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Progression of probable UIP and UIP on HRCT

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ABSTRACT

Purpose: To determine patterns of progression of probable Usual Interstitial Pneumonitis (UIP).
Methods: This HIPPA compliant, IRB-approved study draws patients from our Fibrosis Registry. All patients with a consensus diagnosis of Idiopathic Pulmonary Fibrosis (IPF) were included. Most recent CT scans and all earlier CT scans were reviewed to determine the fibrosis grade in each lobe based on probable UIP (pUIP) findings of ground glass opacities, traction bronchiolectasis and reticulations or UIP findings of subpleural basilar predominant fibrosis with honeycombing (HC) and absence of features that would suggest an alternative diagnosis.
Results: 103 patients with a working diagnosis of IPF are the focus of this report. Among the 68 with pUIP on the initial CT, 32 (47%) progressed; median time to progression was 51 months. The risk of HC progression, adjusted for gender, of patients with emphysema was 2.53 times higher than patients without emphysema (HR = 2.53, 95% CI: 1.06–6.02). Among the 35 with HC on the initial CT scan, 20 (57%) progressed to more advanced HC; median time to progression was 31 months. Increased pulmonary artery size was significantly associated with an elevated risk for more advanced HC progression (HR = 1.16, 95% CI: 1.04–1.31).
Conclusion: Ground glass opacities, traction bronchiolectasis and reticulations, a "Probable UIP Pattern" by ATS criteria progressed to UIP in 47% of patients on follow-up imaging.

1. Background

Idiopathic Pulmonary Fibrosis (IPF) has the worst prognosis of all the Idiopathic Interstitial Pneumonias with a mean life expectancy of 3.8 years after diagnosis [1]. The American Thoracic Society (ATS) provides guidelines for the diagnosis of IPF. First there must be no known cause for a patient's lung fibrosis after a thorough clinical evaluation including serologic studies. Second the patient must have a CT scan showing a "UIP pattern" defined as sub-pleural basilar predominant fibrosis with HC and absence of features that would suggest alternative diagnoses (Fig. 1). If the patient does not have honeycombing but has sub pleural basilar predominant fibrosis they are said to have a "Probable UIP" pattern (pUIP) by ATS criteria and a biopsy may be necessary for diagnosis [2,3] (Fig. 2).

Until recently the only treatment for IPF was lung transplant which limited the need for identification of early, pre-clinical imaging findings of UIP. In 2014, two new anti-fibrotic medications, Pirfenidone and Nintedanib, were approved in the United States. They target multiple pathways of the fibro-proliferative process of UIP [4]. This stimulated effort to detect IPF in its early, possibly preclinical stage before the advanced disease stage with honeycombing develops. Retrospective review of all earlier CT scans of patients who now have advanced disease that currently meets the ATS criteria for a UIP pattern is a critical first step in identifying early signs of UIP on chest CT.

The purpose of our research project is to evaluate the change in IPF related fibrosis over time with particular focus in the transition from "Probable UIP" to "UIP" pattern to better identify early findings. Our goal is to investigate if "Probable UIP" Pattern is an "Early UIP Pattern" and to identify risk factors associated with progression from "Probable UIP" to "UIP".

2. Methods

2.1. Study design

For this retrospective study, data on all patients with a consensus diagnosis of IPF were identified in our Fibrosis Registry. Consent was obtained from all patients according to a HIPAA-compliant, IRB-approved protocol. Between 2014 and 2017, 121 patients were diagnosed with a working diagnosis of IPF based on clinical presentation, CT

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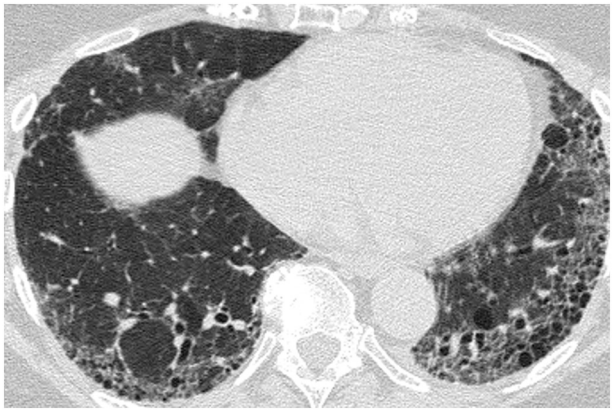

Fig. 1. UIP pattern on HRCT: Subpleural basilar predominant fibrosis with honeycombing which is defined by Webb as "rounded lucencies with shared walls in vertical stacks that are sub-pleural and occur in association with other findings of fibrosis".

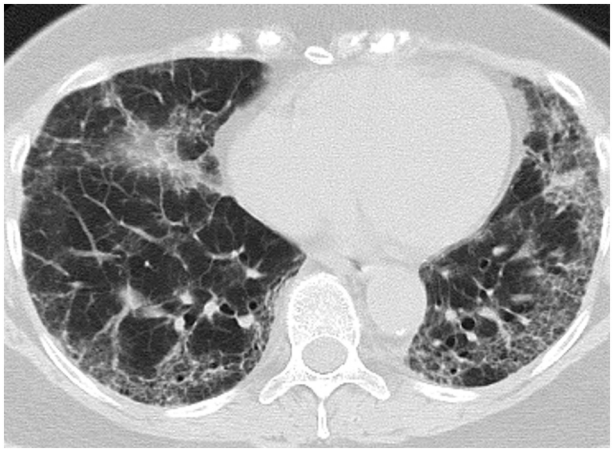

Fig. 2. Early UIP: Same patient several years earlier demonstrates pre-HC findings of sub-pleural, basilar predominant fibrosis with ground glass opacity and traction bronchiectasis representing a combination of alveolar wall thickening giving appearance of GGO and traction bronchiectasis due to increased radial traction on bronchus from collage deposition in alveolar wall.

findings, and pathology when available. This report focuses on the 103 patients (85.1%) who had multiple CT scans. CT readings were performed using standard lung settings (width 1500 HU and level −650 HU). Pattern of Probable UIP or UIP and its extent in each lobe on each CT scan were recorded by consensus agreement of 2 radiologists.

2.2. Probable UIP and UIP patterns

The right upper lobe and right middle lobe were considered as one lobe; thus 4 lobes were evaluated on each CT scan for the presence of reticulations (thickening of the lung interstitium), bronchiolectasis (dilated terminal bronchioles) and honeycombing (clustered cysts in a sub-pleural location) [5–9]. The grading system for extent of Probable UIP (pUIP) and UIP have been previously defined [9] (Table 1). Each lobe was assessed and graded on the stage and extent of disease. If there was HC in any lobe, the patient was considered to have UIP pattern, if not, then the patient was said to have a pUIP pattern. Centrilobular emphysema was defined as focal lucencies measuring up to 1 cm centrally located in the secondary pulmonary lobule with a central pulmonary artery [10].

Advancement of fibrosis on CT, whether it was a change in stage or extent of disease, was called "progression" to distinguish them from clinical "exacerbation". Two groups of patients were defined and classified as either progressors or non-progressors (stable pulmonary fibrosis). Progressors were subcategorized into three groups, progression from pUIP to more extensive pUIP, progression from pUIP to UIP, and progression from UIP to more extensive UIP.

2.3. Statistical analysis

Patients who exhibited only pUIP at initial screening were analyzed separately from patients who presented with HC in at least one lobe on the initial screening. Baseline demographic and CT findings between the two groups were compared. Continuous data are presented as mean (range), or as median (IQR). The Mann-Whitney *U* test was used to assess median differences, and the unpaired *t*-test for mean differences was used for data confirmed to be normally distributed. Categorical data are presented as frequencies and percentages, while group differences were evaluated using Chi-square test and Fisher-exact test.

To evaluate progression to UIP over time, follow-up time was calculated from date of initial CT scan to date of CT scan in which progression to HC was first identified or date of last follow-up scan, whichever came first. Cox proportional hazard regression was used to evaluate risk factors of progression for each analysis. The effect of age, sex and emphysema were each assessed in a univariate model. The effect of relative pulmonary artery (PA) enlargement, defined as a PA to ascending aorta diameter ratio > 1, was also explored. Operating with an entry criteria level set to 0.20, a forward selection procedure was used to arrive at a final adjusted Cox model. Interactions among covariates were also evaluated by likelihood ratio tests. The primary outcome analyses of progression to UIP are demonstrated with Kaplan–Meier survival curves. Log rank test was used to test for significance. All analyses were performed using R software version 3.4.4.

3. Results

Table 2 summarizes the demographic and clinical characteristics of the 103 patients with an average age of 71 (range: 47–91), 64 (62%) men and 39 (38%) women. The average PA size was 28 mm (range: 4–41). The average aorta size was 34 mm (range: 3–48). 25 (24%) had emphysema. The median follow-up time was 25 months. On the initial CT scan, 68 (66%) had only pUIP in all 4 lobes and 35(34%) had honeycombing in at least one lobe of the lung. The frequency of emphysema was significantly higher among patients with HC at baseline compared to those with pUIP at baseline (42% vs. 15%, p = 0.003).

Progression to UIP was observed in 32 (47%) of the 68 patients with pUIP on the initial CT scan (Table 3a), and the median time to progression was 51 months. The difference in duration of follow-up was not statistically significant between patients who had progression and those who did not (29 vs. 23 months, p = 0.28) (Table 3a). Using Cox proportional hazard regression to model time to progression to UIP among the 68 patients with pUIP, univariate analyses showed that gender (p = 0.08), pulmonary artery size (p = 0.10) and emphysema (p = 0.01) met the model entry criteria and were thus eligible for inclusion in the multivariable analysis (Table 3). Patients with emphysema had 3.04 times the risk of progression to HC compared to patients without emphysema (HR = 3.04, 95% CI: 1.32–6.98). Increasing size of pulmonary artery (HR = 1.06, 95% CI: 0.98–1.13) and being male (HR = 2.15, 95% CI: 0.90–5.12) both increased the risk of progression to HC, but were only of borderline significance (Table 4).

The final Cox proportional hazard model included gender and the presence of emphysema (Table 4). Although the risk of progression to HC for males was 1.73 times that for females, (HR = 1.73, 95% CI: 0.69–4.33), the difference was not statistically significant. Comparing patients with and without emphysema, progression to UIP among those with emphysema was 2.53 times higher than those without emphysema (HR = 2.53, 95% CI: 1.06–6.02). Among participants with pUIP on the initial CT scan, emphysema was the only independent predictor for progression to UIP. Fig. 3 shows the Kaplan-Meir estimates of the

Table 1
Grading of idiopathic pulmonary fibrosis on chest CT.

Grade	Description
pUIP1	- Reticulations, traction bronchiolectasis and ground glass opacity 10% of transverse diameter of hemithorax or less
pUIP2	- Reticulations, traction bronchiolectasis and ground glass opacity 11–25% of transverse diameter of hemithorax
pUIP3	- Reticulations, traction bronchiolectasis and ground glass opacity 26% - 50% of transverse diameter of hemithorax
pUIP4	- Reticulations, traction bronchiolectasis and ground glass opacity > 50% of transverse diameter of hemithorax
UIP1	- Peripherally stacked cysts measuring 10% of transverse diameter of hemithorax or less
UIP2	- Peripherally stacked cysts measuring 11–25% of transverse diameter of hemithorax
UIP3	- Peripherally stacked cysts measuring 26% - 50% of transverse diameter of hemithorax
UIP4	- Peripherally stacked cysts measuring > 50% of transverse diameter of hemithorax

Table 2
Patient characteristics.

	All (N = 103)		PREHC baseline (n = 68)		HC baseline (n = 35)		P-value
Age (y)	70.9	(47–91)	70.6	(47–91)	71.5	(52–89)	0.64
Male	64	62%	49	72%	15	43%	0.05
Pulmonary artery size (mm)	27.9	(4–41)	28.1	(17–39)	27.5	(4–41)	0.32
Aorta size (mm)	33.7	(3–48)	34.1	(27–48)	32.6	(3–46)	0.59
PA: A > 1	7	6%	3	4%	4	11%	0.20
Emphysema	25	24%	11	16%	14	40%	0.004
Follow-up time (months), median (IQR)	25	(14, 47)	28	(14, 49)	21	(14.75, 35)	0.23

Summaries presented as mean, (range) unless otherwise indicated. PA:A = relative pulmonary artery (PA) enlargement.

Table 3
Demographics of patients with probable UIP and UIP on initial CT scan.

a) Patients with pUIP on initial scan (N = 68)

	Progression pUIP-UIP		P-value	Total (n = 68)
	No (n = 36)	Yes (n = 32)		
Gender				
Male	22 (61%)	24 (75%)		46 9 (68%)
Female	14 (39%)	8 (25%)	0.34	22 (32%)
Age, mean (SD)	70.2 (8.4)	71.8 (7.4)	0.40	70.9 (7.9)
Follow-up duration (month), median (IQR)	23 (11.00, 50.25)	29 (14.75, 48.00)	0.28	26 (14.00, 50.25)

b) Patients with UIP on initial scan (N = 35)

	Progression UIP-UIP		P-value	Total (n = 35)
	No (n = 15)	Yes (n = 20)		
Gender				
Male	11 (73%)	7 (35%)		18 (51%)
Female	4 (27%)	13 (65%)	0.06	17 (49%)
Age, mean (SD)	69.4 (9.3)	72.4 (9.4)	0.43	70.9 (9.3)
Follow-up duration (months), median (IQR)	20 (5.00, 33.50)	24 (3.00, 38.25)	0.36	21 (14.50, 36.00)

median time to progression for patients with and without emphysema which was 23 months and 66 months, respectively (Log rank p = 0.006).

While 36 patients with pUIP on initial CT had no progression to UIP (Table 3a), 16 of them had progression to more extensive pUIP with a median follow-up of 23 months. Out of the 35 patients with UIP at the initial CT reading, progression was observed in 20 patients (Table 3b), with a median time to progression of 31 months. Women with UIP at initial scan progressed more frequently than men (65% vs. 35%, p = 0.06). The difference in duration of follow-up was not statistically significant between the 20 patients who progressed to more extensive UIP and the 15 patients with stable UIP (24 vs. 20 months, p = 0.36) (Table 3b). Using Cox proportion hazard model with p-value < 0.20 as model entry criteria, univariate analysis suggested that pulmonary artery size (p = 0.02), aorta size (p = 0.18) and emphysema (p = 0.19) met the criteria for inclusion into the multivariable model. Univariate analysis also showed that pulmonary artery size was a significant independent predictor for HC progression (HR = 1.14, 95% CI: 1.02–1.27). The final Cox adjusted model included pulmonary artery size, aorta size, and emphysema (Table 5) but only pulmonary artery size remained significant. A 1 mm increase in pulmonary artery size was significantly associated with a 16% increase in the risk of progression to more extensive UIP (HR = 1.16, 95% CI: 1.04–1.31).

Table 4
pUIP-to-UIP progression.

Variable	Univariate results			Multivariable results		
	HR	P-value	95% CI	HR	P-value	95% CI
Age (y)	1.01	0.55	0.96–1.06			
Male vs. female	2.15	0.08	0.90–5.12[a]	1.73	0.23	1.06 - 6.02
Pulmonary artery size (mm)	1.06	0.10	0.98–1.13[a]			
Aorta size (mm)	1.02	0.64	0.93–1.11			
Emphysema (yes vs. no)	3.04	0.01	1.32–6.98[a]	2.53	0.04	0.69 - 4.33

[a] Variables meeting entry criteria α ≤ 0.20.

4. Discussion

Although the cause of idiopathic pulmonary fibrosis is uncertain, risk factors for increased fibrogenesis within the lung include smoking and genetic mutations [1]. Ultimately, the cause of fibrosis is likely multifactorial. Patients with IPF complain of shortness of breath and cough; on physical exam they may have basilar crackles and finger clubbing and on pulmonary function tests demonstrate a decreased DLCO and FVC with an increased FEV1 [2].

The clinical course of IPF is characterized by exacerbations which decrease patient's functional status and can be deadly. Clinically, we considered the advancement of lung fibrosis on chest CT as “progression” to distinguish them from their clinical counterpart “exacerbation”. Among the 68 patients with pUIP on initial scan, we found that 32 patients had such progressions while 36 remained stable. Although the difference in follow-up duration was not significant, the average follow-up was longer for progressors than for the stable group. Our small sample size may have limited the statistical power to detect the difference in follow-up between these two groups.

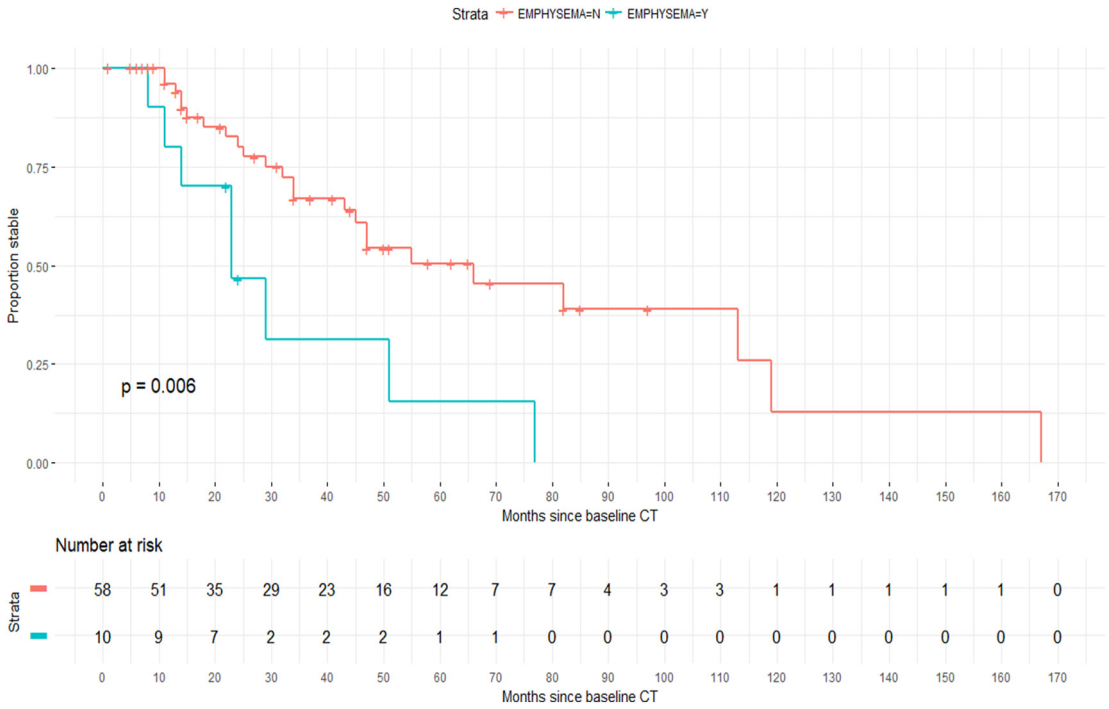

Fig. 3. Kaplan-Meir estimates of the time to progression for patients with and without emphysema.

The ATS have provided criteria for the diagnosis of UIP on HRCT demonstrating sub-pleural, basilar predominant fibrosis with reticulations and honeycombing and absence of features that would suggest an alternative diagnosis. A probable UIP pattern by ATS criteria includes the same criteria but without honeycombing [3]. Raghu found that 79 of 84 patients with clinical IPF and a "possible UIP" pattern on CT when biopsied had UIP proven histology [11]. Our findings of ground glass opacity and traction bronchiectasis representing probable UIP concur with those of Raghu. In another study, Yagihash demonstrated that in a cohort of 64 patients with clinical IPF and a possible UIP pattern on CT, 60 (94%) had UIP or probable UIP on pathology [12] and suggested given a clinical diagnosis of IPF and "possible UIP" pattern on CT, lung biopsy may not be necessary. Chida and Hutchinson found post-operative complications occurred more frequently in patients with lung fibrosis [13,14] providing increased impetus to make the diagnosis of UIP on CT and avoid biopsy.

Our results bring up important questions. First, should pre-clinical disease be treated? Current treatments slow progression but do not reverse disease. Gruden found that of 38 patients with clinical IPF and PREHC pattern, 15 died of lung disease and 16 patients had disease progression [15], supporting the use of pharmacological intervention earlier in the disease before honeycombing is present. Albera's review demonstrated that patients with both early and later stage disease showed similar benefits from the anti-fibrotic medication pirfenidone [16].

Second, what is the appropriate CT follow-up interval for patients with fibrosis? Since the majority of patients in our study showed progression on 12–24 month follow up exam, 1 year would appear to be the appropriate follow-up interval. As many of these patients have a significant smoking history and are thus at increased risk for lung cancer, the one-year follow-up could fulfill the need for lung cancer screening and evaluation of ILD progression.

It is interesting that patients with pUIP were more likely to have emphysema than those presenting with HC. Perhaps it is the emphysema in the first group that brings them to clinical attention and the fibrosis is noted incidentally. Also, the presence of emphysema was a sign of worse prognosis in pUIP group, not only for likelihood to progress but speed of progression. This might support early treatment especially in this subset at highest risk. Pulmonary artery size is available on all CT scans and should also be reported as a one mm increase in pulmonary artery size was significantly associated with a 16% increase in the risk of acceleration which is helpful in counseling patients.

Our study has several limitations. It is a retrospective single institution study with a relatively small sample size. Due to the retrospective nature, assessment of extent of fibrosis can only be performed on available CT images which are often on different machines using different techniques. Patients without any CT scan prior to diagnosis of IPF or prior CT scans that were performed at another institution and unavailable were not included, which may be a source of bias. Long

Table 5
UIP to more extensive UIP progression.

Variable	Univariate results			Multivariable results		
	HR	P-value	95% CI	HR	P-value	95% CI
Age (y)	1.00	0.93	0.95–1.05			
Gender (male vs. female)	0.96	0.94	0.37–2.52			
Pulmonary artery size (mm)	1.14	0.02	1.02–1.27[a]	1.16	0.01	1.04 - 1.31
Aorta size (mm)	1.04	0.18	0.98–1.11[a]	1.05	0.17	0.97 - 1.15
Emphysema (yes vs. no)	0.54	0.19	0.21–1.37[a]	0.50	0.18	0.18 - 1.37

[a] Variables meeting entry criteria $\alpha \leq 0.20$.

term follow-up (after 60 months) was only available in a small number of patients, which may have a negative impact on the reliability of the survival estimates. Future prospective studies with a larger patient population and longer follow-up time might address these issues by increasing power, minimizing selection bias and improving generalizability of the study.

CT is currently the best test for the early, pre-clinical diagnosis of IPF and has the potential to be the best test for evaluation of the extent of disease and its progression in vivo [1]. The earliest CT findings of UIP were sub-pleural, basilar predominant ground glass opacity with traction bronchiectasis. On follow-up imaging this early pattern of fibrosis progressed to honeycombing in a high percentage of patients, particularly if followed for a prolonged period of time suggesting that "probable UIP" may be "early UIP".

Declaration of Competing Interest

Mary Salvatore- Speaker Genentech, Boehriger Ingelheim, Rockpointe, and Eastern Pulmonary Conference.

Maria Padilla-Speaker Genentech, Consultant Boehringer Ingelheim.

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