2023 ILD CASEBOOK

間質性肺病案例集

台灣胸腔暨重症加護醫學會
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出版者 **台灣胸腔暨重症加護醫學會**

發行人

王鶴健 台灣胸腔暨重症加護醫學會 理事長
國立臺灣大學醫學院附設醫院癌醫中心分院 副院長

總編輯

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林聖皓 台灣胸腔暨重症加護醫學會間質性肺病及罕見肺疾病委員會 執行秘書
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陳家弘 台灣胸腔暨重症加護醫學會間質性肺病及罕見肺疾病委員會 委員
中國醫藥大學附設醫院內科部胸腔暨重症系 主治醫師暨肺復原室主任

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藍 冑 進　佛教慈濟醫療財團法人臺北慈濟醫院內科部　副部長暨胸腔內科主任

Spectrum of Non-Infectious Pulmonary Fibrosis : Pathologic Radiologic Considerations and Hypotheses

Introduction

Fibrosis is a pathological wound healing in which connective tissue replaces normal parenchymal tissue, leading to tissue remodeling and the formation of permanent scar tissue. Repeated injury, infection, and chronic inflammation are the common risk factors susceptible to tissue fibrosis.

Causes of pulmonary fibrosis include environmental exposure, drugs, connective tissue diseases, infections, and many interstitial lung diseases of unknown cause.

The main purpose of this article is to classify the pattern of noninfectious lung injury, healing response, and pulmonary fibrosis from the pathologic and radiologic points of view, and to propose several explanatory hypotheses.

Patterns of Lung Injuries and Healing Responses

From the pathologic consideration, lung injuries and healing responses can be categorized into three patterns (Table 1).

Predominant Alveolar Injury

In the pattern of predominant alveolar injury, the characteristic pathologic change is diffuse alveolar damage (DAD). The term “diffuse alveolar damage” was introduced by Katzenstein A, Bloor C, and Liebow A in 1976. Liebow's original intent was to refer to the changes in a single alveolus after a lung injury, meaning all parts of the alveolus (epithelium, endothelium, and interstitial space) are affected by the process (i.e., the alveolus is diffusely involved). In reality, patchy or extensive involvement of lung parenchyma is quite common in DAD both pathologically and radiologically. This article adheres to Liebow's original definition of DAD to classify diseases with

predominant alveolar injury.

Pathologically, DAD can be divided into acute(exudative) stage, organizing (proliferative) stage, and fibrotic stage. The acute and organizing stages may overlap with each other (Fig. 1). It's important to note that DAD does not necessarily progress from the acute to the organizing stage, as the process might halt, and recovery can occur. DAD can be classified into three categories according to the type of disease onset and the extent of disease involvement Table 2.

Acute extensive DAD encompasses conditions such as acute interstitial pneumonia (AIP), acute respiratory distress syndrome(ARDS), acute eosinophilic pneumonia (AEP), and acute hypersensitivity pneumonitis(AHP).

In early exudative phase of acute extensive DAD, intra-alveolar edema and eosinophilic hyaline membranes adhering to edematous alveolar septa can be observed (Fig. 2) On CT scan, patchy ground-glass opacities can be seen in the lung periphery(Fig. 3). Advanced DAD on CT may show extensive ground-glass opacity (GGO)/ consolidation in bilateral lung fields(Fig. 4).

In early organizing (proliferative) stage of acute extensive DAD, granulation tissue plugs (Masson bodies) can be found in airspaces (Fig. 5a,b,c). In the later organizing stage, the Masson bodies may merge into the surrounding parenchyma (Fig .6).

In addition to prominent fibroblast proliferation, alveolar collapse subsequently develops (Fig. 7), and then the Masson bodies fade into the surrounding collapsed parenchyma (Fig. 8). The CT findings of organizing DAD may show patchy or extensive GGO, consolidation, and mild traction bronchiectasis (Fig. 9). Some survivor's lung may progress for several weeks or months to fibrotic stage with extensive restructuring of lung parenchyma and formation of honeycombing (Fig. 10 and Fig. 11).

The most prevalent form of subacute alveolar injury, resulting in focal or multifocal DAD, is organizing pneumonia(OP). The DAD changes seen in OP are primarily localized to the peribronchiolar parenchyma. Masson bodies can be observed within bronchiolar lumens, alveolar ducts, and adjacent airspaces.

A variable degree of interstitial inflammation is also evident. (Fig. 12 and Fig. 13)

Typical CT imaging features of OP include:

(a) patchy GGO or consolidations, especially in subpleural and /or peribronchiolar area (Fig. 14 and Fig. 15);

(b) perilobular pattern (Fig. 16);

(c) peribronchial or peribronchiolar ill-defined small nodules;

(d) large nodules or masses (Fig. 17)

The Masson bodies of OP ordinarily disappear with steroid therapy. However, occasionally they become collagenized or even calcified (Fig. 18). This process has been termed cicatrization. In some areas only fine bands of cicatricial Masson bodies remain. When this was the only pattern seen, it would mimic fibrotic NSIP (Fig. 19 and Fig. 20). In some patients with cicatricial OP, CT shows only patchy peripheral irregular linear and reticular opacities or calcified nodules (Fig. 21).

Acute fibrinous and organizing pneumonia (AFOP) was described by Beasley and Travis in 2002, It's characterized by the deposit of intra-alveolar fibrin and varying degrees of organizing pneumonia within the alveolar ducts and bronchioles. Occasionally, the granulation tissue plugs consist predominantly of fibrin ball (Fig. 22).

Fibrin ball and myxoid granulation tissue plugs can sometimes be observed in the same biopsy (Fig. 23). In fact, OP often appears with extensive DAD, particularly in surgical lung biopsies and autopsies (Fig. 24).

The CT features of AFOP may overlap with extensive DAD (Fig. 25), OP

(Fig. 26), and eosinophilic pneumonia. Based on these pathological and radiological findings, the author hypothesize that acute and/or subacute alveolar injuries can manifest as extensive DAD, AFOP, OP, or a composite of these conditions depending on the acuity and severity of the underlying disease.

(a) interstitial fibrosis in a patchwork pattern (Fig. 27).

(b) architectural distortion (Fig. 27).

(c) presence of multifocal fibroblastic foci (Fig. 28).

(d) microscopic honeycombing (Fig. 32).

UIP(Usual Interstitial Pneumonia) is a chronic, insidiously progressive fibrotic pathologic change of the lung. The major pathologic diagnostic findings include :

The fibroblastic foci ,a variant form of Masson bodies, are believed to represent microscopic foci of alveolar injuries (i.e., a mini-organizing DAD) (Fig. 29 and Fig. 30). In early UIP, the fibrosis might be found directly beneath the pleura or adjacent to the nterlobular septa (Fig. 31). In more advanced UIP, pronounced subpleural fibrosis and honeycombing with fibrosis extending into the deeper parenchyma can be observed (Fig. 27 and Fig. 32).

The CT Feature of early UIP may present an indeterminate form for UIP(Fig. 33). More advanced cases usually show a probable UIP(Fig. 34) or typical UIP (Fig. 35).

According to the above pathologic and radiologic observations, the author offer a hypothesis that the outcomes of alveolar injuries might be influenced by three factors, i.e., the type of onset of injury, the severity of injury, and the frequency of injury (Table 3).

Predominant Interstitial Inflammation

Nonspecific interstitial pneumonia (NSIP) may be idiopathic, but more commonly occurs as a manifestation of connective tissue disease, hypersensitivity pneumonitis, or drug-induced lung disease. Interstitial inflammation and/or fibrosis in NSIP present a spacial and temporal homogeneity (Fig. 36 and Fig. 37), that is quite different from the appearance of UIP.

There's a range from a predominant interstitial inflammation (cellular NSIP) to predominant interstitial fibrosis (fibrotic NSIP). In cellular NSIP, the alveolar septa are thickened by infiltrates of lymphoplasma cells (Fig. 38). In fibrotic NSIP, the alveolar septal thickening is due to uniform collagen deposition with few fibroblasts (Fig. 39). Despite these changes, the underlying lung

architecture is maintained with minimal honeycomb change.

Fibrotic NSIP is much more common than cellular NSIP. In fact, a mixed cellular and fibrotic pattern is not uncommon.

Honeycombing is uncommon in NSIP, but some cases of fibrotic NSIP may exhibit marked focal expansion of alveolar septa, such that they tend to become confluent and eventually develop focal honeycomb cysts. (Fig. 40)

In patients with NSIP, CT typically shows GGO with a subpleural, basilar, and peribronchovascular predominance (Fig. 41). However, relative subpleural sparing can be found in 20%o to 60% of cases (Fig. 42). In patients with fibrotic NSIP, CT displays traction bronchiectasis, irregular reticulation, and GGO with a distribution similar to that of cellular NSIP (Fig. 42)

The majotity of patient with fibrotic NSIP who shows progressive fibrosis on follow-up maintain a CT pattern of NSIP (Fig. 43). However, a significant minority progress to a UIP patten, which is commonly seen in connective tissue disease (CTD)-associated NSIP (Fig. 44 and Fig. 45)

Therefore, a hypothesis is offered here to explain the possible mechanism of this unusual evolution pattern from NSIP to UIP. The author suppose that some CTDs may worsen uniformly over time, causing widespread and marked expansion of alveolar septa, ,which results in progressively extensive confluent fibrous tissue(Fig. 46). Eventually, florid and uniform honeycombing develops. (Fig. 47)

Predominant Granulomatous Inflammation

The major non-infectious causes of granulomatous lung disease include sarcoidosis, granulomatosis with polyangiitis(GPA), hypersensitivity pneumonitis, hot tub lung, and aspiration pneumonia. Among these diseases, sarcoidosis stands out as the most representative and significant.

The typical granulomas of sarcoidosis consist of epithelioid histiocytes, occasionally accompanied by multinucleated giant cells, with few intervening lymphocytes or other inflammatory cells(Fig. 48). Portions of the granulomas, or even entire granulomas, may be replaced by hyalinized fibrous tissue, often appearing as concentric lamellar fibrosis (Fig. 49). Over time, sarcoid granulomas might aggregate to form nodule or mass, characterized by a mixture of granuloma and dense hyalinized collagen.(Fig. 50)

A less common pattern of fibrosis is the formation of peri broncho vascular scars (Fig. 51). Occasionally, diffuse fibrosis in sarcoid can resemble a pattern mimicking fibrotic NSIP. (Fig. 52). Progressive UIP-like pulmonary fibrosis, along with a few non-caseating granulomas, may develop in a minority of cases. (Fig. 53)

The CT features of pulmonary sarcoidosis closely reflect the pathologic findings. The perilymphatic nodules are mainly adjacent to the bronchovascular bundles, interlobular septa, and subpleural regions(Fig. 54). Confluence of granulomas may result in large nodules or masses.(Fig. 55 and 56)

The fibrosis in sarcoidosis is manifested by irregular reticulation, irregular septal thickening, traction bronchiectasis, distortion of fissures, distortion of central bronchi, parahilar conglomerate mass, and, occasionally, honeycombing(Fig. 57-61)

Conclusion

From a pathological perspective, the author classifies the pathogenetic patterns of non-infectious pulmonary fibrosis into three main catagories : predominant alveolar injury, predominant interstitial inflammation, and predominant granulomatous inflammation. These pathological findings serve as a foundation to understand their presentation on CT scans. Some of these hypotheses require further research for validation.

臺中榮民總醫院、中國醫藥大學附設醫院、中山醫學大學附設醫院
彰化基督教醫療財團法人彰化基督教醫院、童綜合醫療社團法人童綜合醫院

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序

肺部間質是肺組織的重要組成部分，包括肺泡、間質和肺泡壁。間質性肺病是指肺泡間的結締組織發生病變的統稱，這些疾病可能由多種原因引起，包括遺傳因素、環境暴露和免疫系統異常等，甚至有些原因不明。此疾病的症狀各不相同，但通常包括呼吸困難、咳嗽和易倦怠等，這些症狀往往會影響病人的生活品質和日常活動。

針對許多會員一開始對於間質性肺病較不熟悉，學會在 2015 年、2020 年發表了「特發性肺纖維化的實證診斷與處置」，2019 年也發行了第一版「間質性肺病案例集」，讓會員們對於此疾病能更加熟悉。目前對肺纖維化也已經有藥物，可以提供治療並改善病人的症狀和病程。

本次出版的「間質性肺病案例集」，特別是挑選學會在 2021 年到 2023 年所舉辦的多科討論會的案例所組成。這些案例呈現了不同類型的疾病、特殊的臨床表現和不同的治療挑戰。讓會員藉由這些臨床上的真實案例 深入了解間質性肺病的臨床特徵、診斷方法和治療選擇。

我們希冀透過本案例集，幫助臨床醫師對此類疾病有更深入的了解，以利後續進一步研究的展開。更期望透過各科不同領域專家的合作，以團隊照顧模式提高病人的生活品質與改善病人的健康。

台灣胸腔暨重症加護醫學會 理事長

王鶴健

序

肺部疾病在臨床上一直以來都備受關注，尤其在 Covid-19 大流行後更是成為全球焦點，近幾年在學會的推廣下，臨床醫師對間質性肺病從不熟悉到現在已經較了解它的診斷與治療方式，但是間質性肺病是一個複雜而多樣化的疾病群體，需要藉由不同的案例學習來增加醫師的診治經驗。

學會從 2021 年到 2023 年間，邀請來自北中南東的 93 位胸腔科講師及 56 位風濕免疫及影像醫學專家，舉辦了 17 場間質性肺病跨領域討論會，熱烈交流困難診治的間質性肺病案例，也實踐了臨床指引所肯定建議的 MDD(Multidisciplinary Discussion) 模式。

這些寶貴的案例資料在間質性肺病及罕見肺疾病委員會的推動下，挑選出不同類型的間質性肺病案例集結成冊，於今年年底出版 2023 年間質性肺病案例集，通過這些案例，幫助醫師更加理解間質性肺病的診斷和治療。

最後感謝這次參與此案例集的編輯醫師群，特別是江自得醫師提供了他多年的智慧洞見，錄製了影像及病理參照的精彩演講，相信可以大幅度幫助醫師深入了解間質性肺病，讓病人得到更好的醫療照護。

台灣胸腔暨重症加護醫學會

間質性肺病及罕見肺疾病委員會 召委

林慶雄

目錄

縮寫對照表

英文縮寫	英文全名
A	
ANA	anti-nuclear antibodies
AsAo	ascending aorta
anti-Scl-70 Ab	anti-scleroderma-70 kD-antigen antibody
anti-SSA Ab	anti—Sjögren's-syndrome-related antigen A antibody
anti-SSB Ab	anti—Sjögren's-syndrome-related antigen B antibody
ALT	alanine transaminase
anti-Jo1 Ab	antihistidyl transfer RNA [t-RNA] synthetase antibody
anti-MDA5	anti-melanoma differentiation-associated gene 5
AST	aspartate transaminase
AMI	acute myocardial infarction
anti-RF	anti-rheumatoid factor antibodies
anti-dsDNA	anti-double strand DNA antibodies
anti-GBM	anti-glomerular basement membrane antibody
anti-CENP	anti-centromere proteins antibodies
anti-ENA	anti-extractable nuclear antigens antibodies
B	
BPM	beats per minute
BP	blood pressure
BAL	bronchoalveolar lavage
BO	bronchiolitis obliterans
C	
CBC	complete blood count
C3	complement component 3
C4	complement component 4
CK	creatine phosphokinase
CRP	c-reactive protein
CT	computed tomography
CPK	creatine Phosphokinase
CPFE	combined pulmonary fibrosis and emphysema
CABG	coronary artery bypass grafting
C-ANCA	cytoplasmic anti-neutrophil cytoplasmic antibody
CXR	chest radiograph
D	
DLCO	diffusion capacity of the lung for carbon monoxide
DLCO/VA	diffusion capacity for carbon monoxide/alveolar volume
DPO	dendriform pulmonary ossification

英文縮寫	英文全名
E	
EMG	electromyography
ESR	erythrocyte sedimentation rate
F	
FEV_1	forced expiratory volume in one second
$FEF_{25\%-75\%}$	forced expiratory flow at 25–75%
FVC	forced vital capacity
FiO2	fraction of inspiration O2
G	
GGO	ground glass opacity
GVHD	graft–versus–host disease
H	
HRCT	high–resolution computed tomography
HP	hypersensitivity pneumonitis
HSCT	hematopoietic stem cell transplantatio
I	
IPF	idiopathic pulmonary fibrosis
ILD	interstitial lung disease
IgG	immunoglobulin G
IgA	immunoglobulin A
IgM	immunoglobulin M
L	
LAD	left anterior descending artery
LV	left ventricle
LA	left atrium
LVEF	left ventricular ejection fractio
LCX	left circumflex artery
LDH	lactate dehydrogenase
LLL	left lowor lobe lung
M	
MSCs	mesenchymal stem cells
M protein	myeloma protein
N	
NYHA	New York Heart Association
NTM	non–tuberculosis mycobacterium
NSIP	nonspecific interstitial pneumonia

英文縮寫	英文全名
	O
OPD	outpatient department
OP	organizing pneumonia
	P
PA	pulmonary artery
PVR	pulmonary vascular resistance
PCR	polymerase chain reaction
PJP	*Pneumocystis jirovecii* pneumonia
PPF	progressive pulmonary fibrosis
P-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
	R
RF	rheumatoid factor
RV	right ventricle
RCA	right coronary artery
RP-ILD	rapid progressive interstitial lung disease
Ribosomal-P	anti-ribosomal P protein
RML	right middle lobe
RLL	increased infiltration and right pleural effusion
RVSP	right ventricular systolic pressure
RNP	antinuclear ribonucleoprotein antibody
	S
SLB	surgical lung biopsy
SpO_2	oxygen saturation
	T
TLC	total lung capacity
TTF-1	thyroid transcription factor 1
TB	tuberculosis
TR	tricuspid regurgitation
TRPG	tricuspid regurgitation peak gradient
TBLC	Transbronchial lung cryobiopsy
TBLB	transbronchial lung biopsy
	U
UIP	usual interstitial pneumonia
	V
VATS	video-assisted thoracic surgery
VA ECMO	veno-arterial extracorporeal membrane oxygenation
	W
WBC	white blood cells

I.

Interstitial lung diseases secondary to specific etiologies

A man suffered from his past - a case of occupational exposure related interstitial lung disease.

Ching-Min Tseng[a,b], *Chi-Wei Tao*[c]

aDevision of Chest Medicine, Department of Internal Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan

bSchool of Medicine, Yang Ming-Chiao Tun University, Taipei, Taiwan

cDepartment of Internal Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan

Clinical pearls

- Initial presentation of interstitial lung disease may not always be shortness of breathing or cough. Infection may occur due to poor lung conditions.
- Detailed interrogation of exposure history is mandatory and helpful for the differential.
- diagnosis of interstitial lung disease, especially in occupational-related ILD (interstitial lung disease).

Main article

Case presentation

- 62-year-old married male.
- A sand-blasting worker.
- Fever flared up to 39.4c for one week. Not relieved after visiting the clinic.
- Cough with some sputum, accompanied by chest and lower back pain. SOB was also noted without hemoptysis.
- After admission, empiric antibiotics treatment was given. His fever subsided.

Medical history

- Gout history.
- Reports no medications.
- Reports smoking 1.5PPD for over 40 years. No alcohol consumption.
- Has no pets.
- Denied bird exposure.
- Unremarkable family history.

Physical examination

- Height: 174 cm Weight: 94 kg.
- SpO_2 (oxygen saturation): 95% under ambient air.
- Basal rales over both lungs, without wheezing.
- No clubbing fingers.
- No leg edema.
- No arthralgia.

Physical examination

- White blood cell counts 14200/ul. AST (aspartate transaminase)/ALT (alanine transaminase)
- 114/153 IU/L. ALK-P 290 U/L. CRP. (c-reactive protein) 13.62 mg/dl
- Negative RF (rheumatoid factor), ANA (anti-nuclear antibodies), anti-ENA(anti-extractable nuclear antigens antibodies), and ds-DNA.
- Sputum culture: candida albicans. (few)

Chest radiograph

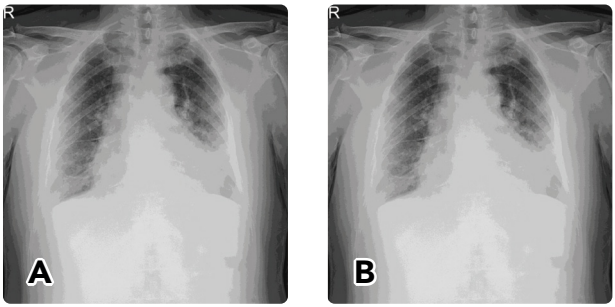

Figure 1A-1B.

Pulmonary function test

Parameter	Value (% predicted)
FVC (forced vital capacity) (L)	2.92(71)
FEV_1 (forced expiratory volume in one second) (L)	2.13(70)
FEV_1/FVC (%)	73
PEF (L)	5.56(61)
TLC (total lung capacity) (L)	4.34(67)
DLCO(diffusion capacity of the lung for carbon monoxide)(ml/min/mmHg)	17(58)
Conclusion: Moderate restrictive pattern with moderate reduction of diffusion capacity	

Bronchial alveolar lavage (via LUL)

- WBC (white blood cells) 1170/ul .
- N/L/E/H 17/68/0/15%.

Chest drainage

- Left side 200cc, Right side 360c.c.
- PE analysis: yellowish, WBC 1629/ul, RBC 1530/ul, N/L/E 61/38/1% LDH (lactate dehydrogenase) 263.
- Protein 3.6, CEA 3.5.

HRCT

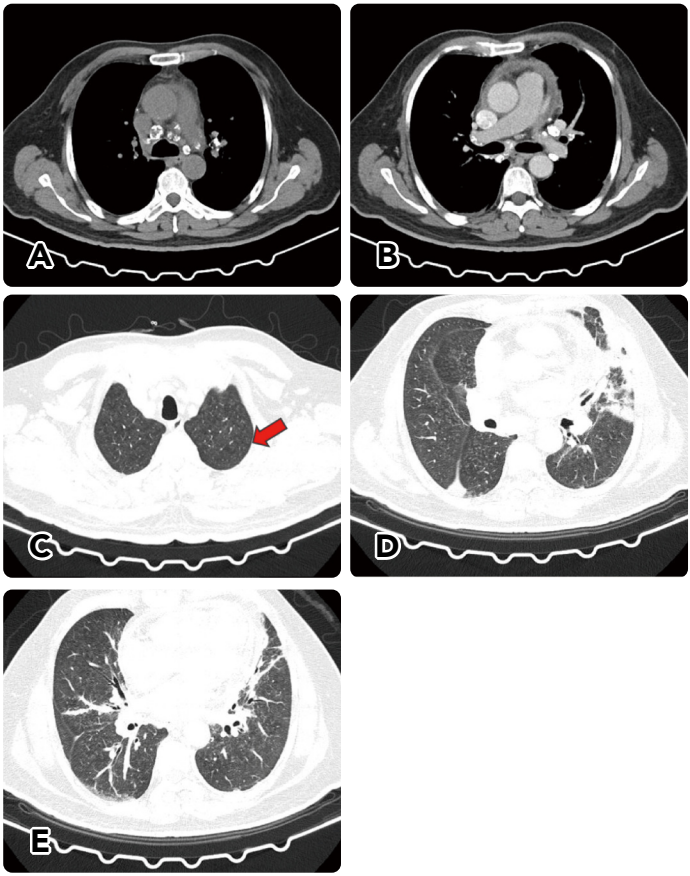

Figure 2A-2E.

Pathology

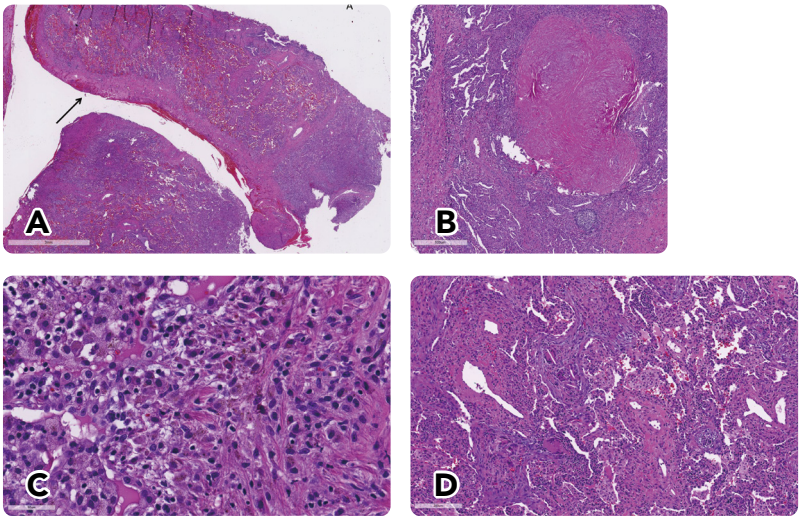

Figure 3A-3D.

Diagnostic process

- According to occupational history and histology, pulmonary silicosis is compatible.
- Chronic exposure to emery sand (金鋼砂), contained with silicon carbide, may induced lung fibrosis.

Discussion

- Fever may be the initial presentation in the patient with interstitial lung disease due to poor lung hygiene. We had to be carefully taking their history, especially the occupational exposure.
- Histology from this patient showed classic silicosis, with intra-alveolar aggregation of pigmented macrophages. And giant cells containing cholesterol clefts may indicate inhaled other organic materials in the emery sand.

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Figure legends

Figure 1

Reticular infiltrates, distributed.

- More at the lung peripheral and basal area.
- Consolidation over left lower lobe.

Figure 2A-2E

Alternative for UIP (usual interstitial pneumonia) pattern, with

- Eggshell calcified lymph node adenopathy in the non-contrast mediastinal window (Figure 2A). Most commonly occur in silicosis or coal workers' pneumoconiosis.
- Pericardial effusion in contrast to mediastinal window (Figure 2B), which is seldom seen in pneumoconiosis.
- Reticular change over bilateral lower lobe with consolidation over left lower lobe .(Figure 2D-2E)

Figure 3A-3D

Surgical lung biopsy specimens from the left upper lobe demonstrated.

- Fibrous thickening of visceral pleural. (Figure 3A, arrow)
- Prolonged inhalational inorganic particles, with pleural dense fibrosis, nodular hyalinized mass, similar to that of silicosis (Figure 3B), accumulation of macrophages with brown pigments. (Figure 3C)
- Intra-alveolar polypoid fibrosis with frequent giant cells containing cholesterol clefts. (Figure 3D)

Pericardium biopsy shows chronic inflammation and fibrosis without malignancy. (Figure not shown)

Amiodarone-related interstitial lung disease – taking care of both the beating and the breathing

Tang-Hsiu Huang[a]

Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Clinical pearls

- Amiodarone has potential pulmonary toxicity and may cause ILD; mechanisms not fully understood.
- For drug-induced ILDs, prompt removal of the triggering agent (if possible) is important.
- No standardization in the dosing and duration of corticosteroid treatment for amiodarone-related ILD.

Main article

Case presentation

- A 65-year-old male presented with progressively worsening non-productive cough and exertional dyspnea for weeks.
- No fever, chest pain, hemoptysis, or edema.

Medical history

- No smoking/vaping.
- Unremarkable travel/contact/family/occupational histories.
- Comorbidities:
  - emergent CABG (coronary artery bypass grafting) for AMI (acute myocardial infarction) 3 years ago.
  - paroxysmal atrial fibrillation, status post ablation.
  - hypertension.

- Current medication: aspirin, bisoprolol, amlodipine, amiodarone. (taken for 3 years, initially 200 mg/day, then 100 mg/day in the past 6 months before this admission)

Physical examination

- Heart rate: 59/minute; respiratory rate: 24/minute; SpO2 88-90% when resting and breathing ambient air.
- No abnormal lesion of the head and neck regions.
- Thoracic examination: mid-sternal healed surgical scars; non-specific crackles auscultated over both lung fields; heart sound was regular without murmurs.
- No hepato-splenomegaly.
- No deformity or swelling of fingers/joints; no edema, tenderness, or weakness of extremities.
- No skin eruption.

Laboratory panels

- Leukocytosis (14000 cells/uL; 79.3% neutrophil, 11.0% lymphocytes, 0.5% eosinophil) and elevated LDH (282 U/L; normal 135-225); otherwise, normal blood biochemistry (including CRP).
- A negative serologic test for connective tissue diseases .(ANA, C3 (complement component 3), C4 (complement component 4), anti-SSA/SSB Ab, anti-Jo 1 Ab, anti-Scl-70 Ab, RF)
- Airway viral swabs (including PCR (polymerase chain reaction) for SARS-CoV-2), and sputum cultures (bacterial, mycobacterial, fungal, viral) and PCRs (TB (tuberculosis), *Pneumocystis* jirovecii) were all negative repeatedly.

Chest radiograph

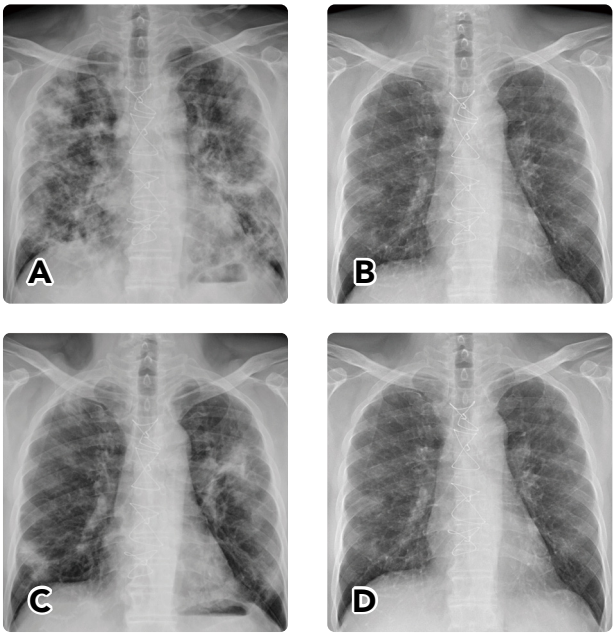

Figure 1A-1D.

Pulmonary function test

Parameter	Value (% predicted)
FVC	4.01 (119)
FEV_1	2.62 (102)
FEV_1/FVC	65
$FEF_{25\%-75\%}$ (forced expiratory flow at 25-75%)	1.03 (31)
DL_{CO}	85
Conclusion: Performed about 6 months after disease onset (briefly after methylprednisolone was discontinued).	

Cardiac evaluation

Adequate left-ventricular systolic function; mild pulmonary hypertension. (31 mmHg)

HRCTX

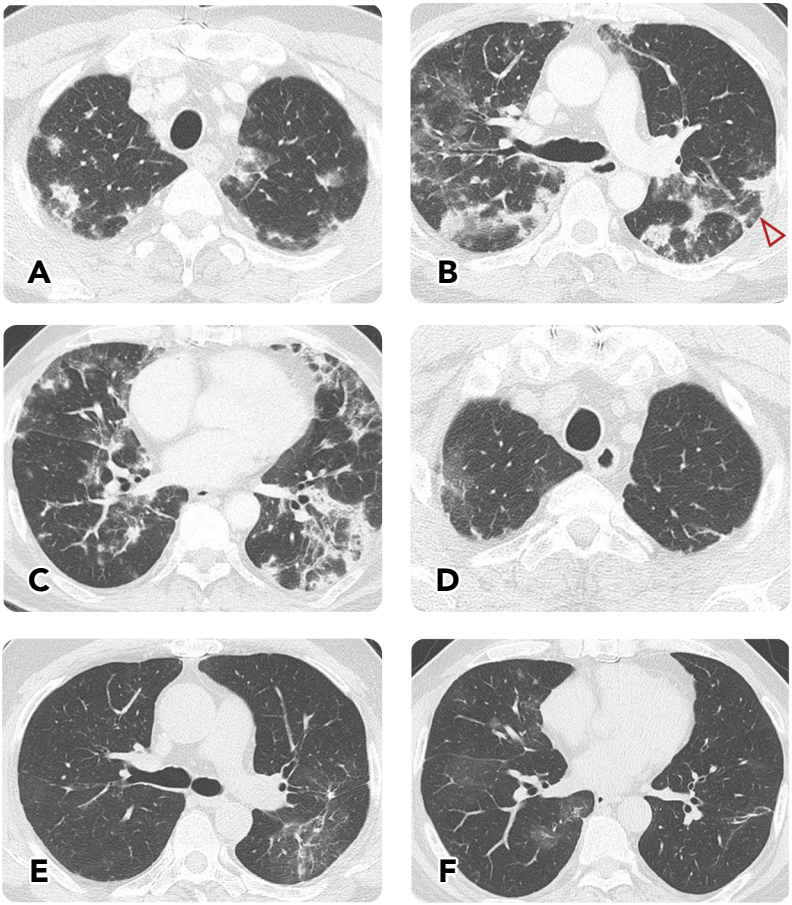

Figure 2A-2F.

Histology

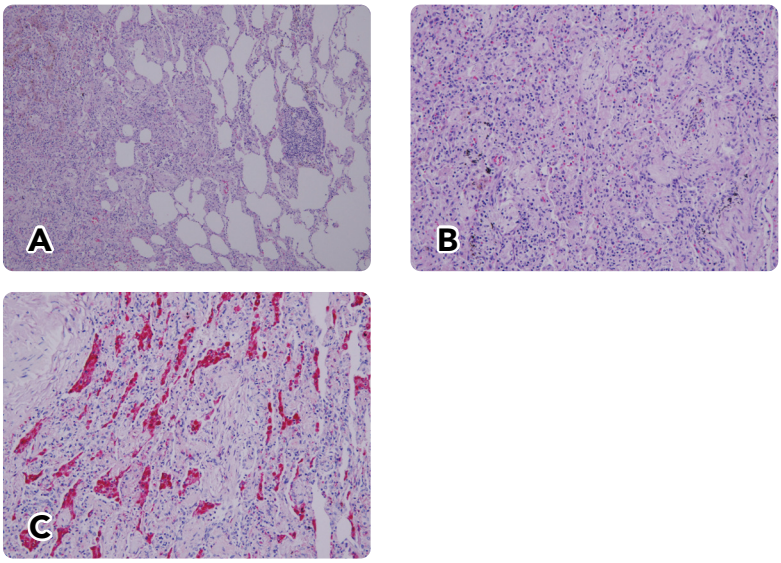

Figure 3A-3D.

Diagnostic process and disease course

- Initial thoracic images (Figure 1A-1D) showed bilateral ill-defined ground-glass, nodular, and consolidating opacities.
- The patient responded poorly to empirical Ceftriaxone + Doxycycline. All microbial workups came back negative. We thus surveyed for other non-infectious etiologies.
- Amiodarone-related toxicity was also suspected; the agent was replaced by diltiazem. VATS (video-assisted thoracic surgery)wedge biopsy (sampling the left upper lobe) was performed based on the following considerations:
  - amiodarone had been an important cardiac medication for this patient, and the daily dosage was low.
  - CT (computed tomography) features were nonspecific, and radiodensities of the lung lesions and liver were not increased. (all < 70 HU)

- Pathology examination reported an organizing pneumonia pattern plus many intra-alveolar clusters of foamy macrophages. (Figure 3A-3C)
- Following amiodarone discontinuation and treatment with systemic methylprednisolone (starting with 1 mg/Kg/day), the patient improved clinically and radiographically (Figure 1B). Methylprednisolone was tapered off over 6 months.
- Despite alternative antiarrhythmic treatments, to the atrial fibrillation kept recurring. Therefore, the cardiologist resumed amiodarone (200 mg/day) about 7 months later.
- 4 weeks after amiodarone resumption, the patient had ILD recurrence, manifesting as a nonproductive cough and new radiographic opacities. (Figure 1C)
- Amiodarone was soon replaced by other agents. Without corticosteroids, the patient improved clinically and radiographically within 3 months. (Figure 1D)
- To avoid re-exposure, amiodarone-related adverse reactions of this patient were registered to the electronic medical system of our hospital and to the personal medication profile of the National Health Insurance.
- No recurrence so far. (Figure 2D-2F)

Discussion

- Amiodarone is a commonly used antiarrhythmic agent, but it has potential pulmonary toxicity and may cause ILD, even at a low daily dose [1-3].
- High radiodensity of the liver and lung lesions is commonly seen in amiodarone-related ILD, but it is neither specific nor pathognomonic [1].
- For patients with new/recurrent/worsening ILD, the search for a possible/controllable etiology is crucial [4].
- For drug-related ILD, prompt removal (if possible) of the causative agent is key to treatment.
- The role, dosing, and duration of systemic corticosteroids in treating amiodarone related ILD have not been standardized.

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Figure legends

Figure 1A and Figure 2A-2C

The initial (1A) chest radiograph and, (2A– 2C) transverse-view HRCT (high-resolution computed tomography) images, of the patient upon admission; the red arrowhead in (2B) indicates the site of wedge biopsy.

Figure 1B-1D

Follow-up chest radiographs (1B) at 6 months (when methylprednisolone was discontinued); (1C) 4 weeks into the second exposure of amiodarone; (1D) 3 months after the second exposure of amiodarone was stopped).

Figure2D-2F

(2D – 2F) Follow-up transverse-view HRCT images. (8 months after the second exposure of amiodarone was stopped)

Figure 3A-3C

Histological examination of the left-upper-lobe wedge-biopsied specimen revealed: (3A) an overall organizing pneumonia pattern (40x; H & E stain), with (3B) intra-alveolar Masson bodies (granulation plugs) and clusters of foamy macrophages (200x; H & E stain) that are highlighted by (3C) the immunohistochemical staining for CD-68 (200x).

Non-specific Interstitial Pneumonitis as an Early Manifestation of Anti-MDA5 Associated Dermatomyositis

Nai-Tzu Chen[a], *Chun-Liang Lai* [b,c]

[a] *Division of Rheumatology and Immunology, Department of Internal Medicine, Buddhist Tzu Chi Medical Foundation Dalin Tzu Chi Hospital, Chiayi, Taiwan*

[b] *Division of Chest Medicine, Department of Internal Medicine, Buddhist Tzu Chi Medical Foundation Dalin Tzu Chi Hospital, Chiayi, Taiwan*

[c] *School of Medicine, College of Medicine, Buddhist Tzu Chi University, Hualien, Taiwan*

Clinical pearls

- Most MDA5-DM cases show a strong association with RP-ILD. (rapid progressive interstitial lung disease)
- Patients may present with interstitial pneumonitis before manifestations of classic skin or myositis which leads to delay in diagnosis and treatment.
- If patients have lung fibrosis noted under chest radiography or HRCT, lung tissue biopsy and evaluation of autoimmune disease can assist in diagnosis.

Main article

Case presentation

- A 50-year-old previously healthy housewife, a never smoker presented to the chest outpatient clinic with 2-month of cough and progressively exertional dyspnea.
- Initial presentation was also accompanied by generalized itchy skin rash and redness on eyelids.
- There was no muscle weakness, fever, chills, orthopnea, or photosensitivity.
- Her skin manifestations including Gottron's sign, Shawl sign, and Heliotrope sign became evident two months later.

Medical history

- Hypertension under Atenolol control.
- No pets and no use of herbs; unremarkable family and travel histories.

Physical examination

- Heart rate: 108/minute; respiratory rate: 25/minute; SpO2 93% when resting and breathing ambient air.
- Thoracic auscultation: Velcro's crackles were heard at bilateral dependent part of lungs, but there was no wheezes or inspiratory squawks. Heart sounds were regular without murmurs.
- No musculoskeletal or mucosal lesions.
- Generalized skin rash spread at trunk and four limbs initially. Helitrope signs, shawls sign, V signs and Grottron's signs presented subsequently two months later.

Laboratory panels

- Normal hemogram but blood biochemistry revealed mild elevation of CRP (2.65 mg/dL), ESR (erythrocyte sedimentation rate) (44), AST (89 IU/L), and ALT (78 IU/L). There was no elevation of CK (creatine phosphokinase) level.
- Her ANA was positive (1:80) but other auto-antibodies screening including anti-SSA/SSB Ab, anti-Jo 1 Ab, anti-Scl-70 Ab, and rheumatoid factor were all negative. However, until skin manifestation flared up 2 months later, myositis antibody profile demonstrated strong positive in anti-MDA5 antibody.
- EMG (electromyography) showed compatible results with dermatomyositis.

Chest radiograph

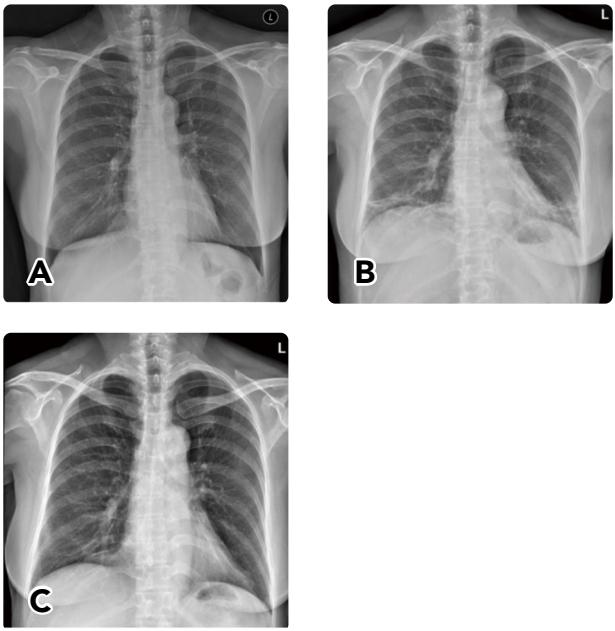

Figure 1A-1C.

Pulmonary function test

Date	Apr. 2021 (onset of symptoms)	Oct. 2021	Mar. 2022	Apr. 2023
FVC, L (% pred.)	1.55(63.1)	2.10(84.9)	2.27 (91.9)	2.41 (98.3)
FEV_1, L (% pred.)	1.23(59.2)	1.72(82.3)	1.84 (88.2)	1.87 (90.5)
FEV_1/FVC, %	79.21	81.8	81.2	77.7
$FEF_{25\%-75\%}$, L/s (% pred.)	1.17 (37.8)	1.19 (38.5)	1.80 (58.7)	1.57 (51.7)
TLC, L (% pred.)	3.13 (76.3)	3.65 (87.4)	3.68 (88)	3.71 (88.9)
D_{LCO}, % pred.	42	49	58	61

Cardiac evaluation

No regional wall motion abnormality with adequate LV (left ventricle) systolic function (LVEF (left ventricular ejection fraction): 71.65%)

HRCT

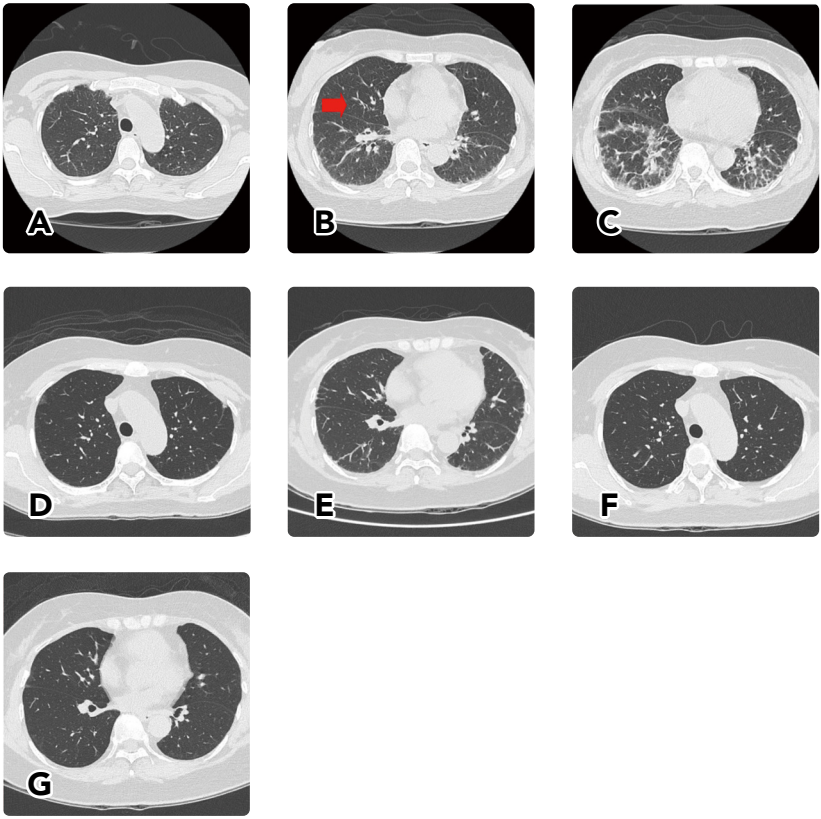

Figure 2A-2G.

Histology

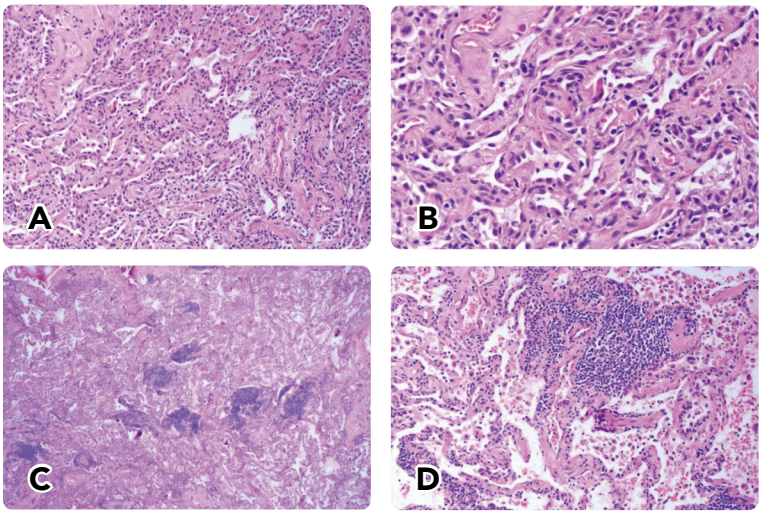

Figure 3A-3D.

Skin manifestation

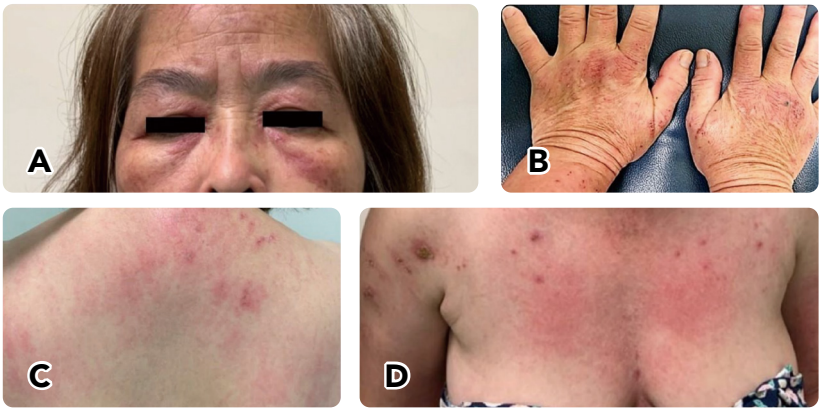

Figure 4A-4D.

Diagnostic process

- The patient had an initial chest radiograph showing bilateral lower lung fibrosis (Figure 1A-1C). She was firstly treated with one-week of antibiotics for possible bacterial infection. As no improvement documented, she was admitted for ILD workup.
- The initial HRCT revealed interlobular septal thickening in both lower lobes, right middle lobe, and both upper lobes,especially severer, more severe at lower lobes. Interstitial lung disease was considered. (Figure 2A-2C)
- VATS right-middle-lobe S4 segmentectomy (indicated by the red arrow in Figure 2B) was performed for definite diagnosis. The pathologic examination reported interstitial lung disease, and the histology was in favor of NSIP (nonspecific interstitial pneumonia) in the morphological aspect. (Figure 3A-3D)
- After an open lung biopsy, the patient started treatment with oral prednisolone (1 mg/kg/day) after rheumatologist consultation. Her autoantibodies disclosed all negative findings except for positive ANA (1:80).
- Two months after diagnosis of NSIP, her skin manifestations including Gottron's sign, Shawl sign, and Heliotrope sign became evident, and hence dermatomyositis was diagnosed with a serology confirmed anti-MDA5 variant. (Figure 4A-4D)
- The patient exhibited a good response to induction steroid pulse therapy and received 6 cycles of cyclophosphamide pulse therapy.
- The interstitial fibrosis pattern showed dramatic regression after medication management. (Figure 2D-2G)

Discussion

- Most Anti-MDA5 DM cases show a strong association with RP-ILD. In our case, it had an initial presentation of NSIP which is a rare clinical presentation in MDA5-DM.
- Our case showed a good response to systemic steroids and immunosuppressants. The interstitial pneumonitis resolved dramatically accompanied by improvement of pulmonary function test and all respiratory symptoms. The follow-up chest CT scan also revealed dramatic regression of interstitial lung fibrosis.

Acknowledgment

We are thankful to Professor Teh-Ying Chou of Taipei Veterans General Hospital for his professional comments on the histological findings.

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Figure legends

Figure 1A-1C

Chest radiograph (1A) at baseline (2 years before this present illness), and (1B) upon symptoms onset (1C) after treatment for 3 months.

Figure 2A-2C

The initial HRCT images showing: (2A-2C) thickening of interlobular septa without honeycombing or ground-glass opacities in lower lobes and upper lobes were relatively spared.

Figure 2D-2G

The interstitial fibrosis pattern showed dramatic regression after steroid treatment for 3 months (2D-2E), and 12 months later after titrating down steroids and immunosuppressants, showing resolution of interstitial lung fibrosis. (2F-2G)

Figure 3A-3D

Histological examination revealed: (3A-3B) interstitial fibrous widening with foci of lymphocyte aggregation. (200x, 400x), with (3C-3D) diffuse lymphocytic. infiltration accompanied by lymphoid aggregates in the septa is compatible with a pathologic pattern of NSIP. (40x-100x). All H & E stain.

Figure 4A-4D

Skin manifestation: (4A) Heliotrope sign, (4B) Gottron's signs, (4C) shawl sign, and (4D) V sign which are the classic presentation of dermatomyositis.

As the lungs turned hazy after hematopoietic stem cell transplantation – hoping for the best but expecting the worst

Chung-Fu Lin[a], *Tang-Hsiu Huang*[a]

[a] *Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*

Clinical pearls

- Recipients of hematopoietic stem cell transplantation are susceptible to various infectious and noninfectious respiratory complications, of which BO (bronchiolitis obliterans) is a major concern.
- OP (Organizing pneumonia) may develop in the late (> 100 days) transplantation period. Unlike BO, OP responds well to systemic corticosteroids.
- Correct diagnosis and appropriate treatments rely on a comprehensive assessment integrating histories and the clinical, laboratory, radiographic, and histologic presentations.

Main article

Case presentation

- A 64-year-old male, presenting with exertional dyspnea and non-productive cough for several weeks.
- No associated fever, sore throat, hemoptysis, abdominal pain, diarrhea, of the skin and oral mucosa.

Medical history

- Long-term olmesartan, diltiazem, and furosemide for hypertension.
- He underwent peripheral-blood HSC (hematopoietic stem cell transplantation) for myelodysplastic syndrome 7 months earlier and then received prednisolone and cyclosporin (together with prophylactic trimethoprim/sulfamethoxazole and ganciclovir) for 4 months. All the immunosuppressants were tapered off 3 months before his present illness.
- A factory worker color-coating electric wires but retired several years ago.
- Quit smoking for 1 yea.r (previously 1 pack per day)
- No pets and no use of herbs; unremarkable family and travel histories.

Physical examination

- Heart rate: 115/minute; respiratory rate: 20/minute; SpO2 93% when resting and breathing ambient air.
- No oral thrush or mucosal lesion.
- No palpable lymphadenopathy.
- Thoracic auscultation: no wheeze, inspiratory squeak, or velcro crackles. Heart sound was regular without murmur.
- No hepato-splenomegaly.
- No deformity or swelling of fingers/joints; no edema, tenderness, or weakness of extremities.
- No skin eruption/discoloration.

Laboratory panels

- Normal hemogram and blood biochemistry.
- Negative auto-antibodies. (ANA, anti-SSA/SSB Ab, anti-Jo 1 Ab, anti-Scl-70 A, rheumatoid factor)
- BAL (bronchoalveolar lavage): clear and neutrophil-predominant fluid (582 WBC/uL with 75% neutrophils, 5% lymphocytes); all the bacterial, mycobacterial, fungal, and viral cultures and galactomannan serology was negative but positive for *Pneumocystis jirovecii*-PCR. (polymerase chain reaction)

Chest radiograph

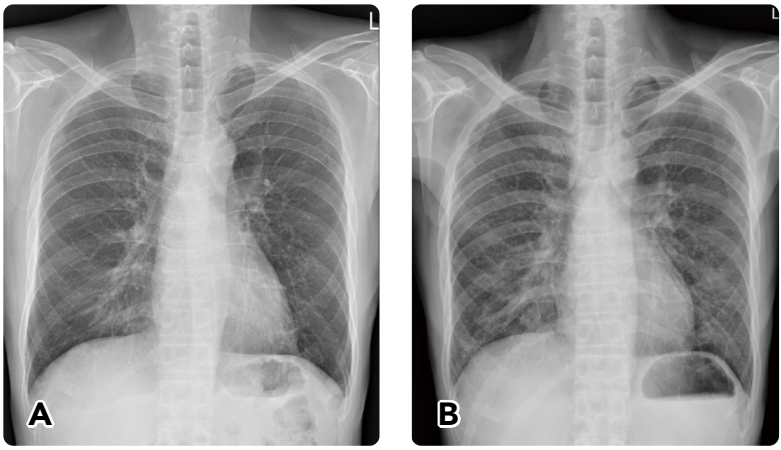


Figure 1A-1B.

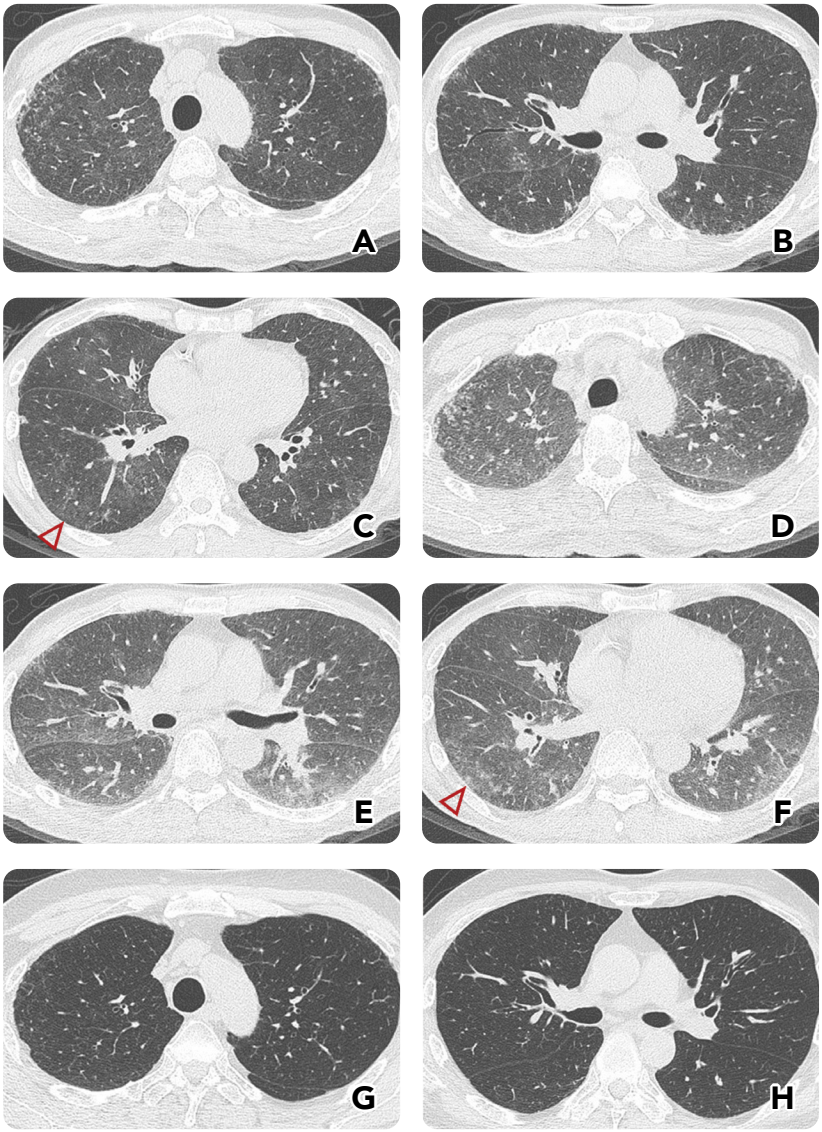
Pulmonary function test

Date	Feb. 2021	Oct. 2021 (onset of present illness)	Dec. 2022
FVC, L (% pred.)	4.22 (118)	3.17 (90)	3.82 (108)
FEV_1, L (% pred.)	2.95 (102)	2.36 (83)	2.74 (97)
FEV_1/FVC, %	70	74	72
$FEF_{25\%-75\%}$, L/s (% pred.)	1.81 (51)	1.92 (55)	1.77 (51)
TLC, L (% pred.)	-	6.01 (107)	6.82 (122)
D_{LCO}, % pred.	-	41	112

Cardiac evaluation

Adequate left-ventricular systolic function; mild pulmonary hypertension (35 mmHg).

HRCTX



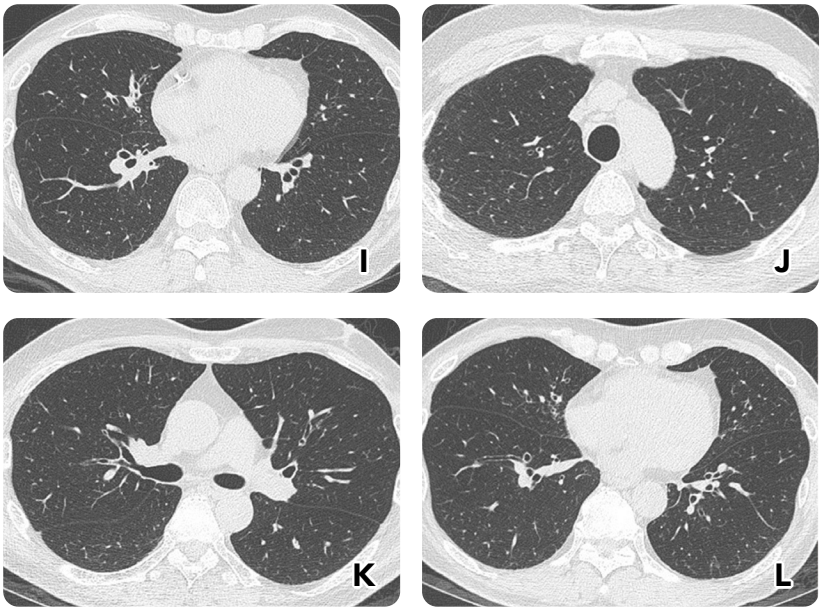


Figure 2A -2L.

Histology

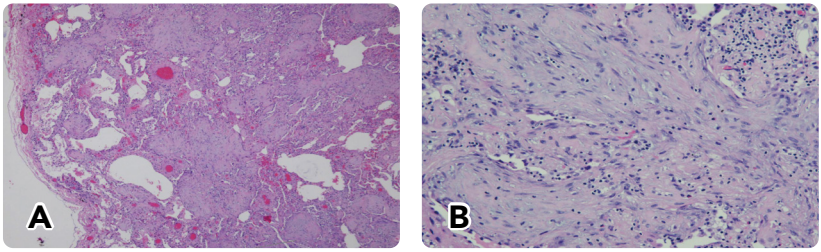


Figure 3A-3B.

Diagnostic process

- In addition to respiratory symptoms, the initial chest radiograph showed bilateral extensive haziness. (Figure 1)

- Although the patient received continuous prophylaxis while he was taking immunosuppressants, and all immunosuppressants were discontinued 3 months ago, the possibility of PJP (Pneumocystis jirovecii pneumonia) could not be completely excluded. He received a complete the course of therapeutic-dose trimethoprim/sulfamethoxazole.
- The initial HRCT revealed diffuse GGO (ground glass opacity) and end-expiratory patchy mosaic attenuation suggesting multifocal air-trapping (Figure 2A-2F). VATS right-lower-lobe wedge biopsy was performed to confidently exclude BO and opportunistic infection.
- Pathologic examination reported a diffuse pattern of OP without evidence of infection (including PJP and virus-related cytopathic changes) or GVHD (graft-versus-host disease).(Figure 3A-3B)
- The patient responded well to systemic methylprednisolone treatment (starting with 0.5 mg/kg/day), which was tapered off over 6 months.
- No recurrence so far (Figure 2G-2L).

Discussion

- Important non-infectious respiratory complications in the late period (> 100 days) after HSCT (hematopoietic stem cell transplantatio) include BO (due to GVHD), cryptogenic OP and other idiopathic interstitial pneumonia, pulmonary toxicity of immunosuppressants, and veno-occlusive disease [1-2].
- OP can occur after autologous or allogeneic HSCT [1-2], with distinct histologic features from those of BO. Typical CT findings are peripheral or peribronchial GGO and consolidation. Linear opacity and "reverse halo sign" are also possible.
- OP generally responds well to systemic corticosteroids, but it is essential to identify a possible triggering etiology and to closely monitor for recurrence [3].

Acknowledgment

We are thankful to Professor Teh-Ying Chou of Taipei Veterans General Hospital for his professional comments on the histological findings.

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Figure legends

Figure 1

Chest radiograph (1A) at baseline (2 months before this present illness), and (1B) upon admission.

Figure 2A-2F

The initial HRCT images show: (2A-2C) diffuse GGO at the end-inspiratory phase, and (2D-2F) patchy mosaic attenuation suggesting air-trapping at the end-expiratory phase. The red arrowhead in (2C) and (2F) indicates the site of wedge biopsy.

Figure 2G-2L

Follow-up HRCT images: (2G-2I) briefly after cessation of methylprednisolone treatment, and (2J-2L) 18 months later, showing resolution of the ground-glass opacities without recurrence.

Figure 3A-3B

Histological examination of the right-lower-lobe wedge-biopsied specimen revealed: (3A) a diffuse pattern of organizing pneumonia (40x), with (3B) intra-alveolar Masson bodies (granulation plugs) and interstitial infiltration of mixed inflammatory cells (100x). There was no evident feature of graft-versus-host reaction (such as apoptosis, perivasculitis, and bronchiolar concentric fibrosis). All H & E stain.

Unraveling the Lines and Dots – A Case of Pulmonary AL Amyloidosis in a Patient with Multiple Plasmacytoma

Hung-Jui Ko[a], *Kuang-Yao Yang*[a,b,c]

[a]*Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

[b]*Faculty of Medicine, School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*

[c]*Institute of Emergency and Critical Care Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*

Clinical pearls

- On HRCT, pulmonary AL amyloidosis may present with diffuse micronodules, interlobular septal thickening and ground glass opacities. Usually, the findings are located over the basal and lower lung field.
- Pulmonary function test typically showed reduced DLCO and restrictive ventilator impairment.
- Tissue biopsy by TBLB (transbronchial lung biopsy) or surgical lung biopsy is needed to establish the diagnosis.

Main article

Case presentation

- 65-year-old woman.
- A housewife without smoking history or electronic cigarette usage.
- Abnormal chest imaging during follow-up of plasmacytoma and rectal adenocarcinoma.

Medical history

- Plasmacytoma, IgG (immunoglobulin G)/Lambda, with multiple lymph node involvement.
- Rectal adenocarcinoma, pT3N1bM0, stage IIIB.
- Chronic hepatitis B.

Physical examination

- SpO_2: 98% under room air.
- No abnormal breathing sound.
- No leg edema.
- No arthralgia.

Laboratory panels

- Normal CBC (complete blood count) and biochemistry.
- Negative sputum and serum bacterial, mycobacterial, and fungal examinations.
- Autoimmune and rheumatology profile: not examined.
- Elevated serum IgG (2445mg/dL; 700-1600), elevated serum free Lambda (30.16mg/L; 5.71-26.30), presence of M protein(myeloma protein) over beta-2 globulin and gamma globulin region, presence of monoclonal protein as IgG/Lambda by serum immunofixation electrophoresis.

Chest radiograph

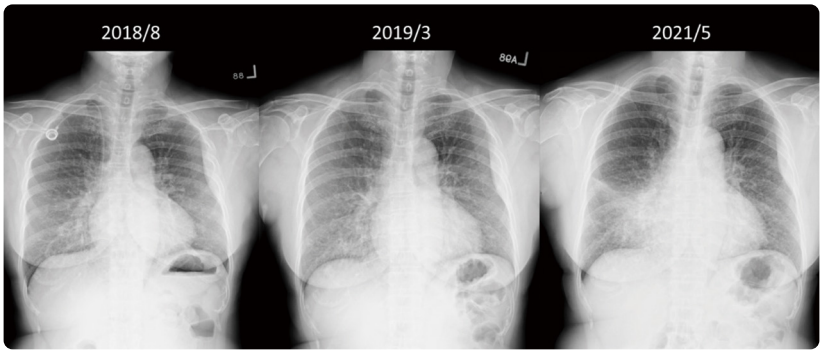

Figure 1.

Pulmonary function test

Date	Value (% predicted)
FVC (L)	2.31 (97)
FEV_1 (L)	2.01 (106)
FEV_1/FVC (%)	87
$FEF_{25\%-75\%}$ (L/sec)	1.76(93)
PEF (L/sec)	4.88(86)
TLC (L)	4.13 (106)
DLCO (ml/min/mmHg)	14.34 (65)
Conclusion: Mild reduction of gas exchange	

Cardiac evaluation

RVSP (right ventricular systolic pressure) 38.1 mmHg.

HRCT

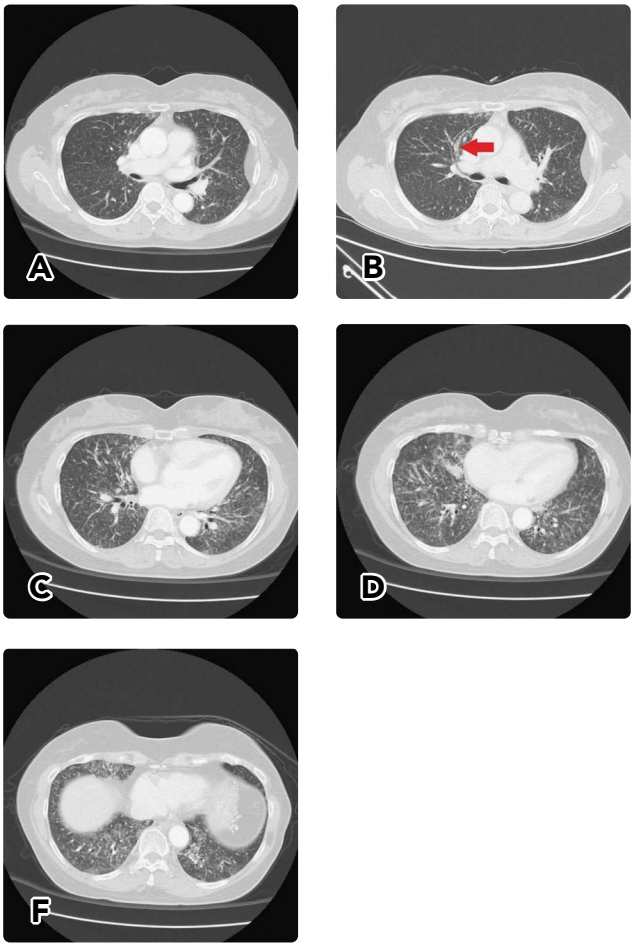

Figure 2A-2F

Bronchoscopy showed

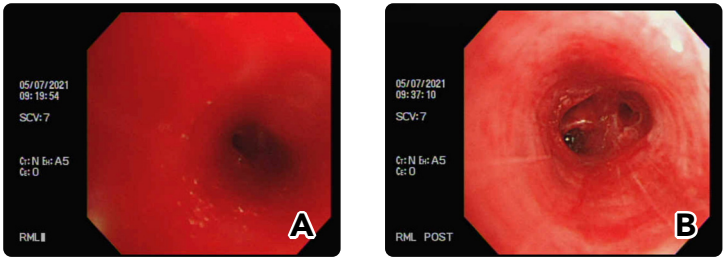

Figure 3A-3B.

Histology

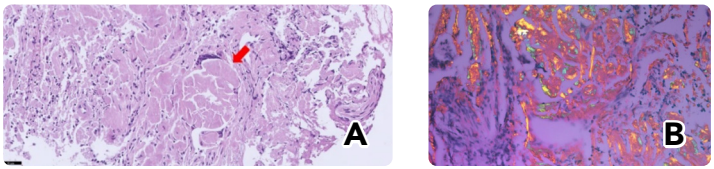

Figure 4A-4B.

Diagnostic process

- Chest CT revealed centrilobular nodules and broncho-vascular bundle thickening.
- Bronchoscopy was done. Culture from BAL fluid yielded *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*. RML (right middle lobe) mucosal irregularity was revealed and TBLB was done (Figure 3A-3B). Pathology showed amorphous eosinophilic material (Figure 4A, red arrow) and green birefringence under cross-polarized light by Congo red. (Figure 4B)
- Repeated TBLB was done, and pathology showed amyloidosis again. Pulmonary AL amyloidosis was diagnosed.

Discussion

- Opportunistic infection and metastatic lesions from rectal adenocarcinoma were first considered. Serology test and sputum examination for infection were done and showed negative finding.

  Though culture from BAL fluid yielded bacteria but clinical symptoms and laboratory tests were not favoring infection. RML mucosal irregularity was found incidentally during bronchoscopy so biopsy was performed. Pathology under Congo red stain showed green birefringence under cross-polarized light. Amyloidosis was suspected. This case was presented to multidisciplinary conference and a re-biopsy were suggested. Repeated TBLB was done and pathology was also consistent with amyloidosis.

- Laboratory test showed elevated serum free Lambda, serum IgG, M protein on serum electrophoresis and IgG/Lambda monoclonal protein on serum immunofixation electrophoresis.

- Pulmonary amyloidosis could be categorized into diffuse alveolar-septal, nodular, or tracheobronchial type. Typically, diffuse alveolar-septal pulmonary amyloidosis would present with exertional dyspnea and fatigue. Pulmonary function test would show restrictive ventilatorimpairment and reduction in DLCO. Chest HRCT might have interlobular septal thickening, 2-4 mm micronodules, and linear, reticulonodular, and patchy ground glass opacities. The distribution would be middle and basilar lung field predominant, extending from hilum to subpleural space.

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Figure legends

Figure 1

- Increased reticular infiltrates and multiple tiny nodules.
- Bilateral lower lung field predominant.
- With gradual progression.

Figure 2A-2E

- Centrilobular tree-in-bud nodules.
- Interlobular and intralobular septal thickening.
- Lower lung predominant and progressive change.

Figure 3A-3B

Bronchoscopy showed

- Mucosal hyperemia and irregularity.

Figure 4A-4B

Pathology of TBLB specimen demonstrated

- Amorphous eosinophilic material within lung parenchyma(red arrow).
- Green birefringence under cross-polarized light by Congo red stain.

II.

Rare diffuse parenchymal lung diseases

Bone in the Lung! A rare case of diffuse pulmonary ossification

Lih-Yu Chang

Department of Internal Medicine, National Taiwan University Hospital, HsinChu branch, Hsin-Chu City, Taiwan

Clinical pearls

- When thin-slice CT showed Multiple punctuate and branching lesions of bone density in subpleural area, DPO (diffuse pulmonary ossification) should be considered; differential diagnosis including bronchiectasis, pulmonary fibrosis, and lymphangitic metastasis.
- Definite diagnosis depends on histopathologic analysis.
- TBLC (transbronchial lung cryobiopsy) is a valid replacement test for SLB (Surgical lung biopsy) in undiagnosed ILD.

Main article

Case presentation

- 40 y/o male.
- No specific occupation exposure history.
- No airway symptom.
- Incidentally found lung lesion by chest CT for renal transplantation evaluation.

Medical history

- Diabetes mellitus.
- Hypertension.
- End-Stage Renal Disease, idiopathic.

Physical examination

- HR 74bpm.
- SpO_2 98% under room air.
- No wheeze nor crackles.
- No clubbing fingers.
- No arthralgia.

Laboratory panels

- Normal CBC and biochemistry, except renal function.
- Negative RF, ANA, anti ENA, and anti CENP; normal C3 and C4.

Chest radiograph

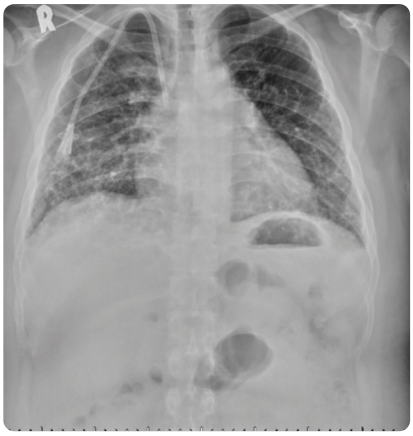

Figure 1A-1C.

Pulmonary Function Test

Parameter	Value (% predicted)
FVC	2.31 (61)
FEV_1	2.77 (63)
FEV_1/FVC	83 (99)
$FEF_{25\%-75\%}$	2.09(55)
Conclusion: Suspect moderate restrictive ventilatory defect	

Cardiac Evaluation

- Diastolic dysfunction.
- Mild tricuspid valve regurgitation.
- TRPG (tricuspid regurgitation peak gradient) 9.0mmHg.

Non-contrast CT/ HRCT

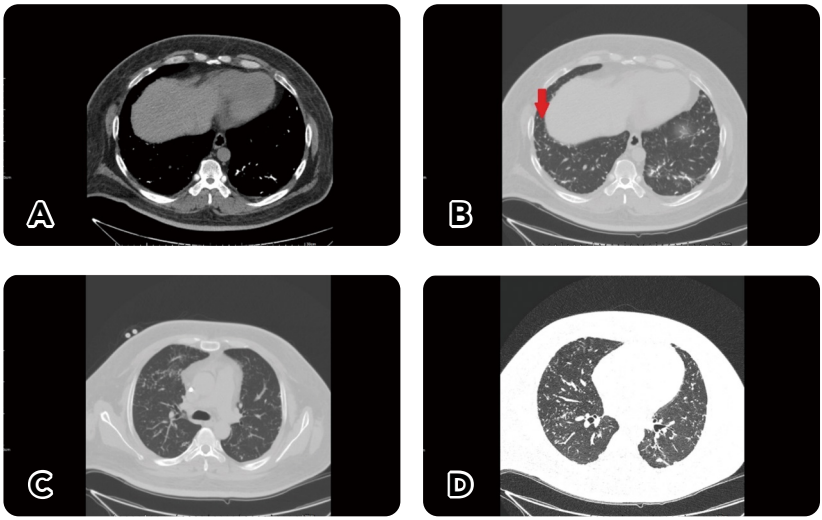

Figure 2A-2D. Non-contrast

Histology

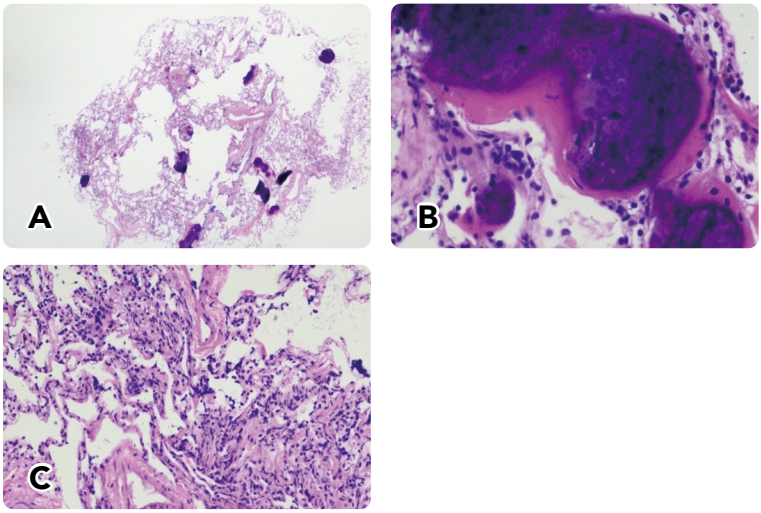

Figure3A-3C.

Diagnostic process

- Multiple branching, calcified nodules in bilateral, subpleural lungs.
- Serum calcium and alkaline phosphate are both within normal limit.
- The histopathologic result of(TBLC) showed ossification and interstitial fibrosis. (Figure 3A-3C)
- Bronchoscope and endobronchial blocker pass through the rigid bronchoscope or endotracheal tube together, plus the rigidity of the cryoprobe, sometimes manipulating the TBLC is not easy Middle or lower lobes were easier for TBLC.
- For slowly progressive course, no extra-medication administration.

Discussion

Pulmonary ossification is a relatively rare disease. The differential diagnoses include amyloidosis,histoplasmosis, prior tuberculosis,or granulomatosis. The final diagnosis depends on histology evidence with bone tissue formation, not calcification only, in lung parenchyma. TBLC is an effective and minimally invasive procedure to get adequate tissue samples for ILD/ diffuse parenchymal lung disease. According to the TBLC guidelines, TBLC is recommended while histopathological data is necessary for undiagnosed ILD. However, TBLC should be performed in experience. institution.

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Figure legends

Figure 1

- Mild fibrotic change/ infiltrate at both lungs.
- More at the lower lung.

Figure 2A-2D

- RS8 segment is the target area of TBLC (red arrow). Calcified nodules
- Branching/ coral-like calcified nodules.
- Bilateral lower, basal, and sub-pleural are more dominant.
- Combined with tree-in-bids nodules.

Figure 3A-3C

Transbronchial lung cryobiopsy specimens demonstrated

- Interstitial fibrosis.
- Ossification was noted at alveolar space and terminal bronchiole.

Cysts in the lung- A case of sporadic lymphangioleiomyomatosis mimics pulmonary Langerhans cell histiocytosis

Yao-Wen Kuo[a], *Hao-Chien Wang* [b]

[a]*Department of integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan*

[b]*Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*

Clinical pearls

- Differential diagnoses of multiple lung cysts as the main feature include lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and Birt-Hogg-Dube syndrome (BHD).
- For definite diagnosis and possible specific medication use in the future, surgery is indicated in this patient.
- Therapy with sirolimus may be useful in patients with LAM.

Main article

Case presentation

- 58-year-old female, never smoker.
- A housewife.
- Exertional dyspnea for 1 year, especially after walking for 100m or climbing two flights of stairs, still could tolerate daily activity.
- No cough, sputum, or skin lesions.

Medical history

- Hypertension under bisoprolol and candesartan.
- Status post cholecystectomy.

Physical examination

- No grey hair.
- No skin lesions.
- Breath sound: no velcro crackles.
- SpO2 93% under ambient air.

Laboratory panels

- Normal CBC and biochemistry.
- Negative autoimmune profile.

Chest radiograph

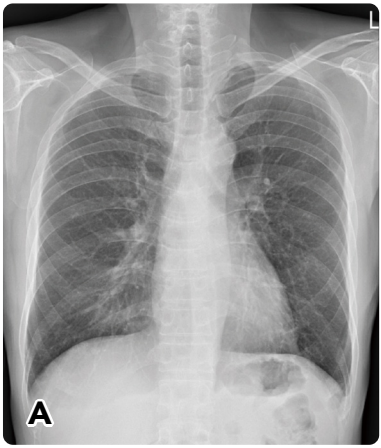

Figure 1

Pulmonary Function Test

Parameter	Observed value
FVC(L)	3.05(120.7)
FEV_1(L)	2.08(99.9)
FEV_1/FVC(%)	68.2(68.2)
$FEF_{25\%-75\%}$(L/S)	1.14(46.1)
TLC(L)	4.75(108.3)
DLco(ml/min/mmHg)	9.98(48.8)
Conclusion: Mild obstructive ventilatory defect and moderate impairment of diffusion capacity	

Cardiac evaluation

LVEF 68.2%, TRPG 24.3 mm Hg.

HRCT

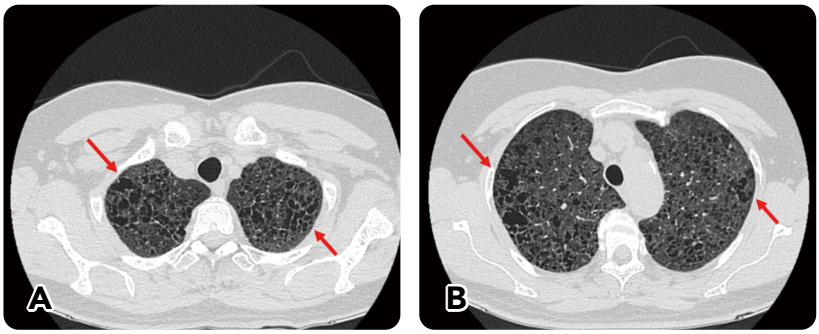

Figure 2A-2B.

Non-contrast CT

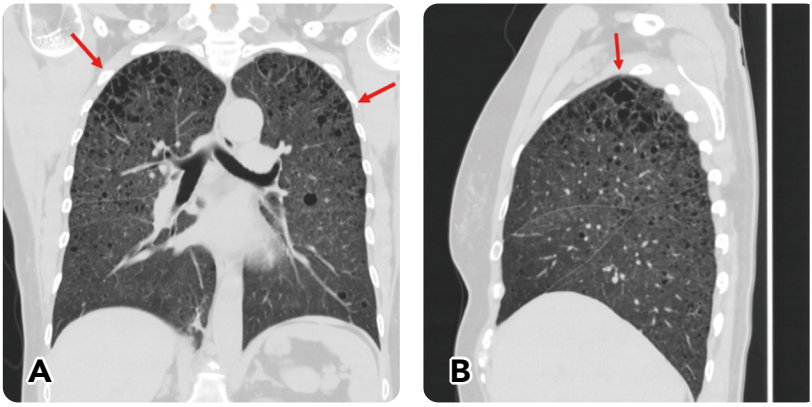

Figure 3A-3B.

Pathology

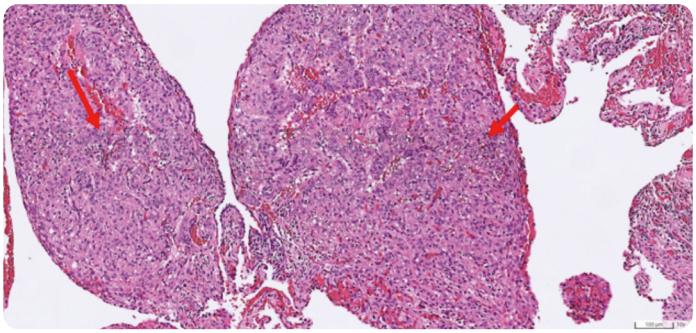

Figure 4.

Diagnostic process

- For definite diagnosis and possible medication use in the future, a surgical lung biopsy was performed, the pathology revealed nodular growth and the formation of irregular lymphatic channels (Figure 4), positive for Cathepsin K, SMA, ER, and PR.
- The diagnosis of lymphangioleiomyomatosis was confirmed and a low dose of sirolimus 1mg/day was prescribed.

Discussion

- *TSC1* or *TSC2* somatic mutations cause sporadic LAM while germline mutations cause Tuberous sclerosis-LAM.
- The clinical characteristics of LAM patients include age around 20-50, mainly female, multiple round cysts (0.5-2cm) with uniform distribution on HRCT, mainly normal or obstructive ventilatory defect on pulmonary function test.
- BRAF V600E somatic mutations are found in around 50% of PLCH patients. Typical HRCT findings include coalescent bizarre cysts and relative sparing of lung bases. Pulmonary function test mainly shows obstructive ventilatory defect. Cladribine may be an effective therapy in patients with progressive PLCH.
- Treatment for LAM includes inhaled bronchodilator, vaccination, and rehabilitation. Estrogen should be avoided. Sirolimus can be started if abnormal lung function (FEV1<70%) and symptomatic chylous effusion.

References

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Figure legends

Figure 1 (Chest radiograph)

Normal heart size and diffuse infiltrative GGO and suspicious some tiny cysts Equally at both lungs; Degenerative change of the T and L spine.

Figure 2A-2B (HRCT) & figure 3A-3B (non-contrast CT)

- Multiple varying-sized bizarre-shaped thin-walled cysts found diffusely in bilateral lungs with upper lobar predominance and costophrenic angle sparing.
- Hyperlucency in bilateral apical upper lobes from coalescent cystic changes.

Figure 4 (Pathology)

A surgical lung biopsy of left upper lobe specimens demonstrated

- Nodular growth composed of oval to spindle cells.
- Formation of irregular lymphatic channels.

Beyond the Halo: A Case of Organizing Pneumonia Presentation in the Reverse Halo Sign

Hsiao-Chin Shen[a,b], *Kuang-Yao Yang*[a,c,d]

[a]*Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

[b]*Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan*

[c]*Faculty of Medicine, School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*

[d]*Institute of Emergency and Critical Care Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*

Clinical pearls

- The diagnosis of organizing pneumonia can be ascertained with clinical and radiological features. The image features include consolidations and other features, like a reversed halo sign.
- Organizing pneumonia usually responds rapidly to oral corticosteroids.
- A significant number of patients with organizing pneumonia will experience a relapse.

Main article

Case presentation

- 71-year-old female.
- Inhaling chemicals while exterminating termites at home about three months ago.
- Productive cough and shortness of breath in recent three weeks.
- Consuming pearl powder in the past year.

Medical history

- Hypertension, under Lercanidipine, Valsartan.
- Type 2 Diabetes mellitus, recent HbA1C 6.8, under Mitiglinide.
- Dyslipidemia, under ezetimibe + atorvastatin.
- Occupation: Unemployed, stays at home.
- Unremarkable family history.

Physical examination

- The oximeter displayed an SpO2 of 96% while breathing room air.
- Bilateral clear breathing sound.
- No clubbing fingers.
- No leg edema.
- No arthralgia.

Laboratory panels

- Elevated CRP (2.9 mg/dL), Other CBC and biochemistry revealed within normal range Negative RF, ANA, SSA (anti–Sjögren's-syndrome-related antigen A antibody), SSB(anti–Sjögren's-syndrome-related antigen B antibody), Sm, RNP (antinuclear ribonucleoprotein antibody), SCL-70, Jo-1, Ribosomal-P(anti-ribosomal P protein), C-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody), P-ANCA (perinuclear anti-neutrophil cytoplasmic antibody), Anti-GBM (anti-glomerular basement membrane antibody); normal C3 and C4.
- Negative bacterial, mycobacterial, and fungal culture results.
- Negative aspergillus galactomannan antigen and cryptococcal antigen lateral flow assays.

Chest radiograph

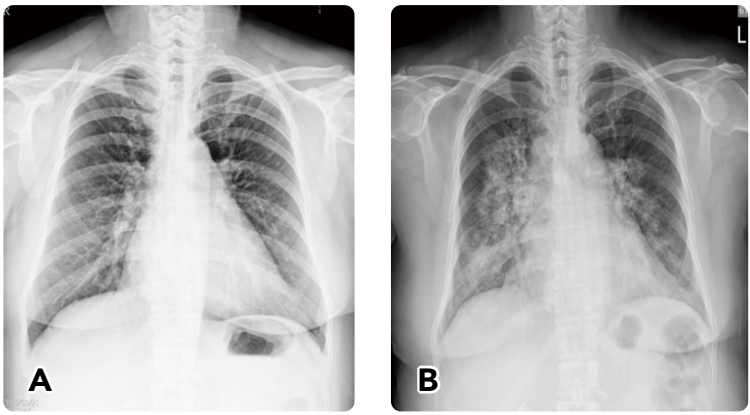


Figure 1A. Baseline CXR(chest radiograph) two years ago ; Figure 1B . CXR upon arrival showed bilateral opacities

Pulmonary Function Test

Parameter	Value (% predicted)
FVC (L)	1.93 (83)
FEV_1 (L)	1.62 (89)
FEV_1/FVC (%)	83 (110)
PEF (L)	5.56 (99)
TLC (L)	3.37 (84)
DLco (ml/min/mmHg)	12.77 (59)
Conclusion: Moderate reduction of of DLco	

HRCT

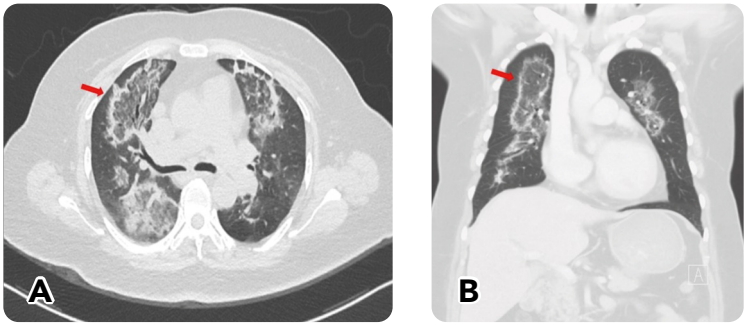


Figure 2. Chest CT revealed multiple GGOs with peripheral consolidations.

Chesst CT and Chest radiograph of lung opacity subsidence

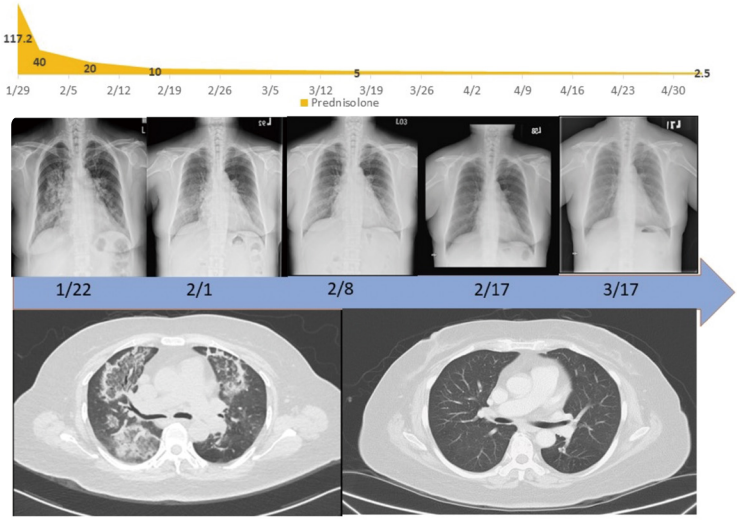


Figure 6.

Diagnostic process

- The "reversed halo sign" on the chest CT demonstrated ground-glass opacity, surrounded by a crescent or ring of consolidated parenchyma. The common etiologies of these signs included organizing pneumonia and hemorrhagic infarction.
- Bronchial lavage was performed over RB3, and the histopathologic findings revealed lymphocyte predominant. (Figure 3)

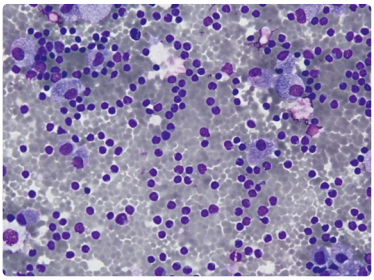
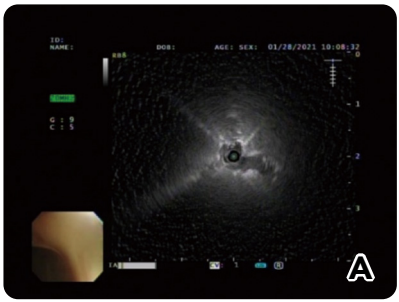


Figure 3.

- The transbronchial lung biopsies over RB8 (Figure 4A-4B). The pathological results revealed heavy inflammation and fibrosis. Masson bodies filling in the alveolar spaces indicated organizing pneumonia. (Figure 5)



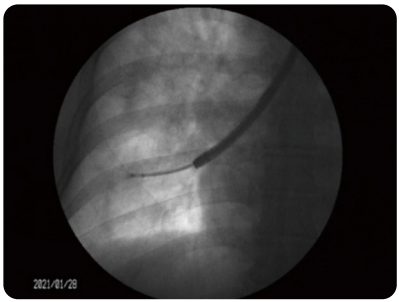


Figure 4A-4B.

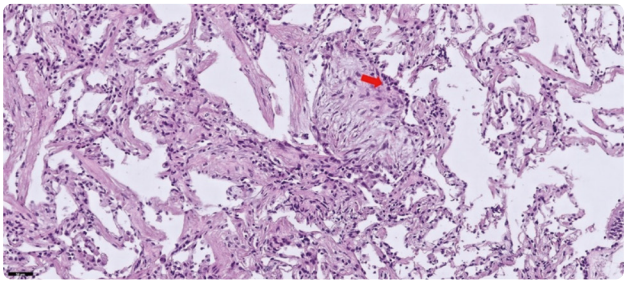


Figure 5.

- After excluding other possible etiologies, organizing pneumonia was diagnosed.
- Corticosteroid was administered and the lung opacity resolved.(Figure 6)

Discussion

- In organizing pneumonia, radiographic images commonly show subpleural or/ peribronchial consolidations in the mid to lower lung zones. Opacities can shift or vanish, and consolidated areas may spontaneously regress[1].
- The Reversed Halo Sign (Atoll Sign) is characterized by ground-glass opacity encircled by a crescent or ring of consolidated parenchyma. It has multiple etiologies, including hemorrhagic infarction, foci of organizing pneumonia, and lymphoma[2].
- Organizing pneumonia is marked by the growth of granulation tissue buds, known as Masson bodies, are mainly found within airspaces like alveoli and terminal bronchioles[1, 3].
- Treatment for organizing pneumonia varies by symptom severity, disease progression, and responsiveness to glucocorticoids. Minimally symptomatic patients are monitored without treatment. Symptomatic patients without rapid progression receive systemic glucocorticoids, usually prednisone with a tapered dose. Poor responders to glucocorticoids should be re-evaluated and may need cytotoxic agents like azathioprine. Patients who can't taper off glucocorticoids or have recurrent relapses may need a second immunosuppressive agent, such as azathioprine or mycophenolate mofetil. Reassessments occur at 8–12-week intervals[4].

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Figure legends

Figure 1A-1B

(A) Baseline CXR two years ago (B) CXR upon arrival showed bilateral opacity.

Figure 2

Chest CT revealed multiple GGOs with peripheral consolidations. GGOs surrounded by a crescent or ring of consolidated parenchyma, also known as the reverse halo sign (red arrow).

Figure 3

Liu's stain of bronchial lavage fluid demonstrated lymphocyte predominant.

Figure 4A-4B

(A)Radial-probe endobronchial ultrasound was inserted into RB8. The lesion was "adjacent to" the RB8 Bronchus. (B) Bronchoscopic biopsies over RB8 several times under fluoroscope assistance.

Figure 5

Masson bodies (red arrow) fill in the alveolar spaces and reactive type 2 pneumocytes are present.

Figure 6

After the diagnosis of organizing pneumonia was confirmed, intravenous corticosteroids were administered, followed by oral corticosteroids, leading to the resolution of the lung opacities.

III.

Special clinical facets of idiopathic pulmonary fibrosis

A case of idiopathic pulmonary fibrosis without typical usual interstitial pneumonia pattern on HRCT imaging

Chung Lee[a], *Mei-Chen Yang*[a,b], *Chou-Chin Lan*[a,b]

[a]*Division of Pulmonary Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation,New Taipei City, Taiwan*

[b]*School of Medicine, Tzu-Chi University, Hualien, Taiwan*

Clinical pearls

- HRCT plays a major role in the diagnosis of IPF (idiopathic pulmonary fibrosis). End-stage IPF with histopathological honeycomb pattern could only show early-stage IPF or probable UIP pattern on HRCT.
- Surgical lung biopsy is the only decisive way for early diagnosis of IPF.
- Even the normal lung fields on HRCT could show fibrotic change with honeycomb on histopathological results.

Main article

Case presentation

- 59-year-old female.
- A department store saleswoman who used to work part-time as catering.
- Chest tightness off and on, dry cough, exertion dyspnea, for 3 years.

Medical history

- GERD, Allergic rhinitis, left circumflex artery and right coronary artery 50 % stenosis.
- Medications: Aspirin.
- History of tobacco consumption.
- Has no pets.
- Unremarkable family history.

Physical examination

- Heart rate: 88 BPM (beats per minute).
- SpO_2: 97% under ambient air.
- Diffuse wheezing over both lungs, without upper-lower difference.
- No clubbing fingers.
- No leg edema.
- No arthralgia.

Laboratory panels

- Normal CBC and biochemistry.
- Negative RF, ANA, anti-ENA, and anti-CENP (anti-centromere proteins antibodies); normal C3 and C4.
- Negative bacterial, mycobacterial, and fungal culture results.

Chest radiograph

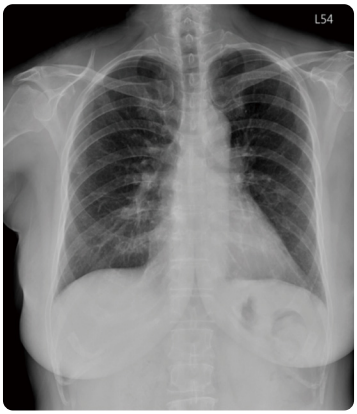

Figure 1.

Chest radiograph

Parameter	Value (% predicted)
FVC	2.34(81)
FEV_1	2.02(86)
FEV_1/FVC	86
$FEF_{25\%-75\%}$	2.64(106)
TLC	3.68(77)
DLco (ml/min/mmHg)	18.94(80)
Conclusion: Low TLC with normal DL_{CO}	

Cardiac evaluation

Adequate LV, RV (right ventricle) systolic function with normal wall motion, LVEF (left ventricular ejection fraction) 73.1%.

HRCT

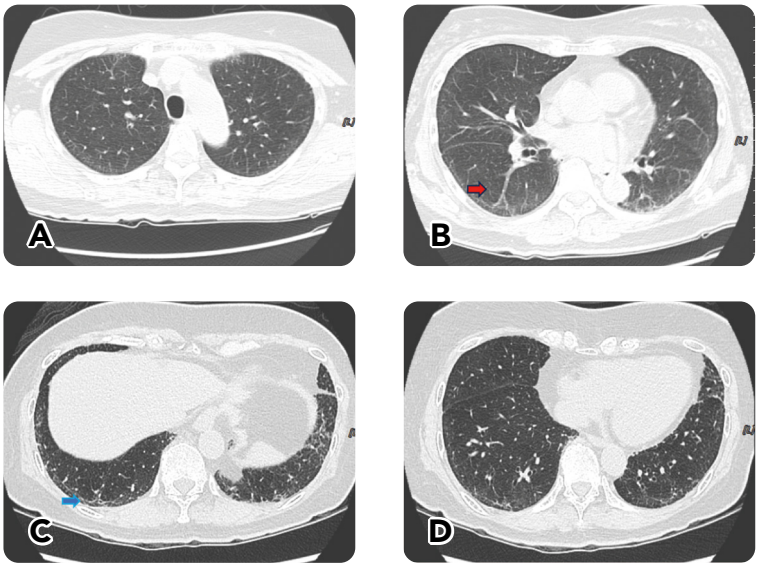

Figure 2A-2D.

Pathology

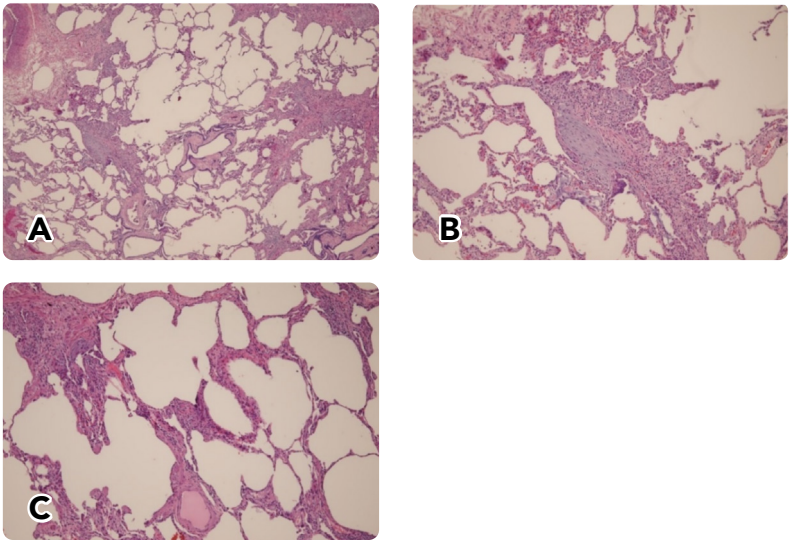

Figure 3A-3C. right lower lobe wedge resection

Pathology

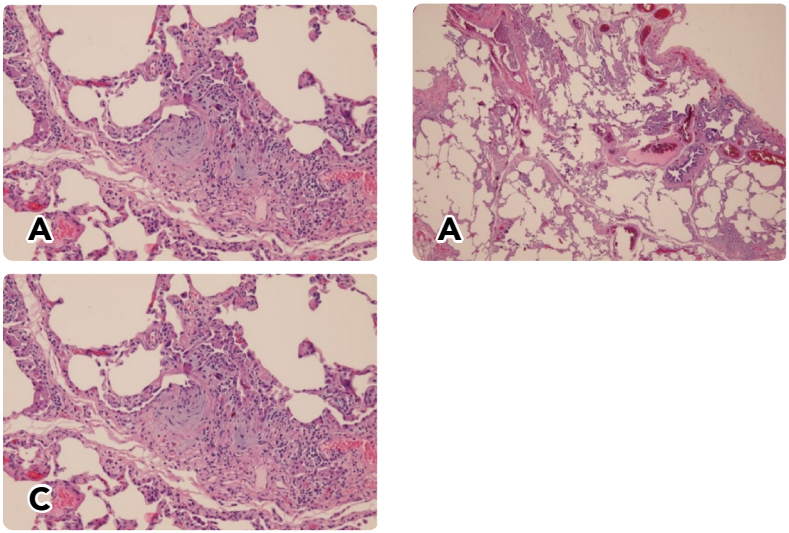

Figure 4A-4C. right middle lobe wedge resection

Discussion

- Unexplained persistent dyspnea on exertion even after bronchodilator use.
- Absences of rheumatologic panels and typical UIP pattern on HRCT could not obtain a definite clinical diagnosis of IPF.
- Enen the normal lung on HRCT imaging showed end-stage fibrosis and honeycomb changes on histopathology.
- For patients with typical symptoms of IPF but normal/atypical HRCT imaging for months to years, surgical lung biopsy is the only crucial and decisive way for timely diagnosis and treatment.

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Figure legends

Figure 1

- No GGO or obvious reticular pattern on bilateral basal lung.
- Mild enlarged cardiac silhouette.
- Normal appearance of both hila.

Figure 2A-2D

Subpleural ground-glass opacity, reticulation, and bronchiectasis and bronchiectasis in bilateral Lungs.

Figure 3A-3C (Right lower lobe with GGO on HRCT)

Alveolar lung tissue with fibroblast foci, and non-uniform interstitial fibrosis. Honeycomb change is focally present. The morphology is compatible with the usual interstitial Pneumonia.

Figure 4A-4C

(Right middle lobe without GGO or fibrotic change on HRCT)

Alveolar lung tissue with fibroblast foci, and non-uniform interstitial fibrosis.

Honeycomb change is focally present.

Unveiling Insights from the Past: A Case Illustrating Pathologically Confirmed Idiopathic Pulmonary Fibrosis Coexisting with Early-Stage Lung Cancer

Yu-Hung Fanga[a,b]

[a]*Division of Thoracic Oncology, Department of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital, Chiayi Branch*

[b] *Department of Nursing, Chang Gung University of Science and Technology, Chiayi Branch*

Clinical pearls

- Diagnosing the early phase of idiopathic pulmonary fibrosis (IPF) poses challenges with HRCT, primarily due to the absence of typical features like traction bronchiectasis and honeycombing.
- This case presents a pathologically confirmed early phase of IPF, with serial HRCT changes observed post-surgical resection of lung cancer and adjuvant chemotherapy.
- Rapid fibrosis progression on HRCT may be linked to procedures like CT-guided biopsies, surgical resection, and chemotherapy during lung cancer diagnosis and treatment.

Main article

Case presentation

- 68-year-old male.
- Employee of a beverage store.
- The patient sought cardiovascular outpatient care for chest tightness and palpitations, leading to a referral to the chest outpatient department (OPD) following a chest X-ray revealing a mass-like lesion.

Medical history

- Hypertension.
- Chronic hepatitis B.

Physical examination

- Diffuse basal rales over both lungs.
- No clubbing fingers.
- No leg edema.

Laboratory panels

- Normal CBC and biochemistry.
- Negative for RF, ANA, anti-SSA, anti-SSB, anti-Jo-1, anti-Scl-70 and CPK. (Creatine Phosphokinase)
- Negative for bacterial, mycobacterial, and fungal culture results.

Chest radiograph

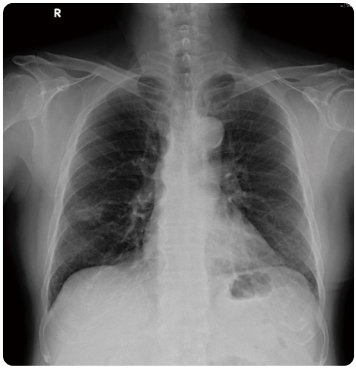


Figure 1. Chest X-ray on 2021/04/09: Initial Chest X-ray showed right lower lung mass

Pulmonary function test

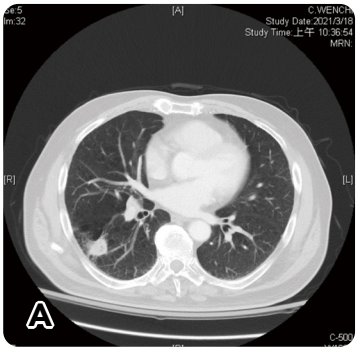
Pre-operation (2021/04/21):

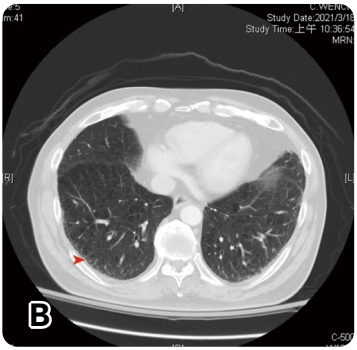
Parameter (Post Bronchodilation)	Value (% predicted)
FVC (L)	3.82(115)
FEV_1 (L)	2.89(110)
FEV_1/FVC (%)	75.7
PEF (L/s)	9.54
Conclusion: Normal baseline spirometry	

Post-operation (2021/10/26)

Parameter (Post Bronchodilation)	Value (% predicted)
FVC (L)	3.35 (107)
FEV_1 (L)	2.58 (118)
FEV_1/FVC (%)	77.0 %
PEF (L/s)	8.75
TLC (L)	4.66 (76)
DLco/VA (ml/min/mmHg)	12.63(66)
Conclusion: Normal baseline spirometry, decreased TLC and DLco/VA (diffusion capacity for carbon monoxide/alveolar volume)	

Chest radiograph





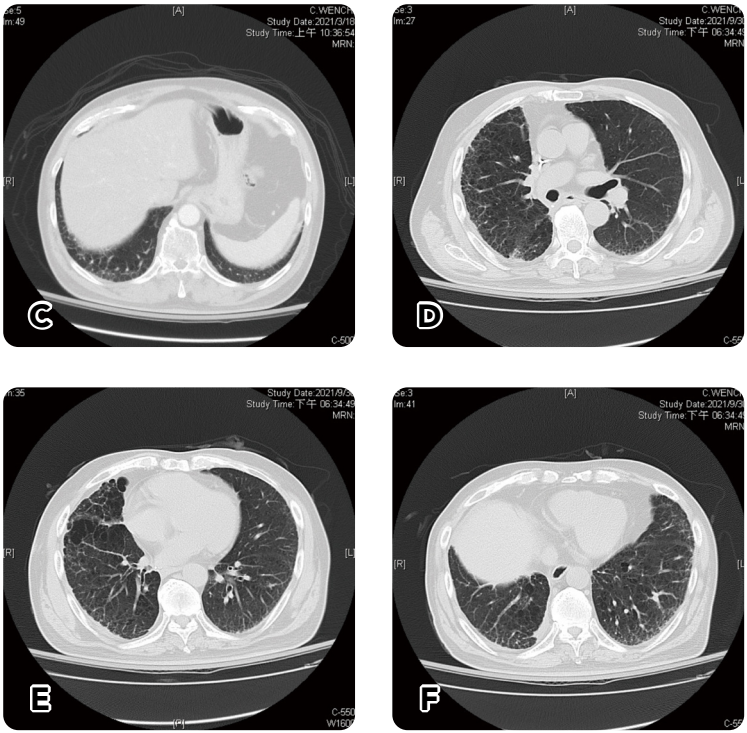


Figure 2A-2C .Pre-operation; Figure 2D-2F. Post operation

Histology

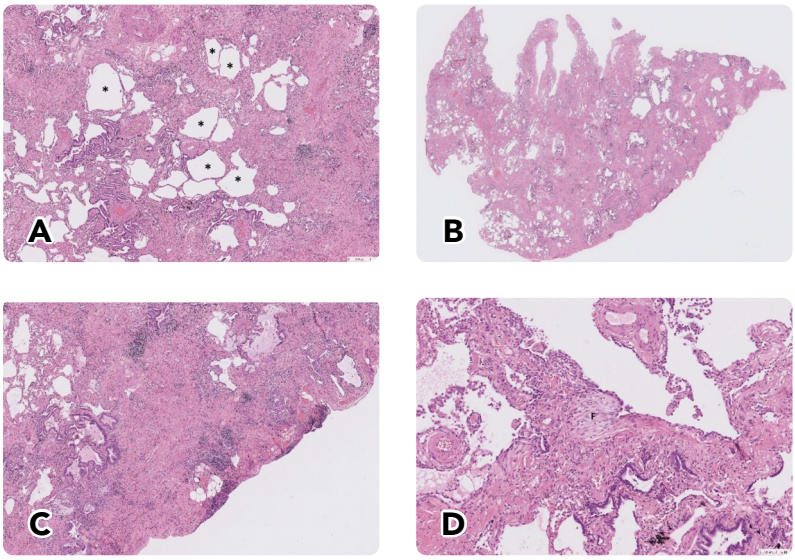


Figure. 3A-3D

Diagnostic process

- A preoperative CT scan revealed a right lower lung tumor and a mild subpleural reticular pattern over the bilateral lower lung (Figure 2A-2C). Post-surgery, the confirmed diagnosis was lung adenocarcinoma, pT2aN0M0, stage 1B. Subsequent to surgery, the patient underwent four cycles of postoperative chemotherapy, combining Docetaxel and cisplatin.
- Post-chemotherapy, the patient experienced increased exertional dyspnea. Follow-up CT scans disclosed rapid progression of bilateral lung lobe fibrosis, featuring bilateral subpleural reticular patterns, traction bronchiectasis, and honeycombing (Figure 2D-2F).
- Upon revisiting the initial surgical specimen, the pathologist identified typical idiopathic pulmonary fibrosis (IPF) pathological changes in a non-tumor area (Figure 3A-3D).

Discussion

1. There is an elevated risk of concurrent lung cancer in individuals with idiopathic pulmonary fibrosis (IPF). A retrospective analysis of lung cancer patients revealed that 1 in every 20 also had IPF[1]. In this patient, the initial Chest CT did not show a pronounced subpleural reticular pattern. For other lung cancer patients, when assessing lung cancer staging, it is also important to consider the coexistence of interstitial lung disease, as it can have a significant impact on subsequent diagnosis and treatment
2. Procedures such as biopsy, surgical resection, and chemotherapy may precipitate acute exacerbation of IPF. Early recognition of IPF allows for the administration of anti-fibrotic medications before invasive treatments, reducing the occurrence of acute exacerbations and slowing the decline in lung function[2].

References

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2. Iyoda A, Azuma Y, Sakamoto S, Homma S, Sano A. Surgical treatment for patients with idiopathic pulmonary fibrosis and lung cancer: postoperative acute exacerbation of idiopathic pulmonary fibrosis and outcomes. Surg Today. 2022;52(5):736-744.

Figure legends

Figure 1

- Initial Chest X-ray showed right lower lung mass.

Figure 2A-2C

Pre-operation chest CT without contrast (2021/03/18)

- Right lower lung tumor.
- Bilateral subpleural mid-reticular pattern.
- ➢ Site of specimens for histology.

Figure 2D-2F

Post-operation and adjuvant chemotherapy HRCT (2021/09/30)

Rapid progressive bilateral subpleural reticular pattern, traction bronchiectasis and honeycombing, favor typical UIP patterns. Also, bilateral upper lung field emphysematous changes, compatible with CPFE (Combined Pulmonary Fibrosis and Emphysema).

Figure 3A

Surgical lung biopsy specimens demonstrated sharp demarcation between the advanced fibrosis and the normal-appearing alveolar walls.

Figure 3B

- Advanced fibrosis with architectural distortion.

Figure 2D-2F

- Dilated cystic spaces (*) embedded within advanced fibrosis. The cysts are lined by ciliated respiratory epithelium.

Figure 2D-2F

- Evidence of active injury in the form of fibroblast foci (F).

Lung Transplantation to Rescue a Case with Idiopathic Pulmonary Fibrosis Complicated with Pulmonary Hypertension, Pulmonary Artery Thrombosis, and Lung Cancer

Kuan-Hsun Lian[a], *Hsao-Hsun Hsu*[b]

[a] *Department of Surgery, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan*

[b] *Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan*

Clinical pearls and take-home message:

- Diagnosis approach and treatment options of idiopathic pulmonary fibrosis.
- Several comorbidities are associated with idiopathic pulmonary fibrosis, including pulmonary hypertension and lung cancer. Annual chest CT scan or immediate chest CT when the presence of an organ donor is suggested.
- Patients with IPF have the highest death rate among the diagnostic groups on the transplant waiting list, so early referral for transplant evaluation should be considered, even before the response to initial medical therapy.

Main article

Case presentation

- 64-year-old male.
- A retired spray painter with 200 pack years of smoking history.
- His younger brother was diagnosed with idiopathic pulmonary fibrosis.
- Exertional dyspnea has troubled him since 2012, and idiopathic pulmonary fibrosis was diagnosed in 2016. however, the symptoms deteriorated, and he depended on a high-flow nasal cannula (FiO2 (fraction of inspiration O2)=50%). Functional class=NYHA (New York Heart Association functional class) class III-> IV.

- He was transferred to our department for lung transplant evaluation after 3 years of treatment with nintedanib and MSCs (mesenchymal stem cells).

Medical history

- Coronary artery disease, status post balloon angioplasty at left circumflex artery.
- NTM (Non-tuberculosis mycobacterium) pulmonary disease (M.gordonae), treated with rifampin, ethambutol & and zithromax for half a year.
- Right upper lobe aspergilloma, treated with voriconazole for 6 months.

Chest radiograph & HRCT

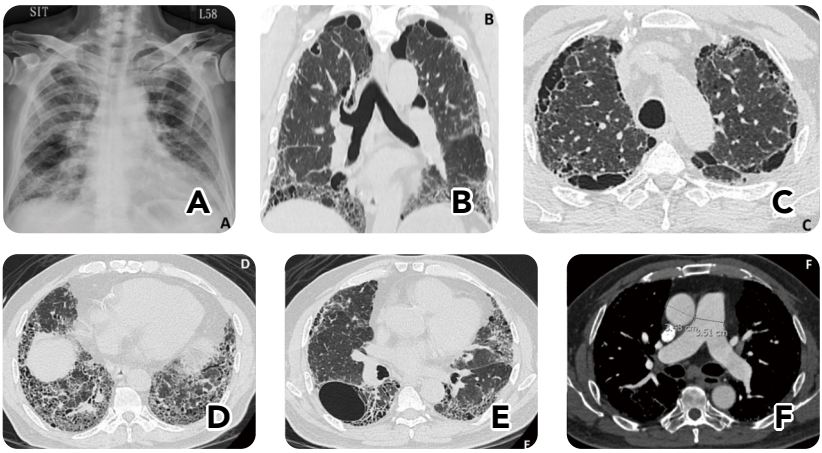
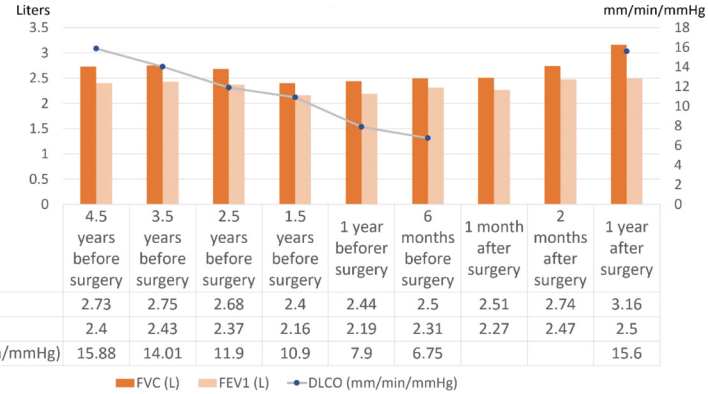


Figure 1A-1F. basilar predominant reticulation in the bilateral lungs; subpleural honeycombing and bullae formation in right lower lobe; UIP (usual interstitial pneumonitis) pattern; AsAo (ascending aorta) diameter=3.46cm; Main PA diameter=3.51cm

Pulmonary function test



	4.5 years before surgery	3.5 years before surgery	2.5 years before surgery	1.5 years before surgery	1 year beforer surgery	6 months before surgery	1 month after surgery	2 months after surgery	1 year after surgery
FVC (L)	2.73	2.75	2.68	2.4	2.44	2.5	2.51	2.74	3.16
FEV1 (L)	2.4	2.43	2.37	2.16	2.19	2.31	2.27	2.47	2.5
DLCO (mm/min/mmHg)	15.88	14.01	11.9	10.9	7.9	6.75			15.6

Figure 2.

The donor lungs

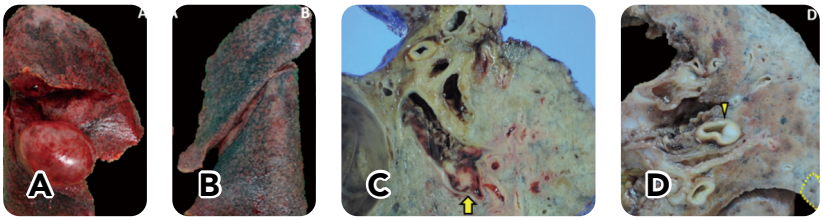


Figure 3A-3D.

Cardiac evaluation

[Echocardiography]

- The LV is grossly normal in size & shape; LV systolic function is normal [LVEF= 71.8%]; dilated LA (left atrium), RA & RV;
- Mild-moderate TR (tricuspid regurgitation); severe pulmonary hypertension, TRmaxPG= 78.6mmHg.

[Cardiac catheterization]

Coronary Angiography: LM: Patent; LAD (left anterior descending artery): Ectasia; LCX (left circumflex artery): Ectasia; RCA (right coronary artery): Ectasia.

- Right heart catheterization:

Main PA (pulmonary artery) BP (blood pressure)= 65/16mmHg; mean BP= 32mmHg; average cardiac output= 6.38L/min; PVR (pulmonary vascular resistance)= 2.65 Wood unit.

Pulmonary ventilation-perfusion(VQ) scan

- Several VQ matched defects in bilateral lungs.
- severe decreased perfusion (with fibrotic change on CT images) at bilateral basal lungs.
- Perfusion tracer distribution: right= 59.14%, left= 40.86%.
- Ventilation tracer distribution: right= 56.48%, left= 43.52%.

Treatment process

- Bilateral sequential lung transplantation was performed via clamshell thoracotomy with partial support of VA ECMO (Veno-arterial extracorporeal membrane oxygenation) six months after listing for lung transplantation.
- Macroscopically, the donor lungs presented with an uneven pleural surface and a 7 cm cyst in the right lower lobe. Consolidation, fibrosis, and honeycombing changes were shown in the periphery, especially in the lower lobes; one thrombus was also retrieved from PA(pulmonary artery). (Figure 3)
- Microscopically, the lung parenchyma was consistent with usual interstitial pneumonia. Intimal hyperplasia and medial hypertrophy of the PA suggested pulmonary hypertension. Aspergillosis was also noted from the cyst in the right lower lobe;one 15 mm adenosquamous carcinoma was unexpectedly found in the singular segment of the left lower lobe with visceral pleural invasion, which was positive for TTF-1 (thyroid transcription factor 1) and P40. No regional lymph node metastases were reported.

- he was weaned off the ventilator on postoperative day 28 and was discharged home 69 days after surgery. At 1-year follow-up, his FEV1 and& FVC were restored to more than 100% of the predicted values. No tumor recurrence was revealed by the CT images.

Discussion

1. The treatment options for idiopathic pulmonary fibrosis: The fibrotic process could not be cured by any medication. Nintedanib and pirfenidone slow. down the disease progression but have significant gastrointestinal side effects. Immunomodulation achieved by MSCs has shown promising results in preclinical data. Its safety and efficacy are concerns being investigated in current clinical trials. Thrombosis and embolization resulting from MSC incompatibility and interactions with the innate immune system has been reported in animal and human patients. The large thrombosis in the pulmonary artery of this patient may be associated with the MSC therapy and may help explain the exacerbation of symptoms before the lung transplantation.
2. The role of surgery in the treatment of IPF:
   ILD, in particular IPF, carries the worst prognosis among the common disease indications for lung transplantation. Early referral for transplant evaluation should be considered, even before the response to initial medical therapy.

▶ Timing of referral for transplantation

- Histopathologic or radiographic evidence ofUIP, regardless of lung function.
- FVC< 80% or DL_{CO}<40% of predicted.
- Any dyspnea or functional limitation attributable to lung disease.
- Any oxygen requirement, even if only during exertion.

▶ Timing of listing

- Decline in FVC≥ 10% or DL_{CO}≥ 15% during 6 months of follow-up.
- Desaturation< 88%.
- On 6-minute-walk test: SpO_2<88%, <250m or >50m decline in distance walked.

- Pulmonary hypertension on right heart catheterization or echocardiograph.
- Hospitalization due to respiratory decline, pneumothorax, or acute exacerbation.

3. Possible complications after lung transplant:

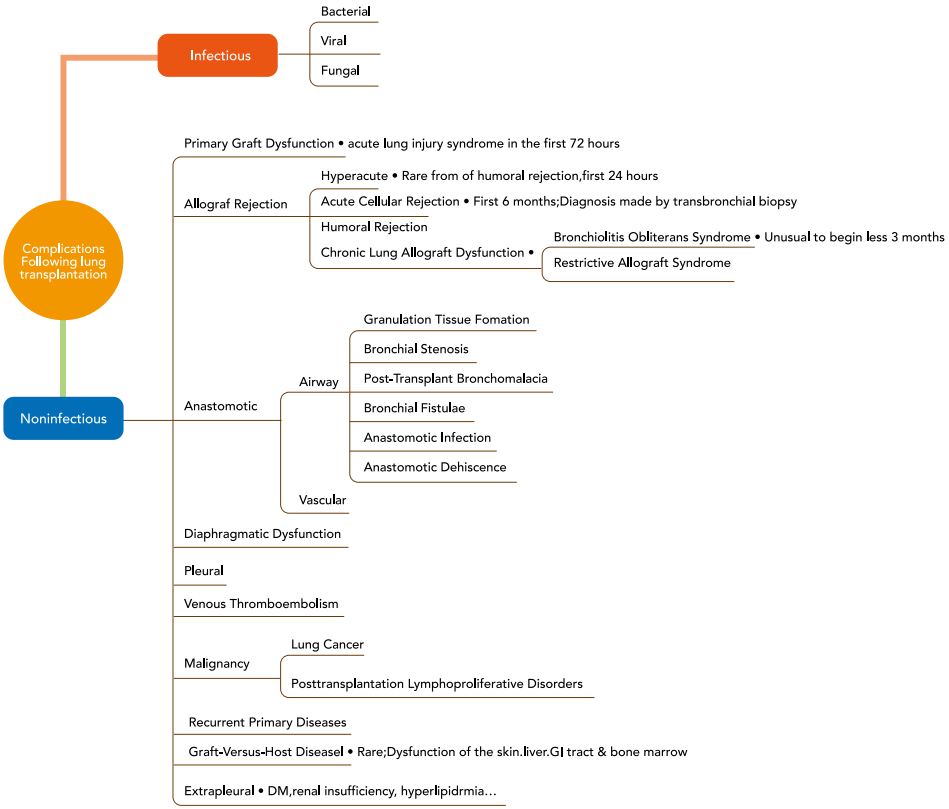


Figure 4.

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Figure legends

Figure 1A-1F

- The chest radiograph and (B-F) CT images 6 months pre-surgery. The basilar predominant reticulation in the bilateral lungs, subpleural honeycombing, and bullae formation in RLL; enlarged pulmonary artery trunk indicated pulmonary hypertension.

Figure 2

The spirometry and diffusion capacity before and after lung transplantation.

Figure 3A-3D

(A, B) The gross image of the diseased lungs: uneven pleural surface and a 7 cm cyst in the right lower lobe. Consolidation, fibrosis, and honeycombing changes were shown in the periphery, especially in the lower lobes; (C) Organizing thrombus in the pulmonary artery (arrow), (D) Intimal fibrosis and medial hypertrophy of the pulmonary artery (arrowhead) and a 15 mm adenosquamous carcinoma (dotted line).

Figure 4

Possible complications after lung transplant.

IV.

Interstitial lung diseases and COVID-19

From Virus to Fibrosis—A case with interstitial lung disease after COVID-19 infection

Meng-Yun Tsai[a]

[a] *Department of Pulmonary and Critical care medicine, Kaohsiung Chang-Gung Memorial Hospital*

Clinical pearls and take-home message:

- ILD occurred in a cohort of patients post-COVID-19 infection, but the diagnosis should be made by excluding other possible diagnoses.
- Early administration of corticosteroids may help patients with post-COVID-19 ILD.
- Anti-fibrotic agent may be helpful for patients with PPF (progressive pulmonary fibrosis)but still need more data to prove it.

Main article

Case presentation

- 62-year-old male.
- A civil servant, without any special contact history or occupational history.
- Progressed shortness of breath, especially during exertion, since diagnosed to have COVID-19 on 2022/05/22.
- Productive cough with yellowish sputum since then.

Medical history

- Gout.
- Hypertension.
- Under Bisoprolol 5mg/QD, Colchicine 0.5mg/QD.
- Reports no history of alcohol, betel nut or drug use.
- Tobacco used in the past: 1PPD, quit for 10 years.
- Has no pets.
- Denied any family history.

Physical examination

- Heart rate: 112 BPM.
- SpO_2: 96% under ambient air.
- Dry crackles over both lower lungs.
- No clubbing fingers.
- No leg edema.
- No arthralgia.

Laboratory panels

- Normal CBC and biochemistry.
- ANA: 1:160(AC-15), Anti-RF (anti-rheumatoid factor antibodies) IgM (immunoglobulin M): 45 IU/ml, Normal anti- dsDNA (anti-double stranded DNA antibodies)/Anti-Scl-70/Anti-SmD/Anti-RN SLB.
- Negative bacterial, mycobacterial, and fungal culture results.

Chest radiograph

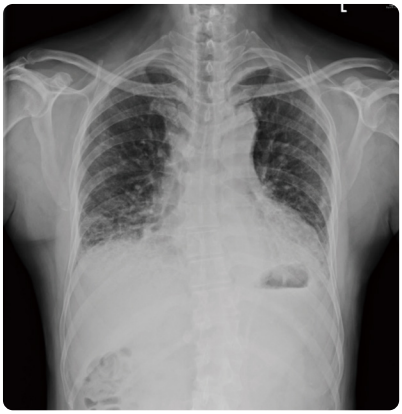

Figure 1.

Pulmonary Function Test

Parameter	Value (% predicted)
FVC (L)	1.71(43.5)
FEV_1 (L)	1.53(49.7)
FEV_1/FVC (%)	90.03
PEF (L)	5.98(74.6)
TLC (L)	3.10(46.62)
DLco (ml/min/mmHg)	8.04(29.79)
Conclusion:	Severe reduction of TLC and severe reduction of DLco

Cardiac evaluation

TRPG 30 mm Hg.

HRCT

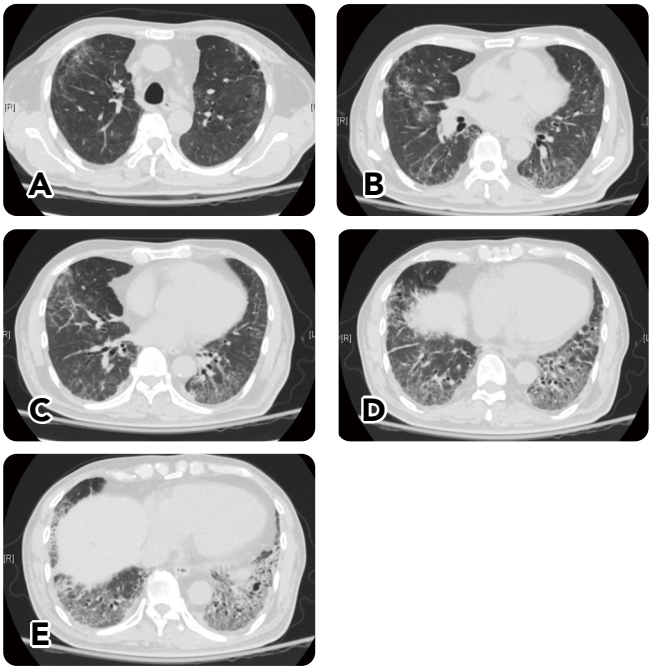

Figure 2A-2E. on 2022/11/14

HRCT

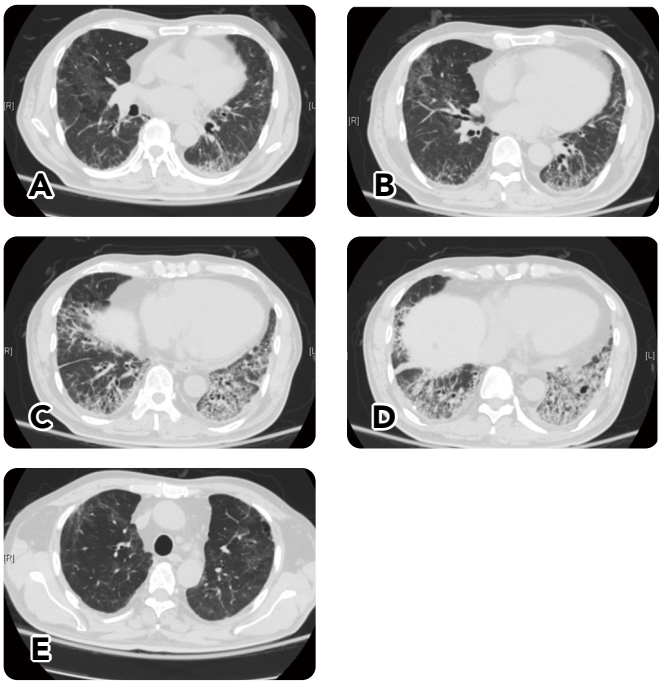

Figure3A-3E. on 2022/12/15

Diagnostic process

- Persisted cough with dyspnea on exertion after COVID-19 infection, PFT revealed Severe reduction of TLC and severe reduction of DLco, CXR revealed peri-bronchial infiltration and mucus plugging densities over bilateral lungs.(Figure 1)
- Chest CT performed on 2022-11-14, revealed traction bronchiectasis and ground glass opacities over bilateral lungs, especially bilateral lower lobes (Figure 2A-2E), pulmonary fibrosis suspected, started treatment of oral prednisolone 5mg BID, check autoimmune profile and sputum culture.
- No positive finding from the evaluation of infection disease, but ANA: 1:160(AC-15), consult rheumatologist, suggests COVID-19-related autoimmune disease.

- Symptom progressed under medications, repeat chest CT on 2022-12-15 to rule out pulmonary embolism due to elevated D-dimer at the scene revealed traction bronchiectasis with multiple wedge-like ground glass opacities over RML, RLL (increased infiltration and right pleural effusion), left lingular lobe and LLL (left lower lobe lung), with progression compared with previous examination.(Figure 3A-3E)
- MDD with radiologist, pulmonologist, and rheumatologist, suspect PPF by image, started anti-fibrotic agent since 2022-12-27 after discussing with the patient.

Discussion

- Following COVID-19 infection, a cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficit.
- But the diagnosis of post-COVID-19 ILD should be established by excluding other possible causes of ILD, such as autoimmune disease or infection.
- Autoimmune disease should be checked and discussed with a rheumatologist if any positive findings, in this case, there was not any autoimmune disease that could be diagnosed despite positive findings of ANA and anti-RF-IgM.
- The major treatment for post-COVID-19 ILD is a steroid, the usage of anti-fibrotic agents is still controversial.
- In this case, the anti-fibrotic agent was prescribed due to PPF was considered during follow-up.
- Post-COVID-19 ILD mainly occurs in patients with severe COVID-19, but there is still risk for patients with mild to moderate disease.

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Figure legends

Figure 1

Peri-bronchial infiltration and mucus plugging densities over bilateral lungs.

Figure 2A-2E

Traction bronchiectasis and ground glass opacities over bilateral lungs, especially bilateral lower Lobes.

Figure 3A-3E

Traction bronchiectasis with multiple wedge-like ground glass opacities over RML, RLL, left singular lobe, and LLL, with progression compared with the previous examination, suspect PPF.

From Virus to Fibrosis, then to Normal Lung—A case with interstitial lung disease after COVID-19 infection

Tingh-Han Chen[a]

[a] *Department of Pulmonary and Critical care medicine, China Medical University Hospital*

Clinical pearls :

- Following COVID-19 pneumonitis, a cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficits.
- Age, ICU stay, severity of COVID infection, and smoking history would be the frisk factor of post-COVID ILD.
- Early treatment with corticosteroids was associated with significant improvement in clinical condition and images.
- The effect of anti-fibrotic agents on the patient with post-COVID ILD needed more evidence.

Main article

Case presentation

- 70-year-old male.
- A retired laborer, without a smoking history and any travel history.
- Contact history: Wife and Mother had COVID infection within one week.
- He complained of progressive shortness of breath and fever for 2 days.
- Productive cough, headache, and general weakness were also noted.

Medical history

- Aortic root aneurysm, s/p Bengal's procedure bioprosthesis valve repairment in 2019/2.
- Hypertension.

Physical examination

- Heart rate: 109 BPM ; Body temperature: 38.9 ; Respiratory rate: 20-22.
- SpO_2: 94% under Non-rebreathing mask 10L/min.
- Crackle breathing sound in bilateral lung fields.
- No heart murmur.
- No clubbing fingers.
- No leg edema.
- No arthralgia nor joint deformity.
- No discoid rash nor malar rash, no Gottron sign, no Heliotrope sign.

Laboratory panels

- Normal CBC and biochemistry, except elevated hsCRP level.
- ANA: Cytoplasm pattern, >1: 160
  - Negative RF, ANA, anti-ENA (SS-A, SS-B, Scl-70), ANCA, and anti-CENP; normal IgG,IgA (immunoglobulin A), IgM, C3 and C4.
- Negative bacterial, mycobacterial, and fungal culture results.
- COVID-19 rapid screen was positive.

Chest radiograph

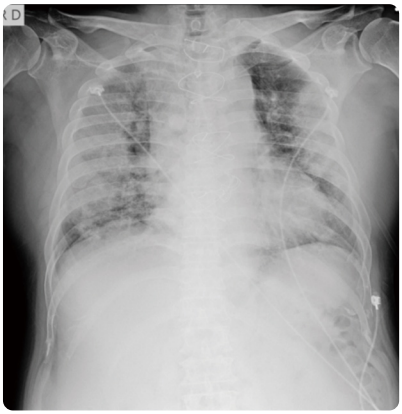

Figure 1.

Pulmonary Function Test

Date	20210621	20220323
FVC, L (% pred.)	2.78 (76)	2.90 (87)
FEV1, L (% pred.)	2.18 (78)	2.30 (82)
FEV1/FVC, %	78(103)	83(107)
FEF25%-75%, L/s (% pred.)	1.89(64)	2.59(89)
TLC, L (% pred.)	4.84(73)	6.38 (95)
DLCO, % pred.	44	63

HRCT

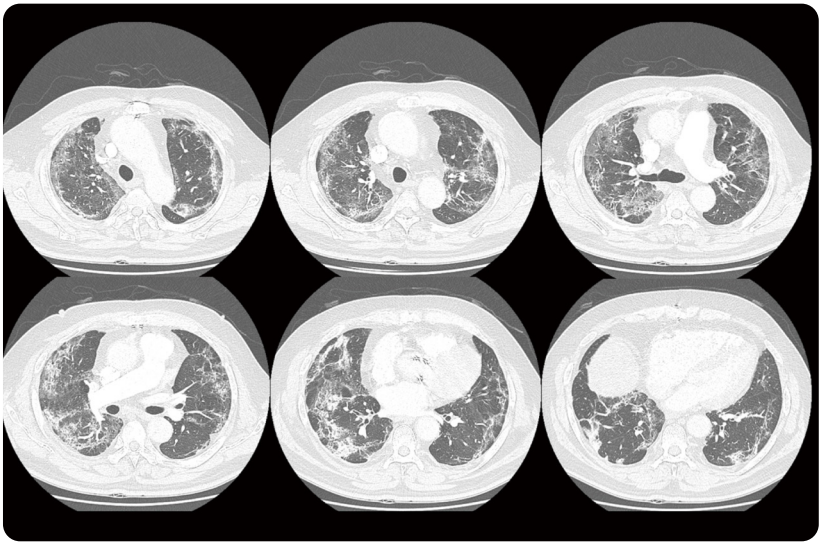

Figure 2. on 2021/06/15

HRCT

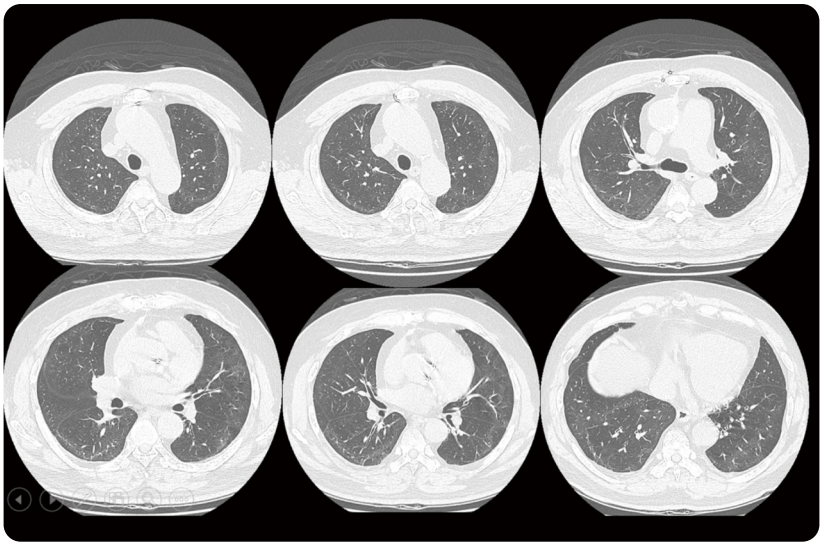

Figure 3. on 2022/01/07

Diagnostic process

- In our clinical experience, some patients had interstitial lung abnormalities after being infected with COVID-19. Although interstitial lung abnormalities usually recover after discharge, Other causes of ILD should be excluded in case of progressive ILD develops.
- In this patient, post-COVID interstitial lung abnormalities were noted even after the clinical condition improved. Autoimmune antibody was screened for excluding CTD-ILD. Early treatment with corticosteroids was prescribed for the patient for about one month. Then, the clinical condition and further chest CT reported significant improvement even without further medication control.

Discussion

- According to several evidence, up to 30% of patients have interstitial lung abnormalities following COVID-19 hospitalization. The radiographic abnormalities improve or resolve in most of these patients.
- Up to one-third of patients with post-COVID ILD have irreversible fibrotic features.
- The risk factors for post-COVID ILD include moderate-to-severe acute disease, age >50 years, intensive care unit stay with lengthy mechanical ventilation, chronic tobacco smoking, or chronic alcohol intake.
- There were several studies that had proven the therapeutic effect of corticosteroid which was well tolerated and associated with significant improvement in both pulmonary function and images.
- The effect of anti-fibrotic agents in the patient with post-COVID ILD needed more evidence.

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Figure legends

Figure 1

Bilateral peripheral distributed ground glass pattern.

Figure 2A-2E

Organizing pneumonia and ground glass opacities over bilateral lungs, especially lower lobes.

Figure 3

Significant improvement was noted, only less ground glass opacities was seen.

Pulmonary fibrosis induced by COVID-19

Chia-Hung Chen[ab]

[a]*Department of Internal Medicine, China medical university hospital, Taichung, Taiwan*

Clinical pearls :

- The most common imaging findings of chest CT scans in COVID-19 patients were infiltration pattern and earliest to be detected, GGOs show bilateral, subpleural, and peripheral distribution in the lungs of most patients. GGOs are usually accompanied by consolidations. and/or crazy paving appearance over time and it may take up to 14 days for CT findings to progress. Parenchymal findings are expected to be completely resolved by around day 26 at the absorption stage.
- Pulmonary fibrosis related to COVID-19 pneumonia was due to fibrous stripes, distortion of the parenchyma, and deformities in the bronchi. These fibrous lesions, which represent the replacement of cellulaPr components, might occur during the healing of chronic inflammation.

Main article

Case presentation

- 58-year-old male.
- An investigative reporter for thirty years.
- fever, fatigue, cough, and diarrhea complaints, and no known history of chronic diseases was referred to our hospital due to a positive COVID-19 RT-PCR test. Acute respiratory failure, COVID-19 pneumonia-related ARDS was noted, and an endotracheal tube was insertion.
- Chest HRCT on day 7 after admission revealed ground glass opacities in the bilateral lungs with inter- and intralobular septal thickening with a crazy paving appearance.
- Follow-up chest HRCT images on day 20 after admission revealed replacement of resolved infiltrations by subpleural honeycombing with traction bronchiectasis and reticular opacifications of both lungs. COVID-19-related pulmonary fibrosis was suspected.

Medical history

- Reports no medications.
- Reports no history of tobacco, alcohol, or drug use.
- Has no pets.
- Unremarkable family history.

Physical examination

- Heart rate: 122 BPM.
- SpO_2: 80-88% under mechanical ventilation with FiO2 100%.
- Diffuse rales over both lungs, without upper-lower difference.
- No clubbing fingers.
- No leg edema.
- No arthralgia.

Physical examination

- Negative RF, ANA, anti-ENA, and anti-CENP; normal C3 and C4.
- Negative bacterial, mycobacterial, and fungal culture results.

Pulmonary function test on 140 admission days

Parameter	Value (% predicted)
FVC (L)	2.32(53)
FEV_1 (L)	2.11(60)
FEV_1/FVC (%)	91(80)
PEF (L)	8.11(94)
TLC (L)	3.71(53)
DLco (ml/min/mmHg)	11.88(40)
Conclusion:Moderate restrictive ventilatory defect	

Chest radiograph

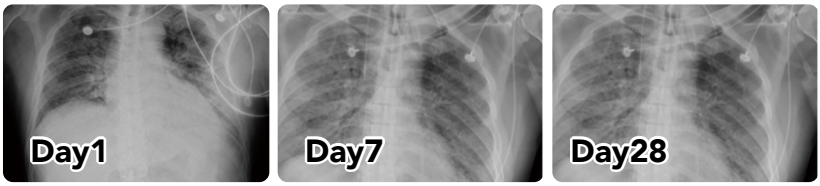

Figure 1.

HRCT

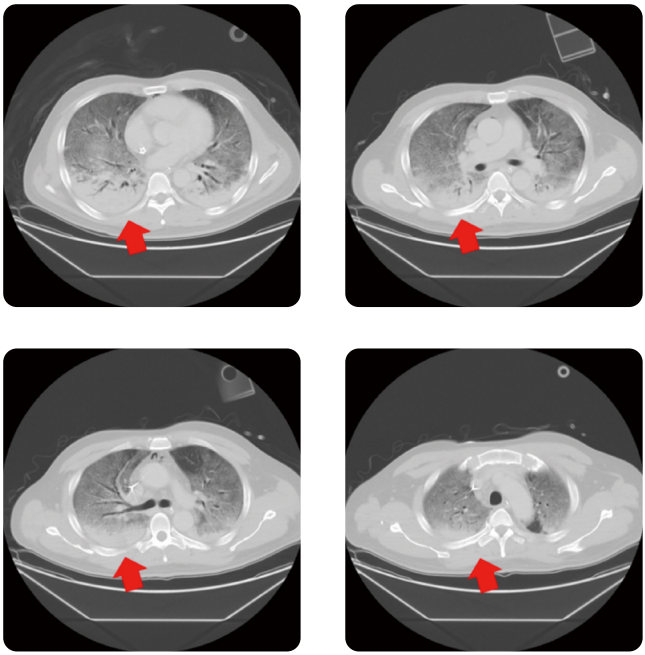

Figure 2. Day 7

HRCT

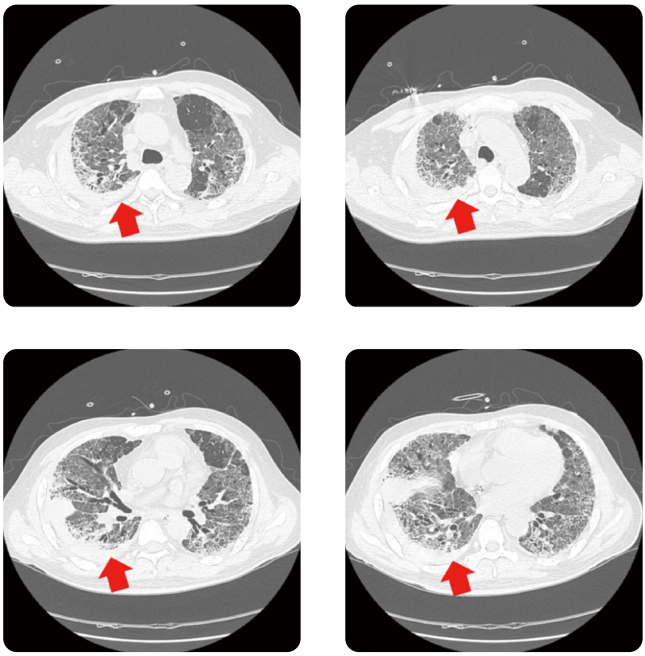

Figure 3. Day 20

Diagnostic process

- the clinicians should be aware that COVID-19-related pulmonary fibrosis may demonstrate similar CT imaging manifestations were seen in the UIP pattern.

Discussion

- The most common abnormalities from CT after COVID-19 are ground-glass opacity, parenchymal or subpleural bands, reticular abnormality, evidence of fibrotic abnormality, and air trapping.
- A Precise radiologic description is important; the term fibrosis should be reserved for those with clear evidence of fibrosis (traction bronchiectasis or bronchiectasis, honeycombing, or architectural distortion).

- GGOs show bilateral, subpleural, and peripheral distribution in the lungs of most patients. GGOs are usually accompanied by consolidations and/or crazy paving appearance over time and it may take up to 14 days for CT findings to progress.
- Parenchymal findings are expected to be completely resolved by around day 26 at the absorption stage. Fibrotic bands may appear during the healing process of pulmonary opacities.
- The etiology of COVID-19-related pulmonary fibrosis is unclear for now. The abnormal systemic immune response due to the hyperinflammatory state caused by COVID-19 might play a pivotal role in promoting pulmonary fibrosis.

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Figure legends

Figure 2

Chest HRCT images on day 7 after admission. CT images revealed ground glass opacities in the bilateral lungs with inter- and intralobular septal thickening with a crazy paving appearance.

Figure 3

Follow-up chest HRCT images on day 20 after admission. CT images revealed replacement of resolved infiltrations by subpleural honeycombing with traction bronchiectasis and reticular opacifications of both lungs.

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總 編 輯：林慶雄

作　　者：王鶴健、方昱宏、李 中、沈曉津、林聖皓、林重甫、柯宏叡、陶啟偉、徐紹勛 、連冠勳、陳乃慈、陳鼎翰、陳家弘、張立禹、郭耀文、陽光耀、楊美貞、黃國棟、黃堂修、温岳峯、曾敬閔、廖偉志、蔡孟耘、賴俊良、藍冑進

地　　址：100229 台北市常德街一號台大景福館四樓 413 室

電　　話：02–2314–4089

傳　　真：02–2314–1289

電子信箱：tspccm.t6237@msa.hinet.net

網　　址： https://www.tspccm.org.tw/ a.h

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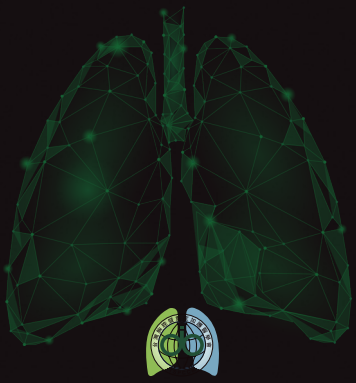

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