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Idiopathic Chronic Eosinophilic Pneumonia Evolving to Pulmonary Fibrosis: A Retrospective Analysis

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Abstract. *Background:* Patients with idiopathic chronic eosinophilic pneumonia (ICEP) may have pulmonary fibrosis. *Objectives:* To investigate the predictors of pulmonary fibrosis in ICEP, to describe the timeline of pulmonary fibrosis after ICEP diagnosis, and to detail the radiologic pattern of fibrosis. *Methods:* A retrospective computer-assisted search was performed to identify patients with ICEP seen at Mayo Clinic in Rochester, Minnesota, from January 1, 1997, through September 1, 2019. Patients with follow-up chest computed tomography (CT) beyond 12 months after the ICEP diagnosis were included in the study. Demographic, clinical, radiologic, and histopathologic characteristics were analyzed. Proportional hazards regression was used to assess the predictors of pulmonary fibrosis. *Results:* We identified 62 patients (mean [SD] age at ICEP diagnosis, 60 [13] years; female sex, 37 [60%]). Cough (87%) and shortness of breath (85%) were the most common presenting symptoms. Of patients, 27 (44%) had a history of smoking and 27 (44%) had a history of asthma. During follow-up, 23 patients (37%) had CT evidence of pulmonary fibrosis, of whom 16 patients (70%) had a CT pattern inconsistent with usual interstitial pneumonia. In 29% of the patients, the CT evidence of pulmonary fibrosis developed within 2 years after ICEP. Age and male sex were predictors of pulmonary fibrosis. Of note, a history of asthma decreased the likelihood of pulmonary fibrosis. *Conclusions:* Development of pulmonary fibrosis is not uncommon in patients with ICEP, especially older men, and is associated with increased risk of death.

Key words: eosinophilia; eosinophilic alveolitis; interstitial lung disease

Introduction

Idiopathic chronic eosinophilic pneumonia (ICEP) is characterized by respiratory symptoms or radiologic infiltrates of more than 1 month and pulmonary eosinophilia detected in either bronchoalveolar lavage (BAL) or lung biopsy in the absence of an identifiable cause for the pulmonary infiltrates or eosinophilia (1-3). The prognosis of ICEP is generally favorable with infiltrate resolution through glucocorticoid therapy.

Although the robust response of eosinophils to glucocorticoids is well established (4-7), some investigators have reported ICEP leading to pulmonary fibrosis and worsening lung function (8, 9). Furthermore, patchy areas of eosinophilic pneumonia like infiltrates have been observed in the background of usual interstitial pneumonia (UIP) in lung biopsies of patients diagnosed with idiopathic pulmonary fibrosis (IPF) (10). In some animal studies, investigators have shown that injury to the lungs leads to pulmonary fibrosis, which in turn leads to release of several cytokines and recruitment of eosinophils to the site of injury. After eosinophils reach the injury site, they secrete toxic chemicals (eg, major basic proteins, eosinophil peroxidase, ribonuclease, deoxyribonucleases, lipase) from their granules and cause further damage (11).

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A detailed description is lacking for the clinical and radiographic characteristics of pulmonary fibrosis in ICEP. The chronology of ICEP leading to pulmonary fibrosis also is not clear. Another question is which factors determine the fibrosis development that occurs in some persons.

The overall goal of the present study was to compare ICEP patients who had pulmonary fibrosis with ICEP patients who did not. The central hypothesis of this study was that ICEP patients who have pulmonary fibrosis have certain demographic or clinical characteristics that differ from those without pulmonary fibrosis.

The aims of this retrospective study were to investigate the predictors of pulmonary fibrosis in ICEP through the comparison among ICEP patients, to describe the timeline of pulmonary fibrosis after ICEP diagnosis, and to detail the radiologic pattern of fibrosis.

Methods

Patient Selection

The Mayo Clinic Institutional Review Board approved this study (19-006448). Patients were excluded if they did not authorize the research use of their electronic health records (EHRs). A computer-assisted search of EHRs was conducted to retrospectively identify all adult ICEP patients evaluated at Mayo Clinic in Rochester, Minnesota, from January 1, 1997, through September 1, 2019. To be all inclusive, we used the term *eosinophilic pneumonia* that was mentioned anywhere in the clinical notes. For all identified patients, we performed a complete EHR review to confirm the ICEP diagnosis.

Diagnostic Criteria for ICEP

The criteria for ICEP used in the present study included symptoms or radiologic infiltrates of more than 1 month. Pulmonary eosinophilia evidenced with BAL (>20% eosinophils) or lung biopsy was another criterion. In tissue biopsy, tissue eosinophilia was graded as 0 (absent), 1 (mild; rare dispersed eosinophils in a few foci), 2 (moderate; readily recognizable small aggregates of eosinophils in multiple foci), or 3 (marked; large aggregates of eosinophils in multiple foci). The presence of organizing pneumonia and interstitial thickening or fibrosis was recorded in each case. (Peripheral eosinophilia was not required.) Absence of any identifiable cause for pulmonary infiltrates or eosinophilia was a criterion. Among these causes were, for example, drug use, fungal or parasitic infections, eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, and connective tissue disease.

Inclusion Criteria

Study inclusion criteria required that patients were older than 18 years, met the diagnostic criteria for ICEP, and had follow-up chest computed tomography (CT) at least 12 months after the initial diagnosis. Patients who had preexisting pulmonary fibrosis at diagnosis of ICEP were not included in the study.

Of the 2,258 patients identified, 2,102 were excluded for various reasons. These were lack of diagnostic evidence for eosinophilic pneumonia (eg, eosinophilic pneumonia merely included in the differential diagnosis; n=1,886); diagnostic criteria not known (n=73); EGPA (n=48); organizing pneumonia or organizing pneumonia with no concurrent characteristics of eosinophilic pneumonia (n=35). Other reasons for exclusion were a drug-related cause (n=29), hypereosinophilic syndrome (n=17), infection (n=7), autoimmune disease (n=5), and acute eosinophilic pneumonia (n=2). The other 156 patients had ICEP, but 94 were excluded from the study because of a lack of follow-up after the initial visit (n=64), no follow-up chest CT beyond 12 months after the diagnosis (n=18), and preexisting fibrotic lung disease (n=12).

Clinical and Laboratory Data

Data extracted from the EHRs included age, sex, smoking status, and body mass index (BMI). The data also included presenting symptoms and duration; date of ICEP diagnosis; and presence of asthma and atopy. In addition, the extracted data were initial pulmonary function test results, laboratory results (peripheral eosinophilia [defined as ≥500 eosinophils per mL] and BAL eosinophilia), bone marrow biopsy results, treatment, follow-up, and outcome. Of the patients who died, the cause and date of death were recorded.

Radiologic Analysis

Chest CT images were evaluated by 2 thoracic radiologists (T.F.J. and Y.K.T.) and were classified according to the Fleischner Society White Paper Guidelines (12) for patterns of fibrosis. Chest CT images were reviewed in their entirety and spanned a timeframe between January 1, 1998, and December 20, 2020. Chest CT images were obtained at our institution and the other referring medical centers, with various acquisition and reconstruction parameters. Most examinations included a high-resolution lung reconstruction, which allowed for evaluation of lung parenchyma. On review, the presence or absence of honeycombing was noted. CT characteristics of honeycombing, reticular opacities, or traction bronchiectasis or bronchiolectasis, or a combination, were considered evidence of fibrosis.

The fibrosis pattern was classified as *typical UIP*, *probable UIP*, *indeterminate for UIP*, and *inconsistent with UIP*. For cases inconsistent with UIP, the reason for the inconsistency was noted, such as excessive ground-glass opacity, consolidation, upper lung predominance, or air trapping. When possible, these examinations were then categorized into patterns of nonspecific interstitial pneumonia (NSIP), obstructive pneumonia, chronic eosinophilic pneumonia, or alternatively, an unclassifiable pattern. Additional pulmonary findings were noted also, such as nodularity, emphysema, or cystic change. Fibrosis was categorized craniocaudally as diffuse or upper or lower lung predominant, categorized axially as diffuse or central or peripheral predominant, and scored in terms of percentage of disease involvement.

For each patient, the earliest CT was documented and the first CT with fibrosis noted. Across the patient CT jackets, progression of fibrosis was noted as absent or present and, when present, described as *mild*, *moderate*, or *severe*. The presence of lymphadenopathy (short axis dimension, >10 mm) was recorded, along with any abnormal enlargement of the main pulmonary artery that was classified as exceeding 29 mm. After the CT scans were reviewed independently, any discrepancies were resolved by consensus.

Pathologic Analysis

An expert thoracic pathologist (E.S.Y.) reviewed all lung biopsy slides. Pertinent histopathologic changes were described, including degree of tissue eosinophilia, presence of organizing pneumonia, and interstitial thickening. When appropriate, terminology of the American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonia was applied (13).

Statistical Analysis

Data were summarized as mean (SD) and median (IQR) for continuous variables and as frequency counts and percentages for categorical variables. Proportional hazards regression was used to assess characteristics potentially associated with development of pulmonary fibrosis. For this analysis, time zero corresponded to the date of ICEP diagnosis; data for patients who did not have pulmonary fibrosis were censored at death or last follow-up. The characteristics assessed in these analyses included age, sex, BMI, smoking status (ever vs never), history of asthma, duration of prior symptoms, and presence of peripheral eosinophilia and BAL eosinophilia. In addition to univariate analysis, each characteristic was assessed with a multivariable model that included age and sex as covariates. To account for missing data, we performed multiple imputations, using fully conditional specification methods, to obtain 20 complete data sets. The results from the analyses of the imputed data sets were combined with use of Rubin's rules (14).

An additional proportional hazards regression analysis was performed to assess whether the development of pulmonary fibrosis was associated with survival. For this analysis, pulmonary fibrosis was treated as a binary time-dependent covariate. Results of the proportional hazards regression analyses are summarized by presenting hazard ratio estimates with 95% CI. In all cases, 2-tailed *P* values were reported, with $P<.05$ considered statistically significant.

Results

In total, 62 patients with ICEP were included in the present study (Table 1). The mean (SD) age at the time of ICEP diagnosis was 60 (13) years, and 37 female patients (60%) were in the cohort. Of patients with data available, the majority (73%) had symptoms for 1 year or less, and the most commonly reported symptoms were cough and shortness of breath.

Table 1. Baseline Characteristics of 62 Study Patients

Characteristic	Summary statistics[a,b]
Age, y	
Mean (SD)	60 (13)
Median (IQR)	59 (48-67)
Sex	
Female	37 (60)
Male	25 (40)
BMI (n=54)	
Mean (SD)	26.8 (4.2)
Median (IQR)	25.9 (23.8-30.4)
Ever-smoker	27 (44)
History of asthma	27 (44)
Symptoms	
Cough	54 (87)
Shortness of breath	53 (85)
Wheezing	23 (37)
Fever	19 (31)
Chest pain	16 (26)
Duration of symptoms, mo (n=57)	
≤3.0	16 (31)
3.1-6.0	9 (18)
6.1-12.0	12 (24)
12.1-36.0	6 (12)
≥36.1	8 (16)
Peripheral eosinophilia (n=47)	39 (91)
BAL eosinophilia (n=44)	24 (62)

Abbreviations: BAL, bronchoalveolar lavage; BMI, body mass index.

[a] Values are presented as number (percentage) of patients unless specified otherwise.

[b] Data were complete for all variables with the exception of BMI (n=54), duration of symptoms (n=57), peripheral eosinophilia (n=47), and BAL eosinophilia (n=44).

The pulmonary function test results are summarized in Table 2. At the time of ICEP diagnosis, the percentage predicted forced vital capacity (FVC) and the percentage predicted diffusing capacity of lung for carbon monoxide (DLCO) were significantly less in patients who developed pulmonary fibrosis than those who did not. The degree of airway obstruction, as shown in percentage predicted forced expiratory volume in the first second of expiration (FEV_1), the FEV_1 to FVC ratio, and percentage predicted residual volume (RV), was more in the ICEP group without fibrosis than in the group with it.

The median (IQR) duration of follow-up was 8.6 (5.4-13.5) years; 23 patients (37%) had CT evidence of pulmonary fibrosis during the interval. Most patients who developed pulmonary fibrosis were diagnosed within 2 years following the diagnosis of ICEP (Figure 1). The Kaplan-Meier estimate (95% CI) for the cumulative percentage of ICEP patients who had pulmonary fibrosis was 16.1% (6.5%-24.8%) at 6 months, 25.8% (14.1%-35.9%) at 1 year, and 29.1% (16.8%-39.6%) at 2 years. The CT findings for the 23 patients who had pulmonary fibrosis are presented in Table 3 . According to Fleischner Society White Paper Guidelines, the most common pattern of fibrosis was inconsistent with UIP (Figure 2); the most common interstitial pneumonia pattern among these cases was NSIP (35%) followed by atypical/unclassifiable patterns (26%). Lower lobe (83%) and peripheral (70%) distributions were commonly seen as fibrosis locations.

Of patients who had ICEP *with* fibrosis, 18 patients (78%) underwent lung biopsy: 10 (55%), surgical lung biopsy; and 8 (44%), transbronchial lung biopsy. Patterns of fibrosis or descriptions suggestive of damage or injury seen on lung biopsy were diffuse alveolar damage (n=3), reactive pneumocyte hyperplasia (n=2), desquamative interstitial pneumonitis (DIP) (n=2), UIP (n=2), and fibrinous organizing pneumonia (n=2). Among the patients with ICEP **without** fibrosis, 35 (90%) underwent lung biopsy. Twenty-five patients (71%) had transbronchial lung biopsy; 7 (20%), surgical lung biopsy; and 3 (8%), needle biopsy.

Proportional hazards regression analysis was used to assess characteristics associated with development of pulmonary fibrosis (Table 4). The likelihood of pulmonary fibrosis increased with older age (univariate hazard ratio [HR] [95% CI], 2.15 [1.34-3.46] per 10 years; sex-adjusted HR [95% CI], 2.02 [1.26-3.24] per 10 years) and male sex (univariate HR [95% CI], 2.97 [1.25-7.05]; age-adjusted HR [95% CI], 2.39 [1.00-5.75]). The likelihood of pulmonary fibrosis was decreased in patients with a history of asthma (univariate HR [95% CI], 0.19 [0.06-0.56]; age- and sex-adjusted HR [95% CI], 0.24 [0.08-0.72]).

A majority of patients in both ICEP groups were treated with oral glucocorticoids for various durations (range, a few months to years). In the ICEP

Table 2. Pulmonary Function Data of Cohorts

	No pulmonary fibrosis (n=39)		Pulmonary fibrosis (n=23)		
Pulmonary function data[a]	**No.**[b]	**Mean (SD)**	**No.**[b]	**Mean (SD)**	***P* value**
At time of ICEP diagnosis					
TLC	19	95.7 (20.2)	16	71.6 (12.2)	<.001
FVC	28	84.4 (18.8)	20	73.4 (17.6)	.046
FEV_1/FVC ratio	27	72.3 (15.3)	19	80.3 (6.3)	.04
FEV_1	27	72.5 (19.5)	20	74.8 (18.3)	.69
RV	18	118.1 (43.0)	15	78.9 (18.2)	.003
DLCO	24	78.9 (18.0)	20	60.0 (19.1)	.002
Last measurement in follow-up[c]					
TLC	18	97.8 (17.7)	17	69.2 (17.4)	<.001
FVC	33	91.0 (19.6)	23	68.0 (18.0)	<.001
FEV_1/FVC ratio	33	73.1 (13.8)	23	83.4 (13.2)	.007
FEV_1	33	81.2 (21.2)	23	68.7 (20.6)	.03
RV	16	130.6 (47.1)	17	70.4 (20.8)	<.001
DLCO	30	78.1 (14.9)	20	56.4 (16.5)	<.001

Abbreviations: DLCO, diffusing capacity of lung for carbon monoxide; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; ICEP, idiopathic chronic eosinophilic pneumonia; RV, residual volume; TLC, total lung capacity.
a Pulmonary function data are written in percentage predicted values.
b Number of patients with information available.
c The median (IQR) time from ICEP diagnosis to the last measured pulmonary function tests was 6.6 (3.1-8.9) years for those who developed pulmonary fibrosis and 4.1 (2.9-7.4) years for those who did not (rank sum test P=.31).

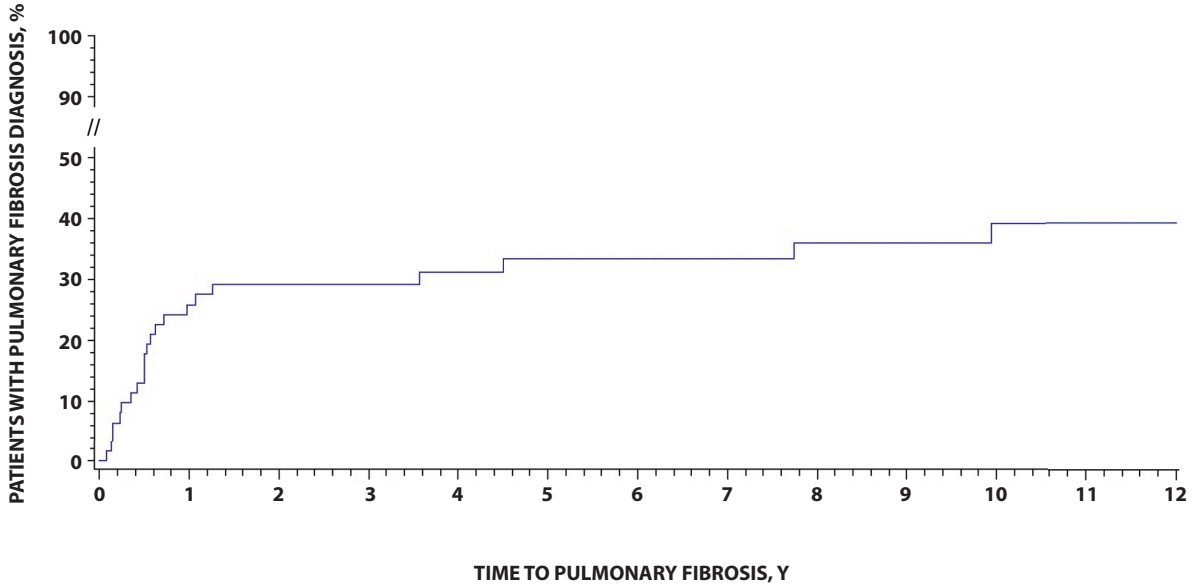

Figure 1. The Estimated Cumulative Percentage of Patients with Pulmonary Fibrosis Diagnosis After Diagnosis of Idiopathic Chronic Eosinophilic Pneumonia.

Table 3. Computed Tomography Findings of the 23 Patients in Whom Pulmonary Fibrosis Developed

Characteristic	Patients, No. (%)
Fleischner Classification	
Inconsistent with UIP	16 (70)
Indeterminate for UIP	5 (22)
UIP	2 (9)
Interstitial pneumonia pattern (inconsistent with UIP)	
NSIP	8 (35)
Atypical/unclassifiable	6 (26)
NSIP plus OP	1 (4)
OP	1 (4)
Lung predominance	
Lower lung	19 (83)
Upper lung	2 (9)
Diffuse	2 (9)
Peripheral and axial predominance	
Peripheral	16 (70)
Diffuse	6 (26)
Axial	1 (4)
Honeycombing	
No	20 (87)
Yes	3 (13)

Abbreviations: NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

group with no pulmonary fibrosis, treatment was not clear for 2 patients. The duration of corticosteroid treatment was minimum of 4 weeks to maximum of 12 years. In 9 cases (23%) in the group without pulmonary fibrosis and 3 (23%) in the pulmonary fibrosis group, use of glucocorticoids was intermittent for several years. The treatments of 3 patients were switched to other immunosuppressants (2 to azathioprine and 1 to mycophenolate mofetil). Twenty-seven patients in this group had at least 1 relapse, and 7 patients did not have a relapse; the relapse rate was not clear for 5 patients. In the ICEP group with fibrosis, the use of corticosteroids was not clear in 2 patients. The minimum duration of corticosteroid treatment was 7 months; the maximum, 12 years. Again, it was intermittent for several years in some patients. Four patients were treated with immunosuppressants (2 with azathioprine and 2 with mycophenolate mofetil). In this group, 15 patients had at least 1 relapse; the relapse rate was not clear in 7 patients, and 1 did not relapse in this group.

During follow-up, the pulmonary function tests of patients who developed pulmonary fibrosis declined significantly compared with those who did not (Table 2). Total lung capacity, FVC, FEV_1, and DLCO were significantly less than in those who did not have pulmonary fibrosis. The latter group continued to have increased RV and a lower FEV_1 to FVC ratio, indicating a worse obstructive pattern.

Of the 12 patients who died, 8 had pulmonary fibrosis before death and 4 died with no pulmonary fibrosis. In the group with pulmonary fibrosis, the cause of death was not clear for 2 patients, and 2 patients died of advanced lung disease leading to respiratory failure. The other 4 patients died of ischemic cardiomyopathy, intracranial hemorrhage, ischemic stroke, and lung cancer, respectively. In the group without pulmonary fibrosis, the causes of death were respiratory failure, end-stage renal disease, intracranial hemorrhage, and septic shock, respectively. From proportional hazards regression with pulmonary fibrosis treated as a time-dependent covariate, development of pulmonary fibrosis was associated with increased risk of death (HR [95% CI], 9.53 [2.02-44.94]; *P*=.004).

Discussion

In the present retrospective single-center study, we described patients with ICEP who had follow-up chest CT beyond 1 year after initial diagnosis of ICEP. Through review of CT evidence, we observed pulmonary fibrosis in 37% of patients with ICEP; pulmonary fibrosis inconsistent with UIP was the most common type. On comparison with a group of ICEP patients who did not have pulmonary fibrosis, we observed that age and male sex were predictors of fibrosis, whereas history of asthma was a protective factor.

In the past, a few studies evaluated the risk factors of frequent relapses in ICEP (15, 16). Studies also assessed the long-term follow-up of pulmonary function tests in this population (17, 18). Detailed evolution of HRCT with special attention to pulmonary fibrosis was missing in these studies. Regarding pulmonary function tests, our results were similar to what has been described previously. We found persistent obstructive and restrictive defects (actually worse on repeat measures) in our cohort. Suzuki et al (18) attributed the restrictive defects to the findings of reticulation on HRCT. We specifically excluded

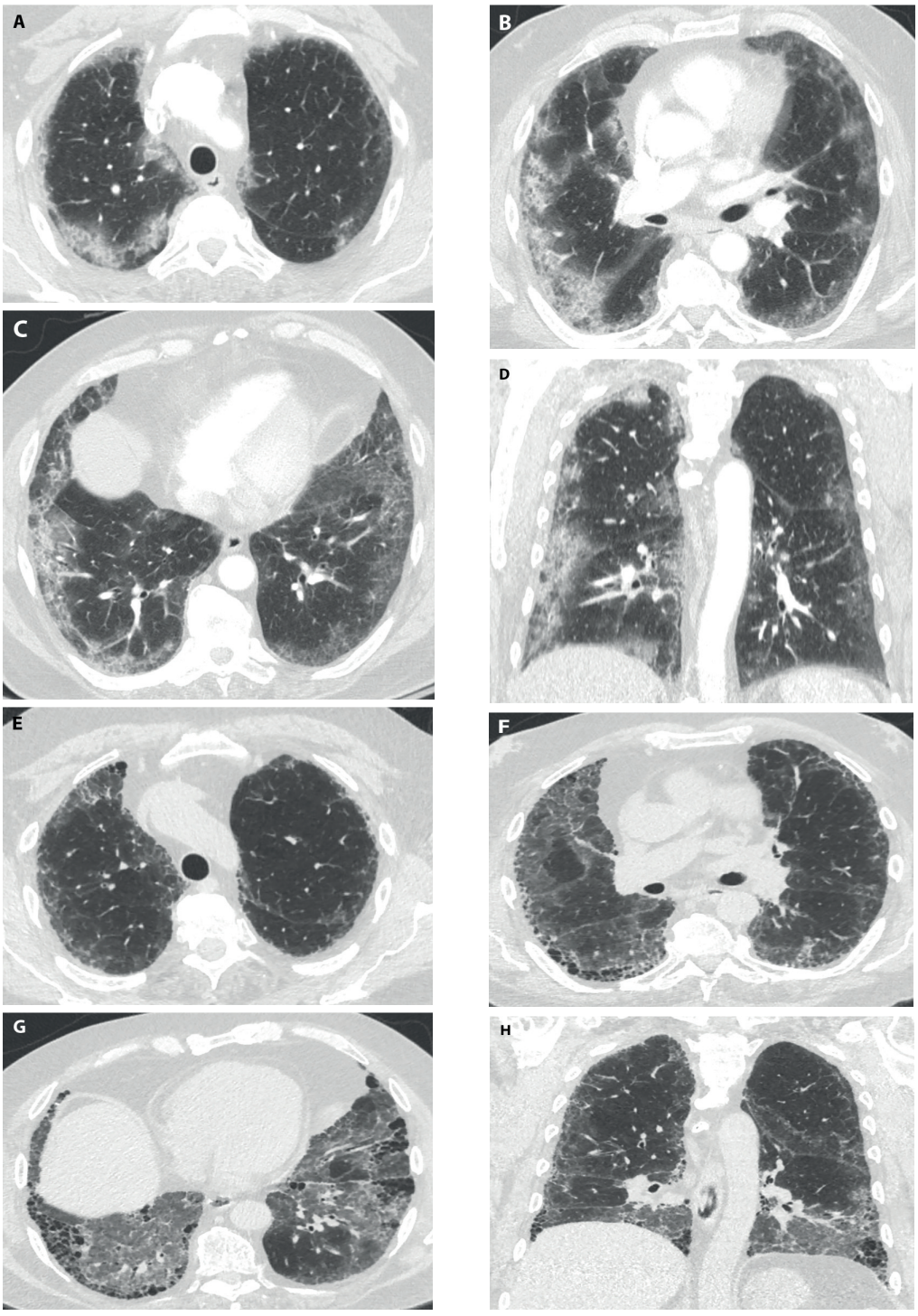

Figure 2. Chest Computed Tomography Images of a Patient With Idiopathic Chronic Eosinophilic Pneumonia. A-D, In images from 2016, peripheral predominate consolidation and ground-glass opacity heterogeneously are distributed in the (A) upper, (B) mid, and (C) lower lungs. These findings show well on the coronal reformat (D). E-H, Follow-up images from 2020 show reticular opacities in the peripheral (E) upper lungs consistent with fibrosis with extensive ground-glass opacity and mixed traction bronchiolectasis and honeycombing in the peripheral and lower lungs, seen in the (F) mid and (G) lower lungs. H, The coronal reformat. Given the degree of ground-glass opacity, the findings are inconsistent with usual interstitial pneumonia.

Table 4. Characteristics Associated With Development of Pulmonary Fibrosis in Patients With Idiopathic Chronic Eosinophilic Pneumonia

	Univariate[a]		Age- and sex-adjusted value[a]	
Characteristic	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age, per 10 y	2.15 (1.34-3.46)	.002	2.02 (1.26-3.24)	.003
Male sex	2.97 (1.25-7.05)	.01	2.39 (1.00-5.75)	.05
BMI, per 5 kg/m^2	1.38 (0.85-2.22)	.19	1.13 (0.68-1.87)	.06
Ever-smoker	1.24 (0.54-2.81)	.61	1.07 (0.46-2.49)	.88
History of asthma	0.19 (0.06-0.56)	.003	0.24 (0.08-0.72)	.01
Duration of symptoms, per mo	0.99 (0.98-1.01)	.20	1.00 (0.98-1.01)	.57
Peripheral eosinophilia	0.67 (0.16-2.86)	.58	0.64 (0.15-2.81)	.55
BAL eosinophilia	0.97 (0.35-2.66)	.95	0.96 (0.36-2.56)	.93

Abbreviations: BAL, bronchoalveolar lavage; BMI, body mass index; HR, hazard ratio.
[a] Data were analyzed with proportional hazards regression. In the accounting for missing data, 20 imputations were performed with use of fully conditional specification methods to obtain complete data sets. Results summarized as point estimates and corresponding 95% CIs, reflecting the combined analysis of multiple imputations.

patients with pulmonary fibrosis at the time of ICEP diagnosis, especially when we did not have previous chest images. A possibility exists that some patients still developed fibrosis at the tissue level, which continued to progress, as shown in repeat pulmonary function tests and HRCT. Our study has been a step forward based on the previous work.

The phenomena of eosinophilic pneumonia leading to pulmonary fibrosis have been described in a few cases (8, 9). In 1 study, Katoh et al (19) determined that the BAL of patients with idiopathic eosinophilic pneumonia had elevated levels of periostin and tumor growth factor $_1$ (TGF- $_1$). The levels of these profibrotic mediators in idiopathic eosinophilic pneumonia were significantly more than in IPF and sarcoidosis. Eosinophils and various stimuli (eg, interleukin 13, TGF-β) induce fibroblast and epithelial cells of the bronchi to produce periostin, an extracellular protein involved in remodeling and fibrosis of the lung. Periostin also increases adhesion of eosinophils and upregulates the functions of eosinophils such as the granulation and production of the cytokine of TGF-β and hence causes a vicious cycle (19). This eosinophil-mediated remodeling of extracellular tissue can explain the persistent obstructive defect as well (20).

Although the profibrotic nature of the eosinophils has been recognized, not all patients with ICEP develop fibrosis. This information leads to consideration of some of the intrinsic factors that put a person at risk for pulmonary fibrosis development. Our study pointed out that older age and male sex are risk factors. The same factors were recognized by Suzuki et al (18) when they compared patients with CEP with and without persistent impaired lung functions. We found the presence of asthma as a protective factor against development of fibrosis. In a previous study, the investigators recognized this as associated with fewer relapses in ICEP (16). Asthma seems to be a protective factor against fibrosis; it could mean that the usual outcome of ICEP is asthma and recurrent bouts of eosinophilic pneumonia. However, in a subset of patients, the outcome is restrictive lung disease in the form of fibrosis rather than obstructive lung disease in the form of asthma. A possible link or confounding factor between ICEP and fibrosis may be cigarette smoking. Smoking is recognized as a precipitating factor for eosinophilic pneumonia (2, 21, 22) and has been associated with increased risk of relapse in ICEP (15). It is also associated with such smoking-related interstitial lung diseases as DIP and respiratory bronchiolitis-interstitial lung disease (23). First, we found only 2 patients with DIP on lung biopsy, and second, in our predictor model, smoking status did not come up as a risk factor for lung fibrosis. Another possible explanation for different outcomes in ICEP could be the role of genetics, which we could not explore in this study.

Of note, although fibrosis developed in some individuals late after the initial diagnosis of ICEP, 29% of patients had pulmonary fibrosis in the first 2 years after the diagnosis. We diagnosed chronic eosinophilic pneumonia on the basis of the duration of respiratory symptoms before the ICEP diagnosis. This

phenomenon of acute respiratory distress syndrome or diffuse alveolar damage has been described in previous studies in relation with acute eosinophilic pneumonia (24, 25). But, as mentioned earlier, a number of patients continued to have pulmonary fibrosis development years after the ICEP diagnosis. Not surprisingly, the mortality rate among patients in whom fibrosis developed was higher than among those who did not have fibrosis.

The clinical implication of our study is to recognize this phenomenon and to keep following up with patients who have ICEP, especially those with risk factors for pulmonary fibrosis. Early initiation of prednisone treatment should be considered. Some reports cite beneficial effects of interleukin-5 inhibitors on eosinophilic pneumonia (26-28). The role of antifibrotic agents is not explored herein, but it probably could be considered when fibrosis is detected.

Our study has limitations. It is a retrospective single-center study. We do not have follow-up data on all patients. The exact details about relapses were missing. The exact dose and duration of corticosteroid therapy were not possible to assess because our center is a referral center and not all details about continuous medical treatment and relapses can be captured in our EHRs. The number of patients who underwent surgical lung biopsy was different in both groups, making pathologic findings difficult to compare. For the same reason, correlation between pathologic and radiologic findings was not possible. We cannot comment on the frequency of patients with ICEP having pulmonary fibrosis because we looked only at those patients who had chest CT at least 1 year after their ICEP diagnosis. We do not know whether eosinophilic pneumonia secondary to other causes (eg, drugs, parasites) also leads to pulmonary fibrosis. For the sake of clarity and to eliminate the confounding effects of external factors, we focused only on the group with idiopathic eosinophilic pneumonia. For the assessments of characteristics potentially associated with development of pulmonary fibrosis, we attempted to address issues related to missing data by using multiple imputation methods. However, given the amount of missing data for peripheral eosinophilia and BAL eosinophilia, findings from the analyses of these characteristics should be considered exploratory.

In conclusion, ICEP can lead to pulmonary fibrosis, especially in older men. Yet, those patients with a history of asthma were less likely to have pulmonary fibrosis.

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Abbreviations: BAL, bronchoalveolar lavage; BMI, body mass index; CT, computed tomography; DIP, desquamative interstitial pneumonitis; DLCO, diffusing capacity of lung for carbon monoxide; EGPA, eosinophilic granulomatosis with polyangiitis; EHR, electronic health record; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HR, hazard ratio; ICEP, idiopathic chronic eosinophilic pneumonia; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; TGF-β_1, tumor growth factor β_1; UIP, usual interstitial pneumonia Presented as an abstract at the CHEST 2021 Annual Meeting, October 17-20, 2021. Portions of this manuscript have been published in abstract form: CHEST. 2021 Oct;160(4) Suppl:A1245.

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