

Diffuse Pulmonary Ossification in Fibrosing Interstitial Lung Diseases: Prevalence and Associations¹

Ryoko Egashira, MD, PhD
Joseph Jacob, MRCP, FRCR, DTM&H
Maria A. Kokosi, MD
Anne-Laure Brun, MD
Alexandra Rice, MB, BChir, FRCPath
Andrew G. Nicholson, DM, FRCPath
Athol U. Wells, MD, FRCP
David M. Hansell, MD, FRCP, FRSM

Purpose:

To investigate the prevalence of diffuse pulmonary ossification (DPO) in patients with fibrosing interstitial lung disease (ILD) and determine whether there are differences among the types of ILDs.

Materials and Methods:

Institutional review board approval was given and patient consent was not required for this study. The study population comprised 892 consecutive patients with fibrosing ILD, including 456 patients with idiopathic pulmonary fibrosis (IPF) (men, 366; women, 90; median age, 72 years [range, 38–93 years]), 244 with nonspecific interstitial pneumonia (men, 79; women, 165; median age, 60.5 years [range, 23–86 years]), and 192 with chronic hypersensitivity pneumonitis (men, 76; women, 116; median age, 66 years [range, 35–88 years]). Pulmonary ossifications were recorded when nodules (<4 mm diameter) were identified on bone window images (width, 2500 HU; level, 500 HU). DPO was defined as 10 or more bilateral nodular ossifications (definition 1) or as one or more lobes with five or more bilateral nodular ossifications (definition 2). Relationships among pulmonary ossification and parenchymal patterns, clinical parameters, and multidisciplinary team diagnoses were examined. The prevalence of DPO was compared with the χ^2 statistic or Fisher exact test, and multivariate analysis was performed with logistic regression.

Results:

In the whole population, the prevalence of DPO was 166 (18.6%) and 106 (11.9%) of 892 patients according to definitions 1 and 2, respectively. The prevalence of DPO (definition 1) was significantly higher in patients with IPF (28.5%) than in those without IPF (8.3%, $P < .001$). Nine of 192 (4.7%) had chronic hypersensitivity pneumonitis ($P < .001$), and 27 of 244 (11.1%) had nonspecific interstitial pneumonia ($P < .001$). At multivariate analysis, DPO according to definition 1 was an independent predictor of IPF diagnosis ($P < .001$) and male sex ($P = .003$). Coarseness of fibrosing ILD ($P = .011$) and IPF diagnosis ($P = .016$) were independently associated with pulmonary ossification profusion.

Conclusion:

DPO is common in patients with fibrosing ILD and is significantly more prevalent in patients with IPF than in those with other fibrosing ILDs, and thus, computed tomographic signs of DPO may be helpful for diagnosis of IPF.

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Online supplemental material is available for this article.

¹ From the Department of Radiology (R.E., J.J., A.L.B., D.M.H.), Interstitial Lung Disease Unit (M.K., A.U.W.), and Department of Histopathology (A.R., A.G.N.), Royal Brompton and Harefield NHS Foundation Trust, London, England. From the 2015 RSNA Annual Meeting. Received November 23, 2015; revision requested January 8, 2016; revision received April 20; accepted May 20; final version accepted December 8. Address correspondence to R.E., Department of Radiology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga-City, Saga 849-8501, Japan (e-mail: egashira@cc.saga-u.ac.jp).

D.M.H. supported by the National Institute of Health Research Senior Investigator Award.

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Diffuse pulmonary ossification (DPO) in patients without background lung disease is a rare condition (1.63 of 1000 cases at autopsy) (1). The cause of the deposition of numerous small ossified nodules throughout the lung parenchyma is unknown (2,3). DPO has been reported in various contexts, including in patients with normal lungs (idiopathic DPO) (4,5); in those with preexisting cardiac diseases, particularly pulmonary congestion secondary to mitral stenosis (6,7); after severe lung injury (8,9); and in association with fibrosing interstitial lung disease (ILD) (10–15). Previous studies of DPO have been limited by small patient numbers (11,14) or have been based on autopsy studies (1,16) and thus do not provide a clear idea of the frequency of ossification in fibrosing ILDs or its associations. The aims of our study were to determine the prevalence of DPO in patients with different types of fibrosing ILD and to determine whether there are differences among them.

Advances in Knowledge

- Diffuse pulmonary ossification, defined as at least one bilateral ossification with at least 10 small dense nodules, is significantly more prevalent in patients with idiopathic pulmonary fibrosis (IPF, 28.5%) than in those without IPF (8.3%, $P < .001$).
- The profusion of nodular ossifications was independently associated with male sex ($P = .003$), coarseness of interstitial lung disease ($P = .011$), and the diagnosis of IPF ($P = .016$).
- Ninety-six percent of pulmonary ossifications were seen in areas of fibrotic interstitial lung disease, predominantly in areas of reticulation.
- Diffuse pulmonary ossification at CT was independently associated with a diagnosis of IPF ($P < .001$), whereas ossification at biopsy was not associated with this diagnosis when CT findings were considered.

Materials and Methods

Institutional approval for the assessment of clinically indicated computed tomographic (CT) examinations and analysis of patient data were granted. Informed patient consent was not required for this retrospective study.

Study Population

Medical records for all consecutive new patients ($n = 2411$) in the Department of Interstitial Lung Disease at our institution between January 1, 2007, and November 30, 2013, were retrieved from the inpatient and clinic computerized databases and were reviewed. Patients without a diagnosis of fibrosing ILD that was made by a multidisciplinary team were excluded ($n = 580$). Patients with a clinically indicated volumetric thin-section CT examination performed at our institution formed the initial study population ($n = 1548$) from which further exclusions were made, which is detailed in Appendix E1 (online).

Each patient was assigned to one of three diagnostic categories on the basis of multidisciplinary evaluations: (a) idiopathic pulmonary fibrosis (IPF) ($n = 456$); (b) nonspecific interstitial pneumonia (NSIP) ($n = 244$), including NSIP of unknown cause (idiopathic) ($n = 42$), NSIP with background classic connective tissue disease ($n = 150$) (17–23), NSIP with interstitial pneumonia with autoimmune features ($n = 52$) (24); or (c) chronic hypersensitivity pneumonitis ($n = 192$). The patients with connective tissue disease-related NSIP included those with systemic sclerosis ($n = 58$), overlapping connective tissue disease ($n = 28$, 15 of

28 with overlapping systemic sclerosis), polymyositis or dermatomyositis ($n = 22$), rheumatoid arthritis ($n = 15$), mixed connective tissue disease ($n = 12$), Sjögren syndrome ($n = 11$), and systemic lupus erythematosus ($n = 4$). Basic clinical data including age, sex, smoking history (ever vs never), histopathologic diagnoses, and final multidisciplinary team diagnosis were also gathered.

CT Image Interpretation

CT examination protocols are described in Appendix E2 (online). One chest radiologist (R.E., with 14 years of experience in thoracic radiology) reviewed the CT studies without reference to any clinical or histologic information. Evaluation of interobserver variation was undertaken by comparing the readings for a random subgroup of 100 patients from the main cohort with those of a second radiologist (A.L.B., with 13 years of experience in thoracic radiology). By using a Mersenne Twister random number generator, 100 CT examinations of patients with IPF, NSIP, or chronic hypersensitivity pneumonitis were selected. The proportion of the diagnostic groups in the sample of 100 patients reflected the proportion

<https://doi.org/10.1148/radiol.2017152419>

Content codes: **CH** **CT**

Radiology 2017; 284:255–263

Abbreviations:

DPO = diffuse PO
ILD = interstitial lung disease
IPF = idiopathic pulmonary fibrosis
NSIP = nonspecific interstitial pneumonia
PO = pulmonary ossification
UIP = usual interstitial pneumonia

Author contributions:

Guarantors of integrity of entire study, R.E., D.M.H.; 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; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, R.E., J.J., A.L.B.; clinical studies, R.E., J.J., M.K., A.L.B., D.M.H.; experimental studies, A.L.B., A.R.; statistical analysis, R.E., J.J., A.U.W.; and manuscript editing, R.E., J.J., A.L.B., A.G.N., A.U.W., D.M.H.

Conflicts of interest are listed at the end of this article.

Implication for Patient Care

- The observation of the strong association between nodular ossification and IPF, when compared with nonspecific interstitial pneumonia and chronic hypersensitivity pneumonitis, may improve diagnostic specificity in patients with IPF, particularly in those without the characteristic honeycombing pattern of usual interstitial pneumonia.

of the diagnostic groups in the parent cohort. All findings were scored on a lobar basis; the left upper lobe was considered as two lobes (the lingula was considered as a separate lobe).

Evaluation of pulmonary ossification.—Small opacities were recorded as pulmonary ossifications (POs) if they were intrapulmonary nodules of calcific attenuation identifiable on bone window settings with a width of 2500 HU and a level of 500 HU and maximal short-axis diameter less than 4 mm. Calcified nodules greater than 4 mm in diameter and/or those suspected of being calcified granulomata were recorded separately. All POs were analyzed for shape and number. For analysis of shape, POs were categorized as nodular or dendriform (the latter were defined as branching structures on contiguous CT images). Individual small rod-like opacities were classified as nodular. For analysis of number, nodular POs were individually summed per lobe. Dendriform PO was evaluated as a volume of affected lung, and thus, individual dendriform structures were not recorded.

In cases where five or more nodular POs were present in a lobe and for all lobes with dendriform POs, the extent, background fibrotic lung parenchymal pattern, and distribution on the axial plane were analyzed. For analysis of extent, a visual estimation was made to determine if nodules occupied more or less than 50% of a lobe. For analysis of PO distribution, the predominant distribution of PO in the axial plane was classified into one of four categories: (a) pleural (abutting the pleura), (b) cortical zone (peripheral third of the lung in horizontal section), (c) medullary zone (in the rest of the inner lung [25]), and (d) random (no predominance). Whether the PO was located in normal or abnormal lung was also documented. For analysis of the pattern of background lung, the proportion of nodules located in areas of ILD and the predominant abnormal lung parenchymal pattern were recorded.

To allow analyses of dendriform ossifications (which were not considered or recorded as individual nodules), an

average nodule score was constructed to correct for the number of lobes with dendriform ossification:

$$\text{ANS} = \sum (N_{\text{NPOL}}) / 6 - L_{\text{DO}},$$

where ANS is the average nodule score, N_{NPOL} is the number of nodular pulmonary ossifications in each lobe, and L_{DO} is the number of lobes with dendriform ossification. For patients with dendriform ossification in all six lobes (denominator of zero in the formula), lobar nodule scores were imputed as average nodule scores in lobes of patients with dendriform ossification in some but not all lobes.

Definition of DPO.—Because no radiologic definition for the entity of DPO exists (3,11,14,26), we selected two definitions in line with previous descriptions of “bilateral, multiple tiny ossifications or bony nodules,” constructed with ease of application in mind. Definition 1 was one or more ossifications that appear bilaterally, with a total of at least 10. Definition 2 was at least one lobe that contains at least five bilateral ossifications. Interobserver agreement for these two definitions was evaluated after a second radiologist evaluated a random selection of 100 CT examinations.

Evaluation of ILD.—The extent of ILD was scored on a lobar basis for patterns, including ground-glass opacity, fine and coarse reticulation, honeycombing, and areas of consolidation, by using the Fleischner Society’s glossary of terms for thoracic imaging (27), as detailed in Appendix E3 (online). The extent of the individual patterns was scored as 0, 0%; 1, less than 25%; 2, 25%–50%; and 3, greater than 50%. The most extensive parenchymal pattern in each lobe was recorded as a categorical coarseness grade 0, normal lung; grade 1, ground-glass opacity; grade 2, fine reticulation; grade 3, coarse reticulation; and grade 4, honeycombing.

The primary coarseness score represented the sum of coarseness grades (grades 0–4). To remove the effect of pattern extent and prevent underestimation of coarseness severity for patients in whom some lobes had no parenchymal abnormality, the score was

adjusted proportionately to a six-lobe score (28).

$$\text{CS} = (\text{CG}_{\text{ru}} + \text{CG}_{\text{lu}} + \text{CG}_{\text{rm}} + \text{CG}_{\text{lm}} + \text{CG}_{\text{rl}} + \text{CG}_{\text{ll}}) / L_{\text{ILD}} \cdot 6,$$

where CS is coarseness score, CG is coarseness grade, ru is right upper, lu is left upper, rm is right middle, lm is left middle (lingula), rl is right lower, ll is left lower, and L_{ILD} is the number of lobes with ILD. In addition to the predominant parenchymal pattern, the presence or absence of emphysema, calcified hilar or mediastinal lymph nodes, and pleural plaques were recorded.

Histopathologic Evaluation for Ossification

Biopsy material was available for review by a thoracic pathologist (A.R., with 13 years of experience) in 119 of 149 patients who had undergone surgical lung biopsy, and the following features were recorded: presence or absence of ossification, condition of the background lung of ossification, highest number of ossifications seen on a slide, and presence or absence of calcified granulomas.

Statistical Analyses

Statistical analyses were performed by using software (Stata version 4; Stata, College Station, Tex). Group comparisons were made by using the Wilcoxon rank-sum, χ^2 statistic, and Fisher exact tests. Correlations were quantified by using the Spearman rank correlation test. *P* values of less than .05 were considered to indicate a statistically significant difference. Independent determinants of a diagnosis of IPF were identified by using stepwise logistic regression analysis (with removal at a level of significance of *P* = .01). A multiple linear regression model was constructed to identify independent determinants of average nodule score. Zero skewness logarithmic transformation was required to remove model heteroscedasticity. Interobserver agreement for the two definitions of pulmonary ossification was established by using the κ coefficient of agreement (poor, κ = 0.00–0.20; 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) (29).

Table 1

Baseline Demographic and Thin-Section CT Data

Characteristic	IPF (n = 456)	Non-IPF (n = 436)	NSIP (n = 244)	Chronic Hypersensitivity Pneumonitis (n = 192)	P Value
Age at time of CT (y)*	72 (38–93)	64 (23–88)	60.5 (23–86)	66.0 (35–88)	<.001
Male sex	366 (80.3)	155 (35.6)	79 (32.4)	76 (39.6)	<.001
Ever smoker (n = 854)	293 (66.9)	172 (41.3)	96/232 (41.4) [†]	76/184 (41.3) [†]	<.001
Extent of ILD at CT* [‡]	12 (2–18)	12 (2–18)	11 (2–18)	14 (3–18)	<.001
Coarseness at CT (n = 887)* [‡]	13 (7.2–24)	12 (6–18)	12 (6–18)	12 (6–18)	<.001
Honeycombing	127 (27.9)	17 (3.9)	3 (1.2)	14 (7.3)	<.001
Emphysema	196 (43.0)	80 (18.3)	42 (17.2)	38 (19.8)	<.001
Calcified granuloma	68 (14.9)	40 (9.2)	20 (8.2)	20 (10.4)	.01
Pulmonary ossification					
Average nodule score (n = 887)* [‡]	0.67 (0–71)	0.17 (0–24)	0.17 (0–24)	0 (0–9.2)	<.001
DPO according to definition 1	130 (28.5)	36 (8.3)	27 (11.1)	9 (4.7)	<.001
DPO according to definition 2	86 (18.9)	20 (4.6)	15 (6.1)	5 (2.6)	<.001

Note.—Unless otherwise indicated, data are number of patients, with percentages in parentheses. Differences between patients with IPF and those without IPF (non-IPF) remained statistically significant when patients with IPF were compared separately with patients with NSIP and chronic hypersensitivity pneumonitis, with the exception of the prevalence of calcified granulomas (IPF vs NSIP, $P = .011$; IPF vs chronic hypersensitivity pneumonitis, $P = .127$).

* Data in parentheses are the range.

[†] Data are for proportion of patients for whom information was available.

[‡] Data for patients with only dendriform ossification were not included in the statistical analyses. $N = 887$.

To examine the applicability of the two definitions for differentiation of IPF from non-IPF diagnoses, diagnostic sensitivity and specificity of different thresholds of the average nodule score were calculated according to the two specified definitions. For the purposes of this study, a multidisciplinary team diagnosis of IPF was the reference standard. The effect of age, sex, and DPO on positive predictive value were also tested (Appendix E4 [online]).

Results

Patient demographics, CT findings, and the prevalence of DPO in patients with IPF compared with the other patients (those with chronic hypersensitivity pneumonitis and NSIP) are shown in Table 1. In the whole study population, DPO had a significantly higher prevalence in patients with IPF (28.5%) than in those without IPF (8.3%, $P < .001$).

Prevalence and Characteristics of Ossification at CT

In the whole cohort (892 patients), nodular and dendriform ossification was present in at least one lobe in 590 (66%) and 37 (4%) patients, respectively. Of the

37 patients with dendriform ossification, only five had purely dendriform ossification in all six lobes (0.6% of the study population). Thirty-two of 37 (86%) patients had coexistent nodular ossification in other lobes. POs were identified more frequently in the lower lobes (59%) than in the upper lobes (28%) and the lung periphery (the cortical [55%] or pleural [39%] areas). Ninety-six percent of POs were located in areas of reticulation and 3% showed honeycombing (Fig 1). POs were conspicuously absent from areas of ground-glass opacity and normal lung parenchyma. As shown in Table 1, the overall prevalence of DPO according to definition 1 ($n = 166$, 18.6%) was higher than that according to definition 2 ($n = 106$, 11.9%; $P = .005$, McNemar χ^2 test); there was good concordance between the results according to definition 1 and those according to definition 2 ($\kappa = 0.63$).

Relationships between Nodular Ossification and Clinical and CT Parameters

In the analysis of the entire cohort, increased nodular profusion was associated with male sex, a positive smoking history, increasing age, honeycombing, emphysema, and a higher coarseness

score (Tables 2, 3). In the multiple linear regression analysis, male sex ($P = .003$), higher coarseness score ($P = .011$), and diagnosis of IPF ($P = .016$) were independently associated with a higher average nodule score. No significant relationship was identified between the presence of lymph nodes or pleural calcification and DPO. Pleural plaques were seen only in 40 patients and were not analyzed further. Nodular POs were observed more frequently in patients with NSIP with underlying systemic sclerosis ($n = 73$, 55 patients with pure systemic sclerosis and 18 with overlapping systemic sclerosis; $P < .001$) than in those with other causes of and associations with NSIP.

Differentiation of Patients With and Patients Without IPF

Univariate logistic regression analysis results showed that a diagnosis of IPF (as opposed to chronic hypersensitivity pneumonitis or NSIP) was associated with age, sex, smoking history, the presence of honeycombing, emphysema, ILD coarseness score, and DPO (according to either definition) (Table 1). At stepwise multivariate logistic regression analysis, a diagnosis of IPF was

Figure 1

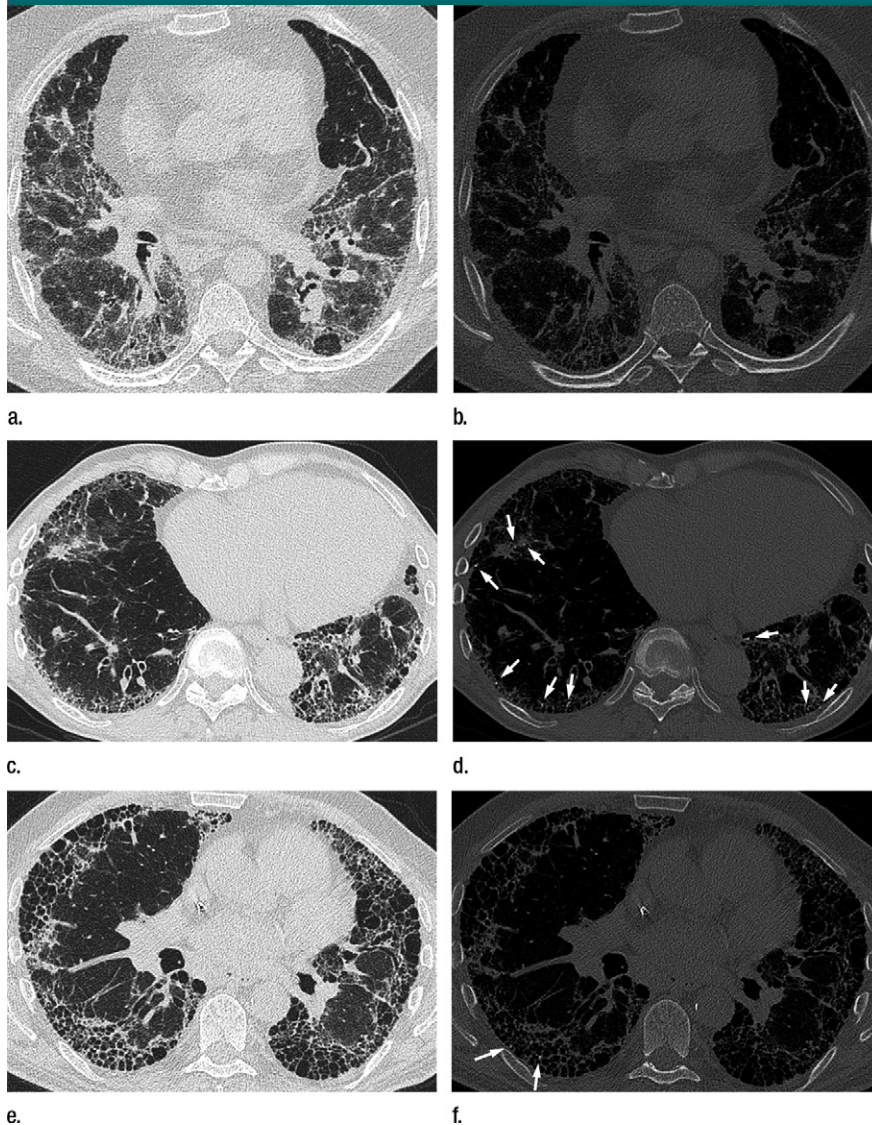


Figure 1: (a, b) Sample CT images in a 55-year-old woman with chronic hypersensitivity pneumonitis. (a) Axial thin-section CT image (width, 1500 HU; level, -500 HU) through lower zone shows extensive ground-glass opacity with some fine reticulation and some lobules of decreased attenuation. Coarseness grade was 8. (b) Bone window image shows no apparent highly attenuating nodules (width, 2500 HU; level, 500 HU). Average nodule score was 0. (c, d) Sample CT images in a 76-year-old man with IPF. (c) Axial thin-section CT image through lower zones (width, 1500 HU; level, -500 HU) shows mixed fine and coarse reticulation with subpleural distribution. Coarseness grade was 16. (d) Bone window image (width, 2500 HU; level, 500 HU) shows numerous highly attenuating small nodules (arrows), appearing mainly in areas of reticulation. Some nodules are seen on pleural surface. Average nodule score was 63.67. (e, f) CT images in an 80-year-old man with IPF. (e) Axial thin-section CT image (width, 1500 HU; level, -500 HU) shows subpleural coarse reticulation and extensive honeycomb destruction. Coarseness grade was 18. (f) Bone window image (width, 2500 HU; level, 500 HU) shows two highly attenuating nodules (arrows) in an area of honeycombing in right lower lobe. Average nodule score of this case was 13.67 (*Fig 1 continues*).

independently associated with DPO (according to definition 1), age, sex (male), history of smoking, honeycombing, and ILD coarseness score (Table 4).

Sensitivity, Specificity, and Interobserver Agreement

To examine the applicability of the two definitions for differentiating IPF from non-IPF diagnoses, diagnostic sensitivity and specificity of different thresholds of the average nodule score, including the two specified definitions, were plotted (Fig 2). Specificity reached a plateau beyond an average nodule score of 2. Although sensitivity decreased slightly with increasing average nodule score, overall, both sensitivity and specificity remained similar among all the chosen nodule thresholds. The positive predictive value for the presence of IPF was found to be 90% in men aged older than 65 years when DPO definition 1 was used and 93% when DPO definition 2 was used (Appendix E4 [online]). Interobserver agreement in 100 randomly selected patients was good (definition 1, $\kappa = 0.66$; definition 2, $\kappa = 0.61$).

Thin-section CT Features and Pathologic Examination of Lung Biopsy

Average nodule scores were higher (median, 1.83; range, 0–40.2) in the 31 patients with nodular ossification at biopsy than in the remaining 88 patients (median, 0.2; range, 0–6; $P < .001$). The presence of ossification at histologic examination of a biopsy specimen was associated with a higher prevalence DPO on thin-section CT images according to definition 1 (18 of 31 [58%] vs four of 88 [5%]; $P < .001$) and the more-stringent definition 2 (14 of 31 [45%] vs two of 88 [2%]; $P < .001$). Ossification was seen at biopsy of fibrotic lungs in all 31 patients but was also present in histologically normal lung tissue in three patients. Calcified granulomas were present in only nine (7.5%) patients and were not associated with a significant difference in average nodule score.

Diagnostic Distinctions in Patients Who Underwent Lung Biopsy

Ossifications were identified at pathologic examination of lung biopsy more

Figure 1 (continued)

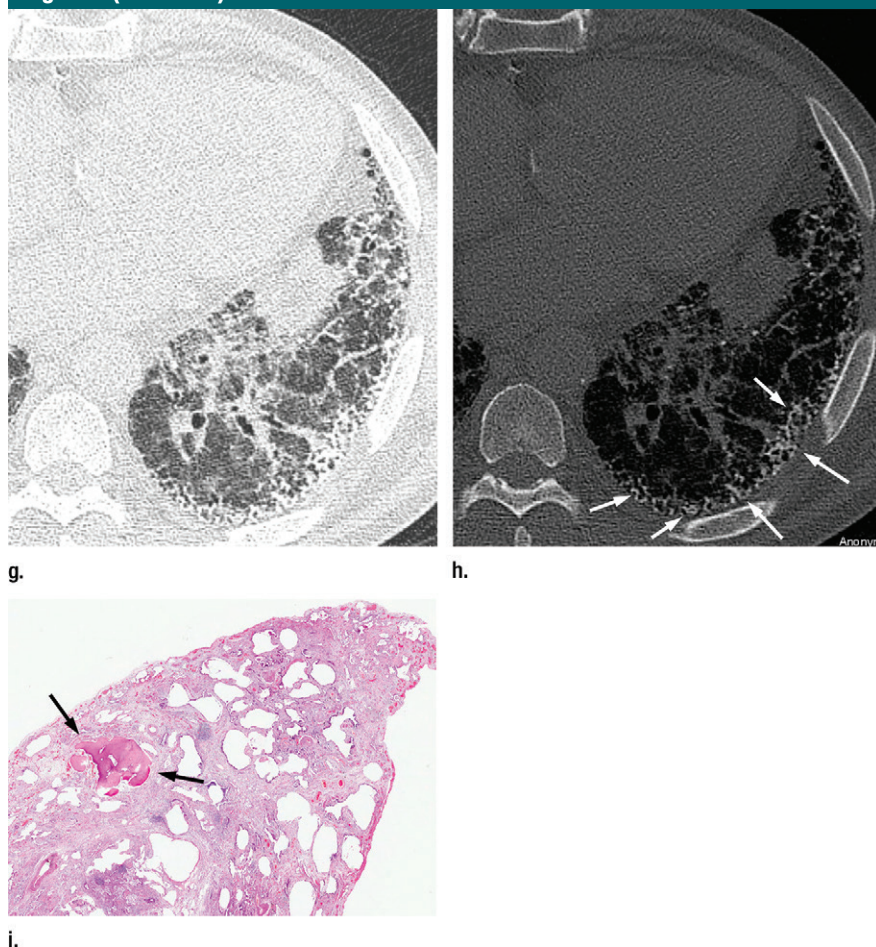


Figure 1 (continued): (g, h) CT images in a 77-year-old man with IPF. (g) Axial thin-section CT image (width, 1500 HU; level, -500 HU) through lower zone shows mixed coarse and fine reticulation with subpleural predominance. Coarseness grade was 12. (h) Extensive network-like or branching highly attenuating structures (arrows) are seen, with some coexisting nodules classified as dendriform type (width, 2500 HU; level, 500 HU). (i) Photomicrograph of single focus of nodular ossification (arrows) measuring 2.03 mm × 1.52 mm on background advanced pulmonary fibrosis shows features of usual interstitial pneumonia (UIP) (hematoxylin-eosin stain; magnification, ×20).

frequently in patients with IPF (21 of 56, 39%) than in those with NSIP (three of 26 [12%], $P = .014$) or hypersensitivity pneumonitis (seven of 37 [19%], $P = .045$). Average nodule scores were higher in patients with IPF (0.83; range, 0–40.2) than in those with NSIP (0.17; range, 0–6.7; $P < .001$) or hypersensitivity pneumonitis (0.17; range, 0–4.8; $P < .001$). The prevalence of DPO according to definition 1 was higher in patients with IPF (19 of 56 [34%]) than in those with NSIP (one of 26 [5%], $P = .003$) or hypersen-

sitivity pneumonitis (two of 37 [5%], $P < .001$). The prevalence of DPO according to definition 2 was higher in patients with IPF (14 of 56 [25%]) than in those with NSIP (one of 26 [5%], $P = .021$) or hypersensitivity pneumonitis (one of 37 [3%], $P = .004$). A logistic regression model was constructed to identify morphologic associations with a diagnosis of IPF. Thin-section CT findings (increased average nodule scores, DPO according to definitions 1 and 2, examined in separate models) remained strongly associated with a diagnosis of

Table 2

Correlations between Average Nodule Scores and Variables

Variable	<i>R</i>	<i>P</i> Value
Age	0.21	<.001
Extent of ILD	0.03	.356
Coarseness score	0.38	<.001

IPF. In comparison, the presence of nodular ossification at biopsy was not independently associated with a diagnosis of IPF, once thin-section CT findings were considered.

Discussion

We have shown a significantly higher prevalence of DPO in patients with IPF compared with those with two other non-IPF fibrosing ILDs, namely, NSIP and chronic hypersensitivity pneumonitis. At CT, POs seen in fibrotic lungs were small (< 4 mm diameter) highly attenuating nodules, with the dendriform pattern being extremely uncommon. As Kim et al (11) reported, histopathologically defined dendriform ossifications usually were observed as minute but not obviously branching opacities at CT, and this was mirrored by the qualitative pathologic assessment of the morphology of ossifications in the patients who underwent lung biopsy in our study. Thus in practice, nodular ossification on CT images likely includes both nodular and dendriform ossification at a histopathologic level.

At CT, POs were located almost invariably in the lung periphery superimposed on predominantly subpleural pulmonary fibrosis of UIP or IPF, and this was in accordance with the pathologic distribution of ossifications. The risk factors for PO that were identified in our study included increasing age, male sex, a positive smoking history, CT features of honeycombing, emphysema, and a coarser interstitial pattern—all of which are strongly associated with IPF (30,31). However, most POs were seen mainly in areas of reticulation, not in areas of honeycombing. The diagnosis of IPF itself was proven to be an independent risk factor for the presence of PO.

Table 3

Group Comparisons in Average Nodule Scores for Dichotomous Variables

Variable	Average Nodule Score	P Value
Honeycombing		
Presence	0.8 (0–63.7)	<.001
Absence	0 (0–71)	
Sex		
Male	0.5 (0–71)	<.001
Female	0.2 (0–18)	
Smoking history		
Ever smoker	0.4 (0–71)	<.001
Never smoker	0.2 (0–63.7)	
Emphysema		
Presence	0.5 (0–40.2)	<.001
Absence	0 (0–71)	
Diagnosis		
IPF	0.67 (0–71)	<.001
Non-IPF	0.2 (0–24)	

Note.—Data in parentheses are the range.

Table 4

Univariate and Multivariate Logistic Regression Analyses—Differentiation of IPF from Others

Variable	Univariate		Multivariate	
	Odds Ratio	P Value	Odds Ratio	P Value
Age	1.09* (1.07, 1.11)	<.001	1.08 (1.06, 1.10)	<.001
Male sex	7.37 (5.45, 9.98)	<.001	6.1 (4.1, 9.0)	<.001
Ever smoker	2.87 (2.17, 3.79)	<.001	1.76 (1.20, 2.56)	<.005
Extent of ILD	0.99* (0.98, 1.02)	.510
Coarseness	1.69* (1.55, 1.84)	<.001	1.50 (1.36, 1.66)	<.001
Honeycombing	9.5 (5.62, 16.12)	<.001	2.97 (1.48, 5.98)	<.005
Emphysema†	3.35 (2.47, 4.55)	<.001
DPO (definition 1)	4.43 (2.98, 6.59)	<.001	2.50 (1.49, 4.20)	<.001
DPO (definition 2)†	4.83 (2.91, 8.02)	<.001

Note.—Data in parentheses are 95% confidence intervals.

* Unit odds ratio for continuous variable.

† DPO according to definition 2 was not included in the multivariate analysis.

Descriptions of DPO are mainly confined to the histopathology literature with no equivalent comprehensive CT reports of morphologic correlates. In a histopathologic study, Travis et al (15) reported metaplastic bone in 12 of 56 (20%) cases of UIP and in two of 22 (9%) cases of fibrotic NSIP. The relatively low frequency of DPO at CT in the study by Kim et al (11), who reported a prevalence of 6.7% for UIP, is likely to relate to the study's small

sample size and interspaced CT section acquisition.

The much higher prevalence of DPO in patients with UIP identified in our study when compared with other non-IPF fibrosing ILDs is striking, although the reason is unclear. The pathogenesis of DPO in fibrotic lungs is obscure but may be related to repeated localized lung injury (32–34); there have been reports (8,9) of extensive and severe lung injury resulting in florid and

widespread ossification of the lungs. Transforming growth factor- β , which is released by damaged epithelial cells, has been shown to be more strongly expressed in UIP lungs than in NSIP lungs (35). As well as being a promoter of lung fibrosis (36), transforming growth factor- β also stimulates proliferation of chondrocytes and osteocytes (2). In the NSIP group, the higher prevalence of ossification associated with systemic sclerosis could indicate a phenomenon similar to dystrophic calcinosis of skin or other organs (37) or represent cases with radiologic-histopathologic discordance between UIP and NSIP (38).

The differentiation of the various fibrosing ILDs can be challenging. Our results have shown that DPO at CT is an independent predictor of IPF. Nevertheless, nodular PO is clearly not entirely specific for IPF; it is seen in both NSIP and chronic hypersensitivity pneumonitis, albeit less frequently. However, this lack of specificity applies to other CT signs of IPF, including honeycombing (30). Thus, when DPO is considered along with other CT signs, it may be regarded as a useful corroborative indicator of IPF.

The differential diagnosis for the CT pattern of profuse minute nodules of calcific opacity is not wide. Pulmonary alveolar microlithiasis theoretically could represent a differential diagnosis for DPO at CT. However, calcifications in alveolar microlithiasis are generally much smaller than POs (sometimes described as “sand-like”) and tend to aggregate along interlobular septa or bronchovascular bundles (39), unlike DPO. Small calcified granulomata related to pulmonary tuberculosis and other granulomatous diseases can show similarities to PO; however, the preferential superimposition of nodules on the background of fibrosing ILD is not a feature of granulomatous disease. Furthermore, in the sample of our patients with calcifications identified pathologically, only 7.5% were granulomas, and authors of previous histopathologic studies have not identified calcified granulomas as being a common finding in the diffuse fibrosing ILD (3).

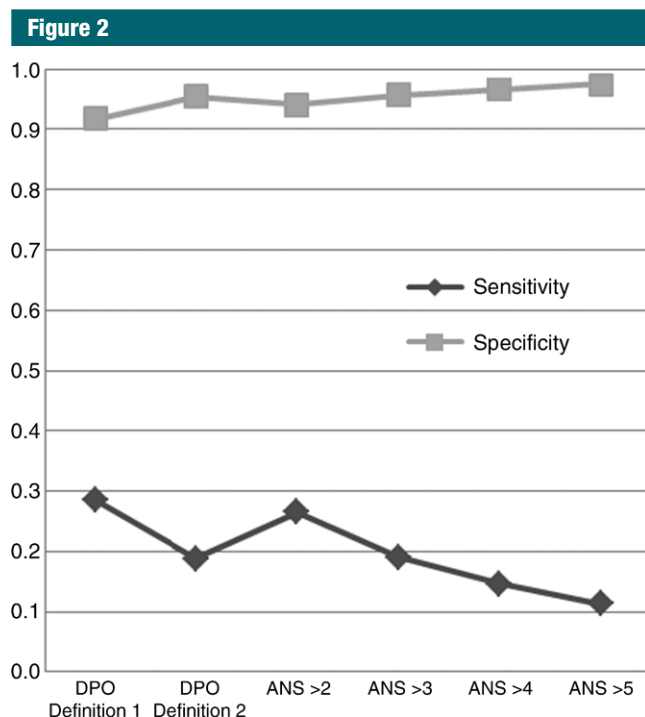


Figure 2: Diagnostic sensitivity and specificity of IPF versus non-IPF cases using different nodule threshold criteria. The two definitions used in this study showed similar sensitivity and specificity compared with other average nodule score thresholds. ANS = average nodule score.

The histopathologic purity of our large study population could be questioned as only 16.8% had a lung biopsy as part of their multidisciplinary team diagnosis. The previously mentioned radiologic-histopathologic discordance between UIP and NSIP (38) could explain the prevalence of ossification in the NSIP group. Any contamination of our subgroups would diminish what are already significant differences; thus, in our observations, we may have underestimated differences in the prevalence of DPO between patients with UIP and those with NSIP. The lack of histopathologic material is inevitable in a sizeable population study in which multidisciplinary team diagnosis is used rather than purely histopathologic diagnosis. Indeed, analyses confined to patients undergoing surgical lung biopsy have their own inherent bias (a preponderance of cases that are atypical as judged by clinical or CT criteria). Nevertheless, analysis of the sample of patients with lung abnormalities available reinforced

the CT findings by showing that there was a clear relationship between the presence of nodular ossifications at biopsy and nodular ossifications (whether definition 1 or 2 was used) at CT. In addition, the different prevalence of ossifications at biopsy between the three fibrosing lung diseases was similar to that shown at CT. At logistic regression analysis, CT parameters of nodular ossifications remained robust, whereas the presence of ossification at biopsy was not independently associated with a diagnosis of IPF, likely reflecting the inevitable problem of sampling error associated with lung biopsy.

Regarding the evaluation of ossification at CT, we chose a generally accepted bone window settings (width, 2500 HU; level, 500 HU). Although we tried the osteoporosis window settings (width, 818; level, 273) advocated by Kim et al (11), we found that the osteoporosis window setting was responsible for some false-positive identification of calcific opacities because of an

occasional highly attenuating appearance of small areas of fibrotic lungs. Whether the presence of DPO has any prognostic significance, over and above its potential diagnostic utility in patients with fibrosing ILD was not explored in the current study but, given the observations by Travis et al (15), this aspect warrants further investigation.

In summary, our study had several limitations. First and foremost, our study was retrospective, with CT data from the archives of our hospital, and accordingly, only a proportion of cases have histopathologic confirmation of both their underlying ILD diagnosis and the nature of the visualized ossification. In our study we also have not questioned the prognostic utility of the finding of pulmonary ossifications, which we believe would constitute a logical follow-up investigation. DPO is common in fibrosing ILDs and is significantly more prevalent in patients with IPF than in those with other fibrosing ILDs and thus may be a helpful corroborative CT sign for diagnosis of IPF.

Disclosures of Conflicts of Interest: R.E. disclosed no relevant relationships. J.J. disclosed no relevant relationships. M.K. disclosed no relevant relationships. A.L.B. disclosed no relevant relationships. A.R. disclosed no relevant relationships. A.G.N. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: Consultant for Boehringer Ingelheim, Roche, and Sanofi; lecture fee from Intermune. Other relationships: disclosed no relevant relationships. A.U.W. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: consulting and lecturing for Bayer, Boehringer Ingelheim, and Intermune/Roche; lecturing for Actelion and Chiesi, consulting for Gilead and Glaxo Smith Kline. Other relationships: disclosed no relevant relationships. D.M.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: consultant for AstraZeneca, Boehringer Ingelheim, Roche, and Sanofi. Other relationships: disclosed no relevant relationships.

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