PULMONARY JOURNAL CLUB

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Articles for Discussion

Oka N, et al. Flat cell variant of lung adenocarcinoma in situ. Mod Pathol. 2025;38:100876.

BACKGROUND

- Adenocarcinoma in situ (AIS) of the lung has been increasingly diagnosed worldwide following the establishment of its diagnostic criteria along with advances in computed tomography imaging technology

METHODS AND RESULTS

- The authors encountered a series of AIS cases with a peculiar flat cell morphology that were challenging to diagnose
- Histologically, all 5 tumors showed a lepidic pattern consisting of flat tumor cells with minimal nuclear atypia
- Intra-alveolar mucin was identified in 4 cases (cytoplasmic mucin was inconspicuous)
- All tumors harbored genetic or immunohistochemical features of neoplasms identical to those of conventional AIS
    - Driver mutations were detected in 3 tumors (2 EGFR mutations and 1 ERBB2 mutation)
    - 4 tumors were positive for hepatocyte nuclear factor 4 alpha, although the intensity was very low
- The authors also identified a case of minimally invasive adenocarcinoma with flat cell features, suggesting a stepwise progression similar to that in conventional AIS

CONCLUSIONS

- The authors suggest that AIS with flat cellular features is a morphologic variant of AIS, which may be challenging to diagnose

Yeh YC, et al. Tumor cell invasion of the external elastic lamina designates visceral pleural invasion and predicts poorer patient outcomes in pulmonary nonmucinous invasive adenocarcinoma. J Thorac Oncol. 2025;20:1791-1800.

BACKGROUND

- Both the American Joint Committee on Cancer and the College of American Pathologists classify visceral pleural invasion (VPI) as follows
    - PL-0 for tumors that do not invade the external elastic lamina
    - PL-1 for tumors that invade the external elastic lamina but not up to the pleural surface
    - PL-2 for tumors that invade up to the pleural surface without involvement of adjacent anatomic structures
    - PL-3 for tumors that invade the parietal pleura
- Staging of tumors smaller than 3 cm in size will be upgraded from T1 to T2 if VPI (PL-1 or PL-2) is present
- Currently, it is recommended that tumor cells invading the external elastic lamina, rather than the internal elastic lamina, serve as the criterion for diagnosing VPI
- Nevertheless, there is scarce evidence supporting this widely adopted recommendation

OBJECTIVE

- To further validate the clinical significance of lung cancer invading the external versus internal elastic lamina of the visceral pleura

METHODS

- The authors retrospectively reviewed the clinicopathologic characteristics of 1217 patients with lung cancer with surgically resected nonmucinous invasive adenocarcinoma between 2011 and 2016
- Using the scheme with two-layered elastic laminae, VPI was categorized into
    - PL-n (no pleural invasion)
    - PL-i (tumor invading into or beyond the internal elastic lamina)
    - PL-e (tumor invading into or beyond the external elastic lamina)
    - PL-p (tumor reaching the parietal pleura)
- The authors analyzed the relationship between categories of VPI and prognosis, along with other pertinent clinical and histopathologic parameters

RESULTS

	5-year overall survival (%)	5-year recurrence-free survival (%)
PL-n	89.7	88.1
PL-i	89.5	85.8
PL-e	71.3	55.8
PL-p	53.3	48.6

- PL-e demonstrated
    - Significant differences in univariate analyses in the overall survival analysis
    - Significant differences in both univariate and multivariate analyses in the disease-free survival analysis

CONCLUSIONS

- Tumor cells invading the external elastic lamina (PL-e) were a significant prognostic factor for recurrence and associated with worse overall survival for pulmonary nonmucinous invasive adenocarcinoma
- The study provides evidence supporting the use of the outmost external elastic lamina as the landmark of visceral pleural invasion

Brcic L, Tazelaar HD. Is Pleural Invasion Always Pleural Invasion? J Thorac Oncol. 2025;20:1741-1743.

Sanchez SI, et al. Cytopathologic and histopathologic characteristics of SMARCB1 deficient neoplasm and correlation with molecular and immunohistochemical findings. Hum Pathol. 2025;166:105980.

BACKGROUND

- SMARCB1 (INI-1) deficient neoplasms are an aggressive and heterogeneous group of tumors
- Recent clinical trials have shown that targeted therapy with EZH2 inhibitor tazemetostat can improve the patients' survival

OBJECTIVE

- To review morphological features of a series of SMARCB1 deficient neoplasms

MATERIAL AND METHODS

- Pathology archives were searched for SMARCB1 deficient neoplasms and aberrant expression of SMARCB1
- Morphological, immunohistochemical, and molecular findings were reviewed

RESULTS

- 54 cases with complete loss and 10 cases with partial loss of SMARCB1 (/INI-1) were identified
- The 54 cases with complete loss of SMARCB1
    - Included 5 serous fluids, 10 FNAs, 18 biopsies, and 21 surgical resections
    - The median age of patients was 35.8 years, ranging from 14 days to 87 years
    - The female to male ratio was 1.07:1.00
    - The most involved anatomic sites in descending order were head and neck (n = 14), CNS (n = 11), lymph node (n = 8), thorax/lung (n = 6), liver (n = 5), and others (n = 10)
    - Characteristic cytomorphology included poorly differentiated neoplasm, poorly differentiated carcinoma, basaloid/sarcomatoid carcinoma, and rhabdoid neoplasm
    - The tumors were frequently positive for cytokeratin
    - Complex genetic abnormalities included aberrant SMARCB1/INI-1, PIK3C2B, RAF, MAP3K14, FBXO11, and others

CONCLUSIONS

- The ancillary testing for SMARCB1/INI-1 should be considered in patients whose tumor demonstrates bizarre morphology

Moriyama H, et al. Is giant cell interstitial pneumonia pathognomonic for hard metal lung diseases? - pathological and elemental analyses of 84 cases. Histopathology. 2025;87:923-932.

BACKGROUND

- Giant cell interstitial pneumonia (GIP) is a rare type of interstitial lung disease (ILD) caused by hard metal dust
- However, instances of GIP without clear exposure to hard metals have been documented (Khoor A, et al. Giant cell interstitial pneumonia in patients without hard metal exposure: analysis of 3 cases and review of the literature. Hum Pathol. 2016;50:176-82.)

OBJECTIVE

- This study aimed to determine whether GIP is pathognomonic for hard metal lung disease (HMLD)

METHODS AND RESULTS

- The authors evaluated 263 patients with ILD with occupational history from Jan 1993 to Aug 2023
- Physicians sent clinical information and tissue samples with pathological diagnoses to request elemental analyses of lung specimens
- The authors prepared 3-μm-thick sections from paraffin-embedded tissues for pathological examination and elemental analysis using an electron probe micro-analyzer (EPMA)
- After identifying centrilobular fibrosis in the pathology reports, the authors collected X-ray data with EPMA
- 84 of the 263 patients were suspected of having HMLD
    - 56 exhibited a GIP pattern
        - Tungsten was found in lung specimens from 40 of the 56 GIP patients, confirming HMLD
        - 3 patients with GIP had cobalt, but no tungsten detected
        - 13 patients with GIP showed elements like silicon, aluminum, iron, magnesium, and others in their specimens but no tungsten or cobalt
    - 28 displayed various other ILD forms

- Among the 28 non-GIP cases, 19 were diagnosed with HMLD upon detection of tungsten

CONCLUSION

- Among the 59 HMLD cases, only 40 had GIP
- Only cobalt was found in 3 cases (5.3%), and neither tungsten nor cobalt was detected in 13 patients (23.2%)
- These findings suggest that GIP is not pathognomonic for HMLD

Articles for Notation: Neoplastic

Elsner F, et al. Current practice of pathologic response assessment following chemoimmunotherapy for non-small cell lung cancer (NSCLC) in Germany: first real-world data from the multicentre Re-GraDE study. Histopathology. 2025;87:869-879.

BACKGROUND

- Given that pathologists now frequently assess pathologic response following neoadjuvant or perioperative chemoimmunotherapy for NSCLC, the authors set up a multicenter study to evaluate the current practice of regression grading in Germany (Re-GraDE NSCLC).

METHODS

- 133 cases of NSCLC resection specimens following chemoimmunotherapy were collected from 9 high-volume lung cancer centers in Germany
- Case characteristics were obtained from pathology reports/electronic medical records
- In 107 cases, pretreatment biopsies were available on-site

RESULTS

- Residual viable tumor (% RVT) was commonly used to measure therapy response (106/133 resection specimens, 79.7%)
- The entire tumor bed was submitted for histology in 55.6% of cases; however, in 18%, a tumor bed of ≤3 cm was not completely submitted
- Either Junker or IASLC regression grading was applied in 97.7% of primary tumors and 60.2% of lymph nodes with comparable results
- Almost half of the tumors (45.9%) showed pathological complete response (pCR) and/or regression grade (RG) III with a very weak correlation between % RVT and pretreatment PD-L1 TPS ($r^2 = 0.078$, $P = 0.007$)
- Pretreatment PD-L1 levels ranged from 0% to 100% (median, 60%) in cases with complete regression, and pCR was observed in 40% of cases with pretreatment PD-L1 TPS <1%.

CONCLUSIONS

- This multicenter study describes the current practice of histopathological regression grading of NSCLC after chemoimmunotherapy in Germany, highlighting

the widespread use of the Junker system, which is basically comparable to IASLC regression grading
- For standardization, the authors recommend following the IASLC guidelines (submitting of the complete tumor bed if ≤3 cm), while the reporting of % RVT might represent a continuous parameter for therapy response
- Germany's digital nationwide registry, which aims to integrate biopsy results, molecular profiling and % RVT in resection specimens, might develop into a valuable tool to investigate novel predictive biomarkers of chemoimmunotherapy efficacy

Wu J, et al. Histomorphological and molecular spectrum of ciliated muconodular papillary tumors with implication for malignant potential: Insights from a literature review and series report. Hum Pathol. 2025;166:105981.

BACKGROUND

- Bronchiolar adenoma/ciliated muconodular papillary tumor (CMPT) of the lung is defined as a benign tumor by the 5th WHO classification
- However, recent studies have shown that it harbors multiple aberrant genes and has undetermined malignant potential
- On the other hand, CMPT is easily misdiagnosed as mucinous adenocarcinoma

OBJECTIVE

- To further study the relationship between histomorphology and genetic alterations in CMPT

METHODS

- 15 cases of CMPT were identified
- Histomorphology, IHC, and gene status (2 cases) were analyzed

RESULTS

- CMPT exhibited double-layered structures with papillary, glandular, and micropapillary formations
- IHC
    - Basal cells showed p40/p63/CK5/6 immunoreactivity
    - Both luminal and basal cells showed TTF-1 immunoreactivity
    - 2 cases expressed ALK protein

    - 1 case overexpressed BRAF (V600E) protein
- NGS
    - 2 cases harbored ALK rearrangements
- Most cases followed an indolent clinical course with no recurrence or metastasis after surgical resection

CONCLUSIONS

- According to the authors, the study highlights the importance of recognizing CMPT's distinct histological and molecular features

Yan P, et al. Claudin18.2 expression and its clinicopathological feature in adenocarcinoma from various parts. J Clin Pathol. 2025;78:815-821.

OBJECTIVE

- To clarify claudin18.2 expression and its clinicopathological features in various cancers, especially in lung adenocarcinoma.

METHODS

- IHC staining and FISH were performed to detect claudin18.2 expression and CLDN18 gene rearrangement in adenocarcinoma from different organs

RESULTS

- The results showed that claudin18.2 expression was found in 68% (27 of 40) of lung mucinous adenocarcinoma, 52% (16 of 31) of cholangiocarcinoma, 2% (10 of 423) of colorectal adenocarcinoma tissue microarray, 27% (6 of 22) of colorectal mucinous adenocarcinoma and 30% (3 of 10) of cervical adenocarcinoma, but not in all 39 cases of invasive breast adenocarcinoma by IHC staining
- There was significantly positive correlation between ratio of claudin18.2-positive carcinoma cells and staining intensity in lung mucinous adenocarcinoma and cholangiocarcinoma
- Claudin18.2 expression was much more in female patients than male patients with lung mucinous adenocarcinoma
- In addition, cholangiocarcinoma with claudin18.2 expression was more aggressive and had perineural invasion
- Intraductal papillary neoplasm of the bile duct and epithelial dysplasia of the adjacent bile in cholangiocarcinoma also showed claudin18.2 expression

- All three cases of cervical adenocarcinoma with claudin18.2 expression were moderately differentiated adenocarcinoma including one human papillomavirus (HPV)-associated carcinoma, two non-HPV-associated and gastric-type carcinoma
- CLDN18 gene rearrangement was not found in all 22 cases with high claudin18.2 expression by FISH

CONCLUSIONS

- The results suggest claudin18.2 might be a potential biomarker for targeted therapy on lung mucinous adenocarcinoma, cholangiocarcinoma, colorectal mucinous adenocarcinoma and gastric-type cervical adenocarcinoma

Zhang N, et al. Combined detection of SHOX2 and PTGER4 methylation with serum marker CYFRA21-1 for improved diagnosis of malignant pleural mesothelioma. J Clin Pathol. 2025;78:836-842.

OBJECTIVE

- To investigate the performance of a combined biomarker approach using the methylation status of the short stature homeobox 2 (SHOX2) and prostaglandin E2 receptor EP4 (PTGER4) genes, along with the serum levels of CYFRA21-1, for differential diagnosis of malignant pleural mesothelioma (MPM) from benign reactive mesothelial hyperplasia (RMH)

METHODS

- The authors analyzed 48 MPM tissue or pleural effusion cell block specimens and 42 cases with RMH
- Real-time quantitative methylation-specific PCR was used to examine the methylation status of SHOX2, PTGER4, ras association domain family 1 isoform A, septin 9 gene and homeobox gene A9 genes
- Additionally, the authors used electrochemiluminescence immunoassay to measure nine serum tumor markers commonly used in pan-cancer screening tests

RESULTS

- The receiver operating curve indicated that SHOX2, PTGER4 gene methylation and serum biomarker CYFRA21-1 exhibited good diagnostic performance in identifying MPM, with area under curves (AUCs) of 0.761, 0.904 and 0.847, respectively
- The combination of SHOX2, PTGER4 methylation and CYFRA21-1 yielded an AUC value of 0.972

- The diagnostic sensitivity and specificity of this panel in differentiating MPM from RMH were 91.3% (42/46) and 97.6% (41/42), respectively
- Both tissue and cell block specimens can be used in the diagnostic process
- Furthermore, elevated CYFRA21-1 levels were associated with poor prognosis ($p<0.05$)
- Hypermethylation level of PTGER4 may indicate an unfavorable prognosis of MPM, but the difference was not statistically significant

CONCLUSIONS

- The combined detection of SHOX2 and PTGER4 methylation alongside serum CYFRA21-1 level significantly enhances the diagnosis of MPM
- Additionally, CYFRA21-1 can serve as a prognostic indicator for MPM

Hong L, et al. Distinct Clinicogenomic Features and Immunotherapy Associations in Pulmonary Sarcomatoid Carcinoma: A Multicenter Retrospective Study. J Thorac Oncol. 2025;20:1763-1777.

BACKGROUND

- Pulmonary sarcomatoid carcinoma (PSC) is a rare NSCLC subtype with poor prognosis

OBJECTIVE

- To compare PSC and other NSCLC subtypes regarding genomic features and response to immune checkpoint inhibitor (ICI) therapy

METHODS

- The authors analyzed 4841 patients including 165 PSC cases treated with ICI-based therapy from three institutions and 201 PSC cases from National Cancer Database (NCDB)
- In the MD Anderson Cancer Center (MDACC) cohort, 65 (4.3%) were PSC, 1138 (75.1%) lung adenocarcinoma (LUAD), and 312 (20.6%) lung squamous cell carcinoma (LUSC).

RESULTS

- Patients with PSC were older and more likely to present with metastatic disease

- In both the MDACC and NCDB cohorts, ICIs resulted in better outcomes for patients with PSC compared with chemotherapy; in these patients, there was no difference in outcome between ICI-monotherapy and ICI-chemotherapy
- Across the three institutional cohorts, 37% to 43% of patients with PSC who received ICIs were responders, compared with 26% to 29% in LUAD and 22% to 46% in LUSC ($p < 0.05$)
- Improved ICI outcomes in PSC appeared driven by high PD-L1 (≥50% in 73%-77% cases)
- Among patients with high PD-L1, response rates were similar across histologic subtypes
- Conversely, TMB was similar in PSC compared with LUAD or LUSC and was not associated with ICI outcomes
- Across cohorts, PSC tumors were enriched for TP53, NF1, NF2, and NRAS, with relative depletion of STK11 and KEAP1 compared with LUAD
- Case observation revealed relatively better outcomes to ICI than targeted therapies in patients with PSC with MET exon 14 skipping or KRAS G12C

CONCLUSIONS

- PSC exhibits improved outcomes to ICI relative to other therapies, potentially driven by high PD-L1 expression
- Genomic analysis highlights a distinct genomic landscape of PSC when compared with LUAD

Herbst RS, et al. Digital versus manual PD-L1 scoring in advanced NSCLC from the IMpower110 and IMpower150 trials. J Thorac Oncol. 2025;20:1778-1790.

BACKGROUND

- Treatment selection in patients with advanced NSCLC is based on PD-L1 expression, which is usually scored manually and is subject to intra- and inter-pathologist variability
- A PD-L1 clone-agnostic artificial intelligence (AI) model for AI-based measurement of PD-L1 (AIM-PD-L1) was developed and assessed in advanced NSCLC using clinical samples from two phase 3 trials

METHODS

- IMpower110 evaluated atezolizumab versus chemotherapy in PD-L1-positive metastatic, stage IV, squamous or non-squamous NSCLC
- IMpower150 evaluated atezolizumab, carboplatin, and paclitaxel, with or without bevacizumab, versus carboplatin, paclitaxel, and bevacizumab in patients with metastatic non-squamous NSCLC
- AIM-PD-L1 was developed and deployed on SP263-stained whole slide images (IMpower110, n = 509; IMpower150, n = 766) for digital scoring of tumor cell (TC) PD-L1 expression and identification of human-interpretable features (HIFs) associated with survival outcomes

RESULTS

- Overall percentage agreements between scoring methods for TC more than or equal to 50% and more than or equal to 1% cutoffs were high
- Survival analyses were similar for PD-L1 subgroups between scoring methods at both TC cutoffs
- A nonsignificant improvement in survival outcomes was observed in patients treated with atezolizumab-containing regimens and classified as positive by digital scoring but missed by manual scoring
- Two HIFs in the cancer epithelium-density of all PD-L1-positive TC and immune cells-were nominally associated with overall survival
- Many HIFs were identified to be predictive of significantly improved progression-free survival with atezolizumab-containing regimens versus control

CONCLUSIONS

- AIM-PD-L1 digital SP263 PD-L1 scoring is concordant with manual scoring, revealing similar predictivity for benefit, and could potentially be used as a predictive marker for patient stratification and selection for anti-PD-(L)1 therapy

von der Thüsen J. Assessment of Immunohistochemical PD-L1 Expression by AI Algorithms in NSCLC: The Time has Come for Validation in Prospective Clinical Trials. J Thorac Oncol. 2025;20:1744-1746.

Yolchuyeva S, et al. Whole-slide imaging and radiological features predict clinical outcomes in patients with neuroendocrine tumors of the lung. Mod Pathol. 2025;38:100897.

BACKGROUND

- Neuroendocrine tumors are rare and heterogeneous cancers that vary in clinical presentation, biology, and treatment response
- They exhibit slow growth with varying levels of aggressiveness, highlighting the need for reliable biomarkers to guide personalized treatment

OBJECTIVE

- To develop predictive models for overall survival (OS) and progression-free survival (PFS) using CT scans, whole-slide images, and clinical data

METHODS

- This retrospective analysis included 83 patients
- Predictive models were developed using radiomics features from CT scans and morphologic or pathomics features from whole-slide images
- The Cox model was trained using the most significant features from both radiomics and pathomics
- By integrating these features with clinical data, the authors built predictive models combining clinical-radiomics and clinical-pathomics information
- The authors also assessed how image harmonization across different acquisition parameters affects model performance

RESULTS

- The radiomics model's concordance indices (C-indices) for predicting OS and PFS in the validation cohort were 0.64 ± 0.06 (95% CI, 0.55-0.73) and 0.60 ± 0.05 (95% CI, 0.52-0.67), respectively.
- Combining radiomics with clinical data slightly improved performance, with C-indices of 0.643 ± 0.04 (95% CI, 0.58-0.70) for OS and 0.61 ± 0.04 (95% CI, 0.54-0.68) for PFS.
- For the pathomics model, combining morphologic features with clinical data also showed better improvements, with C-indices for OS increasing from 0.65 ± 0.08 (95% CI, 0.53-0.76) to 0.70 ± 0.03 (95% CI, 0.57-0.82), and for PFS from 0.60 ± 0.15 (95% CI, 0.39-0.81) to 0.68 ± 0.08 (95% CI, 0.57-0.80).
- Harmonizing radiomics features did not significantly enhance the model's performance for predicting survival outcomes.

CONCLUSIONS

- This study developed and validated models that integrate radiomics and pathomics with clinical data, improving prognostic accuracy for OS and PFS
- These multimodal approaches, supported by large data sets, offer significant potential for enhancing patient risk stratification

Ho DJ, et al. Deep Learning-Based Segmentation of Lung Adenocarcinoma Whole-Slide Images for Objective Grading, Tumor Spread Through Air Spaces Identification, and Mutation Prediction. Mod Pathol. 2025;38:100907.

BACKGROUND

- Manual quantification of morphologic patterns in lung adenocarcinoma is subject to reproducibility issues due to interpathologist variability

OBJECTIVE

- To develop a deep learning-based multiclass segmentation model providing a modality for objective and quantitative grading of digitized lung adenocarcinoma images from resected specimens.
- To detect tumor spread through air spaces and show enrichment of specific morphologic patterns in tumors with different genomic alterations

METHODS

- The study was based on 766 resected nonmucinous lung adenocarcinomas
- Deep Multi-Magnification Network was trained to segment 14 tissue subtypes based on annotations of 108 internal whole-slide images at pixel level by thoracic pathologists
- The trained model was validated on an external cohort of 130 cases for determining predominant patterns and on the remaining 528 internal cases for the 3 clinical tasks

RESULTS

- The model graded nonmucinous lung adenocarcinomas based on the International Association for the Study of Lung Cancer Pathology Committee recommendation and successfully stratified patients into well, moderately, and poorly differentiated morphologies ($P < 1 \times 10\text{-}4$)
- Pixels categorized as spread through air spaces significantly correlated with pathologists' interpretations

- For molecular analysis, solid pattern was enriched with TP53 mutations and depleted of EGFR kinase domain mutations
- Lepidic pattern was inversely associated with TP53 mutations
- Acinar was enriched with EGFR mutations, whereas papillary was associated with RET fusions

CONCLUSIONS

- The study demonstrated that deep learning-based segmentation can accurately quantify histologic patterns in lung adenocarcinoma and identify additional prognostic features

Roche JJ, et al. Current and future applications of artificial intelligence in lung cancer and mesothelioma. Thorax. 2025;80:957-965.

BACKGROUND

- Considerable challenges exist in managing lung cancer and mesothelioma, including diagnostic complexity, treatment stratification, early detection and imaging quantification
- In this context, artificial intelligence (AI) offers a range of assistive/automated functions that can potentially enhance clinical decision-making

OBJECTIVE

- To synthesize evidence on this topic, focusing on routine pathology and radiology images

METHODS

- The authors summarize the strengths and weaknesses of AI applied to common multidisciplinary team (MDT) functions, including histological diagnosis, therapeutic response prediction, radiological detection and quantification, and survival estimation
- They also review emerging methods capable of generating novel biological insights and current barriers to implementation, including access to high-quality training data and suitable regulatory and technical infrastructure.

RESULTS

- Neural networks trained on pathology images have proven utility in histological classification, prognostication, response prediction and survival

- Self-supervised models can also generate new insights into biological features responsible for adverse outcomes
- Radiology applications include lung nodule tools, which offer critical pathway support for imminent lung cancer screening and urgent referrals
- Tumor segmentation AI offers particular advantages in mesothelioma, where response assessment and volumetric staging are difficult using human readers due to tumor size and morphological complexity
- AI is also critical for radiogenomics, permitting effective integration of molecular and radiomic features for discovery of non-invasive markers for molecular subtyping and enhanced stratification

CONCLUSIONS

- AI solutions offer considerable potential benefits across the MDT, particularly in repetitive or time-consuming tasks based on pathology and radiology images
- Effective leveraging of this technology is critical for lung cancer screening and efficient delivery of increasingly complex diagnostic and predictive MDT functions
- Future AI research should involve transparent and interpretable outputs that assist in explaining the basis of AI-supported decision making

Carillo AM, et al. A challenging case of enteric-type lung adenocarcinoma metastatic to the thyroid harboring RET-fusion diagnosed on fine-needle aspiration. Virchows Arch. 2025;487:1433-1438.

BACKGROUND

- Enteric-type lung adenocarcinoma is a histological entity where the enteric component exceeds 50% and showS the expression of at least one immunohistochemical marker of enteric differentiation
- The most common differential diagnosis is colorectal carcinoma
- Molecular alterations less commonly observed in colorectal adenocarcinoma but more frequently associated with enteric-type lung adenocarcinoma can be helpful in differential diagnosis

REPORT OF A CASE

- In this report, the authors show a case of a thyroid lesion diagnosed on FNA as metastasis from colorectal carcinoma and then recognized as a metastasis from enteric-type lung adenocarcinoma thanks to the identification of a RET-fusion through NGS testing

CONCLUSION

- This is the first case of enteric-type lung adenocarcinoma with RET-fusion reported

Lawrence L. Oral TKI zongertinib gains accelerated approval for HER2-mutant NSCLC. Cancer. 2025;131:e70145.

Articles for Notation: Non-neoplastic

Sand JMB, et al. Basement membrane repair response biomarker PRO-C4 predicts progression in idiopathic pulmonary fibrosis: analysis of the PFBIO and PROFILE cohorts. Thorax. 2025;80:935-944.

BACKGROUND

- Idiopathic pulmonary fibrosis (IPF) is characterized by damage to the epithelial layer, closely associated with the alveolar basement membrane (BM).

OBJECTIVE

- The authors aimed to investigate how type IV collagen (COL4) in the BM changes with the progression of IPF

METHODS

- COL4 synthesis (PRO-C4) was detected in blood by the nordicPRO-C4 biomarker in patients with IPF from the two prospective, multicenter, observational, longitudinal cohorts, pulmonary fibrosis biomarker (PFBIO) and prospective observation of fibrosis in the lung clinical endpoints (PROFILE)
- PRO-C4 trajectories over 12 months were compared between progressors and non-progressors by linear mixed effects regression models
- Rate of change in PRO-C4 and lung function were compared by Bayesian bivariate longitudinal models
- Cox proportional hazards models analyzed baseline PRO-C4 and 3 years mortality
- COL4 staining in IPF and non-IPF lungs was evaluated by immunohistochemistry

RESULTS

- In PFBIO and PROFILE, 51/220 (23.2%) and 221/459 (48.1%) patients, respectively, had progressive disease at 12 months
- Longitudinal PRO-C4 levels were higher in progressors versus non-progressors (average differences: PFBIO 21.5% (95% CI 3.4% to 42.9%, p=0.0184); PROFILE 10.9% (95% CI 0.8% to 22.1%; p=0.0340)
- Monthly rate of change in PRO-C4 was steeper in non-survivors versus survivors (mean difference up to 3.12% (95% CI 0.35% to 5.91%)) and was inversely correlated with the change in lung function
- High baseline PRO-C4 was associated with increased mortality risk in PFBIO (HR 2.55 (95% CI 1.27 to 5.12), p=0.0083)

- COL4 staining was higher in IPF versus non-IPF lung but was less obvious in end-stage tissue

CONCLUSIONS

- High and increasing serological PRO-C4 levels were prognostic for progression in two independent IPF cohorts
- This study suggests that COL4 synthesis assessed by PRO-C4 is a pathologically relevant biomarker of alveolar BM repair in IPF

Geudens V, et al. Distinct Morphological Types of Small Airway Obstructions in Smokers with Emphysema and End-Stage Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2025;211:2307-2317.

BACKGROUND

- The precise nature of small airway obstructions in chronic obstructive pulmonary disease (COPD) remains poorly understood, especially at early disease stages
- The authors hypothesized that obstruction subtypes would differ in morphology, nature, and number from early to end-stage COPD

OBJECTIVE

- To characterize small airway obstructions and numbers up to the terminal bronchioles (TBs) in smokers with limited emphysema and end-stage COPD

METHODS

- Whole lungs were inflated and processed from
    - 7 control donors declined for extrapulmonary reasons
    - 8 donors with a history of smoking (3 with <5% emphysema [smokers with no emphysema] and 5 with >5% emphysema [smokers with emphysema])
    - 8 patients with end-stage COPD
- Micro-computed tomography of tissue was used to assess number of TBs, aerated TBs, and number and type of obstructions and was cross-correlated with histopathology

RESULTS

- Obstructions were mainly present in smokers with emphysema and patients with COPD, resulting in less aerated TBs

- Based on emphysema extent, more nonaerated TBs were present in regions with no emphysema than in regions with mild emphysema; however, destruction was more prominent in mild emphysema
- Multiple types of obstructions were identified, comprising occlusions, webs, and collapses
- In smokers with emphysema, obstructions primarily comprised of webs and occlusions, whereas all obstruction types were present in COPD.
- On histopathology, obstructions were identified as mucus plugs

CONCLUSIONS

- Multiple types of obstruction characterized as mucus plugs were identified in smokers with emphysema and patients with end-stage COPD
- Their morphology, nature, and number evolved from smokers with emphysema to end-stage COPD
- A shift from obstruction-dominant dysfunction to destruction-dominant pathology was found in smokers based on the presence of emphysema

Wang S, et al. A Case of Rapidly Progressive Dyspnea and Diffuse Pulmonary Lesions. Chest. 2025;168:e179-e182.

REPORT OF A CASE

- A 55-year-old woman presented to the emergency department with fever, cough, and progressive dyspnea for 3 days
- Chest CT scan showed diffuse pulmonary lesions, and arterial blood gas analysis showed a PaO2 of 56 mm Hg on room air
- She was transferred to the respiratory ICU because of rapidly progressing respiratory failure
- She had a 20-year history of psoriasis was started on ixekizumab (an interleukin-17 inhibitor) 3 months earlier
- A chest radiograph before ixekizumab treatment showed no abnormalities
- After administration of ixekizumab therapy, her skin lesions demonstrated significant improvement
- She denied any history of tobacco use or chronic lung disease

DIAGNOSIS

- Drug-induced interstitial lung disease caused by ixekizumab.

Dalland JC, et al. Dual amyloidosis: A clinicopathologic and proteomic analysis of 111 patients. Hum Pathol. 2025;166:105954.

BACKGROUND

- Patients with two different amyloid types are rare
- It is critical to identify all types of amyloid in a patient as amyloid therapies vary dramatically depending on the specific precursor protein

OBJECTIVE

- To analyze the clinicopathologic and proteomic features in patients with two types of amyloid

METHODS

- The authors queried their reference laboratory database of 51,309 amyloid specimens from all anatomic sites typed by mass spectrometry-based proteomics (LC-MS/MS) for patients diagnosed with two different amyloid types
- Demographic data (patient age, sex, and anatomic site), mass spectrometry proteomic features, and clinical history, when available, were reviewed

RESULTS

- The authors identified 111 patients with two amyloid types: 83 male (75 %), 28 female (25 %)
- The median age at initial diagnosis was 78 years (range 45-96 years)
- 56 patients (50 %) had cardiac involvement
- The two amyloid types were present either in the same anatomic compartment within a single specimen (48 patients, 43 %), in different anatomic compartments within a single specimen (43 patients, 39 %), or in two different anatomic locations (20 patients, 18 %)
- The most common combination was AL plus ATTR (69 patients, 62 %), which occurred in 68 % of patients with cardiac involvement

CONCLUSION

- It is crucial to identify all amyloid types in all cases, including careful morphologic review to evaluate distinct areas with different distribution, and consider the possibility of a second amyloid type when the clinical findings are not explained by the initial amyloid type

Ryerson CJ, et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J. 2025;66:2500158.

BACKGROUND

- The 2013 American Thoracic Society/European Respiratory Society statement on the classification of the idiopathic interstitial pneumonias described six major and two rare subtypes of idiopathic interstitial pneumonia

OBJECTIVE

- To update the 2013 classification

METHODS

- Five co-chairs identified a committee of 32 experts in the field
- The classification scheme was developed by consensus

RESULTS

- The multidisciplinary committee of experts identified four major advances to the classification of interstitial pneumonia
    - Expansion beyond idiopathic interstitial pneumonias to also include secondary causes
    - Identification of new subcategories and updated terms, including
        - Addition of bronchiolocentric interstitial pneumonia (BIP) as a major pattern
        - Changing acute interstitial pneumonia (AIP) to idiopathic diffuse alveolar damage (idiopathic DAD)
        - Desquamative interstitial pneumonia (DIP) to alveolar macrophage pneumonia (AMP)
    - Subclassification of interstitial (fibrotic versus non-fibrotic) and alveolar filling disorders
    - Consideration of diagnostic confidence in patient evaluation and management
- The committee also provided a comprehensive update on the status of potential molecular tools and identified future research priorities

CONCLUSIONS

- This update builds upon the previous classification approach by describing major advances in the classification of interstitial pneumonia over the past decade

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