Respiratory Medicine Case Reports 24 (2018) 25–29

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Emphysematous changes in hypersensitivity pneumonitis: A retrospective analysis of 12 patients

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ARTICLE INFO

Keywords:
Emphysema
Fibrosis
Hypersensitivity pneumonitis

ABSTRACT

Introduction: Emphysema is most commonly associated with smoking but also occurs in hypersensitivity pneumonitis (HP). The aim of this study was to further explore this relationship.

Methods: A retrospective, computer-assisted search was performed to identify patients with HP seen at Mayo Clinic in Rochester, Minnesota, from January 1997 through February 2014. Demographic, clinical, and imaging features were analyzed. Patients were excluded if they had a smoking history of 10 pack-years or more.

Results: Twelve patients (9 males) with HP and computed tomographic evidence of emphysema were identified. Ten were never smokers and 2 were ex-smokers. The median age at diagnosis was 47 (range, 29–77) years; median symptom duration was 2.2 (range, 0.2–13.4) years. The most common presenting symptoms were dyspnea (83%) and cough (67%). On pulmonary function testing, 6 patients (50%) had a restrictive defect, 2 (17%) had airflow obstruction, and 4 (33%) had an isolated reduction in diffusing capacity of lung for carbon monoxide. The severity of emphysema ranged from mild to severe to focal bullae. All patients had chronic hypersensitivity pneumonitis (CHP). Centrilobular emphysema was most commonly seen with coexistent paraseptal emphysema in 5 patients.

Emphysema was most frequent in the upper lung but could be seen in any lobe.

Conclusion: Emphysema can occur in patients with CHP independently of smoking history and exposure to specific types of antigens. Emphysematous changes seem to progress at a slower pace compare to reticulations/fibrosis.

1. Introduction

Hypersensitivity pneumonitis (HP) is a complex interstitial lung disease (ILD) caused by inhalation of and sensitization to an aerosolized environmental antigen [1]. These antigens include bacteria (eg, *Saccharopolyspora*, and *Thermoactinomyces*), fungi, mycobacteria, animal proteins (eg, avian antigens), and chemicals [2,3]. Patients with HP most commonly present with respiratory symptoms, although systemic symptoms may also be present. Consensus has not been reached on the criteria for diagnosing HP; the diagnosis relies on several factors, including history of antigen exposure, serologic presence of precipitating antibodies to causative antigens, clinical features, lymphocytosis on bronchoalveolar lavage, and supporting radiologic and pathologic abnormalities [2]. The clinical presentation of HP is divided into acute, subacute, and chronic forms, depending in part on the duration of exposure to the antigen [4]. Chronic HP (CHP), which results from continuous or recurrent low-level exposure to the offending antigen, is often associated with progressive pulmonary fibrosis.

The most commonly described radiologic findings in HP are ground-glass opacities, ill-defined centrilobular nodules, and focal areas of air trapping that result in mosaic attenuation and fibrosis [5]. Reports dating back to 1968 have described emphysematous changes in CHP, but the studies do not clearly delineate the pattern and extent of emphysema [6–11]. In addition, some of these studies did not adequately account for the smoking history, potentially confounding their results.

Our main goal was to investigate the pattern, severity, and distribution of emphysematous changes in HP along with their effects on pulmonary function. Since previous reports described emphysema mainly in farmers and bird breeders, we also explored whether this phenomenon is antigen specific.

2. Methods

2.1. Patient selection

A computer-aided search identified all adults at Mayo Clinic in

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https://doi.org/10.1016/j.rmcr.2018.03.012
Received 2 March 2018; Received in revised form 19 March 2018; Accepted 20 March 2018

Abbreviations

α_1-AT	α_1-antitrypsin
CHP	chronic hypersensitivity pneumonitis
DLCO	diffusing capacity of lung for carbon monoxide ES, emphysema score
HRCT	high-resolution computed tomography

Rochester, Minnesota, who received a diagnosis of HP from January 1, 1997, through February 28, 2014. Reports from computed tomography (CT) of the chest were reviewed for keywords *emphysema* and *emphysematous changes*. Patients with a smoking history of 10 pack-years or more were excluded from the study. The Mayo Clinic Institutional Review Board approved this study (IRB 13–007760). Patients were excluded if they did not provide written authorization for research use of their medical records.

2.2. Data extraction

Data extracted from the medical records included age, sex, smoking status, exposure history to known antigens, serologic evidence for HP, date of diagnosis, method of diagnosis, pathologic findings, spirometry results, findings from CT of the chest, treatment, outcome, and follow-up duration. A subspecialist thoracic radiologist (D.W.) reviewed all CT scans of the chest.

2.3. Diagnostic criteria of HP

All patients were seen by ILD experts in our ILD clinic. The multidisciplinary diagnosis of HP was made from the integration of several factors:

1. Presence of respiratory symptoms with or without the systemic symptoms of progressive dyspnea, dry cough, fatigue, and weight loss
2. History of exposure to a potential antigen [2,3].
3. Serologic presence of immunoglobulin G precipitating antibodies against a potential antigen [12].
4. Presence of at least 20% lymphocytes on bronchoalveolar lavage [12].
5. High-resolution CT (HRCT) scan supporting features of HP, including presence of ground-glass opacities and centrilobular nodules, and prominent air trapping or fibrosis predominantly in the upper or mid lung
6. Histologic findings of airway-centered interstitial lymphoplasmacytic infiltrates, poorly formed nonnecrotizing granulomas, bronchiolitis or usual interstitial pneumonia (UIP), or “bridging fibrosis” (ie, fibrotic net connecting bronchioles with each other and with the pleural/septal region)

In 10 of 12 patients, the diagnosis of HP was confirmed with lung biopsy. In the other 2, the diagnosis of HP was made from the combination of clinical, serologic, and CT of the chest findings.

2.4. Emphysema scoring

The scoring system used to assess emphysema was adapted from the COPDGene Study [13]. Each lung was divided into 3 zones: upper (above the carina), middle (between the carina and the inferior pulmonary veins), and lower (below the inferior pulmonary veins). The extent of emphysema as a percentage of lung volume within each zone was scored as 0 (absent), 1 ($\leq$5%), 2 (6%–25%), 3 (26%–50%), 4 (51%–75%), or 5 ($>$ 75%).

The patient's emphysema score (ES) was calculated by adding the numerical score for each lung zone. The predominant pattern of emphysema was recorded as centrilobular, paraseptal, panlobular, cicatricial or irregular, or bullae. When more than 1 morphologic type of emphysema was present, the less extensive type was recorded as a secondary pattern.

3. Statistical analysis

Categorical variables were compared between groups with the Fisher exact test. The Wilcoxon rank sum test was used to compare continuous variables between groups. *P* values less than .05 were considered statistically significant. Linear regression was used to assess the relationship between ES and pulmonary function test (PFT) data.

4. Results

Demographics and salient clinical features are summarized in Table 1. Most patients (75%) were men. At diagnosis, the median age was 47 (range, 29–77) years. Ten of 12 patients were never smokers; 1 ex-smoker had used a pipe for 20 years, and another ex-smoker had a smoking history of 5 pack-years. Ten of 12 patients were white; 1 was African American and another was Hispanic American. The median age between the onset of HP symptoms and the diagnosis of HP was 2.24 (range, 0.15–13.43) years. In 7 of 12 patients, the α_1-antitrypsin (α_1-AT) level was normal. An exposure history to known antigens associated with HP was elicited from 8 patients: 2 were farmers, 4 had exposure to avian antigens (2 to birds; 2 to down pillows or comforters), 1 was a potter in a home studio (with exposure to moldy clay), and 1 used a home steam shower (with exposure to mold). HP serology was positive for 6 of 10 tested patients.

The most common presenting symptoms were dyspnea (83%) and cough (67%), and one-third of the patients had lost weight. PFTs showed a restrictive pattern in 6 patients (50%), an isolated reduction in diffusing capacity of lung for carbon monoxide (DLCO) in 4 (33%), and an obstructive defect in 2 (17%) (Table 1). All patients had a reduced DLCO at HP diagnosis. Echocardiographic data were available for 8 of the 12 patients, and 2 had evidence of pulmonary hypertension (estimated right ventricular systolic pressure $>$ 50 mm Hg).

The mean (SD) HRCT patient emphysema score was 9.2 (5.5). The most common type of emphysema was centrilobular, with paraseptal emphysema present as a secondary pattern in 5 patients (Table 2 and Fig. 1).

Two patients presented with large bullae (Fig. 2). Panlobular emphysema was not observed. Emphysema had a predilection for the

Table 1
Demographic and clinical features of 12 patients with emphysematous changes and CHP.

Characteristic	Value[a]
Male sex	9 (75)
Age at HP diagnosis, median (range), y	47 (29–77)
Presenting symptoms	
Dyspnea	10 (83)
Cough	8 (67)
Weight loss	4 (33)
Exposure history—present	8 (67)
HP serology[b]	
Positive	6 (60)
Negative	4 (40)
Pulmonary function test results	
Restrictive	6 (50)
Isolated reduction in DLCO	4 (33)
Obstructive	2 (17)

Abbreviations: DLCO, diffusing capacity of lung for carbon monoxide; HP, hypersensitivity pneumonitis.

[a] Unless otherwise indicated, values are number of patients (percentage).

[b] HP serology was performed for 10 of the 12 patients.

Table 2
Computed tomography of the chest findings in 12 patients with emphysematous changes and chronic hypersensitivity pneumonitis.[a]

Feature	Frequency of Involvement, No. (%)
Distribution (n = 11)	
Right upper zone	10 (91)
Left upper zone	10 (91)
Right middle zone	10 (91)
Left middle zone	9 (82)
Right lower zone	8 (73)
Left lower zone	8 (73)
Predominant pattern of emphysema (n = 12)	
Centrilobular	9 (75)
Bullae	2 (17)
Cicatricial or irregular	1 (8)
Secondary pattern (in 7 of 12; 58%)	
Paraseptal emphysema	5 (71)
Centrilobular	1 (14)
Cicatricial or irregular	1 (14)
Fibrosis (n = 12)	11 (92)
Inconsistent with UIP (n = 12)	12 (100)
Inconsistent features (n = 12)	
Extensive ground-glass opacities	8 (67)
Mid or upper predominance	6 (50)
Central or peribronchovascular predominance	6 (50)
Profuse micronodules	6 (50)
Diffuse mosaic attenuation or air trapping	3 (25)
Consolidation	1 (8)

Abbreviation: UIP, usual interstitial pneumonia.

[a] Only 11 of the 12 patients (92%) had emphysema on the initial computed tomographic scan, but emphysema developed later in the 12th patient. The mean (SD) emphysema score for all 12 patients was 9.2 (5.5).

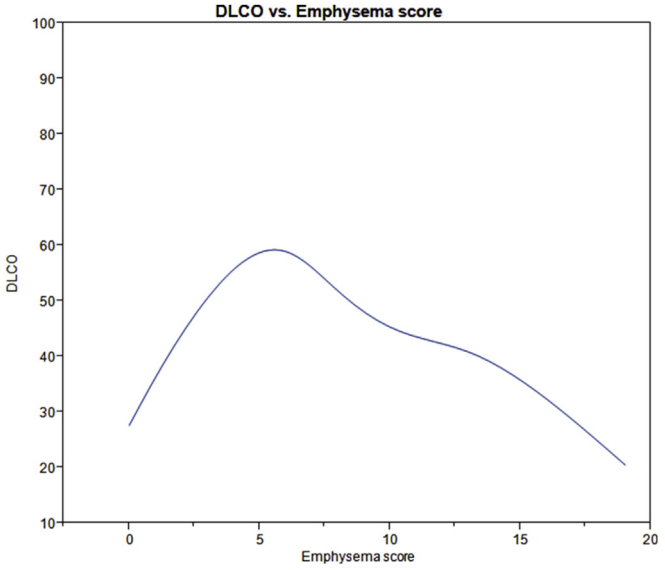

Fig. 1. Computed tomographic scan of the chest of a 70 years old man with chronic hypersensitivity pneumonitis presenting with centrilobular and paraseptal emphysema.

upper and mid lung, and the extent of involvement was greater in the upper and mid lungs than in the lower lungs. Radiologic evidence of fibrosis characterized by intralobular lines, irregular interlobular septal thickening, and traction bronchiectasis was seen in 11 patients. No patient had a pattern of UIP on CT or surgical lung biopsy. All patients had CHP rather than acute or subacute HP clinically.

ESs and PFTs did not have statistically significant correlation, but DLCO did decrease with an increase in ES, especially with high ESs (P = .51) (Fig. 3).

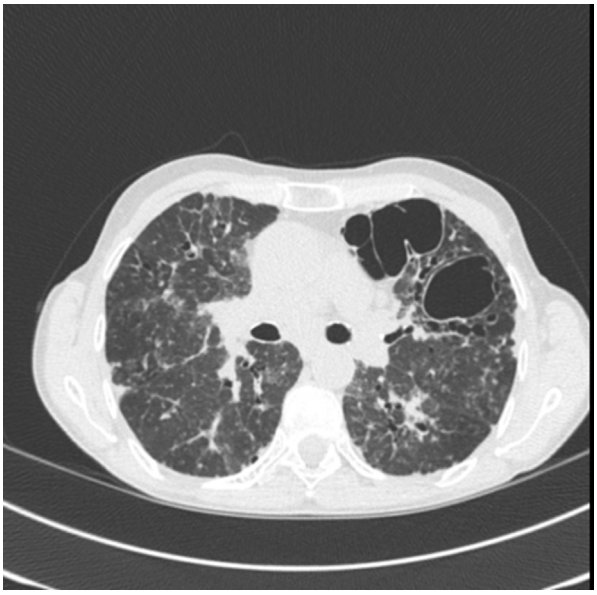

Fig. 2. Computed tomographic scan of the chest of a 68 years old man with chronic hypersensitivity pneumonitis presenting with bullae in the left upper lobe.

Nine patients were treated with prednisone (with or without other immunosuppressants), and 3 patients were managed with the avoidance of allergens only.

This cohort was followed up for a median of 3.62 (range, 0.09–11.82) years. Three patients did not have follow-up CT scans, but all patients had follow-up PFTs. During this time, 2 patients died. One had progressive fibrosis due to CHP leading to respiratory failure, and the other had an acute exacerbation of ILD with pneumothorax and ruptured bullae. In the other 10 patients, PFT results were stable in 5 patients and progressed in the other 5 patients. When available, follow-up qualitative HRCT showed worsening of reticulation alone in 2 patients, worsening of emphysema alone in 1 patient, worsening of both emphysema and reticulation in 3 patients, and stable conditions in 2 patients. The ES score remained stable in 5 patients and worsened in 3

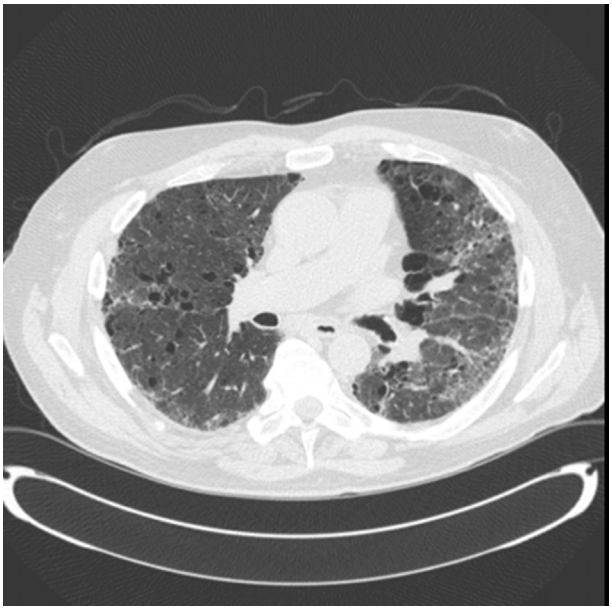

Fig. 3. Relationship between diffusing capacity of lung for carbon monoxide (DLCO) and emphysema score. The relationship is inverse at higher emphysematous scores.

patients. Two patients did not have follow-up HRCT (Table 3).

Follow-up HRCT and PFTs were done at the same time except for 1 patient, for whom they were performed 5 months apart. There was not much difference in treatment strategies between patients whose conditions progressed and those whose conditions remained stable.

5. Discussion

In this retrospective study, we characterized the pattern, extent, and associations of emphysema identified on HRCT in 12 patients with HP and absent or mild smoking history. We found that the patients had emphysema regardless of their smoking status. Most commonly, the pattern of emphysema was predominantly upper lung and centrilobular, but it can occur in any lobe. Paraseptal emphysema was a frequent secondary pattern. The extent of emphysema was also quite variable, from mild to severe to focal bulla. The presence of emphysema was not limited to a specific HP antigen. Although our inclusion criteria included all patients with HP, emphysema occurred only in patients with CHP.

Our results are similar to a recent study [14] in which 16 patients with emphysematous changes on HRCT are compared to 17 patients without these changes in active farming associated HP. They also described upper zone predominance and centrilobular pattern as the most common features of emphysema in their cohort.

Barbee et al. [6] first described the presence of emphysema in patients with CHP in 1968. This finding was readdressed in the early 1990s when Remy-Jardin [11] et al. described emphysema in 14% of subacute cases and 46% of chronic cases (n = 21) among bird breeders with HP. Subsequently, more reports were published, mainly in the radiology literature, and they focused more on farmer's lung. According to a study [10], emphysematous changes are more common than fibrosis in chronic farmer's lung. The same finding was confirmed in a study looking at the long-term outcome with farmer's lung [7]. In another study [8], HRCT findings in 88 patients with farmer's lung were compared with those in 83 control farmers matched for age, sex, and smoking habits: Emphysema was present significantly more often in the patients with farmer's lung than in the control farmers (23% vs 7%).

In previous studies, the findings of emphysema were described in nonsmokers as well, although smokers were not completely excluded from the studies. Some of the previous studies did not check the α_1-AT level, an important cause of emphysema especially in nonsmokers. In our study, we excluded patients with a smoking history of at least 10 pack-years and checked the α_1-AT level, which was normal in 7 of 12 patients.

An important finding of our study was that these emphysematous changes are seen in HP cases caused by a variety of different antigens [15]. This is quite contrary to a previously described concept that HP is divided into two main clusters. Type 1 HP cases are more likely due to massive and intermittent exposure to microorganisms (mainly described in farmers). These antigens tend to cause airways problems leading to chronic bronchiolitis and emphysema. In contrast, chronic exposure to other kinds of antigens mainly avian antigens produces type 2 HP which more likely leads to fibrosis and carries poor prognosis [16].

We used a scoring system to quantitate the type and extent of emphysema associated with HP. We also tried to correlate this scoring to the PFT parameters, especially forced expiratory volume in the first second of expiration, but we could not detect any relationship. This could be due to the small number of patients in our study. Furthermore, in patients with combined restrictive and obstructive defects, one might not see an obvious obstructive defect. In these situations, DLCO is helpful, and we noticed that there might be an inverse relationship between higher ES and DLCO reduction. All patients had a reduced DLCO at baseline. Pulmonary hypertension may also contribute to DLCO reduction. In the present study, 2 patients had echocardiographic evidence of pulmonary hypertension, but this information was available for only 8 patients.

In a median follow-up period of 3.62 (range, 0.09–11.82) years, 2 patients died; 1 died of ruptured bulla, which might not be a common cause of death among patients with HP, but when present, it can have serious clinical implications. During this follow-up period, when 5 patients remained in stable condition and 5 became worse, DLCO was most helpful in detecting the decline in lung function. On HRCT ES score remained stable in more than half (5 out of 8 patients) of the patients whereas in 5 out of 8 patients fibrosis progressed. Treatment was quite variable, ranging from avoiding the offending antigen to taking prednisone with or without another immunosuppressant. There was no difference in these treatment strategies between patients whose condition remained stable and those whose condition progressed. A discrepancy existed between PFT and HRCT data in some of the follow-up data. According to one study, HRCT is more useful than PFTs for predicting mortality of these patients [17]. In our cohort, it is difficult to conclude which was more sensitive for detecting any change.

The pathogenesis of these emphysematous changes probably results from peribronchiolar lymphocytic inflammation. This inflammation leads to partial obstruction of the bronchioles, as commonly described in previous studies. This obliterative bronchiolitis leads to air trapping and rupture of the surrounding alveoli. In some patients with CHP, the same process causes cyst formation [18]. In short, alveolitis seems to be a continuum of the bronchiolitis and the balance between the 2 determines the obstructive, restrictive, or mixed pattern on PFTs [10].

Some of the limitations of our study reflect its retrospective

Table 3
Treatment and results of follow-up studies for 10 patients with emphysematous changes and chronic hypersensitivity pneumonitis.

Patients	Treatment	HRCT of the Chest[a]			PFT Results
		Emphysema		Fibrosis	
		Qualitative	Quantitative (ES)		
1	Avoidance of allergen alone	Stable	Stable	Progression	Progression
2	Prednisone and AZA	Progression	Slight Progression	Progression	Progression
3	Prednisone and MMF	Stable	Stable	Progression	Stable
4	Prednisone and AZA	Stable	Stable	Stable	Progression
5	Prednisone alone	Stable	Stable	Stable	Progression
6	Prednisone alone	Progression	Stable	Stable	Stable
7	Avoidance of allergen alone	Progression	Slight Progression	Progression	Stable
8	Prednisone alone	Progression	Progression	Progression	Progression
9	Prednisone and MMF				Stable
10	Prednisone alone				Stable

Abbreviations: AZA, azathioprine; ES, emphysema score; HRCT, high-resolution computed tomography; MMF, mycophenolate mofetil; PFT, pulmonary function test.
[a] Two patients did not have follow-up HRCT.

approach and the relatively small number of patients. We did not have follow-up HRCT data for 2 patients, and information about possible pulmonary hypertension was available for only 8 patients.

In conclusion, evidence of emphysema of varying severity can be seen on HRCT in patients with CHP independently of the smoking status and exposure to specific types of antigens. These emphysematous changes seem to progress at a slower pace compare to reticulations/ fibrosis.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for- profit sectors.

Conflicts of interest

None.

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