Human Pathology (2019) **86**, 93–101

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Human PATHOLOGY

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Original contribution

Incidental nonneoplastic parenchymal findings in patients undergoing lung resection for mass lesions☆,☆☆,★

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Received 6 November 2018; revised 2 January 2019; accepted 3 January 2019

Keywords:
Interstitial lung disease;
Pulmonary fibrosis;
Usual interstitial pneumonia;
Aspiration;
Pulmonary embolism

Summary The prevalence of incidental nonneoplastic lung disease in patients undergoing resection for mass lesions is unknown. We determined the prevalence and characteristics of parenchymal findings in patients with lung nodules, aiming to increase awareness of findings that could potentially impact patient management. A total of 397 patients with benign or malignant mass lesions with available presurgical chest computed tomography scans resected between January 2001 and July 2015 were included. Retrospective histologic assessment of parenchymal abnormalities in at least 1 section of grossly normal lung was performed for each case by 2 pulmonary pathologists and correlated with original pathology reports, clinical history, and radiologic findings. A total of 233 women and 164 men underwent resections for carcinomas (78%) or benign nodules (22%). One hundred one (25%) patients showed parenchymal abnormalities, including 14 patients with multiple findings. The most common abnormal findings were fibrotic interstitial changes (10%), including usual interstitial pneumonia (1%), followed by granulomatous processes (8%). Other findings included aspiration (4%), intravascular thrombi (2%), Langerhans cell histiocytosis (1.5%), constrictive bronchiolitis (1%), atypical lymphoid infiltrates (1%), and amyloidosis (0.5%). Abnormalities were more likely to have been documented in the original pathology report by pulmonary pathologists (68%) than by general pathologists (15%) ($P < .0001$). Cases with histologic parenchymal abnormalities were more likely to show radiologic interstitial lung abnormalities than those without

☆ Competing interests: Yin P. Hung, Ezra Miller, Rachel Putman, Tetsuro Araki, Hiroto Hatabu, and Marina Vivero have no disclosures. Mizuki Nishino has performed consulting work for Bristol-Myers Squibb, Toshiba Medical Systems, WorldCare Clinical, and Daiichi Sankyo; has received research grants from Merk, Canon Medical Systems, and AstraZeneca and honoraria from Bayer and Roche; and is supported by R01CA203636 (NCI) and U01CA209414 (none relevant to the current work). Lynette M. Sholl performs consulting work for Foghorn Therapeutics and AstraZeneca Pharmaceuticals and is on the scientific advisory board for Loxo Oncology. In the past 5 years, Gary M. Hunninghake has performed consulting work for the Gerson Lehrman Group, Medna LLC, Genentech, and Boehringer-Ingelheim.

☆☆ This study was presented in part at the 105th Annual Meeting of the United States and Canadian Academy of Pathology, Seattle, WA, in March 2016 in poster format.

★ Funding/Support: This research was supported in part by the National Institutes of Health (Bethesda, MD) 5R01HL111024-05.

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https://doi.org/10.1016/j.humpath.2019.01.002

(16% versus 5%; $P = .001$). Evaluation of background lung parenchyma may yield valuable and unanticipated information in patients undergoing surgical resections for lung masses that may correlate with radiographic interstitial lung abnormalities and influence clinical management.

1. Introduction

More than 30 000 surgical lung resections are performed annually in the United States [1], approximately 80%-90% for malignant and 10%-20% for benign lung nodules [1-3]. Reported nonneoplastic findings that account for clinically apparent lesions in lung resections include interstitial fibrosis [3,4], granulomatous inflammation [2,3], and vasculitides [2]. Timely diagnosis of these conditions is crucial for appropriate postsurgical and subsequent patient management. Among the idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis is the most common, occurring more frequently in smokers; can be correlated with the development of lung cancer; and has a median survival of 3-5 years that ultimately necessitates lung transplant as the disease progresses [5-8]. Additionally, idiopathic pulmonary fibrosis, which is characterized by a histologic pattern of usual interstitial pneumonia (UIP), is associated with acute exacerbations and postoperative acute respiratory distress syndrome, resulting in increased morbidity and mortality among both patients with an established diagnosis and those without [9-12]. In addition to UIP, other nonneoplastic lung diseases, including other interstitial lung diseases, thrombotic angiopathy, constrictive bronchiolitis, and the sequelae of aspiration, may be detected in lung resections, with the potential to affect subsequent patient management and prognosis.

Although the histologic correlates of benign processes presenting as mass lesions have been described, incidental lung parenchymal abnormalities in resections performed for unrelated mass lesions have not been systematically characterized. In this study, we evaluated a large series of pulmonary resections in patients undergoing surgery for malignant and benign mass-forming lesions at a single institution. We determined the prevalence and characteristics of histologic changes in the background lung parenchyma and correlated our findings to radiologic imaging and clinical outcomes to evaluate their potential clinical significance.

2. Materials and methods

2.1. Patient selection

Following approval of the Institutional Review Board at Brigham and Women's Hospital, we performed a retrospective study of 397 patients: a consecutive series of 307 patients with primary lung adenocarcinoma or poorly differentiated non–small cell carcinoma resected between January 2001 and December 2012, and a consecutive series of 90 patients with benign mass-forming lesions (including hamartomas, intraparenchymal lymph nodes, or inflammatory nodules) resected between January 2001 and July 2015. To correlate pathologic findings with presurgical radiologic findings, we included only cases with chest computed tomography (CT) imaging performed at our institution within 2 months prior to surgery. We excluded patients with squamous cell carcinoma and patients who had undergone neoadjuvant chemotherapy or radiation for lung tumors to minimize confounding effects of postobstructive pneumonia related to central location and of therapy, respectively, on radiologic and histologic assessment of parenchymal findings. Demographics, clinical history, and radiology reports were obtained from the electronic medical record.

2.2. Histologic assessment

Lung tissue sections were selected by the prosector in surgical pathology, with at least 1 section of lung parenchyma uninvolved by mass lesion routinely obtained in all cases during the study period, per institutional protocol. A median of 2 (range 1-15) whole-tissue hematoxylin and eosin (H&E)–stained slides containing only nonlesional tissue was reviewed per case by 2 pulmonary pathologists (M. V. and L. M. S.). Parenchymal abnormalities were evaluated and categorized according to the following morphologic patterns: fibrotic interstitial changes (including smoking-related interstitial fibrosis [SRIF], UIP, nonspecific interstitial pneumonia [NSIP], and undefined fibrosis), granulomatous disease (including patchy nonspecific granulomatous inflammation and sarcoidosis), evidence of possible aspiration, and other findings (intravascular thrombi, Langerhans cell histiocytosis [LCH], constrictive bronchiolitis, amyloidosis, and atypical lymphoid infiltrates). Cases were recorded as suggestive of aspiration, based on modification of recently published criteria [13], if 2 or more of the 4 following findings were seen affecting 2 or more terminal airways: loosely formed nonnecrotizing granulomas and/or giant cells, fibrin, organizing pneumonia, or aspirated material, in the absence of interstitial granulomas away from airways and clinical evidence of infection or hypersensitivity pneumonitis. Small airways disease without clearly recognized clinical correlates or standard clinical management, including respiratory bronchiolitis in the absence of clinical interstitial lung disease and peribronchiolar metaplasia, was not included. Similarly, all

instances of organizing pneumonia in the study group were associated with the mass lesions and were therefore not recorded as separate abnormalities. Where appropriate, additional immunohistochemical or histochemical stains were performed to confirm the diagnosis.

In addition to histologic review, original pathology reports for all cases were also reviewed to determine whether parenchymal findings were documented by the pathologist(s) of record and whether cases had been reviewed by a general or pulmonary pathologist. Findings noted in the original reports were correlated with the results of our retrospective review.

2.3. Clinical and radiologic correlation

Clinical correlates recorded for specific histologic findings are summarized in Table 1. Comprehensive pulmonary function testing was not available in many subjects and was therefore not recorded as a clinical correlate. Chest CT scans in all cases were evaluated for potential radiologic correlates of histologic findings by up to 3 readers (radiologists) blinded to prior radiologic interpretations, histology, and clinical history, as previously described [14,15]. Briefly, nondependent ground-glass abnormalities, reticular abnormalities, diffuse centrilobular nodularity, cysts, honeycombing, and traction bronchiectasis affecting more than 5% of any lung zone were scored as "interstitial lung abnormalities" (ILA). Focal or patchy findings were considered indeterminate.

2.4. Statistical analysis

Statistical significance for group comparison of variables was performed using GraphPad Prism software (GraphPad http://www.graphpad.com; version 3.10 for Windows; La Jolla, CA), with a predetermined 2-sided $P < .05$ considered to be statistically significant. The Fisher exact test was used when comparing 2 discrete variables between groups, and the χ^2 test was used when comparing 3 or more discrete variables between groups. Continuous variables (age, number of slides) were compared between groups using the 2-tailed Mann-Whitney test.

3. Results

3.1. Clinical characteristics

Our study included 406 separate resection specimens from 233 (58.7%) women and 164 (41.3%) men, with a median age of 66.3 (interquartile range, 59-74) years. Clinical and pathologic characteristics of study patients are summarized in Table 2. The majority of the patients (325, 82%) were either current or former smokers, and most resections (316, 78%) were performed to remove primary lung malignancies. Nine patients had 2 separate resections, which were evaluated separately for histologic parenchymal abnormalities during the study. Parenchymal abnormalities were identified in 101 of the 397 (25%) patients, including 14 patients with more than 1 type of abnormality. Median follow-up among patients with abnormalities was 3.6 years (range, 2 weeks to 15.8 years), with 86 (85%) patients having at least 1 year of follow-up. Older age and current or former smoking status were significantly associated with the presence of histologic parenchymal abnormalities ($P = .003$ and .03, respectively), whereas sex, type of resection, and the benign or malignant nature of the nodule were not (Table 2).

Table 1 Clinical correlates recorded for incidental nonneoplastic histologic findings

Histologic finding	Clinical correlates
Interstitial lung disease	CT imaging consistent with chronic interstitial lung disease
	Clinical diagnosis and/or treatment of chronic interstitial lung disease
	Surgical intervention for diagnosis of pulmonary fibrosis
LCH and nonspecific granulomatous inflammation	Radiologic imaging evidence of pulmonary nodules that resulted in further invasive medical intervention (eg, biopsy, resection)
Aspiration	Treatment for aspiration pneumonia
	Positive barium swallow
	CT imaging consistent with aspiration pneumonia
	Proton pump inhibitor treatment
	Clinical history of gastroesophageal reflux symptoms
Thrombotic angiopathy	Subsequent pathologic evidence of organ infarction
	Clinical and imaging evidence of pulmonary infarct
	Clinical and imaging evidence of stroke
	V/Q scan suggestive of thromboembolic disease
	Clinical and/or ultrasound evidence of deep venous thrombosis
	Clinical evidence of pulmonary hypertension
Atypical lymphoid proliferation	Prior or subsequent documented clinical or pathologic diagnosis of a lymphoproliferative disorder

Abbreviation: V/Q, ventilation-perfusion.

Table 2 Clinical and pathologic characteristics of study patients in relation to presence of histologic lung parenchymal abnormalities

Characteristic	Total n (%)	Histologically normal n (%)	Histologically abnormal n (%)	*P*
Age (median, interquartile range)	66.3 (59-74)	65.3 (57-73)	69.3 (62-75)	.003 *
Sex				
Female	233 (59)	171 (58)	62 (61)	.56
Male	164 (41)	125 (42)	39 (39)	
Smoking status [a]				
Current or former	325 (82)	236 (80)	89 (90)	.03 *
Never	69 (18)	59 (20)	10 (10)	
Specimen type [b]				
Wedge resection/segmentectomy	267 (66)	193 (63)	74 (73)	.07
Lobectomy/pneumonectomy	139 (34)	112 (37)	27 (27)	
Diagnosis				
Malignant	316 (78)	236 (77)	80 (79)	.80
Adenocarcinoma [c]	309 (76)	231 (76)	78 (77)	
Poorly differentiated carcinoma	7 (2)	5 (2)	2 (2)	
Benign	90 (22)	69 (23)	21 (21)	
Pulmonary or chondroid hamartoma	61 (15)	50 (16)	11 (11)	
Intraparenchymal lymph node	21 (5)	14 (5)	7 (7)	
Hyaline, fibrous, or fibroinflammatory nodule	3 (0.7)	1 (0.3)	2 (2)	
Normal lung parenchyma	3 (0.7)	3 (1)	0	
Organizing pneumonia	1 (0.2)	1 (0.3)	0	
Smoking-related pulmonary disease	1 (0.2)	0	1 (1)	

[a] Smoking status was unavailable for 3 patients, including 1 without and 2 with histologic lung abnormalities.
[b] Four hundred six total resections were performed in the 397 study patients, including 296 from patients without and 101 patients with histologic abnormalities.
[c] Includes 1 case of minimally invasive adenocarcinoma.
* Significant value.

3.2. Histologic characteristics of nonneoplastic pulmonary parenchymal findings

Histologic characteristics of the nonneoplastic parenchymal findings in the study cohort are summarized in Table 3 and the Figure. The relationship between specific categories of parenchymal abnormalities and nodule type or smoking status among all study patients is summarized in Supplementary Table 1. Patients with a smoking history were more likely to have fibrotic interstitial changes than never smokers (12% versus 1.4%, $P = .007$), and patients with benign disease were more likely than those with malignant disease to harbor parenchymal abnormalities in the "other" category (including thromboembolic disease, lymphoid infiltrates, and constrictive bronchiolitis; 11% versus 4%, $P = .021$).

The specific categories of histologic abnormalities and their clinical correlates are detailed below:

3.2.1. Fibrotic interstitial changes

Fibrotic interstitial changes comprised the most common category of histologic findings, noted in 41 (10%) patients. Most cases consisted of SRIF (7%) followed by UIP (1%), NSIP (0.7%), and patterns of "undefined" fibrosis (1%) such as desquamative interstitial pneumonia-like patterns, peribronchial fibrosis, and other patterns of fibrosis that did not fall into a recognized category of idiopathic interstitial pneumonia.

Sixteen (53%) patients with SRIF had a clinical diagnosis of chronic obstructive pulmonary disease, and an additional 9 (30%) had emphysema on chest imaging studies, with no other clinical correlates. One patient with UIP pattern had a known clinical history of nitrofurantoin-induced pulmonary fibrosis, whereas the other 3 with a UIP pattern underwent chest CT scans demonstrating unspecified "interstitial fibrosis" but had no documented clinical diagnosis or treatment related to pulmonary fibrosis during 1.0, 5.4, and 5.5 years of follow-up, respectively. Two of the latter 3 patients had undergone chemotherapy and radiation for breast cancer and colon cancer 8 and 2 years prior to lung resection, respectively, with agents that have not been associated with pulmonary fibrosis and otherwise had no histologic or clinical findings suggesting a specific etiology for the interstitial lung disease. No patients with NSIP pattern received rheumatologic or other further workup for interstitial lung disease at the time of last follow-up at 1.5, 3.0, and 5.5 years. One patient with undefined fibrosis was known to have bleomycin-induced lung injury prior to surgical sampling and was alive at follow-up 7 years after surgical sampling. The remainder of the patients within this category did not receive formal diagnoses of or treatment for interstitial lung disease by the time of death or last-follow-up. No patients with fibrotic interstitial changes died of their parenchymal disease.

Table 3 Histologic and reporting characteristics of nonneoplastic lung parenchymal findings in study patients

Lung parenchymal abnormality	Instances of abnormality n = 115 [a] (% total study cases)	Abnormalities reviewed by general pathologists		Abnormalities reviewed by pulmonary pathologists		*P*
		Total	# Reported as abnormal (%)	Total	# Reported as abnormal (%)	
Granulomatous processes	33 (8)	27	4 (15)	6	6 (100)	.0002 *
Nonspecific granulomatous inflammation	32 (8)	27	4	5	5	
Sarcoidosis	1 (0.2)	0	0	1	1	
Fibrotic interstitial changes	41 (10)	37	8 (22)	4	4 (100)	.005 *
SRIF [b]	30 (7)	27	8	3	3	
UIP	4 (1)	3	0	1	1	
NSIP	3 (0.7)	3	0	0	–	
Undefined	4 (1)	4	0	0	–	
Aspiration	17 (4)	12	0 (0)	5	1 (20)	.29
Other findings	24 (6)	20	2 (10)	4	2 (50)	.12
Thrombotic angiopathy	8 (2)	7	0	1	0	
LCH	6 (1.5)	6	1	0	–	
Constrictive bronchiolitis	4 (1)	3	0	1	1	
Atypical lymphoid infiltrate	4 (1)	3	0	1	1	
Amyloidosis	2 (0.5)	1	1	1	0	
Total	115	96	14 (15%)	19	13 (68%)	<.0001 *

[a] Fourteen cases had 2 separate abnormalities that were considered separate instances of abnormality to be reported.
[b] SRIF that was recognized by both general and pulmonary pathologists was reported descriptively.
* Significant values.

3.2.2. Granulomatous inflammation

Granulomatous inflammation was identified in 33 (8%) patients, 32 of whom showed a hypersensitivity-type pattern of sparse, poorly formed granulomas in a peribronchiolar and interstitial distribution. One additional patient was previously diagnosed with sarcoidosis on the basis of mediastinal lymphadenopathy and a prior mediastinal lymph node biopsy containing nonnecrotizing granulomas. In 8 of these cases with available material, special stains for microorganisms were performed during diagnostic workup and were all negative.

In 4 cases presenting with nonspecific granulomatous inflammation, patients complained of chronic cough and/or shortness of breath, including 1 patient who reported relief with prednisone treatment but did not receive a clinical diagnosis of a specific interstitial lung disease. The single patient with sarcoidosis also had a remote history of metastatic leiomyosarcoma with metastases to the lungs as well as primary lung adenocarcinoma and remained asymptomatic without treatment during the study period.

3.2.3. Aspiration

Seventeen (4%) patients showed microscopic evidence of aspiration. In 9 of these cases (53%), clinical evidence of aspiration was subsequently noted at a mean of 26.6 months after surgery either on swallow studies or during episodes of aspiration pneumonia, 2 of which resulted in death.

3.2.4. Constrictive bronchiolitis

Four cases (1%) displayed evidence of constrictive bronchiolitis, characterized by peribronchial fibrosis with luminal narrowing. Three of the 4 patients were current or former smokers with radiologic evidence of emphysema and/or clinical history of chronic obstructive pulmonary disease; however, none had documented treatment for their pulmonary disease during the study time period.

3.2.5. Vascular changes

Organizing or organized thrombi within small arterioles were noted in 8 cases (2%). Four (50%) of these patients experienced subsequent sequelae of thromboembolic disease at a mean of 33 months after surgery. Two were diagnosed with pulmonary hypertension. One of these 2 patients also developed ischemic cerebral infarcts 3 years after surgery and was discovered to have thoracic aortic and popliteal aneurysms with mural thrombi. One developed bilateral deep vein thromboses 2½ years after surgery and died after a motor vehicle accident related to a transient ischemic attack. One additional patient died of ischemic bowel due to thromboembolic disease 3 months after surgery.

Two cases (0.5%) showed amyloidosis, with perivascular deposition of eosinophilic, amorphous material confirmed with Congo red stain. One patient had a known history of monoclonal gammopathy of uncertain significance and amyloidosis corroborated on the subsequent lung biopsy performed for an organizing hematoma.

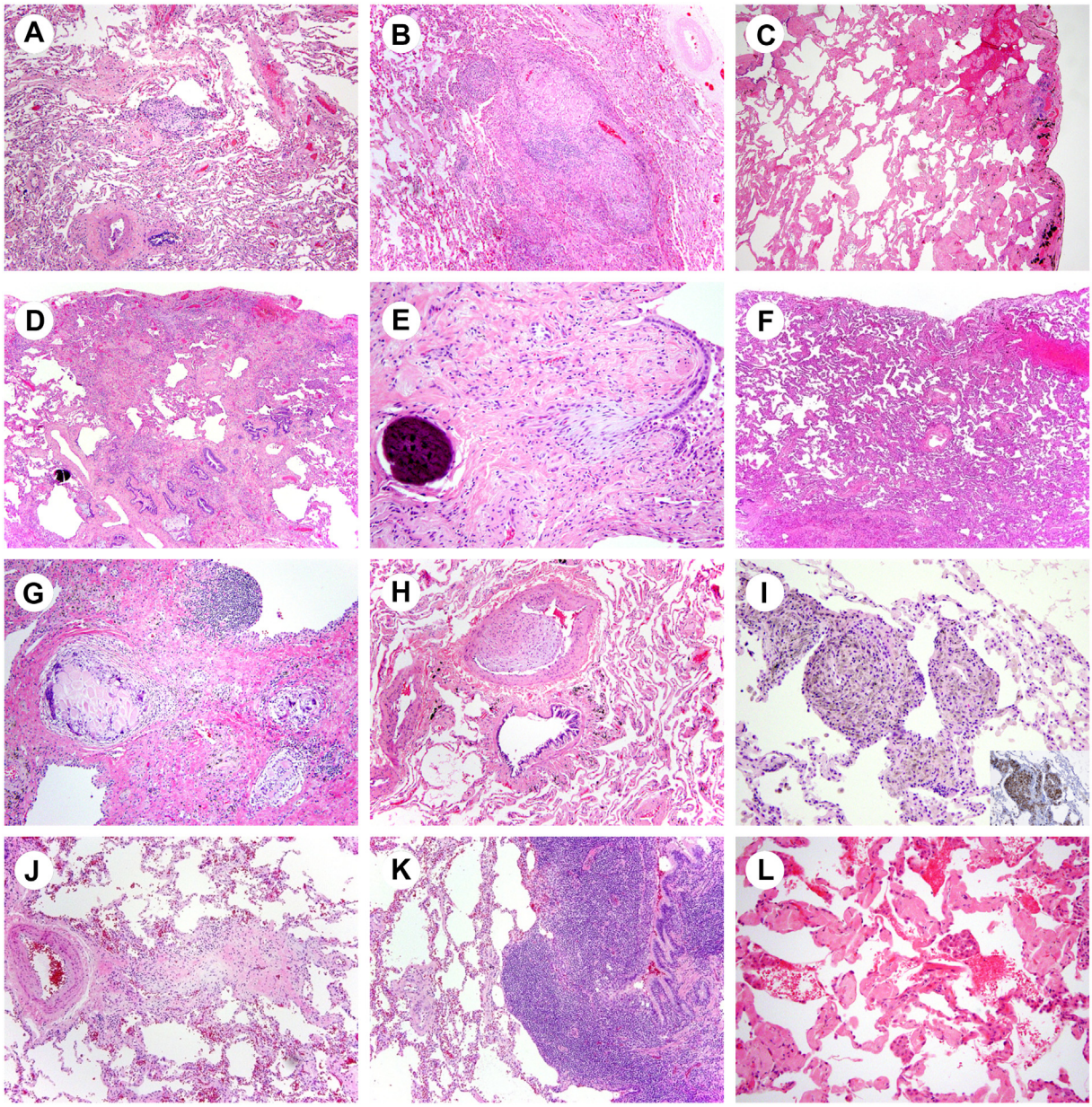

Figure Incidental nonneoplastic pulmonary parenchymal findings (H&E). A, Patchy granulomatous inflammation (original magnification ×100), (B) sarcoidosis (×100), (C) SRIF (×40), (D) UIP (×40), (E) UIP (×200), (F) NSIP (×40), (G) aspiration (×100), (H) thrombotic angiopathy (×100), (I) LCH (H&E ×200; inset: Langerin immunohistochemistry, ×200), (J) small airway obliteration (×100), (K) atypical lymphoid infiltrate (×100), and (L) amyloidosis (×200).

The second patient died 3 months after surgery of complications of small bowel ischemia related to thrombotic disease, as above.

3.2.6. Lymphohistiocytic proliferations

LCH, characterized by nodules or loose aggregates of CD1a and Langerin-positive histiocytoid cells with characteristic nuclear grooves, admixed eosinophils, and scarring [16], was identified in 6 (1.5%) patients. One patient was ultimately diagnosed with LCH based on imaging and smoking history, 3 patients continued to be followed for small persistent but stable pulmonary nodules without a specific diagnosis, and 2 patients had no follow-up imaging.

Atypical lymphoid infiltrates with histologic features of nodular lymphoid hyperplasia or nonspecific nodular fibroinflammatory lesions were observed in 4 cases (1%). One patient had a history of hypothyroidism, and one developed autoimmune hemolytic anemia; none had documented evolution to a lymphoproliferative disorder at a follow-up of 1.3-14.8 (median, 3.7) years.

Table 4 Radiologic correlates of nonneoplastic lung parenchymal findings in study patients

	Associated radiologic ILA[a] n (%)			*P*
	None	Indeterminate	Present	
Cases without parenchymal abnormalities	190 (65)	87 (30)	16 (5)	.001 *
Total cases with parenchymal abnormalities	54 (47)	44 (39)	16 (14)	
Granulomatous processes	15 (45)	16 (48)	2 (6)	.11
Nonspecific granulomatous inflammation	14 (44)	16 (50)	2 (6)	
Sarcoidosis	1 (100)	0 (0)	0 (0)	
Fibrotic interstitial changes	21 (51)	11 (27)	9 (22)	.002 *
SRIF	20 (67)	7 (23)	3 (10)	
UIP	0 (0)	0 (0)	4 (100)	
NSIP	0 (0)	2 (67)	1 (33)	
Undefined	1 (25)	2 (50)	1 (25)	
Aspiration	7 (44)	6 (38)	3 (19)	.18
Other findings	11 (46)	11 (46)	2 (8)	.31
Thrombotic angiopathy	2 (25)	5 (63)	1 (13)	
LCH	3 (50)	2 (33)	1 (17)	
Small airway obliteration	3 (75)	1 (25)	0 (0)	
Atypical lymphoid infiltrate	3 (75)	1 (25)	0 (0)	
Amyloidosis	0 (0)	2 (100)	0 (0)	
Cases with 2 parenchymal abnormalities	4 (29)	7 (50)	3 (21)	.038 *

[a] CT imaging could not be assessed in 12 of 406 cases, including 11 cases without abnormalities and 1 case with abnormality.
* Significant values.

3.3. Impact of specimen type and sampling pattern

The overall prevalence of abnormal parenchymal findings did not significantly differ between specimen types (74 of 267 sublobar resections compared to 27 of 139 lobectomy or pneumonectomy specimens, $P = .07$; Table 2). Although proportions of specimen types did not significantly differ between smokers and nonsmokers ($P = .68$), more patients with malignant disease (41%) than with benign disease (10%) underwent lobectomy or pneumonectomy ($P < .0001$). Identification of parenchymal abnormalities correlated with the number of sections of background lung sampled, with a median of 3 sections (range, 1-15) examined in cases with abnormalities and median of 2 (range, 1-11) in those without ($P = .0009$).

3.3.1. Reporting characteristics of parenchymal findings

Overall and subspecialty-specific reporting characteristics of parenchymal abnormalities are summarized in Table 3. For the purposes of comparison, original reports of unspecified interstitial fibrosis that was classified as SRIF by the authors during the study were considered concordant, as this terminology was first introduced in 2006 [17,18] and was therefore not uniformly recognized as a specific diagnostic entity during the study period. Twenty-seven (23%) of the 115 abnormalities seen in 101 study specimens were documented in the original pathology reports: Of the 101 study specimens, 85 were originally reviewed by a general pathologist, and 16 specimens were reviewed by a pulmonary pathologist. General pathologists documented 14 of 96 (15%) abnormalities in the original pathology reports as compared to 13 of 19 (68%) abnormalities documented in abnormal cases reviewed by pulmonary pathologists ($P < .0001$). Overall, although general pathologists reported aspiration and most nonfibrotic findings at a rate similar to pulmonary pathologists, pulmonary pathologists were significantly more likely to document findings associated with granulomatous processes ($P = .0002$) and fibrotic interstitial changes ($P = .005$).

3.4. Radiologic correlates associated with nonneoplastic pulmonary parenchymal findings

Radiologic correlates of the nonneoplastic parenchymal findings in this cohort are summarized in Table 4. CT imaging could not be assessed in 12 cases, including 11 cases without and 1 case with histologic parenchymal abnormalities. The presence of histologic abnormalities correlated with the presence of ILA on CT imaging: 14% of cases with histologic abnormalities and 5% of cases without histologic abnormalities showed ILA on CT ($P = .001$). Among different histologic categories, only findings consistent with fibrotic interstitial changes were significantly associated with the presence of ILA ($P = .002$).

4. Discussion

Prior to the advent of CT, the majority of surgical lung resections yielded benign nodules [19]. In today's practice,

benign diagnoses account for 9%-24% of resected nodules [2,3,20]. Most studies of parenchymal findings in surgical lung resections to date have therefore aimed to define the characteristics of benign pulmonary mass lesions to avoid unnecessary surgery. These studies, however, did not focus on incidental parenchymal findings and excluded specimens with malignant diagnoses, which comprise most resections in the current era of low-dose CT screening [20-22].

Our retrospective analysis identified incidental histologic parenchymal abnormalities in 25% of all patients undergoing resection for mass lesions, about a quarter of which were mentioned in the diagnostic pathology report. Pathologists with expertise in pulmonary diseases were significantly more likely than general pathologists to report these abnormalities.

Chronic fibrotic interstitial changes were the most common parenchymal finding in our study (10% of patients), mostly consisting of SRIF. UIP and NSIP patterns of fibrosis, as well as undefined patterns, were seen in 3% of patients, comparable to previously described rates of incidental interstitial pneumonias (1.3%-8%) [4,9,23,24]. Interstitial changes, including the specific pattern according to American Thoracic Society/European Respiratory Society criteria, were consistently reported by pulmonary pathologists, but only 22% of cases with interstitial changes were reported by general pathologists and were characterized nonspecifically as "subpleural interstitial fibrosis" in all cases. This latter group corresponded to SRIF based on retrospective review. Although the clinical significance and natural history of SRIF are still undetermined, it is highly prevalent, and characterization as SRIF in diagnostic reports is preferable to nonspecific descriptions of subpleural fibrosis to prevent misinterpretation as potential UIP, which is characterized by a different histologic pattern of subpleural fibrosis and has a poor prognosis. Consistent with other histopathology studies [2,3,25], interstitial and peribronchial nonnecrotizing granulomas were common, identified in 8% of patients in this series. This hypersensitivity pneumonitis-like pattern has been previously described as a secondary cell-mediated response adjacent to malignant tumors or in regional lymph nodes [26]; however, we also observed granulomas in patients with benign diagnoses, suggesting that the pattern is likely not wholly attributable to antitumor response. Correlation with clinical and radiologic findings, and pulmonary function testing if available, is therefore advisable to evaluate the possibility of hypersensitivity pneumonitis. Other findings, including evidence of aspiration, thrombotic angiopathy, LCH, constrictive bronchiolitis, amyloidosis, and atypical lymphoid infiltrates, were each seen in 1%-4% of cases.

Importantly, thrombotic angiopathy and aspiration changes were associated with significant subsequent clinical events including ischemic stroke, pulmonary arterial hypertension, small bowel ischemia, and aspiration pneumonia. Together, thrombotic angiopathy and aspiration were seen in 6% of all patients on retrospective review, but only one (aspiration changes) was documented in the original pathology report. In contrast, interstitial changes, including those documented as a UIP pattern, had no clinical phenotype documented in the study period. Interstitial changes did, however, correlate significantly with radiographic ILA. There is some evidence to suggest that interstitial changes, particularly in smokers, may interfere with diffusion capacity and contribute to pulmonary symptoms out of proportion to pulmonary function defects based on spirometry [14,15]. Longer-term and more systematic follow-up will be required to further characterize these changes.

Nonsmokers were more likely to harbor findings in the "other" category (including thrombolic disease, lymphoid infiltrates, or constrictive bronchiolitis) and as likely to have granulomatous inflammation or aspiration. Patients with benign diagnoses were also as likely to have parenchymal abnormalities as those with malignant diagnoses. These findings indicate the importance of evaluating background lung in all patients undergoing resection for mass lesions, regardless of smoking history or diagnosis.

Optimal sampling protocols to evaluate background lung parenchyma in resections performed for nodules are not well established. One previous study evaluated 27 parenchymal sections per case and found SRIF in 39% of cases [18] compared to 7% in this study. The different detection rate may reflect relative undersampling in our cohort, although our approach likely reflects routine diagnostic practice more closely. We did find that parenchymal abnormalities were more likely to be found in cases with 3 or more sampled nonneoplastic areas, an amount that would be feasible in most practices.

The greatest limitations of this study include its retrospective nature, lack of consistent follow-up and pulmonary function testing in the majority of study patients, and its focus on a single tertiary care hospital. Additionally, the inherent difficulty in determining potential mechanical, obstructive, or inflammatory effects of mass lesions on surrounding parenchyma may preclude optimal evaluation of adjacent parenchyma. We attempted to limit overinterpretation of tumor effects by including only changes noted in normal parenchymal sections and attributing findings directly adjacent to tumor as secondary changes.

In summary, our results show that (1) 77% of incidental parenchymal findings in lung resections performed for mass lesions go unreported, but the majority appear to lack a clear clinical correlate; (2) pulmonary pathologists are significantly more likely than general pathologists to recognize and report the findings; (3) histologic evidence of aspiration and thromboembolic disease, seen in 6% of study patients, may herald subsequent serious clinical events; (4) radiologic ILA are more common in patients with histologic parenchymal abnormalities; and (5) more rigorous sampling of uninvolved lung parenchyma increases the chances of discovering incidental lung parenchymal disease. Our data should be interpreted cautiously in the context of the study's limitations, and additional prospective studies will be necessary to confirm the true clinical impact of our findings in the setting of daily practice. Our results, however, support the judicious use of subspecialty consultation, increased education regarding relevant parenchymal findings, a multidisciplinary diagnostic approach including radiologic evaluation, and thorough sampling of

nonneoplastic parenchyma to improve diagnostic and clinical outcomes.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2019.01.002.

CRediT authorship contribution statement

Yin P. Hung: Investigation, Data curation, Formal analysis, Methodology, writing - original draft, Writing - review & editing. **Gary M. Hunninghake:** Investigation, Funding acquisition, Writing - review and editing. **Ezra R. Miller:** Investigation, Data curation, Writing - review & editing. **Rachel Putman:** Investigation, Writing - review & editing. **Mizuki Nishino:** Investigation, Writing - review & editing. **Tetsuro Araki:** Investigation, Writing - review & editing. **Hiroto Hatabu:** Investigation, Writing - review & editing. **Lynette M. Sholl:** Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Marina Vivero:** Conceptualization, Investigation, Data curation, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing.

Acknowledgments

We thank Dr Geraldine Pinkus and the immunohistochemistry laboratory, Brigham and Women's Hospital, for technical support.

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