CASE REPORT

Immunochemotherapy Disrupts Peripherally Located Lung Squamous Cell Carcinoma Resulting in Pleuritis: A Report of Two Cases, Case Report

Kei Kunimasa, MD, PhD,[a,*] Tomohiro Maniwa, MD, PhD,[b] Motohiro Tamiya, MD,[a] Takako Inoue, MD,[a] Takahisa Kawamura, MD, PhD,[a] Jiro Okami, MD, PhD,[b] Kazumi Nishino, MD, PhD[a]

[a]*Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan*
[b]*Department of General Thoracic Surgery, Osaka International Cancer Institute, Osaka, Japan*

Received 8 April 2022; revised 17 June 2022; accepted 6 July 2022
Available online - 9 July 2022

ABSTRACT

Immunochemotherapy is widely used as the primary treatment for advanced lung cancer and is currently being investigated in the perioperative setting. Immunochemotherapy can produce marked tumor shrinkage and long-term anticancer effects that are not achieved with conventional anticancer drugs. Herein, we present the cases of two patients with relatively large advanced primary lung squamous cell carcinomas located just below the pleura, who developed pleuritis immediately after the initiation of immunochemotherapy, probably owing to leakage of tumor contents after marked tumor shrinkage. Treatment of pleuritis necessitates discontinuation of chemotherapy, and special attention to secondary pleuritis may be required after initiation of immunochemotherapy in patients with lung tumors located just below the pleura.

Keywords: Lung squamous cell carcinoma; Immunechemotherapy; Pleuritis; Adverse event; Case report

Introduction

Lung squamous cell carcinoma (LSqCC) is the second most common histologic subtype of NSCLC after adenocarcinoma and accounts for approximately a quarter of NSCLC. Currently, unlike adenocarcinoma, no druggable driver mutation that can be used in clinical practice has been identified in LSqCC, and in advanced stages, treatment must rely on conventional chemotherapy, immunotherapy, or immunochemotherapy.[1] Recently, immunochemotherapy as the first-line treatment has been found to improve overall survival over conventional chemotherapy and has become the standard treatment for advanced LSqCC.[2]

Immunochemotherapy has strong antitumor effects that are not seen with conventional chemotherapy. Although LSqCC tends to occur centrally within the thorax, it occurs peripherally in approximately one-third of cases.[1] Here, we report the cases of two patients with peripherally located advanced LSqCC who received immunochemotherapy as the first-line treatment. They developed chest

***Corresponding author.**

***Disclosures:** Dr. Kunimasa reports receiving honoraria for lectures conducted for AstraZeneca, Chugai Pharma, and Novartis. Dr. Tamiya reports receiving grants from Ono Pharmaceutical, Japan, Bristol-Myers Squibb, United States, and Boehringer Ingelheim; and honoraria for lectures conducted for Taiho Pharmaceutical, Japan, Eli Lilly, Asahi Kasei Pharmaceutical, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, and Bristol-Myers Squibb. Dr. Nishino reports receiving a grant from Nippon Boehringer Ingelheim and honoraria for lectures conducted for Chugai Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Eli Lilly Japan, Roche Diagnostics, Novartis, Pfizer, and Merck. The remaining authors declare no conflict of interest.*

Address for correspondence: Kei Kunimasa, MD, PhD, Department of Thoracic Oncology, Osaka International Cancer Institute, 3-1-69 Otemae Chuoku, Osaka City, Osaka 541-8567, Japan. E-mail: kei.kunimasa@oici.jp

Cite this article as: Kunimasa K, Maniwa T, Tamiya M, et al. Immunochemotherapy disrupts peripherally located lung squamous cell carcinoma resulting in pleuritis: a report of two cases, a case report. *JTO Clin Res Rep*. 2022;3:100380.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100380

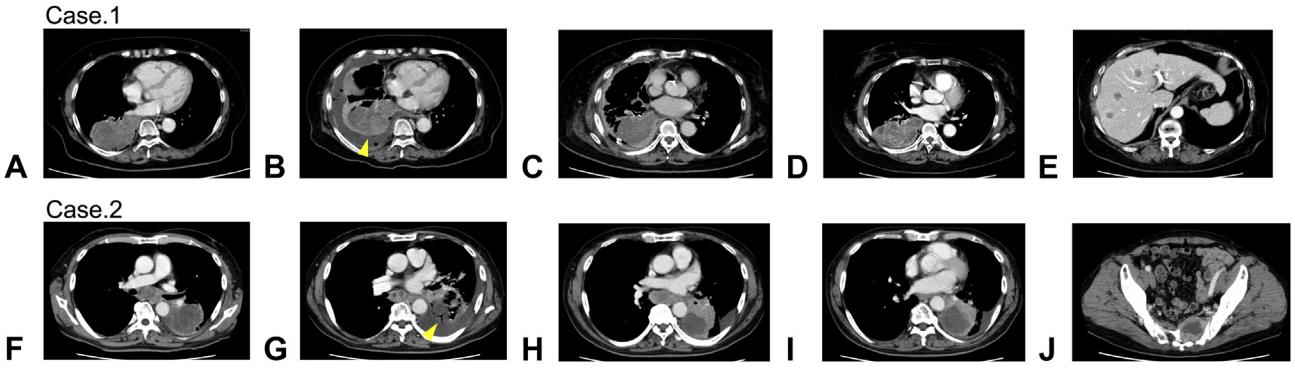

Figure 1. Enhanced chest CT images. Case 1: (*A*) Before induction of immunochemotherapy, a 100-mm mass was found, located just below the right pleura. (*B*) On day 7, there was an emergence of right pleural effusion. The yellow arrowhead indicates rupture of the tumor wall and pleura. (*C*) After insertion of the chest drainage tube, there was (*D*) slight shrinkage of the lung primary tumor, and (*E*) emergence of multiple liver metastases during the treatment for empyema. Case 2: (*F*) before induction of immunochemotherapy, a 77-mm mass was seen located just below the right pleura. (*G*) On day 14, there was an emergence of a left pleural effusion. The yellow arrowhead indicates rupture of the tumor wall and pleura. (*H*) After the treatment for pleuritis, there was a slight shrinkage of the lung primary tumor. (*I*) During the treatment for pleuritis, the lung tumor enlarged, and (*J*) a new bone metastasis emerged in the patient's sacrum. CT, computed tomography.

pain and pleuritis owing to tumor disruption relatively early after treatment initiation, which compelled us to discontinue immunochemotherapy.

Case Presentation

Case 1

A 70-year-old woman, a current 75-pack-year smoker, presented to our hospital with mild cognitive impairment and an abnormal chest shadow. Enhanced brain magnetic resonance imaging and chest computed tomography (CT) revealed a 40-mm mass in the brain and a 100-mm mass in the lower lobe of the right side of the lung, respectively (Fig. 1*A*). Histologic examination of specimens obtained by means of craniotomy and bronchoscopy revealed identical SqCC (Fig. 2*A* and *B*). The patient was diagnosed with clinical stage T4N1M1b LSqCC with a programmed death ligand-1 (PD-L1) tumor proportion score of 75% (Fig. 2*C*). The patient was administered pembrolizumab combined with carboplatin and nab-paclitaxel as the first-line treatment. On day 2 of treatment, she complained of right-sided chest pain; on day 7, she developed fever with pleural effusion on the right side, and tumor disruption was identified on enhanced chest CT (Fig. 1*B*). Pleural effusion culture revealed empyema caused by *Haemophilus influenzae*, and no malignant cells were detected. The empyema was treated using antibiotics and drainage for approximately 1 month (Fig. 1*C* and *D*), during which time the brain metastasis and multiple liver metastases were aggravated (Fig. 1*E*).

Case 2

A 70-year-old man, a current 50-pack-year smoker, was referred to our hospital with an abnormal chest shadow. Enhanced CT revealed a 77-mm mass in the lower lobe of the left lung (Fig. 1*F*). CT-guided biopsy of the lesion revealed LSqCC, which was clinically staged as T4N3M1c with a PD-L1 tumor proportion score of 10% (Fig. 2*D*–*F*). The patient received nivolumab and ipilimumab combined with carboplatin and paclitaxel as the first-line treatment. On day 2, the patient complained of slight left-sided chest pain; on day 14, he developed dyspnea on exertion with left-sided pleural effusion, and enhanced chest CT revealed tumor disruption (Fig. 1*G*). A thoracic drain was inserted, and because no bacteria were detected in the pleural fluid culture, no antibiotics were administered. The patient was followed-up and the drain was removed after the discharge decreased approximately two weeks later (Fig. 1*H* and *I*). In the meantime, the sacral metastasis was found to have increased (Fig. 1*J*) and the primary treatment was deemed ineffective.

Discussion

In the two cases presented here, pleuritis, which is an adverse event leading to treatment discontinuation, was observed immediately after the introduction of immunochemotherapy. The tumors were relatively large and were located just below the pleura, suggesting the possibility that the tumors were exposed on the pleural surface. In our previous experience with LSqCC, we observed a marked tumor collapse on the fourth day after initiation of immunochemotherapy[3]; therefore, the intense inflammation and tumor collapse immediately after the start of treatment in these two cases were expected.

Immunotherapy or immunochemotherapy has been reported to be associated with the frequency of

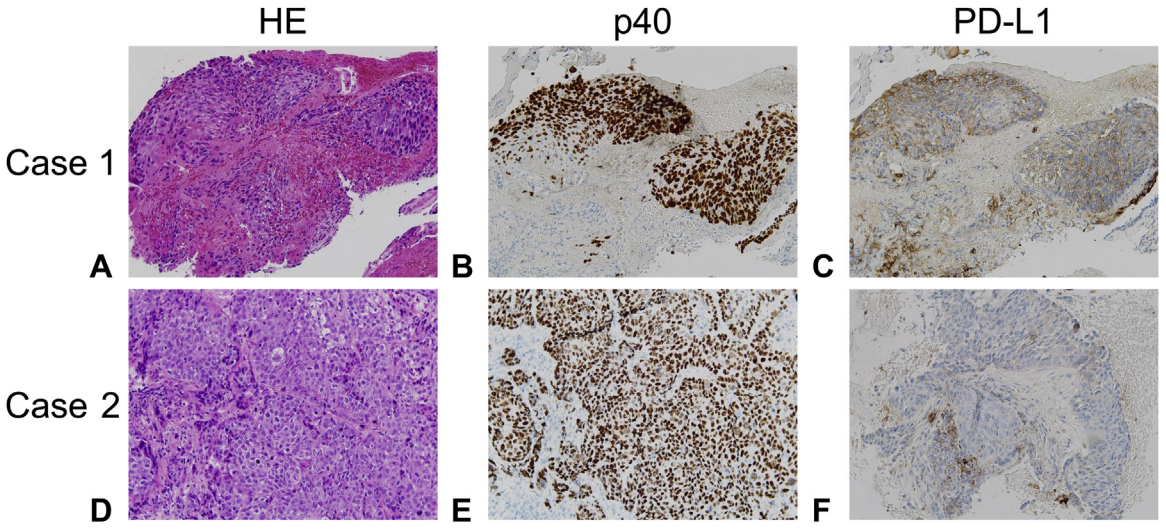

Figure 2. Immunohistopathologic analysis of biopsy samples. Cases 1 and 2: (*A*, *D*) HE-stained images; (*B*, *E*) p40 immunostained images; and (*C*, *F*) PD-L1 immunostained images. HE, hematoxylin and eosin; PD-L1, programmed death-ligand 1.

appearance of immune-related adverse events, and it is known that the effect of immunotherapy or immunochemotherapy can persist even after treatment is discontinued after the first course of severe immune-related adverse events. In the two cases presented, it was expected that the effect of immunotherapy would be sustained afterward, even if the first course of immunochemotherapy was discontinued after a severe adverse event of pleuritis. However, because both cases required nearly a month of treatment for pleurisy and the subsequent appearance of new distant metastases (brain and liver metastases in case 1 and bone metastasis in case 2), they were judged to have tumor progression according to Response Evaluation Criteria in Solid Tumors.

Case 1 developed pyothorax, which required antimicrobial agents, and a longer drainage duration. Both patients underwent a biopsy of the primary lesion before treatment, but no signs of infection were observed at the time of treatment administration, although nearly two weeks had passed until the initiation of immunochemotherapy owing to the biopsy. The presence of bacteria in tumor tissue has been noted, and in lung cancer, chemicals such as nicotine, anthranilate, and toluene, which are present in cigarette smoke, have been reported to form preferred niches for bacteria.[4] Intratumor bacteria mainly include Proteobacteria, and *H. influenzae* is included in Proteobacteria. In Case 1, it is possible that intratumor *H. influenzae* flowed into the pleural cavity owing to tumor collapse and caused empyema.

Immunochemotherapy is being widely applied as neoadjuvant chemotherapy in clinical trials.[5] To safely introduce immunochemotherapy in patients with massive LSqCC located just below the pleura, the first-line treatment may include chemotherapy without immunotherapy, and immunotherapy can be initiated after the tumor has shrunk. Furthermore, patients with relatively stable diseases may undergo surgical resection of large primary tumors before immunochemotherapy. In the case of centrally located squamous cell carcinoma, there is a risk of hemoptysis on tumor lysis with immunochemotherapy. From the phase III, randomised, double-blind, placebo-controlled, multi-centre, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable non-small cell lung cancer (stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy (PACIFIC trial),[6] which compared durvalumab with placebo in patients with unresectable stage III NSCLC and no disease progression after concurrent chemoradiotherapy, hemoptysis was 0.4% in both groups; therefore, the risk of hemoptysis may not be high even with immunochemotherapy. However, it is still necessary to pay attention to the possibility of hemoptysis owing to tumor collapse in central lesions with immunochemotherapy.

We presented two cases with large LSqCC cases located just below the pleura in which the introduction of immunochemotherapy unexpectedly led to the development of pleuritis requiring thoracic drainage. LSqCC just below the pleura may have a tumor-surface outcrop on the pleural surface. Therefore, the strong antitumor effect of immunochemotherapy may result in tumor disruption and subsequent dissemination of intratumoral material into the pleural cavity. To successfully lead to surgical treatment, special attention to

the risk of subsequent pleuritis may be required when introducing immunochemotherapy in patients with large LSqCC just below the pleura.

CRediT Authorship Contribution Statement

Kei Kunimasa: Conceptualization, Methodology, Investigation, Writing - original draft. **Tomohiro Maniwa, Motohiro Tamiya, Takako Inoue, Takahisa Kawamura:** Investigation.

Jiro Okami, Kazumi Nishino: Supervision.

Acknowledgments

Informed consent was obtained from the present cases.

References

1. Drilon A, Rekhtman N, Ladanyi M, Paik P. Squamous-cell carcinomas of the lung: emerging biology, controversies, and the promise of targeted therapy. *Lancet Oncol*. 2012;13:e418–e426.
2. Grant MJ, Herbst RS, Goldberg SB. Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. *Nat Rev Clin Oncol*. 2021;18:625–644.
3. Kunimasa K, Nakamura H, Nishino K, Nakatsuka SI, Kumagai T. Extrinsic upregulation of PD-L1 induced by pembrolizumab combination therapy in patients with NSCLC with low tumor PD-L1 expression. *J Thorac Oncol*. 2019;14:e231–e233.
4. Nejman D, Livyatan I, Fuks G, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science*. 2020;368:973–980.
5. Chaft JE, Shyr Y, Sepesi B, Forde PM. Preoperative and postoperative systemic therapy for operable non-small-cell lung cancer. *J Clin Oncol*. 2022;40:546–555.
6. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.