Pulmonary Pathology Journal Club (November 2012)
Articles from October 2012
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Purpose:
To evaluate whether fibulin-3 in plasma and pleural effusions could meet sensitivity and specificity criteria to serve as a robust biomarker for pleural mesothelioma.

Methods:
- Plasma fibulin-3 levels were measured from patients with mesothelioma (92), asbestos-exposed persons without cancer (136), non-mesothelioma associated pleural effusions (93), and health controls (43).
- Effusion fibulin-3 levels were measured in patients with mesothelioma (74), benign effusions (39), and non-mesothelioma malignancies (54).
- Plasma and effusion fibulin-3 was measured by ELISA.
- Tumor tissue was examined for fibulin-3 by IHC.

Results:
- Plasma fibulin-3 did not vary with age, sex, duration of asbestos exposure
- Plasma levels significantly higher in mesothelioma
- Fibulin-3 IHC (nuclear+cytoplasmic) staining intensity greater in malignant meso (epi, sarc, and biphasic) than in benign pleura
- Plasma levels had a 96.7% sensitivity, 95.5% specificity (52.8 ng, cutoff)
- Early stage meso vs. asbestos exposed non-meso (100 spec, 94.1 sens)

Take home points:
- Plasma fibulin-3 can distinguish healthy persons with exposure to asbestos from patients with mesothelioma
- Effusion fibulin-3 levels + plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions, though the 2 aren’t correlated with one another.
- Fibulin-3 is not necessarily an early detection marker for mesothelioma, owing to the lack of prospective, plasma-based longitudinal collections.

Purpose:
To evaluate the prognostic role of PTEN in non-small cell carcinoma

Methods:
- Tissue microarrays containing 152 resected NSCLCs evaluated PTEN and p53 by IHC and PTEN by FISH.
- KRAS and EGFR mutations were analyzed by mass spec profiling
- Various statistical methods employed for analysis including Fisher’s exact test, Mann-Whitney test, Cochran-Armitage test, & Kaplan-Meier method.

Results:
- PTEN staining absent in 41.4% of cases
- Squamous cell > adenocarcinoma exhibit negative PTEN staining
- Loss of PTEN protein expression associated with shorter DFS.
- No significant associations with p53 or KRAS and EGFR mutations
- Only in adenocarcinomas was absent PTEN staining prognostic

Take home points:
- Absence of PTEN protein expression is an independent prognostic marker in early-stage resected lung adenoCA
- The 138G6 antibody appears to be most specific (from prior studies), and even faint staining appears to matter
- This study showed no correlation between tumor stage and PTEN expression (in contrast to other studies)
- The role of PTEN in these tumors seems functionally important to oncogenesis as its loss results in the dysregulation of pathways that are known to be critical for the progression of cancer.

Purpose: To examine whether IHC for TTF-1 is a useful temporary surrogate marker for choice of treatment guidance in metastatic NSCLC.

Methods:
- Consecutive cases of NSCLC referred for EGRF mutation testing from 2004 to 2010: n = 810
- IHC for TTF-1/NKX2-1 (clone 8G7G3/1, DAKO)
- Intensity scoring system:
  - 3 = strongly positive @ 2.5-4x objective; 2 = moderate @ 10-20x; 1 = weak @ 40x; 0 = no nuclear staining
  - % positive tumors cells for each intensity → H-score = Sum of (Intensity x %+cells)
  - Case with H-score ≥ 30 → = positive for TTF-1
- EGFR mutational analysis: exons 19 to 21

Results: n= 810
- Biopsies (n = 594); resections (n = 162); cytology (n = 54)
- EGFR mutation detected in 114 cases (14%)
- IHC result available in 797 cases (98%): 68% TTF-1+; 32% TTF-neg
- EGFRmut+: 92% are TTF1+, 8% are TTF1-
- In ADCa: probability of neg-EGFRmut is 80% in general, and 96% in TTF-neg ADCa
- Overall negative predictive value of TTF1-neg NSCLC for EGFR mutation is >95%
- 162 resections: 27 (16.7%) were EGFRmut+ and TTF1+
- 593 Bx: 79 (13.3%) were EGFRmut+ of which 8 (10.1%) were TTF1 neg
- 54 cytology: 8 (14.8%) were EGFRmut+ of which 1 (12.5%) was TTF1 neg

Take-home points:
- There is strong concordance between TTF-1+ NSCLC and the presence of EGFR mutation
- In TTF-1-neg cases, the odds of detecting EGFR mutation is about 4% (NPV > 95%)
• If treatment is needed urgently, negative TTF-1 can be used as temporary surrogate marker for starting conventional chemotherapy (until EGFR mutation is confirmed or ruled-out)
• Positive TTF-1 has insufficient PPV to serve as surrogate marker: await EGFR-mutation result before commencing any TKI therapy

Purpose:
- Evaluate histological criteria that can help differentiate connective tissue disease-associated UIP (CTD-UIP) from idiopathic UIP (I-UIP)

Methods:
- Patients with histological Dx of UIP
- Exclusion criteria: coexisting pulmonary disease (neo or non-neoplastic)
- Total # cases included: n = 35
  - CTD-UIP = 17; I-UIP = 18
  - Wedge Bx = 27; Explants = 8 (4 I-UIP and 4 CTD-UIP)
- Types of CTD: RA, SLE, SS, PolyM, DermatoM, Scleroderma, Mixed-CTD, Undiff-CTD
- QUANTITATIVE analysis: Digital scanning of Bx only (explants excluded)
  - I-UIP = 14; CTD-UIP = 13 (RA-CTD = 3; Other-CTD = 10)
  - 2 slides/case analyzed (UIP present on both slides)
  - Order of selection: RLL > LLL > RUL > LUL > Lingula > Right lung > Left lung
- Digital scoring system:
  - Fibroblastic foci (FF), lymphoid aggregates (LA), LA with germinal centers (GC) area outlined on screen and calculated
  - FF count (#); FF area (sum of areas of FF) (same for LA +/- GC)
  - FF count/total area; FF area/total area (same for LA +/- GC)
- QUALITATIVE histological assessment for NSIP-P
  - Both Bx and explants included, using following histological criteria
  - Areas “away” from UIP: x40 field (5mm) away from edge of fibrosis
  - Cellular or Fibrotic NSIP area spanning > x40 field (5mm)

Results:
- CTD-UIP: lower FF count and FF areas than in I-UIP (not significant)
- LA count and LA areas
  - Greatest in RA-UIP (not significant)
  - Similar among Other-CTD-UIP and I-UIP
  - LA+GC: too rare → insufficient for analysis
- In Bx: NSIP-P higher in CTD-UIP than I-UIP (p = .005)
- In explants:
  - I-UIP: ¼ with cellular NSIP in all lobes; ¾ with patchy fibrotic NSIP
  - CTD-UIP: ¾ with cellular NSIP in all lobes

Take-home points:
- CTD-UIP tend to have slightly fewer and smaller FF than I-UIP (p-value not significant)
- LA similar between CTD-UIP and I-UIP, but RA-UIP have a bit more
Significant higher prevalence of NSIP (multilobar) in CTD-UIP than I-UIP (so need multilobar sampling) □ Co-existance of UIP and multilobar NSIP may suggest underlying CTD
SUMMARIES – Articles for Notation (Neoplastic)


**Purpose:**
To understand the utility of an IHC panel in the diagnosis of mesothelioma in a general practice laboratory.

**Methods:**
TMAs composed of 16 adenocarcinomas and 6 mesotheliomas were stained in 36 different pathology laboratories across Canada, resulting in 736 interpretable cores of tumor (sarcomatoid mesotheliomas were stained, but excluded from analysis). CEA, CD15, calretinin and CK5/6 were used. If 3/4 of the markers were concordant with the results, the diagnosis was considered definitive. The original diagnosis made at the Vancouver General hospital (based on clinical, radiologic and pathologic findings) was considered the gold standards.

**Results:**
When 3 of 4 markers were concordant, 166/192 (86.4%) mesothelioma cores and 461/544 (84.7%) adenocarcinoma cores were correctly diagnosed. When 4 of 4 concordant markers were required, then 93/192 (48.4%) mesothelioma cores and 265/544 (48.7%) adenocarcinoma cores were correctly diagnosed.

**Take home points:**
- The authors concluded that a combination of CEA, CD15, calretinin and CK5/6 has a very low false-positive rate when separating pulmonary adenocarcinomas from mesotheliomas.
- 3/4 stains concordant is considered the minimal acceptable result.


**Purpose:**
Immunophenotype and quantify inflammatory cell population, interleukin and cytokines in peri-tumoral microenvironment in comparison to non-neoplastic lung tissue in patients with NSCLC

**Methods:**
The study included 65 patients with completely resected NSCLC ± adjuvant therapy. IHC stains for CD3, CD4, CD8, CD20, CD68, S100, CD1a, NK cell marker, IL-4, IL-6, IL-8, and cytokine TGF-b were used to evaluate innate and adaptive immune response.
Results:
The authors found low numbers of immune cells and levels of cytokines in the tumor environment when compared with surrounding parenchyma. There is an increase in immature DCs and macrophages densities and decreased density of T and B cells and expression of IL-4 and TGF-b.

Conclusion:
They believe this suggests a local environment lacking effective immune responses against cancer cells.


Purpose:
Stemming from the findings that ERCC1 expression is often enhanced in lung adenocarcinomas from never-smokers, the authors aimed at examining the role of P38 MAPK signaling in the oncogenesis of lung cancer.

Methods:
117 adenocarcinomas were tested. Cell viabilities of various cell lines, derived from never or light smokers, were measured after treatment with the p38 MAPK inhibitor SB202190 and cisplatin. The role of p38a (MAPK14) and p38b (MAPK11) isoforms and ERCC1 was evaluated using RNA interference.

Results:
The p38-specific inhibitor SB202190 strongly decreased cell viability (43%-63%). SB202190 plus cisplatin significantly decreased cell viability in every cell line, including cisplatin-resistant NCI-H1793. Genetic in- hibition, targeting both MAPK11 and MAPK14, reduced the viability of the different cell lines: down-regulation of p38b accounted for most of this effect. Cisplatin’s effect was greater after MAPK11 down-regulation for NCI-H1651, and MAPK14 down-regulation for NCI-H1650. In addition, both SB202190 and MAPK11 inhibition reduced excision repair cross-complementing 1 mRNA levels.

Take home points:
- The authors provide substantial molecular evidence in support of the notion that the p38 MAPK signaling pathway can contribute positively to the viability of lung cancer cells derived from never or light smokers.
- They conclude that inhibition of p38 MAPK can also synergize with cisplatin in different models and result in decreased ERCC1 mRNA expression (though this did not appear to definitively reflect ERCC1 protein levels).

Purpose:
The authors sought to examine the prognostic impact of malignant pleural effusions (MPE) in individuals with advanced non-small-cell lung cancer (NSCLC) with distant metastasis (M1b).

Methods:
The study consisted of an examination of more than 57K patients (from the SEER registry 2004-2005). Odds ratio estimates were calculated and a Cox proportional hazard model was used to evaluated independent risk for outcome.

Results:
MPE was identified in 16% of patients. The probability of MPE was higher with larger tumors, mediastinal node involvement and adenocarcinoma or large-cell carcinoma.

Take home points:
- They found that MPE is relatively common in individuals with NSCLC and is associated with decreased overall survival in patients with disatant metastases (stage M1b disease), from 5 months to 3 months when MPE was present.
- The authors identified MPE has an independent predictor for worse survival when adjusted for other demographic factors in multivariate analysis, in which MPE was associated with a 36% increase in the risk of death compared with those without MPE.


Purpose:
The authors conducted a Surveillance, Epidemiology, and End Results (SEER) database analysis to evaluate the prognostic significance of tumor size in patients with unresected stage III NSCLC.

Methods:
The SEER registry was searched and a total of 12,315 patients (age ≥ 21yo) were included in the study: 51.4% with stage IIIA and 48.6% with stage IIIB. Tumor size was defined as: S1 (0.1-3cm), S2 (3.1-5cm), S3 (5.1-7cm), and S4 (7.1-20cm). The histology types include: ADC, SQCC, large cell Ca, among others. Demographic variables are: age at Dx, sex, and race.
Results:
Univariate survival analysis showed that the risk of death from any cause increased significantly with each size category for both stage IIIA and IIIB. Tumor size was a statistically significant predictor for both OS and DSS on multivariate analysis adjusting for age, race, sex, and histology in both stages.

Take-home points:
- Tumor size is an independent predictor for OS and DSS in patients with unresected stage III NSCLC.
- These findings may indicate the relevance of stratifying treatment groups according to tumor size in patients with locally advanced NSCLC.


Purpose:
- This is the Part 2 of a multicenter prospective project known as “Evaluation of the EGFR Mutation status for the administration of EGFR-TKIs in non-small cell lung Carcinoma” (ERMETIC) conducted in France with multi-part objectives.
- The objective of this study is to select and rank clinical, pathological, and biological factors associated with prognosis in EGFR-TKI-treated patients in a large unselected white prospective cohort.

Methods:
A total of 522 patients with advanced NSCLC newly treated with EGFR-TKI were included, but only 307 of these had adequate tissue to reperform EGFR (exons 18, 19, and 21 only) and KRAS mutation analysis for the study.

Results:
The authors have found the following clinical factors to be significantly associated with higher progression risk: former/current smoker, poor performance status (PS >1), non-ADCa histology, >1 metastatic site, prior taxane-based Tx. Presence of EGFR mutation significantly decreased the risk of disease progression (PFS) or death (OS), while KRAS mutation only impacted OS by significantly increasing the risk of death.

Take-home points:
- EGRF and KRAS status independently impacts outcomes in advanced NSCLC patients treated with EGFR-TKI.
- They conclude the necessity of determining EGFR mutation status for selecting patients before administrating EGFR-TKI therapy.

Purpose:
The study seeks to clarify the modern prognostic significance of visceral pleura invasion (VPI) in Stage IB (T2aN0M0) NSCLC (AJCC 7th Edition).

Methods:
A total of 289 patients with completely resected Stage IB NSCLC were included in the study. VPI was defined as PL1 and PL2 involvement (modified Hammar’s diagram). Patients were divided into 3 groups according to size and VPI:

- Group I = “VPI-alone” (tumor ≤ 3cm with VPI; n=83)
- Group II = “Size-alone” (tumor >3cm and ≤5cm, no VPI; n=156)
- Group III = “VPI + Size” (tumor >3cm and ≤5cm with VPI; n=50).

Multivariate cox regression analysis was used to assess the association of VPI and size with survival, adjusting for age, gender, histology and type of resection.

Results:
VPI in Stage IB was identified in 133 patients (46.0%). Survival analysis in these patients identified an optimal cut-off tumor size of 3.1cm, above which the risk of death was significantly higher. Group II had significantly shorter 5-year SR (55.0%) compared to Groups I and II (68.3% and 67.2%, respectively, p=.021). There was no difference between Group I and II. Multivariate analysis showed that VPI associated with size was an independent negative prognostic factor of long-term survival, along with older age and limited resection.

Take-home message:
- Stage IB patients with VPI and tumors >3cm and ≤5cm have significantly worse prognosis than those with size ≤3cm+VPI or any size without VPI.
- The authors suggest upstaging these patients (tumor >3cm and ≤5cm with VPI) from current IB to Stage IIA.

Purpose:
The authors sought to develop a testing algorithm that maximizes the benefits of both DNA-based assay and IHC/cytochemistry testing for rapid response EGFR-TKI treatment.

Methods:
A total of 133 (of which 42 received EGFR-TKIs Tx) patients with NSCLC were analyzed for both types of tests. PNA-LNA PCR clamp assay was used to detect EGFR mutations in exons 19, 20, and 21. The primary antibodies used mutation-specific anti-EGFR Ab against E746-A750 del Specific (6B6) in exon 19 and L858R Mutant Specific (43B2) in exon 21. IHC scoring system is as follows: 0 (negative intensity); 1+ (weak/questionable/possibly negative intensity); and 2+ (easily detected immunoreactivity).

Results:
When excluding the 11 cases with equivocal score 1+, IHC for EGFR mutation-specific Ab showed a sensitivity of 81.4%, specificity of 97.5%, PPV of 94.6%, and NPV of 90.6%. In those treated with EGFR-TKIs, the PFS after the start of therapy was significantly longer in patients with IHC score 2+ than in score 1+ or 0.

Take-home message:
- The authors suggest that IHC for EGFR mutation-specific Ab are good candidates for rapid respond EGFR-TKI therapy.
- The authors propose the following algorithm:

Purpose:
The aim of the study was to investigate the clinical utility of one-step nucleic acid amplification (OSNA) assay, an automated rapid molecular diagnostic method and its optimal mRNA marker for detection of lymph node metastasis in lung cancer.

Methods:
- Sixteen target candidate mRNA markers with high expression in lung cancer from a genetic database were extracted, and then quantified their expression levels by quantitative RT-PCR using surgically dissected lymph nodes with or without metastasis.
- Keratins CK19, CK7 showed significant differences for mRNA expression between metastasis-negative and -positive LNs in quantitative-RT-PCR screening, and were finally selected as potential target markers.
- CK19 and CK7 were quantified using OSNA assay findings of 165 dissected lymph nodes obtained from 49 lung cancer patients.
- Resected LNs were divided in 2 halves: one ½ for routine histopathology FS, the other ½ immediately stored at -80°C until the OSNA assay with CK19 and CK7. These assays were completed within 40 min.

Results:
The positive predictive value, negative predictive value, and accuracy of CK19 OSNA assay compared to histo diagnosis with H&E and IHC were: 95.0%, 99.3%, and 98.8%, respectively. For CK7, the PPV, NPV, and accuracy were 85.0%, 97.9%, and 96.4%, respectively. The best performance was observed when CK19 was used as a marker, while the addition of CK7 mRNA as a marker did not increase sensitivity or specificity.

Take-home points:
OSNA assay using CK19 could be effective for intraoperative rapid molecular diagnosis of lymph node metastasis in lung cancer.

Purpose:
The aim is to describe the clinicopathologic and molecular features of lung granulomas secondary to chickenpox.

Methods:
A series of 8 asymptomatic, immunocompetent adult patients (33-53 yo; mean age 40 yo) with incidentally discovered several bilateral pulmonary granulomas were included: 6 retrospectively, 2 prospectively. Cases were stained with GMS, PAS and AFB. The presence of DNA from varicella-zoster virus (VZV) was studied by real-time PCR (rt-PCR) assay. Another 85 cases of granulomatous inflammation of various cases were arbitrarily selected for molecular analysis.

Results:
Chest CT revealed numerous infra-centimetric bilateral nodules in random distribution. PET scan available in 4 patients was all negative. All had history VZV infection as adults (severe form with general symptoms) 8-37mo prior to detection, but were clinically suspected for metastatic neoplasm or unknown origin.
On histology, the granulomas consisted of well-defined, rounded small nodules with an eosinophilic center of acellular necrosis rimmed by lamellar collagen and chronic inflammation, with or without giant cells. Granulomas did not coalesce, cavitate, or show peripheral histiocytic palisading pattern. GMS, PAS, and AFB were negative in all cases. Real-time PCR analysis detected VZV DNA in all 8 study cases, but not in any of the 85 other cases for granulomatous inflammation of other causes.

Take-home points:
The presentation of incidentally found pulmonary granulomatous nodules with above described peculiar morphology should prompt the consideration of chickenpox-related granulomas and look for history of VZV infection in adulthood.

Purpose:
The study sought to determine the incidence and outcome of drug-induced acute lung injury (DALI) in patients diagnosed with ALI.

Methods:
- “ALI” was defined using the standard American-European Consensus Conference criteria, and a total of 514 patients with true ALI were included in this study.
- “DALI” defined as “development of ALI within 1 year after exposure to any of the pre-specified drugs” (chemotherapeutic/anti-inflammatory agents, amiodarone, and nitrofurantoin).
- Cases were subdivided into: a) probable (12; 2.3%), b) possible (37; 7.2%), c) conditional (8; 1.6%), and d) no DALI (457; 88.9%). Cases from a) and b) were combined as “DALI” (49; 9.5%) and compared to the “Non-DALI” (combining category c and d; 465; 90.5%).

Results:
Of 49 patients of DALI, 36 received chemotox/anti-Inf agents and 14 received amiodarone. All ALI patients have similar baseline characteristics. APACHE III scores, ICU and hospital mortality were significantly higher in DALI than non-DALI group. Even when adjusted for APACHE III score on admission and the presence of malignancy, hospital mortality was still significantly higher in DALI group.

Take-home points:
- Drugs are important risk factor for developing DALI
- Recognizing potential drugs is crucial for early identification of patients at risk, discontinuation of offending agents, and prognosis.


Purpose:
The authors present a small case series of pulmonary lymphatic disease presenting as interstitial lung disease in adulthood accompanied by a nice overview of the spectrum pulmonary lymphatic disease (namely, lymphangiectasis and diffuse pulmonary lymphangiomatosis).

Methods:
The consultation files of the authors were retrospectively searched for cases of pulmonary lymphatic disease in adults. Radiologic and clinical records
were obtained from the referring institutions. Supplemental IHC was employed to aid in the diagnosis and histomorphologic description.

**Results:**
Three cases were found, and the authors provide a detailed description of the above-described features.

**Take home points:**
- Because these rare diseases are typically encountered in a pediatric population, understanding the presentation and histopathology in the adult populations is essential to being about to make identify these lesions and make the correct diagnosis.
- Recognition of the characteristic lymphangitic distribution of abnormally dilated or reduplicated lymphatic spaces is key to the correct diagnosis.


**Purpose:**
The goal was to examine the effect of lactic acid (LA) on myofibroblast differentiation and pulmonary fibrosis.

**Methods:**
Metabolomic analysis was used to examine cellular metabolism in lung tissue with IPF and determined the effects of LA and lactate dehydrogenase-5 (LDH5) overexpression on myofibroblast differentiation and transforming growth factor (TGF)-b activation in vitro. LA concentration was determined by nuclear magnetic resonance spectroscopy. Alpha-SMA, Calponin, and LDH5 expression were assessed by Western blot of cell culture lysate.

**Results:**
The authors found that LA and LDH5 were significantly elevated in IPF lung tissue (n=6) compared with controls (n=6). Physiologic concentrations of lactic acid induced myofibroblast differentiation via activation of TGF-b. TGF-b induced expression of LDH5 via hypoxia-inducible factor 1a (HIF1a). Overexpression of both HIF1a and LDH5 in human lung fibroblasts induced myofibroblast differentiation and synergized with low-dose TGF-b to induce differentiation. Inhibition of both HIF1a and LDH5 inhibited TGF-b–induced myofibroblast differentiation.

**Take-home points:**
This study has identified the metabolite lactic acid as an important mediator of myofibroblast differentiation via a pH-dependent activation of TGF-b. The authors proposed that the metabolic milieu of the lung, and potentially other
tissues, is an important driving force behind myofibroblast differentiation and potentially the initiation and progression of fibrotic disorders.


Purpose:
To identify novel mediators of fibrosis comparing the transcriptional signature of hyperplastic epithelial cells and co- served epithelial cells in the same lung.

Methods:
Laser capture microscope and microarrays analysis were used to identify differentially expressed genes in IPF lungs. Bleomycin-induced lung fibrosis was evaluated in Mmp19-deficient and wild-type (WT) mice. The role of matrix metalloproteinase (MMP)-19 was additionally studied by transfecting the human MMP19 in alveolar epithelial cells.

Results:
A novel mediator, MMP-19, was identified in hyperplastic epithelial cells adjacent to fibrotic regions. Mmp19/2 mice showed a significantly increased lung fibrotic response to bleomycin compared with WT mice. A549 epithelial cells transfected with human MMP19 stimulated wound healing and cell migration, whereas silencing MMP19 had the opposite effect. PTGS2 was overexpressed in IPF lungs and colocalized with MMP-19 in hyperplastic epithelial cells. In WT mice, PTGS2 was significantly increased in bronchoalveolar lavage and lung tissues after bleomycin-induced fibrosis, but not in Mmp19/2 mice.

Take home point:
- Up-regulation of MMP19 induced by lung injury may play a protective role in the development of fibrosis through the induction of PTGS2.


Purpose:
The aim of this study was to investigate the involvement of immune pathways and of the intercellular and vascular cell adhesion molecules (intercellular adhesion molecule and vascular cell adhesion molecule, respectively) in the lungs of patients with pulmonary involvement of leptospirosis.

Methods:
The authors studied the lungs of 18 patients who died of leptospirosis and compared them with 2 groups of controls: normal and noninfectious
hemorrhagic lungs. Using immunohistochemistry and image analysis, they quantified the expression of the C3a anaphylatoxin receptor, intercellular adhesion molecule, vascular cell adhesion molecule, and Toll-like receptor 2 in small pulmonary vessels and in the alveolar septa.

Results:
There was an increased expression of intercellular adhesion molecule (P < .03) and C3a anaphylatoxin receptor (P < .008) in alveolar septa in the leptospirosis group compared with the normal and hemorrhagic controls. In the vessels of the leptospirosis group, there was an increased expression of intercellular adhesion molecule (P = .004), vascular cell adhesion molecule (P = .030), and Toll-like receptor 2 (P = .042) compared with the normal group. Vascular cell adhesion molecule expression in vessels was higher in the leptospirosis group compared with the hemorrhagic group (P = .015).

Take home points:
- Our results indicate that immune receptors and adhesion molecules participate in the phenomena leading to pulmonary hemorrhage in leptospirosis.
- A more complete understanding of the pathogenesis of pulmonary hemorrhage in the setting of leptospirosis is necessary for future development of treatment strategies.