Case Report

A 64 year old Caucasian woman was diagnosed with melanoma (nodular melanoma) of the left arm two years ago. The initial skin lesion measured 3.7 mm in thickness and a size of 1.2 cm. A sentinel lymph node biopsy was negative for any malignant process. She was treated for melanoma with chemotherapy and had a significant response.

The patient has a past medical history of Type II Diabetes Mellitus, hypothyroidism, and hypertension; She has no past history of smoking. Her current medications include atorvastatin, glimepiride, hydrochlorothiazide, canagliflozin, levothyroxine, metformin, oxycodone, quinapril, liraglutide.

Eight months ago, a routine ultrasound of the right upper quadrant revealed multiple hepatic lesions. A subsequent liver biopsy demonstrated metastatic melanoma of the liver. It was also found that the patient has a BRAF V600E mutation. An MRI of the spine demonstrated a metastatic lesion within the T10 with anterior and left lateral epidural extension resulting in moderate canal stenosis. The patient underwent stereotactic body radiotherapy, and immunotherapy. The patient was started on nivolumab. After second cycle of nivolumab treatment, the patient complained of increasing shortness of breath.

On her physical exam, she was alert, awake and oriented. Her pulse was 80 per minute, blood pressure 120/ 80 mmHg, respiratory rate 18 per minute, and oxygen saturation was 96%. Respiratory examinations revealed decreased air entry in both the lung bases. A chest X-ray revealed bilaterally increased lung marking and infiltrates in both lung bases (Figure 1). A PET/CT scan demonstrated new mildly hypermetabolic diffuse bilateral ground glass pulmonary opacities, in view of rapidly deterioration of her pulmonary symptoms after starting nivolumab.

Pulmonary Function Tests (PFTs) suggested restrictive ventilatory defect with moderate decrease in DLCO, thereby suggesting underlying gas exchange abnormality (Table 1). A diagnosis of nivolumab lung toxicity was entertained. Treatment with nivolumab was halted and the patient was started on Prednisone, 20 mg per day. At her subsequent visit after 6 weeks, she reported significant improvement in her dyspnea. Repeat set of pulmonary function tests showed improvement in DLCO as well (Table 1). A repeat chest X-Ray also showed an improvement in the previously reported infiltrates (Figure 2).

Nivolumab, a form of target therapy, is an antibody that blocks the

Keywords: Nivolumab; Drug induced pneumonitis; Steroids; Melanoma; Checkpoint inhibitor; Cryptogenic organizing pneumonia

Table 1: Initial pulmonary function tests vs. follow-up.

<table>
<thead>
<tr>
<th>Date</th>
<th>FVC (Liters)</th>
<th>FEV1 (Liters)</th>
<th>FEV1/ FVC</th>
<th>DLCO (mL/mmHg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Visit</td>
<td>1.86 (66% Predicted)</td>
<td>1.54 (72% predicted)</td>
<td>0.83</td>
<td>11.6 (59% of Predicted)</td>
</tr>
<tr>
<td>Subsequent Visit</td>
<td>2.29 (81% Predicted)</td>
<td>2.13 (100% Predicted)</td>
<td>0.93</td>
<td>15.8 (80% of Predicted)</td>
</tr>
</tbody>
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Figure 1: Chest X-ray at initial presentation shows bilaterally increased lung marking and infiltrates in both lung bases.
challenging because these signs/symptoms are also suggestive of dyspnea, hypoxia that can make diagnosis of drug induced pneumonitis 


[6,7]. Patients generally present with cough, breathlessness and in severe cases, radiographic infiltrates are seen. In patients with grade 2-4 pneumonitis, increased DLCO and initial pulmonary infiltrate were due to drug induced pneumonitis. We believe the patient shortness of breath, decreased DLCO and initial pulmonary infiltrate were due to drug induced pneumonitis (DIP) caused by nivolumab.

**Discussion**

Nivolumab is a human IgG4 programmed death 1 (PD 1) monoclonal antibody that works as an immune check point inhibitor (ICI) [1]. It inhibits the binding of PD 1 to both programmed death- ligand 1 (PD L1) and programmed death- ligand (PD L2), that are found on tumor cells, and help regulate balance of T cell activation [1,2]. In patients with cancer, when these ligands bind to the PD-1 receptor results in declining T- cell activity and in turn allow cancer cells to elude the immune system.

Recent research shows a great promise in this class of medication, as a result they have revolutionized cancer treatments, to a point that they are rapidly becoming standard of care, in various malignancies, such Melanoma [3], Renal cell carcinoma [4], Non-small cell carcinoma (NSCLC) [5].

Yet, the benefits of this novel approach have revealed some unwanted side effects, such as drug related pneumonitis (DIP). Approximately, 2-4% patients treated with nivolumab have developed drug related pneumonitis [6,7]. Patients generally present with cough, dyspnea, hypoxia that can make diagnosis of drug induced pneumonitis challenging because these signs/symptoms are also suggestive of pneumonia, pulmonary edema or alveolar hemorrhage as well [8]. For this reason, DIP is a diagnosis of exclusion. Risk factors associated with DIP are unknown [6]. Study by Naidoo et al. observed that DIP was common in 56% (24 of 43) who were both current and former smokers while, 44% of patients were never smokers [9]. The development of pneumonitis can be variable from the time of initiation of therapy [9]. Study by Naidoo et al., indicated that the median onset of pneumonitis was 2.8 months with a wide range of (9 days to 19.2 months) in 43/915 patients who developed pneumonitis [9]. Similarly, another study by Nishino et al., revealed a median time of 2.6 months (range 0.5-11.5) [10]. The presence of pneumonitis can lead to a decrease in DLCO [11]. Diffusion capacity of carbon monoxide gives the clinicians an idea about the stability of alveolar capillary membrane in the lungs. In the presence of acute pneumonitis, as the gas exchange is impeded the DLCO also decreases. Once the patient recovers, DLCO increases accordingly [11].

As in our case, a chest x-ray can show increased interstitial markings, which is reflective of acute pneumonitis. One can also obtain high resolution CT scan to better evaluate the alveolar/ interstitial structure. DIP may present on CT scan, most commonly, as cryptogenic organizing pneumonia (COP). Aside from COP, it can present as nonspecific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP), or usual interstitial pneumonitis (UIP)/pulmonary fibrosis (PF) [9,10]. In some cases, pneumonitis can appear on CT scan even before any clinical symptoms are apparent, however, some patients can still remain asymptomatic [9,12].

From a clinical perceptive, there is some variability of in severity of DIP. As per Conmon Terminology Criteria for Adverse Events (CTCAE), asymptomatic patients with some radiographic changes are classified as grade 1, while patients with mild to moderate symptoms with varying radiographic infiltrates are considered grade 2 [13]. Furthermore, patients with severe symptoms or symptoms that can lead to life threatening respiratory complications are classified as grade 3 and 4, respectively (Table 2) [13].

Treatment options can range from outpatient management with steroids for grade 2 pneumonitis, to admission in intensive care unit for patients with grade 3-4 severity [13-15]. In more severe cases, anti TNFα, such as infliximab, or immunosuppressive therapy with mycophenolate mofetil can be administered [14]. Patients with grade 3-4 severity, a bronchoscopic evaluation is suggested to rule out infectious or other etiology [13]. Roughly, one third of patients, after treatment with steroids are able to restart PD-1 inhibitor therapy [10]. However, it is not recommended to use any check point inhibitor mediations in patients with moderate to severity pneumonitis [13].

**Conclusion**

With the availability of newer such agents, clinicians may face similar cases much more frequently with the use of Anti-PD1 antibodies. Thus, clinicians must be aware of various presentations of drug induced pneumonitis so it can be diagnosed timely and treated appropriately.

**References**


