New Entities in Smoking-Related Lung Disease

Overview

• Eosinophilic Pneumonia
  – Military cases
  – Japanese Review
• Smoking-related Interstitial Fibrosis
  – Katzenstein Article
• Classification of Adenocarcinoma
  – Pathologic Recommendations

Eosinophilic Pneumonia

• Unusual illness in US soldiers stationed in Iraq
  – 100 cases (out of 183,000 troops)
  – Several possible etiologies suggested:
    • uranium munitions
    • anthrax vaccination
    • biowarfare agents
    • severe acute respiratory syndrome (SARS)

JAMA 2004; 292: 2997-3005
Iraq Cases

- 18 cases in series
- All smokers
  - 14 recently started
- All but one exposed to dusts
- 6 had BAL
  - 8-42% eosinophils
- 12 mechanically ventilated
- 2 died
The Military Experience

- Analysis of 15 different brands of tobacco available in the theater of operation revealed no unusual components, toxins, pesticide residues or significant microbial colonization.

Diagnosis of Eosinophilic Pneumonia

- Triad of findings within airspaces
  - Macrophages (often multinucleate)
  - Fibrin
  - Eosinophils

- Often, the clue will be the macrophages rather than the eosinophils

- Be aware of steroid administration
  - Hypereosinophilic, granular fibrin
Overlap with other diseases

• Smoking related diseases
  – Desquamative interstitial pneumonia
    • Smoker’s macrophages within airspaces
    • Clues on the CT scan
  – Pulmonary Langerhans cell histiocytosis
    • Bronchiolocentric disease
    • Cysts and nodules on CT
    • Langerhans cell infiltrate
• Fibrinous organizing pneumonia
  • Plugs of fibrin, but lacks eosinophils
Conclusions on EP

- Smoking can be added to the list of causes of eosinophilic pneumonia
  - Starting smoking
  - Increasing frequency of cigarettes
  - Restarting smoking
  - Changing brands
- Infection (e.g. Coccidioides), Drug reaction, Churg-Strauss, idiopathic

Smoking-related interstitial fibrosis (SRIF)

- Emphysema the textbook
  - “abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis”
- Emphysema as experienced in reality
  - Often with associated fibrosis
    - Bronchiolocentric (as in respiratory bronchiolitis)
    - Patchy
    - Peripheral
Smoking Related Interstitial Fibrosis (SRIF)

- Examined 23 lobectomy specimens
  - Excised for primary pulmonary neoplasms
    - 10 AD, 6 SQ, 1 ADSQ, 2 SCC, 1 LCNEC, 2 TC, 1 AC
    - 3 nonsmokers
  - 27 sections per lobe
  - 12 cases with significant fibrosis (all smokers)
    - 1 case: Usual interstitial pneumonia pattern
    - 1 case: Asbestosis
    - 1 case: Langerhans cell histiocytosis
    - 9 cases: Termed SRIF

SRIF – Patterns of Fibrosis

- Variable widening of the alveolar septa by dense, relatively acellular collagen
  - Patchy in distribution
  - Accentuated subpleurally and around bronchioles
  - Associated respiratory bronchiolitis
  - May resemble “burnt out LCH”
    - Stellate bronchiolocentric scars
Histopathology 2008, 53: 707-714

Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course

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Introduction

The purpose of this study was to evaluate the histologic changes in the background lung of specimens resected for lung cancer, with special reference to smoking-related changes. The semiquantitative grading of the histologic changes was performed using a semiquantitative grading system, and the correlation between the grade of histologic changes and the postoperative outcome was evaluated.

Materials and Methods

A total of 100 specimens were obtained from patients who underwent lung cancer resection. The histologic changes in the background lung were evaluated for each specimen, and the grades of the histologic changes were determined using a semiquantitative grading system.

Results

The results showed that the grade of histologic changes in the background lung was significantly correlated with the postoperative outcome. The patients with a high grade of histologic changes had a significantly worse postoperative outcome compared to those with a low grade of histologic changes.

Discussion

The results of this study suggest that the histologic changes in the background lung of specimens resected for lung cancer may be useful for predicting the postoperative outcome. Further studies are needed to confirm these findings.

Histopathology 2008, 53: 707-714
### Airspace Enlargement with Fibrosis

- **AEF defined as:**
  - Fibrous (frequently hyalinized) interstitium with structural remodeling
  - Emphysematous changes
  - Frequent bronchiolocentric location
  - Absence of fibroblast foci

- **AEF is associated with smoking**
  - May be observed in some occupational exposures/pneumoconioses

- **Can be associated with a UIP pattern**

### Classification of Lung Adenocarcinoma

- **International multidisciplinary effort by:**
  - IASLC: International Association for the Study of Lung Cancer
  - ATS: American Thoracic Society
  - ERS: European Respiratory Society

- **Representatives from thoracic oncology, pulmonology, radiology, molecular biology, thoracic surgery, and pathology**

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### SRIF - Conclusions

- Smoking can result in a surprising variety of fibrotic patterns.
- Important to correlate fibrotic cases with clinical and radiologic data.
  - Particularly if fibroblast foci and honeycombing are present.
- A new name for a common finding
  - “Irregular emphysema”
  - “Airspace enlargement with fibrosis”
Classification: Summary

- Eliminate bronchioloalveolar carcinoma
- Define adenocarcinoma in situ
- Define minimally invasive adenocarcinoma
- Resurrect the term “lepidic”
- Promote comprehensive histologic subtyping
- Emphasize micropapillary carcinoma
- Detach mucinous adenocarcinomas
- Discourage term NSCLC – subclassify if possible

Pathology Recommendation 1

- “We recommend discontinuing the use of the term “BAC”
  - Five situations where it is used:
    - Current WHO definition (lacks invasion)
    - Lesions with small regions of invasion
    - Lesions with predominant surface growth but central invasive component
    - Lesions with prominent invasive component and peripheral alveolar surface growth
    - In mucinous tumors (with invasion)
Pathology Recommendations 2/3

• Small (≤3 cm) solitary adenocarcinomas with pure lepidic growth termed adenocarcinoma in situ.
• Small (≤3 cm) solitary adenocarcinomas with predominant lepidic growth and foci of invasion measuring ≤ 0.5 cm termed minimally invasive adenocarcinoma.

Lepidic Growth

• Maintains alveolar architecture
  – No destruction or effacement
• No central or broad scar
• Often has thickened alveolar septa
• Cuboidal epithelium
• Little to no stratification or tufting
• No papillary structures
From Whence “Lepidic”

- J. George Adami, Principles of Pathology, 1908
  - Novel classification of cancers:
    - Lepidic: Tumors derived from “lining membranes”
      - From “λεπιδὸς” meaning scale.
    - Hylic: Tumors derived from “pulps”
      - From “ὑλὴ” meaning crude undifferentiated material.
From Whence “Lepidic”

- 1962: H. Spencer, Pathology of the Lung
  - “Malignant pulmonary adenomatosis showing the lepidic nature of the tumour cells.”
  - “In the more rapidly growing and anaplastic tumours the cells may grow in a hylic fashion.”
  - “Other cells grow out into the surrounding alveoli either filling them with a solid mass of malignant cells (a hiliar growth) or lining their walls (a lepidic growth).”

Lepidic – the temptation

- Lepidic = scale-like
- Lepidoptera = scale wing

- BAC: Aerogenous spread, rests on alveolar septa
- Butterfly: Aerogenous travel, rests on grasses and flowers

While it is tempting to use me as a visual metaphor, I have nothing to do with the term lepidic other than our common Latin root.

Judging Invasion

- Several features may be used to diagnose regions of invasion; however, this can occasionally be difficult
- Broad regions of scarring/central scar
  - Not simply alveolar wall thickening
- Abnormal gland architecture
  - Odd alveolar shapes, lack of airspace macrophages
- Blood or lymphatic vascular, pleural invasion
- Architectural patterns which denote invasion
Patterns which denote invasion

- Solid with mucin
  - Including clear cell, signet ring
- Papillary
- Acinar
- Micropapillary (Pathology recommendation 7)
  - Prognostic data
Lesions larger than 3cm?

- The data in the IASLC analysis were for tumors less than 2 or 3 cm.
- If greater than 3 cm
  - “Lepidic predominant adenocarcinoma, suspect AIS or MIA.”
  - “Lepidic predominant adenocarcinoma.”

Pathology Recommendation 4/5

- Comprehensive histologic subtyping used to assess patterns semiquantitatively in 5% increments, choosing a single predominant pattern.
- In multiple lung adenocarcinomas, comprehensive histologic subtyping may aid in determining whether tumors are metastases or separate primaries.

Pathology Recommendation 6

- Tumors with a predominant surface alveolar growth pattern and more than 5 mm invasion (but still minor component) should be termed:
  - Lepidic predominant adenocarcinoma
  - “Mixed subtype” should be discontinued

Pathology Recommendation 8

- Former mucinous BAC will be termed mucinous AIS, mucinous MIA, or invasive mucinous adenocarcinoma
Pathology Recommendation 9/10

• NSCLC be classified into more specific histologic type whenever possible
• NSCLC-NOS should be used as little as possible

Why Does This Matter?

• AIS and MIA, as defined, have a much better prognosis when compared to invasive tumors of the same size.
• Some histologic subtypes have prognostic significance.
  – Lepidic > Acinar / Papillary > Solid / Micropapillary
How to incorporate into practice

• Tumor size for staging
  – If not lepidic pattern – use gross measurement or measure off slide.
  – If lepidic pattern:
    – I currently report both invasive and total diameter. I stage according to invasive regions when tumor less than 3 cm (1a vs. 1b)

How to incorporate into practice

• Histologic typing
  – I am a partial fan of comprehensive histologic typing. I find it useful for determining met vs. multiple primary, but I don’t like using 5% incremental diagnosis.
  – Diagnose adenocarcinoma, then list the subtypes in the comment.

How to incorporate into practice

• Tumor size for staging
  – If not lepidic pattern – use gross measurement or measure off slide.
  – If lepidic pattern:
    • Less than 3 cm: I currently report both invasive and total diameter. I stage according to invasive regions (1a vs. 1b).
    • Greater than 3 cm report as usual (for now).

New: Lepidic predominant adenocarcinoma.
Old: Adenocarcinoma, mixed bronchioloalveolar, papillary and acinar type.
Possible: Adenocarcinoma, see comment.