

Unclassifiable and Newly Described Interstitial Pneumonias
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Definitions (from wordnet.princeton.edu):

Unclassifiable – not possible to classify
Unclassified – not arranged in any specific grouping

Unclassifiable IPs among the idiopathic interstitial pneumonias

Katzenstein and Fiorello were the first to formally recognize that there were interstitial pneumonias that did not fit into the traditional categories of idiopathic interstitial pneumonia, especially UIP (AJSP 1994; 18:136). Nonspecific interstitial pneumonia (NSIP) was used to designate these cases. (The term had been previously used for noninfectious interstitial pneumonias in the setting of AIDS; see Suffredini, et al, in Ann Int Med 1987;107:7).

NSIP is now an important diagnosis; it is recognized that that the cellular variant has a very favorable prognosis and the fibrotic variant a somewhat less favorable prognosis, but nevertheless significantly better than that of UIP in the setting of idiopathic pulmonary fibrosis.

In 1991 I used the term “unclassified interstitial pneumonias” to recognize that “some acute or chronic interstitial pneumonias cannot be put into any of the well-described categories.” (Colby TV, et al. Atlas of Pulmonary Surgical Pathology, W. B. Saunders, 1991) In reviewing figures of those cases, it is clear that most would fit into the category of NSIP.

By creating the category of NSIP, Katzenstein lengthened the list of idiopathic interstitial pneumonias, but still did not leave a category of cases that could not be classified.

The recent 2002 ATS/ERS Consensus Classification of Idiopathic Interstitial Pneumonias (Am J Respir Crit Care Med 2002;165:277-304) does recognize “unclassifiable interstitial pneumonia.” This “small subset” remains unclassifiable after extensive clinical, radiologic and/or pathologic examination due to:

1. Inadequate clinical information.
2. Inadequate radiologic data.
3. An inadequate or nondiagnostic biopsy (e.g. small size or sampling).
4. Major discrepancy between clinical, radiologic and pathologic findings.
5. The effects of previous therapy resulting in alterations of radiologic or histologic findings.
6. Discrepancy between histologic findings in different lobes that is not resolved after correlation with clinical and radiologic data.

One of the reasons for this category is cases in which multiple histologic patterns are present that cannot be reconciled; for example, well-established eosinophilic pneumonia in one lobe and UIP in another; sarcoidosis in one biopsy, UIP in another (or both together, etc.). Obviously then, some “unclassifiable” cases could represent the manifestations of two different disease processes.

My current approach to “unclassifiable” cases: I list the various histologic features that are present (a descriptive diagnosis) and usually prefer the designation “difficult to classify” since it better conveys the essence of the problem than does the words “unclassified” or “unclassifiable.”

Recently Described (Idiopathic) Interstitial Pneumonias

Judging from recently described interstitial pneumonias pulmonary pathologists seem to have a fixation with the centrilobular regions of the lung and/or the bronchioles.

I. Bronchiolitis With Peribronchiolar Organizing Pneumonia (B-POP): A New Clinical Pathologic Entity in Bronchiolar/Interstitial Lung Disease? (Abstract Only)

3 patients with severe dyspnea and diffuse bilateral micronodules on imaging. Pathology showed bronchiolocentric lesions including “both inflammatory and fibrotic bronchiolitis (obliterans)” and intra-alveolar buds of connective tissue limited at the alveoli immediately adjacent to the involved bronchiole (B-POP). All patients improved on steroids.

The authors concluded that “*although B-POP and BOOP have common elementary pathologic bronchiolar and alveolar lesions, their distribution is strikingly different. We therefore consider that B-POP merits to be individualized within the group of bronchiolar/interstitial lung disorders because of both its clinical radiological and pathologic distinct features.*”

Comment: I have seen several of these cases and probably would have included them as COP/BOOP (if they weren't the residue of some recognizable prior infection).

Reference: Thivolet F, Loire R, Cordier J-F. Bronchiolitis with peribronchiolar organizing pneumonia (B-POP): A new clinicopathologic entity in bronchiolar/interstitial lung disease? *Eur Respir J* 1999;14:272S.

II. Centriobular Fibrosis: A Novel Histological Pattern Among Idiopathic Interstitial Pneumonias

49 patients with open lung biopsy showing “pulmonary fibrosis.” 24 classified as UIP, 13 as NSIP, 12 “... with severe lobular derangement and bronchocentric lesions in all the 12 cases in a fairly homogeneous pattern... termed centriobular fibrosis (CLF) group.” “The distribution of the lesion was bronchiolocentric, although the whole secondary lobule was involved...”

The demographics and functional status did not show any differences among the 3 groups except for the fact that the NSIP patients were younger. The UIP and CLF patients could not be distinguished with any of these parameters.

Comment: I cannot understand how these cases are called centriobular. To my eye, the figures look like UIP.

Reference: Pilotto de Cabalho M-E, et al. Centriobular fibrosis: A novel histologic pattern in idiopathic interstitial pneumonia. *Pathol Res Pract* 2002;198:577-583.

III. Idiopathic Bronchiolocentric Interstitial Pneumonia (BrIP)

10 patients “with a distinctive idiopathic bronchiolocentric interstitial pneumonia...” Cases identified from a search of “unclassified” interstitial pneumonias and those showing features “suggestive of” hypersensitivity pneumonitis.”

All 10 cases showed centrilobular bronchiolocentric chronic inflammatory infiltrate with some involvement of peribronchiolar alveolar septa. 7 had peribronchiolar fibrosis with peribronchiolar metaplasia.

8 women, 2 men, mean age 46.7 years. Chest x-rays described as bibasilar interstitial infiltrates in 9 of 10; CT reports available in six cases “confirmed” the chest x-ray findings. PFTs showed mild restriction.

Followup of 9: 3 died of pulmonary disease, 5 had persistent or progressive disease, and 1 was NED.

Comment: The authors noted “histologic similarities to hypersensitivity,” and nowadays many of us would give a descriptive diagnosis and put HP high in the differential.

Reference: Yousem SA, Dacic S. Idiopathic bronchiolocentric interstitial pneumonia. *Mod Pathol* 2002; 15:1148-1153.

IV. Airway Centered Interstitial Fibrosis: A Distinct Form of Aggressive Diffuse Lung Disease

12 cases selected from a group of well-characterized interstitial pneumonias followed in Mexico City. The authors distinguished their cases from those described as idiopathic bronchiolocentric interstitial pneumonia. The key finding at low power magnification was “a distinctive pattern of airway centered interstitial fibrosis centered on membranous and respiratory bronchioles.” The bronchioles were often narrowed and distorted, but not overtly obstructed by granulation tissue or fibrosis. Some subepithelial fibrosis was present. Variable degrees of interstitial fibrosis extended away from the affected airways. Honeycombing was not present. Criteria of UIP were not met.

2:1 female predominance; mean age 54 years. Mild restrictive PFTs. Chest radiographs showed diffuse reticulonodular infiltrates with central predominance and thickening of bronchial walls. CT scan in 5 cases suggested peribronchovascular interstitial thickening and traction bronchiectasis. Some cases had conglomerate fibrotic masses adjacent to the airways. Bronchioloectasis and/or honeycombing were seen in 3 cases. 8 patients had some exposures that could have been significant; two had birds.

Followup: 5 had progressive disease of which 4 died; 3 improved or healed; 2 remained stable; 1 lost to followup; 1 recently diagnosed.

Comment: I could not entirely convince myself that the figures showed centrilobular lesions, but this does appear to be a distinctive pattern of lung injury that does not fit into the accepted patterns of idiopathic interstitial pneumonia.

Reference: Churg A, Myers JL, et al. Airway centered interstitial fibrosis: A distinct form of aggressive diffuse lung disease. *Am J Surg Pathol* 2004;28:62-68.

V. Peribronchiolar Metaplasia: A Common Histologic Lesion in Diffuse Lung Disease and a Rare Cause of Interstitial Lung Disease: Clinical Pathologic Features of 15 Cases

These authors also distance themselves somewhat from two of the above studies, but do acknowledge that “some of the cases included in those reports are likely similar to our cases.”

A study of 15 cases in which peribronchiolar metaplasia (PBM) “was the only major histologic finding in surgical lung biopsies from patients with interstitial lung disease (PBM/ILD)...”

Mean age 57 years, 13 women, 2 men, 1 with pigeon exposure, 1 a welder. Three patients had collagen vascular disease. PFTs in 10 patients: 1 obstructive, 5 restrictive, 2 mixed, 2 normal. CT findings in 7 patients, mosaic attenuation in 3; mild air trapping only on expiration in 1, patchy subpleural GGO in 1; 3 normal.

Followup in 11: All alive (but few details), 5 with improvement of their symptoms.

Comment: Reasonably homogenous series on the basis of histology, but probably include a heterogenous group in terms of exposure history, associated connective tissue disease, etc.

Reference: Fukuoka J, Franks TJ, Colby TV, ... Travis WD. Am J Surg Pathol 2005;29:948-954.

VI. Bronchiolitis Interstitial Pneumonia (BIP): A Distinctive Disease with Clinical and Pathological Features Intermediate between Bronchiolitis Obliterans, Organizing Pneumonia, and Usual Interstitial Pneumonia (Abstract Only)

32 patients who had respiratory disease that led to surgical lung biopsy. The cases were compared with bronchiolitis obliterans, BOOP, NSIP, UIP, airway centered interstitial fibrosis, and idiopathic bronchiolocentric interstitial pneumonia (BrIP).

“The common feature of all our cases was a combination of both prominent bronchiolitis and interstitial inflammation and fibrosis but little or no organizing pneumonia, little or no peribronchiolar fibrosis, and no hyperplasia of bronchus associated lymphoid tissue.”

Followup after treatment with steroids in 20 cases: 7 improved with PFTs improving as well, 5 subjectively improved with unchanged PFTs, 1 remained unchanged, 2 worsened, and 5 died following worsening of disease.

Comment: The abstract includes a little diagram that compares the 6 entities mentioned above. I believe I have seen a number of these cases and if the bronchiolar component is most prominent, I have probably concluded that the case is primarily bronchiolitis with secondary scarring, and if the interstitial pneumonia is predominant, I probably concluded that the bronchiolitis is an incidental finding.

Reference: Ruangchira-Rai R and Mark EJ. Bronchiolitis interstitial pneumonitis: A distinct disease with clinical and pathologic intermediate between bronchiolitis obliterans organizing pneumonia and usual interstitial pneumonia. Mod Pathol 2007;20:329A.

VII. Summary

A casual observer not immersed in the splitter's world of pulmonary pathology might wonder why we have described so many "entities" that appear to have considerable similarities. All the series are small; follow-up is relatively short and inconsistent, and the follow-up in some of the series is not described in detail (see below).

	M	F	Mean Age	Follow-up	DOD		Improved/NED
Yousem	2	8	47	9	3	5 stable or worse	1
Churg	4	8	54	9	4	2 stable	3
Fukuoka	2	13	57	11	0	6 ? stable	5
Ruangchira-Rai	?	?	?	20	5	1 stable 2 worse	12

There probably is something in these series. There is a definite female predilection and most of the patients are in the fifth and sixth decades. Beyond that, I don't think much can be said

Clearly an important lesion in differential diagnosis is chronic hypersensitivity pneumonitis with some fibrosis and in which granulomas are lacking. In such cases, the exposure history is important. Airways changes of the type shown in these series may also be seen distal to bronchiectasis and as part of connective tissue diseases.

For interest, I gave our statistician a summary of the of the available followup in these 4 series, and there was no statistically significant difference among them. According to our statistician, Dr. Dueck: When you pool the data across the 4 studies you do not end up with a significant result (p value of 0.26); in fact, the results are not significant in any one study as well. In terms of sample size needed to prove the significance of these studies. If the true probability of death from disease is 0.60, a sample size of 170 is needed; if the true probability of death from disease is 0.80, a sample size of 20 is needed.

Comment: None of these "entities" is ready yet for prime time among the accepted IIPs.

VIII. Definitional Issue

I use the terms broncho and bronchiolocentric to refer to processes which appear to center on airways from bronchi to alveolar ducts. This is best appreciated at scanning power microscopy and contrasts with typically subpleural and paraseptal preferential involvement in usual interstitial pneumonia. How much of a pathologic process should be airway centered before one uses the term? There is no answer and one must look at the case as a whole. Occasional airway-centered pathology is common in cases of UIP and when fibrosis develops in some airway-centered processes, notably hypersensitivity pneumonitis, some of the scarring may be subpleural and paraseptal and be indistinguishable from UIP.

Minimally invasive pulmonary adenocarcinoma

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- **Solitary non-mucinous bronchioloalveolar carcinomas (BAC) are non-invasive tumors associated with excellent 5 and 10 year survival.**
- **Radiographic pure ground glass opacities (GGO) are often BAC pathologically, and small (<1.0 cm) GGO and mixed GGO have excellent prognosis.**
- **Mixed subtype adenocarcinoma (invasive adenocarcinoma in a background of BAC pattern) with small foci of invasion ($\leq 0.5\text{cm}$) are also associated with favorable 5 and 10 year survival.**
- **Histopathologic criteria for invasion and methods of quantifying invasion need to be developed.**
- **A decision tree incorporating radiologic, pathologic and molecular parameters may help guide therapy including limited versus anatomic resections.**

The histopathology of adenocarcinoma has long been recognized to be heterogeneous. Over the last decade or so, due to a combination of careful histopathological characterization, utilization of radiographic techniques, and molecular discoveries there have been advancements in the understanding of the biological significance of some of this histologic heterogeneity.

The term bronchioloalveolar carcinoma has at its core a tumor type arising in the periphery with replacement or lepidic growth along pre-existing alveolar walls. As many peripheral adenocarcinomas contained elements of lepidic growth, the term was used to include tumors with variable amounts of this pattern. In 1999, the WHO classification defined bronchioloalveolar carcinoma as completely noninvasive, and in 2004 created the term mixed subtype adenocarcinoma for tumors that had invasion in association with a portion of the tumor having a replacement or lepidic growth pattern.

In doing so, the WHO classification created a category of noninvasive carcinoma that if narrowly defined, should not have distant metastatic potential. It could however have solitary or multicentric growth, with tumoral seeding along pre-existing air spaces but without invasion of connective tissue, vessels or pleura. While patients with bronchioloalveolar carcinoma may not experience metastatic tumor, patient with multicentric disease could develop respiratory compromise due to replacement growth of lung tissue. In addition, as bronchioloalveolar carcinomas are thought to be precursor lesions of the mixed subtype adenocarcinomas, acquisition of invasiveness within a multicentric bronchioloalveolar carcinoma could occur with the consequences of the same metastatic potential of any mixed subtype adenocarcinoma.

The mixed subtype adenocarcinoma category however can include tumors with very small foci of invasion or foci of invasion that involve the majority of the tumor. This raises the question as to the minimum size of invasion that increases the risk of metastatic disease resulting in reduced survival in solitary mixed subtype tumors. As in microinvasive cervical cancer or microinvasive breast carcinoma there may represent an extent of invasion than is usually biologically insignificant, or perhaps has an

intermediate significance in terms of risk of lymph node metastasis, distant metastasis and death.

While this definition of bronchioloalveolar carcinoma was established in 1999 by the WHO, the concept of noninvasive replacement type adenocarcinoma began years earlier in studies conducted in Japan. As early as 1980, Shimosato et al¹ reviewed adenocarcinomas less than 3 cm and concluded that the presence of fibrosis within tumors was more important than tumor size - that is the amount of fibrosis was more predictive of survival than gross size under 3 cm versus gross size under 2 cm. In 1994, Kurokawa et al, studied 178 peripheral adenocarcinomas less than 2 cm. Focusing on 56 cases that were solitary, node-negative, and BAC patterned (likely mixed subtype tumors), they found that higher scar grade predicted recurrence and distant metastases². In 1995, Noguchi et al³ examined 236 lung adenocarcinomas from 1962-1993 and attempted to classify them into six groups, A-F:

Table 1 Noguchi classes

Type A – Localized BAC – replacement growth, no alveolar collapse, no fibrosis

Type B – Localized BAC with alveolar collapse, fibrosis, pleural indent.

Type C – Localized BAC with foci of active fibroblastic proliferation.

Type D – Invasive solid

Type E – Invasive acinar

Type F – Invasive papillary.

No Noguchi type A and B tumors had lymph node metastasis while 28% of type C tumors had lymph node metastasis. Despite finding pleural invasion in three and vascular invasion in two of 28 A and B tumors, the five-year survival was 100% for these patients with a significantly lower median survival for the Noguchi type C patients.

Given the impact of the WHO classification in 1999 and the establishment of a narrower definition of bronchioloalveolar carcinoma, studies performed after 1999 may better reflect the current classification of tumors. In their study of 100 adenocarcinomas from 1987-1992 that were 3 cm or less, Suzuki et al⁴ measured invasion as defined by the size of fibrosis on low-power view. Similar to the finding of Shimosato et al published 20 years before, stratification of gross tumor size higher and lower than 2 cm did not

- **Fibrosis size predictive of survival**
- **Excellent survival <6mm fibrosis**
- **No lymph node metastasis with <6 mm fibrosis**

have survival impact. Using strata of less than or equal to 5 mm, >5 to 15 mm, and > 15mm of fibrosis size, they reported 100% 5 yr survival for <6mm group, 72% 5 yr survival for 6-15 mm and 57% 5 yr survival for >15 mm. Lymph node metastasis and vascular invasion correlated with fibrosis size and these parameters but not pleural invasion were

significant in multivariate analysis. No lymph node positives were seen in tumors under 6 mm.

Some authors have used a grading system for the fibrosis. In a study of 200 adenocarcinomas under 3 cm, Yokose et al⁵ identified male gender, age, vascular invasion, pleural invasion, node metastasis, and high fibrosis grade as an indicator of poor prognosis. Using a modified scar grading system, Maeshima et al⁶ studied 239 adenocarcinomas and demonstrated better survival in patients with scar grades of one and 2 than 3 and 4 after 10 years. Scar grade was an independent predictor of survival along

with stage, nodes, lymphatic permeation, and pleural involvement. Scar grade was significant in patients with stage 1A disease and in tumors under 2 cm. In light of the significance of these findings, examination of scar grade definition is warranted. These authors used the following scheme:

- Grade 1 – no desmoplasia
- Grade 2 – sparse desmoplastic reaction
- Grade 3 – Dense desmoplastic reaction < or equal to 1.0 cm
- Grade 4 - Dense desmoplastic reaction > 1.0 cm.

While the significant difference between low and high scar grade was reported, the ten year survival was 89% in the Grade 2 and 100% in the grade 1, and 9 of 61 (15%) patients with modified scar Grade 2 had lymph node metastasis. Therefore while modified scar Grade 2 identified a group of patients with better survival than those of grade 3 and 4, it perhaps defined a group that was intermediate between the pure BAC and the frankly invasive mixed subtype carcinoma rather than defining an amount of invasion that was clinically and biologically insignificant.

In a more recent study, Sakurai et al⁷ examined 380 peripheral adenocarcinomas less than or equal to 2 cm. These authors used a differing grading system, attempting to define differences between invasion at the periphery of the scar and invasion into the scarred area. While one of the conclusions of the study was that invasion into the scar was associated with both pleural and vascular invasion as well as with node positivity and poor outcome, a second conclusion of the study was that only 3.3% of the 91 patients with fibrosis less than 6 mm had recurrence, and importantly 100% were alive at seven years.

All of the above studies were conducted in Japan. This has led to speculation that lung adenocarcinoma in Japan represents a distinct epidemiological entity. Also possible is that early detection of cancer as well as potentially a better understanding of the histopathological features of invasiveness was the underlying cause of this regional concentration. In a study of a European population, Rena et al⁸ studied 28 bronchioloalveolar carcinomas and 80 adenocarcinomas, with the finding that there was a lower rate of recurrence and a higher rate of disease-free survival among bronchioloalveolar carcinoma patients. In a recent study from New York University, Yim et al⁹ demonstrated a survival difference between tumors with less than or equal to 5 mm of invasion and those with greater than 5 mm of measured invasion among stage 1 and 2 lung adenocarcinomas. In addition to showing results similar to prior study of Japanese patients, they also confirmed that the micropapillary pattern has a poor prognosis. In a series of 178 patients with lung adenocarcinomas resected between 1996-2000 Columbia Presbyterian in New York, measured invasive size was associated with survival in all

- Different scar assessments in various studies identifies somewhat different survival strata.
- Measured invasion in European and US based studies show similar findings to Suzuki et al – up to 5 mm of invasion shows excellent survival

patients, stage 1 and 2 patients, and stage 1 patients only. In multivariate analysis, measured invasive size but not gross size, age, node metastasis and visceral pleural invasion were associated with survival, and among stage 1 patients, only age and invasive size were associated with survival after multivariate analysis. When examining tumors with less than 6 mm of invasion, no

cases of lymph node metastasis were recorded. When comparing these results of those of Suzuki et al⁴ published in 2000, there are more similarities than differences in the conclusions despite different observers studying different patient populations.

In the course of these studies there has been a focus on non-mucinous bronchioloalveolar carcinoma, and despite differences in methodology, some similarities in the conclusions reached. Pure non-mucinous bronchioloalveolar carcinomas, when solitary, are associated with a very high 5 and 10-year survival and are not associated with lymph node metastasis. When measured invasive size (whether by size of fibrosis as a surrogate for invasion or linear extent of invasion) is greater than 5 mm, the rate of node metastasis increases and survival rates decrease. What remains unclear is the best threshold for measurement of microinvasion, the best method for measurement of invasion, and importantly the reproducibility of measurements of invasion. It is likely that establishing clear criteria for invasion and methods for its measurement may improve reproducibility.

Pathologic reproducibility was examined by Noguchi et al¹⁰ in 2005. They reviewed 32 cases with expert and non-expert evaluators. They also assessed the effect of training and education. The co-incidence rates with high among experts, and improved among non-experts with education. In the Columbia series, one year of cases were reviewed by 3 pathologists using criteria for invasion and invasion measurements obtained. The intraclass correlation coefficient was .854, and the kappa for pure BAC, “microinvasive” foci ≤ 0.5 cm and >0.5 cm ranged from .49 to .64, a moderate level of agreement.

Therefore, criteria for invasion are of importance. When tumor breaks into vessels, lymphatics, airways or pleura, invasion is easier to identify. True desmoplasia is a helpful feature, and as are architectural patterns of invasive adenocarcinoma such as solid or papillary growth. Somewhat more subjective are growth patterns not consistent pre-existing alveoli such as single cells, angulated glands or cribriform structures, but these too favor invasion. Alveolar collapse and fibrosis may also indicate invasion, but these criteria in isolation may be difficult to apply.

Papillary growth and stratification are frequently problematic in mixed subtype tumors versus BAC and likely contribute to some difficulties in reproducibility in classification. It is unclear whether any stratification is allowable in BAC, but true papillary growth is an invasive pattern and places a tumor out of the BAC category. Aida et al¹¹ studied predominantly papillary tumors as well as BAC tumors. Papillary tumors had survival similar to other invasive adenocarcinomas.

Micropapillary patterns have been shown to be associated with lower 5 year survival. It is unclear whether small foci of micropapillary pattern invasion would have a different impact on a microinvasive definition than other patterns.

As noted previously, this discussion is focused on non-mucinous BAC. While mucinous BAC also grow along pre-existing alveolar walls, their radiologic appearance may be more solid due to intra-alveolar mucin. They are less often solitary, and may be less indolent. In addition, the molecular basis of mucinous BAC appears to differ from that of non-mucinous and mixed non-mucinous/mucinous tumors. Several studies have confirmed a high rate of EGFR mutations in non-mucinous BAC and mixed subtype tumors, ranging from 47% to 88%, while lower rates (0-22%) in mucinous BAC¹²⁻¹⁵. In contrast, activated Kras mutations were seen in 67-85% of mucinous BAC and a low rate

(0-17%) in non-mucinous BAC, mixed subtype AdCa with non-mucinous BAC component and mixed non-mucinous/mucinous BAC¹²⁻¹⁵. Given the difference in molecular pathogenesis and possibly biologic behavior, it remains justified to consider mucinous BAC a different entity.

It could be argued that an important decision regarding the surgical approach of bronchioloalveolar carcinoma or mixed subtype adenocarcinoma, that is wedge resection versus anatomic resection, may need to be reached prior to the time that the pathologist can entirely submit the tumor. One approach would be evaluation of radiologic parameters such as CT scanning and PET scanning. As will be shown in the brief comments that follow, these methods also require examination for reproducibility and prognostic ability.

Given the increasing role of CT scan in the evaluation of pulmonary nodules, this methodology may be useful in determining microinvasion and invasion. The correlation between a bubble-like¹⁶ or air-density containing tumor (called a ground glass opacity or GGO) and BAC histology is very good. When solid components are identified, this is frequently associated with invasion. In a series of 69 cases of CT scan detected GGO, Suzuki et al¹⁷ found that of 38 pure GGO without solid areas, 32 were BAC and 6 were AdCa. In a study of pure GGO and mixed GGO, Nakata¹⁸ reported 62 of 70 pure GGO were BAC, and no pure GGO were over 1.5 cm. They also noted that of pure GGO and mixed GGO lesions less than 1.0 cm, 4 of 60 or 6.6% were AdCa. Takashima et al¹⁹ studied reproducibility among radiologists for 5 parameters including percent GGO and found kappas ranging from .51 to .75. Patients with Noguchi A and B lesions had better survival than those with C and D lesions, and lesions with GGO percentage over 57% had better survival. Other studies have shown that high percentage GGO lesions are more likely BAC, although mixed adenocarcinomas are also seen as GGO lesions, and BAC lesions are identified among tumors with <50% and <10% CT scan GGO²⁰. In another series, 94% of Noguchi A were pure GGO, and Noguchi A, B and C lesions had 92%, 52% and 20% GGO component, respectively²¹. Therefore while not perfectly predictive and subject to interobserver differences, GGO percentage as an estimate of tumor invasiveness and subsequent survival has been demonstrated by several groups^{20, 22}, and this is especially useful in tumors under 1 cm.

- **Pure GGO are frequently but not exclusively BAC**
- **Not all BAC are pure GGO**
- **Some mixed GGO are BAC**
- **Some threshold GGO percentage is associated with improved survival**
- **Interobserver reliability is moderate**

Given the observation that pure and mixed/part solid GGO frequently are histologically proven to be non-invasive BAC tumors, a challenge has been made to the accepted data favoring anatomic lobectomy over wedge in the treatment of lung cancer. In 1995, Ginsberg and Rubinstein²³ reported 122 limited versus 125 anatomic resections for T1N0 lung cancers. Recurrence and locoregional recurrence rates were higher for the limited resection group. However, as the basis for this observation is thought to be microscopic spread within the vascular/lymphatic bed of the primary tumor, the lack of

invasion in BAC (Noguchi A) and low frequency of lymph node metastasis in < 6mm invasive mixed subtype adenocarcinoma (?Noguchi B) may allow for limited resection in this subgroup of patients. Asamura et al²⁴ reported no recurrence for the 12 patients with tumors under 1 cm and GGO appearance that were removed by wedge. Watanabe et al²⁵ reported 14 GGO patients proven to have BAC were free of death or relapse after 32 months. The answer to the question of limited versus anatomic resection may require a randomized prospective trial within this subgroup of tumors and such trials are underway that may address this issue further (e.g. CALGB 140503: A Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (≤ 2 cm) Peripheral Non-Small Cell Lung Cancer). For the pathologist, some aspects of this decision tree may be quite challenging. Intraoperative consultation, for example, in deciding limited resection versus anatomic lobectomy, may be quite difficult, and perhaps more accurate in cases of unequivocal invasion than in diagnosing pure BAC. If limited resection would apply to all cases under 2 cm independent of histology the decision tree would be simplified, but this remains to be determined.

While it appears that small pure and mixed GGO may correlate with pathologic BAC, it is also clear that some cases are not predicted by this approach and that interobserver reliability may impact this clinical decision. PET scanning may contribute to the decision tree, as a positive PET lesion may have a greater likelihood of invasion. It is also possible that the contribution of molecular data may also help stratify and guide therapy.

The identification of a solitary GGO leads to a period of watchful waiting and eventually resection if non-resolving. A high percentage GGO and possibly absence of PET positive signal followed by pathologic diagnosis of BAC is associated with an excellent prognosis. It is likely that a small focus of invasion in such lesions, up to 5mm of invasion, does not change this excellent prognosis. In mixed subtype adenocarcinoma, measurements of invasion may be more accurate at survival prediction than gross size alone, but consensus regarding this measurement has yet to be reached. Whether radiologic assessment can accurately guide decisions regarding limited resection in these lesions, and whether limited resection is equivalent to anatomic resection remains to be determined.

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Current problem areas in the classification of lung tumours

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This talk concentrates on diagnosis of 'rare' lung cancers, using cases referred to our institution for specialist opinion in the past five years to explore controversies over proposed new entities, and what is and what is not neoplastic. Auditing of such referrals reveals fairly consistent numbers in the UK where both specialist and general pathologists have the greatest difficulty. Problem areas can be divided into (a) diagnosing adenocarcinoma on small biopsies, (b) the differential diagnosis of mesothelioma, (c) putative rare lung tumours (the subject of this talk), (d) interstitial pneumonias and other diffuse lung diseases and (e) rare non-neoplastic diseases including vascular and systemic disorders.¹

In the group of rare lung tumours, problems not infrequently arise when putative tumour has a prominent lymphoid component. This not only relates to diagnosing lymphoproliferative disease but also distinguishing other tumours or mimics of tumours that are rich in lymphocytes. Whilst primary pulmonary lymphomas comprised a significant number of such referrals in the 1990s, pathologists are now comfortable diagnosing the vast majority of primary pulmonary marginal zone lymphomas and diffuse large B-cell lymphomas, with referral limited to those with atypical presentation. There are however a few cases each year that fail to show light chain restriction or clonality, where the infiltrate is particularly well organised and these should be accepted as nodular lymphoid hyperplasia.² Cases of lymphomatoid granulomatosis (LYG) continued to be referred, and it remains important for the pulmonary pathologist to co-report such cases with experts in lymphoma pathology in order to ensure the best chance of a correct diagnosis. Cases of LYG can show classic morphology without evidence of EBV and/or clonality.

In this area, a new potential entity to consider in addition is hyper IgG4 disease. This term relates to many lymphoproliferative lesions throughout the body, these including idiopathic retroperitoneal fibrosis and sclerosing pancreatitis.³ It manifests as lymphoplasmacytic inflammation with abundant IgG4-positive cells and sometimes exuberant fibrosis which leaves dense fibrosis on resolution. Its relationship to pulmonary hyalinising granuloma therefore requires investigation and such cases need to be distinguished from inflammatory myofibroblastic tumours⁴ and teased from the spectrum of inflammatory pseudotumors,⁵ as during the acute phase, there is usually a good response to steroid therapy.

The group of miscellaneous tumours in the 2004 classification system also remain a source of referral material, although the purist would argue that most cases in this subgroup should now be moved to other categories in order to maintain histogenetic accuracy. Sclerosing haemangiomas (pneumocytomas) were initially thought to be endothelial in origin,⁶ but there is now a consensus that they are predominantly benign epithelial tumors^{7;8} Although most cases are readily diagnosable on biopsy, and criteria are also given for frozen section and cytological diagnosis, rare cases remain where diagnosis is problematic. Such problems tend to arise when presentation is atypical (sites other than the lung and parenchyma such as endobronchial,

mediastinal, nodal metastases, liver metastases) or the tumour itself is atypical (marked pleomorphism, cystic degeneration, 'giant'). Furthermore patients with multiple small bilateral sclerosing hemangiomas combined with tumourlets have been identified, such cases being a recent focus of referral. Follow-up suggests that patients remain stable over years without need for treatment.

Hamartomas should also no longer be considered a miscellaneous tumour, rather classified as a mesenchymal neoplasm on the basis that they show gene mutations similar to those pure mesenchymal tumours, such as lipomas, these relating to the high-mobility group (HMG) proteins.⁹ As for sclerosing haemangiomas, most cases are readily diagnosable on histology, cytology and frozen section, with rare difficulties only occurring when presentation is grossly atypical. Malignant change, although exceptional, can occur. Furthermore, recent publications have described combination of hamartomas with salivary gland-type lung tumours showing myoepithelial differentiation¹⁰ and pulmonary pathologists should be aware of this and other morphological variations in hamartoma. Likewise, clear cell tumors or 'sugar tumors' represent a tumour from the family of PEComas, neoplasms originating from the perivascular epithelioid cells (PEC)¹¹, and should be grouped with other mesenchymal tumours, and thymomas when primary in the lung should be classified as epithelial, thus leaving only melanoma and teratoma in the miscellaneous category.

Unusual variants of salivary gland-type tumours also appear sporadically, especially in the light of recent publications describing new entities such as pulmonary microcystic fibromyxoma.¹² Such tumours may represent monophasic growth of the stromal component of mixed tumours.¹³ Indeed, when confronted with a myxoid/spindle cell endobronchial lesions, one should always consider equally inflammatory polyps or primary/metastatic mesenchymal tumours.

Another area where there have been questions over lung disease being neoplastic is mucinous proliferation in type 1 congenital cystic adenomatoid malformations (CCAM). Mucinous cell hyperplasia without evidence of malignant transformation is reported in about one third of cases, and some have viewed such proliferations as reactive. However, cases with co-existent atypical adenomatous hyperplasia are now described and both intracystic and intra-alveolar areas of mucinous proliferation have been shown to contain K-ras mutation and LOH and/or microsatellite instability at the p16 locus, displaying similar molecular abnormalities and differentiation profiles to those in mucinous bronchioloalveolar carcinoma 'de novo'. Gains in chromosomes 2 and 4 have also been reported in areas of intra-alveolar mucinous proliferation and metastatic disease is occasionally seen, indicating classification as adenocarcinoma is justified.^{14;15} Neoplasms can also cause cystic change as an integral part of the tumour, for example pleuropulmonary blastoma, another area of controversial overlap between neoplastic and non-neoplastic disease given its histological similarities to type 4 CCAMs.^{16;17}

Finally, in relation to carcinoids, the last three years has seen a significant increase in the number of cases presenting with neuroendocrine cell hyperplasia (NEH) and associated neuroendocrine tumours. Whilst the published literature contains only two series of six and five patients, together with scattered case reports, 11 cases have been identified in one department within the past three years. This has come about

primarily through increased accuracy and frequency of screening of patients for metastatic disease identifying small nodules presumed to be metastases. It is now apparent that NEH may also be associated with atypical as well as typical carcinoids, and may be part of the spectrum of Type 1 MEN syndrome.¹⁸ Indeed peripheral carcinoids, which are those typically seen with NEH, may have a differing biology to the more common central tumours, with the peripheral lesions being more commonly spindle in morphology and TTF-1 positive.¹⁹

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