Chronic Hypersensitivity Pneumonitis: Differentiation from Idiopathic Pulmonary Fibrosis and Nonspecific Interstitial Pneumonia by Using Thin-Section CT[1]

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Purpose: To retrospectively assess the accuracy of thin-section computed tomography (CT) in distinguishing chronic hypersensitivity pneumonitis (HP) from idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP), with histologic results as the reference standard.

Materials and Methods: This retrospective study was approved by the institutional research boards of the participating centers, and informed consent was waived. There was HIPAA compliance for all U.S. patients. The study included 66 patients (36 men, 30 women; mean age, 58.8 years ± 10.9 [standard deviation]) with proved chronic HP ($n = 18$), IPF ($n = 23$), or NSIP ($n = 25$) who underwent CT. Two independent readers assessed the CT images, made a first-choice diagnosis, and noted the degree of confidence in the diagnosis. A general linear model was used to identify CT features that independently differentiated chronic HP from IPF and NSIP. Weighted κ statistic was used to assess interobserver agreement.

Results: The CT features that best differentiated chronic HP were lobular areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower zone predominance of abnormalities ($P \leq .008$). The features that best differentiated NSIP were relative subpleural sparing, absence of lobular areas with decreased attenuation, and lack of honeycombing ($P \leq .002$). The features that best differentiated IPF were basal predominance of honeycombing, absence of relative subpleural sparing, and absence centrilobular nodules ($P \leq .004$). A confident diagnosis was made in 70 (53%) of 132 readings. This diagnosis was correct in 66 (94%) of 70 readings. The accuracy for the entire cohort was 80%. Interobserver agreement for confident diagnosis was good to excellent ($\kappa = 0.77$–0.96).

Conclusion: Characteristic CT features of chronic HP, IPF, and NSIP allow confident distinction between these entities in approximately 50% of patients.

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Chronic hypersensitivity pneumonitis (HP) is often difficult to diagnose because the clinical and functional manifestations are nonspecific and frequently mimic those of chronic interstitial pneumonias, particularly idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP). The distinction of HP from IPF and NSIP is important because each disease is managed differently (1). Avoidance of the inciting antigen is the most important factor in the management of HP (1).

A multicenter study by Lacasse et al (2) showed that thin-section computed tomography (CT) can play an important role in the diagnosis of HP. Lacasse et al demonstrated that a combination of clinical and thin-section CT findings often enables a confident diagnosis of HP (2). However, the study did not assess the reliability of CT in helping to distinguish chronic HP from NSIP and IPF. Previous studies suggested that thin-section CT can be used to distinguish HP from IPF and other chronic interstitial diseases (3–6).

These studies, however, predate the new American Thoracic Society and European Respiratory Society classification of idiopathic interstitial pneumonias and did not assess the accuracy of CT in helping to distinguish chronic HP from NSIP (7). Furthermore, although HP can have a distinctive histologic appearance characterized by bronchiolocentric interstitial pneumonia, noncaseating granulomas, and cellular bronchiolitis, recent studies have shown that chronic HP can manifest histologic patterns of usual interstitial pneumonia or NSIP (8–10).

The aim of our study was to retrospectively assess the accuracy of thin-section CT in helping to distinguish chronic HP from IPF and NSIP by using histologic findings as the reference standard.

Advances in Knowledge

- The thin-section CT findings most helpful in differentiating chronic hypersensitivity pneumonitis (HP) from idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) are lobular areas with decreased attenuation and vascularity, centrilobular nodules, and lack of lower zone predominance of abnormalities.
- The thin-section CT findings allow confident distinction of chronic HP from IPF and NSIP approximately 50% of the time.

Materials and Methods

This retrospective study was approved by the institutional research boards of the three centers (Vancouver General Hospital, Vancouver, Canada; University of Colorado, Denver, Colo; and Sungkyunkwan University, Seoul, Korea) participating in the study and informed consent was waived. There was Health Insurance Portability and Accountability Act compliance for all U.S. patients.

Patients

Patient selection was made by using a review of the medical records of all patients who had received a diagnosis of HP, usual interstitial pneumonia, or NSIP on the basis of surgical lung biopsy retrieval at a large academic institution between 1998 and 2005. Only those patients with a final clinical diagnosis of chronic HP and known causative antigens, IPF, and NSIP and who underwent thin-section CT of the chest were included.

Chronic HP was defined by the presence of fibrosis at thin-section CT. All consecutive patients with chronic HP diagnosed since 1998 and an equivalent number of patients with biopsy-proved NSIP and IPF at two other academic centers that had CT images and pathologic slides for review were also included in the study. The patient group (n = 66) consisted of 18 patients with chronic HP, 23 with IPF, and 25 with NSIP.

The causative antigens of chronic HP were determined on the basis of clinical history or serum precipitin studies. Exposure to bird antigens (bird-breeder lung) was the most common etiologic agent of HP, being identified in nine (50%) of 18 patients. Other sources included mold (n = 4), red cedar (n = 2), feathers (n = 1), down-filled bedding (n = 1), and isocyanate (n = 1). Seven of the NSIP patients manifested a clinical syndrome consistent with underlying connective tissue disease: scleroderma (n = 2), rheumatoid arthritis (n = 1), polymyositis (n = 1), mixed connective tissue disease (n = 1), and undifferentiated connective tissue disease (n = 2). The remaining 18 patients had idiopathic NSIP.

The 66 patients (Table 1) included 36 men and 30 women with a mean age of 58.8 years ± 10.9 (standard deviation). The proportion of men to women was statistically different in chronic HP, IPF, and NSIP. There was a larger proportion of men in IPF (17 of 23, 74%) and chronic HP (13 of 18, 72%) than in NSIP (six of 25, 24%) ($P < .001$). There was no significant difference in age between the chronic HP (mean age, 61.1 years ± 10.2) and IPF groups (mean age, 62.0 years ± 6.9), but the av-

Implications for Patient Care

- CT can play an important role in the differential diagnosis of chronic HP from IPF and NSIP.
- Diagnosis of HP at CT prompts a thorough clinical history to determine inciting antigens and removal of the patient from the source.

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Abbreviations:
GGO = ground-glass opacification
HP = hypersensitivity pneumonitis
IPF = idiopathic pulmonary fibrosis
NSIP = nonspecific interstitial pneumonia

Author contributions:
Guarantors of integrity of entire study, C.I.S.S., N.L.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, C.I.S.S., N.L.M., D.A.L.; clinical studies, C.I.S.S., N.L.M.; statistical analysis, D.C.; and manuscript editing, all authors

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erage age of the patients with NSIP (mean age, 54.1 years ± 12.9) was lower than that of patients with chronic HP and IPF ($P = .02$).

Reference Standard for Histologic Diagnosis

The histologic diagnosis of chronic HP, IPF, or NSIP was initially made at each institution and was confirmed by an experienced lung pathologist (A.C., with 32 years experience) by using current diagnostic criteria (7,8,11,12). The interval between the surgical lung biopsy retrieval and CT ranged from 1 day to 36 months (median, 1 month). The 25 patients with NSIP included 21 with fibrotic NSIP, three with mixed fibrotic and cellular NSIP, and one with cellular NSIP.

CT Scanning Protocol

The thin-section CT examinations were performed with a variety of scanners, with 1.0–1.5-mm collimation ($n = 36$) at 10- or 20-mm intervals from the apex of the lung to the diaphragm or volumetrically with a multidetector CT scanner ($n = 30$) with 1.00–1.25-mm reconstruction. The scans were obtained with the patient in supine position at full inspiration and were reconstructed by using a high-spatial-frequency algorithm. Expiratory CT scans were obtained in 32 (48%) of 66 patients, including 12 (67%) of 18 patients with chronic HP, 10 (43%) of 23 with IPF, and 10 (40%) of 25 with NSIP. The expiratory images consisted of three to 12 thin-section images obtained at preselected levels ($n = 18$) or volumetrically with a multidetector CT scanner ($n = 14$).

Image Evaluation

The thin-section CT scans were randomized and reviewed independently by two thoracic radiologists (N.L.M. and C.I.S.S., with 22 and 4 years experience, respectively) without knowledge of clinical information or histologic diagnosis. The readers knew that only patients with chronic HP, IPF, and NSIP were included in the study, but did not know the frequency of occurrence for each. All images were reviewed at a workstation at window settings optimized for assessment of lung parenchyma (width, 1000–1500 HU; level, −600 to −700 HU). The images were assessed for the presence of reticulation (irregular linear opacities), areas of ground-glass opacification (GGO), consolidation, lobular areas with decreased attenuation associated with decreased vascularity, centrilobular nodules, cysts, honeycombing, traction bronchiectasis, and traction bronchiolectasis. The CT findings were interpreted on the basis of the recommendations of the Nomenclature Committee of the Fleischner Society (13).

The anatomic distribution was classified as peribronchovascular if there was a predominance of abnormalities along the bronchi and vessels, as peripheral if there was a predominance of abnormalities in the outer third of the lung, and as random if there was no peribronchovascular or peripheral predominance. Zone predominance was assessed as being upper, lower, or random. Upper lung zone predominance was considered present when the parenchymal abnormalities were most extensive above the level of the tracheal carina; and lower zone predominance, when they were most extensive below this level.

Relative subpleural sparing in the lung immediately adjacent to the pleura in the dorsal regions of the lower lobes (14), relative sparing of the lung below the level of the dome of the diaphragm (4), presence of fibrosis in upper lobes, basal and peripheral predominance of

Table 1

Demographic Data of Patients with Chronic HP, IPF, and NSIP

Characteristic	Chronic HP ($n = 18$)	IPF ($n = 23$)	NSIP ($n = 25$)	*P* Value
Sex				<.001
Male	13 (72)	17 (74)	6 (24)	
Female	5 (28)	6 (26)	19 (76)	
Age (y)				
Mean ± standard deviation	61.1 ± 10.2	62.0 ± 6.9	54.1 ± 12.9	.02
Range	44–75	52–74	24–79	NA

Note.—Numbers in parentheses are percentages. NA = not applicable. $P < .05$ indicates significant difference.

Table 2

Diagnostic Criteria for Chronic HP, IPF, and NSIP at Thin-Section CT

	Level of Confidence	
Diagnosis	Confident	Probable
Chronic HP	Centrilobular nodules, lobular areas of decreased attenuation and vascularity, mild to moderate extent of GGO away from fibrosis, no or minimal honeycombing, relative basal sparing	Mild to moderate extent of GGO, predominant peribronchovascular distribution and/or upper or middle zone predominance, no or minimal honeycombing, cysts
IPF	Reticulation in all lobes, extensive honeycombing, no or minimal GGO, peripheral and basal predominance	Bilateral reticulation, minimal honeycombing, minimal to moderate GGO, peripheral and basal predominance
NSIP	Extensive GGO, no or only mild reticulation, traction bronchiectasis, no honeycombing, basal predominance, relative subpleural sparing	Moderate GGO, moderate reticulation, traction bronchiectasis, no or minimal honeycombing, basal predominance

fibrosis, and basal predominance of honeycombing were also assessed. Subpleural refers to the region immediately adjacent to the costal pleura, for example, within 1 cm or less of the pleura, whereas peripheral refers to the outer third of the lung. The overall extent of areas of GGO, consolidation, and centrilobular nodules was classified independently as involving less than 25%, 25%–50%, or more than 50% of the lung parenchyma.

The extent of lobular areas with decreased attenuation when present was evaluated by counting the number of secondary lobules with decreased attenuation on all inspiratory images and was classified into one of the following categories: class 1 (up to four lobules), class 2 (five or more lobules and involving two to four lobes), and class 3 (five or more lobules in more than four lobes, the lingula being considered a separate lobe). Quantification of lobular areas with decreased attenuation and vascularity was limited to presence in nondependent lung and away from the superior segment of the lower lobe or the tip of the lingula or right middle lobe or within areas of severe fibrosis (15).

Cysts were considered as circumscribed, thin-walled, low-attenuating areas in the lungs. The number, size (<5 mm, 5–9 mm, or >9 mm), location (upper, middle, or lower lung zone), and distribution (peripheral or central) of lung cysts were also noted. The predominant background parenchymal pattern of lobes containing lung cysts (ie, areas of GGO or centrilobular nodules) was also recorded (16).

Following the initial assessment of

Table 3

Thin-Section CT Features of Patients with Chronic HP, IPF, and NSIP

Characteristic	Percentages			*P* Value
	Chronic HP ($n = 18$)	IPF ($n = 23$)	NSIP ($n = 25$)	
Reticulation	100 (36/36)	100 (46/46)	100 (50/50)	NA
GGO	100 (36/36)	96 (44/46)	100 (50/50)	.15
<25%	36 (13/36)	70 (32/46)	40 (20/50)	≤.007
25%–50%	36 (13/36)	23 (11/46)	30 (15/50)	.72
>50%	28 (10/36)	7 (3/46)	30 (15/50)	≤.02
Consolidation	6 (2/36)	0 (0/46)	4 (2/50)	.31
Lobular areas of decreased attenuation and vascularity	80 (29/36)	43 (20/46)	34 (17/50)	<.001
Class 1	19 (7/36)	26 (12/46)	26 (13/50)	.74
Class 2	22 (8/36)	13 (6/46)	8 (4/50)	.17
Class 3	39 (14/36)	4 (2/46)	0 (0/50)	<.001
Centrilobular nodules	56 (20/36)*	15 (7/46)	14 (7/50)	<.001
Cysts	39 (14/36)	0 (0/46)	12 (6/50)	<.001
Honeycombing	64 (23/36)	67 (31/46)	8 (4/50)	<.001
Traction bronchiectasis	94 (34/36)	100 (46/46)	100 (50/50)	.07
Traction bronchiolectasis	100 (36/36)	100 (46/46)	100 (50/50)	NA
Relative subpleural sparing	11 (4/36)	4 (2/46)	64 (32/50)*	<.001
Zonal predominance				
Upper	11 (4/36)	2 (1/46)	0 (0/50)	.02
Lower	31 (11/36)†	83 (38/46)	94 (47/50)	<.001
Random	58 (21/36)	15 (7/46)	6 (3/50)	<.001
Anatomic distribution				
Peripheral	25 (9/36)	78 (36/46)	72 (36/50)	<.001
Peribronchovascular	22 (8/36)	0 (0/46)	0 (0/50)	<.001
Peripheral and peribronchovascular	17 (6/36)	9 (4/46)	10 (5/50)	.50
Random	36 (13/36)	13 (6/46)	18 (9/50)	.03
Fibrosis				
Upper lobe	100 (36/36)	96 (44/46)	62 (31/50)	<.001
Peripheral predominance	78 (28/36)	100 (46/46)	92 (46/50)	.002
Basal predominance	39 (14/36)	76 (35/46)	84 (42/50)	<.001
Basal predominance of honeycombing	11 (4/36)	52 (24/46)*	4 (2/50)	<.001
Relative sparing of lung bases	39 (14/36)*	11 (5/46)	6 (3/50)	<.001
Air trapping‡	75 (18/24)	35 (7/20)	10 (2/20)	<.003

Note.—NA = not available. Numbers in parentheses are readings by two independent observers. $P < .05$ indicates a significant difference (Fisher exact test).

* Higher than other two percentages.

† Lower than other two percentages.

‡ Expiratory CT images were available in 32 of 66 patients (64 readings).

Figure 1

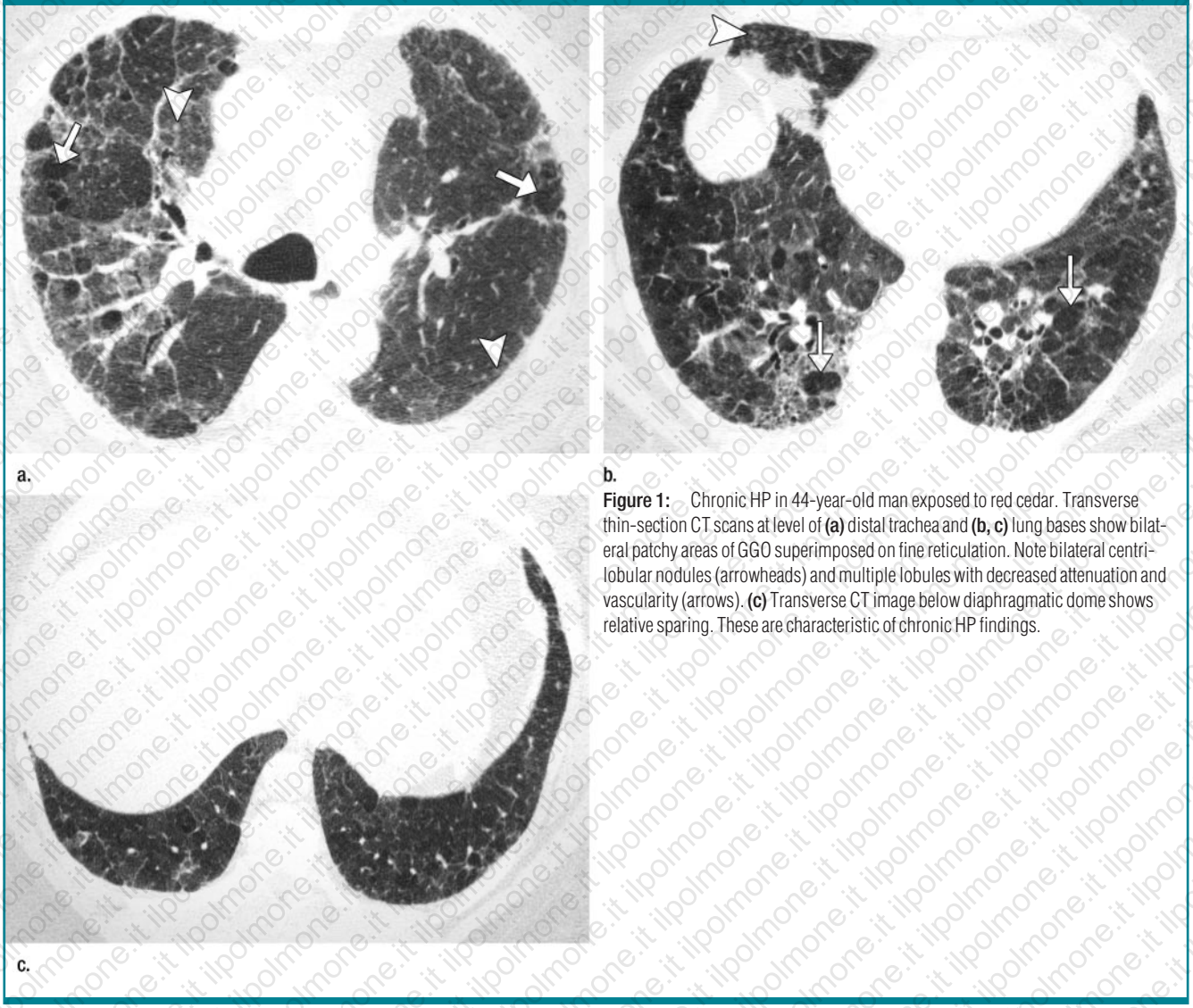


Figure 1: Chronic HP in 44-year-old man exposed to red cedar. Transverse thin-section CT scans at level of **(a)** distal trachea and **(b, c)** lung bases show bilateral patchy areas of GGO superimposed on fine reticulation. Note bilateral centrilobular nodules (arrowheads) and multiple lobules with decreased attenuation and vascularity (arrows). **(c)** Transverse CT image below diaphragmatic dome shows relative sparing. These are characteristic of chronic HP findings.

the thin-section CT images, each reader made a first-choice diagnosis of chronic HP, IPF, or NSIP for each patient and graded the degree of confidence in this diagnosis as being high (confident diagnosis) or low (probable diagnosis) according to specific diagnostic criteria (Table 2) (3–5,17–23). When the CT findings did not fit into any of the three diagnoses, the first-choice diagnosis was "indeterminate."

After reviewing the inspiratory CT images and making the first-choice diagnosis, the readers reviewed the expiratory CT images, when available, and noted the presence of air trapping. The readers also assessed whether the presence of air trapping on expiratory CT images changed the first-choice diagnosis and the level of confidence.

Statistical Analysis

Results are given as means ± standard deviations or medians and ranges (for nonnormally distributed variables). Comparisons between thin-section CT findings and the extent and distribution of abnormalities of chronic HP, IPF, and NSIP were performed with a two-tailed Fisher exact test. Group comparisons of the average CT scores of the two readers with their degree of confidence in the CT diagnosis for chronic HP, IPF, and NSIP were assessed by using a general linear model (eg, analysis of variance and regression) in which the two readers were considered to be replicates, duplicate observers whose readings could differ.

CT features predictive of chronic HP, IPF, and NSIP were identified by using a two-step process. First, for each reader, stepwise logistic regression was used to identify the CT features that predicted each disease type. These variables were then pooled and used in a general linear model in which the two readers were considered to be repli-

cates. A *P* value of less than .05 was considered to indicate a significant difference.

Sensitivity, specificity, positive predictive value, and accuracy of CT in helping distinguish these diseases were calculated with standard methods. The accuracy of CT for differentiating chronic HP from IPF and NSIP was calculated by comparing the CT diagnosis by the two readers with the final histologic and clinical diagnoses. Agreement between the observers in the assessment of findings and CT diagnosis was assessed by using the weighted κ statistic. The interobserver agreement was classified as follows: poor, κ = 0–0.20; fair, κ = 0.21–0.40; moderate, κ = 0.41–0.60; good, κ = 0.61–0.80; and excellent, κ = 0.81–1.00 (24).

Results

Thin-Section CT Findings

Interobserver agreement in the assessment of the CT findings was good to excellent (κ = 0.68–1.00). All 66 patients had reticulation, and at least 94% had traction bronchiectasis and bronchiolectasis and GGO according to both readers (Table 3). Although GGO was commonly seen at CT in patients with IPF (96%), it was more likely to involve less than 25% of the lung parenchyma ($P \leq .007$). Only 7% of readings in patients with IPF had a greater than 50% extent of GGO, compared with 28% for HP and 30% for NSIP ($P \leq .02$). Patients with chronic HP (Fig 1) were more likely to have lobular areas with decreased attenuation (80%), centrilobular nodules (56%), and cysts (39%) than patients with IPF (43%, 15%, and 0%, respectively) and NSIP (34%, 14%, and 12%, respectively) ($P \leq .001$).

One to three cysts were identified in 10 of 14 readings of chronic HP with cysts, and four or more cysts were seen at four of 14 readings. The cysts were always present in areas of GGO. Centrilobular nodules and areas of decreased lobular attenuation occurred in 86% and 100% of patients with chronic HP who had cysts, respectively (Fig 2). Cysts, when present in patients with NSIP, were three or fewer in number and were not associated with centrilobular nodules.

Lower zone predominance of abnormalities was more common in patients with IPF (83%) and NSIP (94%)

Figure 2

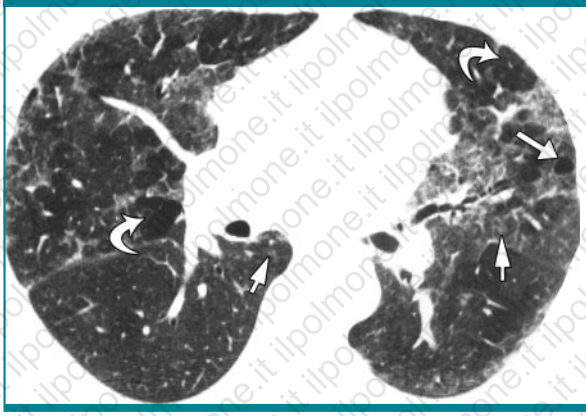


Figure 2: Chronic HP in 55-year-old man exposed to red cedar. Transverse thin-section CT scan at level of bronchus intermedius shows patchy GGO and fine reticulation with associated ill-defined centrilobular nodules (short straight arrows). Note lobular areas with decreased attenuation and vascularity bilaterally (curved arrows) and isolated cyst in left upper lobe (long straight arrow).

Figure 3

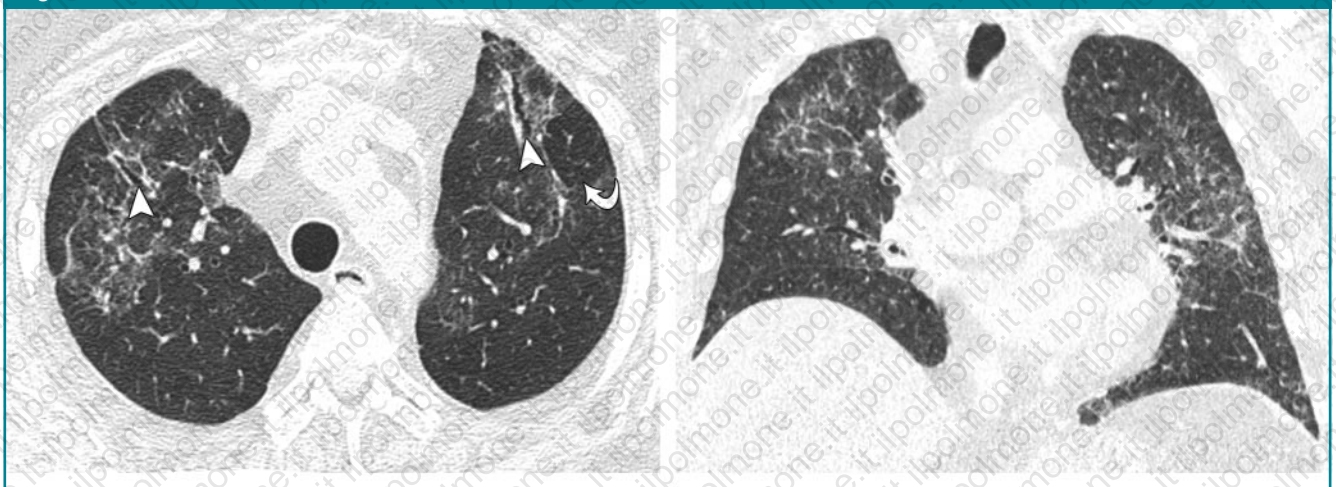


Figure 3: Chronic HP in 72-year-old man exposed to birds. **(a)** Transverse thin-section CT scan of upper lobes shows patchy GGO and superimposed reticulation in predominant peribronchovascular distribution. Note bronchial tortuosity and irregularity (traction bronchiectasis, arrowheads) due to fibrosis and peripheral lobule (arrow) with decreased attenuation and vascularity in left upper lobe. **(b)** Coronal reformation shows predominant distribution of abnormalities in upper lobes.

than in those with chronic HP (31%) ($P < .001$). Although upper zone predominance of abnormalities was uncommon, it was seen more frequently in patients with chronic HP (11%) than in those with IPF (2%) or NSIP (0%) ($P < .02$) (Fig 3). Upper lobe fibrosis was seen in all patients with chronic HP, compared with those with IPF (96%) and NSIP (62%) ($P < .001$). Random distribution of abnormalities was more common in patients with chronic HP (58%) than in those with IPF (15%) or NSIP (6%) ($P < .001$). Peribronchovascular distribution of abnormalities was uncommon but was seen only in patients with chronic HP (22%) ($P < .001$) (Fig 3).

Patients with IPF and NSIP were more likely to have peripheral predominance of abnormalities (78% and 72%, respectively) ($P < .001$) and fibrosis (100% and 92%, respectively) than those with chronic HP (25% and 78%, respectively) ($P = .002$). Similarly, basal predominance of fibrosis was seen more commonly in IPF (76%) and NSIP (84%) than in chronic HP (39%) ($P < .001$). No significant difference was observed in the frequency of honeycombing in patients with chronic HP (64%) and IPF (67%); however, patients with IPF (52%) were more likely to have basal predominance of honeycombing than were those with chronic HP (11%) ($P < .001$).

From the general linear model, the CT features that best differentiated chronic HP from NSIP and IPF were lobular areas with decreased attenuation, absence of lower zone predominance, and presence of centrilobular nodules ($P \leq .008$). Extensive lobular areas with decreased attenuation (class 3) ($P < .001$) and centrilobular nodules involving more than 25% of the lung parenchyma ($P < .001$) were more common in chronic HP; lower zone predominance was uncommon ($P < .001$). Although relative sparing of the lung below the level of the diaphragmatic dome was more common in patients with chronic HP ($P < .001$), it was not an important predictor (Figs 1, 3).

The best predictors of NSIP were relative subpleural sparing, absence of honeycombing, and absence of lobular areas with decreased attenuation ($P \leq .002$) (Fig 4).

The CT features that best differentiated IPF were basal predominance of honeycombing and an absence of relative subpleural sparing and centrilobular nodules ($P \leq .004$).

Expiratory scans were obtained in 32 (48%) of 66 patients. Air trapping was significantly more common in patients with chronic HP (75%) than in those with IPF (35%) or NSIP (10%) ($P < .003$); however, its presence did not change the first-choice diagnosis or the level of confidence for any patient.

Figure 4

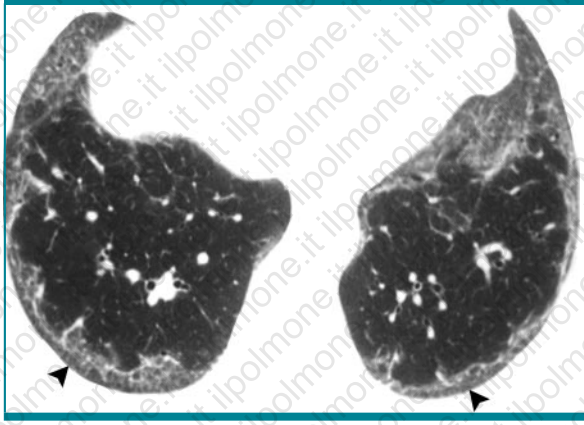


Figure 4: NSIP in 62-year-old woman. Transverse thin-section CT scan of basal segments of lower lobes shows peripheral GGO and mild reticulation with relative subpleural sparing (arrowheads) of lung immediately adjacent to pleura in dorsal lung regions. Note dorsal subpleural region is not normal but is less severely involved than region more than 1 cm away from pleura.

Table 4

Thin-Section CT Diagnosis of Chronic HP, IPF, and NSIP

Diagnosis	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Accuracy (%)
Chronic HP				
First-choice diagnosis ($n = 40$)	78 (28/36)	88 (84/96)	70 (28/40)	85 (112/132)
Confident diagnosis ($n = 24$)	61 (22/36)	98 (94/96)	92 (22/24)	88 (116/132)
Probable diagnosis ($n = 16$)	17 (6/36)	90 (86/96)	38 (6/16)	70 (92/132)
IPF				
First-choice diagnosis ($n = 31$)	57 (26/46)	94 (81/86)	84 (26/31)	81 (107/132)
Confident diagnosis ($n = 15$)	33 (15/46)	100 (86/86)	100 (15/15)	77 (101/132)
Probable diagnosis ($n = 16$)	24 (11/46)	94 (81/86)	69 (11/16)	70 (92/132)
NSIP				
First-choice diagnosis ($n = 42$)	76 (38/50)	95 (78/82)	90 (38/42)	88 (116/132)
Confident diagnosis ($n = 31$)	58 (29/50)	98 (80/82)	94 (29/31)	83 (109/132)
Probable diagnosis ($n = 11$)	18 (9/50)	98 (80/82)	82 (9/11)	67 (89/132)

Note.—Numbers in parentheses are readings of two independent observers.

Accuracy of CT Diagnosis

There was good interobserver agreement for overall CT diagnosis ($\kappa = 0.64$). The interobserver agreement for confident CT diagnosis of chronic HP, IPF, and NSIP was $\kappa = 0.90$, 0.77, and 0.96, respectively.

A first-choice diagnosis of chronic HP, IPF, or NSIP independent of the level of confidence was made in 113 (86%) of 132 readings (Table 4). These included 40 readings of chronic HP, 31 of IPF, and 42 of NSIP, as well as 19 of indeterminate diagnosis. A correct first-choice diagnosis was made in 92 (81%) of 113 readings, including 28 (70%) readings of chronic HP, 26

(84%) of IPF, and 38 (90%) of NSIP (Fig 5). A diagnosis with a high level of confidence was made in 70 (53%) of 132 observations. This diagnosis was correct in 66 (94%) of 70 readings, including 22 (92%) of 24 readings for chronic HP, 15 (100%) of 15 readings for IPF, and 29 (94%) of 31 readings for NSIP. In only one patient was chronic HP misdiagnosed as NSIP with a high level of confidence by both readers. In two patients, one of the observers misdiagnosed IPF as chronic HP (Fig 6) with a high level of confidence, but none of the observers misdiagnosed chronic HP as IPF when they made a confident diagnosis with CT imaging.

The overall accuracy of the entire cohort for a confident diagnosis was 80% (326 of 405), with a sensitivity of 50% (66 of 132), a specificity of 98% (260 of 264), and a positive predictive value of 94% (66 of 70).

Discussion

In our study, a confident first-choice diagnosis at thin-section CT was made in 70 (53%) of 132 readings in patients with chronic HP, IPF, and NSIP and was correct in 94% of these readings. These results are similar to those obtained by Lynch et al (4) in a study that included patients with IPF and HP; in that study, a first-choice diagnosis with a high level of confidence was made in 62% of cases, and this diagnosis was correct in 90% of observations. However, the study by Lynch et al predates the American Thoracic Society and European Respiratory Society classification of idiopathic interstitial pneumonias (7), included three patients with a histologic diagnosis of desquamative interstitial pneumonia as part of the spectrum of IPF, and did not include patients with NSIP. Furthermore, their analysis also included patients with subacute HP, which is easier to distinguish from IPF at CT because of the lack of fibrosis.

An important aspect of our study was the inclusion of patients with NSIP, a disease that has a variable appearance at CT and may mimic IPF or chronic HP (21). Although initial reports suggested that the CT findings of NSIP were nonspecific, more recent studies have shown that CT may allow distinction of NSIP from IPF in approximately 70% of patients (19,22). The findings that favor a diagnosis of NSIP include extensive GGO, mild reticulation, and absence of honeycombing. In our study, we added relative subpleural sparing as a characteristic feature of NSIP and found that it was one of the best predictors of NSIP, being present in 64% of patients with NSIP, in 11% with chronic HP, and in 4% with IPF (14,25). This may explain the higher diagnostic accuracy with confident diagnosis of NSIP in our study.

The thin-section CT features that best differentiated chronic HP from IPF and NSIP were the presence of lobular areas with decreased attenuation and centrilobular nodules and the lack of lower zone predominance. The extent of centrilobular nodules was greater in patients with chronic HP and is commonly associated with subacute changes. At histologic examination, centrilobular nodules correspond to cellular bronchiolitis, noncaseating granulomas, and bronchiolocentric interstitial pneumonitis (11).

The lobular areas with decreased attenuation and air trapping are presumed to be secondary to small airway obstruction due to cellular bronchiolitis or, less commonly, constrictive bronchiolitis (23,26). The presence of lobular areas with decreased attenuation in patients with chronic HP seen in our study (80%) was similar to that seen in the studies by Hansell et al (19 of 22 patients, 86%) (23) and Small et al (15 of 20 patients, 75%) (26), although the majority of patients in those studies had subacute HP.

In our patients with HP, the presence of centrilobular nodules (56%) was similar to that described by Lynch et al (4) in eight (42%) of 19 patients with chronic HP and Hansell et al (23) in 12 (54%) of 22 patients. Centrilobular nodules appear to be less common in chronic HP than in subacute HP and were seen in 14 (70%) of 20 patients with subacute HP reported by Small et al (26).

Cysts were also seen more commonly in patients with chronic HP (39%) than in those with IPF or NSIP. Recently, Franquet et al (16) described lung cysts in 13% of patients with subacute HP. Similar to the cysts described in subacute HP, the cysts in chronic HP were only seen in areas of GGO. They are presumed to result from bronchiolitis and bronchiolar obstruction (16).

Figure 5

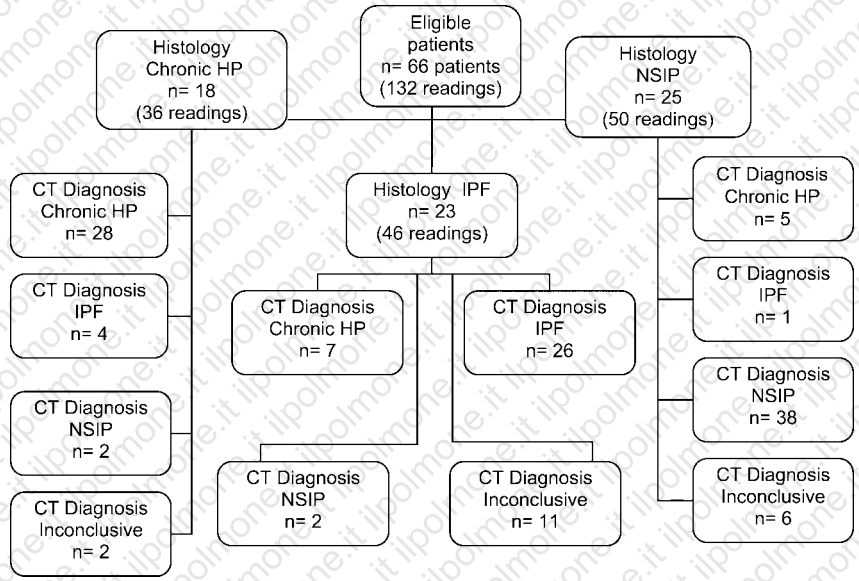
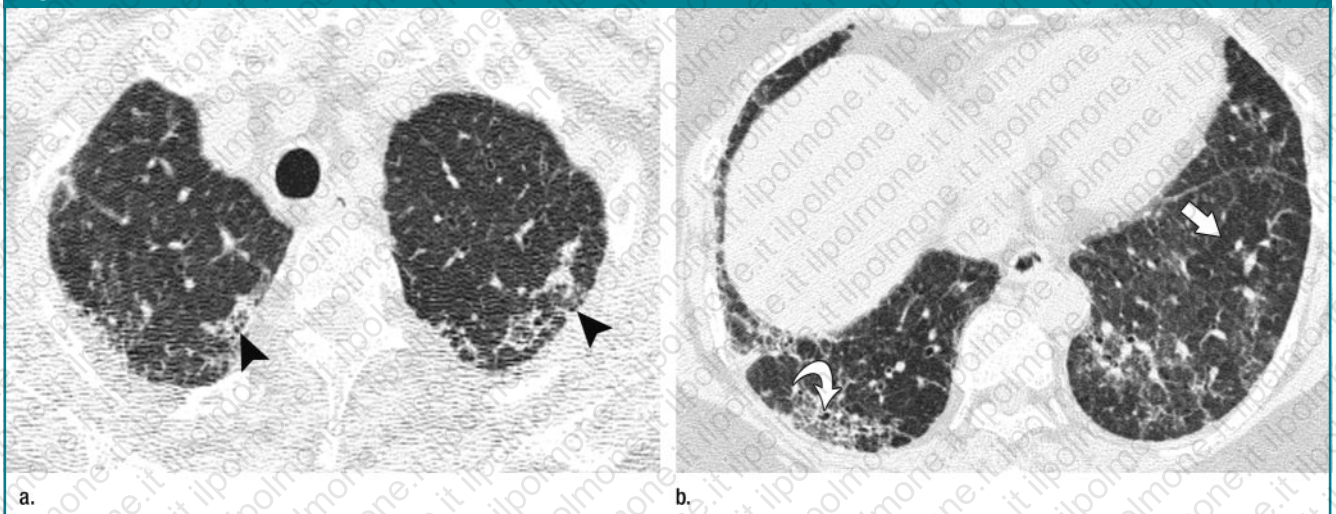


Figure 5: Patient flow diagram.

Figure 6



a. b.

Figure 6: IPF mimicking chronic HP in 76-year-old woman. **(a)** Transverse thin-section CT scan of upper lobes shows minimal GGO and fine reticulation in predominantly peripheral distribution and honeycomb cysts (arrowheads). **(b)** Transverse thin-section CT scan of lung bases shows mild reticulation and traction bronchiectasis (curved arrow), patchy GGO, and several lobules with decreased attenuation and vascularity (straight arrow). Two observers made incorrect first-choice diagnosis of chronic HP, one with low and one with high level of confidence. The histologic findings were characteristic of IPF. No etiologic agent was identified.

The higher prevalence of cysts in patients with chronic HP compared with that seen in patients with subacute disease in the study by Franquet et al (16) may be related to the greater duration of the disease or the presence of fibrosis.

Lobular areas with decreased attenuation were seen in 43% of patients with IPF and in 34% with NSIP. The anatomic cause of decreased attenuation in these conditions is unclear. It may be the result of fibrosis leading to compensatory overinflation of adjacent relatively uninvolved lobules. To minimize this potential effect we did not assess lobular areas with decreased attenuation in areas of severe fibrosis. Honeycombing was seen in 64% of patients with chronic HP in our study, which is similar to the frequency seen in the study by Adler et al (5) in patients with chronic HP (11 of 16, 69%), but higher than that seen by Lynch et al (three of 19, 16%) (4).

No significant difference was observed in the frequency of honeycombing in patients with chronic HP and IPF; however, patients with IPF were more likely to have basal predominance of honeycombing than were those with chronic HP ($P < .001$). Similar to previous studies, we found that patients with IPF were more likely to have basal predominance of honeycombing and lower zone and peripheral predominance of abnormalities (22,27). As shown in previous studies (7,14,19,25), we found that patients with IPF tend to be older than those with NSIP. The average age of patients with chronic HP in our study (61 years) was similar to that of patients with IPF.

Our study had limitations. It was retrospective, included a small sample size, and only included patients with proved chronic HP, IPF, and NSIP. In clinical practice the differential diagnosis would include other interstitial lung diseases. However, the selection of patients was intentional, owing to the considerable overlap of the clinical, functional, and radiologic manifestations of chronic HP, IPF, and NSIP. Most of the other interstitial lung diseases can be readily distinguished by their characteristic clinical, functional, or CT findings. The presence of only three considerations in the differential diagnosis also may have resulted in an artificially high interobserver agreement and sensitivity and specificity of CT in each diagnosis.

Another limitation of our study was that we only included patients with biopsy-proved disease from three large referral centers, creating bias toward patients with less typical findings. Patients with characteristic thin-section CT findings of IPF and clinical history consistent with IPF seldom undergo lung biopsy. Also, patients with characteristic CT findings of chronic HP and history of exposure seldom require lung biopsy for definitive diagnosis. A selection bias may also have been introduced into the study by only including patients with proved chronic HP and known inciting antigens.

In clinical practice a histologic and clinical diagnosis of chronic HP is sometimes made without the inciting antigen ever being identified. On the other hand, the inclusion of a small number of patients with NSIP associated with connective tissue disease may have resulted in an overestimation of small airway diseases in NSIP and led to an underestimation of the value of thin-section CT in distinguishing chronic HP from NSIP. Despite these limitations, our study demonstrates that the CT findings are often characteristic enough to allow confident distinction of chronic HP from IPF and NSIP.

In conclusion, the features that best differentiate chronic HP from IPF and

NSIP at thin-section CT are lobular areas with decreased attenuation, presence of centrilobular nodules, and a lack of lower zone predominance of the abnormalities. NSIP can be differentiated from chronic HP mainly by the presence of relative subpleural sparing, absence of lobular areas with decreased attenuation, and lack of honeycombing. IPF can be differentiated from chronic HP by the basal predominance of honeycombing and absence of relative subpleural sparing and centrilobular nodules. In approximately 50% of patients the characteristic pattern and distribution of findings at thin-section CT allow confident distinction between chronic HP, IPF, and NSIP. The CT findings combined with the clinical history, which was not available to the readers in our study, may preclude the need for biopsy in selected patients.

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