Multi-organs perioperative immune-related adverse events and postoperative bronchial anastomotic fistula in a patient receiving neoadjuvant immunotherapy with NSCLC

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Abstract
The safety of neoadjuvant chemoimmunotherapy before surgery in patients with non–small cell lung cancer (NSCLC) remains unclear in the perioperative stage. We describe a case of a 63-year-old man with IIIC stage NSCLC who received neoadjuvant chemoimmunotherapy and radical lobectomy. After the second cycle of pembrolizumab and chemotherapy (paclitaxel + carboplatin), the patient was diagnosed with immunologic enterocolitis and relieved by glucocorticoid therapy. Radical lobectomy of the right upper lobe was then performed. On postoperative day 4 (POD 4), the patient suddenly suffered suffocated wheezing during sleep. Interstitial lung disease was, therefore, identified by chest computed tomography scan. Glucocorticoids and mechanical ventilation were applied and the symptoms were relieved. On POD 10, the patient developed a bronchial fistula and underwent emergent repair surgery. This is the first case of multi-organs, multi-time point immune-related adverse events (irAE) in perioperative NSCLC patients who received neoadjuvant chemoimmunotherapy. Clinicians should be on high alert for signs of irAEs in neoadjuvant chemoimmunotherapy patients, promptly requiring multidisciplinary management.

KEYWORDS
immune-related adverse events, interstitial lung disease, neoadjuvant chemoimmunotherapy, non–small cell lung cancer, pembrolizumab

INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionized the therapy of non–small cell lung cancer (NSCLC), significantly advanced stage lung cancer. Recently, for resectable NSCLC, neoadjuvant chemoimmunotherapy, including ICI, chemotherapy, and surgery, has attracted the lung cancer treatment field. Forde et al. reported that in patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival (31.6 months vs. 20.8 months) and a higher percentage of patients with a pathological complete response (PCR) (24.0% vs. 2.2%) than chemotherapy alone in the CheckMate 816 clinical trial. Provencio et al. also reported that at 24 months, progression-free survival of resectable stage IIIA NSCLC, who received neoadjuvant nivolumab, was 77.1% (95% CI, 59.9–87.7) in the NADIM clinical trial.

ICI may induce an immune “attack” in organs, therefore, revealing a new spectrum of toxicities called immune-related adverse events (irAEs). IrAEs are incredibly diverse and can affect the skin, the endocrine glands, the gastrointestinal tract, the nervous system, the lungs, the kidney, the heart, the eyes, or other organs. However, irAEs were primarily reported in advanced cancer. IrAEs in neoadjuvant chemoimmunotherapy in the perioperative stage were not clarified clearly. Here, we reported a patient...
who developed irAEs in the colon and the lung around neoadjuvant chemoimmunotherapy.

**CASE REPORT**

A 63-year-old male with a history of intermittent hemoptysis for 6 months was referred to our hospital. He had a history of smoking and drinking for 40 years. His father died of lung cancer. Computed tomography (CT) scan showed a mass lesion in the anterior segment of the right upper lobe (RUL) (Figure 1(a),(c)), approximately 5.6 x 5.6 x 5.9 cm in size. Positron emission tomography/CT (PET/CT) showed the mass had increased radioactive uptake, with a standardized uptake value (SUV) maximum of 18.1. It showed lymph nodes with increased radiological uptake (SUVmax, 14.4) in both lung hilum and mediastinum. No significant abnormalities were seen in the head-enhanced magnetic resonance imaging (MRI). The mass was suggestive of squamous carcinoma after the puncture and evaluated as stage IIIB (cT3N2M0). After multi-disciplinary treatment (MDT) discussion, the patient was entered into neoadjuvant immunotherapy.

This patient was administered two cycles of neoadjuvant chemoimmunotherapy (paclitaxel 270 mg [156 mg/m²], carboplatin 450 mg [Area Under Curve (AUC) 4], and pembrolizumab 200 mg). Because of the recurrent abdominal pain and diarrhea after the second cycle, the patient was diagnosed with ICI-induced enterocolitis after laboratory tests and colonoscopy. The symptoms improved significantly after glucocorticoid therapy (methylprednisolone 40 mg qd x 3 days and reduced by 5 mg per 3 days until complete discontinuation). The third cycle of neoadjuvant therapy only included paclitaxel and carboplatin.

After three cycles (76 days) of neoadjuvant therapy, a CT scan showed a significant reduction in tumor and lymph node size (Figure 1(b),(d)). The patient was reevaluated as clinical stage IIIA (ycT2aN2M0), and partial response (PR) according to response evaluation criteria in solid tumors (RACIST). A radical resection surgery of RUL and complete nodal dissection (2 + 4R, 7, 9, 11, 12) was performed via video-assisted thoracic surgery (VATS). The surgery proceeded normally within 90 minutes.

On postoperative day 1 (POD 1), the patient’s temperature rose to 39.5°C, but dropped to normal after symptomatic treatment. Subsequently, his temperature had remained

![FIGURE 1](a) and (c) Computed tomography (CT) scan of the chest showed a mass lesion (a) and enlarged lymph nodes (4R,7) (c) in the anterior segment of RUL. (b) and (d) After 3 cycles of neoadjuvant therapy, CT scan showed a significant reduction of the primary foci. Abbreviations: CT, computed tomography; RUL, right upper lobe

![FIGURE 2](a) CT scan demonstrated new reticular opacities (POD 4). (b) The interstitial lung infiltrates resolved after glucocorticoid therapy (POD 8). Abbreviations: CT, computed tomography; POD, postoperative day
normal—with no abnormalities in laboratory tests (including white blood cell and procalcitonin) and chest X-ray until POD 4. In the morning POD 4, the patient suddenly suffered suffocated wheezing without apparent cause while sleeping. The blood oxygen saturation dropped to 60%–65%, with a 130–150 bpm heart rate and blood pressure of 130/70 mm Hg. A right pulmonary respiratory wet rhotic sound and clear left pulmonary breath sounds were heard on auscultation. Arterial blood gases (ABG) showed CO₂ partial pressure 24 mm Hg, O₂ partial pressure 39 mm Hg, c-Lactate 8.7 mmol/L, pCO₂(T) 24.4 mm Hg, cHCO₃⁻(P)c 14.1 mmol/L. An electrocardiogram (ECG) showed tachycardia. A bedside cardiac ultrasound showed an enlarged right heart. The physician considered pulmonary embolism (PE) and administered low-molecular heparin subcutaneously and bedside tracheal intubation. The patient’s oxygenation returned to 85%–90%.

Subsequent CT pulmonary angiography (CTPA) ruled out PE but showed new reticular opacities in both lung fields (Figure 2(a)), which indicated ICI-interstitial lung disease (ICI-ILD). The therapy was rapidly adapted to methylprednisolone (80 mg q12h × 5 days → 80 mg qd), gamma globulin (20 g qd × 5 days), tocilizumab (240 mg qd × 2 days), and empirical anti-infective therapy. The interstitial lung infiltrates resolved after glucocorticoid therapy (Figure 2(b)).

On POD 10, the patient presented with subcutaneous emphysema of the left anterior chest wall and bilateral neck (Figure 3(a),(b)). Bronchoscopy found a 5 mm hole near anastomotic stoma (Figure 3(c)). Emergency surgery was performed to repair the patient’s bronchial fistula. Abbreviations: CT, computed tomography.
was performed to repair the fistula (Figure 3(d)). The fistula was sutured and enhanced with thymus gland and peripheral adipose tissues. The patient recovered well after bronchial fistula repair and was discharged on POD 21. The tumor achieved PCR on pathological examination. Chest CT at the second (Figure 4(a)) and the fourth week (Figure 4(b)) after discharge showed no pathological abnormalities. After MDT discussion, considering the patient’s severe irAEs and favorable pathology, no further adjuvant therapy was administered postoperatively.

DISCUSSION

To our knowledge, this is the first case report of neoadjuvant chemoimmunotherapy-induced irAEs, involving ICI-enterocolitis before surgery and ICI-ILD after surgery. Additionally, the glucocorticoids and mechanical ventilation used in ICI-ILD treatment might cause bronchial stump fistulas (Figure 5).

Although ILD was relatively rare, ICI-ILD was explored in previous studies. Prior studies explored the time point of irAE appearance in advanced lung cancer patients. A population-based study among patients with NSCLC who received ICI therapy pointed out that 31.2% experienced an irAE at 3 months, and 52.5% experienced an irAE at 12 months. However, in resectable cancer patients, the surgical time points led to complications in the timing of irAE appearance. Fujita et al. reported one case of pembrolizumab-induced ILD triggered by thoracic surgery. However, in that case, the patient was misdiagnosed as advanced lung cancer instead of resectable lung cancer. Sasaki et al. reported a case of laparoscopic hepatectomy after receiving lenvatinib plus pembrolizumab and developed hypothyroidism and hypopituitarism after surgery. Regarding surgery after neoadjuvant chemoimmunotherapy, it is essential to recognize that irAEs might occur in the postoperative period.

According to the latest expert opinion, this case was diagnosed as a grade 4 (very severe) ICI-ILD. It was recommended to use mechanical ventilation, steroid therapy (2 mg/kg/day intravenous prednisolone or equivalent) and even intravenous immunoglobulins. We have implemented these treatments in compliance with the expert opinion.
Although the patient’s CT showed improvement of ILD, he developed a postoperative bronchial fistula. As most reported irAEs occurred preoperatively, experience for the management of postoperative irAEs is scarce. This case suggests that unexpected complications may occur, such as bronchial fistula. In contrast, for irAE presenting in the perioperative period, management measures may result in complications unexpected by clinicians, such as bronchial fistula. Moreover, preoperative chemotherapy may also increase the risk of bronchial fistula.

In this case, multidisciplinary cooperation was essential for the patient to turn out well in such a complex clinical situation. This case report suggests a series of possible consequences of perioperative irAEs that physicians and surgeons should be aware of when using neoadjuvant chemoimmunotherapy for resectable NSCLC patients.

In conclusion, this is a neoadjuvant chemoimmunotherapy case, with irAEs involving multiple organs, multiple time points, and series reactions. Clinicians should be on high alert for signs of irAE in neoadjuvant chemoimmunotherapy patients, both pre- and post-operatively. The multidisciplinary management is needed in a timely manner.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Written informed consent was obtained from the patient for participation in this case report.

CONSENT TO PUBLISH
The written informed consent to publish this information was obtained from the study participant.

AVAILABILITY OF DATA AND MATERIALS
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS
The authors of this manuscript declare no competing of interests.

AUTHOR CONTRIBUTIONS
Hongsheng Liu evaluated the patient clinically, operated the patient (main surgeon), and read and revised the manuscript. Yuan Xu evaluated the patient clinically, helped to operate the patient (co-surgeon), prepared the first draft, and revised the manuscript. Yingzhi Qin, Dongjie Ma evaluated the patient clinically, helped to operate the patient (co-surgeon). Mengzhao Wang, Juhong Shi, Yun Long and Bo Tang participated the multidisciplinary management. Xiaohong Lyu wrote the manuscript. All the authors have read and approved the manuscript.

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