Leslie Case 1.

A 60 year old woman presents to the hospital emergency room with progressive shortness of breath. She has no prior medical history. Her illness began 2 month earlier when she developed an apparent upper respiratory infection and a dense left-sided infiltrate on imaging. She saw her LMD who prescribed a course of empiric antibiotics. Initially she improved slowly after a 6 week course of IV and oral antibiotics. She was transitioned to Diflucan and doxycycline. In a follow-up visit her initial left sided disease was much improved, but then developed breathlessness associated with non-productive cough and night sweats with new right sided infiltrates. Her symptoms over the week before hospitalization escalated and she was hospitalized profoundly hypoxic. She progressed to respiratory failure and required intubation. Progression of infiltrates is seen in the right lung on CT scan. Several days after admission she is taken to the operating room for a surgical lung biopsy by video-assisted thoracoscopy (VAT).

Diagnosis: Acute eosinophilic pneumonia. Case presented to discuss the role of the pathologist in the management and diagnosis of acute lung disease.

It is intuitive that acute lung damage can occur from a wide variety of extrinsic (inhalational) and intrinsic etiologies that injure the lungs directly. Less intuitive is the concept of disease outside of the lung secondarily inflicting damage diffusely on this organ. Early terms for diffuse acute lung injury occurring indirectly in the setting of overwhelming non-thoracic trauma accompanied by hypovolemia were “shock lung”, “postperfusion lung”, “traumatic wet lung” and “congestive atelectasis”. [1, 2]

Ashbaugh and coworkers (1974) formally described a syndrome in which patients developed severe respiratory distress of acute onset following an identifiable injury. Patients developed dyspnea, reduced lung compliance, diffuse chest radiographic infiltrates, and hypoxemia refractory to supplementary oxygen. [3] In current practice, this sequence of clinical events is referred to as the adult respiratory distress syndrome or simply “ARDS”. The clinical course is rapid and the mortality rate is high, with more than half of patients affected dying of respiratory failure within days to weeks. [2, 4, 5] Things have improved over the years in our management of the ARDS patient underscored by a recent meta-regression analysis performed by Zambon and Vincent [6] showing mortality rates from 72 published studies of ARDS where a decrease of 1.1% per year for the period of 1994-2006, with an overall pooled mortality rate for all studies of 43%. It is essential to remember that not all patients with DAD have clinical ARDS.

Several randomized clinical trials have underscored inefficacy of corticosteroid therapy in the treatment of ARDS patients. What is less clear is the role corticosteroids have in acute injury scenarios other than ARDS. Acute eosinophilic pneumonia is the main disease that argues in favor of short term, high dose corticosteroids in patients with unexplained acute injury, particularly when extravascular eosinophils are visible in lavage fluid or biopsy samples. In our experience, patients with DAD may respond
favorably to acute immunosuppressive therapy with intravenous Solumedrol, so the pathologist’s role in the emergent evaluation of the cytology sample or biopsy is to exclude infection. For the normal host, AFB and GMS are sufficient (although rarely positive). In my own practice I cannot recall seeing a positive stain for a true pathogenic organism in this setting in the absence of at least focal tissue necrosis. For the patient known to be immunocompromised, additional stains are required (Warthin-Starry, Dieterle, Gram, anti-HSV, anti-CMV, primarily). Here, the footprints of infection may be subtle or non-existent, so the stains can be very helpful.

**Acute eosinophilic pneumonia**

Acute eosinophilic pneumonia (AEP) was firstly described in 1989[7] as a disease of rapid onset leading to acute respiratory failure, fever of days to weeks duration, diffuse pulmonary infiltrates radiologically, and eosinophilia in bronchoalveolar lavage (BAL) fluid or lung biopsy specimens in the absence of infection, atopy, and asthma.[8] Peripheral eosinophilia is frequently described, but is not a consistent finding at initial presentation.[9, 10] Acute eosinophilic pneumonia is easily confused with acute interstitial pneumonia (AIP) because both present as acute respiratory distress without an obvious underlying cause.[8]

Histopathologically, the disease is characterized by acute and organizing lung injury showing classical features: 1) alveolar septal edema, 2) eosinophilic airspace macrophages, 3) tissue and airspace eosinophils in varying numbers, and 4) marked reactive atypia of alveolar type II cells. Intra-alveolar fibroblastic proliferation (patchy organizing pneumonia) and inflammatory cells are present to variable degree. Hyaline membranes and organizing intraalveolar fibrin may be present as seen in the patient under discussion. The most significant feature is the presence of interstitial and alveolar eosinophils. Infiltration of small blood vessels, especially veins, by eosinophils also may be seen. It is important to distinguish AEP from other causes of DAD because patients typically benefit from immediate systemic corticosteroid treatment with prompt recovery.

The real challenge for the pathologist encountering AEP today is the widespread use of corticosteroid before lung biopsy is undertaken. This eliminates eosinophils from the tissue! To navigate this challenge, any unexplained (i.e. blood and lavage cultures negative, tissue special stains negative, no tissue necrosis) should be considered occult AEP until an alternate explanation is identified (such as an offending drug or an occult autoimmune disease causing acute lung damage).


**Leslie Case 2.**

A 37 year old woman was gardening in her back yard when she suddenly felt a “pop” in her posterior chest, followed by pain and shortness of breath. A CT scan revealed a pneumothorax and multiple cysts.

**Diagnosis:** Metastatic low grade endometrial stromal sarcoma.

Three main pulmonary disease processes are highlighted with this case 1) pneumothorax, 2) lung cysts, and 3) bland spindle cell tumors in the lung. Each of these topics is broad and alone would be sufficient for a presentation, but when all 3 occur together in the same patient, it is hard not be fascinated!

Our main focus in this case is “bland spindle cell lesions in the lung” and it is no coincidence that this patient also had cysts and a pneumothorax. Spindle cell neoplasms that may have deceptively bland cytologic appearance that occur in the lung include:

1. Alveolar adenoma
2. Lymphangioleiomyomatosis (LAM)
3. Benign metastasizing leiomyoma
4. Endometrial stromal sarcoma
5. Metastatic dermatofibrosarcoma protuberans (DFSP)
6. Benign metastasizing dermatofibroma (!)
7. Metastatic low grade gastrointestinal stromal tumor (GIST)
8. Infantile pleuropulmonary blastoma (embryonal rhabdomyosarcoma)

The majority of these tumors grows slowly within the lung interstitium and because of this may become cystic. If by chance or design they arise in the periphery of the lung, they may present with pneumothorax, in a manner similar to other lung conditions with “cysts”:

1. Langerhans cell histiocytosis
2. Subpleural bullous emphysema (technically not a true cyst)
3. Honeycomb cysts of UIP
4. Lymphocytic interstitial pneumonia (LIP) of Sjogren syndrome (a cystic lung disease)
5. Cystic disease in Birt-Hogg-Dube syndrome
6. Bronchiecstatic cysts

**Endometrial stromal sarcoma (ESS)**

15-25% of uterine sarcomas are classified as endometrial stromal in type and the low grade form is the most common. Low grade ESS has a very favorable prognosis but local pelvic recurrences can occur. Distant metastasis of ESS is rare and lung is the most common site of spread, sometimes occurring many years after the original tumor has been treated. In the series of 16 patients presented by Aubrey et al in 2002 (1), solid lung nodules were most commonly identified. Three (3) patients presented with cystic lung lesions radiologically and in two of these patients cysts predominated. Only one patient in this series presented with pneumothorax (recurrent and bilateral). Interestingly, none of the reviewed primary uterine tumors were cystic.

The histopathology of the lung metastases was dominated by short spindle cells arranged in ill-defined whorls around uniformly distributed small pulmonary arteries. The neoplastic cells had bland nuclear features and little visible cytoplasm in most cases. Rarely admixed cells with more abundant eosinophilic cytoplasm were present suggesting smooth muscle differentiation. Mitotic figures were rare in most cases (0-1/10 hpf) but one patient’s tumors had abundant mitoses (12/10 hpf). Nearly all of the cases demonstrated areas that appeared biphasic, where tumor cells were seen to grow into lung interstitium producing microscopic cysts lined by TTF-1 positive non-neoplastic respiratory epithelium.

Follow-up was available for all 16 patients. One patient died 19 months following the discovery of metastatic lung disease and 20 years after her initial diagnosis of low grade ESS in the uterus. The remaining 15 patients were alive 3 months to 13 years after the first lung metastasis was discovered. Recurrent lung metastasis was identified in 4 patients.

**Reference:**

Leslie Case 3.

A 66 year old woman is discovered to have a peripheral 0.7 cm lung nodule on screening chest radiographs. A PET scan is described as moderately avid. She is a never smoker and the lesion is identified in the left upper lobe (lingula). A wedge excision is performed.

Diagnosis: Pulmonary adenocarcinoma, minimally invasive, 0.7 cm in maximum diameter. No angiolymphatic or pleural invasion. AJCC TNM:T1a

The purpose of this case presentation is to underscore the salient features of the proposed new guidelines for diagnosing and classifying lung adenocarcinomas. The statements and comments that follow are taken from, and directed at, the recent published works by Travis et al. (J. Surg Oncol 6(2) 2011 and Travis et al Archives Pathol Lab Med 137:685). For biopsy sample management the reader is referred to the longer JSO article where numerous recommendations are made. The bottom line for the small biopsy sample is: be cautious, save tissue for molecular studies and never diagnose “adenocarcinomas in situ” without having the whole lesion in hand.

The new classification is as follows:

“Table 1 IASLC/ATS/ERS Classification of lung adenocarcinomas in resection specimens.

Pre-invasive lesions
   Atypical adenomatous hyperplasia
   Adenocarcinoma in situ (≤3.0 cm, formerly, BAC)
      - Nonmucinous
      - Mucinous
      - Mixed mucinous/nonmucinous
   Minimally invasive adenocarcinoma (<3 cm lepidic-predominant tumor with ≤5 mm invasion)
      - Nonmucinous
      - Mucinous
      - Mixed mucinous/nonmucinous
Invasive adenocarcinoma
   Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
   Acinar predominant
   Micropapillary predominant
   Solid predominant with mucin production
Variants of invasive adenocarcinoma
   Invasive mucinous adenocarcinoma (formerly mucinous BAC)
   Colloid
   Fetal (low and high grade)
   Enteric
Abbreviations:  BAC= bronchioloalveolar carcinoma.
*International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society.”


We should begin by asking the obvious question of why a reclassification of adenocarcinoma was deemed necessary. The answer is BAC. Bronchioloalveolar carcinomas have been a problematic issue for many years. The reason is not that pathologists are unable to recognize this distinctive form of lung cancer, but more that the histopathologic diagnosis conferred quite different clinical outcomes beyond stage, that is to say, small BACs seemed to behave in an extraordinarily benign fashion compared to their small conventional invasive adenocarcinoma counterparts. What this seemed to imply is an adenocarcinoma that may not yet have acquired the ability to invade and metastasize, i.e. an in situ adenocarcinoma of the lung.

In the paper by Travis and colleagues, the existence of this elusive AIS tumor was felt to be proven by studies by Noguchi et al and others in small series of patients with BAC who demonstrated 100% survival. Along the way it also became apparent that not all BACs are alike. In fact two forms of the tumor are described in the 2004 WHO classification: a mucinous “classical” form and a cuboidal non-mucinous form. The available data suggested that the mucinous form of “AIS” was exceedingly rare in real life, and that the non-mucinous form was the dominant, but still rare, manifestation for the case that might meet the proposed criteria.

This brings us to the nuts and bolts. The new proposed definition of AIS requires that the lesion in question be:

1. Solitary and circumscribed in the lung
2. 3.0 cm or less in maximal diameter
3. Have no areas of solid growth or excessive complexity to suggest invasion
4. Be completely examined microscopically (i.e not a biopsy diagnosis)

Furthermore, if “invasion” is felt to be present in the above lesion, the term “Minimally invasive adenocarcinoma (MIA)” should be applied if the invasive area is less than 5mm in maximal size. More than 5mm means that your lesion is simply “invasive adenocarcinoma” with the descriptor “lepidic predominant”.

We can gain considerable insight into a few of the major scientific shortcomings of these publications and their recommendations by looking over Table 5 from Travis et al (2) where the authors underscore areas of continued uncertainty and need for more research. Perhaps this nicely articulated set of [further] “research recommendations” should have been published in advance of making strong recommendations without these data.
**Table 5. Pathology Research Recommendations Applicable to Resection Specimens**

1. Criteria for minimally invasive adenocarcinoma are based on limited published data and require further validation. Persistent questions include the following: What is the optimal method for measuring the size of cutoff? If multiple areas of invasion are present, should the greatest dimension of the largest invasive focus be used or the total size multiplied by the percentage of the invasive components? What should be the impact of scar size or prominent stromal desmoplasia and stromal inflammation on determining size of the invasive component? Should criteria for MIA be different for mucinous versus nonmucinous tumors?

2. Lepidic growth may also be composed of neoplastic cells with nuclear atypia resembling that of the adjacent invasive patterns. Whether there is any clinical implication is unknown, that is, it is not established if this is lepidic (non-invasive) growth or invasive carcinoma.

3. The level of reproducibility for identifying predominant histologic patterns is untested. In particular, how should the lepidic pattern be distinguished from other invasive patterns such as acinar and papillary?

4. Are tumors that meet criteria for minimally invasive adenocarcinoma associated with 100% disease-free survival if the invasive component is predominantly solid, micropapillary or if they show giant cell and spindle cell components that fail to qualify for a diagnosis of pleomorphic carcinoma?

5. What is the long-term follow-up for completely resected solitary mucinous minimally invasive adenocarcinoma? Can this be the initial presentation for multifocal invasive mucinous adenocarcinoma?

6. Does the micropapillary pattern have a similar poor prognostic significance in advanced stage as well as early stage tumors?

7. Is there any prognostic significance to the aggressive micropapillary or solid components when present in relatively small amounts if they do not represent the predominant pattern? If so, what percentage is needed for such significance?

8. The ability of pathologists to distinguish adenocarcinoma in situ from invasive disease at frozen section is not proven.

9. Currently, we cannot recommend any specific grading system. Further investigation is needed to determine whether the optimal grading system should include architectural versus nuclear assessment or both.”


Finally, can these recommendations be implemented in the real world, by even the most dedicated and well schooled among us? Eric Thunnissen and colleagues (3) attempted to answer this question in a nicely written paper summarizing the experience of a large group of experts who shared digital images and attempted to implement the Travis et al recommendations (particularly subclassification in 5% increments and determining AIS/early invasive disease). The paper is filled with agreement statistics (kappa value)
arguing that a major pattern is discernible in most cases with good agreement. I leave you with the challenges of their study, summarized in the statement below from page 1583:

“Post-study discussion also identified variation in interpretation of various morphological features. First, some pathologists interpreted a stromal component as tumor-related stroma with fibroblasts (also called desmoplastic stroma), whereas others considered the same feature as benign scarring/fibroelastosis (Figure 4c and i). Second, the presence of elastin was variably weighed as representing native alveolar wall by some pathologists but not by others (Figure 4e and f). Third, inflammation in alveolar walls implied invasive disease to some. Fourth, although there was good agreement between pathologists in cases with a prominent micropapillary component, there was variation in interpretation between what some interpreted as focal micropapillary component and tangential cutting of both lepidic and true papillary structures. Finally, some pathologists interpreted a mucinous lepidic component as being invasive, based upon the reasonable assumption that elsewhere in the tumor an invasive component with scarring is highly likely, whereas others interpreted the image in itself as non-invasive (Figure 4h). It is therefore notable that much of the interobserver variation stems from interpretation based on operator experience and opinion, and improved definitions and better education on their usage are required to reduce interobserver variability.”

Time will be the judge.

References

