


AM J CLIN PATHOL

Purpose:
- Beta-catenin is a double-functional molecule. When it accumulates in the nucleus, it loses its function as a cell-adhesion molecule, which activates the wingless/int (WNT) signaling pathway and switches on transcription of target genes such as c-myc or cyclin D1, resulting in proliferation and metastasis of tumor cells.
- Axin is an important regulator of the WNT signaling pathway. When the activity or expression of the axin complex decreases, beta-catenin accumulates in the cytoplasm and nucleus.
- Also, as candidate mechanisms for the aberrant accumulation of nuclear beta-catenin, mutations in exon 3 of the beta-catenin gene have been documented in several tumor types.
- The purpose of this study was
  o To study the expression of axin and beta-catenin in non-small cell lung cancer (NSCLC),
  o To explore the relationship between the expression of axin and beta-catenin and clinicopathologic factors, and
  o To further test the hypothesis that abnormal beta-catenin expression is related to mutation in exon 3 of the beta-catenin gene.

Methods:
- 100 non-small cell lung cancers (NSCLCs) were analyzed by immunohistochemistry.
- The mutation in exon 3 of the beta-catenin gene was examined by polymerase chain reaction and direct sequencing.

Results:
- Reduced membranous expression of beta-catenin was shown in 80 cases, whereas 26 cases had aberrant nuclear expression.
- Poor differentiation and lymph node metastasis were associated significantly with reduced beta-catenin expression.
- Preserved axin expression was significantly higher in well- and moderately differentiated NSCLC samples than in poorly differentiated ones.
- Lower axin expression was related significantly to higher nuclear beta-catenin expression.
- This study failed to detect any exon 3 mutation in the beta-catenin gene in the 100 NSCLC samples.

Take-home message:
- Reduced beta-catenin and axin expression might predict poor differentiation in NSCLC.
- Reduced axin expression, but not mutation in exon 3, might be an important explanation for the abnormal beta-catenin expression in NSCLC.
AM J SURG PATHOL

Purpose: To examine the expression of h-caldesmon (a smooth muscle marker) in epithelial mesotheliomas versus lung adenocarcinomas.

Methods:
- 70 cases of epithelial mesotheliomas and 70 cases of lung adenocarcinomas
- Immunohistochemistry
  - h-caldesmon
  - Additional muscle markers: desmin, alpha-smooth-muscle actin, muscle-specific actin, myoglobin, myogenin, myosin and MyoD-1 (mesothelioma cases)
  - Other antibodies used for the diagnosis of mesothelioma: calretinin, cytokeratin 5/6, thrombomodulin, EMA, CEA, TTF-1, Ber-EP4, B72.3, CD15

Results:
- Reactivity for h-caldesmon was obtained in 68 (97%) of the 70 epithelial mesotheliomas, but in none of the adenocarcinoma cases
- All mesothelioma cases were found to be negative for the other muscle markers examined
- See Tables 3 and 4 for details

Take-home message:
- h-caldesmon might be a highly sensitive and specific mesothelioma marker
- Further studies are necessary to confirm the results
- Shortcomings of the paper include omission of our adenocarcinoma versus mesothelioma study from the References (Khoor A, Whitsett JA, Stahlman MT, Olson SJ, Cagle PT. Utility of surfactant protein B precursor and thyroid transcription factor 1 in differentiating adenocarcinoma of the lung from malignant mesothelioma. Hum Pathol. 1999;30:695-700)
ARCH PATHOL LAB MED - RESIDENTS’ PAGES

Case report:
- 2-year-old girl with respiratory distress.
- A chest radiograph and subsequent CT scan demonstrated a pneumothorax, which persisted after chest tube placement. No mass was identified.
- It was thought that the pneumothorax was caused by an underlying congenital cyst and surgical intervention was pursued.
- Several fragments of multicystic pleural tissue with adherent hemorrhagic material were sent to pathology.
- Pathologic diagnosis: Pleuropulmonary blastoma.

Take-home message: Pleuropulmonary blastoma should be in the differential diagnosis of pulmonary cysts in a pediatric patient.
ARCH PATHOL LAB MED

Case report:
- 75-year-old man with a pleural-based mass on a routine chest radiograph.
- No mediastinal mass.
- Thoracoscopy revealed multiple nodules on the visceral pleural and pericardial surfaces.
- Surgical resection of several pleural lesions was performed.
- Pathologic diagnosis: Primary pleural thymoma.

Take-home message:
- Because of their ectopic site and variety of histologic patterns, as well as the occurrence of an “invasive” border, diagnosis of primary pleural thymomas by pleural biopsy can be very difficult.
- A combination of clinical information, histopathology, and immunohistochemistry will often help to distinguish a primary pleural thymoma from other neoplasms.
ARCH PATHOL LAB MED – SPECIAL SECTION – ASTHMA

Comment on: Arch Pathol Lab Med. 2006;130:440-6 (next article).

**Purpose:** During an asthmatic episode, leukotriene C4 (LTC4) and interleukin 13 (IL-13) are released into the airways and are thought to be central mediators of the asthmatic response. The purpose of this study was to determine if the LTC4 and IL-13 signaling pathways interact with each other.

**Methods:** The authors examined airway responsiveness, cysteinyl LTs (Cys-LTs), and Cys-LT and IL-13 receptor transcript levels in wild-type mice and in mice that were deficient in gamma-glutamyl leukotrienase (an enzyme that converts LTC4 to LTD4), STAT6 (signal transducer and activator of transcription 6 [a critical molecule in IL-13 signaling]), and IL-4Ra (a subunit of the IL-13 receptor).

**Results:**
- Wild-type (C57BL/129SvEv) and gamma-glutamyl leukotrienase–deficient mice showed increased airway responsiveness after intranasal instillation of IL-13.
- Similar results were observed after intranasal instillation of IL-13 or LTC4 in a second wild-type strain (BALB/c).
- Interleukin 13 treatment reduced levels of Cys-LTs in bronchoalveolar lavage fluid. This change was unaccompanied by changes in other arachidonic acid metabolites or in RNA transcript levels of enzymes associated with Cys-LT synthesis.
- Interleukin 13 treatment also increased transcript levels of the Cys-LT 1 and Cys-LT 2 receptors, while LTC4 increased transcript levels of the a1 chain of the IL-13 receptor.
- IL-4Ra–deficient mice had increased airway responsiveness to LTC4 but not to IL-13, whereas STAT6-deficient mice failed to respond to either agonist.

**Take-home message:** These findings indicate that LTC4 and IL-13 are dependent on or signal through STAT6 to increase airway responsiveness and that both agonists regulate expression of each other’s receptors.
ARCH PATHOL LAB MED – SPECIAL SECTION – ASTHMA

Review article
ARCH PATHOL LAB MED

Case report:
- A 44-year-old nurse presented with fever, dry cough, hemoptysis, and progressive dyspnea, and died after a downhill course of 2 weeks.
- Chest radiographs showed diffuse parenchymal shadows throughout the entire lung and a nodular lesion in the right lower lobe.
- Grossly, a well-circumscribed tumor (3.7 x 3.0 x 3.0 cm) was found in the right lower lobe.
- Histologically, the tumor showed typical appearance of pure choriocarcinoma.
- Diffuse intravascular spread with occasional tumor emboli was present.
- Alveolar hemorrhage (without capillaritis) was also noted throughout the entire lung.
- Small metastatic foci were found in the liver, adrenal glands, pancreas, and ovaries.

Take-home message: This case shows that primary choriocarcinoma of the lung, on rare occasions, can produce the clinical and pathologic features of diffuse alveolar hemorrhage.
HISTOPATHOLOGY

Purpose: Morphological findings in the human congenital diaphragmatic hernia (CDH) lung consist of retarded development of the pulmonary acinus, fewer alveoli with markedly thickened walls, an increased interstitial area and pulmonary arterial structural changes, including an increased wall thickness. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) play an important role in the turnover of the extracellular matrix (ECM) during development and in tissue remodelling. The aim of this study was to investigate differences in the expression of MMPs and TIMPs between CDH lungs and controls.

Methods: The authors studied 12 lungs of term CDH patients who died < 24 h after birth and 11 normal age-matched control lungs, by immunohistochemistry with antibodies against human MMP-1, -2, -9, TIMP-1 and -2.

Results:
- In CDH lungs, MMP-1 immunoreactivity in the epithelial cells and the arteries was similar to that of the controls. However, many more positive capillary endothelial cells and fibroblasts were recognized in the CDH lungs in comparison with normal control lungs.
- In contrast, TIMP-2 reactivity in capillaries was decreased in CDH lungs.
- The arterial endothelium and medial smooth muscle expressed MMP-2, -9 and TIMP-2 in both CDH and control lungs.
- In small arteries (< 100 lm in diameter), the positive surface area of MMP-2, -9 and TIMP-2 was significantly larger in CDH lungs than in controls.
  o Type IV collagen and elastin are degraded by the cooperation between MMP-2, -9 and TIMP-2. The increase in the positive surface area of MMP-2, -9 and TIMP-2 in the pulmonary arteries in CDH is thought to represent an increase in these enzymes in the arteries, which may be secondary to increased deposition of type IV collagen and elastin.
- There was no difference in the distribution and expression of TIMP-1 between CDH lungs and normal controls.

Take-home message: The differences in staining pattern of MMPs and TIMPs between normal and CDH lungs suggest that these enzymes might play a role in the abnormal remodelling of the interstitium and the pulmonary arteries in CDH lungs.
HISTOPATHOLOGY

**Purpose:** To document the histological features seen in pulmonary involvement by types B and C Niemann–Pick disease and to correlate them with clinical and imaging data.

**Methods:** Surgical lung biopsies from six patients (four with type B and two with type C disease) were reviewed.

**Results:**
- **Histology:**
  - Endogenous lipid pneumonia: ++++, all cases
  - Interstitial foamy macrophages: +, all cases
  - Interstitial fibrosis: +, all cases
  - Foamy change in ciliated epithelium: Type C
  - Foamy change in pneumocytes/Clara cells: No
- **Electron microscopy:** Tissue was available for analysis in two patients with type B disease. Both showed similar features with macrophages containing abundant lysosomes filled by lamellar structures characteristic of those seen at other sites.
- **Clinical and imaging data:**
  - Three patients with type B disease had clinical disease limited to the lung, all adults (mean age of 40 years) with unexplained diffuse parenchymal lung disease and mainly ground-glass shadowing on HRCT.
  - In patients with type C disease, biopsies were undertaken as part of investigations into acute respiratory failure in the context of multiorgan systemic presentation.

**Take-home message:** Niemann–Pick disease should be considered for any patient with unexplained diffuse endogenous lipid pneumonia, even when disease is limited to the lungs and presentation is during adulthood.

**Purpose and Methods:** The pathology of severe acute respiratory syndrome (SARS) due to coronavirus (SARS-CoV) and avian influenza A subtype H5N1 is reviewed and compared based on the literature and the cases examined by the authors.

**Results:**
- **Similarities**
  - Pneumocyte the primary target of infection
  - Diffuse alveolar damage
  - Systemic cytokine activation with reactive hemophagocytic syndrome
  - Lymphoid depletion in spleen
  - Skeletal muscle fiber necrosis
  - Acute tubular necrosis
- **Differences**
  - SARS: less fulminant progression of DAD with combination of acute and reparative patterns; H5N1: more fulminant progression of DAD
  - SARS: more fibrocellular intra-alveolar organization with BOOP-like pattern, multinucleated histiocytes, and pneumocytes in 66%; H5N1: more hemorrhagic and necrotizing alveoli in acute phase, interstitial hyaline and paucicellular fibrosis, scanty intra-alveolar organization with no BOOP-like pattern, inconspicuous multinucleated cells
  - SARS-CoV: recoverable from lung by RT-PCR up to day 42; H5N1 virus: recoverable from lung by RT-PCR up to day 17
  - SARS-CoV: more widespread dissemination to blood, urine, feces, gastrointestinal tract, and liver; H5N1 virus: until recently only isolated from lung, recent report of extrapulmonary isolation from gastrointestinal tract, cerebrospinal fluid, and blood
  - SARS: no documented involvement of brain; H5N1: evidence of cerebral involvement in 2 autopsied cases and one clinical case

**Take-home message:** More pathologic studies are needed.
HUMAN PATHOLOGY

Purpose: To assess matrix metalloproteinase (MMP) and MMP inhibitor expression in the airspace of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) and to determine the prognostic significance of MMP expression in this patient population.

Methods:
- Twenty-eight patients with ALI or ARDS were prospectively enrolled in this study.
- Bronchoalveolar lavage (BAL) fluid obtained from these patients was examined for expression of MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin-1), MMP-8 (neutrophil collagenase), and MMP-9 (gelatinase B).
- Levels of MMP inhibitors (TIMP-1 and TIMP-2) were examined in parallel.
- Expression of MMPs was correlated with clinical outcomes.

Results:
- In nearly all specimens obtained from patients with ALI/ARDS, there were high levels of MMP-2, MMP-8, MMP-9, and TIMP-1.
- In only a small subset of patients (6/28) were there detectable levels of MMP-1 and/or MMP-3.
- In the patients with elevated MMP-1 and/or MMP-3, the mortality rate was higher (83%) than in the group without detectable levels of these enzymes (32%).

Take-home message:
- Also considering previous work in experimental animal models, the authors conclude that the presence of elevated MMP-2, MMP-8, and MMP-9 in BAL fluid is a marker of acute lung inflammation.
- In contrast, the presence of detectable MMP-1 and MMP-3 is an indicator of more serious disease progression.
**HUMAN PATHOLOGY**


**Purpose:** Epidermal growth factor receptor (EGFR) exon 18-21 mutations were shown to be highly predictive of response to gefitinib (Iressa) therapy in lung cancer. Although the frequency of these mutations in US and European lung cancers consistently ranged between 1% and 10%, a much higher mutation frequency (25.9%) has been reported in Japanese lung cancers. The purpose of this study was to investigate the prevalence of EGFR alterations in Saudi Arabia.

**Methods:** EGFR alterations were studied in 47 consecutive non-small cell lung cancers from Saudi Arabia by immunohistochemistry, fluorescence in situ hybridization, and DNA sequencing.

**Results:**
- Detectable EGFR expression was seen in 30 (69.8%) of 43 interpretable samples
  - 18 tumors with strong staining
  - 12 tumors with weak staining
- Epidermal growth factor receptor amplification was found in 6 (15.3%) of 39 interpretable samples
  - 4 tumors with high-level amplification (at least 10 EGFR gene copies)
  - 2 tumors with low level amplification
- Epidermal growth factor receptor amplification was strongly associated with high levels of EGFR expression (p = 0.0047).
- Only 1 exon 18-21 mutation was seen among 34 lung cancers that could be successfully sequenced.

**Take-home message:**
- EGFR exon 18-21 mutations are rare in Middle East patients with lung cancer and occur in a similar range as in Western patients.
- Because of their high rate of EGFR amplifications, Middle East lung cancer populations might be well suited for clinical trials investigating the predictive role of EGFR amplifications for responses to anti-EGFR drugs.

Purpose: To evaluate the sensitivity and specificity of 10 monoclonal and two polyclonal antibodies for distinguishing epithelioid mesothelioma from adenocarcinoma (AdCA) using immunohistochemistry (IHC).

Methods:
- The 133 tumors evaluated included 65 malignant epithelioid mesotheliomas, 22 lung AdCAs, 27 ovarian serous carcinomas, 24 breast carcinomas, and five gastric carcinomas.
- Antibodies directed against the mesothelial-associated antigens: mesothelin, calretinin, cytokeratin 5, thrombomodulin, Wilms’ tumor-1 (WT-1) gene product and HBME-1.
- Antibodies directed against the nonmesothelial antigens: Lewis-Y blood group (antibody BG8), MOC-31, BerEp4, CD15, and carcinoembryonic antigen (CEA) family.

Results:
- Calretinin had the best sensitivity for mesothelioma (95%), followed by HBME-1 (84%), WT-1 (78%), cytokeratin 5 (76%), mesothelin (75%), and vimentin and thrombomodulin (68%).
- Thrombomodulin had the best specificity for mesothelioma (92%), followed by cytokeratin 5 (89%), calretinin (87%) vimentin (84%), and HBME-1 (45%).
- The sensitivity of the nonmesothelial antigens for AdCA was organ dependent, with BG8 performing best in the breast cancer group (96%), and BerEp4, BG8, MOC-31 performing best in the lung cancer group (100%).
- The specificity of the nonmesothelial antigens for AdCA was 98% for BG8 and CEA, 97% for CD15, 95% for BerEp4, and 87% for MOC-31.
- A novel statistical analysis technique employing logic regression analysis identified a three-antibody immunohistochemical panel including calretinin, BG8, and MOC-31, which provided over 96% sensitivity and specificity for distinguishing epithelioid mesothelioma from AdCA.

Take-home message: Would you give up your usual antibody panel for these three antibodies to save a few bucks on a rare neoplasm?
Purpose: To report three cases of severe cystic pulmonary light chain deposition disease (LCDD) leading to lung transplantation.

Case reports:
- Clinical data: Three patients presented with a progressive obstructive pulmonary pattern associated with numerous cysts diffusely distributed in both lungs.
  - Histology
    - The disease was histologically characterized by non-amyloid amorphous deposits in the alveolar walls, small airways, and vessels.
    - It was associated with emphysematous-like changes and small airway dilation.
    - Mild extrapulmonary deposition was found in salivary glands in one patient.
    - No immunoproliferative disorder was identified.
  - IF
    - Monotypic kappa light chain was demonstrated in the deposits, and along the basement membranes.
    - Both kappa and lambda light chains were found in the plasma cells.
  - EM revealed coarsely granular electron-dense deposits.

Take-home message:
- This article widens the spectrum of localized pulmonary LCDD: LCDD may also present as a pulmonary cystic disorder.
CHEST

**Purpose:** To compare clinical, radiographic, and histologic findings of bronchiolitis obliterans syndrome (BOS).

**Methods:** All patients who underwent pulmonary retransplantation for BOS from 1992 to 2004 at Duke University Medical Center were reviewed. The authors developed a semiquantitative scoring system for epithelial, inflammatory, and fibrotic changes in affected airways (details of this scoring system are not explained sufficiently in the article). Pathology findings were compared with clinical and radiographic data.

**Results:**
- Over the 12-year study period, 12 patients underwent pulmonary retransplantation for BOS.
- The median time to BOS was 517 days (396 to 819.8 days).
- At least some degree of bronchiolitis obliterans BO was present in all explanted allografts.
- Only 50% (6 of 12 patients) had severe fibrotic changes, although all had some degree of epithelial injury, fibrosis, or inflammation centered on the bronchi and bronchioles.
- Pathology findings other than BO were present in most explanted allografts and included cholesterol clefts (n = 4), focal invasive aspergillosis (n = 1), interstitial fibrosis (n = 2), and chronic vascular rejection (n = 1).

**Take-home message:**
- The study has provided insignificant amount of new information.
- The new BO scoring system, which also includes epithelial changes, makes little or no sense.