Retrospective analysis of dendriform pulmonary ossification: Possible involvement of inflammation and hemorrhage

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Research

Keywords: dendriform pulmonary ossification, inflammation, hemorrhage, fibrosis, usual interstitial pneumonia, surgical lung biopsy

Posted Date: March 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16553/v1

Abstract

Background

Dendriform pulmonary ossification (DPO) is a rare condition characterized by metaplastic bone formation in the lung parenchyma. DPO has been reported to be often associated with usual interstitial pneumonia (UIP) or chronic aspiration of gastric acid; however, DPO is believed to be a multifactorial disease, and its clinical features and pathophysiology remain unclear. This study aimed to reveal the novel clinical features and pathophysiology of DPO.

Methods

The pathology reports of consecutive cases diagnosed by surgical lung biopsy for diffuse lung diseases (DLDs) between April 1, 2000 and March 31, 2018 were reviewed retrospectively. Cases showing ossification in their specimens were subsequently reviewed and confirmed as calcified density lesions on CT scans. Besides the definite DPO cases, two DPO cases that involved surgical resection of the lung tumor were also included in the study. The clinical, radiological, and pathological features were analyzed.

Results

Three (0.96 %) out of 313 cases with DLDs were identified as cases of definite DPO. Taken together with the two DPO cases showing lung tumors, five DPO cases were analyzed. The patients were predominantly male, with a median age of 69 years. Four cases showed no smoking history. One patient had gastroesophageal reflux disease and UIP, and another had demonstrable hiatal hernia. Laboratory data were not remarkable. Pulmonary function at baseline was almost normal, and no significant decline was observed during the follow-up period. All cases showed interstitial fibrosis accompanied by ossifications. Intriguingly, the histological examination revealed intra-alveolar fibrosis and slight inflammatory cell infiltration, including new bone formation, corresponding to the consolidation on the CT scan in one case. In addition, consolidation, suspected to be caused by inflammation or hemorrhage, was also noted in two other DPO cases, namely in all of three idiopathic cases without UIP or risk factors for gastric acid aspiration.

Conclusions

All five DPO cases were indolent, indicating that the prognosis of DPO might be good. The pathological and radiological findings suggested the possible involvement of pulmonary inflammation and hemorrhage in the pathogenesis of DPO.

Background

Diffuse pulmonary ossification is a rare condition characterized by metaplastic bone formation in the lung parenchyma [1]. It is usually an asymptomatic disease and is invisible on chest radiographs. Some recent cases were diagnosed with diffuse pulmonary ossification on the basis of advancements in radiography; however, the condition often remains underdiagnosed or misdiagnosed [2]. Diffuse pulmonary ossification has been recognized in the following 2 forms: nodular and dendriform. The nodular type of ossification has been linked to passive congestion due to chronic heart failure, mitral stenosis, and hypertrophic subaortic stenosis. The dendriform type of ossification, a.k.a. dendriform pulmonary ossification (DPO), is idiopathic or occurs in association with primary lung diseases [1–3]. DPO has been most often described in association with usual interstitial pneumonia (UIP), and most of the DPO cases without UIP are reported to be associated with chronic aspiration of gastric acid [4]; however, other factors can underlie DPO, which is believed to be multifactorial, and its pathophysiology remains unclear. Therefore, this study aimed to reveal the novel clinical features and pathophysiology of DPO.

Methods

The pathology reports of consecutive cases diagnosed by surgical lung biopsy (SLB) for diffuse lung diseases (DLDs) between April 1, 2000 and March 31, 2018 at Kinki-Chuo Chest Medical Center (Sakai City, Osaka, Japan) were reviewed retrospectively. In the cases showing pathological findings of dendriform ossifications in the SLB specimens, the presence of calcifications on CT scans was evaluated, and the cases that did not show calcified density lesions were excluded. Two DPO cases that involved surgical resection of lung tumors were also included in the study on the basis of the same evaluation criteria. The clinical data (e.g., laboratory data, results of pulmonary function tests, and clinical records) and radiological and pathological features were analyzed in the definite DPO cases. A pathologist (T.K.) reviewed all the pathological slides. He evaluated the existence of ossifications in the SLB specimens and classified the ossifications into nodular or dendriform types. This study was approved by the institutional review board of our hospital (Approval number: 679). We used an opt-out method so that patients and families could refuse to participate in the study.

Results

A total of 313 cases diagnosed by SLB were identified between April 1, 2000 and March 30, 2018 (Fig. 1). Of these, three cases showed pulmonary ossifications, representing an average incidence of 0.96%. All three patients showed dendriform ossifications. One case with fibrotic nonspecific interstitial pneumonia (NSIP) was excluded due to the presence of few calcified density lesions on CT scans. Together with two cases that were diagnosed as showing DPO by surgical resection of the lung tumor, a total of five cases of DPO were examined.

The patient characteristics are shown in Table 1. The median age was 69 years (range, 37–70 years), and the five patients included four men and one woman. Four of the five cases had no smoking history. DPO has been reported to be associated with recurrent acid aspiration [4]. One case (case 4) showed demonstrable hiatal hernia, and another case (case 5) showed gastroesophageal reflux disease (GERD) and UIP. In the two cases with lung tumors, one (case 1) showed sclerosing pneumocytoma and the other (case 3) showed lung adenocarcinoma. Chest CT or high-resolution CT (HRCT) images at the time of diagnosis demonstrated calcified density lesions in all cases (Fig. 2). The lesions of DPO tended to be located in both lower lobes in all cases. Histopathological findings obtained with SLB are shown in Fig. 2. All cases showed bone marrow elements, which included fat marrow tissues, and interstitial fibrosis accompanied by ossifications.

Table 1
Patient characteristics

Case No.	Age, years	Sex	Smoking History	Past medical history	Main location of lesions*	Bone marrow elements**	Interstitial fibrosis**
1	70	F	Never	Sclerosing pneumocytoma, Diabetes mellitus, Uterine fibroids	Both lower lobes	Present	Present
2	37	M	Never	Spinal disc herniation	Both lower lobes	Present	Present
3	69	M	Ex-smoker	Lung adenocarcinoma, Coronary-pulmonary artery fistula, COPD, OMI, HT	Both lower lobes	Present	Present
4	46	M	Never	Demonstrable hiatal hernia	Both lower lobes	Present	Present
5	70	M	Never	UIP, GERD	Both lower lobes	Present	Present

Abbreviations: UIP: usual interstitial pneumonia, COPD: chronic obstructive pulmonary disease, OMI: old myocardial infarction, HT: hypertension,
GERD: gastroesophageal reflux disease.
*: Radiological findings.
**: Pathological findings.

The laboratory findings are shown in Table 2. Surfactant protein-D (SP-D) levels were elevated in case 3. However, the elevation was not significant enough to be regarded as interstitial pneumonia by both pathological and radiological assessment. No other remarkable findings were observed in laboratory tests.

Table 2
Laboratory data

Case No.	WBC /μL	Hb g/dL	Plt x10^4/μL	AST U/L	ALT U/L	LDH U/L	Cr mg/dL	CRP mg/dL	KL-6 U/mL	SP-D ng/mL	SP-A ng/mL	Alb g/dL	Ca mg/dL	PT-INR	aPTT s
1	4100	13.6	25.1	27	20	238	0.72	0.03	284	N/A	N/A	4.6	9.2	1.04	27.6
2	8300	14.5	25.6	14	22	145	0.66	0	365	< 17	39.6	5.3	9.7	0.99	28.8
3	6500	13.1	21.0	16	11	142	0.80	0.18	402	393.7	54.6	4.5	8.9	1.01	23.7
4	5300	15.7	19.3	16	25	154	0.83	0.06	287	65.5	N/A	4.5	9.3	0.96	24.1
5	5700	15.6	22.8	22	22	185	0.79	0.01	438	55.9	41.3	4.5	8.9	1.01	32.7

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase,
Cr: creatinine, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, SP-A: surfactant protein-A, Alb: albumin, Ca: calcium, PTH: parathyroid hormone, PT-INR: prothrombin time-international normalized ratio, aPTT: activated partial thromboplastin time
N/A: not available

Pulmonary function tests at the time of diagnosis are shown in Table 3. Although the values of %VC, %TLC, RV/TLC, %DLco were rather low in cases 2 and 4, they were almost within the normal range. No other remarkable impairments were noted at the baseline. Significant decline was not observed during the follow-up period (Table 3). None of the DPO patients had died at the time of review.

Table 3
Pulmonary function test

Case No.	VC* (L)	%VC* (%)	FEV1* (L/min)	%FEV1* (%)	FEV1%* (%)	%TLC* (%)	RV/TLC* (%)	%DLco* (%)	%DLco/VA* (%)	ΔFVC** per year (%)	ΔDLco** per year (%)	Follow-up period (Y)
1	2.92	128.1	2.19	114.7	71.8	131.8	37.1	113.1	103.9	-0.2	3.1	3.3
2	3.23	81.4	2.54	70.8	77.9	69.7	25.5	69.8	91.8	0.4	-0.2	9.6
3	3.18	96.7	2.27	83.5	70.3	80.8	36.1	102.6	90.1	N/A	N/A	N/A
4	3.21	85.1	2.47	74.0	76.5	71.5	25.9	74.3	102.9	-3.4	0.7	1.3
5	3.84	119.6	2.97	112.5	83.4	97.4	30.6	135.9	124.5	-0.5	-2.5	3.6

Abbreviations: N/A: not available.
: Values at the time of diagnosis
**: Rate of change per year from the diagnosis to the last follow-up. Each parameter was calculated by the formula: ΔFVC per year: [(FVC in the latest pulmonary function test (L) − FVC at baseline (L)) × 100] / [(FVC at baseline (L)) × (follow-up period (year))], ΔDLco per year: [(DLco in the latest pulmonary function test (ml/min/mmHg) − DLco at baseline (ml/min/mmHg)) × 100] / [(DLco at the baseline (ml/min/mmHg)) × (follow-up period (year))].

Case Presentation

Case 1

A 70-year-old woman visited our hospital for pulmonary opacities. She had diabetes, which had been treated with oral hypoglycemic agents and insulin. She had no remarkable family medical history, smoking history, or previous exposure to environmental allergens. An abnormality on a chest radiograph had been noted at a medical checkup when she was about 40 years old; however, no close inspection had been conducted. A nodular shadow in the right lower lobe was noted when she was 54 years old. It had enlarged when she was 70 years old, and she was referred to our hospital. There were no remarkable findings in laboratory and pulmonary function tests. An electrocardiogram and echocardiogram showed no abnormalities. The chest CT scan at the first visit showed diffuse reticulonodular shadows in the bilateral lower lobes and a 3-cm nodule in the right lower lobe (Fig. 3A, B). About two months later, consolidation next to the nodular shadow in the right lower lobe appeared on CT scans, which included calcified density lesions (Fig. 3C, D). At that time, the patient was asymptomatic. Resection of the right lower lobe was performed for diagnosis 13 days after the CT scan.

The nodule in the right lower lobe was diagnosed as a sclerosing pneumocytoma by the histological examination. In addition, the specimens showed multiple interstitial branching spicules of bone, which were mainly located irregularly in the alveolar airspaces and focally involved the walls. Some of them contained fat marrow tissues (Fig. 3E). These findings were compatible with DPO. Furthermore, fibrosis and slight intra-alveolar inflammatory cell infiltration, including new bone formations, surrounded by some osteoblasts were identified, corresponding to the consolidation in the right lower lobe (Fig. 3F). The patient received follow-up observation without treatment. DPO did not show any progression over the 40-month follow-up period.

Cases 2 And 3

Intriguingly, further analysis revealed similar shadows in cases 2 and 3. In case 2, a round 3-cm nodule that was suspected to be a hematoma was observed in the right lower lobe (Fig. 4), and in case 3, consolidation including a calcified shadow that was suspected to be inflammation or hemorrhage was observed in the right upper lobe (Fig. 5) on CT scans before surgery. Both shadows were asymptomatic and regressed spontaneously.

All three cases presented here did not involve UIP or risk factors for gastric acid aspiration.

Discussion

This is the first report to examine DPO in patients with DLDs who underwent SLB. The findings of this study were almost consistent with the previously reported common features of DPO patients, including slow progression, the location of the lesions, and the co-existence of fibrosis; however, we further found that inflammation and hemorrhage were observed in patients diagnosed with idiopathic DPO.

In this study, of the 313 cases with DLDs that involved SLBs, three cases were definitely diagnosed with DPO, representing an average incidence of 0.96%. Diffuse pulmonary ossification has been reported to be present in 0.16–0.40% of autopsies [1, 9]. However, limited to alive DLDs, the incidence of DPO may be rather high. In this study, pulmonary ossifications were located in both lower lobes in all five cases. Similarly, pulmonary ossifications were located in the lower lobes in 36 of 42 cases diagnosed with DPO in a previous study [10]. In our study, pulmonary function tests showed no remarkable impairment at the baseline and significant decline during the follow-up period. None of the DPO patients met the criteria for progressive fibrosing interstitial lung disease [11] or had died at the time of review. DPO is typically considered to be indolent or slowly progressive, inducing a gradual decline in the pulmonary function [5, 12, 13]. On the other hand, a DPO case that showed progressive restrictive ventilatory impairment was reported [14]. Nevertheless, the risk factors for progression in DPO remain unclear.

Dendriform-type ossifications are frequently accompanied by interstitial fibrosis [9, 15, 16], and their association has been suggested. As a factor causing ossification, transforming growth factor-beta, which is strongly implicated in idiopathic pulmonary fibrosis and other fibrotic pulmonary diseases, stimulates osteoblast and chondrocyte proliferation [3]. In this study, all five DPO cases showed interstitial fibrosis in lung tissues. Furthermore, on histopathologic review, ossifications were identified in one (0.6%) of the 174 cases with UIP and one (0.9%) of the 112 cases with NSIP, out of 313 cases with DLDs. Travis et al. reported that ossifications were identified during pathologic examination of lung biopsy specimens in 12 of 56 (21%) cases of UIP and in two of 22 (9%) cases of fibrotic NSIP [17]. Kim et al. reported that ossifications were identified during pathologic examination of lung biopsy specimens in five of 75 (6.7%) cases of UIP and not identified in 44 cases of NSIP [18]. The frequency of ossifications in UIP was lower in this study than in the previous studies. This might be explained by the following reasons. First, the difference in patient characteristics might have influenced the findings. Second, false-negative biopsy results may have occurred due to sampling errors.

In this study, case 4 showed demonstrable hiatal hernia and case 5 showed GERD. In a previous report, 39 of 52 DPO cases without UIP (75%) showed obstructive sleep apnea, GERD, or a chronic neurologic disorder, and DPO was suggested to be associated with recurrent acid aspiration [4]. Local acidity and hypoxemia can cause differentiation of pulmonary fibroblasts and possibly macrophages into osteoblasts, and microscopic and chronic low-level acid aspiration could therefore be expected to cause DPO [15].

As mentioned above, DPO has been reported to be often associated with usual interstitial pneumonia (UIP) or chronic aspiration of gastric acid. However, DPO is believed to be a multifactorial disease and causes other than UIP or acid aspiration should underlie the mechanism of DPO. Three cases (cases 1, 2, and 3), which were considered to be idiopathic due to the lack of any underlying disease, showed neither UIP nor any risk factor of acid aspiration. In case 1, in addition to ossifications compatible with DPO, fibrosis and slight inflammatory cell infiltration were observed in the lung tissues. The ossifications in the fibrosis and slight inflammatory cell infiltration were considered to be relatively recent because they co-existed with osteoblasts. This case suggested that fibrosis, which typically results from chronic inflammation, and inflammation might be related to new bone formations. Furthermore, cases 2 and 3 also showed temporary consolidation, suspected to be caused by inflammation or hemorrhage. Namely, all three DPO cases without UIP or risk factors of acid aspiration did show consolidation suspected to be caused by inflammation or hemorrhage in common. We, therefore, speculated that inflammation or hemorrhage associated with fibrosis could contribute to bone formations in DPO. Inflammation itself is suggested to be involved in the pathogenesis of bone formation by promoting the transformation of cultured fibroblasts into osteoblasts [19, 20]. With respect to hemorrhage, organization of intra-alveolar hemorrhage associated with chronic passive hyperemia and phagocytosis of intra-alveolar hemosiderin deposits are suggested to be involved in the pathogenesis of bone formations [21]. In two cases, DPO was reported to occur secondarily from diffuse alveolar hemorrhage [22, 23]. In addition, in vascular Ehlers-Danlos syndrome, which is caused by mutations of type III collagen (COL3A1) gene, laceration of the lung, vascular disruption, and alveolar injury as a result of tissue fragility caused acute hematoma, hemorrhage, and organizing pneumonia [24, 25]. Subsequently, they often formed fibrous nodules, representing abnormal wound healing with abnormal collagen deposition, and ossifications developed in the background of the fibrous nodules. Asymptomatic mild inflammation or hemorrhage might have been overlooked in previous DPO cases, especially in idiopathic cases.

This study had several limitations. First, the sample size was small. Second, histological specimens corresponding to consolidation suspected to be caused by inflammation or hemorrhage could not be obtained in cases 2 and 3. Third, in the three cases, localized consolidation could not explain the diffuse ossifications in the whole lungs. However, unrecognized repeated inflammation and hemorrhage might have occurred diffusely. In this study, we could not reveal the factors causing inflammation or hemorrhage.

Conclusions

All five DPO cases were indolent, indicating that the prognosis of DPO might be good. The pathological and radiological findings suggested the possible involvement of pulmonary inflammation and hemorrhage in the pathogenesis of DPO. Further studies are warranted to validate the possible mechanisms underlying DPO.

Abbreviations

DLD
diffuse lung disease
DPO
dendriform pulmonary ossification
GERD
gastroesophageal reflux disease
HRCT
high resolution CT
NSIP
nonspecific interstitial pneumonia
SP-D
surfactant protein-D
UIP
usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of our hospital (Approval number: 679). We used an opt-out method, so that patients and families could refuse to participate in the study.

Consent for publication

The consent was obtained from the five patients for publication of this research and any accompanying images.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

YI received honoraria as an advisor and member of the steering committees of Boehringer Ingelheim, Shionogi, Asahi Kasei. YI received a grant from Japanese Ministry of Health, Labour, and Welfare. TA received lecture fees from Boehringer Ingelheim and Shionogi. The other authors declare that they have no competing interests.

Funding

This study was supported by Japanese Ministry of Health, Labour and Welfare (17933470).

Authors' contributions

TE, TT, TA and YI designed the study. TE and TK collected the data. TK performed pathological assessments. TE and MA performed radiological assessments. TE wrote the first draft of the paper. TT, TA and YI revised the paper critically. All authors have participated in revising the manuscript critically and gave their final approval of the version to be submitted.

Acknowledgements

We acknowledge all the subjects who participated in the study.

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Figures

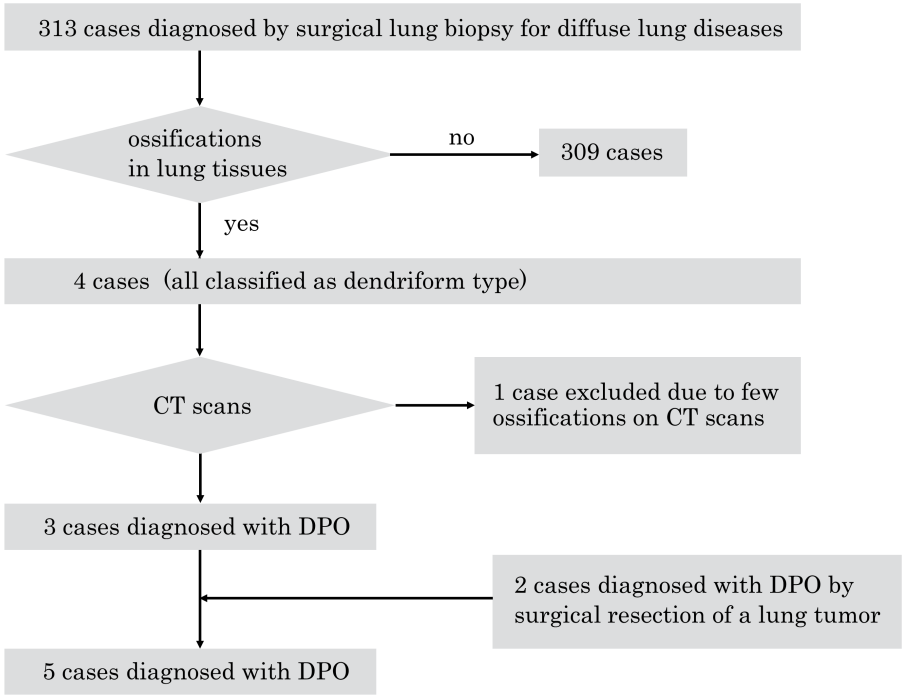

Figure 1

Flowchart of the study. DPO: dendriform pulmonary ossification

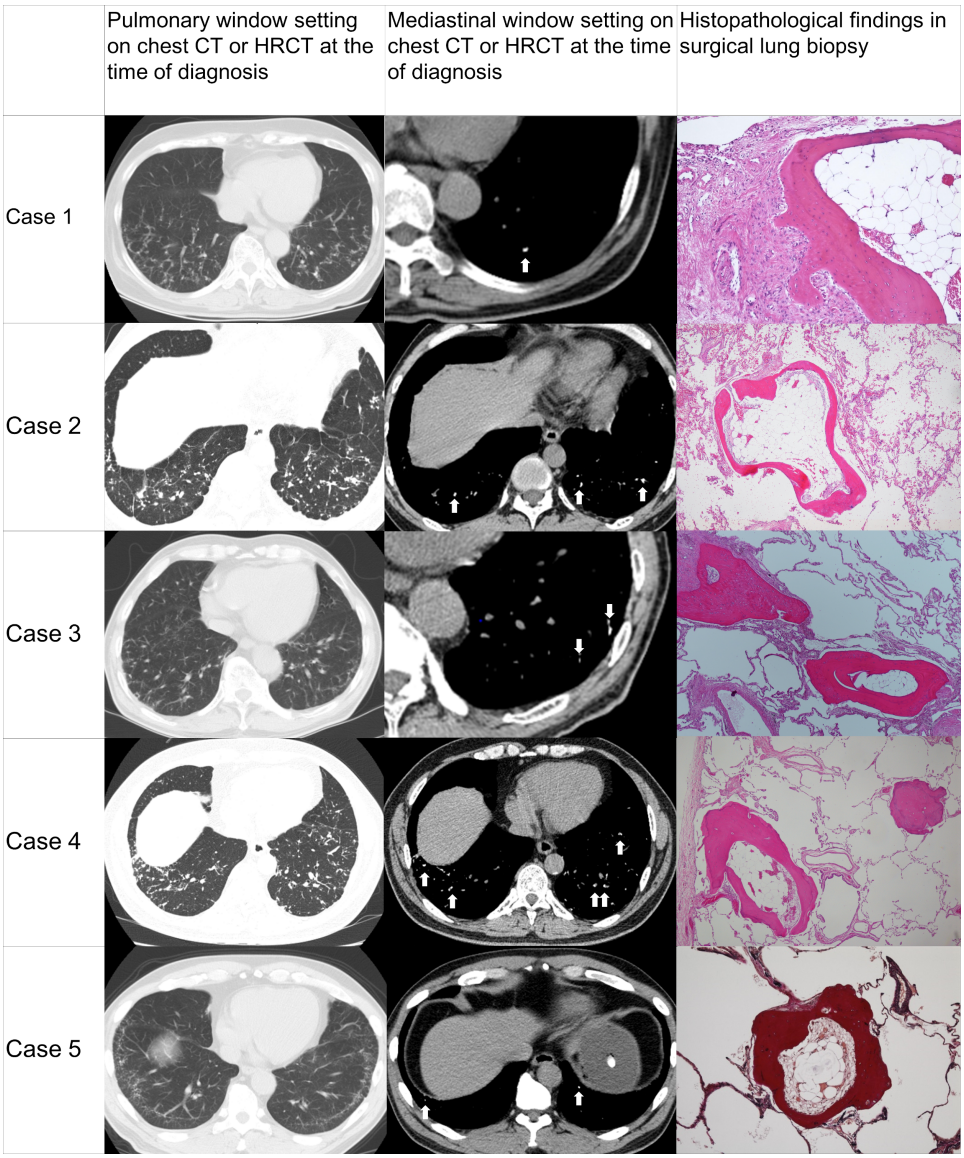

Figure 2

CT or high-resolution CT images at the time of diagnosis and histopathology of surgical lung biopsy. (Case 1) Hematoxylin and eosin stain, ×40. (Case 2, 3, 4) Hematoxylin and eosin stain, ×20. (Case 5) Elastica van Gieson stain, ×20. Arrows indicate calcified density lesions.

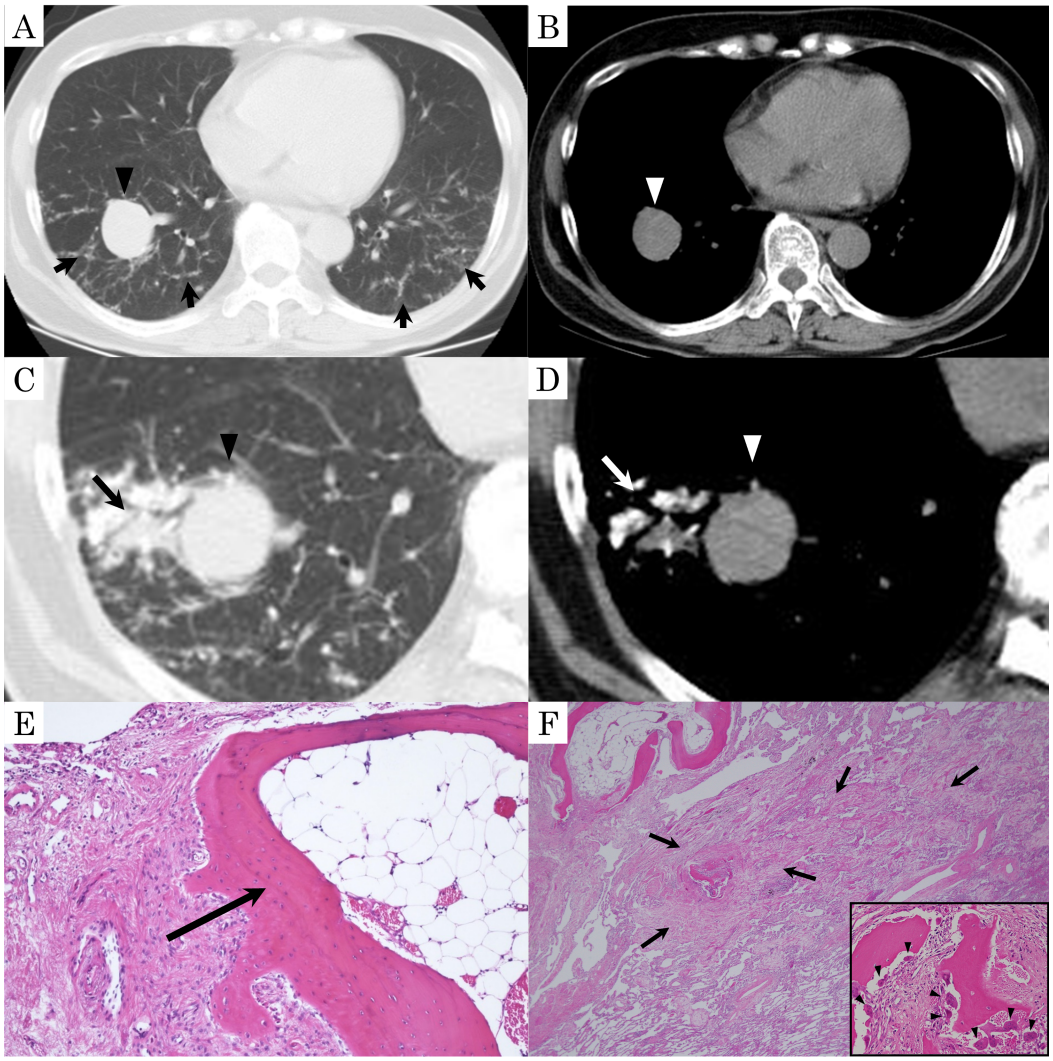

Figure 3

Chest CT images and histopathology of surgical lung biopsy specimens in Case 1. (A, B) Pulmonary window and mediastinal window setting of chest CT at the first visit showed diffuse reticulonodular shadows in both lower lobes (arrows) and a 3-cm nodular shadow in the right lower lobe (arrowhead). (C, D) Chest CT at 13 days before the surgery showed consolidation (arrow) next to a 3-cm nodular shadow (arrowhead) in the right lower lobe, which included calcified density lesions. (E) The specimen obtained with surgical lung biopsy revealed the presence of several irregularly shape interstitial bone, some of which contained fat marrow tissues (arrow) (hematoxylin and eosin stain, ×40). (F) Ossifications (inset) surrounded by some osteoblasts (arrowheads) were included in intra-alveolar fibrosis and slight inflammatory cell infiltration (arrows), corresponding to consolidation in the right lower lobe (hematoxylin and eosin stain, ×10) was observed.

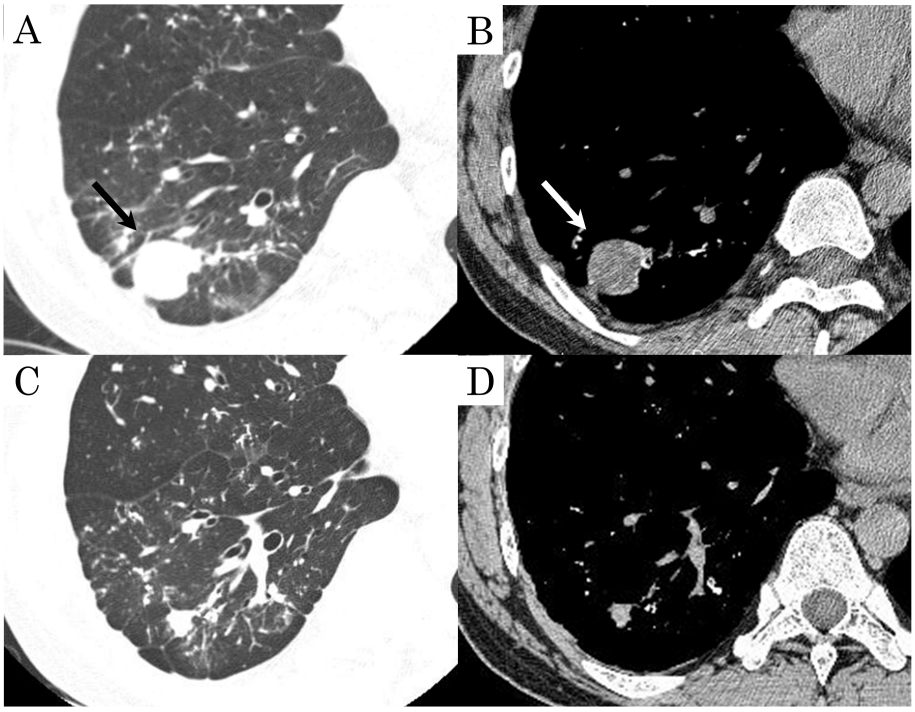

Figure 4

Chest CT images in Case 2. (A, B) High-resolution CT showed a round 3-cm nodule in the right lower lobe (arrow). (C, D) The nodule regressed spontaneously in 7 weeks.

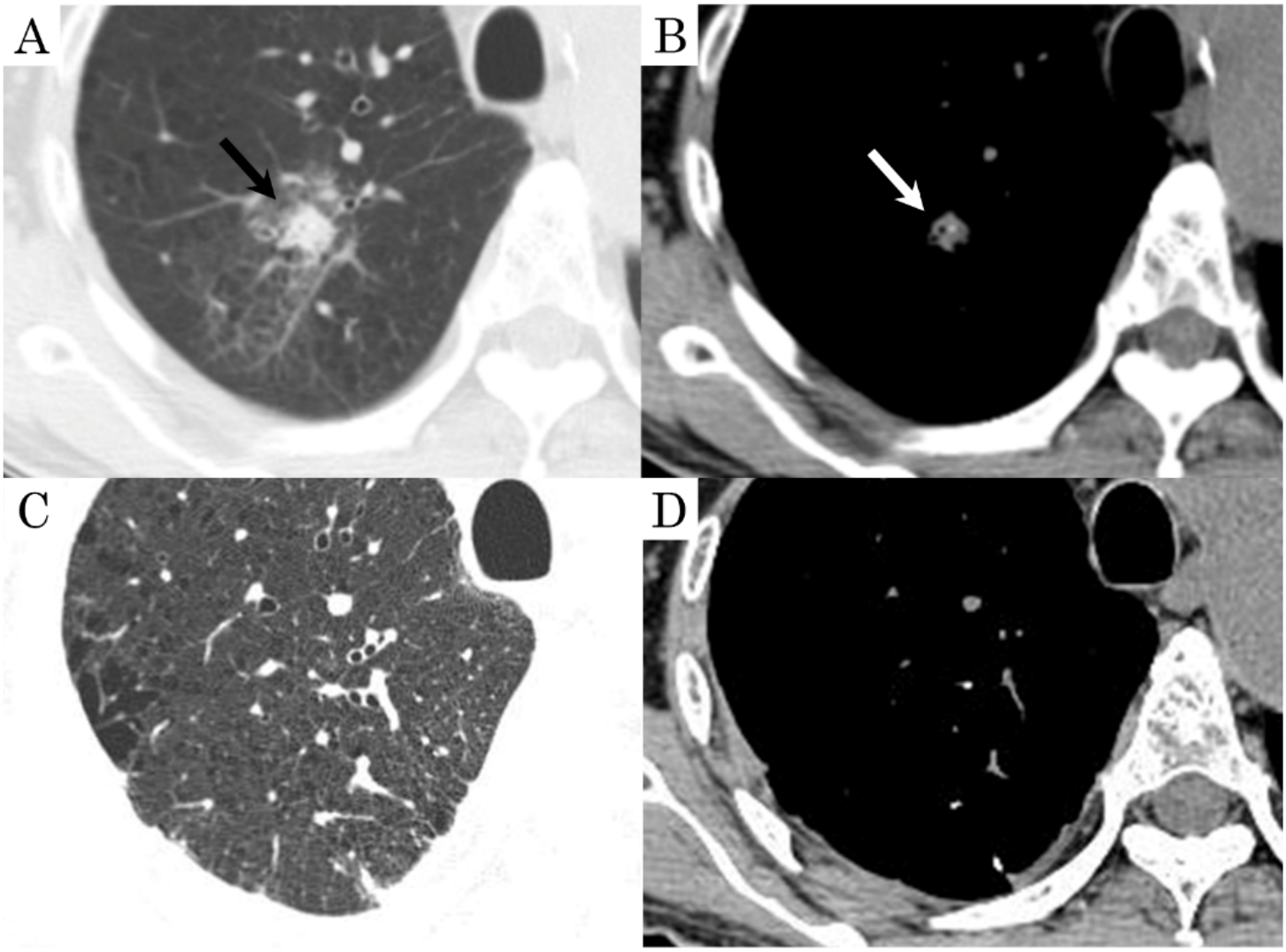

Figure 5

Chest CT images in Case 3. (A, B) High-resolution CT at 2 months after the first visit showed consolidation including a calcified density lesion in the right upper lobe (arrow). (C, D) The consolidation regressed spontaneously in 2 months.