Case Report

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

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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.

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>
<thead>
<tr>
<th>Risk Factors</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Age</td>
<td>Bleomycin(^9)</td>
</tr>
<tr>
<td>Sex</td>
<td>Nitrofurantoin(^10)</td>
</tr>
<tr>
<td>Dose</td>
<td>Bleomycin(^11)</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Amiodarone(^12)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Bortezomib in Japanese population(^13)</td>
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<td></td>
<td>Bortezomib in African American population(^14)</td>
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<td></td>
<td>Tacrolimus and Leflunomide(^15,16)</td>
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<tr>
<td>Drug interaction</td>
<td>Cisplatin and Bleomycin(^17)</td>
</tr>
<tr>
<td>Radiation</td>
<td>In conjunction with bleomycin(^18)</td>
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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.\(^7\) Another method causing DI-ILD is a hypersensitivity reaction to medication that occurs if drug acts as hapten or antigen to activate immune mediated response, consequently leading to fibrosis as
seen in drug induced systemic lupus erythematosus.\(^8\) Some of the risk factors mentioned in the literature are older age, sex, drug dosing and/or past history of radiation (Table 2).\(^8\)

**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, interstitial infiltrates or a decline in oxygen saturation by >5% 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**
