### Articles for Discussion

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### Articles for Notation

**Original Articles**

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**Current Topics/Review Articles**

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Case Reports

Letters and Replies to the Editor
I. Articles for Discussion


Purpose: A report of 3 cases of a rare lesion – only 10 cases reported since 1954- with IHC and EM.

Methods:
- 3 cases of glandular papilloma were identified between 1989-2005.
- IHC with p53, Ki-67, CK17 and HPV.
- EM examination

Results:
- 2M:1W, 53, 72 and 75 yo, 2 former smokers
- 1 endobronchial lesion with presenting symptoms of hemoptysis and obstructive pneumonia and 2 peripheral lesions, incidental
- 2 wedge resections and one lobectomy. FU of 3 mos, 6 and 7 yrs, no recurrence or metastasis
- Size of 1.0 to 1.4 cm in greatest dimension.
- Papillary fronds lined by a combination of cell types, pseudostratified columnar with ciliated cells, basal cells and mucous cells.
- One case had central “scar”, looked like BAC/papillary adeno except for the cell population
- All had CK17 diffuse + in basal cells, Ki-67 2.3 to 12%, p53 <10% labeling and HPV neg in all
- EM confirmed the different cell types and cilia were normal

Take Home Message: These papillomas can be peripheral and mimic low grade papillary adenocarcinoma. The key is the combination of cell types including ciliated cells.


Purpose:
- Lung cancer the most common cause of brain metastasis
  - 10% at time of diagnosis
  - 40% will develop over time
- Possibility that prophylactic cranial radiation may be effective in the prevention of brain met
- Currently, early-staged NSCLC not screened for brain met
- Using markers involved in the different pathways of the metastatic cascade, shown to be possibly associated with poor prognosis, assess if can predict which patients will develop brain met

Method:
• From 1989-2003, group I of patients with NSCLC who developed brain mets, tissue available for both 1ary and met, tx with surgery with or without adjuvant therapy and no immediate post-op death. N=21
• From 1989-2003, control group II of patients with NSCLC and no brain met or met to other organ site. Neurologic exam or imaging negative. N=33
• IHC with Ki-67 (LI), caspase-3 (LI), VEGF-A (% + cells), -C, E-cadherin and EGFR (0=0-10% or less of + cells)

Results
• Gender, age, histology, location, tumor size, T, N and overall stage similar between both groups (no statistical p except for age 60 vs 65 yo). Mostly women, adeno, Stage I cancers.
• In group I, brain mets developed med 12.5 mos (range 1.7-89.4 mos) after lung 1ary. Group II no brain mets, med FU 3.5 yrs (0.8-6.6 yrs). FU time similar for both group (p=.54)
• Risk of developing brain mets associated with Ki-67 \geq 30\%, VEGF-C + (as low as 1\% of cells), and Capspase-3 \geq 20\% with p<0.001. E-cadherin 0-90\% + cells with p=0.05. Cut-offs based on highest odds ratio in predicting brain mets but overlap exists between both group
• No significant differences in overall survival between both groups but Ki-67 predicted for a poorer prognosis, 26 vs 47 mos.

Take Home Message:
• Good logic behind choices of markers and methodology but fell short of making this in anyway clinically useful. Not clear if having only 1 of these markers is sufficient to predict, or if a combination would better predict and then validate this model in a larger group.


Purpose: To describe 4 cases of fibrotic HP who developed a phase of acute exacerbation.

Methods:
• Retrospective study 2005-2007 of the ILD Program at the National Jewish
• Cases with diagnosis of fibrotic HP by clinic-radiologic-pathologic (surgical lung biopsies) correlation
• Clinical acute decline in respiratory status with no specific explanation and pathologic material (surgical biopsy, explant or autopsy) at time of decline available

Results:
• 4 patients, 3M:1F, 47 to 66 yo, 3 remote smokers, 1 with antigen exposure characterized Acute episode occurred between 4mos to 9 yrs after the biopsy proven fibrotic HP (although in 2 cases the fibrosis seems more by radiologic description than pathologic)
• Acute symptoms of dyspnea with/without systemic symptoms duration 4-8 weeks
• New bilateral ground glass infiltrates superimposed on fibrotic infiltrates in all cases
• All requiring mechanical ventilation, no response to treatment, 3 died and 1 had bilateral transplantation.
• All had DAD.

Take Home Message:
• Another chronic fibrosing ILD that can be associated with an acute exacerbation phase.


Purpose: To assess the mutation rate of EGFR in malignant pleural effusions (MPE) and assess the prognostic factors of adenocarcinomas with MPE.

Methods:
• June 2005-Dec 2006, 136 adenocarcinomas with MPE, all specimens obtained before treatment with EGFR TKI
• Control group of 91 surgically resected adeno archived between April 2001-Nov 2004
• EGFR mutation analysis by RT-PCR and direct sequencing
• RECIST guidelines to determine response to treatment

Results:
• In the surgically resected adeno:
  o EGFR mutation in 50.5% and no differences for gender, age, smoking status and Stage between patients with or without mutation.
  o 14 took EGFR TKI after tumor recurrence. 7 with mutations
  o Response was seen in 5 with mutation and in 3 without
• In the MPE group:
  o EGFR mutations in 68.4% and no differences for gender, age, smoking status and Stage between patients with or without mutation (greater than compared to above group p=0.007)
  o 71 patients treated with EGFR TKI, 38 with partial response, 1 with no mutation.
  o Med OS greater for patients with EGFR mutation (21.4mos vs 11.5 mos, p=0.005)
  o In multivariate, age<65 yrs, never smoker, ECOG PS 0-1 and EGFR mutation were associated with longer OS

Take Home Message:
• Study in an Asian population so results likely not applicable in North America although interesting that there was as many mutations in the men and smokers contrary to most studies.
• Clinical trials in USA were on advanced stage lung cancer IIIB and IV but not necessarily distinguishing the cases with MPE vs not so we don’t know if there would be a difference in rate of mutation but not sure how this really matters.
• I think it is nice to confirm that EGFR mutation can be assessed on cytology and we don’t need necessarily tissue
• And this is another study to suggest that EGFR mutation not only predicts for response to treatment but also is a prognostic factor (or the 2 linked really…but can’t tell from this study. In their multivariate had if patient was on TKI but not if there was a response or not, or didn’t look at that subgroup specifically).


**Purpose:** To review the histologic features of surgical biopsies of cases in which congenital alveolar capillary dysplasia (ACD) entered the differential diagnosis and distinguish it from congenital alveolar dysplasia (CAD).

- **ACD:**
  - Persistent PHTN
  - Deficiency in alveolar capillaries, medial hypertrophy of pulm art with muscular extension into intraacinar vessels and malposition of pulm veins adjacent to small pulm art
- **CAD:**
  - Less well defined
  - Rich network of capillaries and abundance of undifferentiated mesenchyme

**Methods:**
- 21 cases (1997-2005) reviewed by 3 pathologists
- **Criteria**
  - Misalignment of veins: present (2), probably present (1), absent (0)
  - Septal development: N/AN
  - Presence of clear cells in interstitium 0-6
  - Presence of type II hyperplasia 0-6
  - Evidence of PAH in preacinar arteries 0-6
  - Evidence of PAH in intra-acinar arteries 0-6
  - Capillary density 0-6
  - Capillary apposition 0-6
  - Coexistent alveolar hypoplasia, interstitial inflammation, AN interlobular septal development present/absent
- **Classification**
  - ACD
  - ACD/CAD overlap
  - CAD
  - Surfactant protein deficiency (SPD)
  - NSIP
- **IHC with CD34, SPD-B**
- **Correlation with clinical data**

**Results:**
- 7 ACD, 7 CAD, 3 ACD/CAD, 3 c/w SPD-B, 1 NSIP
- Histologically no distinguishing criteria between ACD, CAD and SPD except
No misalignment of veins in SPD
- ACD had less capillary density (scores 1 and 2) and apposition than CAD (scores 5-6) and SPD (score 5)
  - Clinically: pre-term not common, dx at 18 d for ACD, 103 d for CAD, cyanosis and/or respiratory distress the usual presentation. Most have an associated congenital abnormality.
  - Survival: all ACD with FU DOD, 1/3 ACD/CAD AWD 3 mos, 2/7 CAD alive 2.5 and 4 yrs FU

Take Home Message:
- Concept still not clear. But at least seems like we can’t really distinguish ACD and CAD based on this article and seems like doesn’t have important clinical significance

6- Berghams et al. EGFR, TTF-1 and Mdm2 expression in stage III non-small cell cancer: A positive association. Lung Cancer 2008; 62:35-44

**Purpose:** Investigate the prognostic significance of Mdm2, TTF-1, EGFR and p53 in Stage III lung cancer and determine relationship with known clinical variables (they had previously looked at TTF-1, EGFR and p 53 which was basically a negative study so now adding Mdm2!)

**Methods:**
- Stage III (by 1997 IIS) cancer 1985-2003; also use their own classification III β as T3-4N3M0 and III α as all others
- Biomarkers evaluated by IHC (score of intensity X % cells, class 1 < 50, 2= 50-100, 3>100). Mdm2 overexpression is a class 3, + for EGFR if 1 cell +, >5% for TTF-1 and >10% p53

**Results:**
- 84 patients, 63M, med age 66 yo, 44 squamous cell ca, 29 IIIA and 55 IIIB or 70 IIIα and 11 IIIβ (although 3 missing in this staging scheme)
- Variable tx from surgery + chemo-radiation, to chemo or radiation alone, and chemotherapy regimen varied,
- 76 dead, 3 alive and 5 lost to FU with 5-yr survival of 5.5%
- No association between expression of these markers and substage (whether using A vs B or α vs β)
- Association between EGFR and TTF-1 which are mutually exclusive (big surprise since EGFR are mostly + in squamous and TTF-1 in adeno!)
- No great association between these markers and overall survival except in squamous cell ca, the cases that were EGFR+ and TTF-1 neg had better survival than other combinations 474d vs 337 d (p=0.02)
- In univariate, only PS and treatment predicted outcome and in multivariate, treatment was the only predictive survival for OS and cancer specific survival

**Take home message:**
Amazing that a study like this gets published.

II. Articles for Notation
Original Articles


**Purpose:** To clarify prognosis of gefitinib treatment between chemonaive and chemotherapy treated patients. Focused on cases with EGFR mutations in exon 19 and 21.

**Methods:**
- Retrospective, Taiwan, Jan 2004 to June 2007
- Response to treatment to Gefitinib assessed by CT according to RECIST criteria:
  - Responders: complete and partial response
  - Non-responders: stable and progressive disease
- EGFR mutational analysis on either paraffin or frozen tissue

**Results:**
- 328 patients, 215F, mean 64.2 yo, 254 never smoker, 301 adeno, 49 IIIB and 279 IV
- 192 with EGFR mutation (75 with L858R, 77 with exon 19 del, 9 with exon 20 mutation and 32 with others) and statistically more women (138), never smoker (164) and adenocarcinoma (188)
  - 62.5% were responders, mostly exon 19 deletion(68.8%) and L858R (65.3) vs exon 20 (12.5%) and others (53.1%)
  - PFS shorter for exon 20 p=0.003 but not OS
- Patients with single mutation L858R and del exon 19
  - 152 patients, 91 chemonaive and 61 prior chemotx, no diff in age, gender, smoking and stage. All 4 non-adeno were in the chemotx group. No difference in OS and PFS.
  - More responders in chemonaive group 75.8% vs 54.1% p=0.005
  - In univariate analysis, female gender and chemonaive predicted for response
  - In multivariate only chemonaive was independent factor to predict response (p=0.006)
  - For OS only response to Gefitinib predicted for better survival (18.8 mos vs 11.2 mos) p=0.001, not mutation type, age, stage, smoking, gender or prior chemotx

**Take Home Message:**
- Well done study that showed Gefitinib to be effective in both chemonaive and chemotx patients without difference in OS and DFS.
- More responders in the chemonaive and response to tx main prognostic factor for OS

2- Cronkhite et al. Telomere Shortening in Familial and Sporadic Pulmonary Fibrosis. Am J Respir Crit Care Med 2008;178:729-737

**Purpose:** To identify mutations of telomerase, *TERT* and *TERC*, gene in familial and sporadic IPF and compare telomere length of circulating leukocytes in both groups
Methods:
- Clinical diagnosis of pulmonary fibrosis/idiopathic interstitial pneumonia/unclassifiable IP with exclusion of all potential cases of secondary pulmonary fibrosis [But in the discussion seems like cases were mostly IPF 50-85% with some NSIP and BOOP].
- Sequencing of TERT and TERC gene and assessed enzyme activity using TRAP assay
- Analysis of telomere length in leukocytes: Terminal restriction fragment length and by RT-PCR determination

Results:
- 25 probands of familial fibrosis and 34 sporadic subjects, 6 new mutations, none of which found in 528 controls
- Telomere length:
  - Control group of 201 normal subjects and determined range of length and establish percentile. Age similar to the study groups
  - Unrelated sporadic group n=75, 2 with mutation and 73 without
    - 2 with mutation, both <10th percentile for telomere length
    - 73 without, 17 <10th percentile, more than the control group (8 of 201) p=0.0000026
  - Familial group n= 77, 18 with mutation and 59 without
    - 18 with mutation, all below the 10th percentile
    - 14 without mutation <10th percentile, more than the control group p=0.000008
  - No distinguishing phenotype between patients with <10th and >10th percentile length telomere
  - Correlation with gender and age (but age similar between subgroups so did not affect the findings within the subgroups)

Take Home Message:
- Patients with “pulmonary fibrosis” do have shorter telomeres, not explained by mutation in the genes, marker of disease?
- Well executed study but poorly written with a lot of results in discussion

3- Park et al. Soluble Mesothelin-related Protein in an Asbestos-exposed Population. Am J Respir Crit Care Med 2008;178:832-837

Purpose: To assess SMRP in asbestos exposed workers and correlate with diagnosis of MM.
Methods:
- Prospective study in workers exposed to asbestos and other dust between Jan and Nov 2006
- Standardized questionnaire, radiology, lung function and physical exam
- Monitored for 12 mos and blood collected
- Chest x-ray mandatory, other exams as indicated; presence of non-neoplastic dust related diseases commented on
- Serum SMRP performed; specimen duplicates with 10% repeated in a “blind” fashion on different days (it should good correlation duplicate assays r=0.9 and repeat assay r=0.85)
If elevated, PET/CT done and results interpreted by radiologist “blinded” to results

Results:

- 621 (47.2%) of potential patients agreed to participate
  - Blood possible to collect in 538 (Normal SMRP <2.5nM), almost all men, mean age 66.9 yo, never smoker in 36%.
  - Healthy asbestos exposed in 223, silicosis in 20, asbestosis in 24, diffuse pleural thickening in 113, asbestosis and DPT in 13, pleural plaques in 142 and a few other combination in 3 (omitted for analysis too small)
    - Mean SMRP levels was for these groups respectively 0.79, 0.90, 1.14, 0.89, 1.08 and 1.06 \( p=0.002 \), healthy vs pp \( p<0.01 \) and healthy vs the others \( p=0.0003 \)
  - SMRP was normal in 523 patients and abnormal in 15 (2.8%) (including one with CRF)
    - 1/15 had CT only, found to have adenocarcinoma of the lung
    - 14 had PET/CT, 4 of which were AN
      - 0 cases of MM
      - Increase uptake in heart, Echo showed possible LA tumor, no further investigation because of age
      - 1 uptake in hilar and mediastinal region and did not want any further investigation
      - 2 with uptake in hilar region and FU CT did not show any malignancy
    - In the population with no elevated SMRP, one subject died of lung cancer, one of metastatic pancreatic cancer and one with asbestosis.

Take Home Message: In a screening setting of subjects exposed to dust, elevated SMRP was uncommon and did not predict for MM (nor for lung cancer) BUT only 1 year FU. Levels of SMRP were elevated in patients with dust related non-neoplastic diseases compared to healthy individuals.


Purpose: To look at relationship between ER\(\beta\) and histologic features of adenocarcinomas

Methods:

- 112 adenocarcinomas from 71M:41W, Jan 2002-March 2007
- Subtyped adenocarcinomas: papillary, acinar, BAC mucinous and non mucinous, mixed BAC, solid, signet ring, mucinous, clear cell
- ER\(\beta\) by IHC, % cells and intensity of staining assessed by 2 pathologists and disagreements resolved with third
  - Proportion Score based on estimated proportion of + cells: Score 1 >0 -1/100, score 2 1/100 – 1/10, score 3 1/10 – 1/3, score 4 1/3 – 2/3, score 5 2/3 – 1
  - Intensity score: score 1 weak, score 2 intermediate, score 3 is strong
  - Final score = PS + IS; high 5-8, low 0-4 and class A 6-8, B 4-5, C 0-3

Results:
19% never smokers, 38% Stage I and 38% Stage III
- Adeno mixed subtype 51%, analyzed each subtype separately
  - Acinar in 49, papillary in 49, solid in 44, non mucinous BAC in 34, mucinous BAC in 2, clear cell in 6, signet ring in 1 and mucinous in 9
- Can’t tell how many cases + because the Score 0 encompassed in the low score or score A but large number had a high score, almost all groups over 60%.
- Solid type has lowest expression on ERβ and mucinous, clear cell adeno and non-mucinous BAC the highest expression. Lowest expression in high grade tumor vs low grade tumor (which correlates well with histologic subtype!)
- No association between ERβ and clinicopathologic features.

**Take Home Message:** Beware of the antibody used for ER in clinical practice because high number of lung cancers positive for ERβ

5- Iwahori et al. Megakaryocyte potentiating factor as a tumor marker of malignant pleural mesothelioma: Evaluation in comparison with mesothelin. Lung Cancer 2008;62:45-54

**Purpose:** Both megakaryocyte potentiating factor (MPF) and SMRP have been shown to be increased in the serum of patients with MPM. This study aims at comparing the value of these proteins.

**Methods:**
- Study groups:
  - 27 consecutive patients with unresectable MPM, 13 epithelial type, 3 sarcomatous, 5 biphasic and 6 unclassifiable (cytology specimens).
  - Control group of 47 patients with lung cancer, 35 with other types of cancers (18 ovarian, 8 stomach and 9 colon cancers), 9 healthy asbestos-exposed adults and 38 healthy adults with no history of asbestos exposure.
- Generate their own monoclonal Abs and prepare ELISA assays for MPF and MSLN (identical to SMRP, soluble variant), with confirmatory immunoprecipitation and Western Blots.
- Measure serum MFP and MSLN in all subjects and determine cut-off values, sensitivities and specificities.

**Results:**
- There are statistical differences in the serum level between MPM and control groups but still overlap in values
- Using cut-off value of MPF at 19.1ng/ml, ROC of 0.879, sensitivity of 74.1% and specificity of 90.4% (patients with lung cancers and other cancers had elevated value above cut-off) and for MSLN cut-off value at 93.5ng/ml ROC of 0.713 with sensitivity of 59.3% and specificity of 86.2%
- Significant correlation between both markers with y=0.77

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<th>Diagnosis</th>
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<th>MSLN (ng/ml)</th>
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<td></td>
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</tr>
<tr>
<td>Type</td>
<td>n</td>
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<tr>
<td>MPM</td>
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<td>Colon cancer</td>
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<td>9.0 (2.9)</td>
<td>8.0</td>
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Significance of median values for the specified control groups compared with MPM. Mann–Whitney’s U test; *p < 0.001.
Significance of median values for the specified control groups compared with MPM. Mann–Whitney’s U test; †p = 0.028.
Significance of median values for the specified control groups compared with MPM. Mann–Whitney’s U test; ‡p = 0.005.
Significance of median values for the specified control groups compared with MPM. Mann–Whitney’s U test; §p = 0.01

Take Home Message: Good efforts in getting a serum test for MPM but still quite a bit away from PSA. This study would indicate that MPF would be better than mesothelin

Current Topics/Review Articles

Special Section of Arch Pathol Lab Med 2008 ; vol 132 on Molecular Signatures of Lung and Pleural Tumors.

- These review articles summarize the proceedings of a special Joint Symposium of the European Working Groups for Molecular Pathology and Pulmonary Pathology at the 21st European Congress of Pathology that took place in Istanbul, Turkey, in September 2007.
  - Allen et al. Basic Concepts of Molecular Pathology. p1551-56
This review focuses on reviewing definition of genes, explaining the different tools to detect genetic abnormalities such as FISH, PCR (including RT-PCR and real time PCR), different gene functions and how their abnormalities associated with lung cancer such as LOH, genes involved in signaling pathways, DNA repair, and cell cycle.

Very easy to read and gives a nice background to those who are unfamiliar with these concepts

- **Muradyan et al. An Integrative Approach for Analyzing the Interplay of Genetic and Epigenetic Changes in Tumors. p1557-61**
  - This article explains the transition from conventional cytogenetic to Comparative Genomic Hybridization (CGH) and CGH methodology in assessing DNA copy number changes by comparing the AN to N.
  - Also describes the recent improvement in CGH methodology with DNA spot arrays
  - Also new technology to better assess epigenetic and post-translational genomic alterations such as ChIP on chip technology and methylation arrays (since these events may alter gene expression independently of DNA copy numbers).
  - Kept it simple but almost too simple to the point may be hard to understand and not so much link with lung cancer

- **Sanchez-Cespedes M. The Impact of Gene Expression Microarrays in the Evaluation of Lung Carcinoma Subtypes and DNA Copy Number. p1562-65**
  - Summarizes the cascade of most important genes involved in lung cancer with a nice schematic and the importance of elucidating these complex interactions
  - Focus on *EGFR* and *PIK3CA*
  - Describes RNA microarray technology and how it has been used in lung cancer, discussing its limitations
  - Introduces microRNAs
  - Good article to read. Gives nice background information on gene interactions in lung cancer

- **Wisniewski JR. Mass Spectrometry-Based Proteomics. Principle, Perspectives, and Challenges. p1566-69**
  - This article reviews how mass spectrometry works, its value and limitations
  - Also explains the principle in that it analyses proteins and thus post-translational events, in contrast the molecular pathology which looks at DNA and mRNA and not always a reflection of the end-product i.e. the protein
  - Does talk much about lung cancer, probably not that much done yet using mass spec
  - Good review, easy to follow

- **Popper et al. Proteomics- Tissue and Protein Microarrays and Antibody Array. What information is provided? p1570-72**
Reviews the principals of TMA and its advantages like evaluating up to 200 tumors using one paraffin blocks, using technologies such as IHC, ISH
- Describes very briefly (so much so that I didn’t understand it) reverse-phase protein microarray and antibody array
  - Murer B. Targeted Therapy in Non-Small Cell Lung Cancer. A commentary. p1573- 75
    - Focus on targeted therapy to \( \text{EGFR} \) and mechanisms of resistance
    - Discussed which pathologic test may be more relevant to predicting tumor response
    - Good review that covers the necessary basics.

**Case Reports**


**Case Summary:** A 50-some yo woman had GI symptoms for almost 20 years when diagnosed with Crohn’s disease following small bowel resection for obstruction. The small bowel resection contained serosal nodules. Mesothelial proliferation with papillary and tubular structures with superficial invasion. See photomicrograph. The authors argue that this is reactive because in the setting of active Crohn’s disease and it mimics a WDPM

![Photomicrograph](image)

**Take Home Message:** Based on the description and the picture, hard for me to call this simply reactive. I think this is truly a WDPM.


**Case Summary:** 67 yo man with past history AVR for rheumatic disease at age 42. He developed CHF and non-sustained VT at age 60 and was started on amiodarone. He was admitted for CHF and found to have a 1cm lung mass which showed some uptake on PET scan, worrisome for lung cancer. He died shortly after of resistant VT. He was also known for a year to have proteinuria but kidney biopsy never performed. At autopsy, the lung mass was comprised of thickened alveolar septum by chronic inflammation associated with intra-alveolar macrophage
accumulation containing myelinoid bodies by EM. A similar lesion was identified in the other lung. The kidneys showed a membranous GN.

Take Home Message: A possible example of amiodarone lung toxicity presenting as a lung mass.

Letters and Replies to the Editor

The authors came suddenly to realize that BAC is defined as an in situ carcinoma following the article by Yousem and Beasley and they propose to drop the terminology of BAC and use carcinoma in situ instead.