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Radiographic Progression and Survival of the Different HRCT Patterns of Idiopathic Pulmonary Fibrosis

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Abstract. *Introduction.* Idiopathic pulmonary fibrosis (IPF) is a chronic disease with a peculiar (typical) HRCT pattern, but biopsy can demonstrate usual interstitial pneumonia in patients with atypical patterns. It is unknown how progression pattern varies among different radiographic presentations of IPF. We sought to investigate the longitudinal radiographic evolution and survival of typical and non-typical patterns. *Materials and Methods.* One-hundred-twenty-three patients diagnosed with IPF in 2 tertiary referral hospitals were included in the study. Longitudinal evolution of non-typical patterns was considered. The HRCT visual fibrosis score was used as a reliable evaluation tool of disease progression. HRCTs were scored by 2 senior chest radiologists with ILD expertise. The primary endpoint was the evolution of the presentation pattern to probable or typical. The secondary endpoint was lung transplant (LTx)-free survival from the time of diagnosis. *Results.* Average interval between HRCTs was 16±5 months; average follow-up after the 2nd HRCT was 17±11 months. Four out of 45 (8.9%) patients with probable pattern "evolved" to a typical pattern of IPF, while 5 out of 31 (16.1%) with indeterminate/alternative pattern "evolved" to probable pattern. An average HRCT fibrosis score increase of 9±11% was observed with typical (n=49), 6±5% with probable (n=43) and 7±8% (n=31) with indeterminate/alternative presentation pattern. LTx-free survival and lung function declines did not show any difference related to presentation HRCT patterns. *Conclusions.* The evolution of a non-typical UIP pattern to a typical one is infrequent. All presentation HRCT patterns of IPF evolve in similar way and are associated with comparable survival time.

Keywords: usual interstitial pneumonia, idiopathic pulmonary fibrosis, high-resolution chest CT scan, fibrosis score, progression.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with a histopathologic pattern of usual interstitial pneumonia (UIP) (1).

High-resolution chest CT scan (HRCT) of the chest has become the standard radiographic evaluation tool in all interstitial lung diseases (ILDs), providing pivotal diagnostic and prognostic information. Key parenchymal abnormalities that can be assessed and quantified include ground-glass opacities, consolidation, reticulation, traction bronchiectasis and honeycombing, as well as their distribution (2). According to current international guidelines, the HRCT plays a key role in establishing a diagnosis

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of IPF by recognizing an "UIP" pattern, based on specific radiographic features (1,2). Both ATS/ERS (1) and Fleischner (2) guidelines describe 4 different HRCT patterns that can be found when a diagnosis of IPF is being considered: "UIP pattern", which eliminates the need for a surgical lung biopsy; a "probable UIP" pattern; a "indeterminate UIP pattern" and "alternate diagnosis" pattern. After excluding all known causes of interstitial lung disease (ILD), a surgical lung biopsy is generally recommended, when possible, in patients presenting with either of the last 2 patterns.

Several methods exist to evaluate the extent of lung fibrosis on HRCT and to assess disease progression: visual scores (3,4) and automated methods (5,6). We recently found that the HRCT visual fibrosis score is a reliable and responsive tool to detect clinically meaningful disease progression (7).

The clinical course of IPF, whether diagnosed based on clinical-radiographic criteria or biopsy-proven, is highly variable and difficult to predict (8). The longitudinal evolution of the presentation pattern of IPF and its prognostic implications have received very little attention in the literature (9,10). The aim of this study was to investigate the differences in terms of longitudinal disease progression among different presentation patterns (typical, probable, indeterminate, alternative diagnosis) of proven IPF, and to investigate the frequency of evolution to a (more) typical pattern among less typical presentations. We utilized HRCT fibrosis visual score (9,11) as a reliable evaluation tool of disease progression and longitudinally followed. Lung function declines and survival according to presentation pattern were considered.

Methods

Subjects

One hundred twenty-three consecutive patients diagnosed with IPF were enrolled by 2 participating centers, London, ON, Canada and Rome, Italy. The diagnosis of IPF was based on the ATS/ERS/JRS/ALAT guidelines (1) in the context of the multidisciplinary discussion (MDD) (12). Patients with radiographic pattern compatible with hypersensitivity pneumonitis (HP) and/or who had an exposure concerning for HP were excluded. Patients with typical or probable pattern were diagnosed with IPF based on clinical-radiographic criteria, after excluding all known causes of ILD. Patients with indeterminate or alternative pattern were diagnosed with IPF based on clinical-radiographic-pathologic criteria. Patients who had 2 consecutive HRCT and at least 1 year of clinical follow up from the time of diagnosis were included in the study. Patients with any other type of ILD were carefully excluded. The follow-up HRCT was ordered by the attending physician, as clinically indicated.

Out of one hundred twenty-three patients, a total of thirty-seven (30%) received a surgical lung biopsy, specifically:

- fourteen out of 49 patients with typical pattern (28%);
- eight out of 43 patients with probable pattern (19%);
- four of 5 patients with indeterminate pattern (80%);
- eleven of 26 patients with alternative diagnosis (42%).

Cases who did not undergo a to undergo a surgical lung biopsy despite a no-typical pattern had contraindications and, as such, were not deemed medically safe to undergo the procedure. Criteria used during multidisciplinary discussion to conclude on a diagnosis of IPF included the radiographic evolution from available, previous x-rays/CT scans, the clinical-functional evidence of progression, the age of the patient and lack of any known cause of interstitial lung disease.

The average interval between baseline and follow-up HRCT was 16±5 months. Demographic characteristics and pulmonary function tests were compared among the different HRCT presentation patterns. transplant (LTx)-free survival was considered from the time of diagnosis (baseline HRCT).

The primary endpoint was the evolution of the presentation pattern to probable or typical.

LTx-free survival was considered as the secondary endpoint. Of note, all patients included in the study who received a LTx were from Ontario, where there is no specific age limit for LTx eligibility. The latter depends on the actual functional status of the patient, frailty, comorbidities, physiotherapy output and supports in place (13).

HRCT

The overall extent of pulmonary fibrosis was evaluated with a quantitative visual score, as previously described (9,11,14). Two chest radiologists from different institutions, with specific ILD expertise and over 20 years' experience in cardio-thoracic imaging (M.Z., G.S.), who were blinded to clinical information, separately assessed the pattern and scored each case and the average score was calculated. HRCT images were assessed for the presence and extent of parenchymal abnormalities, including ground-glass opacities, reticular opacities, traction bronchiectasis and honeycombing. A 5-point scale (0 = absence of lesions, 1, 2, 3, 4 = extent of lesions, respectively, <25, 25-50, 50-75, >75%) was used to determine the extent of overall fibrotic lung disease. The scores assigned for each scan at 4 predefined levels (aortic arch, bronchus intermedius, pulmonary veins, lowest scan) and each hemithorax were summed, and a final value was obtained: score = 100/maximum predicted value (equivalent to 8 times the number of scans performed). The extent of fibrosis was expressed as a percentage of the total lung volume. Baseline and follow-up HRCT fibrosis visual scores were calculated. Examples are shown in Figure 1.

Statistical Analysis

Values are expressed as mean ± standard deviation. The Kolmogorov-Smirnov test was used for distribution analysis. One-way ANOVA analysis was used to compare patients grouped based on the presentation HRCT pattern. Lung transplant-free survival was evaluated using Kaplan-Meier curves and the log rank test. P values <0.05 were considered statistically significant. GraphPad (MacKiev, San Diego, CA) software was used.

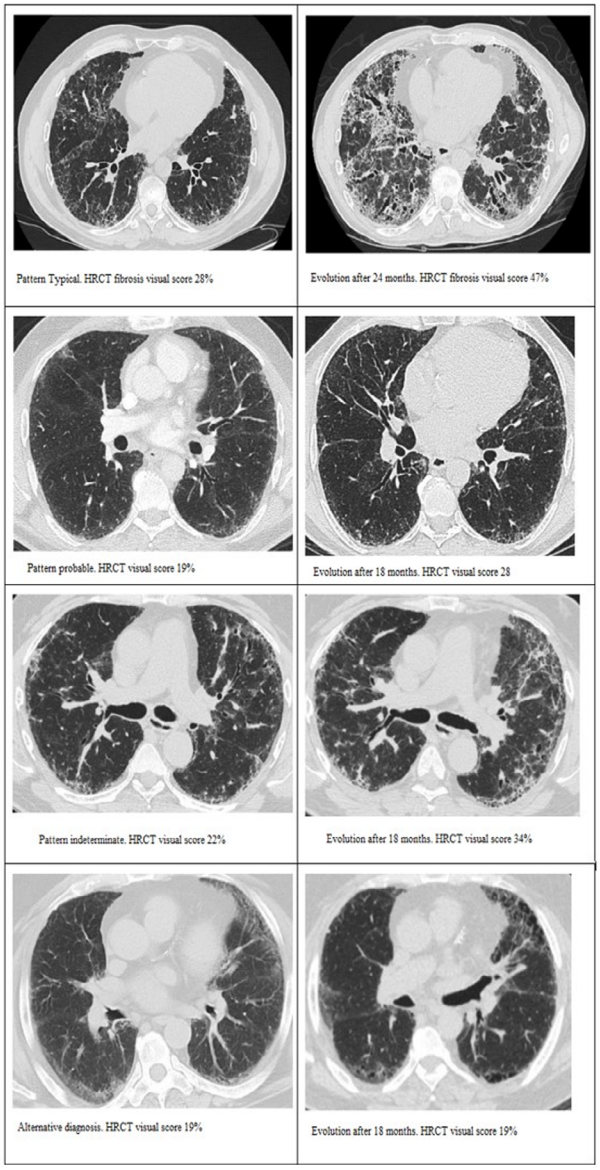

Figure 1. Examples of typical, probable, indeterminate and alternative patterns of UIP and their progression in our cohort.

Results

Average age was 70±8 years, body mass index 30±5 kg/m^2, with male predominance (72%). Forty-six patients (37%) had concomitant emphysema. The average extent of fibrosis at baseline was 24±13%. Lung function at the time of diagnosis was on average mildly compromised, with forced vital capacity of 77±20%, total lung capacity of 72±16% and diffusing lung capacity for carbon monoxide of 51±18%. No significant demographic or functional differences among patients grouped based on the HRCT patterns were observed.

The average interval between baseline and follow-up HRCTs was 20.4 months (range 18-24 months), with no significant different among patients grouped based on presentation patterns. Longitudinal evolution of non-typical patterns was considered. Four out of 45 (8.9%) patients with probable pattern "evolved" to a typical pattern of IPF (Figure 2A).

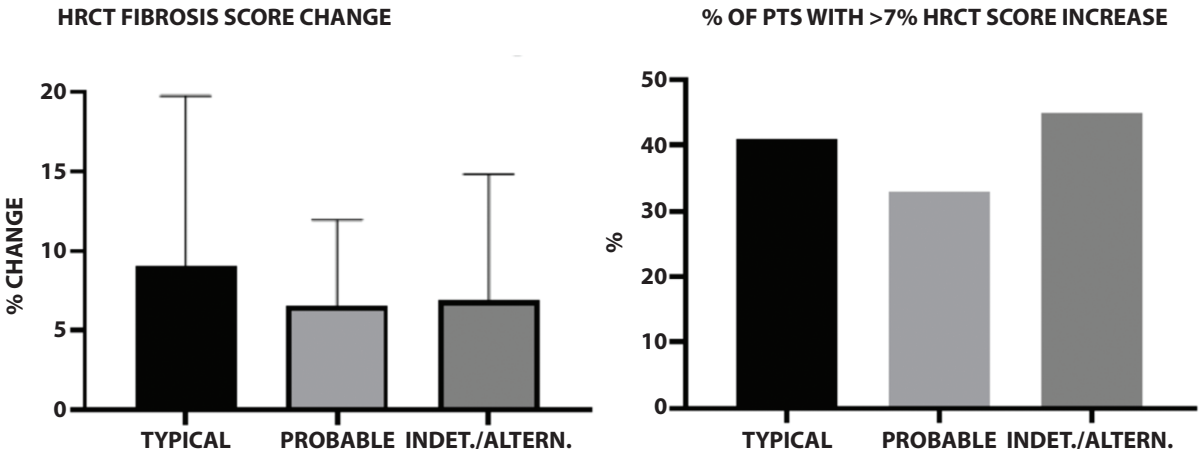

Figure 2. Evolution of HRCT pattern at the follow-up scan. A. Probable at baseline. B. Indeterminate/Alternative at baseline. In the great majority of cases, the pattern did not change.

Among patients with indeterminate/alternative presentation pattern, 5 out of 31 (16.1%) "evolved" to probable pattern, while none evolved to a typical pattern (Figure 2B).

The average progression of fibrosis was 7±8%, and this was a significant increase from baseline. An average HRCT fibrosis score increase of 9±11% was observed with typical (n=49), 6±5% with probable (n=43) and 7±8% (n=31) with indeterminate/alternative presentation pattern (Supplemental Figure 1). There was overall no significant difference among presentation patterns in terms of rate of fibrosis progression (Figure 3). Forty-eight patients had an increase >7% of fibrosis, which is associated with shorter survival. The proportion of patients with >7% of fibrosis was not significantly different among presentation patterns (Supplemental Figure 1). There were 5 cases of acute exacerbations (3 passed away, 1 survived and 1 had an emergent LTx) and 4 cases of lung cancer (1 survived with lung resection, 3 passed away).

Lung function data were also longitudinally followed in all patients. In the typical pattern group, the average change in forced vital capacity (FVC) was -6±16 % pred, total lung capacity (TLC) change was -4±12 % pred and diffusing lung capacity for carbon monoxide (DLCO) change was -10±14 % pred. In the probable pattern group, average change in FVC was -3±10 % pred, TLC change was -5±11 % pred and DLCO change was -7±10 % pred. In the indeterminate/alternative pattern group, average change in FVC was -3±10 % pred, TLC change was -3±8 % pred and DLCO change was -4±11 % pred. No significant differences were observed among the 3 groups in terms of lung function longitudinal changes. These data are consistent with both the expected pattern of progression and with the significant variability in longitudinal deterioration commonly observed among patients with IPF.

Average follow-up after the 2nd HRCT was 17±11 months. After a post-diagnosis follow-up period of 33±10 months, there were 44 deaths (36%) and 11 (%) LTx, while 68 patients (%) were alive without LTx. Outcomes were very similar among different HRCT patterns. LTx-free survival was in fact not significantly different among presentation HRCT patterns (Figure 4).

Discussion

IPF is the most lethal of all ILDs, with average survival of only 3-5 years, in the absence of therapy (15). Consistently, HRCT typical patterns for UIP with honeycombing and peripheral, bibasilar distribution, is associated with poor survival (8). It was however unknown whether other presentation HRCT patterns of IPF are associated with similar progression, and whether an evolution of the pattern in atypical cases towards more consistent features of UIP would be associated with poorer outcome or not.

The results of our study show that evolution of the pattern is very infrequent among atypical presentation of IPF, but, despite this, the rate of progression of fibrosis is very similar among all presentation

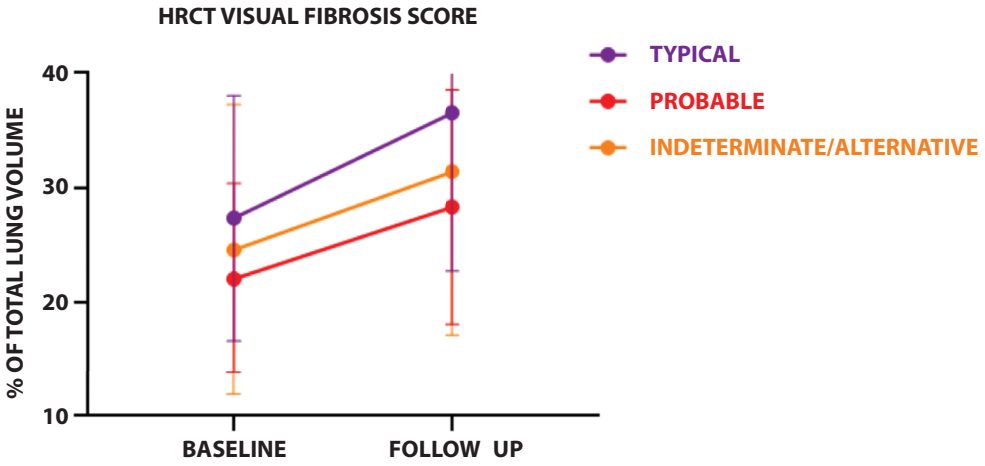

Figure 3. Average progression of the HRCT visual fibrosis score observed in the different patterns of IPF. No significance difference among baseline patterns was observed.

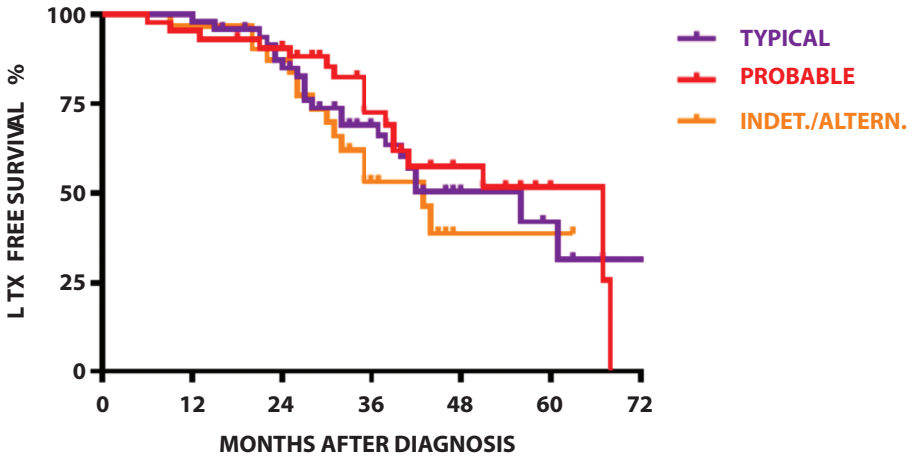

Figure 4. Kaplan-Meier curves showing survival of patients grouped according to their baseline HRCT pattern. No significant differences were observed.

patterns. Furthermore, no differences in LTx-free survival among HRCT patters were observed. The longitudinal decline of pulmonary functional data was also very similar across different radiographic patterns.

The disconnection between atypical radiographic presentations in about a quarter to a third of case of IPF and pathologic findings consistent with UIP (1) remains both interesting and challenging. In particular, the lack of honeycombing development despite significant progression of disease in cases with atypical patterns for UIP suggest that fibrosis assessment should be comprehensive and not limited to typical findings for UIP.

About half of patients with indeterminate or alternative pattern for UIP included in this study had biopsy-proven IPF. When a biopsy was not deemed safe, clinical-functional course, radiographic evolution from previous x-rays and scans, lack of known causes of ILD and age of the patient were taken into consideration, in the context of multi-disciplinary discussion (16) Our findings reinforce the importance of clarifying diagnosis in atypical radiographic presentations of idiopathic interstitial pneumonias, whenever possible, as indeterminate/alternative patterns were associated with a rate of progression and dismal survival very similar to the typical and probable patterns for UIP. Any assumption that these

patients would either not have IPF or have a less aggressive form of it could lead to delay in starting anti-fibrotic therapies and LTx assessment.

Strengths of this study include its multicenter inclusion of patients, rigorous diagnostic criteria, availability of full longitudinal lung function data, and adequate length of follow-up and statistical power, provided by an equal distribution of cases among different patterns and by a combined death/LTx incidence of 45% during the follow-up period.

The main limitation is represented by retrospective design, where patients with rapidly progressive tend to be excluded, due to rapidly fatal disease. Several patients may not even have a follow-up HRCT, especially when the diagnosis is late. Another limitation is represented by the lack of pathologic confirmation of UIP in a number of cases with indeterminate/atypical pattern, due to safety concerns. However, the lack of survival differences observed in this group compared to more typical patterns would mitigate concerns about diagnostic uncertainty.

Our ongoing, prospective study on the risk stratification score for IPF (https://clinicaltrials.gov/ct2/show/NCT02632123), conducted exclusively in newly diagnosed patients, will further clarify the clinical and radiographic evolution of all HRCT patterns of this condition (17).

We previously identified a >7% change in HRCT fibrosis visual score as being clinically significant, as associated with significantly worse survival (7). The use of new software algorithms to obtain an automated, more accurate scoring of all aspect of pulmonary fibrosis**,** applied to different presentation patterns and with longitudinal follow-up may also further improve our understanding of disease progression in IPF.

Another recognized limit in the use of HRCT in ILD is interobserver variability in terms of pattern recognition (8,18). On the other hand, good interobserver agreement in terms of visual quantification of pulmonary fibrosis on HRCT (K: 0.64 (7) and excellent agreement for identification of reticular opacity and honeycombing (K: 0.85-1.00) (10) were observed. Interobserver variability agreement was instead only moderate in distinguishing typical UIP from probable or inconsistent UIP pattern, without substantial change related multidisciplinary team discussion, experience or patient age (9). Another level of multidisciplinary agreement concerns the concordance between radiographic and pathological diagnosis, and this varies with the presentation HRCT pattern. While probable UIP on HRCT is nevertheless associated with higher rate of histologic UIP than the indeterminate pattern (19), only limited radiologic-pathologic agreement was observed in cases of HRCT pattern inconsistent with UIP (20), not surprisingly.

In conclusion, the presentation pattern of confirmed IPF does not usually change over a period of 1 year and half since diagnosis and does not have an impact the rate of progression, lung function decline or average survival of patients with this devastating condition.

Declarations: No personal identifiers of patients are included in the study.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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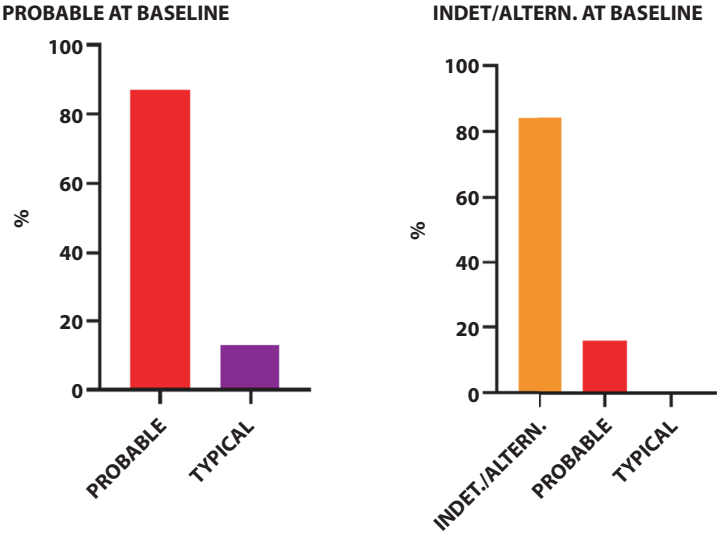

Supplemental Figure 1. Right: Longitudinal changes of HRCT fibrosis score among different patterns of UIP. Left: Proportion of patients among different patterns of UIP with a >7% increase of HRCT fibrosis score, which is associated with significantly worse lung transplant-free survival.