IPF AND LUNG CANCER

*Distinct horns of the same devil*

Αργύρης Τζουβελέκης
Πνευμονολόγος
argyrios.tzouvelekis@fleming.gr
First Respiratory Department, SOTIRIA Hospital
First case
• 78-yrs old, male, ex-smoker (70 p/yrs), DOE (mMRC II/IV)
• GERD symptoms
• No familial Hx/No exposure
• Medical Hx: Arterial hypertension
• No Raynaud, arthralgias or myalgias,
• + Velcro type crackles: + clubbing
• Negative immunologic profile
• FVC: 56%pred, TIF: 81, TLC: 52% pred, DLCO: 48% pred
• 6MWD: 440 m, 96% - 84%
• ECHO: RVSP: 28mmHg
• BAL: 88% МΦ, 8%L, 2% Eos, 2% Polys
EBUS: Mass, 4R, 7 (+): SQUAMOUS – T2bN2M0-IIIA
Management

- Functional deterioration
- Severe disease status
- Male gender
- IIIA-borderline
- 80 yrs
- Nintedanib + CARBOPLATIN + PACLITAXEL
Second case
• 65 yrs – ex-50 p/yrs – IPF last 2.5 yrs – under OFEV last 2 yrs
• Negative immunologic profile
• FVC: 78% pred, TIF: 85, TLC: 65% pred, DLCO: 61% pred
• 6MWD: 480 m, 96% - 90%
• ECHO: RVSP: 24mmHg
• BAL: 85% МΦ, 10% L, 2% Eos, 3% Polys
• 6 mo- HRCT follow-up
FNB – Adenocarcinoma
EBUS/TBNB – N0 - T2aN0M0-Ib
Moderate (stable) disease
Middle age – Male gender - Low TNM
Lung surgery – Segmentectomy

Management
Third case
History

- 80-yrs old, male, ex-smoker (70 p/yrs), DOE (mMRC II/IV)+ GERD symptoms
- No familial Hx/No exposure
- Medical Hx: Arterial hypertension
- No Raynaud, arthralgias or myalgias,
- + Velcro type crackles: + clubbing
- Negative immunologic profile
- FVC: 62%pred, TIF: 82, TLC: 52% pred, DLCO: 29% pred
- 6MWD: 340 m, 96% - 84% - LTOT: 2lt/min
- ECHO: RVSP: 28mmHg
- BAL: 88% МΦ, 8%L, 2% Eos, 2% Polys
- Nintedanib Rx (2 years) – Gradual Progression
- FVC: 54%pred, TIF: 84, TLC: 48% pred, DLCO: 22% pred
Management

- FNB – Adenocarcinoma
- EBUS/TBNB – N1 – T4N1M0-IIIA
- Disease progression - Elderly pt – Male gender - IIIA
- MICO

Graph showing FVC, TLC, and DLCO %predicted.
Hyper-proliferating – Ki67 + Epithelium

CK19 + AEC + Adenoid structures (ADC)
INTRODUCTION

Factors that increased interest in patients with both IPF and lung cancer:

i. IPF **risk factor** for lung cancer development

ii. Patients with IPF and lung cancer have **shorter survival**

iii. **Common pathogenetic pathways**

*Vancheri BMC Med. 2015*
RESEARCH ARTICLE

Lung cancer in idiopathic pulmonary fibrosis: A systematic review and meta-analysis

AliReza JafariNezhad

PLOS ONE | https://doi.org/10.1371/journal.pone.0202360 | August 16, 2018

• 35 (0.18% studies included)
• Prevalence of LC in IPF: 13.54% - x9 in men
• 38% SQCC, 31% ADC, 20% SmCC, 5%LCC, 4% Adeno-squamous
• 31% stage III, 13% stage II
• 84% peripheral area, 16% central – RLL most common
i. **Prevalence of lung cancer in IPF 2.7 - 31.3 %**

Table 1: Studies reporting prevalence of lung cancer in patients with IPF

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with IPF</th>
<th>Incidence of lung cancer</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagai</td>
<td>99</td>
<td>31 (31.3%)</td>
<td>1992</td>
</tr>
<tr>
<td>Park</td>
<td>281</td>
<td>63 (22.4%)</td>
<td>2001</td>
</tr>
<tr>
<td>Le Jeune</td>
<td>1064</td>
<td>29 (2.7%)</td>
<td>2007</td>
</tr>
<tr>
<td>Ozawa</td>
<td>103</td>
<td>21 (20.4%)</td>
<td>2009</td>
</tr>
<tr>
<td>Kreuter</td>
<td>265</td>
<td>42 (16%)</td>
<td>2014</td>
</tr>
<tr>
<td>Tomassetti</td>
<td>181</td>
<td>23 (13%)</td>
<td>2015</td>
</tr>
</tbody>
</table>

ii. **Squamous cell carcinoma (SCC) most frequent histologic type (35-46%)**

Table 2: Studies reporting histologic predominance of lung cancer in patients with IPF

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with IPF-lung cancer</th>
<th>SCC</th>
<th>ADC</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagai</td>
<td>31</td>
<td>45.2%</td>
<td>35.2%</td>
<td>1992</td>
</tr>
<tr>
<td>Park</td>
<td>65</td>
<td>35%</td>
<td>30%</td>
<td>2001</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>53</td>
<td>48%</td>
<td>46%</td>
<td>2001</td>
</tr>
<tr>
<td>Ozawa</td>
<td>21</td>
<td>38%</td>
<td>29%</td>
<td>2009</td>
</tr>
<tr>
<td>Lee</td>
<td>70</td>
<td>40%</td>
<td>30%</td>
<td>2014</td>
</tr>
<tr>
<td>Kreuter</td>
<td>42</td>
<td>30%</td>
<td>31%</td>
<td>2014</td>
</tr>
<tr>
<td>Tomassetti</td>
<td>23</td>
<td>39%</td>
<td>35%</td>
<td>2015</td>
</tr>
</tbody>
</table>

**Abbreviations.** IPF: Idiopathic pulmonary fibrosis, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma
**Greek cohort**

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>BASELINE DATA (N,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients with IPF</strong></td>
<td><strong>608</strong></td>
</tr>
<tr>
<td>Patients with IPF and cancer</td>
<td>63/608 (10.3%)</td>
</tr>
<tr>
<td>Males/ Females</td>
<td>57/6</td>
</tr>
<tr>
<td>Age (mean ± SD), years</td>
<td>72.8 ± 7.5</td>
</tr>
<tr>
<td>FVC %pred (mean ± SD)</td>
<td>75.9 ± 21.5</td>
</tr>
<tr>
<td>DLco %pred (mean ± SD)</td>
<td>47.2 ± 15.8</td>
</tr>
<tr>
<td>Patients with IPF and lung cancer</td>
<td>50/608 (8.2%)</td>
</tr>
<tr>
<td>Other types of cancer</td>
<td>16/608 (2.6%)</td>
</tr>
<tr>
<td>Both lung and other type of cancer</td>
<td>3/608 (0.5%)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>37/50 (74 %)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>20/50 (40 %)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12/50 (24 %)</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>7/50 (14 %)</td>
</tr>
<tr>
<td>Lung cancer post IPF diagnosis</td>
<td>23/36 (63%)</td>
</tr>
<tr>
<td>Median latency time ( months) + SD</td>
<td>14.6 ± 35.5</td>
</tr>
<tr>
<td>Lung cancer and IPF synchronously</td>
<td>11/36 (31%)</td>
</tr>
<tr>
<td>Lung cancer prior IPF diagnosis</td>
<td>2/36 (6%)</td>
</tr>
<tr>
<td>Median latency time (months) + SD</td>
<td>23.8 ± 57.8</td>
</tr>
<tr>
<td>Missing data for time of lung cancer diagnosis</td>
<td>14/50 (28%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>24.0 (95% CI: 18.6 to 38.0)</td>
</tr>
</tbody>
</table>

**Greek cohort**

**Lung Cancer Histology**

- SQLC
- ADC
- SCLC
- OTHER

**Location-Treatment**

- PRIMARY LESION
- UPPER LOBES
- CHEMOTHERAPY
- SURGERY
Is there a direct relationship between fibrotic areas and cancer development?

This phenomenon has been coined out as "scarcinoma"
IPF fibroblasts undergo glycolytic reprogramming towards myofibroblast differentiation ("Warburg effect")

Cell-to-cell communication and signal transduction pathways

- PI3K/AKT (therapeutic target in both)
- Wnt/β-catenin (cancer development, fibrosis progression)
- Tyrosine kinases/phosphatases (nintedanib, SHP2)
Findings In the discovery analysis, we identified four serum biomarkers (surfactant protein D, matrix metalloproteinase 7, CA19-9, and CA-125) that were suitable for replication. Histological assessment of CA19-9 and CA-125 suggested that these proteins were markers of epithelial damage. Replication analysis showed that baseline
Clinical Data

Patients with IPF and LC present with worse prognosis than IPF for the following reasons:

i. Increased perioperative mortality (7.1% vs 1.9%)

ii. Increased likelihood for postoperative AEx (8.7% vs 1.8%)

iii. Relapse of malignancy (36%)

iv. Complications from aggressive therapeutic interventions (chemotherapy-infections, post-radiation pneumonitis/injury)

Negative prognostic factors for surgical interventions:

i. Increased levels of KL-6, LDH

ii. Decreased FVC, DLCo

iii. Male gender, use of corticosteroids, history of AEx, definite UIP pattern

How do we approach a patient with IPF and suspicious lung lesion (?)
Patients with IPF and lung cancer: diagnosis and management

*Argyris Tzouvelakis, Paolo Spagnolo, Francesco Bonella, Carlo Vancheri, Vasilios Tzilas, Bruno Crestani, Michael Kreuter, Demosthenes Bouros

- LDCT/PET scan
- PFS
- Location of the lesion
- Avoid irradiation
- Beware of surgical interventions
- Platin doublets/1\textsuperscript{st} line
- Don’t discontinue antifibrotics
The approval of nintedanib and pirfenidone alters the scenario:

i. Pirfenidone decreases the incidence of lung cancer (2.9% vs 20.3%)

ii. **Prophylactic effect** of preoperative treatment with pirfenidone for postoperative acute exacerbations (3.2% vs 21.1% within 90 postoperative days)

iii. Nintedanib improves the outcome for docetaxel-based second-line therapy especially for patients with adenocarcinoma

iv. Drug repositioning like nintedanib (pan-class I PI3K/mTOR inhibitor ?)

THE ROLE OF LIQUID BIOPSIES

- Similar concept to that of prenatal screening – circulating free DNA

- Inability for molecular tumor profiling in 20% - Low PFS, small tissue
- First PCR-droplet biopsy test for BRAF (V600) and EGFR (T970M) in clinic
• IPF risk of developing LC increases over time- 3.3% (1st yr) – 55% (10th yr)
• 70% of IPF pts have Mediastinal Lnpathy – Reactive or NOT?
• Amenable need for minimally invasive diagnostic/screening tools
• Low dose CT scan + EBUS/TBNB sampling = screening algorithm for early detection of high risk individuals
Diagnosis And Management Of lung cancer and FibrOSIS “DI-A-M-O-R-F-OSIS” survey
Aims

• To identify variations in diagnostic and management strategies across different hospitals and institutions

• To raise awareness on the association between the two conditions

• To provide rationale for a consensus statement (or position paper) for an improved, homogeneous and standardized approach
Design

• Q & A- based survey – Approximately 40 Qs – 10-15 min

• **General Knowledge Questions**: i.e. *What is your medical specialty?*

• **Prevalence-based Questions**: i.e. *What is the most common histologic subtype of lung cancer in your cohort of patients with IPF?*

• **Disease specific Questions (Diagnosis)**: i.e. *What diagnostic modality do you use to screen patients with IPF for lung cancer?*

• **Disease specific Questions (Treatment)**: i.e. *How would you treat a patient with severe IPF (DLCO<35%) and otherwise non-operable NSCLC?*

• **Case report-based Questions**: i.e. *What would it be your next diagnostic step in a patient with severe IPF presenting with a nodular lesion of 9 mm*
i. IPF is an independent risk factor for lung cancer (10-15% prevalence)
ii. Pathogenetic similarities - scacinoma
iii. Need for a consensus for the management of patients with IPF-LC
iv. Pirfenidone and nintedanib alter the scenario? PD-1 inhibitors?
v. Early diagnosis is the key – Role of Liquid biopsies- EBUS/TBNB – low dose CT
Ευχαριστίες

• Κος Παπίρης/Κα Μάναλη/Κος Τόμος – ΒΠΠ Νοσοκομείο «Αττικόν» -ΕΚΠΑ
• Κα Αντωνίου/Τραχαλάκη/Βαρσαμίδη – ΠΑΓΝΗ-Πανεπιστήμιο Κρήτης
• Κα Μαρκοπούλου – ΓΝ Παπανικολάου
• Κος Κολιλέκας – 7η Κλινική ΓΝΝΘΑ «ΣΩΤΗΡΙΑ»
• Κο Παπανικολάου – ΓΝ Κερκύρης
• Κα Παπακώστα- ΓΝ Παπανικολάου –ΑΠΘ
• Κα Δανιήλ/Μπαρδάκα – Πανεπιστημιακό Νοσοκομείο Λάρισας
• Κα Δημάκου – 5η Πνευμονολογική Κλινική – ΓΝΝΘΑ «ΣΩΤΗΡΙΑ»
• Κος Μπούρος/Καραμπιτσάκος/Τζίλας/Γομάτου/Μπούρος Ε/Ντάσιου/Μαρκοζάννες/Τριγγίδου-Α’ΠΠ ΓΝΝΘΑ «ΣΩΤΗΡΙΑ», ΕΚΠΑ