancer

It has remained elusive whether the development of CIP in patients with lymphoepithelial carcinoma is associated with EBV. The present study reported the first case of a presumed association between EBV and CIP, with reasonable speculation regarding potential mechanisms of CIP development.

Case report

A 57-year-old male patient was admitted to another hospital in May 2019 after his annual checkup prompted computed tomography (CT) evaluation, which revealed a distinct right lung mass. Undifferentiated pLELC of pathologic stage T3N1M1c was diagnosed by needle biopsy. The patient was started on a course of combined gemcitabine 1,730 mg and carboplatin 664 mg chemotherapy, which had poor efficacy and was later changed to four cycles of nivolumab 200 mg combined with bevacizumab anti-vascular therapy 90 mg. At this time, the patient had occasional cough with little sputum, no chills or fever, and no shortness of breath. Lymph nodes and multiple bone metastases were detected by positron emission tomography (PET) conducted during the treatment phase to evaluate disease progression in October 2020. The patient was treated with multiple radiotherapy sessions and eventually received maintenance therapy of bleomycin 20 mg plus toripalimab 200 mg.

Following the third course of chemoimmunotherapy, in April 2021, the patient was immediately transferred to the First Affiliated Hospital of Guangzhou Medical University after one month of shortness of breath, which had become aggravated during the preceding three days. The patient presented with cough with expectoration, dyspnea, persistent pyrexia and a maximum body temperature of 40.5°C. CT indicated a right middle lung tumor measuring ~2.3x1.8 cm, with interstitial inflammation in both lungs (Fig. 1) and involvement of the whole lung. It had been six months since the last radiotherapy and imaging did not indicate any shadows or streak-like changes consistent with the irradiated field or area, and radiation pneumonitis was thus excluded.

Laboratory tests revealed a concomitant gram-positive coccus infection. Based on medication history, clinical presentation and imaging, the diagnosis of severe CIP at the highest grade (IV) with concomitant pulmonary infection was considered. The patient was in a critical, life-threatening condition with plasma EBV 5.68×10^4 copies/ml as determined by fluorometric PCR at the pathology department (Fig. 2). Noninvasive assisted ventilation was quickly initiated combined with conventional intravenous corticosteroids 80 mg for anti-inflammation and meropenem for anti-infection, with simultaneous ganciclovir antiviral therapy for EBV. Following this, EBV dropped to 2.98×10^3 copies/ml on follow-up during antiviral treatment and corticosteroid was reduced to 40 mg intravenously (Fig. 2). Of note, the patient improved significantly within 10 days, at which time CT indicated that inflammation in both lungs was significantly reduced and other clinical signs were significantly improved (Fig. 1). The patient was discharged with only methylprednisolone tablets, despite final EBV 1.48×10^4 copies/ml, exceeding the normal level (5×10^2 copies/ml) (Fig. 2).

After three weeks, the patient returned with shortness of breath and cough with a small amount of white

mucous sputum. Chest CT indicated no significant tumor changes and both lungs contained ground glass opacities (Fig. 1). Laboratory examination suggested no other pulmonary infection. Medical history review revealed that the patient had stopped corticosteroids without authorization after discharge and it was determined that the CIP had recurred. At this point, EBV had returned to a high level (1.14×10^5 copies/ml) (Fig. 2). The patient was treated with a conventional protocol of corticosteroid 40 mg combined with antiviral ganciclovir 0.25 g. The patient was stable eight days later, when he was administered chemotherapy combined with anti-vascular therapy to control the tumor, without immunotherapy rechallenge.

The patient returned to the hospital every three weeks for regular antineoplastic treatment. CT review six weeks after resumption of antineoplastic treatment revealed that the right lung tumor (4.5x3.1 cm) and lymph node metastases had all increased in size. In order to better display the changes, the mediastinal window on chest imaging is also provided (Fig. 1).

Discussion

While immunotherapy advances provide novel treatment options for patients with advanced pLELC and increase overall survival (9), unpredictable irAEs may occur. An association between EBV and irAEs was previously reported. Saikawa *et al* (10) reported a case of acute cerebellar ataxia caused by EBV under immunotherapy and Pugh *et al* (11) reported EBV-positive skin ulcers complicated by colitis under immunotherapy. CIP after immunotherapy is rare and potentially fatal. While the mechanisms remain to be fully elucidated, studies have reported possible associations with excessive T-cell activation, imbalanced inflammatory factors and increased autoantibodies (12). A potential link between EBV and immune pneumonia has not heretofore been reported, to the best of our knowledge.

CIP was previously categorized into three types based on clinical factors: Pure type, induced type (IT) and mixed type pneumonitis. IT includes different etiologies, such as radiotherapy, CMV or EBV reactivation, producing specific antigens that lead to specific immune cell activation, which in turn leads to CIP, with no evidence of viral or radiotherapy-induced organ damage (13). As pLELC is closely related to EBV virus, considering the CIP type of the patient was IT pneumonitis, the patient underwent treatment with conventional corticosteroids combined with ganciclovir antiviral therapy and rapidly recovered from severe CIP (grade IV) within just 10 days, which is not a common situation. This circumstance led to speculations regarding a possible connection of EBV with the pathogenesis of CIP.

The CIP of the patient of the present study was hypothesized to be EBV-induced IT pneumonitis, leading us to explore and consider alternative mechanisms of CIP. As immune checkpoint inhibitors are immunotherapeutic agents with specific targets, off-target toxicity is a specific mechanism by which targeted therapies may cause negative effects (14). The possible mechanisms of CIP in previous studies are stimulation of antigen cross-presentation against self-peptides or shared epitopes between it and the tumor, ultimately triggering an

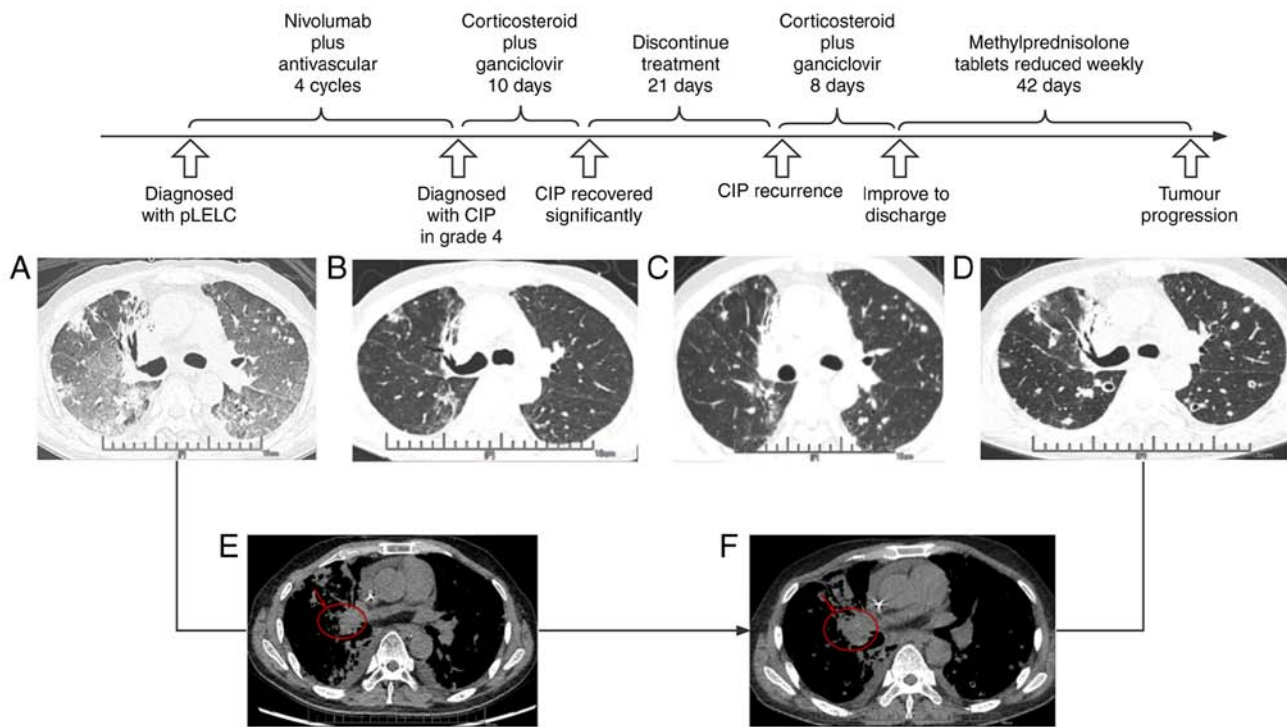


Figure 1. Timeline and CT manifestation. (A) Chest imaging at initial CIP diagnosis. (B) CIP imaging post-treatment with significant recovery. (C) Recurrent CIP images. (D) Routine tumor follow-up, indicating obvious enlargement (scale bars in cm). (E and F) Mediastinal window of the chest imaging at (E) CIP occurrence on first presentation of the patient and (F) follow-up visit (the arrow pointing to the circled area indicates the change of the tumor). CIP, checkpoint inhibitor-associated pneumonitis.

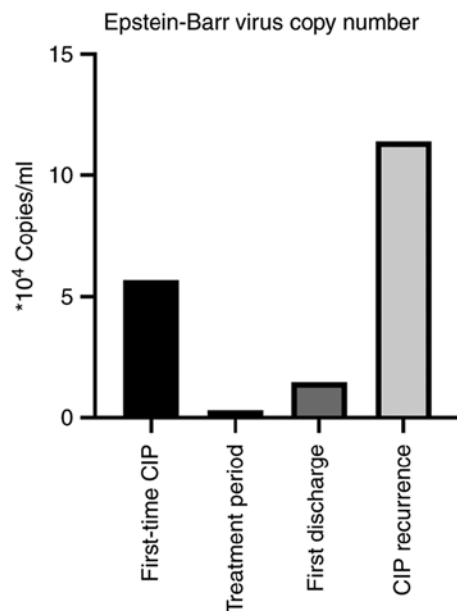


Figure 2. Diagram of Epstein-Barr virus copy number at different time-points. CIP, checkpoint inhibitor-associated pneumonitis.

autoimmune response (15). Thus, it may be hypothesized that a specific T-cell type, EBV-specific T cells, may be produced. These are formed following specific antigen presentation, expressed by infected cells following EBV infection, which may be functionally defective in oncology patients and unable to develop effective cellular immunity. After immunotherapy, a large number of T cells are activated, including EBV-specific

T cells, allowing them to mediate cellular immunity, attack EBV-infected lung tissue and cause lung injury (8,16,17).

The association between viruses and irAEs is not unprecedented and an association between CIP and CMV was previously reported by our group (8). CIP may be an immune reconstitution syndrome associated with CMV infection, which may occur as an immune response to infection manifested by a cascade of T-cell responses to CMV-specific antigens due to the blockage of the programmed cell death 1 (PD-1) pathway. A related study also supports this hypothesis; a recent report of immunotherapy for metastatic prostate cancer, in which clonal expansion of CD8+ T cells preceded the development of grade 2-3 irAEs, suggested a potential role of antigen-specific cytotoxic T cells in the pathogenesis of CIP (16). The authors of another case report of PD-1 inhibitor treatment leading to fatal encephalitis speculated similarly regarding the mechanism of immune encephalitis. In their report, spatial and multivariate analyses of immunotherapy-associated encephalitis revealed that memory CD4+ T cells were highly aggregated at the encephalitis site, and T cell receptor (TCR) clones found in inflamed brain tissue were mainly those recognizing viral proteins rather than autoimmune correlates. The TCR clone sequences shared the same TCR β complementary determinant region 3 sequence as those known to be EBV-specific, identifying a highly oligoclonal T-cell receptor library localized to activated memory cytotoxic CD4+ cells (expression of granzyme B, CD45RO and Ki67) (17).

This cumulative evidence is consistent with our suspicion that EBV-specific T cells may induce CIP. When the patient of the present study recovered from CIP and the antiviral drugs

were discontinued, the EBV copy number exhibited a marked increase. This also supports the notion that EBV in patients with pLELC enables the formation of EBV-specific T cells to mediate the onset of cellular immunity.

The treatment of immune-related pneumonitis is based on systemic corticosteroids. Steroid-insensitive CIP may require second-line immunosuppression, though often with poor prognosis (6). The present case of pLELC had a virus-associated tumor type and, to the best of our knowledge, the present study was the first to report on CIP caused by EBV during immunotherapy. The novel concept that EBV-specific T cells are associated with the incidence of CIP was also proposed. The present study may thus assist clinicians who, in similar cases, should attend closely to virus detection, consider combination therapy and note that a virus may be a factor of irAE etiology.

In conclusion, this is the first reported case indicating possible CIP caused by EBV during immunotherapy. This case and the existing literature suggest that EBV-specific T cell-mediated cellular immunity may contribute to the occurrence of CIP. This cumulative evidence indicates that patients with CIP should be monitored for viral copy numbers in the face of virus-associated tumors and emphasizes the importance of combination therapy in such cases. However, the scenario of this single case report must be confirmed and further explored with larger samples.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JD and XL treated the patient and wrote the manuscript. HD, YY, XX and WG treated the patient. CZ contributed to PET/CT response evaluation. All authors contributed to the article and have read and approved the final manuscript. JD and XL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images and data included in this article.

Competing interests

The authors declare that they have no competing interests.

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