

Mukhopadhyay et al. Pulmonary disease due to aspiration of food and other particulate matter: a clinicopathologic study of 59 cases diagnosed on biopsy or resection specimens. Am J Surg Pathol 2007; 31: 752-759


I. DISCUSSION ARTICLES


• **Purpose:** Report the Mesopath Group’s experience with the lymphohistiocytoid variant of MM and describe the clinicopathologic and immunohistochemical features, EBV status and outcome of this rare variant.

• **Methods:**
  o 1998-2004 Mesopath group filled for MM defined as having “diffuse sheets of histiocyte-like cells with dense and prominent lymphoid infiltrate, comprising >50% of the tumor”
    ▪ 10 epithelioid
    ▪ 2 biphasic
    ▪ 10 sarcomatoid
  o Confirmed by IHC, EBV ISH
  o Comparison to 765 MM from the group during same time period

• **Results:**
  o 14M:8W, mean 69.5 yrs
  o Chest pain in 12, fatigue and weight less in 9
  o 14 with diffuse pleural thickening, 3 localized mass and 7 fibrous plaques
  o 16 DOD med 8 mos; 6 AWD med 8 mos
  o IHC: AE1/AE3 100%, Calretinin 100%, CK5/6 46%, lymphocytes mainly cytotoxic T-cells.
  o EBV negative
  o Compared to other MM, survival of MMLH closer to epithelioid and biphasic than sarcomatoid

• **Take home message**
  o MMLH is a rare variant that doesn’t differ clinically, radiologically and IHC from other types of MM.
  o Important to recognize as to not confuse with malignant lymphoma or other types of lymphoepithelial tumors.
  o Survival dismal but closer to epithelioid than sarcomatoid, contrary to previous reports.

- **Purpose:** To assess if BML is biologically and diagnostically homogenous and to evaluate its relationship to uterine smooth muscle tumors.

- **Methods:**
  - 5 cases available with fresh tissue submitted for cytogenetics.
  - IHC for desmin and SMA performed

- **Results:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Symptoms</th>
<th>#lung nodules</th>
<th>Size of nodules</th>
<th>Histology</th>
<th>Uterine finding</th>
<th>IHC</th>
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<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Incidental</td>
<td>2</td>
<td>2.5-3.9</td>
<td>Hyalinized Bland</td>
<td>HAT SOB</td>
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<td></td>
<td></td>
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<td></td>
<td>No necrosis</td>
<td>No mitosis</td>
<td>No dx of leiomyoma</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>SMA+</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>Incidental</td>
<td>2</td>
<td>Up 2cm</td>
<td>Bland no atypia</td>
<td>2 myomectomies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Branch multiple</td>
<td></td>
<td></td>
<td></td>
<td>1 reviewed no malignancy</td>
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<tr>
<td>3</td>
<td>45</td>
<td>Incidental</td>
<td>2</td>
<td>0.3 and 0.8</td>
<td>Mild atypia</td>
<td>TAHBSO 4 benign leiomyomas</td>
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<td></td>
<td></td>
<td>No necrosis</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1/50 HPF</td>
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</tr>
<tr>
<td>4</td>
<td>55</td>
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<td>1</td>
<td>2.5cm</td>
<td>Bland no atypia</td>
<td>HAT 30 yrs prior</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>No necrosis</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/30 HPF</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>Incidental</td>
<td>Branch multiple</td>
<td>0.1-1</td>
<td>Bland</td>
<td>MRI pelvis 9mm nodule c/w leiomyoma</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>63</td>
<td>DOE</td>
<td>1</td>
<td>14</td>
<td>Cellular</td>
<td>HAT for fibroids</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Mild atypia</td>
<td>Not reviewed</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>1/10 HPF</td>
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<td></td>
<td></td>
<td>Called sarcoma</td>
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</tbody>
</table>

- **Cytogenetic results** complex but all have in common abnormalities of 19q and 22q. The Primary leiomyosarcoma (PPL) had abnormalities of 3,8,11 and 1p

- **Take home message**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Cytogenetics</th>
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<tbody>
<tr>
<td>Met from unrecognized uterine leiomyosarcoma</td>
<td>more complex</td>
</tr>
<tr>
<td>Intravenous leiomyomatosis</td>
<td>12q15</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>12q15, 6p21</td>
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<tr>
<td>Hyperplasia</td>
<td>None</td>
</tr>
<tr>
<td>Multifocal primary</td>
<td>PPL with 3,8,11 and 1p</td>
</tr>
<tr>
<td>Met from benign leiomyoma</td>
<td>60% diploid</td>
</tr>
<tr>
<td></td>
<td>12q or 7q most common</td>
</tr>
<tr>
<td></td>
<td><em>3% 19q and 22q</em></td>
</tr>
</tbody>
</table>
Mukhopadhyay et al. Pulmonary disease due to aspiration of food and other particulate matter: a clinicopathologic study of 59 cases diagnosed on biopsy or resection specimens. Am J Surg Pathol 2007; 31: 752- 759

- **Purpose:** “To alert pathologist to the frequency” of aspiration pneumonia in biopsies and surgical specimens and outline clinical and pathologic characteristics

- **Methods:**
  - 1995-2005 consults and archives
  - 59 cases with exogenous material (excluding lipid).
    - 46 wedge biopsies
    - 6 lobectomies
    - 8 biopsies: 7 TBBx and 1 needle

- **Results:**
  - 40 M: 19F mean 57 yo
  - Symptoms: SOB (39%), Fever (25%), Recurrent pneumonia (25%), Cough (17%), Hemoptysis (11%)
  - Unilateral in 50%, bilateral in 50%, nodule(s) in 18 (unilateral), infiltrates in 15 (bilateral)
  - Predisposing factors: esophageal (11), drugs (10), gastric (8), neurologic (6)
  - Clinical dx: Neoplasm (56%), pneumonia (22%), aspiration (9%)
  - Pathologic dx: BOOP in 15, UIP in 5, DAD in 4, BCG in 3, HSP in 3 and **aspiration in 9**
  - Histologic features:
    - BOOP 52/59
      - 49 granuloma/giant cells (35) and/or acute inflammation (33)
    - No BOOP in 7
      - 4 peribronchiolar fibrosis and chronic inflammation
      - 3 acute bronchiolitis with acute bronchopneumonia, 2 with giant cells
    - Foreign bodies
      - Vegetable matter in 92%
      - Talc, microcrystalline cellulose or crospovidone in 7 cases

- **Take home message**
  - “Healthy” individual with specific risk factors
  - Not suspected clinically
  - Diagnosis can be made on small biopsies
  - BOOP with giant cells, acute inflammation or acute/chronic small airway disease with giant cells
Weydert et al. Comparison of fungal culture versus surgical pathology examination in the detection of *Histoplasma* in surgically excised pulmonary granulomas. Arch Pathol Lab Med 2007; 131: 780-83

- **Purpose:** Surgical resection of necrotizing granuloma for histoplasmosis is common in regions endemic for Histo. Cultures are considered gold standard but some studies suggest low yields. Thus the goal of this study to evaluate the utility of doing routine cultures on surgical resections of solitary granuloma.

- **M&M:**
  - 01/01/2001 – 7/31/2004, new dx of granulomas on wedge resection
  - Non immunocompromised hosts, no systemic mycosis with positive cultures
  - Path review of H&E, GMS< PAS-D and AFB with no discrepancy
  - On the included cases, results of cultures and direct smears recorded.

- **Results:**
  - 30 cases:
    - 24 had cultures
      - 2/24 positive: 1 MAI and 1 Histoplasma
    - 22/30 with positive stains:
      - 20 c/w Histo including the culture + case
      - 1 AFB + (same with MAI on culture)
      - 1 c/w Cocci (culture -)
    - 8/ 30 negative stains; 6/6 had cultures and smears also negative (**but they don’t mention results of serologies or other to see what was the final clinical diagnosis**)

- **Take home message**
  - 66% of granulomas were positive for histo with 0% of false + and 0% of false - (**but we don’t know for sure the true denominator of cases positive for Histo based on serologies so may have had some false -)**
  - At least in this study (? Endemic regions) , cultures should not routinely be done for fungi, only for mycobacteria (mostly to subspeciate)

- **Purpose:** To correlate grade of stromal invasion with prognosis of pT1 adenocarcinoma. To assess if grade 3 stromal invasion can be subclassified based on the presence of micropapillary pattern. To see if micropapillary pattern associated with specific grade of stromal invasion.

- **M&M:**
  - April 1993- Dec 2002, 134 cases of pT1
    - 7 excluded because lost to FU
    - 7 cases had no central fibrotic focus excluded
  - Total 120 cases with complete surgical resection and mean FU 75 mos
  - H&E, EvG,, MUC 1
  - Stromal invasion grading system
    - Gr0 = BAC
    - Gr1 = stromal invasion in area of BAC (not in central scar)
    - Gr 2 = stromal invasion in periphery of fibrotic focus
    - Gr 3 = stromal invasion in center of fibrotic focus
  - Micropapillary areas as absent if 0% or 1+ (<10%), and present if 2+ (10-50%) or 3+ (>50%), done by 2 pathologists with >90% concordance

- **Results**
  - 49 M:71 W, mean 64.8 yo, treated with lobectomy in 73% and limited resection in 27% (**first confounding variable)
  - 49 stromal invasion grade 0-2 and 40 negative for micropapillary pattern

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>Stromal 0-2 Micropap -</th>
<th>Stroma 0-2 Micropap +</th>
<th>Stromal 3 Microp -</th>
<th>Stromal 3 Microp +</th>
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</thead>
<tbody>
<tr>
<td>Stage Ia</td>
<td>101</td>
<td>23</td>
<td>13</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>24</td>
<td>15</td>
<td>16</td>
<td>65</td>
</tr>
</tbody>
</table>

- Patients with micropapillary pattern had more often larger tumors (>1cm), LN metastasis, ****pleural invasion (but all pT1?) and small cluster invasion (in univariate model)
- Survival rates (**which included all Stages) showed statistical differences for grade 0-2 5-yr of 95.2% vs grade 3 5-yr of 69.1% p=0.0048 and for micropapillary negative 5-yr of 83.3% vs positive 5-yr of 64.9 p=0.0196
- Univariate analysis for Stage I, micropapillary and grade 3 poor prognosis; no significant ones for IIIA
- Multivariate, micropapillary positive with shorter overall survival with p=0.0493

- **Take home message**
  - After all these very meticulous analysis and calculations, nothing new.

- **Purpose:** Evaluate agreement in the classification of IIP in academic and community settings and examine the influence of iterative diagnostic approach in these settings.

- **M&M**
  - Data from patients referred to Michigan from Aug 2002 to December 2003. Excluded if no HRCT or SLB.
  - 2 Community groups (3 clinicians, 2 radiologists and 2 pathologists) and 1 Expert group (6 clinicians, 2 radiologists and 4 pathologists) ***Expert group in practice longer and greater amount of time evaluating ILD***
  - Data provided in same order to each group, on separate days through 5 stages
  - 8 category of diagnosis: IPF, NSIP, bronchiolar/airway disease, HP, RBILD/DIP, COP, ILD with CVD, and other ***not all IIP***
  - Kappa perfect agreement >0.8, substantial 0.6-0.8, moderate 0.4-0.6, fair 0.2-0.4, slight 0.0-0.2

- **Results**
  - 39 cases
  - Interobserver agreement from step 1 to 5

<table>
<thead>
<tr>
<th></th>
<th>Academic</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians</td>
<td>0.28 – 0.71</td>
<td>0.20 – 0.44</td>
</tr>
<tr>
<td>Radiologist</td>
<td>0.59 – 0.55</td>
<td>0.38 – 0.32</td>
</tr>
<tr>
<td>Pathologists</td>
<td>0.57 – 0.57</td>
<td>0.14 – 0.41</td>
</tr>
</tbody>
</table>

***Academic clinicians really did better from step 3 to 4 and 5 from 0.37 to 0.62 and 0.71 vs community 0.27 to 0.47 and 0.44***
Final diagnosis -not clear how these were made and gave issues with CVD pathologic diagnosis, IPF vs HP and the fact that the pathologists had to choose from the clinical diagnosis

In table I= IPF, N= NSIP, B= airway/bronchiolar disease, H= HSP, R= RBILD/DIP, C= COP, S= CVD-ILD, O= other

By the last figure, for IIP as IPF, NSIP and COP, to me looks like community does better or as good as experts

Take Home message

Issues are that the aim was to evaluate community vs academic for IIP and data made murky by adding non IIP which were the “debatable” diagnosis
I don’t understand how easily academic pathologists swayed by clinical data

Assumption is that making a precise diagnosis is important due to difference in prognosis and treatment but this was not verified i.e. IPF vs HP did this difference in dx truly impact patient care.

Finally, not clear what was the gold standard for final comparison? Pathology? Clinical? Experts? The reason to ask this question is that the assumption the experts were right (see Editorial)
Luyt et al. **Herpes Simplex virus lung infection in patients undergoing prolonged mechanical ventilation. Am J Respir Crit Care Med 2007; 175: 935-42.**

Editorial by Groeneveld and Vandenbroucke-Grauls p 176.

- **Purpose:** Prospective study to determine the frequency, risk factors and relevance of HSV bronchopneumonia (BPn) in non-immunocompromised host on prolonged mechanical ventilation.

- **M&M:**
  - Oct 2004-Jan 2006, >5d of MVA, n on-immunocompromised
  - If patient febrile or unexplained hemodynamic instability
    - Bronchoscopy for secretions and BAL
    - Any macroscopic lesions noted and BBX
    - Endotracheal aspirate and oropharyngeal swabs before bronch
    - This repeated for each episode of fever or instability
  - Cultures for HSV done on BAL, aspirates and swabs
  - BAL assessed by real-time PCR to quantitate viral load
  - Cytology on aspirate, BAL and biopsies assessed by 2 pathologists
  - HSV BPn defined
    - Clinical deterioration
    - HSV detection in lower respiratory tract
    - Nuclear inclusions identified by pathologists
  - Bacterial ventilator associated pneumonia (VAP) with deterioration and positive cultures in BAL

- **Results:**
- 19 treated with acyclovir and no stat significance in outcome but mortality was 27% vs 57% for treated vs untreated
- Risk factors for HSV BnP
  - Post-surgery, mostly postcardiac surgery
  - HSV-positive serology
  - ARDS
  - Oral-labial lesions*, HSV in throat*, HSV in lower respiratory tract
  - Macroscopic bronchial lesions* and inclusions
  - * factors preserved in multivariate analysis
- Outcome
  - Ventilated longer
  - More VAP episodes (1.5 vs 1.1)
  - **Majority of HSV Bpn had no VAP (23/42, 55%)**
  - Longer stay in ICU
  - No stat diff in mortality (48% vs 42)
- Viral load

**Take home message**
- This study tried to address the concept of passive non clinically significant shedding of HSV vs true infection by HSV (more than half without VAP and 4 with no oral HSV)
- They make a strong argument but questions remains especially in terms of necessity of treatment with acyclovir in these patients
II. ARTICLES FOR NOTATION

**Non-neoplastic lung disease**


This prospective epidemiologic study looked at the role of exposure to the dust of FDNY rescue workforce during the WTC rescue/recovery efforts in development of granulomatous lung disease. The same group had shown that firefighters had an increased incidence (15/100,000) and prevalence of sarcoidosis in the 15 years prior to the WTC. They showed that following WTC, the firefighters had increased incidence of 22/100,000. Airway hyperactivity/asthma was also a common finding, present in 18 of the 26 patients with granulomatous disease. Thus the importance of early detection and treatment following environmental/occupational exposure.


Nice reflection and synopsis on the prevalence and significance of PH in IPF, as well as its potential pathogenesis, and clinical implication in the “treatment” of IPF. It addresses several issues and findings from previous articles discussed in our Journal Club.

**Neoplastic lung disease**


Excellent review on pivotal issues in lung cancer and studies from 2006 looking at these. Topics addressed include lung cancer risk and prevention, need for effective screening and role of CT (NEJM recent paper), need for better non-invasive staging tool and role of EBUS-TBNA, better understanding carcinogenesis of lung cancer, role of adjuvant therapy in early stage disease (seems like data does not support treating IB), identification of novel therapeutics or markers predicting response to therapies (ERCC1, EGFR, VEGF).


One more study adding to the complexity of understanding the biology of EGFR and anti-EGFR therapy. Gefitinib (IRESSA) is an EGFR tyrosine kinase inhibitor. Some studies looking at Gefitinib, showed better outcome for patients with mutation of gene as well as amplification but independent of whether or not Gefitinib was given, suggesting prognostic marker but not marker of response. But other studies showed that amplification was associated with better response. In this study, only mutation, not amplification was a predictor of response and survival.

Interesting study with solid methodology which compared, using microarray, well diff areas of adeno to mod diff areas, primary with met to primary without met, and primary to its met. They showed that expression profiling of well diff areas to mod diff areas were comparable. Same for primary to met. This suggests that genes do not account for difference in morphology thus potentially all adeno comparable. It also suggest that genes conferring metastatic power to the tumor are present very early and thus would be detectable before the tumor has metastasize. And this has potential clinical and therapeutical implications. Finally, they did find 75 genes that could separate non metastatic adeno from metastatic adeno but validated only 3 of them. Promising study which needs more validation to be clinically useful.


This study looks at outcome of patients with 2 synchronous lung cancer treated surgically. They showed overall 2- and 5-yr survival of 61.6 and 34%, median survival of 34.9 and 10-yr overall survival of 19%, much better than what would be predicted by the current staging system of IIIB and IV. They showed that adverse prognostic factors (in multivariate analysis) including male gender, >60 yrs old, symptoms, low FEV1, pneumonectomy, no adjuvant therapy, no complete surgical resection and presence of LN metastasis.