Case

- 57 y/o woman with ESRD on PD since March 2013. Admitted for resection of left lung carcinoid tumor nodules.

- Lung nodules were found incidentally during her pre-kidney transplant evaluation.

- No symptoms of carcinoid syndrome.

- Denied palpitations, hot flashes, diarrhea or wheezing.
Case

- **PMH:** HTN, mild CHF, DM, Diabetic retinopathy, HLD, ESRD on PD (overnight 2x/week) and hiatal hernia.
- **PSH:** Appendectomy, Gastric bypass 2009, ORIF of right femur, Tenkhoff catheter placement 2013
- **Allergy:** NKDA
- **Meds:** Torsemide, Metoprolol, Calcitriol, Pravastatin, Hydralazine, Aspirin 81, Nifedipine, Rena-Vite, Trazodone, Humalog and Lantus
- **SH:** lifelong nonsmoker, drinks socially, works in a nontoxic environment.
- **FH:** DM both father and mother, brother has multiple sclerosis.
Case

- Physical Exam:
- Vitals- BP 144/86 HR 71 RR 14 O2 sat. 100%
- AAOx3, well nourished, white female.
- PERRL, no flushing
- Neck: supple, no lymphadenopathy
- CTAB
- S1S2 RRR
- SNTND, no organomegally, no palpable masses
- Rectal: no masses, no gross blood, guaiac negative
- Ext. +1 edema, no clubbing.
Imaging

- Present CT chest LUL 1.13 cm and RML 0.95 cm
- Patient had CT chest done 2010.
- No difference in size or in contour appearance in the three year interval.
Workup

• CT guided biopsy of the **left side** lesion c/w Pulmonary carcinoid tumor.

• The KI-67 index was <1% and this was considered a peripheral typical carcinoid.

• CT guided biopsy of the **right side** c/w neuroendocrine tumor.
Workup

- CBC - 9.7/9.1/27.1/193
- BMP - 135/3.5/102/24/37/3.6/216
- LFTs - 5.8/3.6/20/21/87/0.4
- HGBA1C 6.4
- Carcinoid tumor markers - negative
  1. Serum Serotonin level.
  2. Urine 5-Hydroxyindoleacetic acid (5-HIAA).
  3. Serum Chromogranin A (CgA).
  4. Pancreastatin.
  5. Neuron Specific Enolase (NSE)
Workup

- CT Abdomen/Pelvis- negative.
- Octreotide scan- negative.
- EGD/ Colonoscopy- negative
- PFT- FEV₁ mild obstructive vent. Defect, Lung volume by helium dilution WNL, DLCO WNL
Plan

• Presence of typical carcinoid lesions as well as the requirement that she be cancer free to qualify for renal transplantation led to decision for surgery...
Factors that Can Rule Out Kidney Transplantation

- Severe CAD.
- Severe cardiomyopathy
- Severe PVD.
- Severe pulmonary disease, such as advanced emphysema, pulmonary hypertension.
- HIV.
- Active infection (active hepatitis, TB, osteomyelitis).
- Cancer, such as colon, breast or pulmonary. Exceptions are skin cancers with evidence of complete excision. Patients may be considered for a renal transplant after a disease free interval.
- Current drug and/or excessive alcohol abuse.
- Serious and incapacitating mental illness
- Repeated noncompliance with medical regimen.
Intra./Postoperative Course

- Patient was taken to the OR on 10/30/13.
- Octreotide drip for Carcinoid crisis prophylaxis.
- Bronchoscopy, left VATS, LUL wedge resection x2 and LLL wedge resection x1.
- Chest tube was removed on POD#1
- Discharged home on POD#2
Pathology

- #1 Lingula, wedge-> Carcinoid tumor 0.4 cm., margin is clear 0.6 cm., KI index 5%.

- #2 LUL, wedge-> pulmonary ossification and interstitial fibrosis.

- #3 LLL, wedge-> interstitial fibrosis
Questions
Historical Perspective

- 1888- Lunarsch first applied a term hormonally active tumors on carcinoids.
- 1907 - Obendorfer first characterized and named midgut Carcinoid (Karzinoid).
- 1937- Hamperl first described Bronchial carcinoids
- 1953- Lembeck showed that abdominal carcinoids contain large amounts of 5-HIAA.
- 1954- Thorson first reported Carcinoid Syndrome symptoms.
- 1972- Arrigoni first described histological differentiation between typical and atypical broncho-pulmonary carcinoid tumors
Introduction

• Bronchial Carcinoid tumors are Cancer.

• It originates from the dispersed neuroendocrine system (Kulchitsky cells)

• Neuroendocrine tumors:
  a) Endocrine organs (pancreas, adrenal).
  b) Dispersed endocrine cells (GI tract, broncho-pulmonary, C cells of the thyroid).
Carcinoid tumors are classified based on embryonic division of the gut

- **Foregut tumors:** Respiratory tract, stomach, 1st part of duodenum, biliary system and pancreas.
- **Midgut tumors:** 2nd part of duodenum, through ascending colon and appendix.
- **Hindgut tumors:** Transverse, descending colon and rectum.
• 2 % of all lung cancers.

• Neuroendocrine cells detect the levels of oxygen and carbon dioxide in the air

• People who live at higher altitudes have more lung neuroendocrine cells

• Spectrum of NEC: TC>AC>NSCLC->SCLC.
Epidemiology

- Incidence rates 0.2 : 2 /100,000 population/yr.
- Women > Men
- White > Black
- Sporadic
- Most common primary lung neoplasm of children
- TC 4x > AC
- 20 : 30 % of all carcinoid tumors
Primary broncho-pulmonary carcinoids comprise a significant proportion of carcinoid tumors.

NOS = not otherwise specified.
Risk Factors

- Smoking - unclear
- MEN1 syndrome (10%)
- Familial pulmonary carcinoids
Typical carcinoids

- 1%-2% of lung tumors
- 90% of lung carcinoids
- 5-15% LNs mets. and 3% distant mets.
- Peripheral
- 5\textsuperscript{th} decade of life.
- Low mitotic activity
- 90% Low-grade (well-differentiated)
- Slowly-growing neoplasms
- Rarely metastasize to extra-thoracic structures.

Histologic features of low- and intermediate-grade neuroendocrine carcinoma (typical and atypical carcinoid tumors) of the lung.
Tsuta K, Raso MG, Kalhor N, Liu DD, Wistuba II, Moran CA
Lung Cancer. 2011 Jan; 71(1):34-41
Atypical carcinoids

- 0.1-0.2% of lung tumors
- 10% of lung carcinoids
- 40-50% LNs mets. and 20% distant mets.
- Central (hilar or perihilar)
- 6th decade of life.
- High mitotic activity
- High-grade (intermediate differentiated)
- Rapid tumor growth (More aggressive)
- Higher rate of metastasis
- Intermediate between typical carcinoids and SCLC.
Signs and Symptoms

- Asymptomatic
- Cough
- Bloody sputum
- Wheezing
- Shortness of breath
- Chest pain
- Post-Obstructive Pneumonia

Review Bronchial typical carcinoid tumors.
Morandi U, Casali C, Rossi G
Signs and Symptoms

- **Carcinoid syndrome** 1%-5%, secondary vasoactive substances
  - Flushing
  - Diarrhea
  - Wheezing
  - Pellagra
  - Tachycardia and
  - Heart-valvular dysfunction.

- **Cushing syndrome** hypercortisolism secondary ACTH
  - Weight gain
  - Weakness
  - DM
  - Increased body and facial hair.
Labs Workup

- **Serotonin** in the blood and urine
- **5-HIAA** in the urine (collected over 24 hrs)
- **Chromogranin A (CgA)**, glycoprotin made in the secretory granules, highly specific.
- **Pancreastatin**
- **Neuron-specific enolase (NSE)**, glycolytic enz.
- **Cortisol**
- **ACTH**
- **Kinins**
- **Substance P**
Imaging Workup

- CXR
- CT scan
- CT guided Needle biopsy
- Bronchoscopy
- Endobronchial ultrasonography (EBUS)
- Octreotide scintigraphy
- I-131 MIBG
- PET scan.
Positive Octreotide Scan.
Histologic features distinguishing among lung carcinoid tumors are **morphology, mitotic activity** and the presence or absence of **necrosis**.
<table>
<thead>
<tr>
<th>Features</th>
<th>Typical Carcinoid</th>
<th>Atypical Carcinoid</th>
<th>Small cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic Pattern</td>
<td>Trabecular, palisading and spindle cell</td>
<td>Trabecular, palisading and spindle cell</td>
<td>Do not grow with specific pattern</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent or rare</td>
<td>Up to 10 per 10 hpf</td>
<td>&gt;10 per 10hpf</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent</td>
<td>Focal</td>
<td>Extensive</td>
</tr>
<tr>
<td>Nuclear pleomorphism, hyperchromasia</td>
<td>Absent</td>
<td>Often present</td>
<td>Extensive</td>
</tr>
</tbody>
</table>
Staging (same TNM staging used for other types of lung cancer)

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>T1 &lt;3 cm</th>
<th>T2 3-7 cm</th>
<th>T3 &gt;7 cm</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T2a 3-5 cm, T2b 5-7 cm) Atelectasis (part of lung) Invasion: Visceral pleura, main bronchus ≥ 2 cm from carina Atelectasis (whole lung) Invasion: Phrenic nerve, diaphragm, chest wall mediastinal pleura, main bronchus &lt;2 cm from carina, parietal pericard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>NO No lymph nodes involvement</td>
<td>N1 Ipsilateral bronchopulmonary/hilar</td>
<td>N2 Ipsilateral mediastinal/subcarinal</td>
<td>N3 Contralateral hilar/contralateral mediastinal/supraclavicular</td>
</tr>
<tr>
<td>Metastasis</td>
<td>M0 No metastasis</td>
<td>M1 Bilateral lesions Distant metastasis malignant pleural effusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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TNM staging system for lung cancer

- **Primary tumor (T)**
  - T1 Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
  - T1a Tumor ≤2 cm in diameter
  - T1b Tumor >2 cm but ≤3 cm in diameter
  - T2 Tumor >3 cm but ≤7 cm, or tumor with any of the following features:
    - Involves main bronchus, ≥2 cm distal to carina
    - Invades visceral pleura
    - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - T2a Tumor >3 cm but ≤5 cm
  - T2b Tumor >5 cm but ≤7 cm
  - T3 Tumor >7 cm or any of the following:
    - Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
    - Atelectasis or obstructive pneumonitis of the entire lung
    - Separate tumor nodules in the same lobe
    - T4 Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
- **Regional lymph nodes (N)**
  - N0 No regional lymph node metastases
  - N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
  - N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
  - N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
- **Distant metastasis (M)**
  - Mo No distant metastasis
  - M1 Distant metastasis
  - M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
  - M1b Distant metastasis (in extrathoracic organs)

### Staging

- **Stage IA** $T_1 \; N_0 \; M_0$
- **Stage IB** $T_{2a} \; N_0 \; M_0$
- **Stage IIA** $T_{1,2a} \; N_1 \; M_0$ // $T_{2b} \; N_0 \; M_0$
- **Stage IIB** $T_{2b} \; N_1 \; M_0$ // $T_3 \; N_0 \; M_0$
- **Stage IIIA** $T_{1,2a,2b} \; N_2 \; M_0$ // $T_3 \; N_{1,2} \; M_0$ // $T_4 \; N_0, N_1 \; M_0$
- **Stage IIIB** $T_4 \; N_2 \; M_0$ // Any $T \; N_3 \; M_0$
- **Stage IV** Any $T$ Any $N$ $M_{1a}$ or $M_{1b}$

Treatment

- **Surgery** - complete resection is the main stay of the treatment.
  - **Resectable**
    Most patients cured with surgery alone and don't need other treatments.
  - **Unresectable**
    Surgery, radiation therapy, chemotherapy, targeted therapy, interferon alpha and somatostatin.
Treatment

- **Typical Carcinoid-**
  - parenchyma-saving resection
  - good prognosis
  - 97% 5 year survival with or without nodal involvement

- **Atypical Carcinoid-**
  - Radical resection with mediastinal LN dissection
  - 78% 5 year survival, 60% with nodal involvement

Treatment

- **Chemotherapy** - used for advanced pulmonary carcinoid. FU+STZ (improved survival but not PFS).
  
  Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281.
  J Clin Oncol. 2005 Aug 1; 23(22):4897-904.

- **Radiotherapy** - local advanced disease.

- **Everolimus+Octreotide** - improved PFS in patients with carcinoid syndrome.
  
Treatment

- **Somatostatin analog** - Lanreotide is a synthetic analog used in treating carcinoid syndrome.
  
  *Neuroendocrine bronchial and thymic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.*
  Oberg K, Hellman P, Kwekkeboom D, Jelic S, ESMO Guidelines Working Group

- **Interferon alpha** - antiangiogenic, retard tumor growth in patients with midgut carcinoids
  
  *Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours.*
  Kölby L, Persson G, Franzén S, Ahrén B

- **Antiangiogenic therapy** - Sunitinib malate is a small molecule kinase inhibitor for patients with metastatic or unresectable carcinoid tumors.
  
  *Activity of sunitinib in patients with advanced neuroendocrine tumors.*

- **Hepatic artery embolization or chemoembolization.**
Treatment Algorithm of Carcinoid Tumors

1. Carcinoid syndrome?
   - Yes: Octreotide or lanreotide
   - No: Surveillance 10 years

2. Carcinoid tumors
   - Atypical: Radical surgery + lymph node dissection
   - Typical: Parenchyma-saving resection + lymph node dissection

3. Metastasis?
   - No: Surveillance 10 years
   - Hepatic metastasis: Local treatment (metastasis surgery or hepatic artery embolization or chemoembolization)
   - Extrahepatic metastasis: Systemic medical therapies: chemotherapy or interferon
     - Or targeted therapy: antiangiogenic therapy and m-TOR inhibitor

4. Inoperable: Endoscopic resection or surveillance
Prognosis

- **Typical carcinoids** — excellent prognosis following surgical resection.
  - 5 year survival rates 87 : 100 %
  - 10 years 82 : 87 %
  - low recurrence rate 2 : 11%.
- **Atypical carcinoids** — greater tendency to metastasize and to recur locally.
  - 5 year survival rates 30 : 95 %
  - 10 year are 35 : 56 %

[Bronchial carcinoid tumor: a retrospective analysis of 62 surgically treated cases].
Iglesias M, Belda J, Baldó X, Gimferrer JM, Catalán M, Rubio M, Serra M
POST-TREATMENT SURVEILLANCE

- TC-> CT chest annually
- AC-> CT chest every 6months x 2 years, then annually.

- These recommendations are suggested by NANETS, not available from the NCCN.
Conclusion

• TC & AC are distinguished by the clinical, histological and radiological presentation.

• Surgery remains a mainstay for the treatment of both types of carcinoids,

• Typical carcinoids are low-grade malignancies with favorable prognosis following complete resection.

• Atypical carcinoids are intermediate-grade malignancies, with higher rate of nodal involvement should receive a radical surgery
Questions 1

• What is the gold standard test for confirming the diagnosis of carcinoid and NETs?

A. Serotonin in the blood
B. 5-HIAA in the urine
C. Chromogranin A
D. Pancreastatin
E. Neuron-specific enolase
Question 1

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A. Serotonin in the blood  
B. 5-HIAA in the urine  
C. Chromogranin A  
D. Pancreastatin  
E. Neuron-specific enolase
Question 2

• Bronchial carcinoid tumors derived from.............. cells.
Question 2

• Bronchial carcinoid tumors derived from Kulchitsky cells.
References


