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RESEARCH ARTICLE

An important radiological clue in idiopathic pulmonary fibrosis: Diffuse pulmonary ossification

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ABSTRACT

An important radiological clue in idiopathic pulmonary fibrosis: Diffuse pulmonary ossification

Introduction: Diffuse pulmonary ossification (DPO) refers to the unusual formation of mature bone tissue within the lung parenchyma. It has been shown to be associated with a number of cardiac and chronic lung diseases. The relation between DPO and idiopathic pulmonary fibrosis (IPF) has been shown in the literature. We examined DPO, which is the supporting computed tomography (CT) finding of IPF. In this way, it was aimed to distinguish cases with an IPF-like pattern non-invasively.

Materials and Methods: A retrospective analysis included 89 cases exhibiting a CT pattern typical of usual interstitial pneumonia (UIP). The cases were divided into two groups: One with an IPF diagnosis and the other with a non-IPF diagnosis. The presence of DPO was then assessed in each case according to the criteria outlined in the literature. Finally, the occurrence of DPO was compared between the IPF group and the non-IPF group.

Results: Forty-seven of 89 cases had a diagnosis of IPF (52.8%). DPO was observed in 31 patients (34.8%). Presence of DPO was detected in 28 (59.6%) patients in the IPF group. The presence of DPO was detected in 3 (7.1%) cases in the non-IPF UIP patient group. A moderate correlation was found between IPF and DPO, and a moderate correlation was found between IPF and the male sex ($r = 0.549$; $r = 0.311$, respectively).

Conclusion: DPO is an important finding to support the diagnosis of IPF.

Key words: Diffuse pulmonary ossification; supporting finding; non-invasive; usual interstitial pneumonia pattern

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ÖZ

İdiyopatik pulmoner fibroziste önemli bir radyolojik ipucu: Yaygın pulmoner ossifikasyon

Giriş: Diffüz pulmoner ossifikasyon (DPO), akciğer parankiminde matür kemik dokusunun beklenmedik şekilde oluşumunu ifade eder. Birçok kalp ve kronik akciğer hastalığı ile ilişkili olduğu gösterilmiştir. Literatürde, DPO ile

idiyopatik pulmoner fibrozis (İPF) arasındaki ilişki gösterilmiştir. Çalışmamızda, İPF'yi destekleyen bilgisayarlı tomografi (BT) bulgusu olan DPO'yu inceledik. Bu sayede, İPF ile benzer radyolojik paterni gösteren vakaları non-invaziv olarak ayırt etmeyi amaçladık.

Materyal ve Metod: Retrospektif olarak olağan interstisyel pnömoni (UIP) tipik BT paternini sergileyen 89 vaka çalışmaya dahil edildi. Vakalar, İPF tanısı olan ve olmayan olarak iki gruba ayrıldı. Her vakada literatürde belirtilen kriterlere göre DPO varlığı değerlendirildi. Ayrıca DPO varlığı ile İPF grubu ve non-İPF grubu arasındaki istatistiksel anlamlılık karşılaştırıldı.

Bulgular: Seksen dokuz vakanın 47 (%52.8)'sinde İPF tanısı vardı. Otuz bir hastada (%34.8) DPO gözlemlendi. İdiyopatik pulmoner fibrozis grubundaki 28 (%59.6) hastada DPO varlığı tespit edildi. Non-İPF UIP hasta grubundaki 3 (%7.1) vakada DPO varlığı tespit edildi. İdiyopatik pulmoner fibrozis ile DPO arasında orta düzeyde korelasyon, İPF ile erkek cinsiyeti arasında ise orta düzeyde korelasyon bulundu (sırasıyla $r = 0.549$; $r = 0.311$).

Sonuç: Diffüz pulmoner ossifikasyon, İPF tanısını destekleyen önemli bir bulgudur.

Anahtar kelimeler: Diffüz pulmoner ossifikasyon; destekleyici bulgu; non-invaziv; olağan interstisyel pnömoni paterni

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) represents a clinical disease characterized by the presence of lung fibrosis, manifesting as the most prevalent and fatal condition with a progressively advancing course and exhibiting both histological and imaging patterns indicative of usual interstitial pneumonia (UIP) (1). Diagnosing IPF depends on identifying the UIP pattern through histological or radiological methods, along with ruling out secondary causes like connective tissue disorders, drug use, or exposure to external substances. IPF is more commonly seen in males and individuals over 60 years old, though cases in younger individuals have been reported, particularly in familial conditions associated with pulmonary fibrosis (2). The European Respiratory Society (ERS) and American Thoracic Society (ATS) have established criteria, including major and minor criteria, for diagnosing idiopathic pulmonary fibrosis (IPF) (3). These criteria were revised in a joint statement released in 2018 by the ERS, ATS, Latin American Thoracic Association and Japanese Respiratory Society. Additionally, the Fleischner Society issued guidelines on the UIP pattern, which constitutes the imaging aspect of these criteria, in 2018 (4). According to this reference, the UIP computed tomography (CT) pattern is categorized into four groups: Typical UIP CT pattern, Probable UIP CT pattern, CT pattern indeterminate for UIP, and CT features most indicative of a non-IPF diagnosis.

Diffuse pulmonary ossification (DPO) is a rare condition marked by the formation of ectopic bone within the lung parenchyma. In an autopsy series, DPO was found in 1.63 out of every 1000 cases (5). It was first described by Luschka in 1856 (6). There are two types as dendriform and nodular form. DPO is observed in a variety of situations. It can be

detected in normal lung (idiopathic form), it can be observed especially in cardiac diseases associated with pulmonary congestion, it can be observed in cases of severe lung damage, and it can be observed in interstitial lung diseases with fibrosis (7-10). Radiologically, DPO is observed as calcified nodules of 1-5 mm in size or confluent clustered trabecular calcified areas and is seen in the subpleural portions.

There are a limited number of case series and a limited number of original articles related to DPO in the literature. The relation between DPO and IPF has been revealed in recent publications (11). However, the extent to which it should be used in the differentiation of diseases with the same radiological pattern has not been sufficiently clarified. Antifibrotic treatments (pirfenidone and nintedanib), which have been popularly used in recent years, reduce disease progression and improve quality of life in IPF patients (14). Being able to diagnose IPF as non-invasively as possible shortens the time to start treatment, increases patient comfort, and also reduces costs.

The aim of our study was to differentiate the UIP pattern associated with IPF from those caused by other conditions that result in a non-IPF UIP pattern. By doing so, we hope to contribute to the existing literature.

MATERIALS and METHODS

The study was carried out retrospectively and received approval from the local ethics committee. The study adhered to the principles established in the Helsinki Declaration.

Case Selection

Individuals with a clinical suspicion of interstitial lung disease who underwent high-resolution thoracic CT (HRCT) between January 2022 and February 2023

were included in our study. Evaluation was done retrospectively. Biopsy was not conducted in patients with unremarkable clinical and radiological findings. The cases with a probable UIP CT pattern were histopathologically confirmed, and the patients whose pathological diagnosis was compatible with the UIP pattern were included in the study. Pathological evaluation was conducted only in cases with a clinically ambiguous probable UIP pattern, while it was not performed in cases with clinically compatible and probable UIP patterns. In addition, the cases with a UIP pattern from non-IPF diseases were also included in the non-IPF-UIP group. Cases with no histopathological diagnosis and clinically incompatible HRCT with a radiological pattern other than the typical UIP CT pattern were not included in the study. Additionally, cases with suboptimal HRCT scans -due to issues like inadequate breath-holding, motion artifacts, or incomplete lung coverage- were excluded from the study. Furthermore, individuals with chronic renal failure or chronic diseases associated with hypercalcemia that could lead to metastatic calcification were also excluded.

Image Evaluation

Image evaluation was carried out by a single radiologist with 10 years of expertise in cardiothoracic radiology. Patients were categorized based on the UIP pattern. The assessment of the UIP pattern followed the glossary of definitions for thoracic imaging outlined by the Fleischner Society (12). Then, DPO evaluation was done on MIP images from the bone window (WW= 2500 HU, WL= 500 HU). MIP images were used to increase the sensitivity of nodule detection. Small intrapulmonary localized calcific attenuated nodules with a maximal short axis of 4 mm were considered as pulmonary ossification (PO) (13). The numbers and rough shapes of POs were evaluated. At least 10 bilateral POs or at least five POs in one lung lobe were evaluated as DPO (13).

Statistical Analysis

Data analysis was conducted using the SPSS 24 statistical software package (IBM Corp., Armonk, NY, USA). Categorical variables were reported as counts and percentages, while continuous variables were summarized with mean, standard deviation, and range (minimum-maximum). Pearson chi-square test was employed to examine the association of DPO with IPF. Given the normal distribution of our data, an independent samples t-test was used for statistical

analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 89 participants were included in the study, comprising 64 males (71.9%) and 25 females (28.1%). Among these patients, 47 were diagnosed with IPF, accounting for 52.8% of the total cohort. Forty-two other patients were included in the non-IPF group (47.2%). HRCT of 80 patients, except nine of the IPF group patients, was typical UIP CT pattern (89.9%). HRCT pattern of nine patients was probable UIP CT pattern (10.1%). UIP diagnosis was confirmed histopathologically in these nine patients. DPO was observed in 31 of 89 patients (34.8%).

Mean age of the participants in the study was 71.98 ± 8.02 years. Among the male patients, mean age was 71.48 ± 6.88 years, while among the female patients, it was 73.2 ± 10.46 years. The analysis showed no statistically significant difference in the mean age between male and female participants ($p=0.368$). Mean age of the patients diagnosed with IPF was 72.45 ± 8.65 years, while that of those in the non-IPF group was 71.43 ± 8.02 years. The comparison revealed no statistically significant difference in the mean age between individuals in the IPF group and those in the non-IPF group ($p=0.553$). Mean age of the individuals with DPO was 73.23 ± 8.05 years, compared to 71.29 ± 8 years for those without DPO. Statistical analysis showed no significant difference in mean age between those with and without DPO ($p=0.281$).

Among the individuals with IPF, 40 (85.1%) were males and 7 (14.9%) were females. The prevalence of IPF was statistically significantly higher in males ($p=0.003$). For those with DPO, 24 (77.4%) were males and 7 (22.6%) were females. No statistically significant difference in sex distribution was observed among those with DPO ($p=0.398$). The presence of DPO was detected in 28 (59.6%) patients in the IPF group (Figures 1, 2). The presence of DPO was detected in 3 (7.1%) cases in the non-IPF UIP patient group. A statistically significantly higher rate of DPO detection was observed in IPF patients ($p<0.001$) (Table 1). DPO was not detected in 19 (40.4%) patients in the IPF group.

DPO was encountered in 3 (33.33%) of nine patients whose pathological result was confirmed as IPF and whose CT pattern was in the probable UIP CT pattern group.

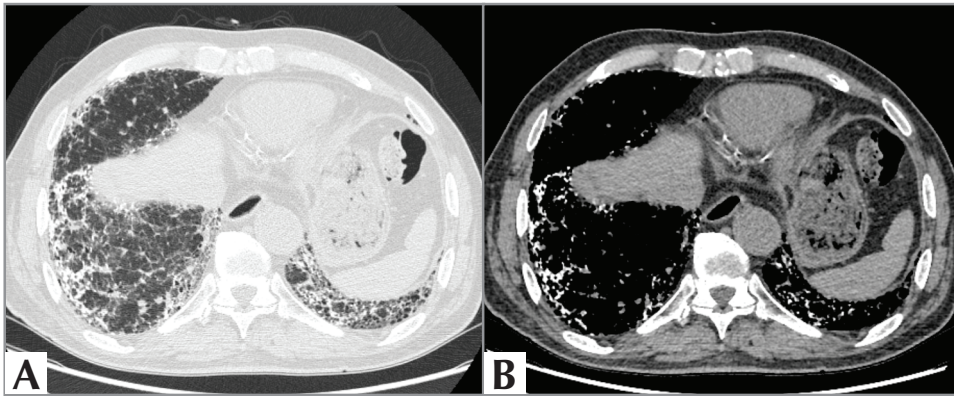


Figure 1. A 77-year-old male patient with a diagnosis of IPF. **A.** Lung parenchyma window. Sub-pleural reticular densities and honeycomb cysts in the lower lobes are consistent with the typical UIP CT pattern. **B.** Mediastinal window. Appearances in bone density compatible with diffuse pulmonary ossification.

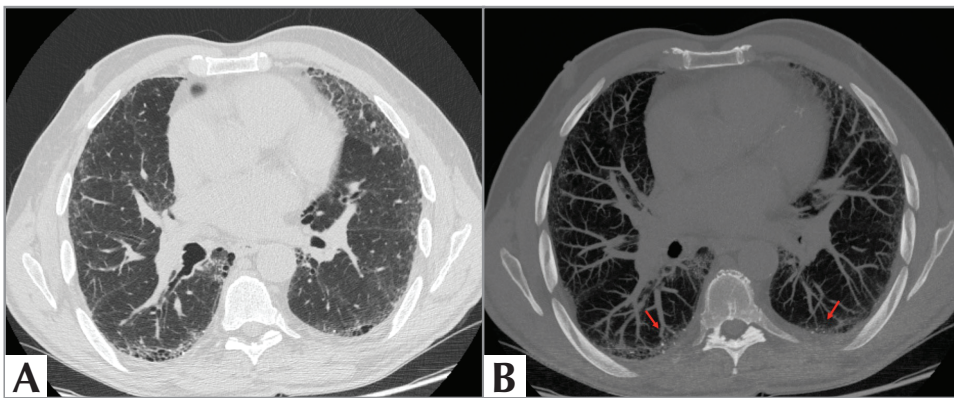


Figure 2. A 72-year-old male patient diagnosed with IPF. **A.** Lung parenchyma window. Sub-pleural reticular densities and honeycomb cysts in the lower lobes are consistent with the typical UIP CT pattern. **B.** MIP images in the bone window. Opacities (red arrows) consistent with nodular diffuse pulmonary ossification in bony attenuation in the fibrotic lung portion.

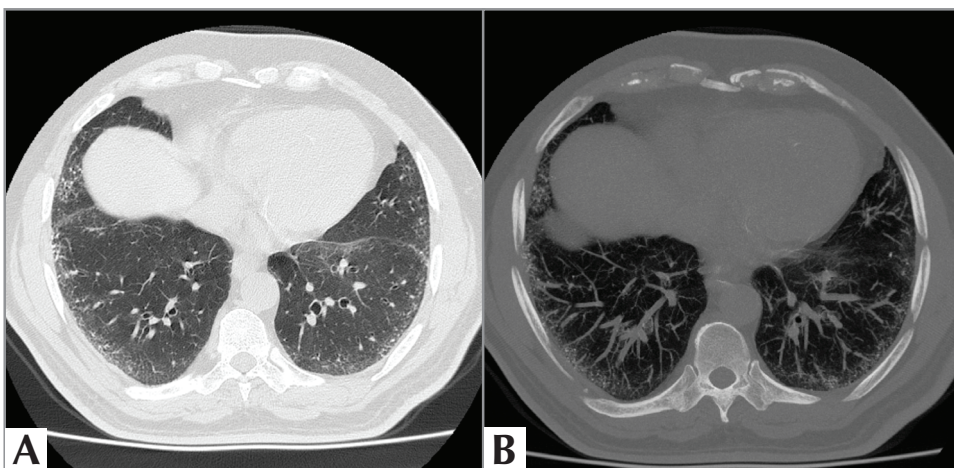


Figure 3. A 67-year-old male patient with histopathologically confirmed diagnosis of IPF. **A.** Lung parenchyma window. Sub-pleural reticular densities and ground glass densities are observed. Traction bronchiectasis is observed. The findings are consistent with the Probable UIP CT pattern. **B.** MIP images in the bone window. High attenuation nodular opacities consistent with diffuse pulmonary ossification in the involved lung.

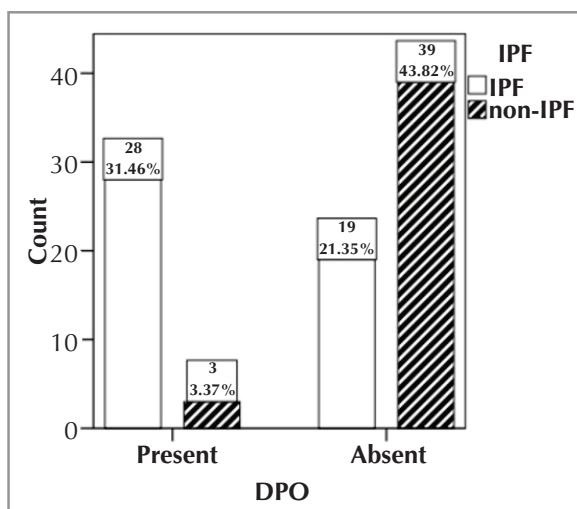


Figure 4. Bar graph of DPO by IPF.

Pearson correlation analysis was applied to investigate the relationship between IPF, DPO, age and sex (Table 2). A moderate correlation was found between IPF and DPO, and a moderate correlation was found between IPF and the male sex ($r = 0.549$; $r = 0.311$, respectively) (Table 2).

DISCUSSION

We think that “diffuse pulmonary ossification” finding, known as ectopic detection of mature bone tissue in the lung parenchyma, will contribute to the differential diagnosis in our study, where we aimed to find a clue on CT images for the non-invasive diagnosis of IPF cases. In our study, a statistically significant higher rate of DPO was found in IPF patients than other diseases with a similar CT pattern.

Consistent with the literature, we detected IPF, which is the patient population we studied, more frequently in male patients and in patients over 60 years of age (2). IPF sometimes exhibits confusing radiological findings. Since antifibrinolytic agents offer a treatment option, it is important to make the differential diagnosis, although it is not always easy. In the literature, various CT findings have been identified to aid in differentiating IPF from other conditions that present with a UIP pattern. Supporting findings for differential diagnosis from lung fibrosis associated with connective tissue diseases: the “exuberant honeycombing” sign, the “anterior upper lobe” sign, and the “straight-edge” sign (14). In addition, the supporting CT finding used

Table 1. Sex, number/percentages of idiopathic pulmonary fibrosis and diffuse pulmonary ossification of patients included in the study

Parameters	IPF (n= 47)	Non IPF (n= 42)	p
Sex			
Male (n= 64)	40 (85.1%)	24 (57.1%)	0.003
Female (n= 25)	7 (14.9%)	18 (42.9%)	
Age	72.45 ± 7.48	71.43 ± 8.65	0.55
DPO			
Present (n= 31)	28 (59.6%)	3 (7.1%)	<0.001
Absent (n= 58)	19 (40.4%)	39 (92.9%)	

IPF: Idiopathic pulmonary fibrosis, DPO: Diffuse pulmonary ossification.

Table 2. Correlation analysis of parameters

		DPO +	Age	Gender
IPF +	r	0.549**	-0.064	0.311**
	p	<0.001	0.553	0.003
DPO +	r	1	-0.115	0.090
	p		0.281	0.404
Age	r	-0.115	1	0.097
	p	0.281		0.368
Sex	r	0.090	0.097	1
	p	0.404	0.368	

Pearson correlation analysis was used. $p < 0.05$ was considered significant.

IPF: Idiopathic pulmonary fibrosis, DPO: Diffuse parenchymal ossification.

for the differential diagnosis of chronic hypersensitivity pneumonia and IPF is “the headcheese sign” (15,16). DPO should be added to these supportive differential diagnosis findings.

There are few studies in the literature regarding DPO. In the literature, the role of DPO in the differentiation of UIP and nonspecific interstitial pneumonia (NSIP) was investigated in a histopathologically confirmed thin-section CT study of dendriform DPO. Seventy-five UIP and 44 NSIP cases were included in the study. It was found that the incidence of DPO in UIP cases was 6.7% (16). Our study included 89 cases of UIP and the DPO rate was 34.8%. We think that this is related to the inability to exclude calcified granulomas in the differential diagnosis of DPO, the fact that the evaluation with MIP increased the diagnostic sensitivity, and the evaluation of both dendriform and nodular DPO. In another autopsy study, they found that the incidence of DPO in respiratory diseases was 0.6%-1.63%. Again, we think that the reason for the low DPO rates compared to our study is related to the above-mentioned factors, as well as the authors’ study of more extensive lung diseases. In addition, in the same study, it was shown that the majority of DPO cases were in the 70-80 age range and was more common in male patients (17). We also found DPO to be more common in male patients with a similar age range. In another histopathological study, it was shown that metastatic bone tissue was found in 20% of UIP patients and 9% in fibrotic NSIP. Fifty-six UIP and 22 fibrotic NSIP patients were included in this study (18,19). Another study evaluated small, highly attenuated nodules (<4 mm diameter) in fibrotic lung tissue as DPO and compared IPF patients with NSIP and chronic hypersensitivity pneumonia. The authors found the prevalence of DPO to be statistically significantly higher in IPF cases. The study demonstrated that calcified granulomas were more prevalent in the IPF group compared to the non-IPF group (13). In this case, without excluding calcified granulomas, which are in the differential diagnosis of DPO and create a similar radiological appearance, we can say that DPO is at a higher rate in the IPF group, although we do not know the true incidence. In addition, it has been shown in the literature that the incidence of DPO is quite different.

Limitations

The limitations of our study are that no pathological examination was performed for DPO, and that other

calcific conditions in the differential diagnosis could not be eliminated in this way. Examining patients without distinguishing between nodular and dendriform DPO may also be a limitation. Furthermore, the study’s limitation includes its single-center nature and the limited number of patients enrolled. Another limitation of the study is the small number of individuals who had a biopsy and did not exhibit a typical UIP pattern.

CONCLUSION

In conclusion, it is sometimes challenging to make the differential diagnosis of various interstitial lung diseases with fibrosis. In our study, it is seen that DPO is an independent predictor for IPF. Although DPO is seen in various diseases, it can be used as a confirmatory finding in the diagnosis of IPF. We hope that studies will be conducted on how DPO may be an early finding in IPF patients and how it changes during the follow-up period.

Main Points:

- Diffuse pulmonary ossification (DPO) is ectopic bone tissue observed in the lung parenchyma.
- Although DPO is observed in many chronic lung diseases, its frequency was found to be statistically significantly higher in IPF.
- DPO examination should be examined in MIP projection in the CT bone window and calcific nodular structures observed more than five should be considered as DPO.

Ethical Committee Approval: This study was approved by Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Committee (Decision no: 23-KAEK-095, Date: 13.04.2023).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: HAK, HİY

Analys/Interpretation: HAK

Data acquisition: HAK

Writing: HAK

Clinical Revision: HAK, HİY

Final Approval: HAK, HİY

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