# Case Series

# Series of rare lung diseases mimicking imaging patterns of common diffuse parenchymal lung diseases

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## ABSTRACT

Diffuse parenchymal lung diseases (DPLDs) encompass a variety of restrictive and obstructive lung pathologies. In this article, the authors discuss a series of rare pulmonary entities and their high-resolution computed tomography imaging appearances, which can mimic more commonly encountered patterns of DPLDs. These cases highlight the importance of surgical lung biopsies in patients with imaging findings that do not show typical imaging features of usual interstitial pneumonia.

**KEY WORDS:** Amyloidosis, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, pleuroparenchymal fibroelastosis, pulmonary capillary hemangiomatosis, usual interstitial pneumonia

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## INTRODUCTION

Diffuse parenchymal lung disease (DPLD) is characterized by various imaging patterns on high-resolution computed tomography (HRCT). Some of the commonly recognized imaging patterns are usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and hypersensitivity pneumonitis (HP). The later two entities are deemed as not consistent with definite UIP as per the American Thoracic Society (ATS) guidelines. These guidelines characterizing the imaging findings of DPLDs into three main categories of definite, possible, and inconsistent with UIP findings.[1] According to the current ATS guidelines, if a high-confidence diagnosis of UIP is made on HRCT and the clinical workup does not reveal any etiology for the fibrotic changes, idiopathic pulmonary fibrosis (IPF) is the most likely diagnosis and a surgical lung biopsy (SLB) is obviated; however, if the HRCT pattern is not consistent with a UIP pattern, a SLB and multidisciplinary discussion should be considered.[2] It is probable that approximately one-third of the IPF patients would need SLB to obtain an accurate diagnosis. The incidence of surgical lung biopsies widely varies between 21%–89% depending on the institution and various clinical trials conducted in the past decade.[3] The lower rate of SLB is likely attributed to the mortality, which can occur shortly after the procedure, although the precise risk limits for complication of SLB procedure are not well known.

Rare pulmonary diseases may manifest HRCT imaging findings that can mimic and be confused with patterns that are observed in more common DPLDs including IPF, connective tissue disease-related interstitial lung disease, and HP. Not all cases that have a possible UIP pattern or inconsistent with UIP pattern are fibrotic lung disease. This article discusses a series of such rare pulmonary entities and reviews the imaging findings that can mimic the above-mentioned patterns. Relevant histopathology correlation is also provided.

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The radiology–pathology correlation of these cases highlights the importance of SLB even in older age group as the imaging features of such rare diseases can mimic imaging patterns of more commonly encountered fibrotic and nonfibrotic DPLDs. An accurate diagnosis is of utmost importance in the correct management of such cases.

## PULMONARY CAPILLARY HEMANGIOMATOSIS

### Case 1
A 73 year old patient with history of diabetes presented with persistent long-term dyspnea and nonproductive cough. He was referred to a pulmonologist who diagnosed restrictive DPLD based on pulmonary function test (PFT) and impaired diffusion capacity. There was no history to suggest a connective tissue disorder, occupational or environmental exposure, or drug intake, and a clinical diagnosis of IPF was suspected. Since the HRCT images showed a pattern that was not consistent with UIP [Figure 1] but possibly NSIP, an open lung biopsy was performed that revealed findings compatible with pulmonary capillary hemangiomatosis (PCH) [Figure 2]. A subsequent right heart catheterization showed mild pulmonary hypertension.

### Discussion
PCH was first described in 1978 by Wagenvoort *et al*.[4] as a vascular proliferation with indolent onset pulmonary hypertension. It is a rare disease occurring in young adults and most often presents as dyspnea, cough, and hemoptysis. It slowly progresses to cor-pulmonale,

and typically, the capillary pulmonary wedge pressure remains normal. Biopsy in patients with PCH is frequently not possible due to the high pulmonary pressure and increased risk of bleeding but typically shows proliferating capillaries causing thickening of the alveolar wall, thereby disrupting the gas exchange mechanism. Precapillary hypertension leads to a restrictive ventilatory pattern. Normal pulmonary capillary wedge pressures on cardiac catheterization confirm that obstruction is proximal to the large pulmonary veins.

HRCT typically shows enlarged main pulmonary artery and diffuse ill-defined ground-glass centrilobular nodules, occasionally mixed with lobular ground-glass opacities. Additional findings of normal or small left atrium, smooth interlobular septal thickening, lymphadenopathy, pleural effusion, enlargement of the right chambers of the heart, and pericardial effusion support this rare diagnosis.[5] The presence of smooth interlobular septal thickening may or may not be present and likely represents an overlap with pulmonary veno-occlusive disease.[6] We describe a rare imaging presentation of PCH that mimics fibrotic lung disease on HRCT. Several previous case reports have described PCH with secondary pulmonary fibrosis without much details about the imaging findings on HRCT except for one case report that described PCH with lung fibrosis on routine chest CT.[7]

This case highlights the importance of open lung biopsy and multidisciplinary discussion not only in establishing the final and correct diagnosis of PCH[8] but also shows that biopsy is of utmost importance for proper patient management in cases with imaging
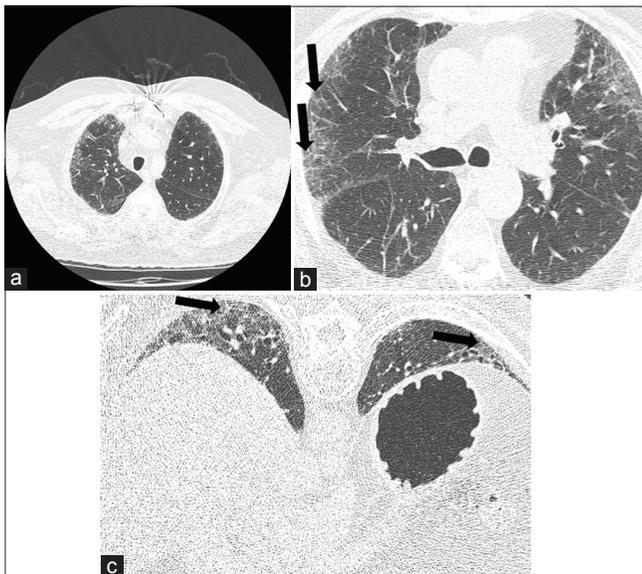


**Figure 1:** Capillary hemangiomatosis: Axial supine (a and b) inspiratory and prone (c) high-resolution computed tomography images show predominant subpleural ground-glass densities with fine reticulations (arrows in a and b) and bibasilar traction bronchiectasis (arrows in c). The ground-glass densities appear greater than reticulations suggesting a pattern not consistent with usual interstitial pneumonia
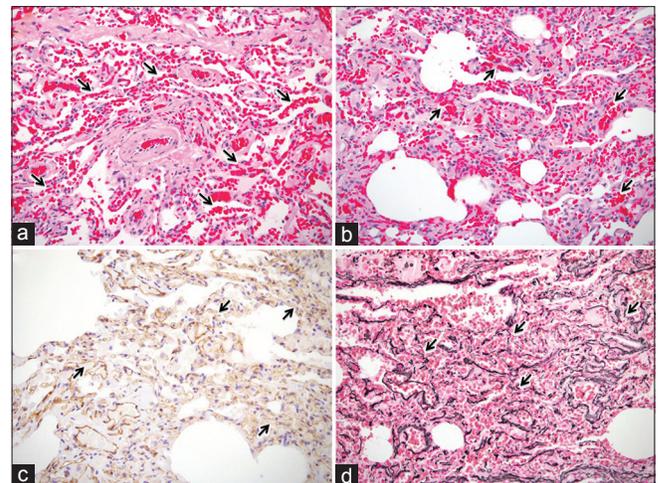


**Figure 2:** Capillary hemangiomatosis: Histopathological examination. (a and b) Demonstrating a proliferating anastomosing network of capillaries causing thickened alveolar walls (H and E, ×200). (c) Immunohistochemical staining with CD31 (an endothelial marker) at ×200 highlights the network of proliferating capillaries (brown staining). (d) Special staining with reticulin at ×200 highlights the invasion of proliferating capillaries into the walls of the airways (black staining)

pattern not consistent with definite UIP. In the absence of the pathological diagnosis, a right heart catheterization would not have been performed in a timely fashion, masking mild pulmonary hypertension. Not only would have the patient been subjected to administration of steroids in the light of imaging findings suggestive of possible NSIP but also to the side effects associated with the same.
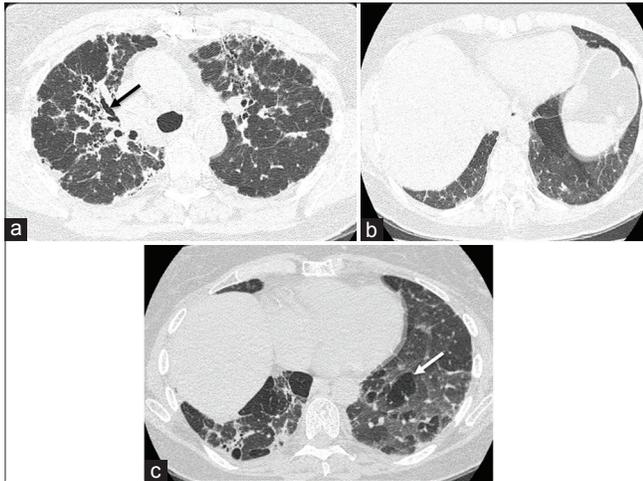


**Figure 3:** Pleuroparenchymal fibroelastosis. High-resolution computed tomography axial images (a and b) show predominantly upper and middle lobe fibrotic pattern with severe central traction bronchiectasis (arrow), peribronchial thickening, and patchy areas of subpleural fibrosis. No significant pleural thickening noted. Expiratory image (c) demonstrates prominent lobular areas of air trapping in the lower lobes (arrow)
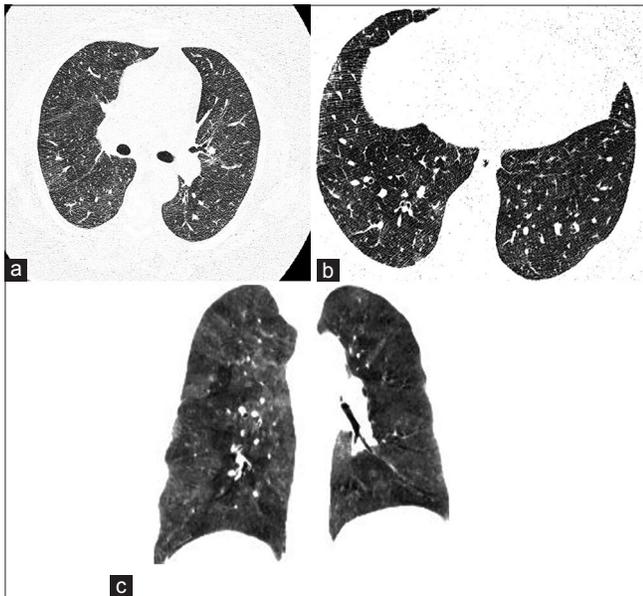


**Figure 5:** Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia – Axial high-resolution computed tomography inspiratory image (a) demonstrates mosaicism and expiratory images (b) shows air trapping as depicted by the lobular low attenuation areas. A coronal mimimum intensity projection (MinIP) reformat (c) highlights the mosaicism secondary to air trapping

# PLEUROPARENCHYMAL FIBROELASTOSIS

## Case 2

A 66 year old patient presented with gradually progressive exertional dyspnea. She also had significant complaints of dry eyes and dry mouth with occasional Raynaud's phenomenon. There was a history of multiple water leaks in the house raising the possibility of mold exposure. Her PFTs showed a restrictive pattern and HRCT of lungs depicted an imaging pattern suggestive of chronic HP (CHP) [Figure 3]. Dedicated pulmonary pathology review
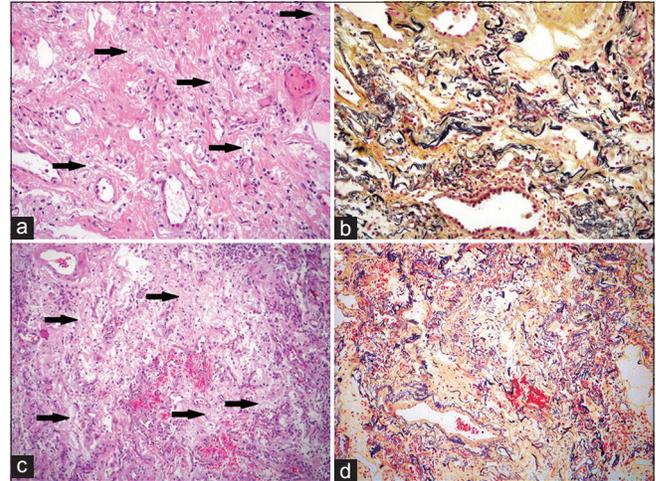


**Figure 4:** Pleuroparenchymal fibroelastosis. (a and c) Representative images of H and E staining of lung parenchyma at ×200 and ×100 showing extensive interstitial fibrosis with a prominent gray-violet elastotic component (arrows). (b and d) Pentachrome (Movat's) stain of the same areas demonstrating extensive elastosis (black fibers)
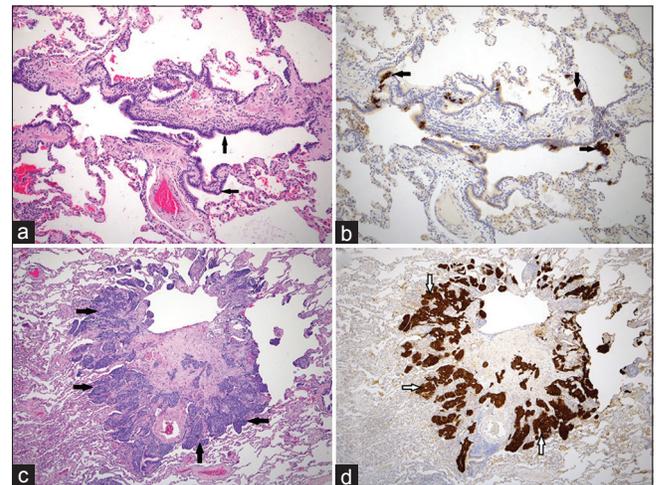


**Figure 6:** Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: (a) Tortuous bronchiolar profiles with focal subepithelial fibrosis and neuroendocrine cell hyperplasia (arrows) (H and E, ×100). Immunohistochemistry (b) for chromogranin at ×100 highlights the neuroendocrine cell hyperplasia (arrows). (c) Numerous aggregates of neuroendocrine cells bulge into bronchiolar lumens and out into surrounding alveolar parenchyma (arrows). (d) Immunohistochemistry staining for chromogranin at ×100 highlights the neuroendocrine cell aggregates (arrows)

of the outside biopsy specimens led to a final diagnosis of pleuroparenchymal fibroelastosis (PPFE) [Figure 4].

### Discussion

PPFE was originally described in 2004[9] and is a rare diagnosis. PPFE is suggested to represent a pattern of chronic lung injury that can be associated with a wide clinic-radiologic spectrum.[10] The exact etiology is unknown, and conditions associated with PPFE include drug exposure, possible genetic predispositions, bone marrow transplant, infections, and autoimmune conditions.[9-16] Typical imaging features of PPFE have been described as predominantly bi-apical pleural thickening, subpleural upper lobe consolidation, and fibrosis.[13] Significant air trapping with upper lobe fibrosis is an imaging pattern commonly observed in CHP and sarcoidosis, but PPFE should also be kept in mind, despite an exposure history and imaging findings that mimic CHP. PPFE is a recently defined clinico-pathologic term with unknown long-term prognosis. It is possible that it may represent a phenotype of lung injury expressed in an airway-centric disease such as CHP. This case reiterates that lung biopsy should be strongly considered in cases with imaging findings that are not consistent with definite UIP. In the absence of biopsy results and given the clinical and imaging features, this patient may be treated with immunosuppressants and steroids for possible HP, thus putting the patient at risk for emergent adverse events and increased morbidity.

## DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE CELL HYPERPLASIA

### Case 3

A 65 year old former female smoker presented with a 6-month history of progressive dyspnea on exertion and restrictive PFT. Her environmental exposure history included bioaerosol and water leaks. Autoimmune serology was negative. HRCT of lungs revealed diffuse air trapping on the expiratory scan, with a few scattered random nodules [Figure 5]. Given her exposure history and imaging findings, nonfibrosing CHP was suggested as plausible diagnosis. Right middle lobe wedge biopsy was performed, and six histopathologies revealed diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) [Figure 6].

### Discussion

DIPNECH is a very rare lung lesion and definitive diagnosis can only be established on histopathology. It is characterized by generalized proliferation of pulmonary neuroendocrine cells that produce fibrogenic peptides causing diffuse constrictive bronchiolitis. DIPNECH is considered a preneoplastic lesion in the spectrum of pulmonary neuroendocrine tumors because it is commonly found in patients with peripheral carcinoid tumors.[17] However, DIPNECH's role in the etiology of predominantly central, high-grade, or malignant pulmonary neuroendocrine tumors is uncertain.[18-21] HRCT typically shows air trapping, small

nodules, bronchial wall thickening, and bronchiectasis, making this condition a mimicker of more commonly encountered lung conditions with small airway disease such as asthma, constrictive bronchiolitis, respiratory bronchiolitis, and HP.[22,23] Results of the SLB as in this case provided a diagnosis which would allow administration of somatostatin analog rather than immunosuppressants and steroids (presumably for prebiopsy diagnosis of HP, given the exposure history and imaging findings). Somatostatin analog has been shown to result in significant resolution in the clinical features in DIPNECH.[24]

## PULMONARY AMYLOIDOSIS

### Case 4

A 74 year old former smoker presented with a 5-year history of dyspnea on exertion and restrictive pattern on PFTs. HRCT was performed, showing a fibrotic pattern suggestive of possible UIP [Figure 7], and concerning for IPF in the absence of any secondary factors known to cause pulmonary fibrosis. A subsequent open biopsy, however, showed diffuse alveolar septal amyloid deposits [Figure 8]. The amyloid protein was found to be transthyretin (TTR). TTR is a rare variant of amyloidosis that deposits more frequently in the peripheral nervous system resulting in peripheral neuropathy. Lung involvement is rare with this variant. The patient was subsequently treated with diflunisal which is a tetramer stabilizer.[25] A dramatic increase in forced vital capacity (FVC) by 800 cc and an increase in the diffusing capacity of the lung for carbon monoxide (DLCO) from 13.8 to 22.3 ml/min/mmHg since treatment has occurred, whereas at 7 months before therapy with diflunisal was initiated, the patient had lost about 22% FVC and 29% of DLCO.
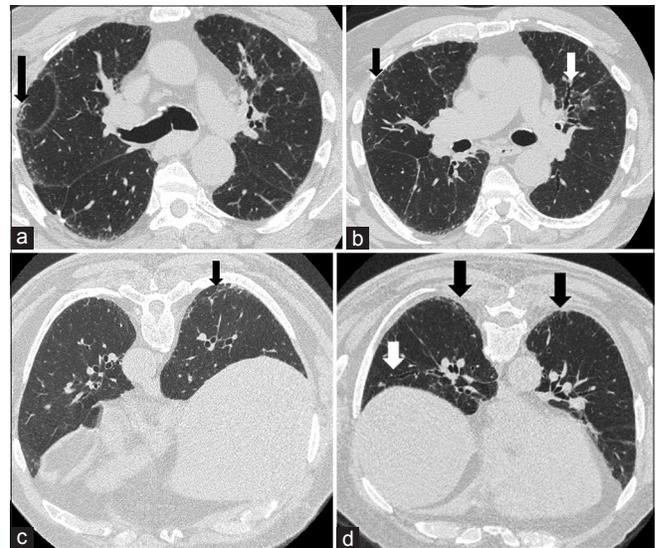


**Figure 7:** Pulmonary amyloidosis with a possible usual interstitial pneumonia pattern. High-resolution computed tomography images show subpleural distribution of reticulations (black arrows in a-d). Minimal architectural distortion and traction bronchiectasis in the lingula and right lower lobe (white arrows in b and d). No honeycombing or subpleural sparing noted
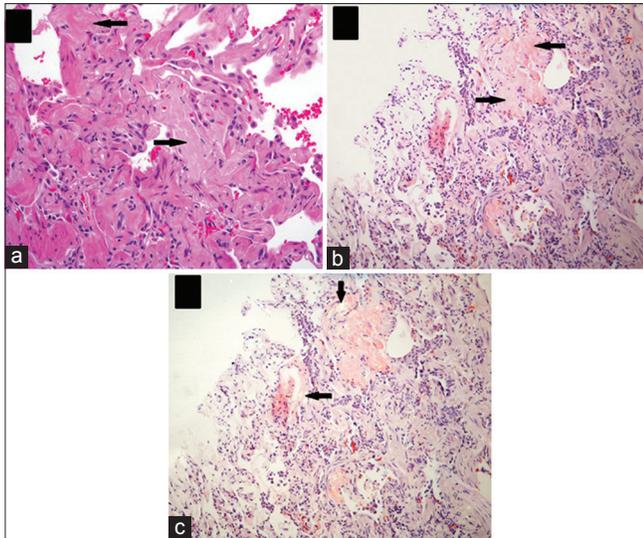
**Figure 8:** Amyloidosis: Histopathological examination. (a) Demonstrating extracellular deposition of amorphous material consistent with amyloid (arrows) (H and E, ×200). (b) Positive for interstitial amyloid material (arrows) (Congo red, ×100). Polarized photomicrograph of Congo red, ×100 (c) characteristic apple-green birefringent amyloid material (arrows)

### Discussion

Amyloidosis encompasses a diverse group of metabolic disorders characterized by extracellular deposition of insoluble proteins. Pulmonary involvement in amyloidosis is rare and presents with one of three distinct morphologies – tracheobronchial, nodular parenchymal, and rarely, diffuse alveolar septal amyloidosis.[26-29] Rarely, cystic lesions with or without nodules can be associated with Sjogren syndrome and amyloidosis.[30,31] Pulmonary fibrotic pattern in amyloidosis has been described in association with amyloid A protein amyloidosis[32] or familial Mediterranean fever,[33] but our case did not have either of the above. Thus, amyloidosis should be kept in mind as a rare differential diagnosis for fibrotic lung disease and can mimic possible UIP pattern on HRCT imaging. This case also reinforces that SLB is important in making the correct diagnosis in cases with imaging findings that are not consistent with definite UIP pattern, even in an older age group. The correct diagnosis not only led to the right treatment that substantially improved the patient symptoms and PFTs but also saved the patient from unwanted side effects of antifibrotic drugs and from progression of the underlying disease in the absence of correct treatment.

## CONCLUSION

PCH, amyloidosis, PPFE, and DIPNECH are rare disease entities that may mimic HRCT patterns that are encountered with more common fibrotic and nonfibrotic DPLD. The radiology–pathology correlation is of utmost importance in obtaining an accurate diagnosis in cases with imaging pattern not consistent with definite UIP. Discounting of surgical biopsy due to associated risks and old age
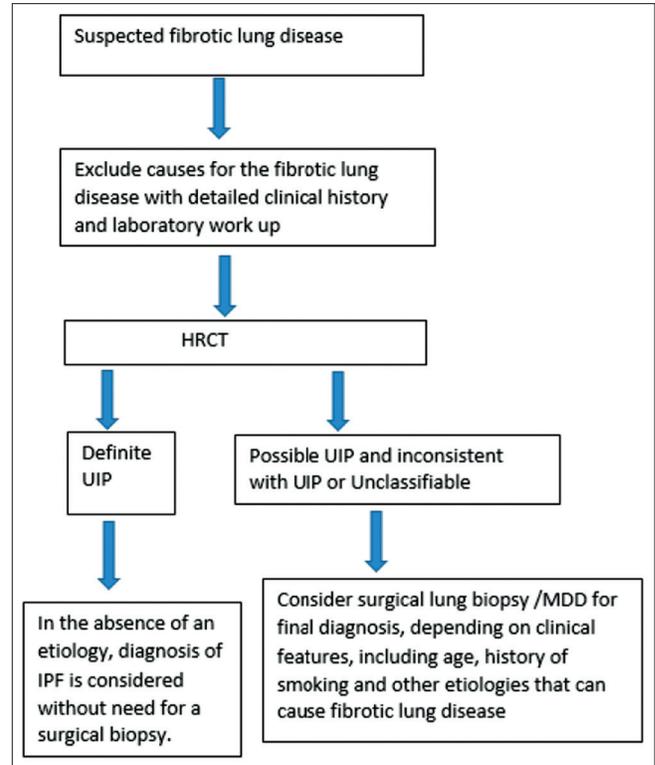


**Figure 9:** Flowchart to approach work up for suspected fibrotic lung disease. IPF: Idiopathic pulmonary fibrosis, MDD: Multididciplinary diagnosis, UIP: usual interstial pneumonia

leads to a missed opportunity for a remarkably effective treatment and in the absence of the correct diagnosis and puts the patient through risks of empiric therapy without a diagnostic confirmation.[34] Therefore, a broad outlook in approach to manage such difficult cases is needed. SLB and a multidisciplinary discussion are advocated for cases that are possible or inconsistent with UIP pattern in order to not miss some rare disease as described above [Figure 9].

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest
There are no conflicts of interest.

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