

Case Report

Idelalisib induced drug toxicity presenting as drug induced pneumonitis: a case report

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ABSTRACT

Idelalisib is a novel treatment option for patients with chronic lymphocytic leukemia. A rare, but, fatal complication of using Idelalisib is drug induced pneumonitis. This article presents a case of Idelalisib induced pneumonitis in a patient with chronic lymphocytic leukemia along with a brief discussion of management plan.

Keywords: Idelalisib, Chronic lymphocytic leukemia, Drug induced interstitial lung diseases, Phosphatidylinositol 3 kinase inhibitor, Steroids

INTRODUCTION

The diagnosis of Interstitial lung diseases (ILD) can be challenging and often requires a multi-disciplinary approach. ILD has many etiologies and identification of an underlying cause can be elusive.¹ However, one frequently underrecognized cause of ILD is drug induced interstitial lung disease (DI-ILD). Here we report a case of Idelalisib induced DI-ILD and review the literature.

CASE REPORT

A 72-year-old male with a history of Chronic Lymphocytic Leukemia (CLL) on Idelalisib (Zydelig®) presented with cough, low grade fevers, dyspnea and hypoxia. He was a distant former smoker but denied any previous toxic exposures, recent travels, or sick contacts. He did not improve with outpatient antibiotic therapy. He did not have any sputum production, hemoptysis, or chest pain. He was awake, alert, oriented and had a pulse of 110/min, blood pressure 110/80, and respiratory rate 18/min with a room air oxygen saturation of 88% on room air. His physical exam was normal except for bilateral inspiratory

crackles. A chest CT scan had bilateral scattered ground glass opacities. (Figure 1)

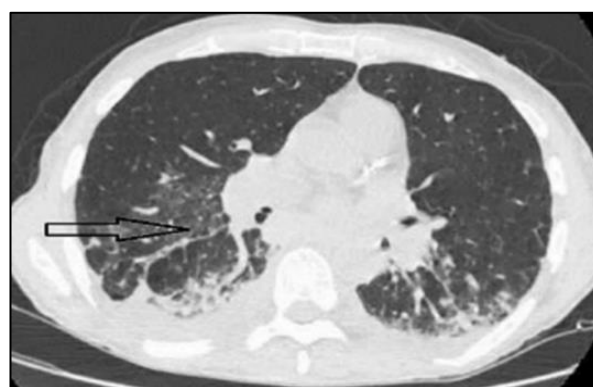


Figure 1: CT scan showing ground glass opacities (arrow) at initial presentation.

The patient ultimately required a bronchoscopy and transbronchial biopsy. The bronchoalveolar lavage was negative for infections, alveolar hemorrhage, and eosinophilia. Transbronchial biopsy showed evidence of

granulomatous inflammation suggestive of granulomatous pneumonitis. (Figure 2)

The acid-fast, fungal, and bacterial cultures from the biopsy specimen were negative. After ruling out infections, and with a multidisciplinary discussion between pathology, hematology, pulmonology, and infectious disease a diagnosis of drug induced interstitial lung disease (DI-ILD) due to Idelalisib was made.

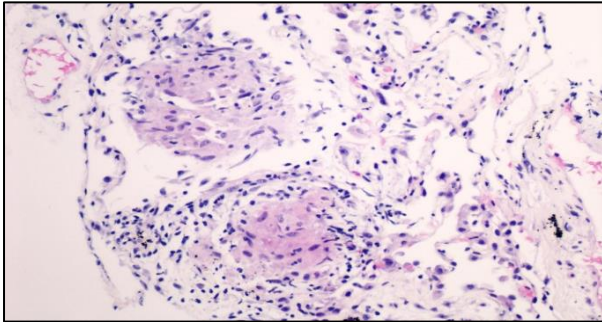


Figure 2: Transbronchial biopsy showing non-necrotizing granulomas in patient treated with Idelalisib.



Figure 3: CT scan shows improvement (arrow) after treatment.

Table 1: Types of ID-ILD.

Histological findings	
Granulomatous Pneumonitis	Inflammation without necrosis
Interstitial Pneumonia	Diffuse pattern involving alveolar wall
Hypersensitivity Pneumonitis	Increase lymphocytes and plasma cells, Non caseating granulomas
Cyrtogenic organizing pneumonia	Intra-alveolar fibroblastic proliferation, preserved lung architecture with plasma cells, lymphocytes and histocytes

Idelalisib was stopped and the patient was treated with a course of prednisone 60mg tapered over 8 weeks. He had significant improvement in his symptoms, physical exam

findings, and oxygenation and resolution of the abnormal CT findings (Figure 3).

Unfortunately, his CLL progressed over the next few months while off therapy and he passed way from CLL related hematological complications.

DISCUSSION

DI-ILD is a recognized subtype of diffuse parenchymal lung disease according to the ATS/ERS classification.¹ (Table 1).

Table 2: Risk factors for DI-ILD.

Risk Factors	Medications
Age	Bleomycin ⁹
Sex	Nitrofurantoin ¹⁰
Dose	Bleomycin ¹¹
Oxygen	Amiodarone ¹²
Ethnicity	Bortezomib in Japanese population ¹³
	Bortezomib in African American population ¹⁴
	Tacrolimus and Leflunomide ^{15,16}
Drug interaction	Cisplatin and Bleomycin ¹⁷
Radiation	In conjunction with bleomycin ¹⁸

However, even with the ATS/ERS classification system, it can be difficult to identify the exact subtype because clinical, radiologic, and pathologic features are rarely able to differentiate between varying interstitial pneumonias. Drug induced interstitial lung disease (DI-ILD) is defined as interstitial abnormality that results secondary to administration of a drug.^{2,3} Non-specific symptoms such as cough, fever, and dyspnea associated with inspiratory crackles are initial presenting manifestation of DI-ILD. Pulmonary function tests may reveal restrictive pattern with low DLCO and radiographic images can rule out indication of any infections, congestive heart failure or malignancy.⁴ A high resolution CT scan (HRCT) is pertinent for a diagnosis of DI-ILD; however, it can't distinguish between all the histological patterns.⁵ DI-ILD accounts for 3-5% of prevalent ILD cases and studies have noted that DI-ILD incidence rates ranged from 4.1 to 12.4 cases per million per year.⁶

The mechanism causing DI-ILD is not yet clearly understood. However, it is believed that drug induced cytotoxic and immune mechanisms may be involved.⁷ Cytotoxic lung injury can manifest its effects on alveolar epithelial cells or alveolar capillary endothelium. In a stepwise method, alveolar damage leads to cytokine release that initiates an inflammatory response thereby leading to interstitial fibrosis.⁴ Another method causing DI-ILD is a hypersensitivity reaction to medication that occurs if drug acts as haptens or antigens to activate immune mediated response, consequently leading to fibrosis as

seen in drug induced systemic lupus erythematosus.⁸ seen in this patient.⁸ Some of the risk factors mentioned in the literature are older age, sex, drug dosing and/or past history of radiation (Table 2).⁸

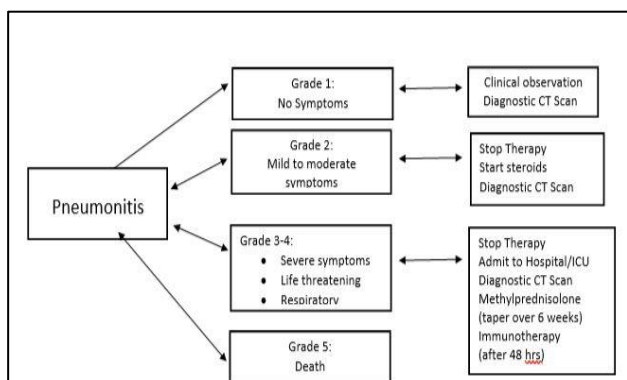


Figure 4: Pneumonitis severity assessment based on CTCAE.

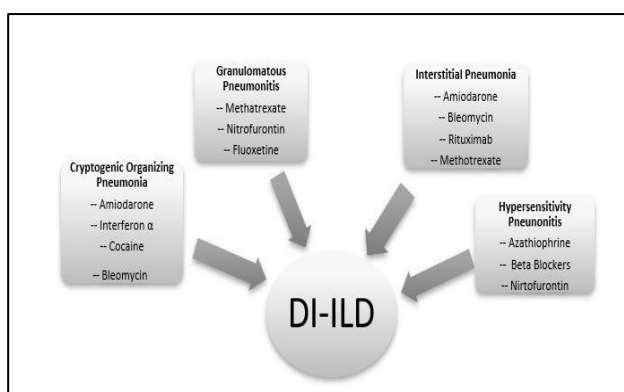


Figure 5: Drug causing drug induced interstitial lung disease (adapted from schwaiblmair).⁸

Idelalisib is a potent phosphatidylinositol 3 kinase inhibitor (PI3K δ) recently approved for the treatment of relapsing CLL in combination with rituximab.^{19,20} Since this medication interferes with regulatory immune system, it has led to some adverse events such as colitis, hepatotoxicity and pneumonitis that required a black box warning.^{21,22} Patients taking Idelalisib who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates or a decline in oxygen saturation by >5% should be evaluated for pneumonitis.²² If an infectious cause is suspected, antibiotic therapy should be started. If infection is not a causative agent, then an HRCT and Bronchoscopy with BAL and/or transbronchial lung biopsy may be necessary with treatment modifications based on the subsequent findings. Once a diagnosis of DI-ILD is made, it is imperative to grade the level of toxicity and start treatment based on the Common Terminology Criteria for Adverse Events (CTCAE).^{23,24} (Figure 4)

In general, advanced pneumonitis is treated with, first discontinuing the inciting drug and then starting the patient

on prednisone. There are more than 300 medications which have been related to DI-ILD. (Figure 5).

CONCLUSION

DI-ILD is an underrecognized form of interstitial lung disease. It is diagnosed in an appropriate clinical setting after other potential etiologies have been ruled out. DI-ILD has radiographic findings consistent with ILD and a temporal relationship between the onset of symptoms and exposure to inciting drug. DI-ILD is characterized by improvement upon withdrawal of the offending agent

Idelalisib is a novel therapy approved for treating relapsing chronic lymphocytic leukemia and follicular B- Cell non-Hodgkin lymphoma. It selectively induces apoptosis by inhibiting a phosphatidylinositol 3-kinase δ and prevents proliferation of cells. Patients presenting with cough, persistent dyspnea and hypoxia should undergo a dedicated evaluation to identify the cause of symptoms. Therefore, DI-ILD, or drug induced pneumonitis, should be included on the differential diagnosis list. Clinicians should be aware of the possibility of drug-related pulmonary manifestations because it is critical to obtain these diagnoses as it requires a change in clinical management.

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REFERENCES

1. Travis WD, Costabel U, Hansell DM. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733-48.
2. Erasmus JJ, McAdams HP, Rossi SE. Drug-induced lung injury. Semin Roentgenol 2002;37:72-81.
3. Ripley BA KT, Gill RR. Deciphering drug-induced interstitial lung disease: A mechanistic approach Appl Radiol. 2016;45:9-18.
4. Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012;13:39.
5. Cleverley JR, Screatton NJ, Hiorns MP, Flint JD, Muller NL. Drug-induced lung disease: high-resolution CT and histological findings. Clin Radiol. 2002;57:292-9.
6. Skeoch S, Weatherley N, Swift AJ. Drug-Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018;7.
7. Pietra GG. Pathologic mechanisms of drug-induced lung disorders. J Thorac Imaging. 1991;6:1-7.
8. Schwaiblmair M, Behr W, Haeckel T, Markl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. Open Respir Med J. 2012;6:63-74.

9. Simpson AB, Paul J, Graham J, Kaye SB. Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours. *Br J Cancer.* 1998;78:1061-6.
10. Mendez JL, Nadrous HF, Hartman TE, Ryu JH. Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005;80:1298-302.
11. Reinert T BC, Nunes FAP, Scheliga AAdS. Bleomycin-Induced Lung Injury. *Journal of Cancer Research.* 2013;2013:9.
12. Crimi E, Sica V, Williams-Ignarro S. The role of oxidative stress in adult critical care. *Free Radic Biol Med.* 2006;40:398-406.
13. Miyakoshi S, Kami M, Yuji K. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. *Blood.* 2006;107:3492-4.
14. Ohri A, Arena FP. Severe pulmonary complications in African-American patient after bortezomib therapy. *Am J Ther.* 2006;13:553-5.
15. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum.* 2006;54:1435-9.
16. Miwa Y, Isozaki T, Wakabayashi K. Tacrolimus-induced lung injury in a rheumatoid arthritis patient with interstitial pneumonitis. *Mod Rheumatol.* 2008;18:208-11.
17. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer.* 1996;32A:550-2.
18. Oya N, Sasai K, Tachiiri S. Influence of radiation dose rate and lung dose on interstitial pneumonitis after fractionated total body irradiation: acute parotitis may predict interstitial pneumonitis. *Int J Hematol.* 2006;83:86-91.
19. Yang Q, Modi P, Newcomb T, Queva C, Gandhi V. Idelalisib: First-in-Class PI3K Delta Inhibitor for the Treatment of Chronic Lymphocytic Leukemia, Small Lymphocytic Leukemia, and Follicular Lymphoma. *Clin Cancer Res.* 2015;21:1537-42.
20. Fruman DA, Cantley LC. Idelalisib--a PI3Kdelta inhibitor for B-cell cancers. *N Engl J Med.* 2014;370:1061-2.
21. Coutre SE, Barrientos JC, Brown JR. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma.* 2015;56:2779-86.
22. Drug statistical FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/2065451bl.pdf. Accessed 10 August 2020.
23. Chuzi S, Tavora F, Cruz M. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. *Cancer Manag Res* 2017;9:207-13.
24. Vulisha AK, Talwar A, Verma S, Gupta A, Lam L. Nivolumab Induced Toxicity Presenting As Pneumonitis- A Case Report. *J Pulm Respir Med* 2018;8.

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