Peribronchiolar Metaplasia: A Cigarette Smoke-Induced Small Airway Injury Associated with Interstitial Lung Abnormality, Interstitial Lung Disease and Emphysema

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Research Article

Keywords: peribronchiolar metaplasia, smoking, interstitial lung abnormality, interstitial lung disease, emphysema, small airway remodeling

Posted Date: April 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1523203/v1

Abstract

Background:

Peribronchiolar metaplasia (PBM) is a non-specific reaction to bronchiolar injury, characterized by both proliferation of bronchiolar epithelium and fibrosis along the peribronchiolar wall. While an association of PBM with diffuse interstitial lung diseases (ILDs) is recognized, its clinical significance in emphysema and interstitial lung abnormalities (ILAs) remains unclear.

Methods: A retrospective review of a cohort (n=352) undergoing surgical resection for suspected lung nodule/mass at a tertiary medical center between 2017 and 2020 was completed to 1) determine the prevalence of PBM and 2) identify association with clinical, radiographic and histologic characteristics. A multivariate logistic regression analysis was performed.

Results:

The study cohort was elderly (mean age 66.15±10.19 years), predominantly female (57.1%), Caucasian and overweight (mean BMI 28.35±6.88). Ninety percent of patients were current or ex-smokers with a median pack year of 40 (IQR 32.5). Thirty-two patients (9.1%) were observed to have PBM as a histological finding. Clinical chronic obstructive pulmonary disease (COPD) was diagnosed in two-thirds of patients with PBM. Comorbid gastroesophageal reflux disease (GERD) was significantly associated with PBM. Conventional measures of pulmonary function tests were not significantly different between the groups with and without PBM. Radiologic and histologic emphysema were observed in all patients with histologic PBM. In addition, radiologic centrilobular ground-glass opacities (CL-GGO) of ILAs, specific ILD patterns, isolated traction bronchiectasis (iTB), histologic fibrosis, desquamative interstitial pneumonia (DIP), anthracosis and honeycomb changes were associated with PBM. A logistic regression model which included CL-GGO ILA, iTB, histologic fibrosis, DIP and anthracosis strongly predicted PBM in the cohort.

Conclusion:

A constellation of radiologic and histologic smoking-related abnormalities predicted PBM in our cohort. This supports a co-existence of tissue responses including small airway disease, fibrosis and emphysema as consequence of cigarette smoking. PBM can function as a histologic marker of small-airway injury in a smoking population.

Introduction

Inflammation and fibrosis of bronchiolar walls and the adjacent alveolar septa may be accompanied by metaplasia of the bronchiolar and/or alveolar epithelium. This bronchiolar epithelial metaplasia can be either goblet-cell or squamous cell-type.[1-3] Parenchymal metaplastic lesions seen more distally have not been characterized in detail. Initially considered the result of bronchiolar epithelium proliferation onto the

alveolar surface following conveyance via the canals of Lambert, its observation was referred to as Lambertosis.[4] This peribronchiolar metaplasia (PBM) is now recognized as a nonspecific reaction to a variety of stimuli including tobacco smoke, air pollutants (e.g. diesel exhaust and ozone), microbes, and gastric content aspiration.[5-8] PBM is often an incidental finding in patients with diverse interstitial lung diseases (ILD) including respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and hypersensitivity pneumonia (HP).[9-11] PBM and cystic changes were also seen in the lungs of patients with long-standing rheumatoid arthritis.[12] Interestingly, PBM has been noted as the only histopathological finding in a small number of patients with ILD and identified as a separate entity of bronchiolocentric interstitial pneumonia (BCIP) and airway-centered interstitial fibrosis (ACIF).[13-16]

Despite these recognized associations, the clinical significance of PBM remains incompletely delineated. Employing a locally identified cohort of patients with lung nodules/masses undergoing surgical resection at a rural Appalachian center after heavy cigarette smoke exposure, we aimed to define 1) the prevalence of PBM on histopathology, and 2) its correlation with clinical, radiographic and histological features in smoking-related lung interstitial lung abnormalities (ILAs) and emphysema.

Materials And Methods

Study design: We conducted a single-center, retrospective, cohort study at the tertiary medical center of West Virginia University Hospital (WVUH). The study protocol was approved by the institutional review board (ID# 2010131995). Patients who were referred to thoracic oncology clinic for suspicious lung nodules/masses and underwent surgical resection were identified (January 1, 2017 to December 31, 2020). Exclusion criteria for the study were 1) a lack of a good quality CT scan of the chest obtained within six months prior to surgery and/or adequate lung tissue to allow independent review, and 2) surgery performed for non-pulmonary malignancy/metastatic disease. Groups with or without the histologic observation of PBM were defined (Figure 1).

Data collection: After identification of patients within the WVUH electronic medical records (EMR), the following data variables were recorded: demographics, smoking status with pack-years of smoking, occupational exposures, comorbidities, baseline supplemental oxygen use, and pulmonary function tests (PFTs). The PFTs included percent predicted values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV), diffusion capacity for carbon monoxide (DL_{CO}) and RV/TLC. Additionally, the ratios for FEV_1/FVC and RV/TLC were collected.

Pathologic evaluation: At least one tissue section, and typically 3-6 sections, were examined for histological features. Areas distant from the tumor were evaluated. Microscopic analysis focused on identifying PBM, fibrosis, honeycombing, emphysema, and a variety of histopathologic patterns and features indicative of specific ILD.[17-19] Retrospective histopathologic review of 352 lung specimens was performed independently by two pathologists. Consensus of pathologic findings was obtained for all specimens.

Radiographic evaluation: Pre-operative CT scans (1 mm slice thickness for lung windows) were analyzed by three study authors. Consensus of radiographic findings were recorded in accordance with the case definitions which included emphysema and its types (centrilobular (CL), paraseptal (PS), bullous and panacinar), ILA patterns of diffuse centrilobular- ground glass opacity (CL-GGO), subpleural reticular changes, mixed CL-GGO and subpleural reticular changes and non-emphysematous cysts involving at least 5% of a lung zone, specific ILD patterns of UIP, probable UIP, NSIP, RB-ILD, pulmonary Langerhans cell histiocytosis (PLCH), DIP, combined pulmonary fibrosis emphysema (CPFE), organizing pneumonia (OP) and unclassifiable patterns.[19-24] Additional radiographic findings included isolated traction bronchiectasis (iTB), honeycombing, and pleural plaques. Important exclusions for radiologic findings were changes restricted to dependent lung zones, focal paraspinal fibrosis, focal or unilateral abnormality, interstitial pulmonary edema or aspiration-related findings of tree-in-bud or patchy ground glass.

Statistical analysis: Means, medians (IQR), standard deviations and proportions were used to describe continuous and categorical variables. Chi-squared or Fisher exact tests were used to detect differences in categorical variables between the groups, while means of continuous variables were compared using two-sided independent-samples t-tests. The Mann-Whitney U test was used when normality could not be assumed. Univariate logistic regression analysis was used to determine significant associations of PBM. Subsequently, a multivariate logistic regression model was developed to determine the predictors of PBM. $p<0.05$ and 95% CI defined statistical significance for all analyses.

Results

Of the total of 392 patients who underwent surgical resection for lung nodules/masses, 40 patients (10.2%) were excluded due to 1) lack of a satisfactory quality CT scan of the chest or lung tissue and 2) presence of non-lung cancer related metastatic lesions (Figure 1). The final cohort included 352 patients (Figure 1). The prevalence of PBM in the cohort was 9.1% (32/352 patients). The remaining 320 patients (90.9%) constituted the comparison group without PBM (Figure 1).

The study cohort was elderly with a mean age of 66.15±10.19 years, predominantly white (96.3%), had approximately equal numbers of male and female patients (57.1% female), and was overweight with mean body mass index (BMI) of 28.35±6.88 kg/m^2 (Table 1). Demographic variables were not different between the groups with and without PBM. Ninety percent of the study cohort was ever-smoker with mean pack years of 43.23±31.86 and median pack years of 40 (IQR 32.5). This reflects the distinct, heavy smoking habit in the Appalachian region. Approximately two-thirds of patients (61.4%) carried a clinical diagnosis of chronic obstructive pulmonary disease (COPD), whereas only a minority of patients carried the clinical diagnosis of ILD (n=5, 1.5%). There were no significant differences between the groups with and without PBM in smoking behavior and prevalence of COPD. All five patients with a history of ILD were in the group without PBM. The PBM group had higher proportion of patients with gastro-esophageal reflux disease (GERD, 19/32 (59.4%) vs. 124/320 (38.7%), p=0.036). The other notable comorbidities for the cohort included hypertension (69.9%), hyperlipidemia (59.3%), coronary artery disease (37.2%),

anxiety (32.7%), diabetes (24.4%), mood disorders (40.6%), pain disorders (31.2%) and hypothyroidism (18.1%) with no differences between the groups. Baseline O_2 requirement was documented in 14.5% patients, predominantly due to a clinical COPD diagnosis, with no difference between the groups (Table 1).

Pre-surgical PFTs were performed for most patients in the cohort (n=336, 95.4%). Corresponding to the diagnoses of COPD, the study cohort showed PFTs consistent with obstructive ventilatory impairment (mean FEV_1/FVC ratio of 67.74±12.17), air trapping (mean percent predicted RV of 141.13±51.41), and mildly decreased percent predicted DL_{CO} (69.06±21.95). None of the indices of pulmonary function showed a statistically significant difference between the groups with and without PBM. Finally, mortality did not differ between the groups (15.6% vs. 10.9, p=0.387) (Table 1).

Radiographic emphysema was extremely frequent in the study cohort (70.4%). The group with PBM showed a significantly higher prevalence of any form of emphysema relative to the group without PBM (100% vs. 67.5%, p<0.0001). Additionally, the group with PBM had a higher prevalence of both CL and PS emphysema (90.6% vs. 59.4%, p<0.0004 and 43.7% vs. 25.6%, p=0.036, respectively). About half of the study cohort (52.9%) noted presence of subclinical ILA (34.3%) and ILD patterns (17.6%) on the CT chest. Additional findings of ILA included subpleural reticular changes (14.8%), CL-GGO (8%), non-emphysematous cysts (8%) and mixed CL-GGO with subpleural reticular changes (7.4%). ILD patterns recognized on the CT scan of the chest included UIP (0.6%), probable UIP (0.6%), NSIP (0.9%), RB-ILD (3.1%), LCH (0.6%), DIP (1.1%), CPFE (3.1%), OP (2.8%) and unclassifiable (4.8%). A combination of ILA and ILD patterns were observed in a greater proportion of the group with PBM compared to the group without PBM (87.5% vs. 49.4%, p=0). The PBM group demonstrated a higher prevalence of CL-GGO ILA pattern (18.7% vs. 6.8%, p=0.031) and any ILD patterns (43.7% vs. 15%, p=0.002). Lastly, isolated traction bronchiectasis on the CT scan was more common in the group with PBM (28.1% vs. 13.1% p=0.032) (Table 2).

Histologically, primary lung malignancy was noted in 92% of resected nodules/masses in the study cohort with no difference between the groups with and without PBM. There were several smoking-associated pathologic findings observed in greater frequency in the group with PBM including emphysema (100% vs. 48.7%%, p<0.0001), any pulmonary fibrosis (56.2% vs. 13.1%, p<0.0001), DIP (12.5% vs. 2.8%, p=0.022), anthracosis (78.1% vs. 32.2%, p<0.0001) and honeycomb changes (15.6% vs. 0.9%, p<0.0001). While organizing pneumonia was solely present in non-PBM group (0 vs. 6.5%, p=0.238), respiratory bronchiolitis was noted in both groups without significant difference (15.6% vs. 12.5%, p=0.581) (Table 2). CT chest images and corresponding pathologic findings of a representative case with PBM are displayed in figure 3 and 4, respectively.

Univariate analysis of significant clinical, radiographic and pathologic predictors for PBM are provided (Figure 2). Comorbid GERD predicted PBM in the study cohort (OR 2.31, 95% CI [1.10 – 4.84]). Subtypes of CL and PS emphysema were associated with PBM (OR 6.61, 95% CI [1.97 – 22.16] and OR 2.25, 95% CI [1.07 – 4.74], respectively). Of the various ILA patterns, CL-GGO increased PBM approximately three-fold

(OR 3.13, 95% CI [1.16 – 8.39]). Combined ILA/ILD correlated strongly with PBM (OR 7.17, 95% CI [2.46 – 20.93]). Additional histologic findings associated with PBM included honeycomb changes, any fibrosis, anthracosis and DIP (OR 19.56, 95% CI [4.43 – 86.33]; OR 8.51, 95% CI [3.94 – 18.38]; OR 7.52 95% CI (3.15 – 17.96); and OR 4.93 95% CI [1.43 – 17.05], respectively).

Based on above mentioned variables, a logistic regression model was developed to predict PBM (Table 3). Considering mutually existing prevalence of both radiologic and histologic emphysema in all PBM patients, they were excluded from the model. Radiologic findings of CL-GGO ILA and isolated traction bronchiectasis were highly predictive of PBM (OR 5.72, 95% CI [1.53 – 21.32] and OR 3.45, 95% CI [1.21 – 9.79], respectively). Histologic findings of fibrosis, DIP and anthracosis were significantly associated with PBM (OR 5.83, 95% CI [2.17 – 15.68], OR 13.60, 95% CI [2.74 – 67.52] and OR 6.66, 95% CI [2.50 – 17.70], respectively). A radiographic ILD pattern and a histologic finding of honeycomb changes trended towards significance.

Discussion

In our study cohort, PBM was observed in 9.1% of lung specimens in the study cohort. Despite considerable interest, differences in study designs (case reports and series) have made it difficult to determine the prevalence of PBM in the general population.[10,13-16,25] However, previous investigations of patients undergoing lobectomy for malignant neoplasms have reported peribronchiolar fibrosis (PBF) and metaplasia in approximately one-fifth of patients (17.4% to 24.2%), similar to the result of this study.[26,27]

Comorbid GERD predicted PBM in our cohort. An inflammatory injury of the bronchioles can be observed in animal models of gastroesophageal reflux.[28,29] A relationship of GERD with PBM can be comparable to its correlation with Barrett's esophagus in which stratified squamous epithelium is transformed to simple columnar epithelium, with interspersed goblet cells, normally present in the small intestine and large intestine. The association may also reflect an ultimate relationship of GERD and PBM (as well as Barrett's esophagus) with smoking.[30,31]

PBM reported in our cohort was strongly associated with concomitant emphysema noted either radiologically and/or histologically. Respiratory and terminal bronchioles are the initial site of deposition and/or retention for cigarette smoke particles and subsequently, the pathological response is initiated here.[32] There have been numerous investigations into how injury proceeds from these small airways, the "silent zone of the lung", to clinical presentation in COPD.[33-35] This series of structural changes in the small conducting airways after smoking is associated with histological evidence of airflow obstruction.[36,37] Contemporary investigations utilizing novel radiographic research tools have suggested that functional small airway dysfunction correlated with narrowing and loss of terminal bronchioles, which is an important event preceding to the advanced stage emphysematous destruction.[38-40] Ultimately, this injury to the small airways may promote emphysema via a loss of support at the distal acinus.[40,41]

Our study cohort demonstrated a significant correlation between PBM and fibrosis noted either radiologically and/or histologically. In addition, there was a unique association of PBM with subclinical CL-GGO ILA on CT chest suggesting an involvement in an injury at the distal (respiratory and terminal) bronchioles. The histopathologic evaluation of ILD patients relies on identification of disease as: 1) primary bronchiolar disorders, 2) interstitial patterns with prominent bronchiolar involvement, and 3) bronchiolar pathology in association with large airway diseases.[42] Recently described entities of bronchiolitis interstitial pneumonia (BIP), bronchiolocentric interstitial pneumonia (BCIP) and airway-centered interstitial fibrosis (ACIF) are usually differentiated by the mixture of organizing pneumonia, interstitial pneumonitis, bronchiolar myxoid fibrous tufts and contiguous PBM/PBF in varying degrees.[43] While the role of injury to the alveolar and adjacent interstitial regions is acknowledged in idiopathic pulmonary fibrosis (IPF), there's recent recognition of a possible contribution of small airways injury in the pathogenesis of fibrotic interstitial pneumonias.[44,45] Such a role has been proposed for PBM in the predominantly bronchiolocentric pathology of chronic hypersensitivity pneumonitis.[46] Bronchiolar cuboidal epithelial cells, rather than type II alveolar cells, were demonstrated to be the major source of epithelial renewal and proliferation in areas of severely fibrotic lung tissue.[47] In addition, animal investigation has identified a differential pro-fibrotic and pro-elastogenic response of small airways relative to lung parenchyma in response to cigarette smoke exposure.[48] Detailed morphological evaluation of both IPF and NSIP lung tissue showed increased inflammation in both bronchioles and peribronchiolar tissue, PBM, and PBF supporting an active involvement of small airways in fibrotic lung diseases.[49] Moreover, there was an overexpression of matrix metalloproteinases in bronchiolar epithelial which could also potentially contribute to local remodeling of peribronchiolar interstitium. Identical to COPD, advanced CT analysis showed the increased measures of airway wall thickness in association with ILAs and IPF.[50] Therefore, emerging histologic and radiographic evidence supports small airway remodeling as a contributory event towards both early stage ILAs and ILD/fibrosis.

Detailed histologic and immunohistochemistry analysis on lung tissue of COPD patients shed significant insights into the origin of PBM and contradict its links with non-specific Lambertosis. PBM was distributed multifocally in lung tissue and was associated with airway remodeling changes of epithelial hyperplasia, goblet cell hypertrophy and inflammation.[51] Moreover, these metaplastic cells exhibited surfactant and mucin production, suggestive of a primitive epithelial phenotype, potentially a consequence of injury with aberrant repair. Collectively, small airways remodeling resulting from cigarette smoke exposure is instrumental for host responses of emphysema and/or fibrosis. Our study notes significant associations of PBM with both emphysema and fibrosis. Considering the assembly of various radiologic and histologic features with PBM in our cohort, PBM may serve as a histologic marker of small-airway injury in a heavily smoking population (Figure 5).

Radiological evidence of peribronchial interstitial thickening and signs of bronchiolar involvement (centrilobular nodules, bronchiectasis, GGO, mosaic attenuation) are consistent with a possible injury due to inhalation or aspiration. Patients with isolated PBM were reported to have a variety of radiographic findings including mosaic attenuation, lobular air trapping, subpleural fibrosis, septal thickening,

centrilobular ground glass nodules and emphysema.[10,25] ACIF is usually represented with prominent peribronchiolar inflammatory infiltrates, PBM and PBF, and importantly, lack bronchiolar myxoid fibrous tufts, OP and advanced fibrosis with honeycombing.[14,43] A large case series of ACIF patients observed patchy GGO (84%), peribronchovascular interstitial thickening (79%), and traction bronchiectasis (63%) as common features on HRCT scans of chest, whereas mosaic attenuation/air trapping and centrilobular nodules were noted in one-third of patients.[14] Identical to these observations, the accumulation of bronchiolar signs of involvement (CL-GGO and isolated traction bronchiectasis) were predictive of PBM in our cohort.

Our study has several limitations. It is a retrospective review which represents an inherent limitation. Histologic evaluation was not performed primarily to detect PBM but metaplasia was noted as incidental finding and therefore, it is likely to be under-recognized. Compared to the pulmonary pathologists, general pathologists' interpretation of lung tissue was associated with less identification of background histologic abnormalities.[52] With 92% of subjects providing resected lung tissue demonstrating a malignant process, determining the potential mechanical, obstructive and inflammatory effects of nodule/mass on adjacent tissue may be difficult. However, we attempted to limit any impact by avoiding evaluation of the lung parenchyma immediately adjacent to tumor. The cohort was predominantly White, and the study was performed at a rural tertiary medical center which may limit generalization of study findings to different settings. In contrast, strengths of the study include relatively large number included in the cohort with consecutively included patients undergoing surgical resection, detailed description of clinical and radiologic findings and their correlation with histological features.

Conclusion

A cohort with heavy smoking (median pack years of 40) undergoing surgical resection for suspected lung nodules/masses provided an opportunity for a comprehensive analysis of the clinical, radiographic and histological predictors of PBM. A constellation of various radiologic and histologic lung abnormalities and injuries demonstrated an association with PBM, suggesting a co-existence of small airway disease, fibrosis and emphysema after smoking. PBM can function as a histologic marker of small-airway response and/or injury following exposure to cigarette smoke particles.

Abbreviations

ACIF: airway-centered interstitial fibrosis

BCIP: bronchiolocentric interstitial pneumonia

BIP: bronchiolitis interstitial pneumonia

BMI: body mass index

CL: centrilobular

COPD: chronic obstructive pulmonary disease

CPFE**:** combined pulmonary fibrosis and emphysema

DL_{CO}: diffusion capacity for carbon monoxide

DIP: desquamative interstitial pneumonia

EMR: electronic medical record

FEV_1: forced expiratory volume in one second

FVC: forced vital

GERD: gastro-esophageal acid reflex

GGO: ground glass opacity

HP: hypersensitivity pneumonitis

ILAs: interstitial lung abnormalities

ILDs: interstitial lung diseases

IPF: idiopathic pulmonary fibrosis

iTB: isolated traction bronchiectasis

NSIP: non-specific interstitial pneumonia

OP: organizing pneumonia

OR: odds ratio

PBM: peribronchiolar metaplasia

PFT: pulmonary function test

PLCH: pulmonary Langerhans cell histiocytosis

PS: paraseptal

RB-ILD: respiratory bronchiolitis- interstitial lung disease

RV: residual volume

SRIF: smoking-related interstitial fibrosis

TLC: total lung capacity

UIP: usual interstitial pneumonia

Declarations

Ethics approval and consent to participate: The study protocol for retrospective review of electronic medical records was approved and “informed consent” was waived by the institutional review board of WVU (ID# 2010131995).

All ethical standards were adhered in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analyzed during this study are included in this published article.

RGS takes the responsibility of the content and accuracy of work presented in the manuscript.

Authors' contributions:

Conception and design of the work: RGS, VD, AJG

Data acquisition: RGS, VD, ZP, EA, JV

Data analysis: RGS, VD, AJG

Data interpretation: RGS, AJG, JV

Manuscript drafting and revisions: RGS, AJG, VD, JV, ZP

All authors have read and approved the manuscript.

Competing interests: The authors declare they have no financial or non-financial competing interests.

Funding: none.

Acknowledgment: none.

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Tables

Table 1: Characteristics of groups of patients with and without histologic finding of peribronchiolar metaplasia (PBM) in the cohort (n=352)

Variables, Values, n (%) or mean ± SD	Group with PBM (n=32, 9.1%)	Group without PBM (n=320, 90.9%)	Total Cohort (n=352)	p-value
Age	66.94 ± 9.73	66.07 ± 10.25	66.15 ± 10.19	0.648
Gender (male)	13 (3.7)	138 (39.2)	151 (42.9)	0.852
Body mass index (BMI, kg/m^2)	28.42 ± 8.48	28.34 ± 6.71	28.35 ± 6.88	0.953
Race (White)	32 (9.1)	307 (87.2)	339 (96.3)	0.617
Smoking status:				
1. Ever-smoker	31 (8.8)	282 (80.1)	313 (88.9)	0.231
2. Current smoker	10 (2.9)	119 (33.8)	129	0.568
3. Pack years				
a. mean±SD	40.97 ± 37.30	39.62 ± 31.76	39.73 ± 32.24	0.565
b. median (IQR)	34.5 (30.5)	40 (35.5)	40 (32.5)	0.888
4. >= 30 pack years	23 (6.5)	199 (56.5)	222 (63.0)	0.339
Other exposure history	5 (1.4)	48 (13.6)	53 (15.0)	1
· Coal	2 (0.6)	25 (7.1)		1
· Silica	0 (0)	11 (3.1)		0.608
· Asbestos	3 (0.9)	21 (7.1)		0.731
Comorbidities				
1. COPD	21 (6.0)	195 (55.4)	216 (61.4)	0.604
2. ILD	0 (0)	5 (1.4)	5 (1.5)	1
3. Hypertension	23 (6.5)	223 (63.3)	246 (69.9)	0.797
4. Hyperlipidemia	20 (5.7)	189 (53.6)	209 (59.3)	0.850
5. CAD	12 (3.4)	119 (33.8)	131 (37.2)	1
6. DM	9 (2.6)	77 (21.8)	86 (24.4)	0.666
7. Atrial fibrillation	6 (1.7)	44 (12.5)	50 (14.2)	0.428
8. VTE	2 (0.6)	46 (13.0)	48 (13.6)	0.282
9. OSA	5 (1.4)	41 (11.7)	46 (13.1)	0.588
10. GERD	19 (5.4)	124 (35.2)	143 (40.6)	***0.036***
11. Mood disorders	8 (2.2)	107 (30.4)	115 (32.6)	0.430

12. Pain disorders	12 (3.4)	98 (27.8)	110 (31.2)	0.428
13. Hypothyroidism	7 (2.0)	57 (16.2)	64 (18.2)	0.629
Home O_2 use	6 (1.7)	45 (12.8)	51 (14.5)	0.436
PFT performed:	30 (8.5)	306 (86.9)	336 (95.4)	0.629
1. FEV_1, % predicted	76.71 ± 20.27	76.37 ± 21.97	76.34 ± 21.75	0.933
2. FVC, % predicted	89.90 ± 19.08	85.49 ± 18.08	85.85 ±18.15	0.198
3. Ratio FEV_1/FVC	65.84 ± 11.53	67.94 ± 12.23	67.74 ± 12.16	0.360
4. TLC, % predicted	108.38 ± 17.57	106.68 ± 20.43	106.82 ± 20.15	0.667
5. RV, % predicted	141.31 ± 42.93	141.13 ± 52.30	141.13 ± 51.40	0.985
6. RV/TLC, actual value	48.55 ± 7.83	50.33 ± 26.96	50.15 ± 25.70	0.724
7. RV/TLC, % predicted	127.11 ± 22.93	126.24 ± 27.44	126.30 ± 27.00	0.872
8. DL_{CO}, % predicted	66.66 ± 19.88	69.40 ± 22.14	69.05 ± 20.92	0.521
Mortality (dead)	5 (1.4)	35 (9.9)	40 (11.3)	0.387

Abbreviations: CAD=coronary artery disease, COPD=chronic obstructive lung disease, DL_{CO}= diffusion capacity for carbon monoxide, DM=diabetes mellitus, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, GERD=gastro-esophageal reflux disease, ILA=interstitial lung abnormalities, ILD=interstitial lung disease, OSA=obstructive sleep apnea, RV=residual volume TLC=total lung capacity, VTE=venous thromboembolism

Table 2. Radiographic and histopathological features of groups with and without histologic peribronchiolar metaplasia (PBM) in the cohort (n=352)

Variables, Values, n (%) or mean ± SD	Group with PBM (n=32, 9.1%)	Group without PBM (n=320, 90.9%)	Total Cohort (n=352)	p-value
CT chest findings:				
1. Emphysema (any)	32 (9.1)	216 (61.3)	248 (70.4)	***<0.0001***
a. Centrilobular emphysema	29 (8.2)	190 (54.0)	219 (62.2)	***0.0004***
b. Paraseptal emphysema	14 (4.0)	82 (23.3)	96 (27.3)	***0.036***
c. Bullous emphysema	2 (0.6)	21 (6.0)	23 (6.6)	0.957
d. Panacinar emphysema	1 (0.3)	32 (9.1)	33 (9.4)	0.338
e. Combination patterns	12 (3.4)	88 (25.0)	100 (28.4)	0.225
2. Any ILA only	14 (4.0)	110 (31.2)	124 (34.3)	0.332
a. Centrilobular GGO	6 (1.7)	22 (6.3)	28 (8.0)	***0.031***
b. Subpleural reticulation	3 (0.9)	50 (14.2)	53 (15.1)	0.444
c. Mixed a+b	5 (1.4)	21 (6.0)	26 (7.4)	0.073
d. Non-emphysematous cysts	2 (0.6)	26 (7.4)	28 (8.0)	1
3. Any ILD patterns only	14 (4.0)	48 (13.6)	62 (17.6)	***0.002***
4. ILA and ILD combined	28 (8.0)	158 (44.9)	186 (52.9)	***0***
5. Isolated traction bronchiectasis	9 (2.5)	42 (11.9)	51 (14.4)	***0.032***
6. Isolated honeycombing	0 (0)	8 (2.2)	8 (2.2)	1
7. Pleural plaques	1 (0.3)	22 (6.2)	23 (6.5)	0.708
Pathological findings:				
1. Primary lung cancer pathology in the resected nodule	30 (8.5)	293 (83.2)	323 (91.7)	1
2. Emphysema	32 (9.1)	156 (44.3)	188 (53.4)	***<0.0001***
3. Any fibrosis^{++}	18 (5.1)	42 (11.9)	60	***<0.0001***

				(17.0)	
4.	RB	5 (1.4)	40 (11.4)	45 (12.8)	0.581
5.	DIP	4 (1.1)	9 (2.6)	13 (3.7)	***0.022***
6.	OP	0 (0)	21 (6.0)	21 (6.0)	0.238
7.	Anthracosis	25 (7.1)	103 (29.3)	128 (36.3)	***<0.0001***
8.	Honeycomb changes	5 (1.4)	3 (0.9)	8 (2.3)	***<0.0001***
9.	Granulomatous inflammation (necrotizing, non-necrotizing, loosely formed-HP like and calcified)	1 (0.3)	35 (9.9)	36 (10.2)	0.227
10.	Miscellaneous*	6 (1.7)	23 (6.5)	29 (8.2)	**0.036**

[++]Any fibrosis included fibrosis, fibroblastic foci, subpleural fibrosis, and architectural distortion

*Miscellaneous findings for PBM group (n=6) includes FB giant cell reaction, cholesterol cliff (n=1), follicular bronchiolitis (n=1) and vascular medial hypertrophy (n=1), calcification or metaplastic bone formation (n=3).

*Miscellaneous findings for non-PBM group (n=23) includes chronic inflammation (n=4), silicotic nodule (n=3), consolidation/necrosis (n=5), pleural plaque (n=4), lymphocytic interstitial pneumonia (n=2), foreign body giant cell reactions (n=1) DIPNECH (n=1), adenomatous hyperplasia (n=1), and bronchiectasis (n=1), calcification or metaplastic bone formation (n=1), and carcinoid (n=1).

Abbreviations: DIP=desquamative interstitial pneumonia, DIPNECH =diffuse idiopathic pulmonary neuroendocrine hyperplasia, GGO=ground glass opacity, HP=hypersensitivity pneumonitis ILA=interstitial lung abnormalities, ILD=interstitial lung disease, OP=organizing pneumonia, RB=respiratory bronchiolitis

Table 3: Logistic regression model showing predictors of peribronchiolar metaplasia (PBM) in the cohort (n=352)

Variables	Odds ratio	95% CI	p-value
Radiologic:			
CL-GGO ILA	5.72	1.53 – 21.32	***0.009***
Any ILD pattern	2.45	0.91 – 6.65	0.076
Isolated traction bronchiectasis	3.45	1.21 – 9.79	***0.020***
Histologic:			
Fibrosis	5.83	2.17 – 15.68	***<0.001***
DIP	13.60	2.74 – 67.52	***0.001***
Anthracosis	6.66	2.50 – 17.70	***<0.001***
Honeycomb changes	5.88	0.99 – 35.15	0.052

Abbreviations: CL-GGO: centrilobular ground glass opacity, DIP=desquamative interstitial pneumonia, ILA=interstitial lung abnormalities and ILD=interstitial lung disease

Figures

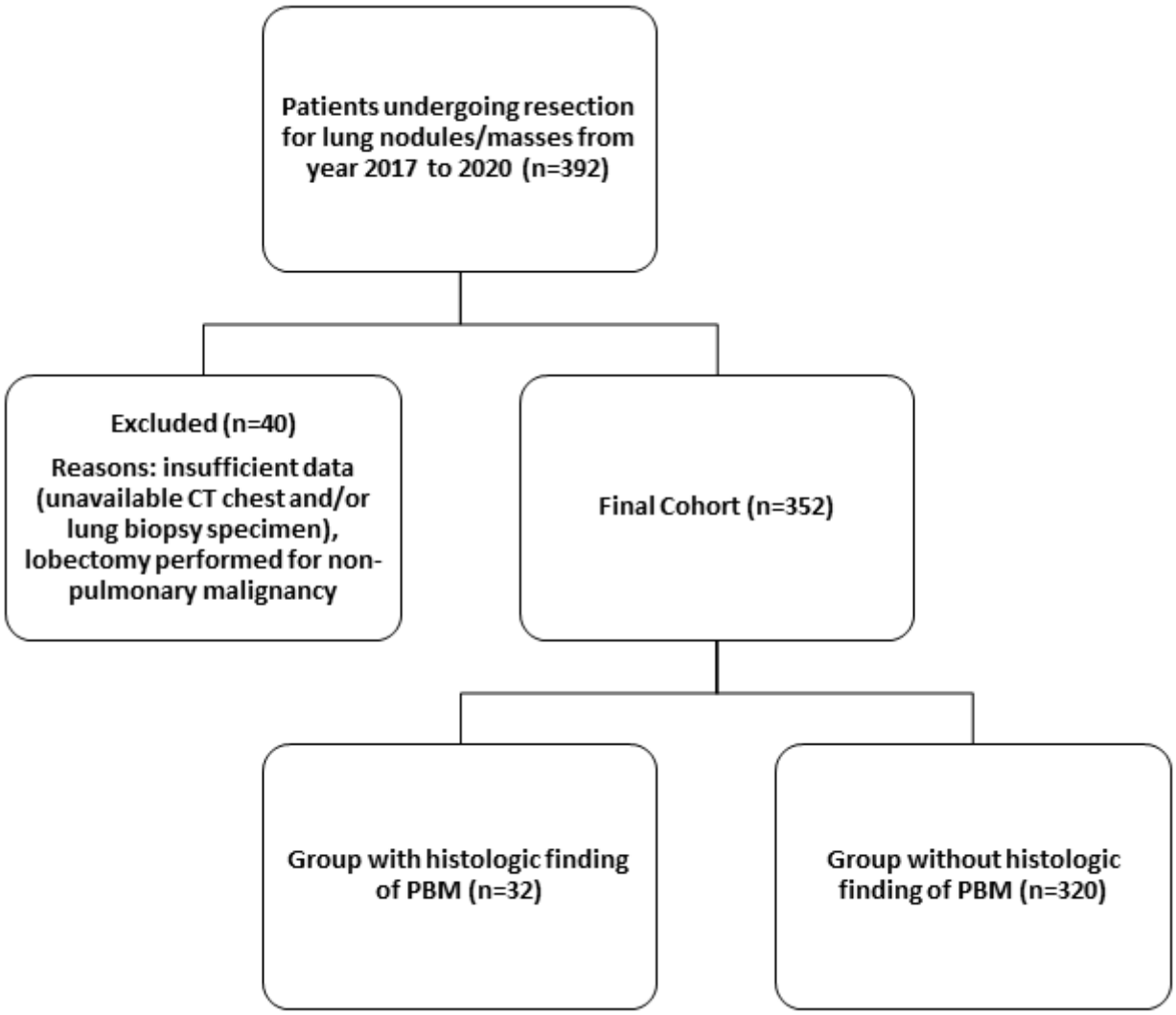

Figure 1

Study approach for creating groups with and without histologic finding of peribronchiolar metaplasia(PBM)

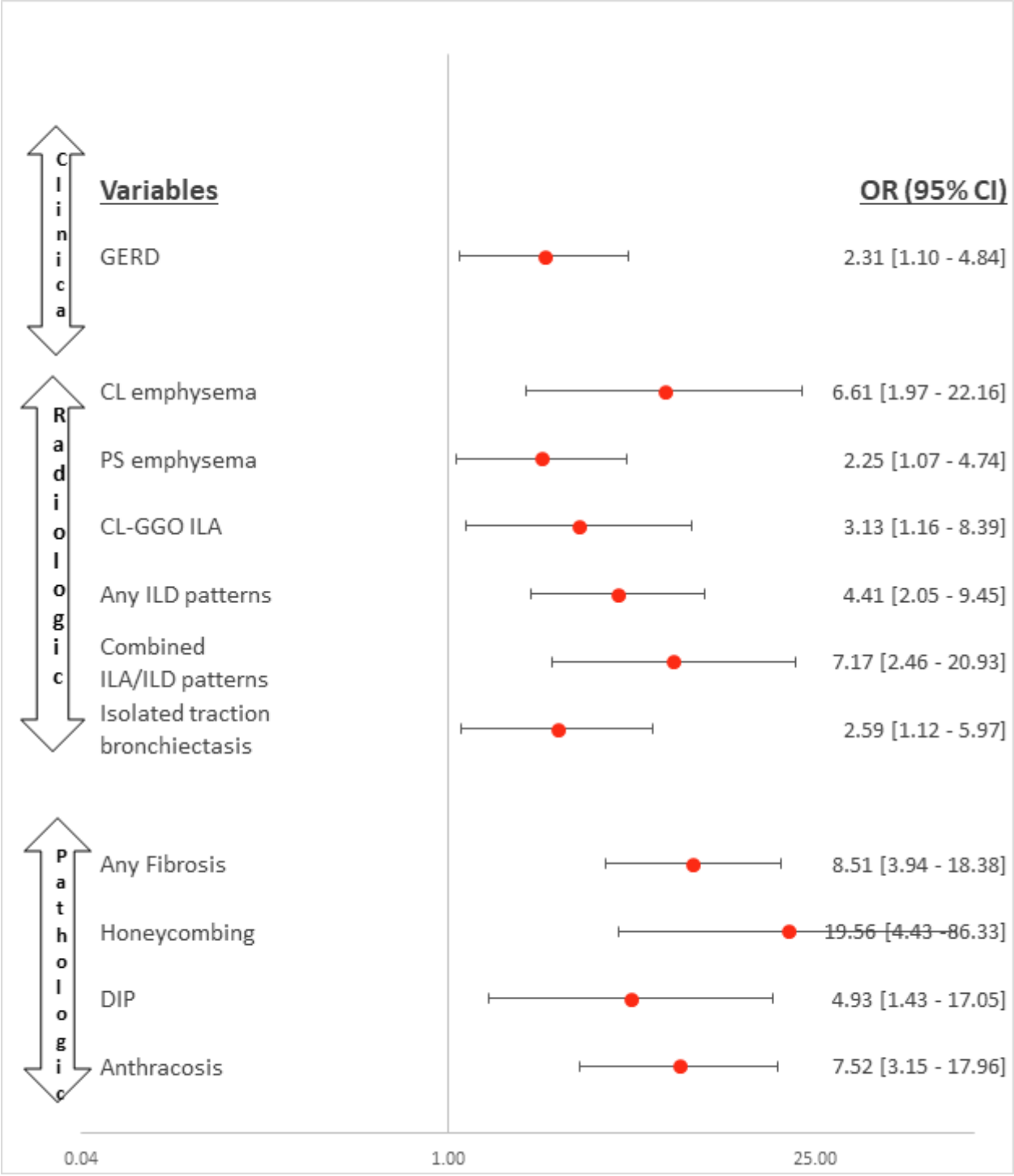

Figure 2

Forest plot of clinical, radiographic and histological factors for peribronchiolar metaplasia in the cohort

Abbreviations: CL=centrilobular, DIP=desquamative interstitial pneumonia, GERD=gastro-esophageal reflux disease, PS=paraseptal, ILA=interstitial lung abnormality, ILD=interstitial lung disease

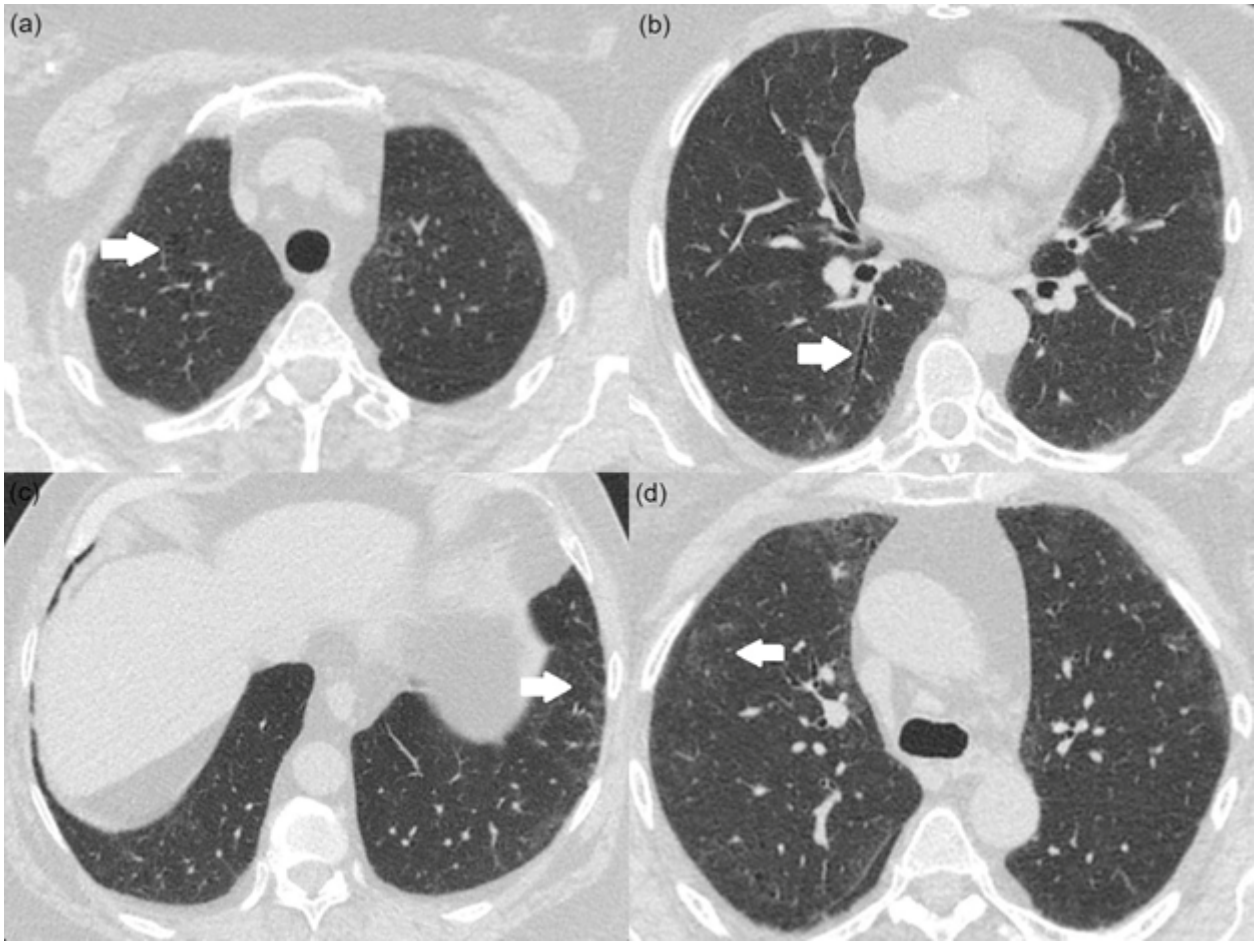

Figure 3

Pre-operative CT chest images of a 67-year-old former smoker (50 pack years) female who underwent left upper lobectomy for suspicious lung nodule showing the significant non-dependent findings of (a) centrilobular emphysema, (b) isolated traction bronchiectasis, (c) subpleural reticulation, and (d) centrilobular ground glass opacities (all represented with white arrows).

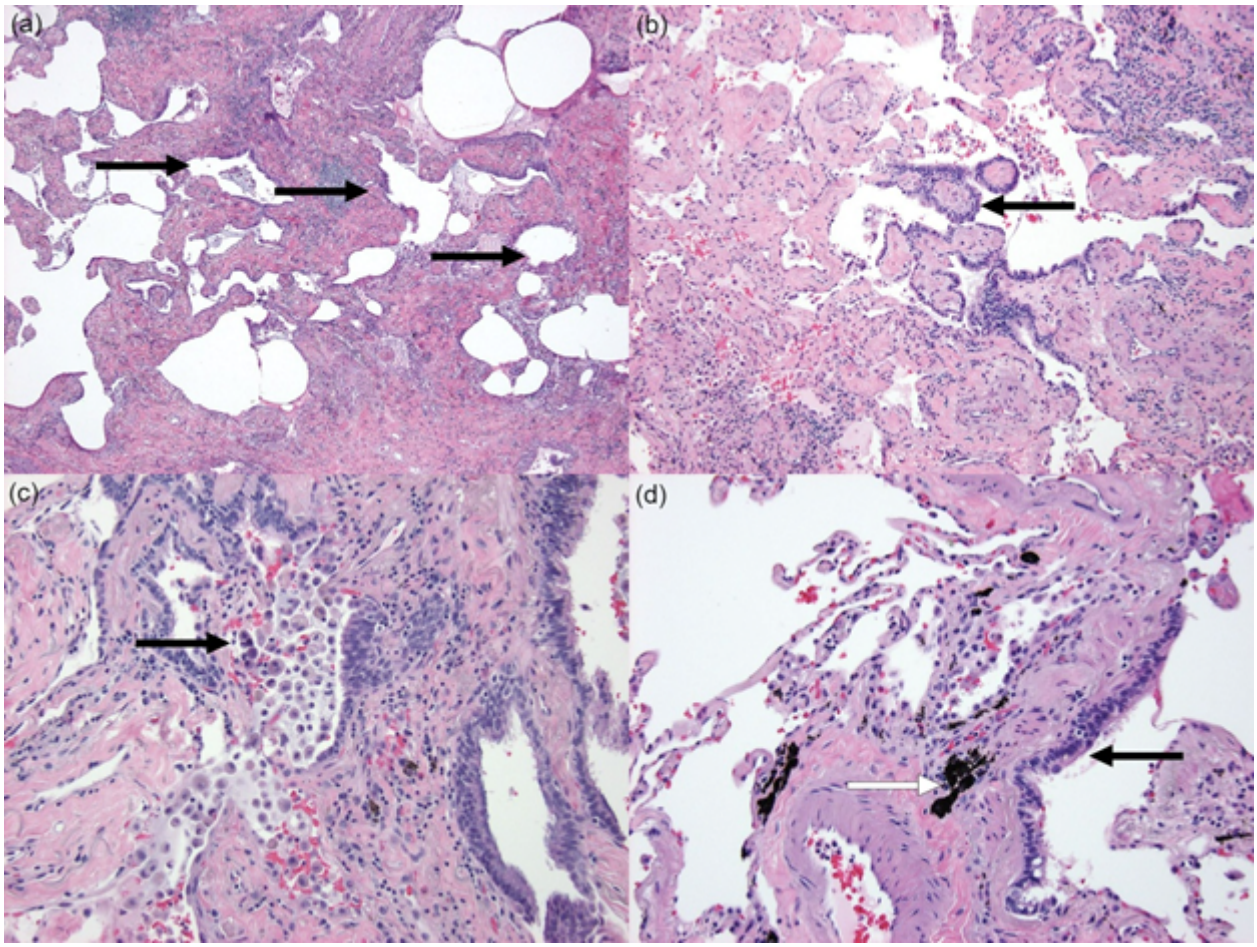

Figure 4

Corresponding histologic findings in addition to invasive adenocarcinoma noted on lobectomy of a representative case of 67-year-old female include:

(a) Microscopic honeycombing showing dense fibrosis, loss of lung architecture and cyst-like spaces (black arrows) lined by metaplastic cuboidal and bronchiolar epithelium (40x), (b) Respiratory-type epithelium lining alveolar walls with septal fibrosis (black arrow), characteristic of peribronchial metaplasia (100x), (c) Accumulations of numerous alveolar macrophages (black arrow), in addition to interstitial fibrosis and mild chronic inflammation, suggests a desquamative interstitial pneumonia (DIP) pattern (200x), and (d) Emphysema, anthracotic pigment deposition (white arrow) and peribronchial metaplasia (black arrow) were noted in a less fibrotic area of the lung (200x).

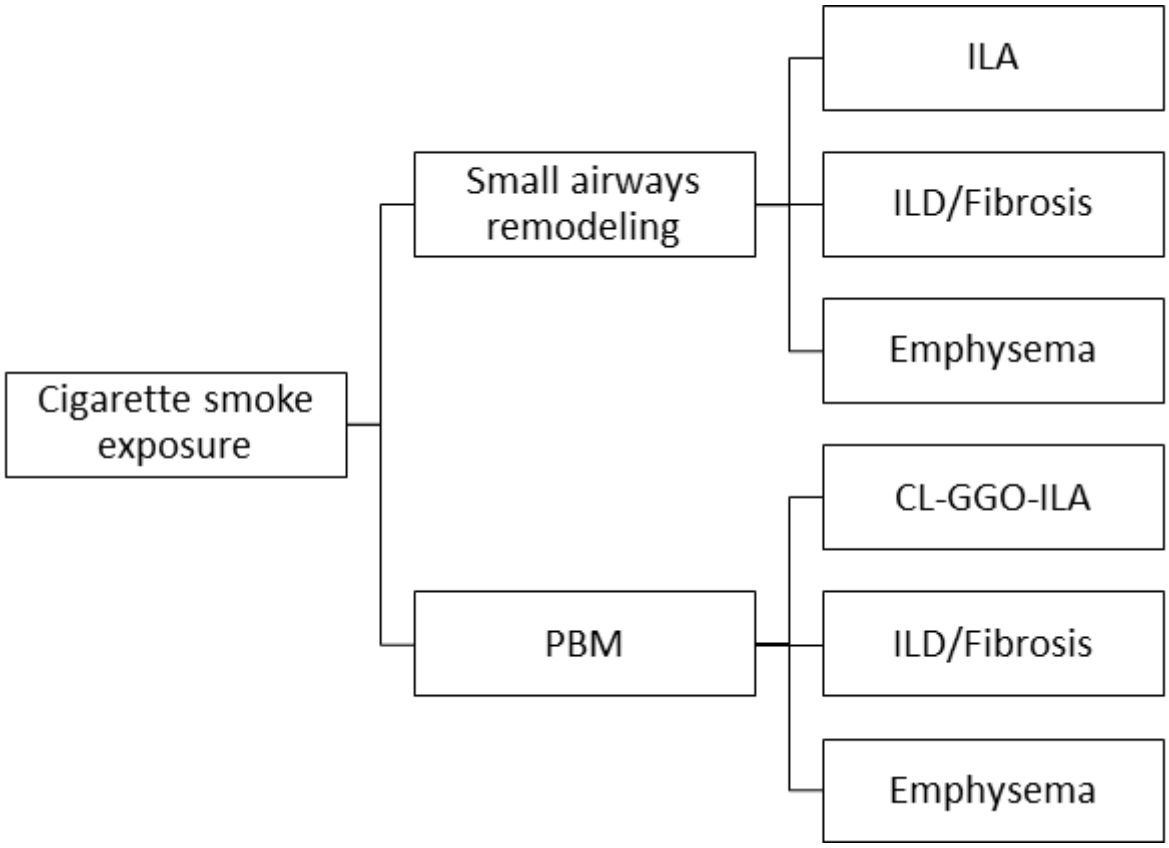

Figure 5

Peribronchiolar metaplasia (PBM) as a histological marker of small airway remodeling resulting from cigarette smoke. Cigarette smoke-induced small airway remodeling has been associated with non-malignant lung injury processes of interstitial lung abnormalities (ILA), interstitial lung disease (ILD) and emphysema. This study demonstrated that PBM, a cigarette smoke-related small airways reaction, is similarly associated with radiologic and histologic tissues responses of ILA, ILD/fibrosis and emphysema.