Diagnostic Snapshot

Can You Establish the Cause of This Patient's Shortness of Breath?

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2023.14.5.8

Abstract

Mr. B is a 56-year-old man diagnosed with metastatic HER2-positive gastroesophageal adenocarcinoma. He received front-line leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) and trastuzumab for 10 months before restaging imaging revealed progressive disease. He then received second-line trastuzumab deruxtecan. His treatment was complicated by several admissions felt to be unrelated to his cancer therapy. He was discharged after an episode of pneumonia on a steroid taper with prophylactic trimethoprim/sulfamethoxazole. Once he recovered, he was given a fourth dose of chemotherapy. About a week later, wheezes were noticed on physical exam, and he was given a 5-day course of levofloxacin. Around the same time, he also finished his steroid taper. Twelve days after his dose of chemotherapy, he presented to the emergency room with 3 to 4 days of progressive shortness of breath and dry cough following the completion of levofloxacin without symptom improvement. A CT scan showed increasing airspace opacities and multifocal areas of consolidation. Blood, nasal, and sputum cultures were negative. A bronchoscopy was performed that did not reveal findings concerning for capillaritis. He was ultimately diagnosed with drug-induced pneumonitis/interstitial lung disease (ILD). Mr. B continued to experience worsening hypoxic respiratory failure despite continuous IV steroids. He was discharged to an inpatient hospice facility where he passed away 2 weeks later. Drug-induced pneumonitis/ILD should be considered in all patients receiving trastuzumab deruxtecan who develop progressive shortness of breath or other respiratory complaints.

BACKGROUND

Mr. B is a 56-year-old male who presented to our institution with a past medical history of renal stones, deep vein thrombosis (DVT) with an inferior vena cava filter, and cerebrovascular accident (CVA). He was initially diagnosed with metastatic gastroesophageal junction (GEJ) adenocarcinoma with hepatic metastases and abdominal lymphadenopathy. Esophagogastroduodenoscopy with biopsies revealed poorly differentiated adenocarcinoma. Pathology was noted to be HER2-positive by fluorescence in situ hybridization. He received front-line leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) and trastuzumab for 10 months before restaging imaging revealed progressive disease.

Second-line therapy was initiated with trastuzumab deruxtecan (T-DXd; Enhertu). He received 6.4 mg/kg intravenously (IV) on an every-21-days cycle. After cycle 2, he developed a subacute right basal ganglia stroke that was felt to be unrelated to treatment. Restaging imaging showed a dramatic response to therapy in the liver and lymph nodes,

and he received a third cycle. Fourteen days later, he was admitted to the hospital for 9 days with hypoxic respiratory failure and pneumonia also felt to be unrelated to his current treatment. He was discharged on a prednisone taper starting at 80 mg and was given prophylactic trimethoprim/sulfamethoxazole for pneumocystis pneumonia. T-DXd was held while he recovered. A follow-up chest x-ray after 1 month showed improvement in his pneumonias. His fatigue improved, oxygen saturations were normal, and respiratory complaints completely resolved, although he continued to wheeze on exam so he was started on a 5-day course of levofloxacin. He also developed minor liver transaminitis without a clear etiology. His treatment was resumed with a dose reduction of 5.4 mg/kg given his current hepatic function and performance status.

CHIEF COMPLAINT

Mr. B presented to the emergency room 12 days after cycle 4 complaining of 3 to 4 days of progressive shortness of breath and dry cough following completion of levofloxacin without symptom improvement. Additionally, he had completed his steroid taper about 2 to 3 days prior to symptom onset. He was taking his trimethoprim/sulfamethoxazole as prescribed. He denied fever but reported chills starting 1 day prior to his visit. He denied hemoptysis, chest pain, palpitations, lower extremity edema, and recent travel history or known exposure to coronavirus. He reported darker stools and complained of several days of bloody nasal secretions. Of note, he was on anticoagulation and antiplatelet therapy for his recent DVT and CVA, respectively.

PHYSICAL EXAM AND DIAGNOSTIC WORKUP

On initial presentation, Mr. B's oxygen saturation was noted to be 95% on room air with respirations 22, heart rate at 116 beats/minute, and blood pressure of 165 mmHg/76 mmHg. He was afebrile on initial presentation but developed fever while in the emergency room. A physical exam revealed rales with no leg edema. Laboratory studies revealed aspartate transaminase at 81 U/L, alanine transaminase at 93 U/L, platelets at 107 K/uL, and hemoglobin at 12.0 g/dL. SARS-CoV-2 polymerase chain reaction (PCR) and an extended respiratory panel were negative. A CT via pulmonary embolism protocol was negative for a pulmonary embolus but showed increasing bilateral airspace opacities with multifocal areas of increasing consolidation and no pleural effusions. He was admitted and started on 4 L of oxygen via nasal canula. He was empirically treated with cefepime, linezolid, and trimethoprim/sulfamethoxazole. He was also started on pulse steroids. Sputum culture was consistent with normal oral flora. Cytomegalovirus PCR, T-SPOT, and blood cultures returned negative. A bronchoscopy was completed, and bronchioalveolar lavage (BAL) resulted as bloody with rare macrophage with hemosiderin and negative cultures. Other relevant findings include repeat proteinase 3 (PR3) equivocal, urinalysis negative, myeloperoxidase antibody (MPO) negative, and antineutrophil cytoplasmic antibody (ANCA) negative.

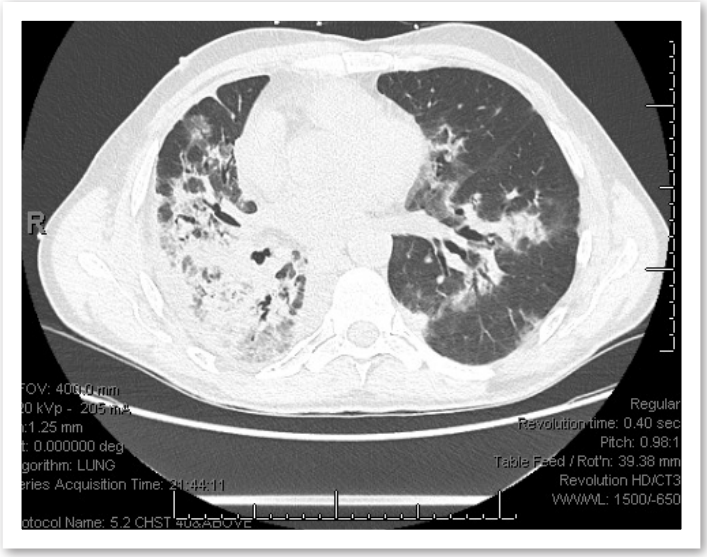

Figure 1. CT chest without contrast showing ground-glass and airspace opacities.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MR. B?

- A ☐ Fungal pneumonia
- B ☐ Bacterial pneumonia
- C ☐ Drug-induced interstitial lung disease/pneumonitis
- D ☐ Paraneoplastic ANCA-associated vasculitis with pneumonitis

SEE BACK FOR ANSWER ▶

WHAT IS THE CORRECT DIAGNOSIS FOR MR. B?

A Fungal pneumonia

B Bacterial pneumonia

C Drug-induced interstitial lung disease/pneumonitis (correct answer)

D Paraneoplastic ANCA-associated vasculitis with pneumonitis

DISCUSSION

A **Fungal pneumonia**. This is less likely as the BAL cultures were negative. Mr. B also reported taking his prophylactic trimethoprim/sulfamethoxazole as prescribed.

B **Bacterial pneumonia.** This is also less likely given the negative BAL, sputum, and blood cultures.

C **Drug-induced interstitial lung disease/pneumonitis.** Antibody-drug conjugates (ADCs) are a relatively new class of anticancer drugs designed to combine the cytotoxic qualities of chemotherapy, referred to as the payload, with the selectivity of monoclonal antibodies (Criscitiello et al., 2021). T-DXd is an ADC approved for advanced unresectable HER2-positive GEJ/gastric adenocarcinoma for patients who have previously received a trastuzumab-containing regimen. It consists of a topoisomerase I inhibitor payload, humanized anti-HER2 antibody, and a newly developed novel enzymatically cleavable peptide linker that attaches them (Takegawa et al., 2017).

Interstitial lung disease (ILD) is a group of lung disorders that includes pneumonitis. It has been associated with irinotecan, a different topoisomerase I inhibitor similar to the payload of T-DXd, and other HER2-directed therapies at rates of 0.5% to 1% (Kumagai et al., 2020). Interestingly, 10% of patients receiving T-DXd had drug-related ILD/pneumonitis of any grade in the DESTINY-Gastric01 trial. While the majority of these cases were grade 1 and 2 events, 2% of patients had fatal outcomes (Shitara et al., 2020).

The mechanism and trigger for drug-related ILD/pneumonitis is still unknown in many ways, and there is limited data in humans. Although there have been several theories proposed, including target-dependent uptake in cells, target-independent uptake in cells, bystander killing by free drug released from cancer cells, and deconjugation of ADC resulting in free payload, it is still unclear why the conjugated drugs are associated with a higher incidence of ILD/pneumonitis than their unconjugated counterparts (Tarantino et al., 2021). In one study by Kumagai and colleagues (2020), cynomolgus monkeys were injected with escalating doses of T-DXd and experienced ILD in a dose-dependent manner, while monkeys injected with deconjugated deruxtecan did not experience ILD even in high doses. Their data also showed that T-DXd was mainly distributed to macrophages in the lungs and liver of monkeys. The macrophages of these monkeys express a lysosomal cysteine protease also expressed in the macrophages in humans and is considered one of the enzymes responsible for linker cleavage of T-DXd. This could support the hypothesis that lung toxicity is induced by target-independent uptake of conjugated ADC in the macrophages followed by release of free DXd rather than HER2 dependent uptake (Kumagai et al., 2020).

Interstitial lung disease/pneumonitis can be difficult to diagnose because laboratory and clinical symptoms such as cough, fever, dyspnea, and hypoxemia, are nonspecific. According to Matsuno (2012), histological findings are often also nonspecific and can mimic other conditions. Mr. B's complex medical history and generalized pulmonary complaints were further clouded by the COVID-19 pandemic, as there is significant overlap in symptoms and radiographic findings. High-resolution CT is the best noninvasive method to assess the presence of drug-induced disease, as it may reveal abnormalities in patients with normal radiographs. However, it is limited in its ability to predict the histological reaction patterns (Matsuno, 2012). Akira and colleagues (2002) reported that the predominant findings in anticancer agent-induced pneumonitis is diffuse or multifocal ground-glass opacities with intralobular interstitial thickening.

Bronchoscopy findings are often limited, as biopsy specimens often reveal nonspecific abnormalities (Ryu et al., 2007). Diagnosis is often ultimately dependent upon temporal association between an exposure to the causative agent and the development of respiratory signs and symptoms, as well as ruling out other causes (Skeoch et al., 2018).

D Paraneoplastic ANCA-associated vasculitis with pneumonitis. Specifically, diffuse alveolar hemorrhage was suspected based on bloody aspirate. It is less likely because BAL did not reveal findings consistent with capillaritis. Furthermore, it is unlikely in the setting of PR3 antibody equivocal with MPO and ANCA negativity (Brown, 2006).

MANAGEMENT

All patients on T-DXd with suspected ILD/pneumonitis should be monitored until symptom resolution or the drug is discontinued. According to prescribing information, for asymptomatic patients (grade 1), clinicians should consider corticosteroids at a dose of at least 0.5 mg/kg/day prednisolone or equivalent (Daiichi Sankyo, Inc., 2021). If symptoms have completely resolved after 28 days, the initial dose can be resumed, but one level dose reduction is recommended if symptoms take more than 28 days to resolve. For grade 2 events or greater, clinicians should promptly initiate systemic corticosteroids with at least 1 mg/kg prednisolone or equivalent and continue for at least 14 days, followed by a gradual taper for at least 4 weeks. T-DXd should be permanently discontinued for patients with symptomatic ILD/pneumonitis (Daiichi Sankyo, Inc., 2021).

Mr. B continued to experience worsening hypoxic respiratory failure despite continuous high-dose IV steroids. He remained on high-flow oxygen during a 2-month admission and required bilevel positive airway pressure periodically. His respiratory failure was felt to be chronic, likely with permanent high supplemental oxygen requirements. Given his metastatic cancer diagnosis, Mr. B was discharged to an inpatient hospice facility where he passed away approximately 2 weeks later.

Disclosure

The authors have no conflicts of interest to disclose.

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