CASE REPORT

Pembrolizumab-induced simultaneous and multiple immune-related adverse events including myasthenia gravis, myositis, hepatitis, and pityriasis lichenoides in a non-small cell lung cancer patient

Mi-ran Han[1], Chang-Hoon Lee[1], So-Yeon Jeon[1], Ho-Young Yhim[1,2], Na-Ri Lee[1,2], Jae-Yong Kwak[1,2], Ho-Sung Park[1,3], Eun-Kee Song[1,2,*]

[1] Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, Republic of Korea. [2] Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Republic of Korea. [3] Department of Pathology, Jeonbuk National University Medical School, Jeonju, Republic of Korea.

*Correspondence: Eun-Kee Song, Department of Internal Medicine, Jeonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju, Republic of Korea, Tel: +82-63-250-1245. Fax: +82-63-255-1609; Email: eksong@jbnu.ac.kr

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ABSTRACT

Pembrolizumab, an immune checkpoint inhibitor (ICI) targeting the programmed cell death protein 1 (PD-1) receptor on T cells, enhances the immune system's ability to recognize and attack cancer cells. However, immune-related adverse events (irAEs) may arise, necessitating careful monitoring during treatment. Here, we present the case of a 47-year-old woman who developed multiple irAEs following pembrolizumab therapy. Initially diagnosed with Stage IIIB non-small cell lung cancer, she underwent chemotherapy followed by concurrent chemoradiotherapy. After two years of monitoring, progression of disease was observed, and pembrolizumab was initiated as second-line chemotherapy. Shortly thereafter, she presented with left-sided ptosis and weakness in both upper and lower extremities. Diagnostic evaluation, including a tensilon test and laboratory findings, confirmed with myositis, hepatitis, and myasthenia gravis. Treatment with steroids and neostigmine led to marked clinical improvement. Two months later, the patient developed additional dermatological symptoms, including rash and pruritus. Skin biopsy confirmed a diagnosis of pityriasis lichenoides. She is currently receiving antihistamines therapy, with no further exacerbation. This case underscores the importance of recognizing and promptly managing irAEs associated with ICIs to ensure patient safety and treatment efficacy.

KEYWORDS: Pembrolizumab; Immune-related adverse events (irAE); Immune-mediated hepatitis; Myasthenia gravis; Myositis; Pityriasis lichenoides chronica (PLC); Non-small cell lung cancer (NSCLC)

1. INTRODUCTION

Pembrolizumab, a humanized monoclonal anti-programmed cell death protein 1 (PD-1) antibody, targets the PD-1 checkpoint, which plays a crucial role in regulation the immune response [1,2]. It has been extensively studied and used in the treatment of various malignancies including melanoma, non-small cell lung cancer (NSCLC), gastric cancer and others [1]. However, pembrolizumab can lead to immune-related adverse events (irAEs), which occur when the activated immune system inadvertently targets and damages normal tissues [3,4]. These irAEs may range from mild skin reactions to more severe conditions such as immune-related pneumonitis, autoimmune hepatitis, hypo- or hyperthyroidism, and even type 1 diabetes [1,3]. We present a case of a patient who developed extremely rare and multiple irAEs, including myositis, immune-mediated hepatitis, myasthenia gravis (MG), and pityriasis lichenoides, following a single dose of pembrolizumab.

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2. CASE PRESENTATION

A 47-year-old woman presented to the emergency department with complaints of left ptosis, generalized pain, and weakness in both upper and lower extremities. The patient with a documented history of stage IIIB non-small cell lung cancer (NSCLC), initially diagnosed in 2021. The primary lesion was identified in the left upper lobe (LUL) with evidence of pleural involvement. Histopathological analysis confirmed squamous cell carcinoma as the NSCLC subtype. Review of the patient's family history revealed no serious or

inherited familial diseases or autoimmune disorders, except for the father's history of hepatocellular carcinoma. She was treated with six cycles of paclitaxel and carboplatin for 4.5 months, but the response was limited. Subsequently, she received concurrent chemoradiotherapy (CCRT) with the intention of surgery, but she eventually declined surgery and continued follow-up care. Throughout her follow-up, the disease remained stable, as assessed by the RECIST criteria. However, a computed tomography (CT) scan in July 2024 revealed progression of the previously noted lesion in the LUL, along with metastases to multiple lymph nodes, pleural metastases, and the presence of pleural effusion. Lung cancer tissue obtained by percutaneous transthoracic needle biopsy revealed that 90% of tumor cells exhibited membrane staining, which was verified by VENTANA PD-L1 (SP263) assay. Pembrolizumab was administered as second-line chemotherapy. The patient received 200mg of pembrolizumab as the first cycle on July 22. Approximately two weeks later, she presented to the emergency department with worsening left ptosis and generalized pain, as well as muscle weakness in the arms and legs. Laboratory results revealed significant elevations in several biomarkers, including aspartate aminotransferase at 524 IU/L (normal range: 0-32 IU/L), alanine aminotransferase at 350 IU/L (normal range: 0-33 IU/L), lactate dehydrogenase (LD) at 1,710 IU/L (normal range: 0-250 IU/L), and creatine kinase (CK) at 11,417 IU/L (normal range: 0-170 IU/L). Additionally, troponin I was elevated at 1.864 ng/mL (normal range: 0-0.0452 ng/mL) and creatinine kinase muscle brain (CK-MB) levels exceeded 300 ng/mL (normal range: 0-5 ng/mL), further indicating substantial metabolic disturbances consistent with systemic involvement. No additional findings suggestive of other causes for the elevated liver enzymes, such as toxic exposure or infection-associated hepatitis, were noted. A chest and abdominal CT scan revealed no significant changes of cancer lesions compared with previous CT scan. Both echocardiography and electrocardiography also showed no notable findings. Regarding neurological symptoms, brain magnetic resonance imaging also showed no lesions to explain the symptoms, aside from a previously identified small vestibular schwannoma in the right internal auditory canal (Figure 1). Due to the severity of the symptoms, immediate treatment was required, and thus a muscle biopsy could not be performed. However, given the clinical presentation such as ptosis, laboratory results, and recent use of immuno-oncology therapy, myasthenia gravis and myositis were considered as possible diagnoses. The tensilon test was performed and yielded positive results. Additionally, the acetylcholine esterase antibody level was elevated at 1.42 nmol/L (normal range $<$ 0.5 nmol/L), indicating a positive finding. In the case of myositis accompanied by myasthenia gravis (MG), treatment with prednisolone (1 mg/kg) and pyridostigmine (60 mg four times daily) was initiated. CK levels were closely monitored during medication tapering. This combined approach aimed to manage both the inflammatory muscle condition and the neuromuscular symptoms of MG, leading to a significant improvement in the patient's clinical status. Furthermore, levels of LD, CK, and liver function tests showed improvement (Figure 2). However, two months later, new skin-related side effects

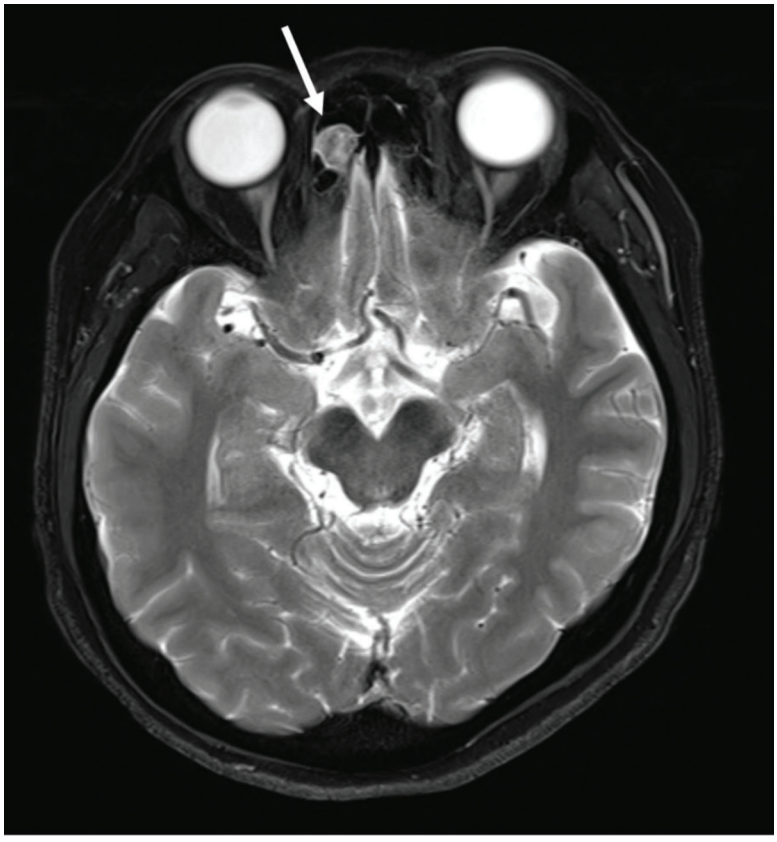

Fig. 1. T2-weighted brain MRI image. On the T2 brain MRI, no new lesions are observed that could cause ptosis or upper and lower limb weakness, aside from the previously noted small vestibular schwannoma in the right internal auditory canal.

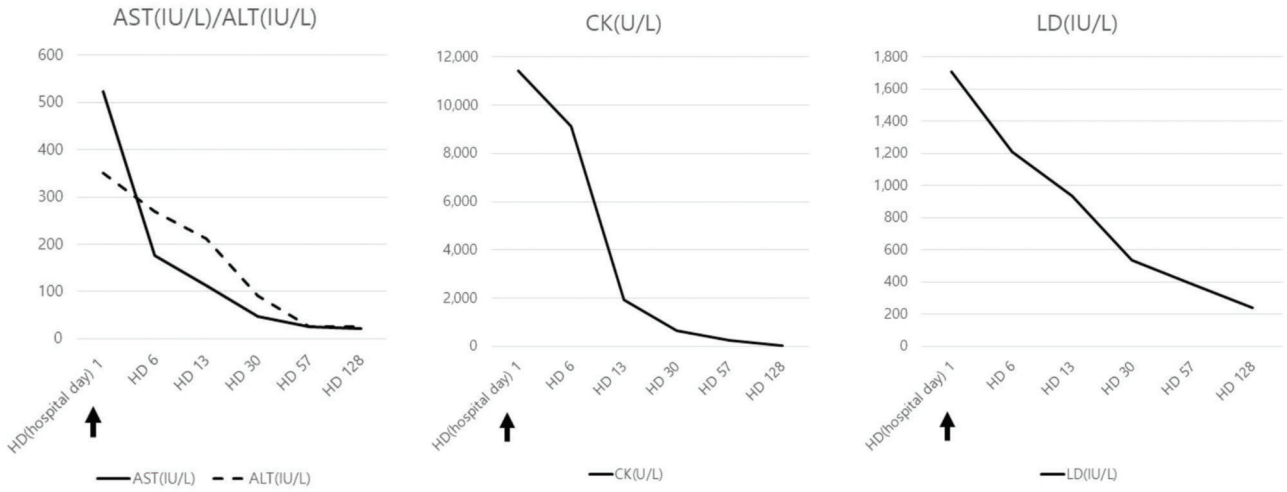

Fig. 2. Laboratory results showing improvement following treatment progression. The bold arrow indicates the initiation of treatment and the day of the emergency room visit. The graph displays laboratory test results from the initiation point to the most recent data. During the course of treatment, it was observed that the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LD) all returned to normal.

emerged. Itchy, erythematous and scaly lesions started on the back and spread throughout the body (Figure 3). A skin biopsy was performed, and diagnosed as pityriasis lichenoides chronica (PLC) (Figure 4). Although phototherapy was recommended, the patient declined, and treatment was continued with topical steroids and antihistamines. The condition is gradually improving with ongoing monitoring. For the treatment of NSCLC, pembroliuzmab was permanently discontinued due to grade 3 irAE and no other antitumor treatment has been initiated until now. A follow-up CT scan in December 2024 revealed no significant changes in the extent of her disease. Immune-related myositis and hepatitis were completely recovered and MG and pityriasis lichenoides were marked improved with ongoing treatment without cancer progression for 5 months.

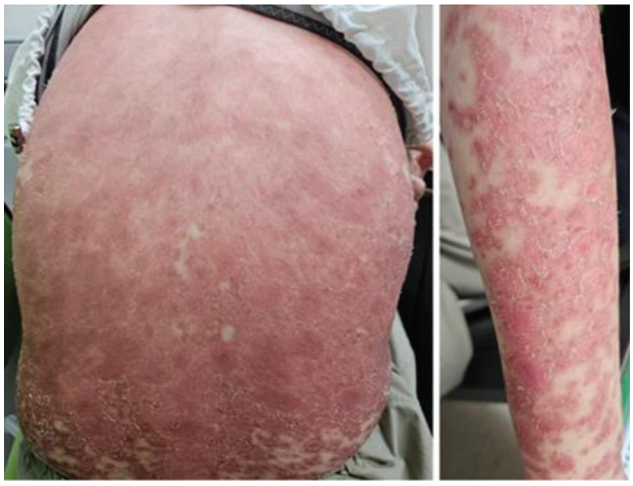

Fig. 3. Skin lesions with erythema and scales. The image shows erythematous, scaly lesions with accompanying pruritus observed throughout.

3. DISCUSSION

Immune checkpoint inhibitors (ICIs) are a class of therapeutic agents that block checkpoint proteins, enabling T cells to attack cancer cells and can generate immune memory, allowing for long-term therapeutic effects. These therapies target molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1/PD-L1. In the treatment of NSCLC, PD-1/PD-L1 inhibitors are recommended as first-line therapy, either as monotherapy or in combination with chemotherapy, based on the expression levels of PD-L1 on tumor or immune cells [3]. PD-1/PD-L1 inhibitors have also been approved for use as second-line therapy in certain cases of small cell lung cancer (SCLC) [1]. The primary mechanism of PD-1/PD-L1 inhibitors involves blocking the interaction between PD-1 on T cells and its ligand, PD-L1, expressed on cancer and other immune or stromal cells. Normally, the binding of PD-L1 to PD-1 downregulates T cell activity to prevent autoimmune reactions. However, cancer cells often exploit this pathway by overexpressing PD-L1, which suppresses T cell activation and allows immune evasion [2]. Pembrolizumab, one such PD-1 inhibitor, disrupts this interaction, reactivating T cells to recognize and attack cancer cells. Despite their effectiveness in treating cancers, ICIs can lead to irAEs, which arise when the activated immune system attacks healthy tissues. IrAEs typically occur within 2 to 16 weeks of treatment initiation and are sometimes regarded as a potential indicators of ICI response [5]. However, in the case of grade 3 or higher irAEs, treatment discontinuation is warranted due to the risk of life-threatening complications, which can even result in death.

While the exact mechanisms behind irAEs remain incompletely understood, several factors are believed to contribute. Autoimmunity and antitumor effects may result from shared antigens between tumors and normal tissues. Pre-existing inflammation may also be unmasked by the treatment, and cytokines and activated T cells generated by the antitumor response could exacerbate organ-specific inflammation. Additionally, about regulatory T cells (Tregs), it plays a vital role in maintaining immune homeostasis and preventing autoimmunity; however, their high expression of checkpoint molecules like CTLA-4, PD-1, and LAG-3 makes them a

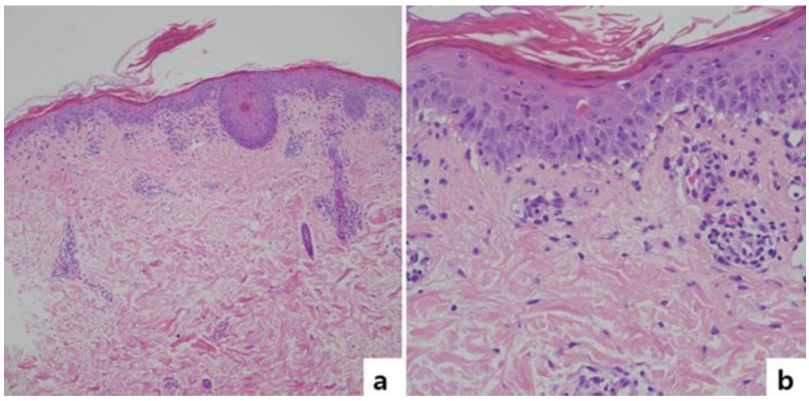

Fig. 4. Histologic findings of left upper arm skin. **a**. Intermediate power view reveals parakeratosis and mild inflammatory infiltrates in the upper dermis (HE, x100). **b**. High power view reveals spongiosis, necrotic keratinocyte, vacuolar change of basal cells, and infiltration of chronic inflammatory cells on perivascular area and upper dermis (HE, x400).

primary target of ICI therapies. Thus, Disrupting Tregs' function can lead to the development of irAEs as their immune regulatory role is impaired [6,7].

IrAEs commonly involve the gastrointestinal system, such as diarrhea and colitis, endocrine glands, skin issues like rashes or pruritus, and liver-related complications. However, irAEs affecting the pulmonary, cardiovascular, and hematologic systems are less well-documented [5,8]. Especially, Neurological and musculoskeletal complications, such as encephalitis, seizures, leukoencephalopathy, myelopathy, polyneuropathy, MG, and myositis, are very rare but can be severe [9]. Immune-related MG, in particular, is a extremely rare but life-threatening complication of ICIs. It is caused by the production of antibodies that attack the acetylcholine receptors, leading to interference with receptor function or a reduction in the number of receptors, leading to impaired neuromuscular transmission [10].

In the present case, the patient developed a combination of MG, myositis, and hepatitis, as evidenced by elevated CK levels, abnormal liver function, drug reaction test using edrophonium and confirmation of acetylcholine esterase antibody. Furthermore, the patient presented PLC, a skin disorder typically associated with autoimmune reactions, which manifested as pustules, keratinization, and skin shedding. These adverse events occurred following a single dose of pembrolizumab, emphasizing the rarity and multiplicity of irAEs in this case.

Treatment of irAEs depends on the organs involved and the severity of the symptoms. The standard treatment for the immunological side effects of ICIs involves discontinuation of the immunotherapy, with the consideration of steroid use. If no improvement is observed within 72 hours, immunosuppressive agents or intravenous immunoglobulin (IVIG) may also be considered [6]. In this case, discontinuation of pembrolizumab was necessary due to the grade 3 irAEs and the patient was treated with 1mg/kg steroids along with disease-specific therapies. For MG, acetylcholinesterase inhibitors, such as pyridostigmine, were used to improve neuromuscular function. For PLC, the treatment plan should include topical corticosteroids, oral antibiotics, and phototherapy [11,12]. Ultimately, the patient was successfully treated with steroids and disease-specific therapies, following the standard of care for each condition.

This case highlights the complexity and challenges of managing multiple irAEs in a patient receiving immunotherapy, and it underscores the importance of close monitoring and tailored treatment strategies for managing these complications.

4. CONCLUSION

This case presents a patient who developed simultaneous and multiple severe immune-related adverse events, including rhabdomyolysis, myasthenia gravis (MG), immune-mediated hepatitis, and pityriasis lichenoides, following a single dose of pembrolizumab. Although the accompanying immune-related side effects were rare and serious, they could be effectively treated with appropriate symptomatic treatment, including steroids. ICIs like pembrolizumab can cause a variety of immune-related adverse events and affect multiple organs. Therefore, early recognition and appropriate management are essential to optimizing patient outcomes and minimizing the associated risks.

Compliance with Ethical Standards

This study was approved by the Institutional ethical committee of Jeonbuk National University Hospital, Jeonju, Republic of Korea.

Consent for Publication

Written informed consent was obtained from the patient for publications of this case reports and any accompanying images.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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