



Case Report

A Reversible Case of Advanced Interstitial Lung Disease in a Patient with HER2 Low Metastatic Breast Cancer Treated with Trastuzumab Deruxtecan

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Abstract

This study presents a case of reversible grade 4 Interstitial Lung Disease (ILD) triggered by Trastuzumab Deruxtecan (T-DXd) in a patient with HER2 low metastatic breast cancer. While T-DXd has shown efficacy in diverse HER2-expressing cancers, it can lead to ILD, ranging from mild to severe. The patient's ILD was initially managed with corticosteroids and immunosuppressants, but with limited success. A unique approach involving the antifibrotic agent Nintedanib was employed due to persistent symptoms and worsening radiographic changes. This led to significant clinical and radiological improvements, presenting an innovative method differing from conventional ILD treatment strategies. The case underscores the challenges posed by T-DXd-induced ILD and suggests potential benefits of antifibrotic therapy, meriting further investigation. This report contributes to understanding and managing ILD resulting from T-DXd treatment, offering insights into a previously unexplored therapeutic avenue.

Introduction

Antibody-drug conjugates (ADCs) are a class of targeted cancer therapies that combine the specificity of monoclonal antibodies with the potency of cytotoxic drugs. One such ADC is trastuzumab deruxtecan (T-DXd), which has been approved by the FDA for the treatment of HER2-positive breast cancer in 2022 [1,2]. Owing to its unique pharmaceutical properties including topoisomerase I inhibitor payload with a high drug-to-antibody

ratio of 8 and a cleavable linker that can induce a bystander effect, T-DXd has demonstrated activity across a broad range of HER2-expressing cancers, including striking efficacy in breast cancers with low levels of HER2 expression, HER2+ gastric cancers and HER2 mutated non-small cell lung cancer, making it one of the most active and versatile HER2 targeting therapies available in the clinic today [2,3]. While the most common toxicities of T-DXd are low-grade and manageable nausea, GI dysfunction, and bone

marrow suppression, it is critical to highlight the risk of interstitial lung disease (ILD) as an important toxicity of this new-generation ADC. ILD from T-DXd can range from asymptomatic grade 1 findings on radiographic images to symptomatic pneumonitis and also includes rare but fatal cases of ILD. In a pooled analysis of heavily treated patients, the incidence of T-DXd-related ILD/pneumonitis was approximately 15% [4] across a variety of cancer types and dose ranges. While the pathophysiology of the lung toxicity is yet unclear, having a heightened awareness of this risk and implementation of routine monitoring of respiratory symptoms and intermittent chest computed tomography (CT) scans with prompt cessation of therapy at the first signs of toxicity and institution of treatment with steroids, the rates of grade 5 ILD events are now typically less than 1% in modern breast trials [5]. Here, we report a case of grade 4 ILD induced by T-DXd that was initially treated with a combination of corticosteroids (CS) and immunosuppressants without significant improvement. Based on a multidisciplinary review, it was decided to add an antifibrotic agent given the presence of concomitant pulmonary parenchymal distortion evident on chest radiographs taken throughout the course of the disease. To the best of our knowledge, this is the first such report in clinical practice, making it highly significant with insights to be shared with the medical community treating patients with this new generation ADC.

Case Presentation

A previously healthy 38-year-old woman, diagnosed with invasive breast carcinoma (ER 70%, PR 70%, HER2 1+, Ki67 30%) underwent four cycles of neoadjuvant chemotherapy using doxorubicin and cyclophosphamide dose-dense, followed by weekly paclitaxel for 12 weeks, right mastectomy, and axillary lymph node dissection. Post-surgery pathology reported residual non-special type invasive carcinoma with clear margins and 9/19 axillary lymph node metastases. She received adjuvant intensity-modulated radiation therapy (IMRT) in the right breast, ipsilateral axilla, and supraclavicular fossa. However, she presented with disease recurrence in the T3 vertebral body five months post-surgery. Treatment involved ablative radiation and systemic treatment with Letrozole, Ribociclib, and Zoladex. Over the next 15 months, she developed neurological symptoms, with imaging revealing a frontal lobe nodular lesion and leptomeningeal disease, suggesting leptomeningeal dissemination. Treatment involved stereotactic radiosurgery on the frontal lesion, systemic treatment with Carboplatin, Paclitaxel, Bevacizumab, and intrathecal Methotrexate (MTX) - discontinued after three months due to neuroinfection. Her condition deteriorated significantly, requiring high doses of CS following a leptomeningeal carcinomatosis diagnosis. In the face of disease progression, treatment with T-DXd was initiated considering her low HER2 expression. This led to significant clinical and functional improvement post

the first cycle. Thirteen days after the second infusion of T-DXd, this patient presented to the hospital complaining of rhinorrhea, shortness of breath, dry cough, and tachycardia that started three days before admission. On physical examination, her temperature, heart rate, and blood pressure were 36.5°C, 110 beats per minute, and 130/65 mmHg, respectively, with a respiratory rate of 25 per minute and oxygen saturation (SpO₂) of 84% on room air. Pulmonary auscultation showed crackles predominantly in the left hemithorax. Due to the significant respiratory impairment and the chronological correlation with T-DXd infusion, the hypothesis of pneumonitis caused by this medication was raised, and the Pulmonology team was contacted for collaborative management of the case with the Oncology team. A 12-lead electrocardiogram demonstrated sinus tachycardia. After stabilization of SpO₂ (nasal cannula oxygen at 3 L/min), the patient underwent a chest CT. It ruled out thromboembolism and revealed the appearance of ground glass opacities with a predominance of the left lung, especially in the upper left lobe. The baseline CT had no significant abnormalities in the lungs and was remarkable only for the presence of a right diaphragm paralysis, restricting the right lung expansion and promoting a subtle mediastinum shift to the left (Figure 1A and 1B). These recently identified opacities on the chest CT scan appeared to exhibit a greater correlation with inflammatory manifestations; however, it is imperative to rule out any infectious etiologies, particularly viral pneumonia, atypical pneumonia, and pneumocystosis. Considering this, antibiotic therapy with cefepime and azithromycin was initiated upon admission, along with CS therapy using methylprednisolone 1 mg/kg/day, and an urgent bronchoscopy was requested. Laboratory tests revealed 8.860 cells/μl leukocytes, 10,3 g/dl hemoglobin, normal platelets count, and elevated C-reactive protein (90,0 mg/l). Serum electrolytes, renal function, troponin, NT-proBNP (< 10 pg/ml), procalcitonin, aspergillus antigen, cytomegalovirus PCR, and echocardiogram were normal. A bronchoscopy was performed, and the bronchoalveolar lavage fluid analysis ruled out an infection. The patient was referred to the intensive care unit and started on a high-flow nasal cannula (HFNC) with a flow rate of 60 L/min and FiO₂ (fraction of inspired oxygen) of 80%, due to worsening hypoxemia after bronchoscopy. Three daily periods of 1-hour non-invasive ventilation were also initiated. ILD induced by T-DXd (grade 4 by the Common Terminology Criteria for Adverse Events Version 5.0) was considered as the main diagnosis after excluding infectious causes. On the second day of hospitalization, pulse therapy with methylprednisolone (0,5 g/day) was started for 3 days followed by 1 mg/kg/day of maintenance. After 7 days of CS therapy, the patient did not show improvement in SpO₂, and the decision by multidisciplinary team was made to initiate infliximab, based on the recommendation from the DESTINY-Breast01 Investigators [2]. Infliximab, a tumor necrosis factor (TNF)-alpha inhibitor, works by binding to TNF and neutralizing

its pulmonary inflammatory effects. Despite these measures, there was no decrease in HFNC parameters 13 days after the infliximab dose and the chest X-ray showed worsening deviation of the trachea to the left side (Figure 2), suggesting progression with pulmonary fibrosis in the left lung. Since the patient could not be transported for a chest CT scan, the team opted to initiate an antifibrotic medication, an intracellular triple tyrosine kinase inhibitor, Nintedanib 150 mg twice daily. The first reduction in HFNC occurred 4 days after starting the antifibrotic medication, with a flow rate of 50 L/min and FiO₂ of 60% to achieve a SpO₂ of 92% on room air. On the 14th day after antifibrotic treatment, the flow rate was reduced to 40 L/min and FiO₂ to 40% to achieve the same SpO₂. On the 20th day, the patient was using a nasal oxygen cannula at 2.0 L/min to maintain a SpO₂ of 92% on room air, which remained stable. A chest CT scan performed 21 days post antifibrotic therapy initiation (Figure 1C) showed left lung volume reduction in parallel to signs of a parenchymal reparative process with more consolidation opacities, including peribulbar configurations that suggested organizing pneumonia, and more marked signs of interstitial distortion characterized by bronchial dilation with irregular walls, all findings consistent with fibrosis. Along with those findings, a pneumomediastinum occurred in the interface with the upper left lung, associated with interstitial emphysema, secondary to local barotrauma. As a mechanism of fibrosis retraction, the mediastinum showed a more marked shift to the left, confirming the suspicion in the bedside chest X-ray. After 2 months of initiating treatment, a final chest CT scan demonstrated a small reduction in the left parenchymal involvement, primarily attributed to ground glass opacities, with the remaining abnormalities compatible with parenchymal distortion. Additionally, the pneumomediastinum had reduced significantly (Figure 1D). She was discharged after 65 days still requiring supplemental oxygen via nasal cannula at 2.0 L/min, undergoing CS tapering with 8 mg of dexamethasone per day, and continuing Nintedanib, with partial resolution of symptoms and a moderate improvement of the radiological abnormalities.

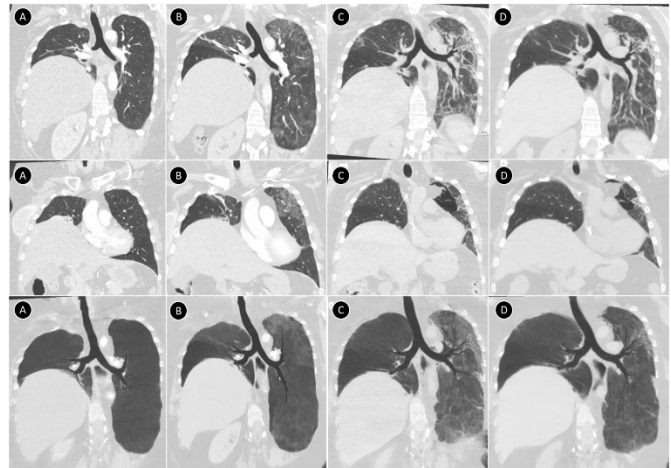


Figure 1: Images are CT scans in four different periods of time (A to D) and divided into three different coronal oblique planes arranged in columns (upper, middle, and inferior images). The upper and middle images in each period are coronal oblique planes that show the lungs in a more central and a more anterior position, respectively. The inferior images are coronal obliques with minimum intensity projection (Minip) which is intended to better depict the airways. (A) The images are the baseline exam, which is remarkable only for the right diaphragm elevation due to paralysis, promoting some restrictive atelectasis over the right lung and a slight shift of the mediastinum to the left side. (B) The images are the first CT scan after two cycles of Trastuzumab Deruxtecan, showing lung compromise of the lungs with ground glass opacities, with a predominance of the left lung that were compatible after clinical correlation with drug pneumonitis. Besides, in the inferior image is well demonstrated a subtle dilation of the airways in the left lung due to inflammatory impairment and a small increase in the mediastinum shift to the left, which was attributed partially to the right lower lobe and middle lobe hyperinflation (valve obstructive mechanism due to the diaphragm paralysis) but also due to a potential early parenchymal distortion in the left lung. (C) CT control images after the therapeutics (including antifibrotic and

corticosteroid therapies). In the upper image is demonstrated a left lung volume reduction in parallel to signs of parenchyma reparative process, with more consolidative opacities, including perilobular configurations that suggest organizing pneumonia, and more marked signs of interstitial distortion characterized by reticular opacities and bronchial dilation with irregular walls along to the volume reduction. In the inferior image, the signs of distortion are better depicted, with Minip serving as a useful tool for this specific evaluation in the reparative phase. In the middle image, a pneumomediastinum occurred in the interface with the upper left lung, associated with interstitial emphysema (not demonstrated) and a fat pad from the prevascular compartment protruding into it, indicating barotrauma in the airways and a retractile mechanism from the interstitial lung fibrosis. In the middle image, it is also seen that the heart is more dislocated to the left and rotated superiorly. (D) The images are the final CT control, demonstrating a little reduction in the left lung impairment, mostly at the cost of the ground glass opacities, remaining the other abnormalities compatible with parenchymal distortion. In the middle image, the pneumomediastinum had a significant reduction.

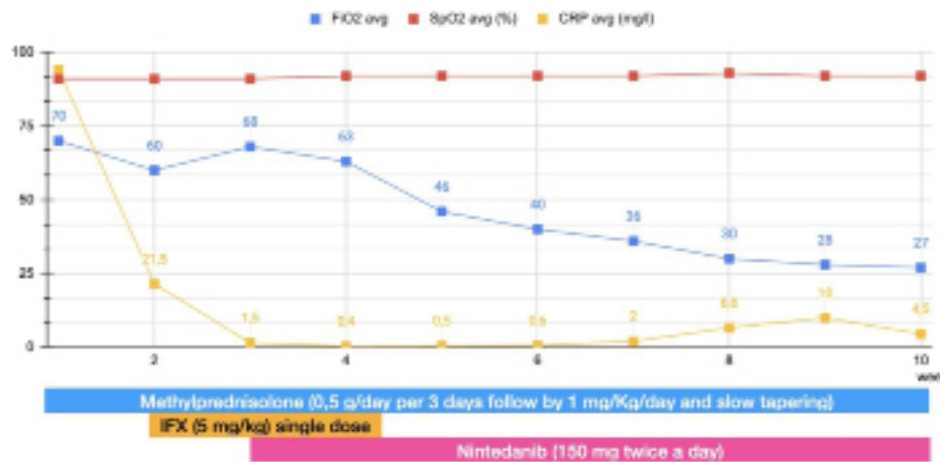


Figure 2: Clinical course using SpO2, FiO2, CPR parameters and therapeutic interventions over time.

SpO2: oxygen saturation; **FiO2:** fraction of inspired oxygen; **CPR:** c-reactive protein; **IFX:** infliximab

Discussion

In the case of suspected ILD related to T-DXd, there are now widely available guidelines to help clinicians in the early recognition and prompt intervention of this important and potentially serious toxicity. It is generally recommended that the drug should be interrupted while investigations are pursued to work up alternate etiologies. Steroids should be initiated promptly, even for asymptomatic cases to expedite the resolution of radiographic findings to allow the potential for drug rechallenge. There is no role for T-DXd rechallenge in cases of grade > 1 toxicity. Although the pathophysiology underlying TDXd-related ILD is yet elusive, there are two leading hypotheses to explain the histological and radiological findings. The first mechanism involves an allergic reaction, which results in histopathological patterns that are more responsive to CS (e.g., organizing pneumonia, nonspecific interstitial pneumonia), typically observed in grades 1 and 2 ILDs. The second mechanism, direct cytotoxicity, manifests histologically as diffuse alveolar damage (DAD), which is the histological hallmark of acute respiratory distress syndrome (ARDS) and is characterized in its exudative phase most commonly by diffuse or

patchy ground-glass or consolidation opacities on CT scans, while in its fibrotic phase, there is usually a reduction in consolidations with variable persistence of ground glass, along with the appearance of reticulation and traction bronchiectasis [6]. DAD is seen in more advanced stages of toxicity (grade 3/4) and generally exhibits reduced responsiveness to CS [5]. The pathophysiology of DAD involves a cascade of events including the activation of pro-inflammatory cytokines, infiltration of immune cells such as neutrophils and macrophages, and dysregulated coagulation pathways (exudative phase). This orchestrated response results in extensive hyaline membrane formation, fibroblast proliferation (organization phase), and ultimately, fibrosis, which compromises the gas exchange capacity of the lungs (resolution or fibrotic phase). Other histologic patterns may be encountered in patients with DAD, such as acute eosinophilic pneumonia and acute fibrinous and organizing pneumonia [7,8]. Antifibrotic drugs were initially studied and subsequently used for idiopathic pulmonary fibrosis (IPF), the most common and poorest prognostic idiopathic interstitial pneumonia among fibrotic ILD. The medical therapies currently approved for IPF are Nintedanib and pirfenidone.

Nintedanib inhibits inflammation and fibrosis by blocking several tyrosine kinase receptors, including those for platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor [9]. The primary antifibrotic effect of pirfenidone is the down-regulation of transforming growth factor-beta [10]. Over time, the mechanism of these medications has gained interest in other pathologies beyond IPF, as they share pathophysiological pathways with conditions such as the subacute phase of radiation pneumonitis [11] and acute SARS-CoV-2 infection [12]. It is also noted the potential of these drugs to prevent acute exacerbations of fibrotic diseases, which are moments described as a potential picture of when DAD occurs [13]. In the case of our patient, we considered her initial presentation to be consistent with an inflammatory phase as is described for grade 3 and 4 ILD, exhibiting DAD as the primary histological component, which is traditionally managed with anti-inflammatory therapies such as CS and infliximab as was done during the initial weeks of her treatment. However, it is essential to consider the introduction of antifibrotic therapy in refractory cases or those with radiological findings indicative of pulmonary parenchymal disorganization (e.g., traction bronchiectasis or volume reduction) as was manifest in our patient. After several weeks of Nintedanib, she eventually had clinical improvement and could leave the hospital 2 months after the initial presentation. Although this case resulted in a successful recovery from treatment-related ILD, there are several important points to consider and discuss. Foremost in this case, it is not possible to precisely establish a causal relationship between the administration of the antifibrotic agent and the clinical improvement observed in the patient, precluding the possibility of a delayed response to CS or infliximab. Secondly, there are no clinical studies supporting the use of antifibrotic agents during the reparative phase of DAD, with the present application being solely based on experiences derived from other pathologies exhibiting similar histological patterns. Lastly, the literature lacks descriptions of analogous cases. Despite these limitations, the management and positive outcome in this case are worthy of further study to determine if antifibrotic agents have a role to play in the management of late-stage ILD/pneumonitis.

Conclusion

To summarize, this report presents a unique approach to treating T-DXd-induced grade 4 ILD. The addition of an antifibrotic agent, Nintedanib, was associated with clinical improvement, making this the first of a kind case to be reported. Based on our experience, further studies investigating the role of antifibrotic therapies for refractory treatment related ILD should be undertaken and administration of an antifibrotic agent in selected cases including those with radiological signs of pulmonary parenchymal disorganization could be considered.

Author contributions: G.N.B.S. and F.C.M. described the patient data on oncological disease and M.T.C. on pulmonary involvement. A.K.M. described the imaging exam. S.M. and F.M.C. analyzed and interpreted all data and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Competing interests: All authors declare no financial or non-financial competing interests.

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