Two cases of trastuzumab deruxtecan-induced interstitial lung disease in advanced breast cancer

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INTRODUCTION

An antibody–drug conjugate (ADC) consists of a monoclonal antibody that targets cancer cells linked to a compound that blocks topoisomerases. ADCs are being developed as next-generation chemotherapeutic agents because they selectively and effectively kill tumour cells and cause less systemic toxicity. Trastuzumab deruxtecan (T-DXd) is an ADC used for anti-human epidermal growth factor receptor 2 (HER2)-positive breast and gastric cancers. Here, we report two cases of interstitial lung disease (ILD) induced by T-DXd. To the best of our knowledge, this is the first such report in clinical practice, making it highly significant.

CASE REPORT

Case 1

A 57-year-old Japanese woman presented to our hospital with dyspnoea and fever. She did not have any smoking history or respiratory disorders. She suffered post-operative recurrence and had advanced breast cancer for 15 years with multiple lung and lymph node metastases. She received 4 cycles of T-DXd as 11th-line chemotherapy with a good therapeutic response. On examination, her temperature, heart rate and blood pressure were 38.5°C, 115 beats per minute and 140/72 mmHg, respectively, with a respiratory rate of 24 per minute and oxygen saturation of 84% on room air. On chest auscultation, there were fine crackles in the lungs. Laboratory studies revealed elevated C-reactive protein (14.9 mg/dl), Krebs von den Lungen-6 (KL-6) (1486 U/ml) and Surfactant protein D (SP-D) (641 ng/ml) levels. β-D glucan, Aspergillus antigen and cytomegalovirus antigenaemia were all negative.

Chest computed tomography (CT) showed diffuse consolidation, reticular shadow and metastatic shrinking nodules in both the lung fields (Figure 1A,B). The consolidation and reticular shadow had a mosaic pattern. We diagnosed ILD, which showed a non-specific interstitial pneumonia pattern on CT. The CT prior to T-DXd chemotherapy showed multiple metastatic nodules in the lung but no interstitial lung abnormality.
ILD induced by T-DXd was considered as a differential diagnosis. The severity of ILD was grade 4 as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The patient was administered oxygen therapy, corticosteroid therapy and pulse methylprednisolone; chemotherapy was discontinued. After 1 month of initiating treatment,

**FIGURE 1** Case 1. (A, B) Computed tomography (CT) images on admission illustrating diffusely distributed consolidation, reticular shadow and shrinking metastatic nodules in both the lung fields. (C, D) CT images obtained 1 month after initiating corticosteroid therapy. Interstitial lung disease remained widespread, improved poorly and was complicated with pneumomediastinum.

**FIGURE 2** Case 2. (A, B) Computed tomography (CT) images on admission showing ground-glass opacity predominantly in the left lung, and bilateral pleural effusion and metastatic nodules in the right upper lobe. Patchy consolidation and interlobular septum thickening with ground-glass opacity were observed. (C, D) CT images obtained 3 weeks after initiating corticosteroid therapy. Interstitial lung disease improved; however, mild fibrosis persisted.
ILD remained widespread and poorly improved. This condition was complicated by pneumomediastinum, an adverse effect of steroid therapy (Figure 1C,D). Even with long-term steroid therapy, ILD was difficult to improve and respiratory failure persisted. Best supportive care was provided, and the patient died 6 months after the ILD complication.

Case 2

A 72-year-old Japanese woman presented to our hospital with dyspnoea. She was a former 20 pack-year smoker until the onset of breast cancer. She suffered post-operative recurrence and had advanced breast cancer for 9 years. She had moderate cancerous pleural effusion and had recently received 3 cycles of T-DXd as seventh-line chemotherapy at our hospital.

On examination, her temperature, heart rate and blood pressure were 37.0°C, 117 beats per minute and 110/82 mmHg, respectively, with a respiratory rate of 20 breaths per minute; her oxygen saturation was 87% on room air. On chest auscultation, there were diminished breath sounds and fine crackles in the lung were heard.

Laboratory studies revealed hypoalbuminaemia (2.9 g/dl) and slight elevation of KL-6 (651 U/ml) and SP-D (128 ng/ml) levels. None of the findings suggested infectious disease, and brain natriuretic peptide level was not elevated.

CT prior to T-DXd chemotherapy showed bilateral pleural effusion and a metastatic nodule in the right upper lobe but no interstitial lung abnormality. The CT at admission showed ground-glass opacity predominantly in the left lung, bilateral pleural effusion and metastatic nodules in the right upper lobe (Figure 2A,B). There was patchy consolidation and thickening of the interlobular septum with ground-glass opacity. The pleural effusion remained the same as that 2 months ago. She underwent bronchoscopy and a lymphocyte increase (50% of all cells) was found in the bronchoalveolar lavage of the left middle lobe. We diagnosed ILD, which showed a non-specific interstitial pneumonia pattern on CT, induced by T-DXd. The severity of ILD was grade 3 as defined by CTCAE Version 5.0. She was given oxygen and corticosteroid therapy, including pulse methylprednisolone. Three weeks after treatment initiation, ILD had improved; however, mild fibrosis persisted, and she was weaned from oxygen therapy (Figure 2C,D). ILD was alleviated by long-term corticosteroid therapy; however, her performance status weakened due to steroid therapy and the progression of breast cancer. She was subsequently transferred to a palliative care centre.

DISCUSSION

To the best of our knowledge, our cases are the first reports of T-DXd-induced ILD in advanced breast cancer patients in a real-world clinical setting. The DESTINY Breast study reported that T-DXd has a beneficial therapeutic effect with a response rate of 60.9% and response duration of nearly 15 months for patients who have received treatment with TDM-1 for HER2-positive advanced breast cancer. Conversely, the results also showed that patients receiving T-DXd may have an increased risk of ILD. ILD occurred in 13.6% of participants and most ILD cases were mild or moderate in severity. Similarly, in a study on the effectiveness of T-DXd for advanced gastric cancer, ILD was reported in 9.6% of the patients. The frequency of ILD in these two studies was remarkably higher than that in previous studies. Powell et al. analysed these two studies and found that the only potential risk factor associated with treatment-related ILD in both univariate and multivariate analyses was residence in Japan. This result is consistent with our cases, and it is a known fact that Japanese patients have more frequent chemotherapy-induced ILD than other populations.

One of the pharmaceutical features of T-DXd is ADC. The structure of ADC contributes to its therapeutic effect. Trastuzumab emtansine is an ADC for HER2-positive advanced breast cancer; however, the frequency of trastuzumab-induced ILD is only 0.5%, which is lower than that of T-DXd-induced ILD. This result suggests that ILD caused by T-DXd is caused by deruxtecan, which is a part of T-DXd, not trastuzumab. Deruxtecan is a camptothecin derivative with topoisomerase I inhibitory action. It exerts an inhibitory action on tumour growth through DNA damage and by causing cancer cell apoptosis. Camptothecin is a known cause of ILD and is banned for use in patients with ILD. ILD induced by T-DXd can be attributed to deruxtecan. Conversely, Kumagai et al. reported that high-dose deruxtecan did not cause ILD in a study with monkeys. They suggested that target-independent uptake of T-DXd by lung macrophages may be involved in T-DXd-induced ILD. However, detailed pathogenesis of ILD remains unclear.

Kudoh et al. reported a high frequency of drug-induced ILD and some risk factors for ILD in Japanese patients with lung cancer. One of the risk factors is reduced normal lung function on CT. In our cases, pulmonary function tests were not performed before chemotherapy, and the level of pulmonary function was unclear. Moreover, the cases did not have interstitial lung abnormalities. However, they had reduced normal lung due to cancerous pleuritis and multiple intrapulmonary metastases, which might have been involved in the development of ILD.

The severity of ILD in our cases was grades 3 and 4. Case 1 in particular presented very severe ILD with diffuse ground-glass opacity. Although the original ILD severity and treatment response were different in the two cases, both the cases survived ILD. Their performance status deteriorated due to long-term corticosteroid therapy and breast cancer disease progression. Subsequently, these patients were unable to continue breast cancer chemotherapy.

T-DXd is a useful drug for patients with advanced breast cancer. However, the continuation of cancer treatment is difficult when ILD develops, and drug-induced ILD can greatly affect patient prognosis. In the future, T-DXd may be indicated not only for breast and gastric cancer, but also
for various HER2-positive cancers. Therefore, it is important to detect and treat ILD at an early stage.

CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTION
All authors have revised, approved and agreed to all aspects of the work. They have ensured that disagreements related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT
The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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REFERENCES
1. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610–21. https://doi.org/10.1056/NEJMoa1914510
2. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419–30. https://doi.org/10.1056/NEJMoa2004413
3. Powell CA, Camidge DR, Modi S, Qin A, Taitt C, Lee C, et al. 289P risk factors for interstitial lung disease in patients treated with trastuzumab deruxtecan from two interventional studies. Ann Oncol. 2020;31:S357–8. https://doi.org/10.1007/s10549-020-05754-8
4. Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med. 2008;177:1348–57. https://doi.org/10.1164/rccm.200710-1501OC
5. Hackshaw MD, Danysh HE, Singh J, Ritchey ME, Lader N, Taitt C, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2020;183:23–39. https://doi.org/10.1007/s10549-020-05754-8
6. Kumagai K, Aida T, Tsuchiya Y, Kishino Y, Kai K, Mori K. Interstitial pneumonitis related to trastuzumab deruxtecan, a human epidermal growth factor receptor 2-targeting Ab-drug conjugate, in monkeys. Cancer Sci. 2020;111:4636–45. https://doi.org/10.1111/cas.14686

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