June 2018 Pulmonary Case of the Month

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History of Present Illness
The patient is a 53-year-old man who presented in January 2018 for a second opinion on interstitial lung disease first diagnosed in 2011. He lives in Los Angeles and had one year of increasing dyspnea on exertion prior to diagnosis. He had an outside surgical lung biopsy and was treated with prednisone, then started on azathioprine and the prednisone tapered. He was followed regularly and had limited progression over next 7 years. However, recently he had increasing shortness of breath.

Past Medical History, Social History, Family History
He has no significant past medical history. He is a nonsmoker and denies any significant occupational exposures.

Physical Examination
Physical examination was unremarkable without rales or clubbing.

Which of the following should be obtained at this time?

1. Prior chest x-rays, CT scans, pulmonary function testing and lung biopsy
2. Repeat CT scan, pulmonary function testing
3. Rheumatological serologies
4. 1 and 3
5. All of the above
Correct!

5. All of the above

In order to determine if his increasing shortness of breath is secondary to progression of his interstitial lung disease it will be necessary to obtain his baseline data and compare it with his current data.

His pulmonary function testing is shown in figure 1 and his CT scans are shown in figure 2.

<table>
<thead>
<tr>
<th>2011</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUNG VOLUMES</strong></td>
<td><strong>LUNG VOLUMES</strong></td>
</tr>
<tr>
<td>TLC (Pleth) (L)</td>
<td>6.38</td>
</tr>
<tr>
<td>SVC (L)</td>
<td>5.10</td>
</tr>
<tr>
<td>RV (Pleth) (L)</td>
<td>4.41</td>
</tr>
<tr>
<td>RV/TLC (Pleth) (%)</td>
<td>*2.39</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>3.11</td>
</tr>
<tr>
<td>SPIROMETRY</td>
<td>SPIROMETRY</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.41</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>*2.31</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>3.57</td>
</tr>
<tr>
<td>FEF 25-75% (L/sec)</td>
<td>*1.34</td>
</tr>
<tr>
<td>FEF Max (L/sec)</td>
<td>77</td>
</tr>
<tr>
<td>FEF Max (L/sec)</td>
<td>64</td>
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<tr>
<td>FEF50% (L/sec)</td>
<td>3.24</td>
</tr>
<tr>
<td>FEF Max (L/sec)</td>
<td>3.24</td>
</tr>
<tr>
<td>FEF50% (L/sec)</td>
<td>1.97</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>87</td>
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<tr>
<td>DLOCunc (ml/min/mmHg)</td>
<td>28.85</td>
</tr>
<tr>
<td>VA (L)</td>
<td>6.38</td>
</tr>
<tr>
<td>DLOCunc (ml/min/mmHg)</td>
<td>*15.35</td>
</tr>
<tr>
<td>VA (L)</td>
<td>*2.99</td>
</tr>
</tbody>
</table>

Figure 1. Pulmonary function tests from 2011 and 2018.

Figure 2. Representative images from thoracic CT scan in 2011 and 2018.
His lung biopsy was requested and mailed, however, only the report was available at that time. The report read “nonspecific interstitial pneumonia pattern with mild interstitial inflammation accompanied by fibrosis. Differential diagnosis would include drug reaction, systemic autoimmune disease or idiopathic nonspecific interstitial pneumonia.”

Rheumatological work up including rheumatoid factor, anti-nuclear antibody, erythrocyte sedimentation rate, C-reactive protein, anticitrulline antibody, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane were all negative.

What should be **done at this time**?

1. Begin pirfenidone or nintedanib
2. Bronchoscopy with bronchoalveolar lavage to assess for alveolitis
3. Continue to observe with one-month follow-up
4. Repeat the lung biopsy
5. Retreat with prednisone followed by azathioprine
Correct!

3. Continue to observe with close follow-up

Although he has increasing shortness of breath it is unclear at this time if this is due to his interstitial lung disease. His pulmonary function tests are not worse although there has been progression of his disease at his lung bases on CT scan. Furthermore, interpretation of his lung biopsy is not totally clear.

It was decided to await the biopsy and have the patient return in about a month. His biopsy was reviewed and thought compatible with nonspecific interstitial pneumonitis. He returned a month later in February 2018 reporting increasing shortness of breath.

What should be done at this time?

1. Begin pirfenidone or nintedanib
2. Bronchoscopy with bronchoalveolar lavage to assess for alveolitis
3. Continue to observe with close follow-up
4. Repeat the lung biopsy
5. Retreat with prednisone followed by azathioprine
Correct!

5. Retreat with prednisone followed by azathioprine

The patient has idiopathic nonspecific interstitial pneumonia (NSIP) which is a distinct form of idiopathic interstitial pneumonia (1,2). It is clinically, radiologically and histologically distinct from idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP). A diagnosis of NSIP requires exclusion of other causes of NSIP patterns (drugs, CVD). NSIP exhibits a uniform alveolar septal infiltrate of lymphocytes and plasma cells (1,2). Neutrophils, eosinophils, and histiocytes are inconspicuous and granulomas are rare in NSIP and, if present, should raise other considerations. Most important is that the character of the inflammatory process in NSIP is the same throughout the affected areas, without the temporal heterogeneity inherent in UIP (Figure 3).

![NSIP and UIP](image)

**Figure 3.** Typical low power biopsy of NSIP (left) and UIP (right). Note the uniform alveolar septal infiltrates of lymphocytes and plasma cells in NSIP. In UIP fibrosis predominates over inflammation. "Fibroblast foci" represent microscopic zones of acute lung injury set against a backdrop of chronic scarring, thus contributing to the variegated appearance or temporal heterogeneity of UIP.

On thoracic CT NSIP usually shows ground glass opacities in a patchy distribution with subpleural sparing. IPF/UIP usually shows honeycombing with basilar predominance and subpleural disease.

Importantly, prognosis and treatment are different for NSIP. Prognosis is considerably better with NSIP which usually responds to corticosteroids, azathioprine or mycophenolate.

Our patient was restarted on prednisone 40 mg/day and transitioned from azathioprine to mycophenolate. His breathing subjectively improved and a taper of prednisone was started. However, after 2 months when his prednisone had been tapered to 20 mg/day and he became much shorter of breath and returned for a follow up visit. His SpO2 was 91% on 6 lpm continuous flow. His chest exam revealed bilateral crackles.
What should be *done at this time*?

1. Chest CT scan
2. Start pirfenidone or nintedanib
3. Treat with high-dose corticosteroids
4. 1 and 3
5. All of the above
A thoracic CT scan was performed (Figure 4).

2011  Jan 2018  April 2018

Figure 4. Thoracic CT scans from 2011, January 2018 and April 2018.

The CT scan suggests progression as well as increased ground glass consistent with an exacerbation of his underlying NSIP. In NSIP exacerbations occur in 4-5% of patients per year and are likely to respond to steroid therapy. In contrast, exacerbations occur in 10-15% of IPF patients per year; occur most often in patients with an FVC < 70% predicted; are less likely to respond to corticosteroids; and prognosis is poor with >50% mortality.

Our patient was treated with high dose corticosteroids and clinically improved. He is currently on prednisone 60 mg/day and being evaluated for lung transplantation.
References