ACUTE ON CHRONIC: A CASE OF IDIOPATHIC PULMONARY FIBROSIS AND ACUTE EXACERBATION

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CASE OVERVIEW

A case of a patient with idiopathic pulmonary fibrosis (IPF) complicated by acute exacerbation and the development of pulmonary hypertension. This case highlights the difficulties in making an accurate diagnosis of IPF and also demonstrates the impact of an acute exacerbation of IPF and pulmonary hypertension on final patient outcomes. The case further highlights the importance of involving a multidisciplinary team of specialists in any discussion on diagnosis.
MEDICAL HISTORY AND TESTS

Initial visit (mid 2008)
• Male, 60 years old
• Obese
• Smoking history:
  – Ex-smoker until 20 years ago; 10 pack-years
• Occupation:
  – Former baker; regular contact with flour dust
• Family history
  – No family history of pulmonary disease
• Pets
  – None
MEDICAL HISTORY AND TESTS

Initial visit (mid 2008)

- Comorbidities:
  - Coronary artery disease (myocardial infarction in 2004), hypertension and gout

- Current medications:
  - Statin, acetylsalicylic acid, angiotensin receptor antagonist, furosemide and β-blocker
MEDICAL HISTORY AND TESTS

Initial visit (mid 2008)

• Physical examination:
  – Nonproductive cough for more than 6 months
  – Exertional dyspnoea
  – No gastroesophageal reflux disease
  – Bradycardia
  – No heart murmurs, oedema
  – No abdominal signs or symptoms
Initial visit (mid 2008)
• Bibasilar inspiratory (velcro) crackles on lung auscultation
LUNG FUNCTION

Lung function measurements (mid 2008)
• Mild-moderate diffusion defect, mild-moderate restrictive lung disease
LUNG FUNCTION

Lung function measurements (mid 2008)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( pO_2 ) at rest</td>
<td>76 mmHg</td>
</tr>
<tr>
<td>AaDO(_2)</td>
<td>24 mmHg</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>82% predicted</td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>2.6 L (75% predicted)</td>
</tr>
<tr>
<td>FVC</td>
<td>3.1 L (69% predicted)</td>
</tr>
<tr>
<td>TLC</td>
<td>4.5 L (63% predicted)</td>
</tr>
<tr>
<td>DLCO</td>
<td>52% predicted</td>
</tr>
<tr>
<td>KCO</td>
<td>88% predicted</td>
</tr>
</tbody>
</table>
LUNG FUNCTION

Additional information (mid 2008)

- 6-minute walk test (400 m) showed minimal impairment; some deoxygenation under exertion (initial SaO2 = 95%; minimal SaO2 = 89%)
IMAGING

HRCT scan (2008)
• Traction bronchiectasis
• Possible usual interstitial pneumonia pattern (UIP)
  • Subpleural, basal predominance, reticulation, traction bronchiectasis but no honeycombing
• Absence of features inconsistent with UIP

→ The multidisciplinary team (Interdisciplinary Interstitial Lung Disease Board) could not establish a definitive diagnosis, as either idiopathic non-specific interstitial pneumonia (NSIP) or IPF were on the differential diagnosis list due to the HRCT pattern.
IMAGING – HRCT (IMAGE1)

(Image heading)
HRCT 2008
HRCT 2008:
Traction bronchiectasis
HRCT 2008:
Possible UIP: subpleural, basal predominance, reticulation, traction bronchiectasis but no honeycombing; absence of features inconsistent with UIP
## Antibodies (2008)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>1:640</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Negative</td>
</tr>
<tr>
<td>Extractable nuclear antigen antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Jo-1</td>
<td>Negative</td>
</tr>
<tr>
<td>Double-stranded DNA</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-cyclic citrullinated peptide antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibodies</td>
<td>Negative</td>
</tr>
</tbody>
</table>

- There were no clinical signs of infection or connective tissue disease
Bronchoscopy results (2008)

- Results of bronchoalveolar lavage (BAL) were unspecific but typically consistent with that of a patient with idiopathic pulmonary fibrosis (IPF)

- Transbronchial histology (right lower lobe and right upper lobe) revealed interstitial fibrosis and chronic inflammation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar macrophages</td>
<td>82%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>7%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>9%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1%</td>
</tr>
</tbody>
</table>
Summary of pathologic findings (2008)

- Revealed evidence of marked fibrosis/architectural distortion and honeycombing in a predominantly subpleural/paraseptal distribution

- Presence of patchy involvement of lung parenchyma by fibrosis and fibroblast foci
PATHOLOGY (IMAGE 1)

Surgical lung biopsy (2008)

- Evidence of marked fibrosis/architectural distortion and honeycombing in a predominantly subpleural/paraseptal distribution
- Presence of patchy involvement of lung parenchyma by fibrosis and fibroblast foci
PATHOLOGY (IMAGE 2)

Surgical lung biopsy (2008)
Surgical lung biopsy (2008)
Fibroblast focus in higher magnification
Surgical lung biopsy (2008)
Fibroblast focus in higher
Diagnosis 2008

→ The multidisciplinary team made a diagnosis of IPF (with moderate lung function impairment) and discussed the different therapeutic options

→ Initially, the patient was observed and monitored at regular intervals. However, due to a further deterioration in lung function (decline in FVC >10%), triple therapy with azathioprine 150 mg, prednisolone 7.5 mg, and N-acetylcysteine 600 mg tid was initiated
MEDICAL HISTORY AND TESTS

Follow-up visit (2012)
• Severe cough, combined with cough syncopes
• Progressive dyspnoea on exertion
• Gastroesophageal reflux disease
• Echocardiography: regular right ventricular function
• Elevated brain natriuretic peptide levels but no evidence of pulmonary hypertension on echocardiography
• Current medication: N-acetylcysteine and prednisolone
LUNG FUNCTION

Lung function measurements (2012)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 2008</th>
<th>Value 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂</td>
<td>76 mmHg</td>
<td>53 mmHg</td>
</tr>
<tr>
<td>FVC</td>
<td>3.1L (69% predicted)</td>
<td>2.2 L (56% predicted)</td>
</tr>
<tr>
<td>TLC</td>
<td>4.5 L (63% predicted)</td>
<td>3.3 L (50% predicted)</td>
</tr>
<tr>
<td>DLCO</td>
<td>52% predicted</td>
<td>36% predicted</td>
</tr>
</tbody>
</table>

- Pulmonary function tests revealed a progressive worsening of the patient’s condition
The new thin section HRCT now shows definitive UIP pattern with an increased reticulation and a newly developed honeycombing.

- Newly developed honeycombing and increasing reticulation and traction bronchiectasis

→ Definitive UIP pattern
Following the multidisciplinary team diagnosis of IPF (2008) the current radiological and functional investigations led to the diagnosis of moderate IPF.

Therapy with N-acetylcysteine was stopped and prednisolone tapered off; pirfenidone (3x 267 mg capsules tid) was initiated plus NaCl inhalation and long-term oxygen therapy prescribed.
IMAGING

HRCT scan (2012)
The new thin section HRCT now shows definitive UIP pattern with

- Increased reticulation and traction bronchiectasis
- Increased and newly developed honeycombing
- Basal predominance
The HRCT shows definitive UIP pattern with an increased reticulation and a newly developed honeycombing.
IMAGING- HRCT (IMAGE 2)

HRCT (2012)

Newly developed honeycombing (arrow) and increasing reticulation and traction bronchiectasis (circle)
IMAGING- HRCT (IMAGE 3)

**HRCT (2012)**

Definitive UIP pattern (increased reticulation and honeycombing) with basal predominance
LUNG FUNCTION

Lung function measurements (August 2013)

• Patient presented to the emergency department following rapid deterioration in his condition
• Test revealed a significant decline in lung function
• Evidence of aggravated hypoxaemia
LUNG FUNCTION

Lung function measurements (August 2013)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 2008</th>
<th>Value 2012</th>
<th>Value 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂</td>
<td>76 mmHg</td>
<td>53 mmHg</td>
<td>50 mmHg (with 6L O₂)</td>
</tr>
<tr>
<td>FVC</td>
<td>3.1L (69% predicted)</td>
<td>2.2 L (56% predicted)</td>
<td>1.75 L (46% predicted)</td>
</tr>
<tr>
<td>TLC</td>
<td>4.5 L (63% predicted)</td>
<td>3.3 L (50% predicted)</td>
<td>3.2 L (49% predicted)</td>
</tr>
<tr>
<td>DLCO</td>
<td>52% predicted</td>
<td>36% predicted</td>
<td>23% predicted</td>
</tr>
</tbody>
</table>
IMAGING

HRCT scan (August 2013)
• A new thin section HRCT revealed diffuse, newly developed ground glass opacifications
→ Acute exacerbation of IPF
IMAGING- HRCT (IMAGE 1)

HRCT (2013)
IMAGING - HRCT (IMAGE 2)

HRCT (2013)
IMAGING- HRCT (IMAGE 3)

HRCT (2013)
IMAGING- HRCT (IMAGE 4)

HRCT (2013)
IMAGING- HRCT (IMAGE 5)

HRCT (2013)
IMAGING- HRCT (IMAGE 6)

HRCT (2013)
IMAGING- HRCT (IMAGE 7)

HRCT (2013)
IMAGING- HRCT (IMAGE 8)

HRCT (2013)
Diagnosis and medication after HRCT scan (August 2013)
Diagnosis: Acute exacerbation of IPF
Medication:

- Patient treated with high-dose methylprednisolone 500 mg (days 1-3) plus empirical antibiotic (aminopenicillin/β-lactamase inhibitor and a macrolide)
- N-acetylcysteine was added later during the course of treatment; pirfenidone was continued throughout
QUESTIONS

Question 1: Which statement is correct?

- An acute exacerbation is a well-defined event during the course of IPF
- Mortality in patients with an acute exacerbation of IPF is very high (correct answer)
- An acute exacerbation of IPF is comparable to an acute exacerbation of chronic obstructive pulmonary disease with some more productive cough, purulent sputum and increased dyspnoea
- An acute exacerbation of IPF is always due to a viral respiratory infection
Acute exacerbations of IPF are believed to reflect disease progression in IPF and have been associated with high mortality rates.\textsuperscript{1,2} In patients with IPF, the presence of comorbidities such as pulmonary hypertension, itself associated with a high risk of morbidity and mortality, may increase the risk of having an acute exacerbation of IPF.\textsuperscript{1}

QUESTIONS

Question 2: Which statement is incorrect?

- Treatment of an acute exacerbation of IPF should include high-dose steroids
- Alternative causes of respiratory deterioration have to be excluded before the diagnosis of an acute exacerbation of IPF can be made
- Alternative causes of an acute exacerbation of IPF include pulmonary embolism, heart failure and pulmonary infection
- Bronchoalveolar lavage should always be performed in patients with an acute exacerbation of IPF (correct answer ie the incorrect one)
Answer 2
Bronchoalveolar lavage is generally regarded as a safe diagnostic procedure and is a valuable diagnostic tool in patients with IPF. However, bronchoalveolar lavage may also predispose patients to the development of an acute exacerbation of IPF, especially older patients; as such, bronchoalveolar lavage should be used with caution in these patients (if used, patients should be carefully monitored after a diagnostic bronchoalveolar lavage procedure).

MEDICAL HISTORY AND TESTS

Echocardiography followed by right heart catheterisation (August 2013)

- Right atrium and right ventricle enlarged
- Reduced right ventricular function (TAPSE 1.6 cm)
- Systolic pulmonary artery pressure = 100 mmHg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure</td>
<td>55 mmHg</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure</td>
<td>6 mmHg</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.7 L/min/m²</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>726 dyn<em>s</em>cm⁻⁵</td>
</tr>
</tbody>
</table>
DIAGNOSIS

Diagnosis and medication (August 2013)

• A diagnosis of precapillary pulmonary hypertension was made during the acute exacerbation

• The patient was treated with sildenafil 20 mg tid empirically plus pulmonary rehabilitation

• A lung transplant was discussed but declined
LUNG FUNCTION

Lung function measurements (October 2013)
• Some clinical improvement in pulmonary function tests (October 2013)
• Echo: TAPSE 1.4 cm; PASP = 65 mmHg
LUNG FUNCTION

Lung function measurements (October 2013)

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<tr>
<td>pO₂</td>
<td>69 mmHg (with 6L O₂)</td>
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<tr>
<td>FVC</td>
<td>1.9 L (48% predicted)</td>
</tr>
<tr>
<td>TLC</td>
<td>2.9 L (44% predicted)</td>
</tr>
<tr>
<td>DLCO</td>
<td>22% predicted</td>
</tr>
</tbody>
</table>
LUNG FUNCTION

Lung function measurements (April 2014)

• Evidence of a moderate increase in dyspnoea and new onset of cough syncopes

• Stabilisation of pulmonary function but progression of pulmonary hypertension (evaluated using regular echocardiography, 6-minute walk test and measurement of brain natriuretic peptide levels)
LUNG FUNCTION

Lung function measurements (April 2014)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO$_2$</td>
<td>48 mmHg (with 6L O$_2$)</td>
</tr>
<tr>
<td>FVC</td>
<td>1.9 L (50% predicted)</td>
</tr>
<tr>
<td>TLC</td>
<td>3.5 L (53% predicted)</td>
</tr>
<tr>
<td>DLCO</td>
<td>24% predicted</td>
</tr>
</tbody>
</table>
1. Initial HRCT scans revealed a possible UIP pattern. Following surgical lung biopsy, a diagnosis of mild-moderate IPF was made

2. During progression of the disease, the HRCT scan showed a definitive UIP pattern

3. A rapid clinical and functional deterioration, associated with an acute exacerbation, followed

4. During this acute exacerbation, the patient was diagnosed with precapillary pulmonary hypertension

5. On follow-up in April 2014, the patient’s pulmonary function had stabilised but his pulmonary hypertension had progressed
LEARNINGS FROM THE CASE

1. Demonstrates how the natural pathology of IPF may vary from patient to patient

2. Highlights that the diagnosis of IPF may be difficult (since the cause is unknown and symptoms may mimic those of other pulmonary diseases) and discussions on diagnosis should involve an interdisciplinary team of specialists

3. Highlights that IPF may be treated with both pharmacological and nonpharmacological therapies

4. Demonstrates the impact of an acute exacerbation of IPF and pulmonary hypertension on final patient outcomes