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Case Report

Venetoclax-associated interstitial pneumonitis

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ABSTRACT

Venetoclax is a selective inhibitor of the antiapoptotic protein B-cell lymphoma 2 (BCL-2). It is approved for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and acute myeloid leukemia (AML) in combination with chemotherapy or hypomethylating agents. Interstitial pneumonitis due to venetoclax has not been described in the literature. We describe a case of a 79-year-old female who experienced SLL relapse and developed interstitial pneumonitis associated with venetoclax, which completely resolved after discontinuation of the medication.

1. Introduction

Drug-induced interstitial lung disease is associated with significant morbidity and mortality. Early diagnosis and treatment can potentially improve outcomes. Common pulmonary adverse effects include cough, dyspnea, pneumonia and upper respiratory tract infection. There are no reports in the literature regarding the association between venetoclax and interstitial pneumonitis.

2. Case presentation

A 79-year-old female with a significant medical history of diabetes mellitus, hypertension, hyperlipidemia and SLL was diagnosed and treated with fludarabine, cyclophosphamide and rituximab thirteen years prior. She was in remission for several years. Her SLL relapsed six months prior, and she was diagnosed by biopsy of the abdominal lymphadenopathy. The patient was started on venetoclax for relapsed small lymphocytic lymphoma six months prior. She presented to the emergency department with shortness of breath, cough and low-grade fever. Her current dose of venetoclax was 400 mg daily. On initial evaluation, her heart rate was 98/min, respiratory rate was 18/min, oxygenation saturation was 80 % on room air, temperature was 100.4 F, and blood pressure was normal. She required 2 L of oxygen via a low-flow nasal cannula. Chest examination revealed scattered rales. The rest of the physical examination was unremarkable. Initial laboratory data showed a white cell count of 2.3 k/UL, a hemoglobin level of 9.3 g/dL and a platelet count of 98 k/UL. Serum chemistries were normal. Blood, sputum and urine cultures were negative. Serum histoplasmosis antibodies, urine histoplasmosis antigen, serum coccidioidomycosis antibodies, and a rapid respiratory pathogen panel were negative. Extensive immunological workup results, including serum antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) panel, anti–glomerular basement membrane (anti-GBM) antibody, anti-Ro (SS-A) and anti-La (SS–B) antibodies, rheumatoid factor (RF), antisynthetase antibody panel, anti-DNA topoisomerase I (Scl-70) antibody and anti-centromere antibodies, were negative. Computed tomography (CT) of the chest showed bilateral diffuse ground glass opacities with an acute interstitial pneumonia (AIP) pattern [Fig. 1]. The patient was started empirically on vancomycin, cefepime and fluconazole for infection. Bronchoscopy with bronchoalveolar lavage (BAL) was performed. BAL fluid analysis showed predominant lymphocytes. The results of BAL studies including bacterial, fungal, viral, and acid-fast bacillus (AFB) staining; AFB culture; and *Mycobacterium tuber-*

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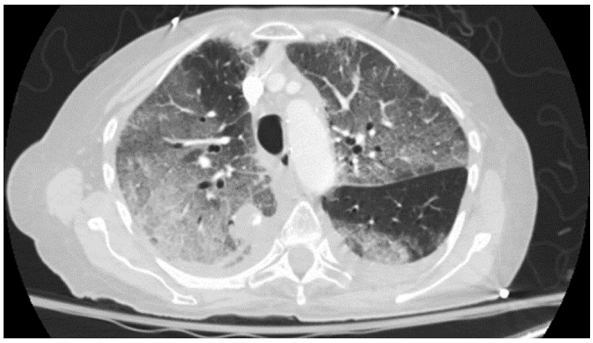

Fig. 1. CT of the chest showing diffuse bilateral ground glass opacities.

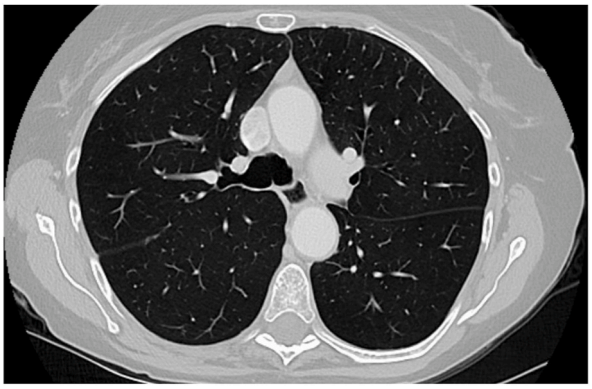

Fig. 2. CT of the chest at the 2-month follow-up showing resolution of diffuse bilateral ground glass opacities.

culosis (MTB) polymerase chain reaction (PCR), were negative. In the setting of persistent symptoms and a negative diagnostic workup, drug-induced interstitial pneumonitis was considered, and all the medications were carefully reviewed. The patient was taking losartan, atorvastatin, insulin and venetoclax. The patient completed seven days of antibiotics without improvement. We stopped venetoclax as a therapeutic intervention. She was treated with systemic steroids for 4 weeks. Her symptoms gradually improved, and she was weaned off oxygen at the 2-month follow-up. Her CT chest imaging showed resolution of interstitial pneumonitis [Fig. 2]. Rechallenge with venetoclax after 2 months led to the recurrence of interstitial pneumonitis within 4 weeks with the same AIP pattern on chest imaging; therefore, venetoclax was stopped, and the patient was switched to obinutuzumab for SLL treatment.

3. Discussion

BCL-2 inhibitors are critical regulators of cell survival, resulting in evasion of programmed cell death [1]. The ability to evade apoptosis is an important hallmark of cancer [2]. Venetoclax is a member of BCL-2 inhibitor family that selectively inhibits the anti-apoptotic protein BCL-2, which is overexpressed in CLL cells, SLL cells and AML cells. BCL-2 mediates tumor cell survival and has been associated with chemotherapy resistance. Venetoclax has been shown to have substantial antitumor activity in patients with relapsed CLL/SLL, including those with poor prognostic features. Venetoclax is well tolerated in patients with hematologic malignancies. The most common adverse events are self-limited diarrhea and nausea, along with upper respiratory tract infection. The most common serious adverse events are febrile neutropenia, pneumonia and immune thrombocytopenia [3,4]. Common side effects are described in the full prescribing information of venetoclax and can involve multiple organ systems [Table 1]. Common pulmonary adverse effects include cough, dyspnea, pneumonia and upper respiratory tract infection. It is very unusual for venetoclax to cause interstitial lung disease because animal studies have shown potential benefits of bcl-2 inhibitors in bleomycin-induced interstitial pneumonitis [5,6]. However, venetoclax-induced interstitial pneumonitis has never been described in the literature. To the best of our knowledge, this is the first case report of venetoclax-associated interstitial pneumonitis. Furthermore, we were able to rechallenge the venetoclax that caused the recurrence of her symptoms and pneumonitis, which further validated the association of interstitial pneumonitis with venetoclax. The exact mechanism and pathophysiology by which venetoclax causes interstitial pneumonitis are not well understood.

Table 1
Venetoclax toxicities.

Organ system	Common adverse effects including all grades
Cardiovascular	Edema (22 %)
Dermatologic	Skin rash (18 %)
Gastrointestinal	Abdominal pain (18 %), constipation (16 %), diarrhea (43 %), nausea (42 %), stomatitis (13 %), vomiting (16 %)
Hematologic and oncologic	Anemia (33 %–71 %), leukopenia (4–89 %), lymphocytopenia (9 %–74 %), neutropenia (33 %–87 %), thrombocytopenia (4 %–64 %)
Nervous system	Dizziness (14 %), fatigue (32 %), headache (18 %)
Neuromuscular & skeletal	Arthralgia (12 %), musculoskeletal pain (29 %)
Hepatic:	Increased serum aspartate aminotransferase (53 %)
Neuromuscular & skeletal	Arthralgia (12 %), musculoskeletal pain (29 %)
Respiratory	Cough (22 %), dyspnea (13 %), lower respiratory tract infection (11 %), pneumonia (14 %), upper respiratory tract infection (36 %)
Endocrine	Hyperglycemia (67 %), hyperkalemia (59 %), hypoalbuminemia (49 %), hypocalcemia (87 %), hyponatremia (40 %), and hypophosphatemia (45 %)

4. Conclusion

Clinicians need to be highly suspicious of drug-induced pulmonary toxicity in patients who are receiving BCL-2 inhibitors and who present with respiratory symptoms. Corticosteroids may be considered for severe life-threatening disease. Early recognition of venetoclax toxicity and appropriate discontinuation can prevent significant morbidity and adverse outcomes.

CRediT authorship contribution statement

Atif Saleem Siddiqui: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

BCL-2: B-cell lymphoma-2
*CLL:*Chronic lymphocytic leukemia
*SLL:*Small lymphocytic lymphoma
*AML:*Acute myeloid leukemia
CT: Computed tomography
*BAL:*Bronchoalveolar lavage
AFB: Acid fast bacillus
MTB: Mycobacterium tuberculosis
PCR: Polymerase chain reaction
ANA: Antinuclear antibody
ANCA: Antineutrophil cytoplasmic antibodies (ANCA)
GBM: Glomerular basement membrane
*SS-A:*Ro antibody
*SS-B:*La antibody
RF: Rheumatoid factor
Scl-70: Anti-DNA topoisomerase