Received: 11 June 2022 | Accepted: 16 June 2022

DOI: 10.1111/1759-7714.14567

ORIGINAL ARTICLE

WILEY

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

Yuan Xu[1] | Xiaohong Lyu[1,2] | Yingzhi Qin[1] | Dongjie Ma[1] | Mengzhao Wang[3] | Juhong Shi[3] | Yun Long[4] | Bo Tang[4] | Hongsheng Liu[1]

[1]Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China

[2]Eight-Year Program of Clinical Medicine, Peking Union Medical College, Beijing, China

[3]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

[4]Department of Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Hongsheng Liu, Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China.
Email: hongshengliu16@163.com

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.[1] Recently, for resectable NSCLC, neoadjuvant chemoimmunotherapy, including ICI, chemotherapy, and surgery, has attracted the lung cancer treatment field.[2] Forde et al.[3] 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.[4] 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,[5] the endocrine glands,[6,7] the gastrointestinal tract,[8] the nervous system,[9] the lungs,[10] the kidney,[11] the heart,[12] the eyes,[13] 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

Yuan Xu and Xiaohong Lyu contributed equally to this work and are co-first authors.

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 × 5.6 × 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/m^2], 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 × 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).[14] 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

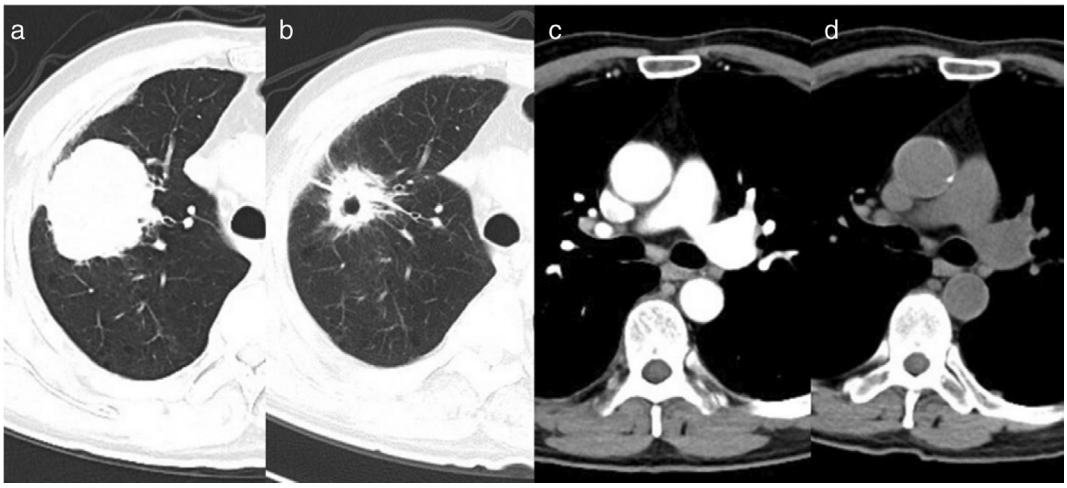

FIGURE 1 (a) and (c) Computed tomography (CT) scan of the chest showed a mass lesion (a) and enlarged lymph nodes (4R,7) (c) in the anterior segment of RUL. (b) and (d) After 3 cycles of neoadjuvant therapy, CT scan showed a significant reduction of the primary foci. Abbreviations: CT, computed tomography;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

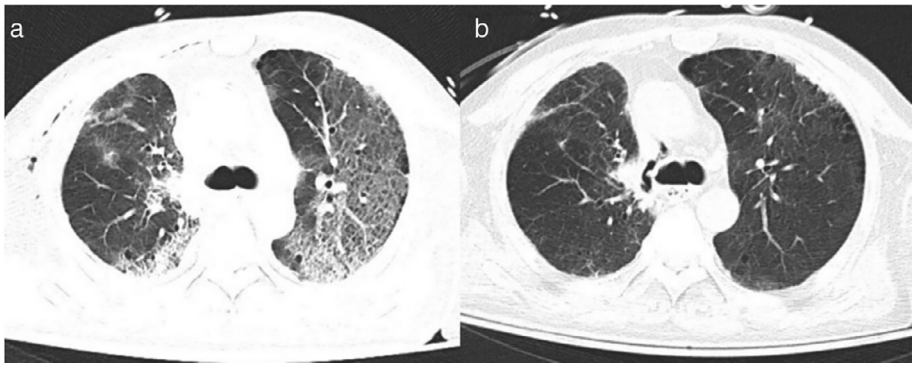

FIGURE 2 (a) CT scan demonstrated new reticular opacities (POD 4). (b) The interstitial lung infiltrates resolved after glucocorticoid therapy (POD 8). Abbreviations: CT, computed tomography; POD, postoperative day

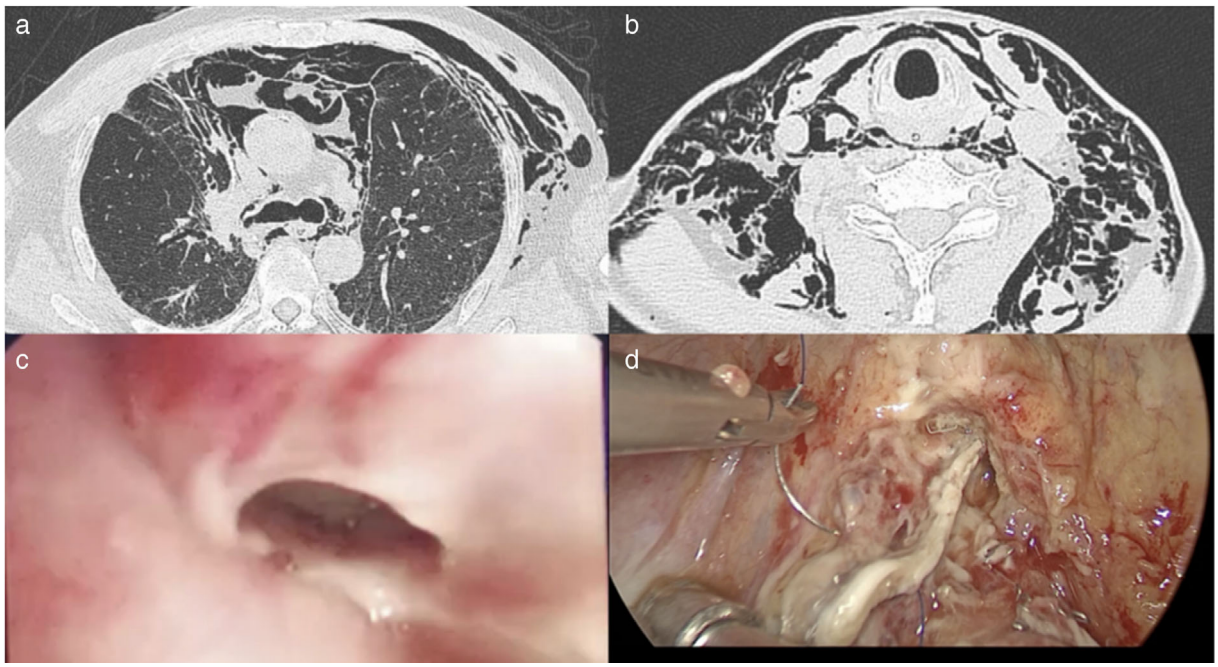

FIGURE 3 (a) and (b) Subcutaneous emphysema in CT. (c) Bronchoscopy found a 5 mm hole near anastomotic stoma. (d) Emergency surgery was performed to repair the patient's bronchial fistula. Abbreviations: CT, computed tomography

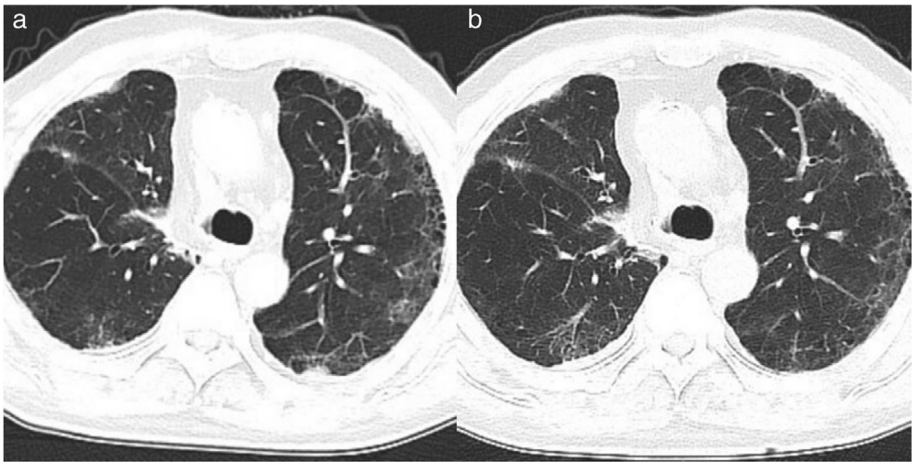

FIGURE 4 (a) Chest CT at the second week after discharge. (b) Chest CT at the fourth week after discharge. Abbreviations: CT, computed tomography

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 CO_2 partial pressure 24 mm Hg, O_2 partial pressure 39 mm Hg, cLactate 8.7 mmol/L, pCO_2(T) 24.4 mm Hg, $cHCO_3^-$(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

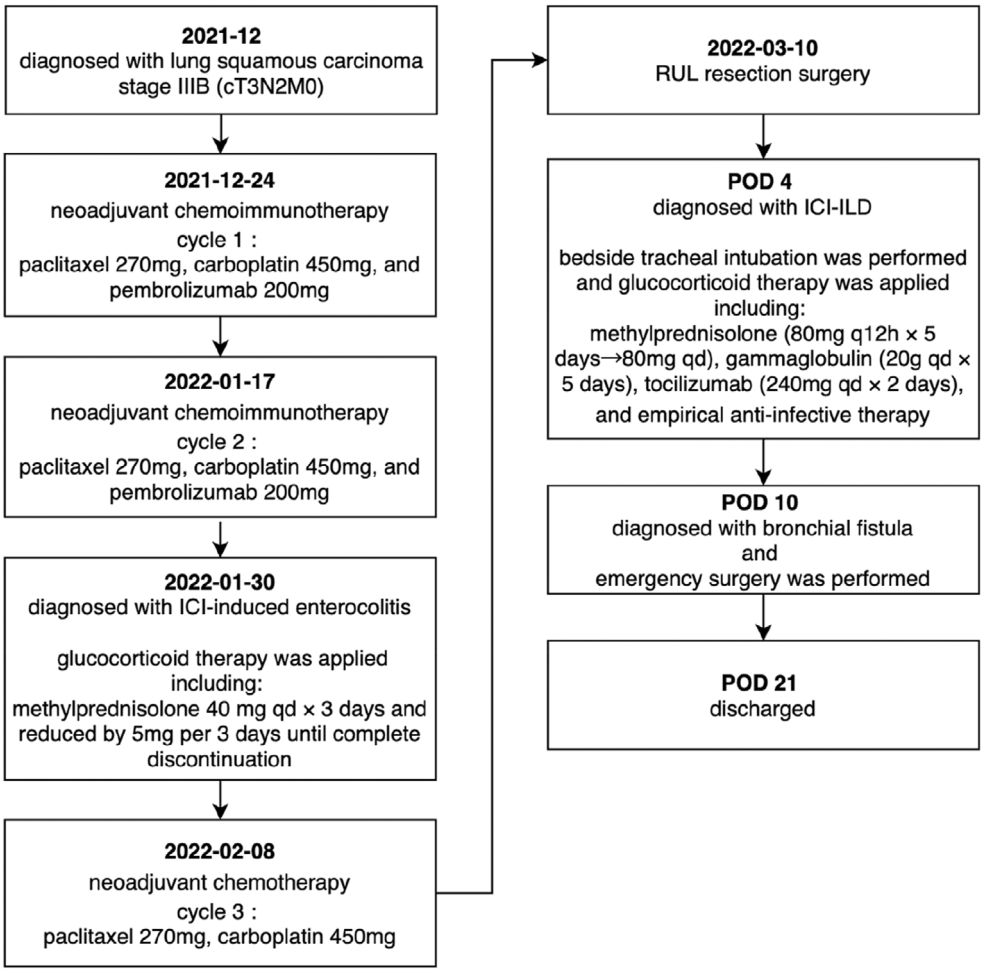

FIGURE 5 Timeline of the case. Abbreviation: ICI, immune checkpoint inhibitors, RUL, right upper lobe; ILD, interstitial lung disease; POD, postoperative day

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).

This case report involved multi-organ and multi-time point irAEs in neoadjuvant chemoimmunotherapy. IrAEs can affect multiple systems, as reported by various studies.[15] Although ILD was relatively rare, ICI-ILD was explored in previous studies.[16–20] 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.[21] However, in resectable cancer patients, the surgical time points led to complications in the timing of irAE appearance. Fujita et al.[22] 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.[23] 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.[24] 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 occured preoperatively, experirence 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.[25] Moreover, preoperative chemotherapy may also increase the risk of bronchial fistula.[26,27]

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.

ACKNOWLEDGMENTS

We all express our gratitude to the patient who kindly gave consent for this case to be presented in this paper.

ORCID

Hongsheng Liu https://orcid.org/0000-0003-4188-9638

REFERENCES

1. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
2. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med. 2018;378(21):1976–86.
3. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med. 2022;386:1973–85.
4. Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(11):1413–22.
5. Keiser MF, Patel AB, Altan M. Cutaneous toxicities in lung cancer patients on immune checkpoint inhibitor therapy. Clin Lung Cancer. 2021;22(3):195–200 e1.
6. Iyer PC, Cabanillas ME, Waguespack SG, Hu MI, Thosani S, Lavis VR, et al. Immune-related thyroiditis with immune checkpoint inhibitors. Thyroid. 2018;28(10):1243–51.
7. Iqbal I, Khan MAA, Ullah W, Nabwani D. Nivolumab-induced adrenalitis. BMJ Case Rep. 2019;12:11.
8. Bergqvist V, Hertervig E, Gedeon P, Kopljar M, Griph H, Kinhult S, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. Cancer Immunol Immunother. 2017;66(5):581–92.
9. Mikami T, Liaw B, Asada M, Niimura T, Zamami Y, Green-LaRoche D, et al. Neuroimmunological adverse events associated with immune checkpoint inhibitor: a retrospective, pharmacovigilance study using FAERS database. J Neurooncol. 2021;152(1):135–44.
10. Xu C, Chen YP, du XJ, Liu JQ, Huang CL, Chen L, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018;363:k4226.
11. Franzin R, Netti GS, Spadaccino F, Porta C, Gesualdo L, Stallone G, et al. The use of immune checkpoint inhibitors in oncology and the occurrence of AKI: where do we stand? Front Immunol. 2020;11:574271.
12. Slawinski G et al. Immune checkpoint inhibitors and cardiac toxicity in patients treated for non-small lung cancer: a review. Int J Mol Sci. 2020;21(19):7195.
13. Alba-Linero C, Alba E. Ocular side effects of checkpoint inhibitors. Surv Ophthalmol. 2021;66(6):951–9.
14. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205–16.
15. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev. 2016;44:51–60.
16. Nakahama K et al. Association between imaging findings of airway obstruction adjacent to lung tumors and the onset of interstitial lung disease after nivolumab. In Vivo. 2018;32(4):887–91.
17. Sugano T, Seike M, Saito Y, Kashiwada T, Terasaki Y, Takano N, et al. Immune checkpoint inhibitor-associated interstitial lung diseases correlate with better prognosis in patients with advanced non-small-cell lung cancer. Thorac Cancer. 2020;11(4):1052–60.
18. Yamagata A, Yokoyama T, Fukuda Y, Ishida T. Impact of interstitial lung disease associated with immune checkpoint inhibitors on prognosis in patients with non-small-cell lung cancer. Cancer Chemother Pharmacol. 2021;87(2):251–8.
19. Kato T, Masuda N, Nakanishi Y, Takahashi M, Hida T, Sakai H, et al. Nivolumab-induced interstitial lung disease analysis of two phase II

studies patients with recurrent or advanced non-small-cell lung cancer. Lung Cancer. 2017;104:111–8.
20. Christy J, Rafae A, Kandah E, Kunadi A. Early presentation of pembrolizumab-associated pneumonitis. BMJ Case Rep. 2021;14(7): e242493.
21. Cathcart-Rake EJ, Sangaralingham LR, Henk HJ, Shah ND, Riaz IB, Mansfield AS. A population-based study of immunotherapy-related toxicities in lung cancer. Clin Lung Cancer. 2020;21(5): 421–427 e2.
22. Fujita T, Hayama N, Kuroki T, Shiraishi Y, Amano H, Nakamura M, et al. Pembrolizumab-induced interstitial lung disease following thoracic surgery in a patient with non-small cell lung cancer. Thorac Cancer. 2019;10(11):2179–82.
23. Sasaki K, Kobayashi S, Kudo M, Sugimoto M, Takahashi S, Nakamura Y, et al. Hypothyroidism and hypopituitarism as immune-related adverse events due to lenvatinib plus pembrolizumab therapy in the immediate postoperative period after laparoscopic hepatectomy for liver metastases from gastric cancer: a case report. Surg Case Rep. 2021;7(1):267.
24. Conte P, Ascierto PA, Patelli G, Danesi R, Vanzulli A, Sandomenico F, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. ESMO Open. 2022;7(2):100404.
25. Cerfolio RJ. The incidence, etiology, and prevention of postresectional bronchopleural fistula. Semin Thorac Cardiovasc Surg. 2001;13(1):3–7.
26. Sonobe M, Nakagawa M, Ichinose M, Ikegami N, Nagasawa M, Shindo T. Analysis of risk factors in bronchopleural fistula after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg. 2000;18(5):519–23.
27. Okuda M, Go T, Yokomise H. Risk factor of bronchopleural fistula after general thoracic surgery: review article. Gen Thorac Cardiovasc Surg. 2017;65(12):679–85.

How to cite this article: Xu Y, Lyu X, Qin Y, Ma D, Wang M, Shi J, et al. Multi-organs perioperative immune-related adverse events and postoperative bronchial anastomotic fistula in a patient receiving neoadjuvant immunotherapy with NSCLC. Thorac Cancer. 2022;13(16):2340–5. https://doi.org/10.1111/1759-7714.14567