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# HISTOLOGICAL SPECTRUM OF NON-NEOPLASTIC LESIONS IN THE LUNG-A RETROSPECTIVE STUDY DONE ON LOBECTOMY SPECIMENS

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## ABSTRACT

To study the histolopathological spectrum of non-neoplastic lesions of lung and to evaluate in relation to age, gender and clinico-radiological findings. This study is done over a period of 1 year (Nov 2020 to Nov 2021) in the Department of Pathology, LNMC, Bhopal. Total of 33 lobectomy specimens were studied. Specimens were fixed in formalin and paraffin embedded H&E-stained tissue sections were studied. Special stains (Gomorri's methenamine silver stain and Periodic acid Schiff stain) were done where ever required. Non-neoplastic lesions from 3 (9.09%) women and 30 (90.90%) men, with a median age of 43.86 (Interquartile range: 23-60 years) were collected. Fibrotic interstitial changes comprised the most common category of histologic findings, noted in 20 (60.6%) patients. Most cases consisted of usual interstitial pneumonia (UIP) (30.30%), followed by smoking related interstitial fibrosis/SRIF (desquamative interstitial pneumonia like patterns and respiratory bronchiolitis like pattern) (12.12%), non-specific interstitial pneumonia (NSIP) (9.09%) and patterns of "undefined" fibrosis (6.06%) such as peribronchial fibrosis, organizing pneumonias and other patterns of fibrosis that did not fall into a recognized category of idiopathic interstitial pneumonia. Granulomatous pathology was identified in 4 (10.81%) patients. On chest X-ray/CT scan chest, majority of lung lesions presented as diffuse and patchy opacities with honeycombing and bronchiectasis. Cigarette smoking was associated with 4 lung lesions. Histopathologic classification plays an important role in separating variable forms of non-neoplastic lung lesions & further subcategorising idiopathic interstitial pneumonia into clinically meaningful categories have important differences in natural history, prognosis, and treatment.

**KEYWORDS:** Lung, Smoking, Non-neoplastic lung, Idiopathic interstitial pneumonias, Idiopathic pulmonary fibrosis, Nonspecific interstitial pneumonia, Usual interstitial pneumonia, Tuberculosis, Fungal.

## INTRODUCTION

Lungs are the foundational organ of respiratory system and participate in transporting oxygen to and removing the excess carbon dioxide from the body and this emphasize its role in vital functioning of their organs. Non neoplastic lung diseases include a wide range of pathological disorders from asthma to interstitial lung diseases to pulmonary hypertension, infectious and occupational lung diseases, causing significant morbidity and account for the large number of workdays lost with morbidity in the general population. Although these lesions are not neoplastic, they are nevertheless important to recognize, as their diagnosis by surgical pathologists and an improved understanding of pathophysiology may help in understanding the outcome of these much harmless conditions (1).

Respiratory tract infections are quite frequent and can be caused majorly by viruses (2).

Familiarity with the histopathologic classification of the non-neoplastic conditions of lung may expedite treatment of patients as they are often confused with malignant neoplasms. Idiopathic interstitial pneumonia accounts for substantial subset of diffuse lung diseases that surgical pathologists are likely to encounter. It can be clinically and microscopically categorised into entities considering the pattern and microanatomic distribution of inflammation, fibroblast proliferation, collagen deposition, and architectural remodeling. The most common idiopathic interstitial pneumonias are Usual interstitial pneumonias (UIP). Other forms of idiopathic interstitial pneumonia include desquamative interstitial pneumonia, respiratory bronchiolitis–associated interstitial lung disease, acute interstitial pneumonia, and nonspecific interstitial pneumonia.

These latter categories differ from UIP in that the histopathologic findings, spatial and temporal synchrony

of progression do not allow specific diagnosis in most cases and require careful correlation with clinical and radiologic findings and hence their treatment (3).

A large number of diseases in which granulomatous inflammation is a dominant feature involve the lung, which may be infectious (mycobacteria and fungi) and non-infectious lung diseases (sarcoidosis, necrotising sarcoid granulomatosis, hypersensitivity pneumonitis, etc.) Precise clinical evaluation, laboratory testing and often histomorphological assessment contribute to make a specific diagnosis of granulomatous lung diseases (4).

In this study, we estimate the prevalence and characterise the parenchymal findings of these non-neoplastic lung lesions aiming to increase awareness of findings that could potentially impact patient management.

## MATERIALS AND METHODS

This retrospective study was done over a period of 1 years (Nov 2020 - Nov 2021) in the Department of Pathology, LNMC, Bhopal. Total of 33 cases were studied, which presented with lesions on CT scan or X-ray chest to the cardio-thoracic department. Demographics, clinical history, and radiology reports were collected from the medical record. Clinical correlation was recorded for specific histologic findings. Chest CT scans or X ray findings in all cases were evaluated for potential radiologic correlates of histologic findings. The lung lobectomy specimens were fixed in 10% buffered formalin. Tissues were processed by routine paraffin processing and H&E staining was performed. Special stains (Gomorri's methenamine silver stain and Periodic acid Schiff, ZN) were done where ever required, following which histological assessment was done (5).

Morphological evaluation and categorisation of parenchymal abnormalities was done into: fibrotic interstitial changes (including smoking-related interstitial fibrosis [SRIF], usual interstitial pneumonia [UIP], nonspecific interstitial pneumonia [NSIP], undefined fibrosis), granulomatous disease (including infectious & non-infectious) and other miscellaneous group (6).

## RESULTS

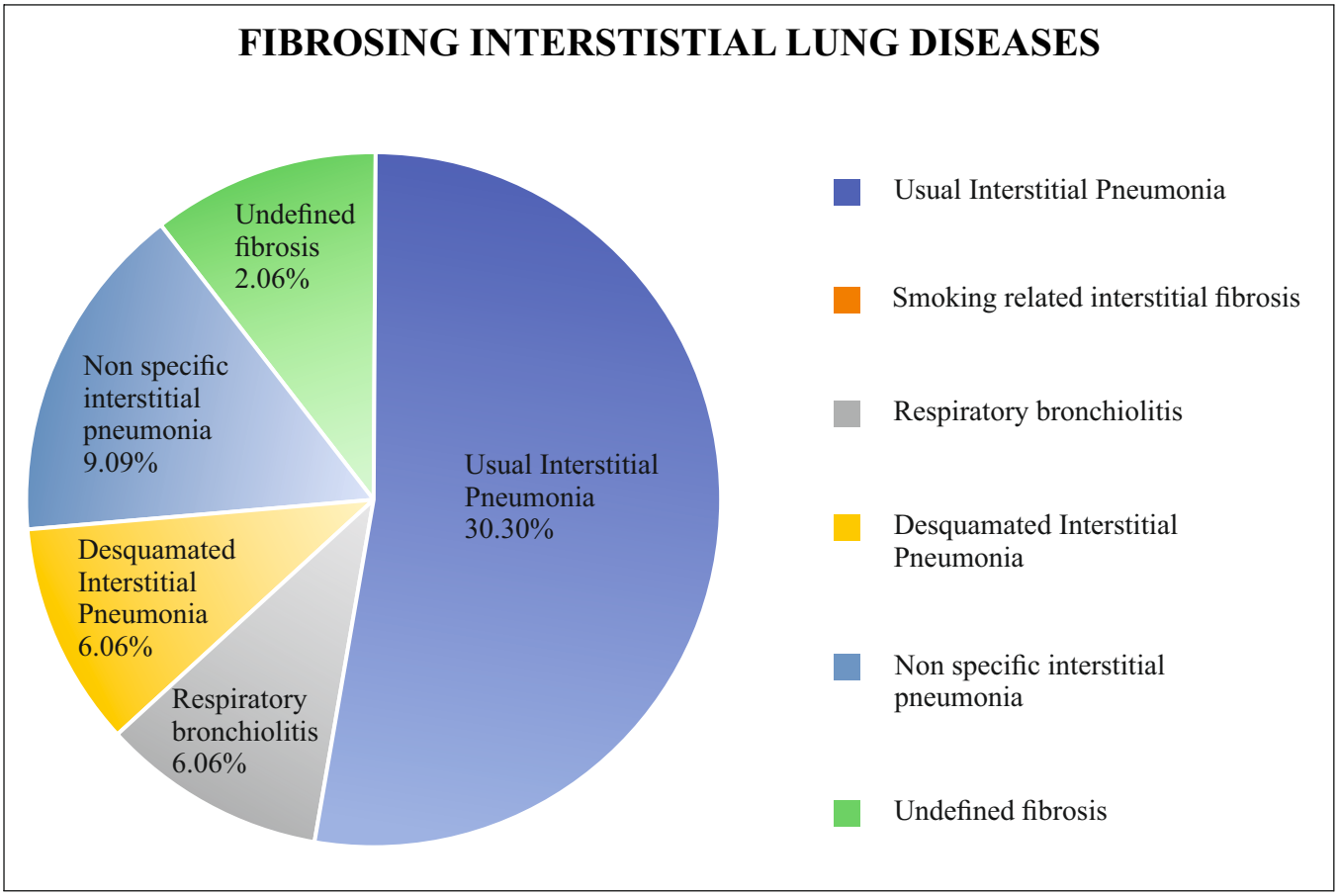
Retrospective histologic assessment of parenchymal abnormalities was correlated with original pathology reports, clinical history, and radiologic findings.

Our study included 33 separate resection specimens from 3 (9.09%) women and 30 (90.90%) men, with a median age of 43.86. There were 4 cases of either current or former smokers and they added upto smoking related interstitial fibrosis (SRIF).

They added up to smoking related interstitial fibrosis (SRIF). The most common abnormal findings were fibrotic interstitial changes (60.6%), including usual interstitial pneumonia (30.30%), smoking related interstitial fibrosis (SRIF) (12.12%), non-specific interstitial pneumonia (NSIP) (9.09%), undefined fibrosis (6.06%) and subpleural fibrosis (3.03%) followed by granulomatous lesions (12.12%). There were 2 cases of fungal etiology (6.06%), 1 case of hydatid cyst (3.03%), 2 cases of emphysematous lesions (6.06%), 3 cases were bronchiectasis (9.09%) and 1 case of lung abscess (3.03%). (Pie chart 1, Table 1)

| **Non neoplastic lung lesions** | **Total no of cases (n=33)** |
|---|---|
| **Fibrosing interstitial lung diseases-** | **No. of cases (n=20)** |
| Usual interstitial pneumonia pattern (UIP) | 10 (30.30%) |
| Smoking related interstitial fibrosis pattern (SRIF) - Respiratory bronchiolitis | 2 (6.06%) |
| Desquamative interstitial pneumonia (DIP) | 2 (6.06%) |
| Non-specific interstitial pneumonia pattern (NSIP) | 3 (9.09%) |
| Undefined fibrosis | 2 (6.06%) |
| **Subpleural fibrosis** | 1 (3.03%) |
| **Infective etiology-** | **No. of cases (n=7)** |
| Tubercular granulomas | 4 (12.12%) |
| Fungus | 2 (6.06%) |
| Hydatid cyst | 1 (3.03%) |
| **Miscellaneous-** | **No. of cases (n=6)** |
| Emphysema | 2 (6.06%) |
| Bronchiectasis | 3 (9.09%) |
| Lung Abscess | 1 (3.03%) |

*Table 1: Spectrum of Non-neoplastic Lesions in Lung Lobectomy Specimens*




***Graph 1: shows the Spectrum of Fibrosing Interstitial Lung diseases in the Lobectomy Specimens***

Pathologic features of UIP/IPF showed heterogeneous and variegated appearance with architectural derangement. Alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change results in a distinctive "patchwork" distribution at low magnification (Fig. 3).

"Fibroblast foci" against a backdrop of chronic scarring, showing variegated appearance or temporal heterogeneity of UIP present. (Fig. 4). Obliterative architectural distortion with fibrotic scars (dense eosinophilic collagen without associated honeycomb change), smooth muscle hyperplasia of vessel wall & mild interstitial inflammation consisting of patchy alveolar septal infiltrates of mononuclear cells. Peribronchiolar lymphoid aggregates were seen in few cases (Fig. 5-7). Secondary ("traction") bronchiectasis (Fig. 8) and peribronchiolar fibrosis with associated epithelial hyperplasia, peribronchiolar metaplasia (Fig. 9). Subpleural fibrosis also noted in a case. (Fig.10) Desquamative interstitial pneumonia (DIP) shows filling of distal airspaces by numerous pigmented alveolar macrophages. (Fig. 11)

Nonspecific Interstitial Pneumonia shows uniform alveolar septal infiltrates of lymphocytes and plasma cells with mid congestion in alveolar septa. (Fig. 12)

Organizing pneumonia shows airway plugged with organizing exudates with surrounding inflammation and fibrosis. (Fig. 13)

Tuberculosis shows confluent granuloma with focal collection of inflammatory cells at sites of tissue infection and includes epithelioid cells, langhans' giant cells, and lymphocytes with or without caseous necrosis. (Fig. 14-16)

Fungal granulomatous lesions show granulomas with central necrosis and contain hyphae. The dilated bronchi are filled with eosinophilic debris and filled with mucoid impaction. Necrotizing granulomatous inflammation destroying a bronchiole seen. Note the necrotic debris filling the bronchiolar lumen. (Fig. 17-18)

Hydatid cyst shows laminated chitinous wall with degenerating protoscolex along with focal perivascular chronic inflammatory infiltrate (Fig. 19).

## GROSS APPEARANCE OF LOBECTOMY SPECIMENS

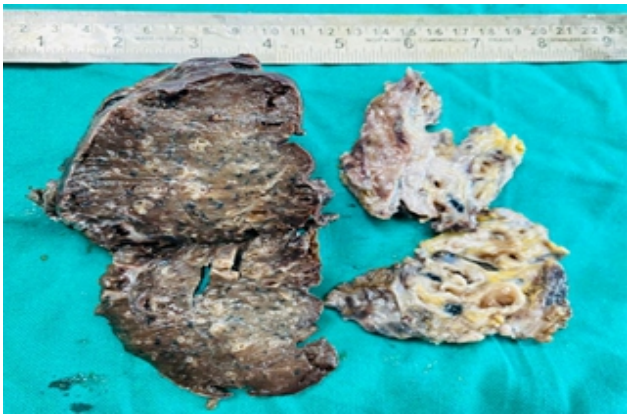


*Fig. 1: Gross of interstitial lung disease showing bronchiectasis, honeycombing, consolidation and fibrosis*

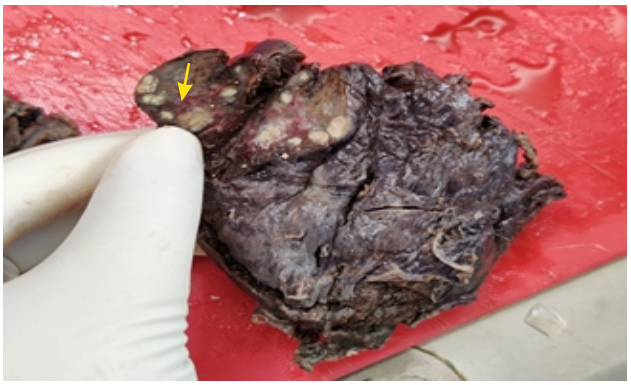


*Fig. 2: Gross of lung tuberculosis showing scattered tan nodules in the upper lobe of lung with caseous necrosis*

## HISTOPATHOLOGICAL IMAGES OF THE CASES

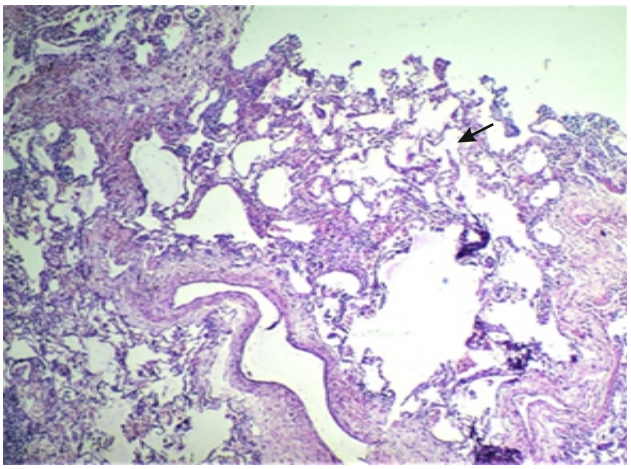


*Fig. 3. Photomicrograph illustrating variegated honeycomb change, patchwork distribution of abnormalities in a classical usual interstitial pneumonia (UIP) (H&E stain; X40)*

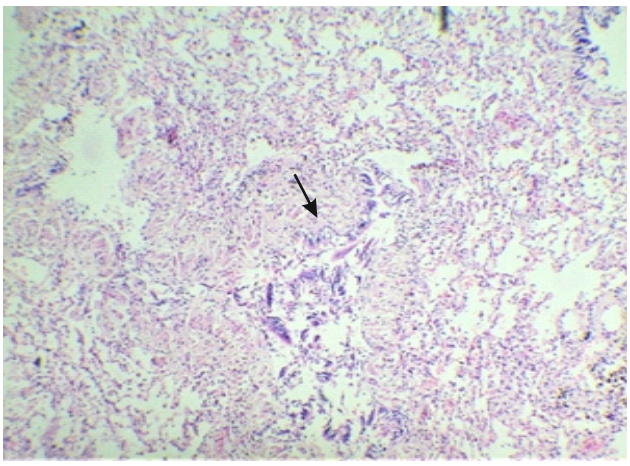


*Fig. 4: Photomicrograph illustrating fibroblast focus in a patient with UIP. The fibroblast focus comprises a localized area in which spindle cells are distributed in a somewhat linear fashion within pale-staining interstitial matrix associated with overlying hyperplastic pneumocytes (H&E stain, X40)*

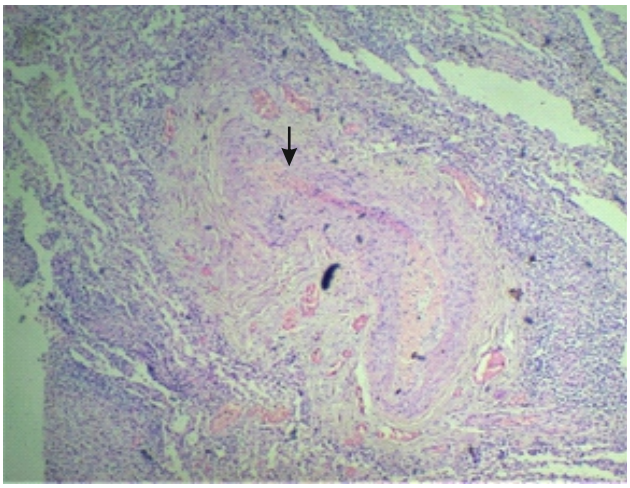


*Fig. 5. Photomicrograph shows smooth muscle cell hyperplasia and interstitial inflammation (H&E stain, X40*

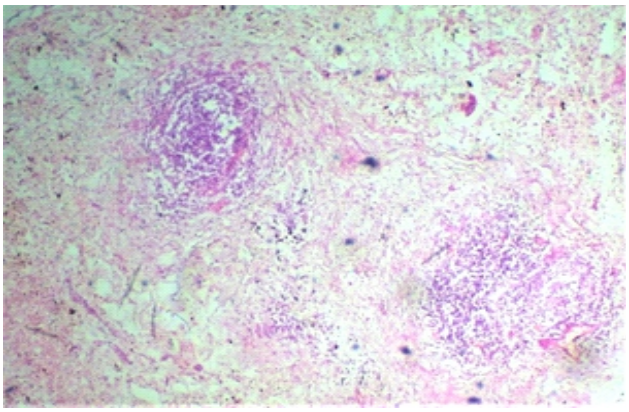


*Fig. 6. Photomicrograph shows Lymphoid aggregates with Peribronchial Fibrosis. (H&E stain,*

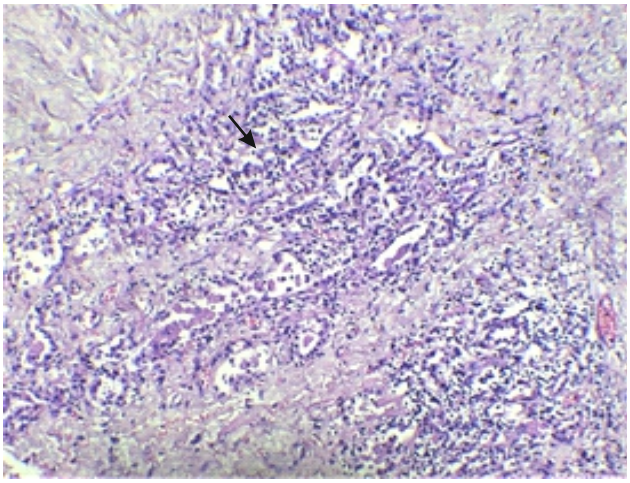


*Fig. 7: Photomicrograph shows Pneumocyte Hyperplasia. (H&E stain, X40)*

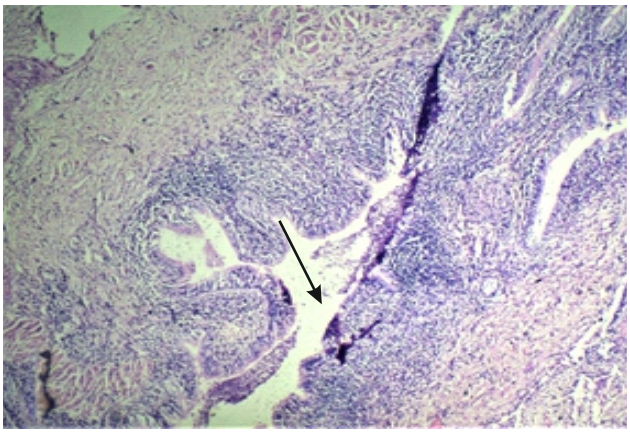


*Fig. 8: Photomicrograph illustrates bronchiectasis showing chronic inflammation, thickened pleura and fibrosis. (H&E stain, X40)*

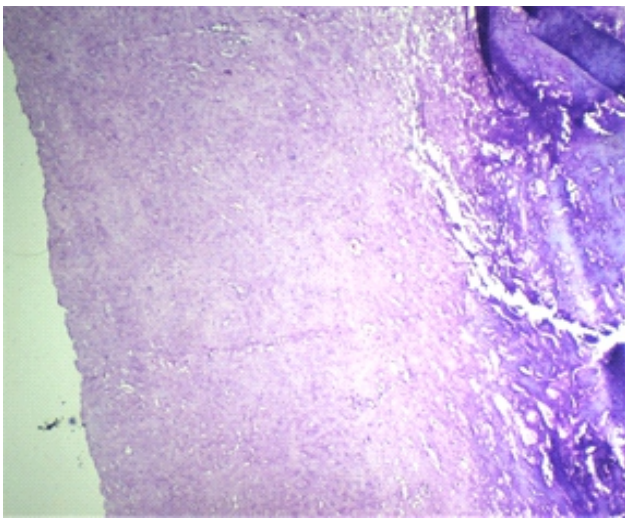


*Fig. 9: Photomicrograph shows pleural fibrosis with collapsed adjacent lung parenchyma. (H&E stain, X10)*

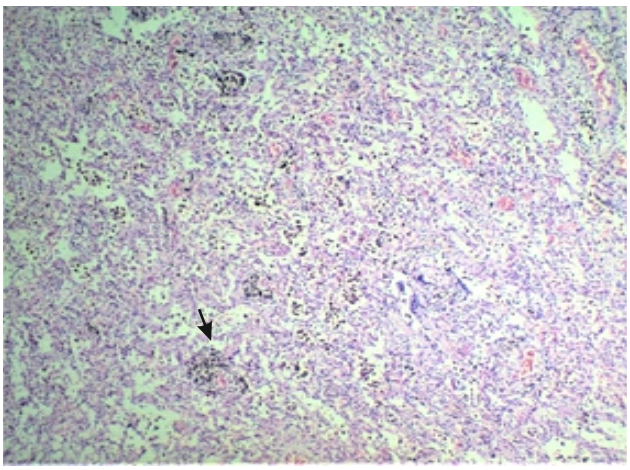


*Fig. 10: Photomicrograph illustrates desquamative interstitial pneumonia (DIP) showing diffuse and massive accumulation of intra-alveolar macrophages. (H&E stain, X10)*

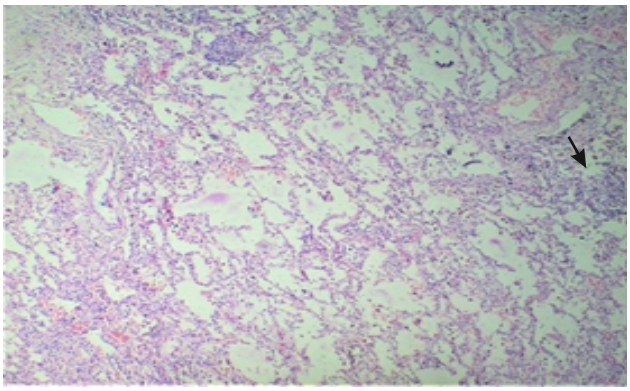


*Fig. 11: Photomicrograph illustrates non-specific interstitial pneumonia (NSIP) showing uniform alveolar septal infiltrates of lymphocytes and plasma cells with mid congestion in alveolar septa. (H&E stain, X40)*

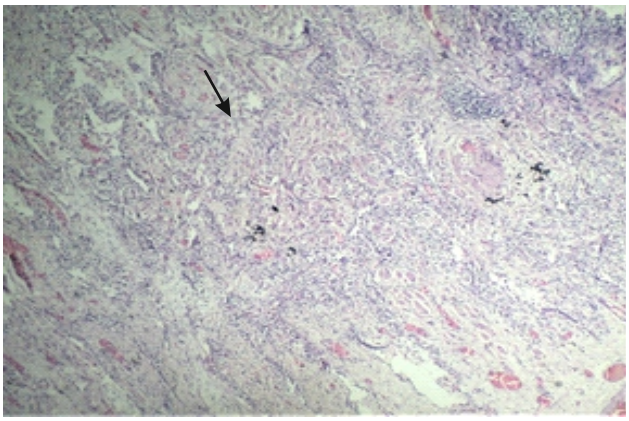


*Fig. 12: Photomicrograph illustrates organizing pneumonia, showing airway plugged with organizing exudates with surrounding inflammation and fibrosis. (H&E stain, X40)*

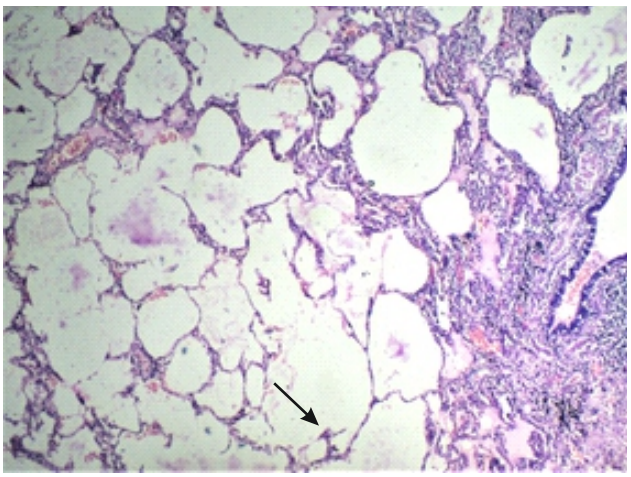
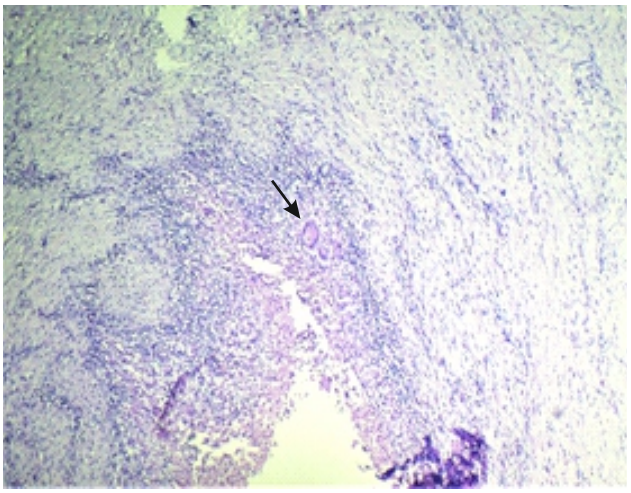


*Fig. 13. Photomicrograph illustrates emphysematous lesion showing enlarged airspaces with mild fibrotic change and inflammation*



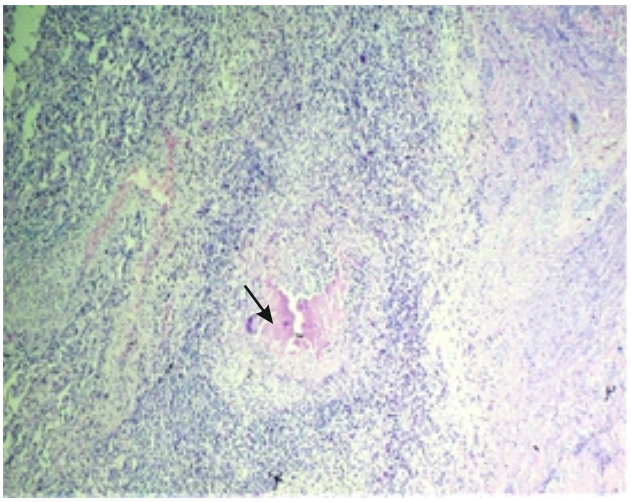


*Fig. 14-15 Photomicrograph illustrates granulomatous lesion showing well formed granuloma comprising of Langan's type of giant cells, lymphocytes, plasma cells and fibrosis. (H&E stain, X10)*

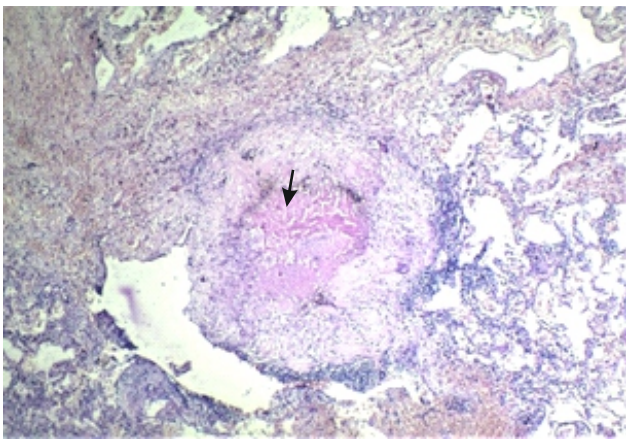
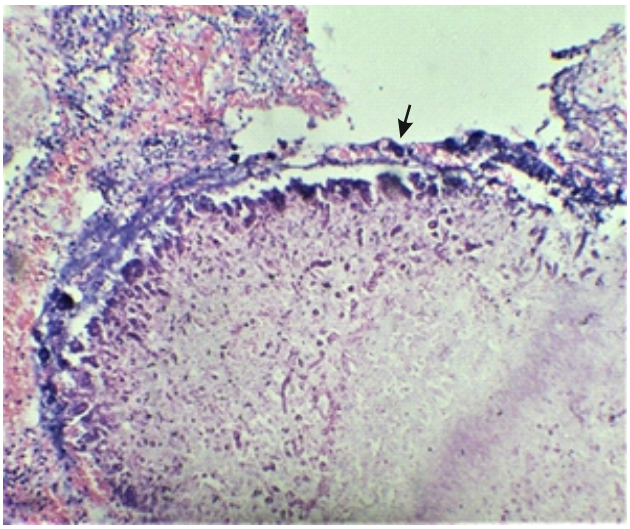


*Fig. 16: Photomicrograph Illustrates Granulomatous lesion showing Granuloma with Caseating Necrosis. (H&E stain, X10)*



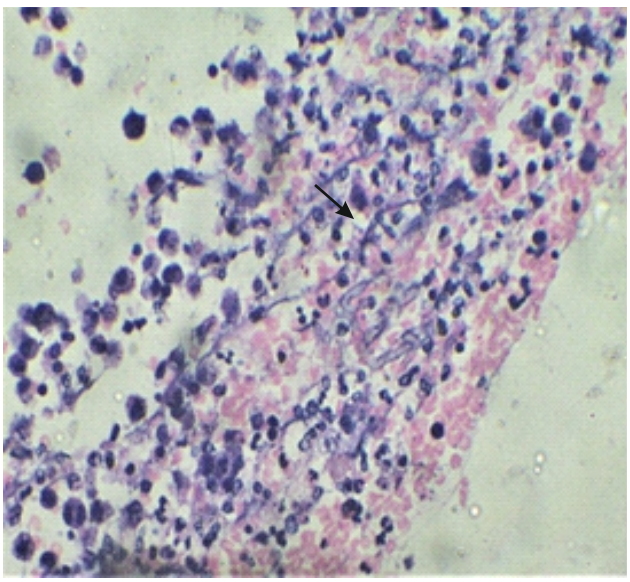


*Fig. 17, 18: Photomicrographs Illustrates Fungal Balls showing Fungal Hyphae*

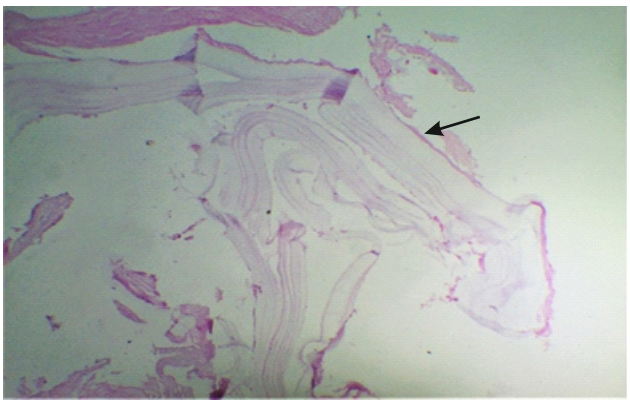


***Fig. 19: Photomicrograph shows Laminated wall of Hydatid Cyst***

## DISCUSSION

Most incidental lung parenchymal findings are under-recognized and under-reported.

The prevalence of non-neoplastic lung diseases in patients that undergo resection for mass lesions is still not well documented. We estimate the prevalence and evaluate the characteristics of parenchymal findings in patients with lung lesions, as this could potentially impact patient management and increase the awareness of these findings. Radiological findings of these non-neoplastic lesions may or may not contribute to the specific diagnosis. Their findings briefly include reticular abnormalities, diffuse centrilobular nodularity, non-dependent ground-glass abnormalities, cysts, traction bronchiectasis and honeycombing.

Over 30,000 surgical lung resections are performed annually in the United States, approximately 80–90% for malignant and 10–20% for benign lung lesions. In majority, interstitial fibrosis, granulomatous inflammation, and vasculitides are reported non-neoplastic findings that account for clinically apparent lesions in lung resections. Timely diagnosis of these conditions is crucial for appropriate post-surgical and subsequent patient management (8-10).

## FIBROSING INTERSTITIAL LUNG DISEASES: USUAL INTERSTITIAL PNEUMONIA/ IDIOPATHIC PULMONARY FIBROSIS

UIP was initially a term used to designate a pattern (e.g., UIP caused by asbestos, UIP caused by drug reaction), but eventually, after the series of Carrington *et al.* in the *New England Journal of Medicine* in 1978, UIP became recognized as a specific pattern of chronic interstitial pneumonia synonymous with IPF (11-14).

UIP/IPF is the most common of the idiopathic interstitial pneumonias, accounting for more than 60% of cases (15).

Most patients of UIP fall into a clinical category of IPF (idiopathic pulmonary fibrosis), a syndrome that classically have an insidious onset characterised by a combination of breathlessness and cough with a relentlessly progressive evolution, many of the patients dying of respiratory failure after 3-4 years.

Among the idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) is the most common, that occurs more frequently in smokers, can be correlated with the development of lung cancer, and has a median survival of 3–5 years that ultimately necessitates lung transplant as the disease progresses (16-21).

Idiopathic interstitial pneumonias are characterized by expansion of the interstitial compartment by inflammatory cells. Fibrosis, either in the form of abnormal collagen deposition or proliferation of fibroblasts capable of collagen synthesis, occurs in many cases. An important principle developed by Liebow is that pathologic classifications were histologic patterns rather than freestanding diagnostic entities, and that each could occur in a variety of clinical contexts (22-25).

## DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP) & RESPIRATORY BRONCHIOLITIS INTERSTITIAL LUNG DISEASE (RBILD)

Desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis interstitial lung disease (RBILD) are related and associated with heavy smokers with "respiratory bronchiolitis" that is an inflammatory reaction around respiratory bronchioles. It is characterised by accumulation of lightly pigmented alveolar macrophages within respiratory bronchioles spilling into neighbouring alveoli. Most affected patients are between 25 and 55 years of age, and all (by definition) are smokers. Absence of architectural distortion and temporal variegation are key features in separating DIP from UIP (26-27).

## NONSPECIFIC INTERSTITIAL PNEUMONIA

NSIP was originally used for cases that could not be classified into major categories of interstitial pneumonias. However, now considered NSIP may be idiopathic or may occur as a manifestation of systemic connective tissue diseases, hypersensitivity pneumonia, drug-induced lung disease, and chronic interstitial lung disease complicating DAD (28).

The main morphological difference of UIP is that NSIP lags heterogenous pattern of lung involvement characteristic of the former. NSIP generally has better prognosis than UIP.

## GRANULOMATOUS LESIONS

A diverse group of disorders that have a widespread of pathologies with different clinical manifestations and outcomes are granulomatous lung diseases. Granulomas appear to be a defensive mechanism that stimulates the body to "wall off" foreign invaders such as bacteria or fungi to keep them from spreading. As we know that infection is a common cause of pulmonary granulomas, it is always important to rule

out infectious lung diseases. Mycobacteria and fungi are the most commonly found organisms in pulmonary granulomas. The histochemical stains commonly used for the evaluation of infective organisms are the GMS stain for fungi and the ZN stain for Mycobacteria. The PAS stain is useful histochemical stain for fungi (29).

Generally, fever, prolonged cough, night sweats, weight loss and lymphadenopathy are suggestive of TB, but are nonspecific. The Radiological findings that are typical for TB include focal infiltration of the upper lobe(s), tissue destruction, cavitation, fibrosis with enlargement of hilar/mediastinal lymph nodes traction bronchiectasis, small nodular lesions and pleural effusions. For a specific diagnosis, detection of *Mycobacterium tuberculosis* in sputum, bronchoscopy specimens, pleural fluid or gastric secretions is essential.

Diagnosis of fungal infection is made predominantly by serological rather than histological examination. Sporadically, fungal organisms persist in a well-formed necrotising granuloma, similar to TB (*e.g., Cryptococcus, Coccidioides* and *Histoplasma*). Fungal infection infrequently progresses, resulting in chronic fungal lung disease. The manifestation of this form of pathology consists of complicated necrotising granulomas combined with underlying predisposing diseases (*e.g.,* emphysema and cavities) (30-32).

Histological picture is determined by necrotizing granulomas containing *Aspergillus* hyphae. The granulomas may cause extensive parenchymal consolidation or it may lead to bronchiectatic cavities or may be entirely bronchocentric.

## CONCLUSION

This study concludes that the most common non neoplastic lung lesions include UIP, followed by SRIF and Granulomatous lesions amongst the cases that were studied.

The retrospective nature of the study, lack of consistent follow-up and unavailability of pulmonary function tests are the major limitations of the study. This is a complex group of non-neoplastic pulmonary diseases that often require correlation of morphology, clinical and radiological findings. Our results, however, support the judicious use of subspecialty consultation, increased education regarding relevant parenchymal findings, a multidisciplinary diagnostic approach with utmost extensive sampling of non-neoplastic parenchyma to improve diagnostic and clinical outcomes.

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