CASE REPORT

DOI: 10.4274/nkmj.galenos.2025.33154
Nam Kem Med J 2025;13(4):439-443

Long-lasting Steroid Tapering Scheme in the Management of Relapsed Atezolizumab-induced Grade 3 Pneumonitis: A Case Report

Tekrarlayan Atezolizumab İlişkili Pnömonit Yönetiminde Uzun Süreli Steroid Azaltma Şeması: Olgu Raporu

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ABSTRACT

Immune checkpoint inhibitors, like atezolizumab, have significantly improved survival outcomes in cancer patients, including those with extensive-stage small cell lung cancer (SCLC). However, their use is associated with potentially severe immune-related adverse events, including pneumonitis, which can be life-threatening. We present a case of a 52-year-old male patient with SCLC who developed grade 3 pneumonitis during atezolizumab maintenance therapy. The patient, a chronic smoker, developed symptoms of dry cough and shortness of breath after the third maintenance dose. Radiologic imaging showed bilateral consolidation and ground-glass opacities. A diagnosis of atezolizumab-induced pneumonitis was confirmed, and treatment with high-dose methylprednisolone (1 mg/kg/day) was initiated, leading to clinical improvement. Following discharge, the patient experienced a relapse of symptoms while tapering steroids, prompting a steroid dose increase. After resolution of acute symptoms, the long-lasting steroid tapering regimen was used, ultimately resulting in the successful discontinuation of steroids. This case highlights the challenges of managing immune checkpoint inhibitor-induced pneumonitis, especially when it relapses, and underscores the importance of a personalized steroid tapering protocol. A tailored approach, combined with vigilant monitoring, can effectively manage this complication, emphasizing the need for individualized treatment strategies to balance immunotherapy efficacy and toxicity risks. Further research is necessary to optimize steroid tapering protocols and better understand long-term outcomes of immunotherapy-related pneumonitis.

Keywords: Lung cancer, immune-related pneumonitis, atezolizumab

ÖZ

Atezolizumab gibi immün kontrol noktası inhibitörleri, yaygın evre küçük hücreli akciğer kanseri (SCLC) olanlar da dahil olmak üzere kanser hastalarında sağkalım sonuçlarını önemli ölçüde iyileştirmiştir. Bununla birlikte, kullanımları, yaşamı tehdit edebilen pnömonit de dahil olmak üzere potansiyel olarak ciddi bağışıklık ile ilişkili yan etkilerle ilişkilidir. Bu yazıda, atezolizumab idame tedavisi sırasında grade 3 pnömonit gelişen 52 yaşında SCLC'li (SCLC) erkek hasta sunulmuştur. Kronik sigara içicisi olan hastada üçüncü idame dozundan sonra kuru öksürük ve nefes darlığı semptomları gelişmiştir. Radyolojik görüntülemede bilateral konsolidasyon ve buzlu cam opasiteleri görüldü. Atezolizumab kaynaklı pnömoni tanısı doğrulandı ve yüksek doz metilprednizolon (1 mg/kg/gün) tedavisi başlanarak klinik iyileşme sağlandı. Taburcu edildikten sonra, hasta steroidleri azaltırken semptomlarda bir nüksetme yaşamış ve bu da steroid dozunun artırılmasına neden olmuştur. Akut semptomların çözülmesinden sonra, uzun süreli steroid azaltma rejimi kullanılmış ve sonuçta steroidlerin başarılı bir şekilde kesilmesiyle sonuçlanmıştır. Bu olgu, özellikle nüks ettiğinde immün kontrol noktası inhibitörüne bağlı pnömoniti yönetmenin zorluklarını vurgulamakta ve kişiselleştirilmiş bir steroid azaltma protokolünün öneminin altını çizmektedir. Dikkatli izleme ile birlikte özel bir yaklaşım, immünoterapi etkinliği ve toksisite risklerini dengelemek için bireyselleştirilmiş tedavi stratejilerine duyulan ihtiyacı vurgulayarak bu komplikasyonu etkili bir şekilde yönetebilir. Steroid azaltma protokollerini optimize etmek ve immünoterapiyle ilişkili pnömonitin uzun vadeli sonuçlarını daha iyi anlamak için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Akciğer kanseri, immünoterapi ilişkili pnömonit, atezolizumab

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Received: 04.12.2024 **Accepted:** 09.01.2025 **Publication Date:** 19.12.2025

Cite this article as: Büyüktuna MA, Yergin Taçyıldız S, Koç T, Karaboyun K. Long-lasting steroid tapering scheme in the management of relapsed atezolizumab-induced grade 3 pneumonitis: a case report. Nam Kem Med J. 2025;13(4):439-443

INTRODUCTION

Cancer cells carry neoantigens resulting from genetic and epigenetic alterations that can potentially be recognized by the immune system. However, this immune response usually fails due to resistance mutations in tumor cells, tumor-induced local immunosuppression, weakened T-cell signaling and increased immune self-tolerance. Immune checkpoint inhibitors are new anti-cancer therapeutic agents whose efficacy in various cancer types has been proven by many studies[1].

Immunotherapies can have a wide spectrum of side effects due to the strengthening of the immune response. The skin, liver, gastrointestinal tract, lung and endocrine system can be attacked. Pneumonitis is one of the relatively rare but lethal side effects of this group of drugs. However, little is known about the clinical and radiologic features of checkpoint inhibitor-induced lung disease.

The standard first-line treatment for extensive stage small cell lung cancer (SCLC) has been platinum chemotherapy with etoposide for many years[2]. Given for more than 20 years, there has been limited progress, despite response rates of 60 to 65%, with a median overall survival of about 10 months[3,4]. SCLC has high mutation rates. Because of this feature, the addition of immune checkpoint inhibitors to treatment has been shown to positively contribute to survival in the IMpower133 clinic study[5]. We herein report successful management of a patient with SCLC of grade 3 pneumonitis related atezolizumab olarak düzeletelim geçen her yerde treatment.

CASE REPORT

A 52-year-old male patient with extensive stage SCLC was admitted to medical oncology outpatient clinic with complaints of dry cough and shortness of breath lasting for three days while he was on Atezolizumab maintenance therapy (he was taken 3rd maintenance dose before 10 days ago). He was previously performed Atezolizumab 1200 mg/21 days in combination with platinum - etoposide for 4 cycles, and then his treatment was switched to maintenance Atezolizumab 1200 mg/21 days treatment upon after partial response. The patient had been a smoker for more than 30 years and was in otherwise good health with no other signs of disease. Physical examination revealed decreased breath sounds bilaterally, velcro type rales on the auscultation of the right side of the lung, the heart rate 115/min, the blood pressure 115/80 mmhg, the respiratory rate 18 per minute, without fever and the oxygen saturation 85% while ambient air. Electrocardiogram showed no findings except sinus tachycardia. The peripheral blood sampling verified that white blood cell, neutrophil and monocyte counts were normal and increased C-reactive protein level. Influenza A-B and coronavirus disease-2019 rapid tests and two blood cultures were negative. chest computed tomography (CT) showed patchy distributed bilateral consolidation and ground-glass opacities (Figure 1). After initial rapid work-up, patient was hospitalised and 1mg/kg methylprednisolone was initiated due to high suspicion of immunotherapy related pneumonitis. Few days after corticosteroid treatment, the patient's symptoms tended to improve, the acute-phase response was declined, oxygen saturation recovered and dyspnea resolved. After a period of one week with no sign of disease, the patient was discharged with a steroid tapering scheme (8 mg dose reduction every 5 days), pneumocystis carinii pneumonia (PCP) prophylaxis and calcium and vitamin D replacement.

Twenty days after discharge, while taking 20 mg/day methylprednisolone, the patient re-presented to our outpatient clinic with the complaint of shortness of breath. The patient with elevated acute phase response and dyspnea was hospitalized and chest CT and angiography were performed. No pulmonary embolism was observed. As radiologic images were compatible with lobar pneumonia (Figure 2), IV antibiotic therapy covering pseudomal infection was initiated. Chest CT was repeated after 48-72 hours with no acute phase reactants response and no growth in blood and sputum cultures. Methylprednisolone was increased again to 40 mg dose with the concern of recurrence of pneumonitis due to ground glass opacity and increased bilateral infiltrations on imaging. After receiving methylprednisolone 40 mg/5 days, clinical and laboratory response was observed. Antibiotic treatment was discontinued. 40 mg methylprednisolone was completed to 7 days and the patient was discharged with a slow dose reduction scheme (4 mg every 10 days). In outpatient follow-up, corticosteroids were safely discontinued with slow dose reduction and atezolizumab was permanently discontinued. The patient continues follow-up without treatment for SCLC.

DISCUSSION

This case highlights the complexities of managing immune checkpoint inhibitor-related pneumonitis, particularly in the context of relapsed pneumonitis. While immune checkpoint inhibitors like atezolizumab have revolutionized the treatment landscape for cancer, their potential for causing severe immune-related adverse events, such as grade 3-4 pneumonitis, requires careful and often prolonged management. The success of the steroid tapering regimen in this patient underscores the need for personalized and adaptive therapeutic strategies to balance the benefits of immunotherapy with the risks of such life-threatening complications.

According to the Common Terminology Criteria for Adverse Events version 5, immunotherapy-associated pneumonitis that affects daily vital activities and/or is life-threatening in addition to the need for oxygen is evaluated as grade 3-4[6]. European Society for Medical Oncology (ESMO) and National

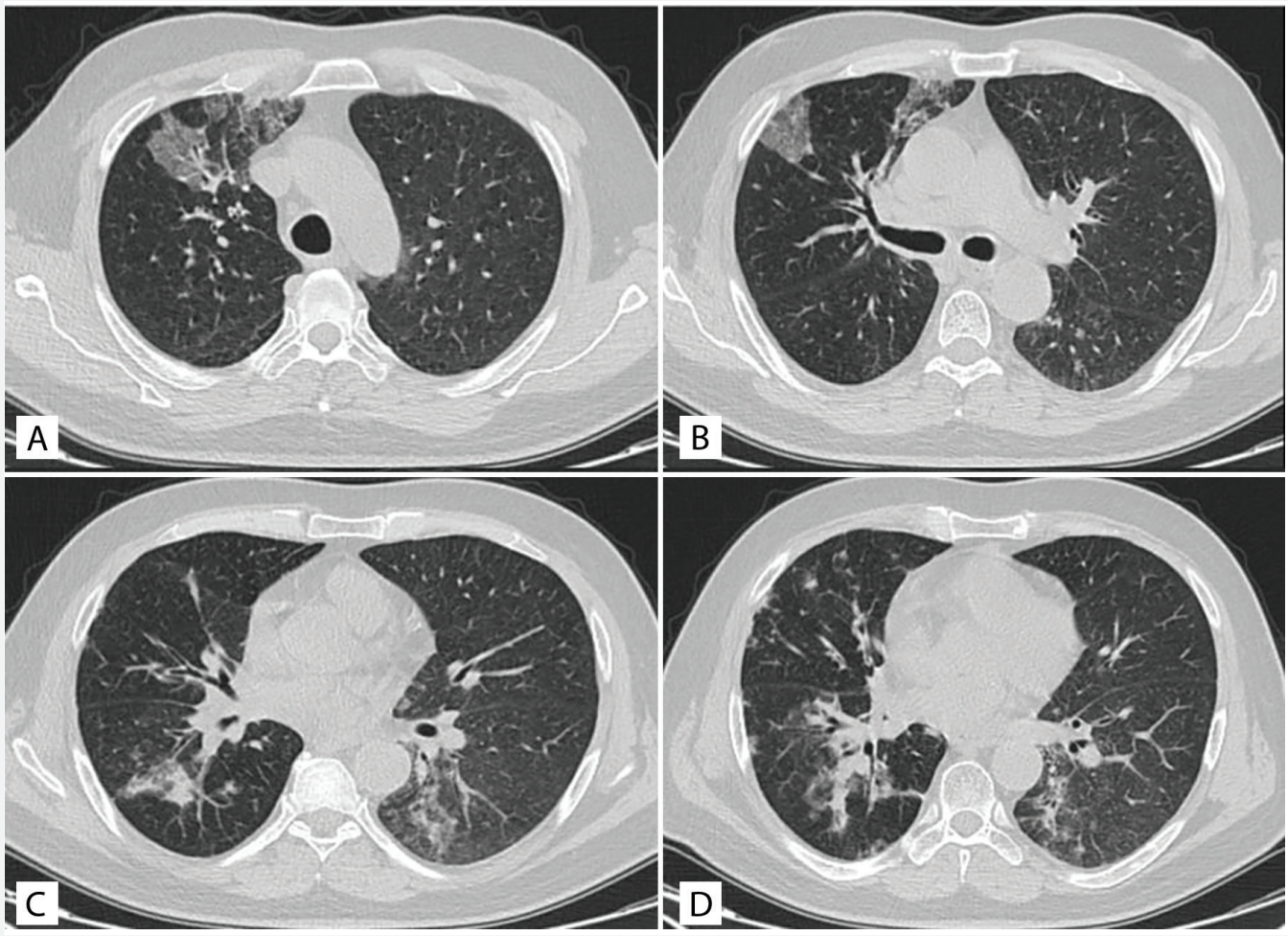

Figure 1. Multifocal ground-glass areas in both lung parenchyma
A) Upper lung slice B) Slice at carina level C, D) Slices at post-arch

Comprehensive Cancer Network guidelines recommend that patients with grade 3-4 pneumonitis should be hospitalized for management[7,8]. Glucocorticoids treatment and holding immunotherapy constitute the backbone of management. In addition, in terms of differential diagnosis, a rapid work up for pseudomonal pneumonia, PCP infection, disease progression, and vascular thromboembolic diseases should be performed. Blood culture, nasal swabs, sputum culture, metabolic and biochemical panels are usually performed on the inpatient setting. Bronchoalveolar lavage may be useful for microorganism production or disease invasion assessment. Finally, it is recommended to add antibiotherapy covering the pseudomonal pneumonia and PCP infection.

In studies performed before the prevalent use of immunotherapies in different cancer types, the risk of pneumonitis was reported to be higher in NSCLC and RCC and in combined immunotherapies than in melanoma[9]. Immunotherapies, which are now indicated for almost every type of cancer, need to be evaluated for these fatal side effects. Grade 3-4 pneumonitis was seen in 3.1% of patients in durvalumab condensation immunotherapy[10], which is the new standard treatment in early-stage SCLC, while it was seen in 0.5% patients in the IMpower133 study evaluating patients receiving atezolizumab in extensive stage SCLC.

Although the optimal dose reduction and duration for grade 3-4 pneumonitis responsive to corticosteroid therapy is not clear, ESMO guidelines recommend steroid dose reduction for at least 6-8 weeks. If symptoms or imaging studies worsen significantly during tapering, we will return to the last well-tolerated dose of prednisone (or equivalent) for two weeks before continuing tapering. In cases of grade 4 pneumonitis, immunotherapy is completely discontinued, while in grade 2 cases, immunotherapy can usually be restarted. For grade 3 cases, there is no certainty and patient characteristics such

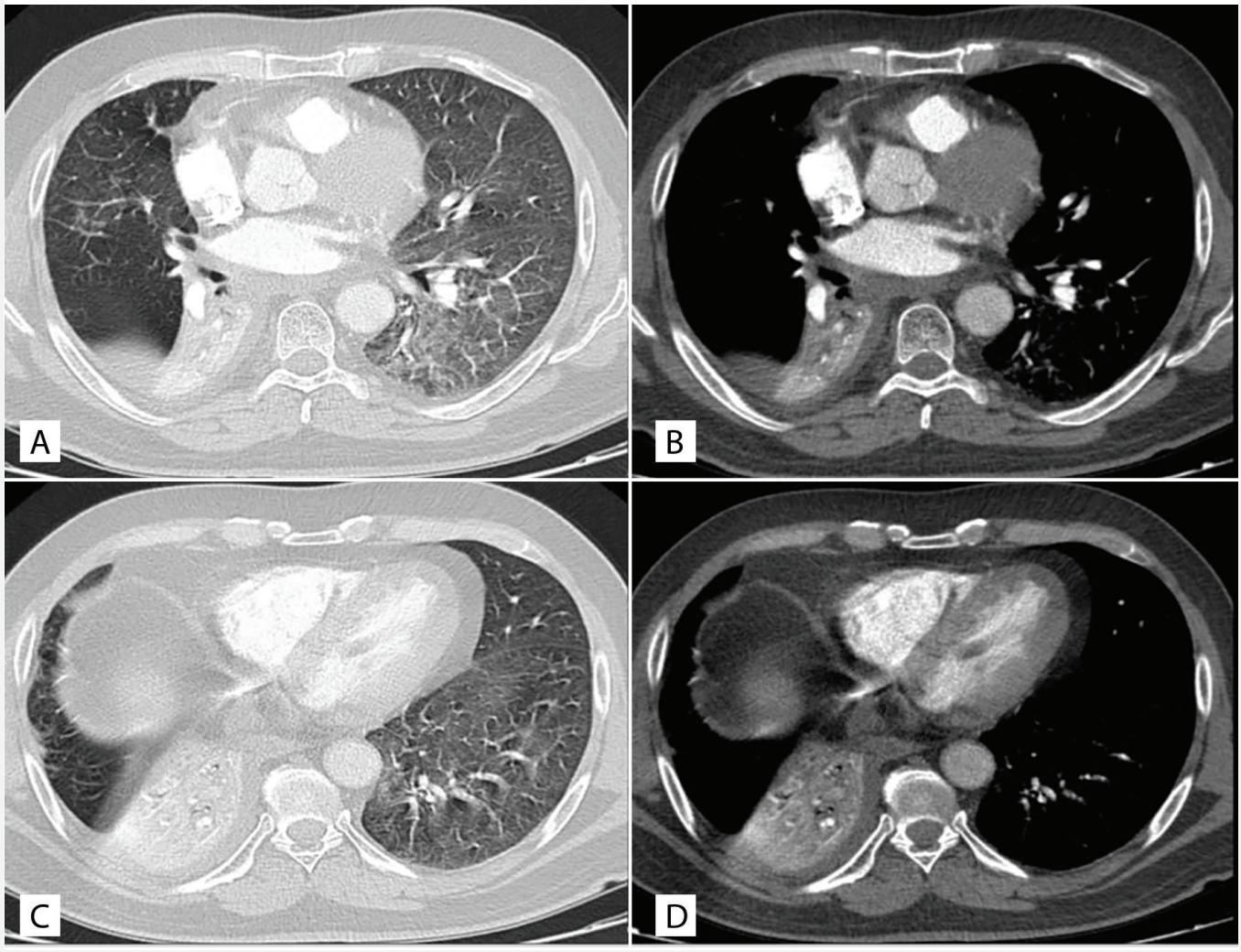

Figure 2. Consolidation with air bronchograms in the lower lobe of the right lung
A-D) Slices at air bronchograms level

as the course of pneumonitis, response to treatment and life expectancy need to be taken into account.

CONCLUSION

A tailored steroid tapering regimen, coupled with appropriate monitoring, proved effective in managing this life-threatening complication. Despite the risks associated with immune checkpoint inhibitors, careful management can allow for favorable outcomes, emphasizing the importance of individualized steroid treatment strategies and close follow-up. Further studies are needed to refine the optimal approach for steroid tapering and to better understand the long-term implications of immunotherapy-related pneumonitis.

Ethics

Informed Consent: The patient provided written informed consent for the publication of this article.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.B., Concept: M.A.B., T.K., K.K., Design: S.Y., Data Collection or Processing: S.Y., Analysis or Interpretation: T.K., K.K., Literature Search: T.K., K.K., Writing: S.Y., K.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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