832_EPAT CARE: PATIENT CASE DR. AGUILANIU
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CASE#1
RECEIVED 12/06/2014
Short description:
An asymptomatic smoker was diagnosed with mild interstitial lung disease (either early interstitial pulmonary fibrosis (IPF) or non-specific interstitial pneumonia (NSIP)).
Initially, the patient refused lung biopsy, but he eventually agreed because his symptoms worsened over the years. Seven years after his first visit, he received a lung transplant.
Here we discuss the natural history of this case of IPF, which was detected by chance before the presence of significant symptoms, and the clinical management problems caused by this unusual situation.
The patient requested a pulmonary check-up because his brother had died after a surgical lung biopsy conducted for the diagnosis of interstitial lung disease.

Initial visit (1/1999)
- 58-year-old male
- Smoker
- No occupational or environmental hazards
- Brother died after surgical lung biopsy (conducted for diagnosis of interstitial lung disease)

Clinical data
- No symptoms
- No drugs
- $\text{SpO}_2$: 97% (normal)
- Heart rate: 72 bpm (normal)

Physical examination
- No cyanosis
- No clubbing
- No clinical sign of systemic disease
- The first pulmonary auscultation was *almost* normal, but minimal crackles were heard in the posterior regions of the thorax.
IMAGING – 1999 – CHEST RADIOGRAPH

- Chest radiography (1999) was considered normal
LUNG FUNCTION - 1999

Forced expiration measurement:

• Forced vital capacity is within the normal range
• No bronchial obstruction observed

Pulmonary diffusion measurement:

• Pulmonary diffusion measurements show a low DL\(_{\text{CO}}\)

Cardiopulmonary exercise testing (CPET):

• CPET shows a mild pulmonary gas exchange disturbance, whilst the maximal work capacity is modest

Conclusion

Because of “minimal crackles” at auscultation and the low DL\(_{\text{CO}}\) value, a CT scan was performed.
## LUNG FUNCTION - 1999

Forced expiration measurement (1999)

<table>
<thead>
<tr>
<th>Value</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>4.0</td>
<td>97</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.3</td>
<td>100</td>
</tr>
<tr>
<td>FEV₁/ FVC (%)</td>
<td>82</td>
<td>100</td>
</tr>
</tbody>
</table>
LUNG FUNCTION - 1999

Lung volume measurement (1999)

<table>
<thead>
<tr>
<th>Value</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (L)</td>
<td>5.6</td>
<td>83</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>3.1</td>
<td>90</td>
</tr>
<tr>
<td>IC (L)</td>
<td>2.6</td>
<td>78</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.4</td>
<td>61</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>25</td>
<td>74</td>
</tr>
<tr>
<td>SVC (L)</td>
<td>4.3</td>
<td>96</td>
</tr>
</tbody>
</table>
Pulmonary diffusion measurement (1999)

<table>
<thead>
<tr>
<th>Value</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$DL_{CO}$ (mlCO/min/mm Hg)</td>
<td>20.2</td>
<td>72</td>
</tr>
<tr>
<td>$K_{CO}$ ($DL_{CO}$/VA)</td>
<td>3.52</td>
<td>84</td>
</tr>
</tbody>
</table>
Cardiopulmonary exercise testing (CPET) (1999)

<table>
<thead>
<tr>
<th>Value</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{O_2}^{\text{Max}}$ (mlO$_2$/kg/min)</td>
<td>23.7</td>
<td>80</td>
</tr>
<tr>
<td>$W_R^{\text{MAX}}$ (Watts)</td>
<td>104</td>
<td>80</td>
</tr>
<tr>
<td>$P_{a_{O_2}}^{\text{rest}}$ (mmHg)</td>
<td>94</td>
<td>$\Delta = -12$</td>
</tr>
<tr>
<td>$P_{a_{O_2}}^{\text{max}}$ (mmHg)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>$P(A-a)_{O_2}^{\text{max}}$ (mmHg)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>$V_D/V_{\text{I}_{\text{max}}}$ (%)</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
CT scan in 1999 shows:

- Intralobular reticulation
- Subpleural localisation
- Predominance in lower lobes
IMAGING – 1999 - CT
QUESTION 1

What pattern does the CT scan show?
• UIP
• Inconsistent with UIP
• Possible UIP*
The CT scan shows:
• Intralobular reticulation
• Subpleural localisation
• Predominance in lower lobes

Traction bronchiectasis and honeycombing are absent. This means that the patient exhibits a possible radiological UIP pattern.

## Laboratory results in 2000:

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>Normal</td>
</tr>
<tr>
<td>Immunology</td>
<td>No positive auto-antibodies</td>
</tr>
<tr>
<td>ACE</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum precipitins</td>
<td>Normal</td>
</tr>
<tr>
<td>Haematology</td>
<td>Normal</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Normal inflammatory markers; Creatine kinase normal</td>
</tr>
</tbody>
</table>
Bronchoscopy performed in 2000

- Macroscopic assessment: Normal
- Bronchoalveolar lavage (BAL) differential cell count:
  Abnormal, due to polymorphonuclear (neutrophilic and eosinophilic) pattern

<table>
<thead>
<tr>
<th></th>
<th>BAL differential cell count: patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar macrophages</td>
<td>78 %</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>12 %</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>6 %</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>4 %</td>
</tr>
</tbody>
</table>
Lung biopsy was proposed in 2000, but this was rejected by the patient (because his brother had died after a surgical lung biopsy).
Radiologically, the patient exhibits a possible UIP pattern (no honeycombing)

Other possible diagnoses are negative

This leads to the conclusion that this asymptomatic smoker has an idiopathic interstitial pneumonia with the following possible diagnoses:

- Early IPF
- Non-specific interstitial pneumonia
What are the next steps that need to be taken?
The treating physician should inform the patient that his lung function could deteriorate in the future and that he therefore needs to be followed up every six months.
2001 (surveillance every 6 months)

- Patient is still asymptomatic
- Slight worsening of the reticular pattern on CT
- Stable pulmonary function at rest and on exercise
- Patient still refuses lung biopsy
IMAGING – 2001 - CT

A second CT scan in 2001 shows slight worsening of the reticular pattern.

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>TLC (ml/min/mmHg)</td>
<td>5.6</td>
<td>5.9</td>
</tr>
<tr>
<td>DL$_{CO}$ (ml/min/mmHg)</td>
<td>20.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Pa$_{O_2}^{\text{rest}}$ (mmHg)</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>VO$_2$ Max (mlO$_2$/(kg*min))</td>
<td>23.7</td>
<td>23</td>
</tr>
<tr>
<td>WR$_{\text{MAX}}$ (Watts)</td>
<td>105</td>
<td>98</td>
</tr>
<tr>
<td>Pa$_{O_2}^{\text{max}}$ (mmHg)</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>P(A-a)$_{O_2}^{\text{max}}$ (mmHg)</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>V$<em>D$/V$</em>{T\text{max}}$ (%)</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>
PATIENT ANAMNESIS - 2002

2002 (surveillance every 6 months)
The patient exhibits an onset of symptoms late in 2002.

- Mainly dry cough
- No dyspnoea
IMAGING – 2002 - CT

CT scan in 2002 shows a mild increase of intralobular reticulation compared to 1999, without honeycombing or traction bronchiectasis.

1999 vs. 2002
IMAGING – 2002 - CT

1999

2002

[Images of lung CT scans from 1999 and 2002, with a red circle highlighting a difference.]
LUNG FUNCTION - 2002

- Decreased DL\textsubscript{CO}
- Increased P(A-a)\textsubscript{O\textsubscript{2}max} and V\textsubscript{D}/V\textsubscript{tmax}

Conclusion: Deterioration of rest (DL\textsubscript{CO}) and exercise pulmonary gas exchange without significant change in lung volume

Rest and exercise pulmonary function (2002)

<table>
<thead>
<tr>
<th>Metric</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>4.0</td>
<td>4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (L)</td>
<td>3.3</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>TLC (ml/min/mmHg)</td>
<td>5.6</td>
<td>5.9</td>
<td>5.8</td>
</tr>
<tr>
<td>DL\textsubscript{CO} (ml/min/mmHg)</td>
<td>20.2</td>
<td>18.8</td>
<td>16.3</td>
</tr>
<tr>
<td>PaO\textsubscript{2}\textsubscript{rest} (mmHg)</td>
<td>94</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>V\textsubscript{O\textsubscript{2}}\textsubscript{Max} (mLO\textsubscript{2}/(kg*min))</td>
<td>23.7</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>WR\textsubscript{MAX} (Watts)</td>
<td>105</td>
<td>98</td>
<td>105</td>
</tr>
<tr>
<td>PaO\textsubscript{2}max (mmHg)</td>
<td>82</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>P(A-a)\textsubscript{O\textsubscript{2}max} (mmHg)</td>
<td>31</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>V\textsubscript{D}/V\textsubscript{Tmax} (%)</td>
<td>26</td>
<td>26</td>
<td>31</td>
</tr>
</tbody>
</table>
Question: What diagnostic procedure should be suggested to the patient?

- Perform chest radiography in order to compare it with the CT results.
- Repeat the BAL measurements conducted in 2000.
- Perform a lung biopsy in order to determine histological UIP pattern.*
- Repeat the CT scan to exclude scanning artefacts.
Author’s solution:
Correct answer: Perform a lung biopsy in order to determine histological UIP pattern.

Lung function tests show a functional aggravation, in particular in pulmonary gas exchange and the CT scan of this patient shows a possible UIP pattern.

In order to confirm or reject the diagnosis of IPF, a surgical lung biopsy is needed.

The patient consented to Video-Assisted Thoracoscopic Surgery (VATS) in 2003. Samples were taken from the superior and inferior lobe of the left lung.
Pathology

The biopsy shows:

- Fibroblastic foci
- Honeycombing
- Sub-pleural predominance
- Temporal heterogeneity

Histological conclusion: The lung biopsy pattern is consistent with a UIP pattern.

Pathology

Honeycombing

Sub-pleural predominance

Fibroblastic foci
Based on the radiological (possible UIP) and histological (UIP) patterns detected, the final diagnosis of this patient is idiopathic pulmonary fibrosis (IPF).

PATIENT ANAMNESIS – 2003, 2004, 2005

Overview of the treatment the patient received

2003

Combination of azathioprine, prednisone and N-acylcysteine

2004

Cyclophosphamide bolus for an episode of subacute exacerbation (administered on 15 days over a time period of three months).


2005

- Oxygen therapy during walking
- Pulmonary rehabilitation
- Treatment with interferonγ-1b

• Despite treatment, the patient exhibited a decline of over 20% in FVC in 2004 after the exacerbation.

• Pulmonary function parameters remained relatively stable between 2004 and 2005 whilst on treatment with interferon-1b.


<table>
<thead>
<tr>
<th></th>
<th>11/2003</th>
<th>05/2004</th>
<th>05/2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.1</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.7</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>DL₃CO (ml/min/mmHg)</td>
<td>8.2</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td>WR₅₀MAX (Watts)</td>
<td>98</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>VO₂₅₀Max (mlO₂/(kg*min))</td>
<td>24</td>
<td>16.7</td>
<td>13.4</td>
</tr>
<tr>
<td>PaO₂₅₀max (mmHg)</td>
<td>55</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>P(A-a)O₂₅₀max (mmHg)</td>
<td>62</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>V₄/D/V₅₅₀max (%)</td>
<td>43</td>
<td>52</td>
<td>41</td>
</tr>
</tbody>
</table>
IMAGING - 2005

The CT scan in 2005 shows aggravation cysts.
IMAGING - 2005

The CT scan in 2005 shows traction bronchiectasis and honeycombing.
LUNG FUNCTION - 2006

During the course of six months, the patient exhibits a further decline in FVC of 10%.

Lung function testing (2006)

<table>
<thead>
<tr>
<th></th>
<th>03/2006</th>
<th>10/2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (L)</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>TLC (</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>DL\textsubscript{CO} (ml/min/mmHg)</td>
<td>5.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Pa\textsubscript{O2} \textsubscript{rest} (mmHg)</td>
<td>82</td>
<td>55</td>
</tr>
</tbody>
</table>
This deterioration lead to an alteration of treatment in 10/2006:

- Stop treatment with interferonγ-1b
- Start treatment with octreotide

The patient underwent a lung transplant in 2007 and is currently well with a good quality of life despite recurrent infectious complications.
OPERATING THEATRE - 2007

1999

2007
The most important take home messages of the case are:

1) Lung crackles and even slight decrease in DL$_{CO}$ over several successive measurements can be early signs of IPF and should not be ignored.

2) Reduction of pulmonary gas exchange during exercise can precede the decrease in lung volumes measured at rest.

3) IPF may be present without visible honeycombing on CT. In this case, IPF can be confirmed by lung biopsy.

4) Being asymptomatic does not exclude the diagnosis of IPF.