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Case Report

A Case of Nonsmall-Cell Lung Cancer with Anaphylaxis after 41 Courses of Pembrolizumab along with Adrenal Insufficiency as an Immune-Related Adverse Event

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Keywords

Lung cancer · Pembrolizumab · Anaphylaxis · Adrenal insufficiency · Immune-related adverse event

Abstract

In this report, we present a case of nonsmall-cell lung cancer with anaphylaxis after 41 courses of pembrolizumab along with adrenal insufficiency as an immune-related adverse event (irAE). A 73-year-old man with no allergic disease started pembrolizumab for postoperative recurrence of lung cancer. After four courses, tumor shrinkage was observed and maintained thereafter. After the 39th course, his serum sodium level and random serum cortisol level decreased. Adrenal insufficiency was considered; however, the patient was asymptomatic. Furthermore, his serum sodium level improved spontaneously; therefore, he was followed up. At the end of the 40th course, rhinorrhea and pharyngeal discomfort were noted; however, they were mild and resolved spontaneously. Immediately after administration of the 41st course, he developed pembrolizumab-induced anaphylaxis with percutaneous oxygen saturation decreased. The symptoms quickly improved after intramuscular adrenaline were administered and did not recur. Three months after discharge, the patient was urgently examined for vomiting and anorexia. His serum sodium levels decreased to 119 mEq/L, and an adrenocorticotropic hormone stimulation test was performed. It showed a low response, and the patient was diagnosed with secondary adrenal insufficiency as an irAE of pembrolizumab and treated with hydrocortisone, which quickly improved his serum sodium levels and symptoms. When adrenal insufficiency develops due to irAEs, patients may be susceptible to allergic reactions.

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Introduction

Pembrolizumab, a humanized immunoglobulin subclass 4 monoclonal antibody that specifically targets programmed death receptor-1, has been widely used because of its therapeutic efficacy against lung cancer as well as other neoplasms compared to conventional chemotherapy [1]. Programmed death ligand-1 (PD-L1) is the only predictive biomarker approved to date for immune checkpoint inhibitor (ICI) treatment in nonsmall-cell lung cancer patients [2]. However, other biomarkers that have recently been noted as predictors of treatment response include tumor-infiltrating lymphocytes, tumor mutational load, several other biomarkers, and the use of certain drugs [3–5].

Because pembrolizumab enhances the host immune system, it often develops unique side effects called immune-related adverse events (irAEs) [6]. In addition, ICIs, like other drugs, have been reported to cause anaphylaxis, but most develop after the first few courses [7, 8]. Herein, we present a case of nonsmall-cell lung cancer with anaphylaxis after 41 courses of pembrolizumab along with adrenal insufficiency as an irAE.

Case Report/Case Presentation

A 73-year-old man with hypertension, dyslipidemia, and no allergic disease underwent thoracoscopic upper lobectomy of the right lung for an 11-mm part-solid ground-glass nodule in the right upper lung lobe, which was incidentally identified. He was diagnosed with lung adenocarcinoma (pT1aN2M0, stage IIIA), which was negative for EGFR mutation, ALK fusion, ROS-1 fusion, and BRAF mutation. PD-L1 expression with a tumor proportion score of 30% was confirmed by immunohistochemistry with a 22C3 antibody. Contrast-enhanced computed tomography and positron emission tomography-computed tomography performed 6 months after adjuvant chemotherapy confirmed recurrence in the right supraclavicular lymph node. Therefore, pembrolizumab 200 mg every 3 weeks was started; after four courses, tumor shrinkage was observed and maintained thereafter. By the end of 38 courses, there were no side effects of pembrolizumab.

After the 39th course, his serum sodium level decreased (127 mEq/L), random serum cortisol level was 3.23 μg/dL, and adrenocorticotropic hormone level was normal. Eosinophil count had previously been around 300, but was elevated (540/μL) at this time. Adrenal insufficiency was considered; however, the patient was asymptomatic. Furthermore, his serum sodium level improved spontaneously; therefore, he was followed up. At the end of the 40th course, rhinorrhea and pharyngeal discomfort were noted; however, they were mild and resolved spontaneously (only follow-up observation). The 41st course was administered with antihistamine premedication. The eosinophil count remained high at 550/μL in the blood drawn prior to administration. Immediately after administration, he developed rhinorrhea and nasal obstruction; furthermore, wheezing was noted, and percutaneous oxygen saturation decreased to 90% on room air. There was no skin rash, including wheals. He was diagnosed with pembrolizumab-induced anaphylaxis. The symptoms quickly improved after intramuscular adrenaline and intravenous famotidine and hydrocortisone were administered and did not recur.

Three months after discharge, the patient was urgently examined for vomiting and anorexia. His serum sodium level decreased to 119 mEq/L, and thyroid function and renin and aldosterone levels were normal. Considering the possibility of inadequate solute intake, a solute load with saline solution was administered; however, there was no improvement. Pre-admission contrast-enhanced magnetic resonance imaging of the head showed no pituitary abnormalities. The adrenocorticotropic hormone stimulation test was performed by consulting an endocrinologist. It showed a low response, and the patient was diagnosed with secondary adrenal insufficiency as an irAE of pembrolizumab and treated with hydrocortisone,

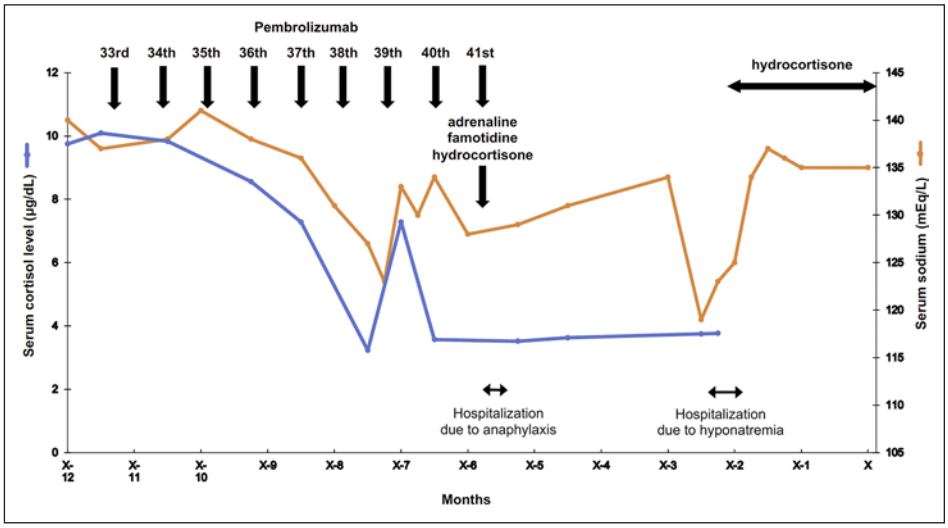

Fig. 1. Patient's clinical course in the last 12 months. Around course 38, the patient had hypocortisolemia and hyponatremia, probably due to an immune-related adverse event caused by pembrolizumab. After 41 courses, he developed anaphylaxis and was treated with adrenaline, famotidine, and hydrocortisone. He was subsequently hospitalized for hyponatremia due to adrenal insufficiency and treated with steroid replacement. His serum sodium levels improved and are maintained.

which quickly improved his serum sodium levels and symptoms. Pembrolizumab was not resumed; he was followed up without treatment, with no tumor growth. Patient's clinical course in the last 12 months is shown in Figure 1.

Discussion/Conclusion

Pembrolizumab has been widely used because of its therapeutic efficacy against lung cancer and other neoplasms. Because it enhances the host immune system, it often causes unique side effects called irAEs [6].

We encountered a case in which anaphylaxis first occurred after a very late treatment course, after 41 pembrolizumab courses. No similar case has been reported hitherto. Anaphylaxis frequency associated with pembrolizumab monotherapy for lung cancer is only 0.2% [9]. There are no consistent reports on the timing of anaphylaxis onset with pembrolizumab. Avelumab, an anti-PD-L1 antibody, is known to cause most infusion reactions during or just after the first four courses. Furthermore, infusion reactions with nivolumab are often reported to occur within a few courses [8].

Our patient simultaneously developed adrenal insufficiency as an irAE, which led to a decrease in endogenous glucocorticoids (GCs). GCs inhibit the transcription of allergy-related cytokines, which are important for triggering allergic inflammation. Furthermore, GCs inhibit eosinophil migration and induce eosinophil apoptosis by downregulating adhesion molecules such as intercellular adhesion molecule-3 [10]. Low GC levels due to adrenal insufficiency may have led to the dysregulation of these parameters, promoting an overshoot of the allergic reaction and making the patient more susceptible to anaphylaxis. For example, adrenal insufficiency triggered by lymphocytic hypophysitis was reported to induce repeated anaphylaxis [11].

The patient had signs of adrenal insufficiency, including low cortisol levels and transient hyponatremia, prior to anaphylaxis. However, hydrocortisone supplementation was not performed because of temporary improvement of symptoms. The diagnosis of adrenal

insufficiency is often difficult because it is made by a combination of findings rather than by a single marker [12]. Therefore, regular follow-up of cortisol and attention to signs of adrenal insufficiency are necessary to reach the earliest possible diagnosis. Furthermore, adrenal insufficiency as an irAE also occurs infrequently and may be underestimated in relation to the development of anaphylaxis due to its diagnostic difficulties [6]. To clarify this, it is necessary to accumulate many cases of adrenal insufficiency due to ICI and show its association with the development of anaphylaxis.

In conclusion, anaphylaxis usually occurs after the first few pembrolizumab doses; however, we encountered a case after 41 doses, with adrenal insufficiency. When adrenal insufficiency develops due to irAEs, patients may be susceptible to allergic reactions. Anaphylaxis occurs despite repeated pembrolizumab exposure; therefore, careful monitoring after each administration is important.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The manuscript was reviewed and approved by all authors and is not under consideration for publication elsewhere. All authors contributed to the work in this report. Tomoaki Nakamura collected clinical data and wrote the initial draft of the manuscript. Ryosuke Imai and Naoki Nishimura supervised and edited the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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