

ABSTRACT

Diffuse parenchymal lung diseases (DPLD) constitute a group of over 200 diverse etiologic entities which present with respiratory symptoms and diffuse lung infiltrates. Flexible bronchoscopy is a useful tool for the early diagnosis of DPLD so that definitive treatment can be instituted and long term outcomes are improved. In immune compromised patients presenting with DPLD, Bronchoalveolar lavage analysis is helpful in establishing diagnosis of infections. Bronchoscopic lung biopsy has a high yield in certain DPLD such as Sarcoidosis, Hypersensitivity pneumonitis, Organizing pneumonias, Eosinophilic pneumonias and Pulmonary alveolar proteinosis. Bronchoscopic biopsy can help in making clinical decisions in majority of DPLD by excluding differential diagnosis such as infections and malignancy.

INTRODUCTION

Diffuse parenchymal lung diseases (DPLD) constitute a group of over 200 diverse etiologic entities (listed in table 1) which present with respiratory symptoms and diffuse lung infiltrates and account for 15% of patients seen by a pulmonary physician.¹ Bronchoscopy is an important tool in the practice of Pulmonary Medicine in the era of Evidence based medicine. Flexible bronchoscopy gives easy access to respiratory samples for cytological studies and lung tissue for histopathology in DPLD. Lung biopsy studies have unravelled the complex cellular and molecular events in pathogenesis of various types of interstitial lung diseases and have led to development of novel therapeutic agents for idiopathic pulmonary fibrosis.² Over the last five decades, greater awareness and easy availability of CT thorax and fiberoptic bronchoscopy has led to diagnosis of diseases such as sarcoidosis, which were earlier considered to be rare in our country.³

While dealing with DPLD, the aim is to make early diagnosis for institution of definitive treatment and improvement in long term outcomes. The focus of this chapter would be on immense impact that flexible bronchoscopy has made on the diagnosis of DPLD.

BRONCHOSCOPY IN DPLD

Till the development of fiberoptic bronchoscope by Prof Shigeto Ikeda in 1966 treatment of diffuse lung diseases was largely empirical and rigid bronchoscopy was done only in selected cases. First trans-bronchial lung biopsy was obtained through rigid bronchoscopy under general anaesthesia in 1965 and being cumbersome it was infrequently done. Flexible bronchoscopy has

revolutionized the practice of pulmonary medicine over the last five decades by providing access to lower respiratory tract in a minimally invasive manner. With better equipment and training in bronchoscopy, expertise of pulmonologists in doing bronchoscopic lung biopsy has increased and complications are very few. As a result, TBLB is the most common lung biopsy submitted for evaluation of DPLD.^{2,4}

Using flexible bronchoscope under local anaesthesia with or without sedation, various lower respiratory cytology and tissue samples can be obtained for diagnosis of DPLD. These include Bronchoalveolar lavage fluid (BAL), bronchial brushings, endo-bronchial biopsy (EBB), bronchoscopic lung biopsy (BLB) and transbronchial needle aspiration (TBNA) of mediastinal lymph nodes, TBNA with endobronchial ultrasound bronchoscope (EBUS-TBNA). Often in patients with DPLD such as Sarcoidosis and Tuberculosis most or all of the above samples are obtained in the same sitting to increase the diagnostic yield by adding microbiological and molecular tests and saving precious time for diagnosis.

BRONCHOALVEOLAR LAVAGE (BAL)

BAL sample is obtained by wedging the bronchoscope in the segment of maximum radiological abnormality and instilling aliquots of sterile saline (total 100-150 ml) followed by aspiration into a sterile chamber. BAL fluid appearance is helpful for the diagnosis of certain DPLD. Appearance of uniformly hemorrhagic BAL fluid (Figure 1) suggests diffuse alveolar hemorrhage in appropriate settings. Milky BAL (Figure 2) is characteristic of pulmonary alveolar proteinosis. Floating oily layer on top of BAL fluid is suggestive of lipoid pneumonia. BAL cytology and cellular subtype analysis is helpful in various pulmonary diseases (listed in Table 2). BAL flow cytometry for CD1a positive cells >5% confirms the diagnosis of Pulmonary Langerhans' cell histiocytosis.⁵

BAL fluid sample can be subjected to many microbiological tests including special stains (eg Grams, ZN, PAS, Grocott stains), appropriate cultures (bacterial, fungal, mycobacterial) and molecular testing (eg PCR for mycobacterium tuberculosis, fungal, Pneumocystis jirovecii, CMV etc). The yield of BAL is high (70-80%) in patients with infectious causes of DPLD especially in Immuno-compromised hosts such as post chemotherapy neutropenia, post bone marrow transplantation, solid organ transplant recipients and HIV infection.⁶

Table 1: Classification of DPLD

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| 1. Idiopathic Interstitial Pneumonias (IIP) : | e. Sjogren's syndrome |
| a. Usual Interstitial Pneumonia (UIP) -Idiopathic pulmonary fibrosis (IPF) | f. Mixed connective tissue disease |
| b. Non UIP IIP: | g. Overlap syndrome |
| i. Non-specific Interstitial Pneumonia (NSIP) | 7. Drug induced DPLD: |
| ii. Desquamative Interstitial Pneumonia (DIP) | a. Amiodarone |
| iii. Cryptogenic organizing pneumonia (COP) | b. Methotrexate |
| iv. Lymphocytic Interstitial Pneumonia (LIP) | c. Nitrofurantoin |
| v. Acute Interstitial Pneumonia (AIP) | d. Chemotherapeutic drugs (Bleomycin, Busulfan, Paclitaxel, Gemcitabine) |
| vi. Respiratory bronchiolitis- interstitial lung disease (RB-ILD) | 8. Diffuse alveolar hemorrhage with or without vasculitis : |
| 2. Granulomatous DPLD: | a. Granulomatosis polyangitis or Wegener's granulomatosis |
| a. Pulmonary Sarcoidosis | b. Microscopic polyangitis |
| b. Hypersensitivity pneumonitis (Farmer's lung, Bird fancier's lung etc) | c. Allergic angitis& granulomatosis (Churg Strauss syndrome) |
| 3. Occupational DPLD: | d. Systemic lupus erythematosus (SLE) |
| a. Silicosis | e. Good Pasture's syndrome (Anti Glomerular basement membrane disease) |
| b. Coal workers pneumoconiosis | f. IgA mediated lung disease |
| c. Asbestosis | g. Idiopathic pulmonary hemosiderosis (IPH) |
| 4. Infectious DPLD: | 9. Rare DPLD: |
| a. Miliary Tuberculosis | a. Lymphangioleiomyomatosis (LAM), |
| b. Fungal : Histoplasmosis, Aspergillosis, Candidiasis | b. Pulmonary Langerhans cell histiocytosis (PLCH), |
| c. Viral pneumonias: CMV, Influenza | c. Inherited ILD (Tuberous Sclerosis, Neurofibromatosis) |
| d. Pneumocystis jerevecii pneumonia | 10. Neoplastic DPLD: |
| 5. Eosinophilic DPLD : | a. Lymphangitis carcinomatosis |
| a. Tropical pulmonary eosinophilia (TPE) | b. Miliary metastasis |
| b. Acute eosinophilic pneumonia | c. Radiation pneumonitis |
| c. Chronic eosinophilic pneumonia | 11. Miscellaneous DPLD: |
| d. Allergic bronchopulmonary aspergillosis (ABPA) | a. Pulmonary alveolar proteinosis |
| 6. Connective tissue diseases with DPLD: | b. Alveolar microlithiasis |
| a. Systemic Lupus Erythematosus | c. Mitral stenosis with pulmonary hemosiderosis |
| b. Progressive systemic sclerosis | d. Pulmonary veno-occlusive disease (PVOD) |
| c. Polymyositis – dermatomyositis | e. Pulmonary capillary hemangiomatosis (PCH) |
| d. Rheumatoid arthritis | |

BRONCHOSCOPIC LUNG BIOPSY (BLB)

The distribution of lesions in lung parenchyma has an impact on the yield of lung biopsy in DPLD. The yield of BLB is high in diseases where the lesions are peri-bronchial in distribution such as in Sarcoidosis, hypersensitivity pneumonitis and organizing pneumonias. The yield of BLB is also high in diseases which have easily identifiable pattern such as eosinophilic pneumonias pulmonary

alveolar proteinosis and diffuse alveolar hemorrhage. Ensminger et al found the information from bronchoscopic lung biopsy to be immensely useful in clinical decision making in almost 75% of their cases by excluding other differential diagnosis as infections and malignancy.⁷ BLB is a safe procedure for making the diagnosis in miliary tuberculosis, with 67% cases showing granulomatous lung lesions.⁸

Table 2: Analysis of BAL cytology in DPLD

Predominant BAL Cells	Lymphocyte > 25%	Neutrophils > 50%	Eosinophils > 25%
Diseases	Tuberculosis	IPF	TPE
	Sarcoidosis	Pneumonia	Drugs induced
	Hypersensitivity pneumonitis	ARDS	Eosinophilic Pneumonias
	CTD related ILD	AIP	Churg Strauss syndrome
	Organizing pneumonia		Hypereosinophilic syndrome

Table 3: Contraindications for BLB

1. Advanced interstitial lung disease with respiratory failure and /or pulmonary hypertension
2. Cardiovascular diseases: Unstable angina, acute myocardial infarction (< 6 weeks), heart failure
3. Recent or ongoing exacerbation of DPLD or recent pneumonia (<6 weeks)
4. Severe hypoxemia : PaO₂ < 75 mmHg on oxygen (Venturi mask FiO₂=0.5)
5. Coagulopathy (INR 1.5, PTTK > 1.5 times control)
6. Thrombocytopenia (platelet count < 1 lakh/uL)
7. Renal failure (Serum creatinine > 3.5 mg/dl)

On the flip side, BLB has a very poor yield in idiopathic interstitial lung diseases especially in Idiopathic Pulmonary Fibrosis (IPF) and fibrotic Nonspecific Interstitial Pneumonia (NSIP) and Desquamative interstitial pneumonias (DIP). Due to small size of BLB tissue, classical findings of UIP such as spatial and temporal heterogeneity of inflammation, fibroblastic foci and honeycombing cannot be recognized and there are large inter-observer variations in interpretation among pathologists. Current guidelines recommend surgical lung biopsy (SLB) for accurate diagnosis in these diseases.⁹

Bronchoscopic cryo-biopsy is an exciting addition to the armamentarium of the pulmonologist in the last few years. The use of cryobiopsy resulted in larger lung biopsy (mean size 1-2 cm), had greater diagnostic yield 70-80% and reduced the need for SLB in idiopathic ILD to 1.2%.¹⁰ In view of larger biopsy there is increased risk of bleeding and pneumothorax following cryobiopsy in 2-4% cases and patients need to be observed. The initial encouraging results of cryobiopsy need to be compared with SLB in idiopathic ILD in larger randomized trials.

ENDO-BRONCHIAL BIOPSY (EBB)

In cases of pulmonary sarcoidosis, bronchial mucosal infiltration, nodularity and erythema may be present and bronchial biopsies are positive in 35-50 %. Even when bronchial mucosa is normal in appearance, bronchial biopsy may show classical non caseating granulomas and must be done in all cases.

MULTIPRONGED APPROACH IN DPLD

A recent meta-analysis shows the yield of sarcoidosis in BLB is 68% and EBB is 49% when used singly but

**Fig. 1: Hemorrhagic BAL in alveolar hemorrhage****Fig. 2: Milky BAL in Pulmonary alveolar proteinosis**

goes up to 81.4% when both are combined together. The yield increases to 86.9% when BLB and EBB are combined with transbronchial needle aspiration (TBNA) of hilar and mediastinal lymph nodes. Endobronchial ultrasound guidance bronchoscopy (EBUS-TBNA) improves sensitivity over conventional TBNA from 22% to 57%. When conventional TBNA is combined with BLB + EBB the diagnostic yield is equivalent to EBUS TBNA

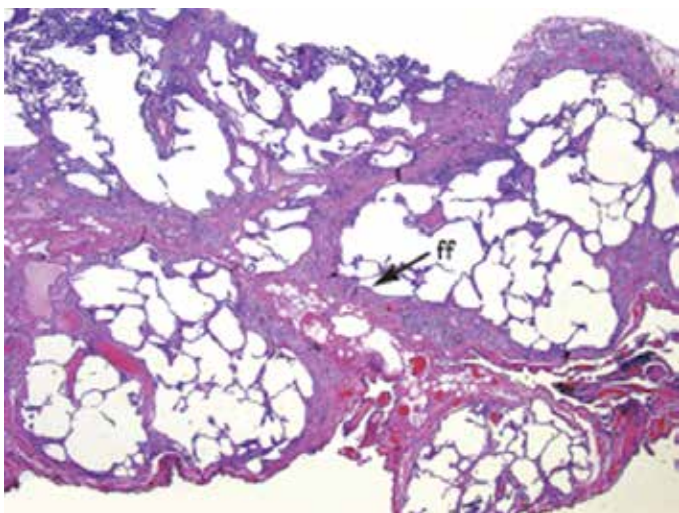


Fig. 3: Usual Interstitial pneumonia

combined with BLB +EBB, 86.9 vs 86.4%. Therefore, using the multipronged approach doing TBNA, EBB and BLB using conventional bronchoscopy in same sitting, majority of sarcoidosis can be diagnosed.¹¹

SURGICAL LUNG BIOPSY IN DPLD

Many pathologists consider bronchoscopic lung biopsy to be unsuitable in idiopathic pulmonary fibrosis and Non-specific interstitial pneumonia. Problems with BLB are that samples may not be from representative area of disease and small tissue size. As a result, pathologists are not able to pick up the classical findings to make confident diagnosis. Surgical lung biopsy (SLB) is the gold standard till date for diagnosis of IPF and NSIP.⁹ Adequate lung tissue samples from multiple lobes can be obtained by mini thoracotomy or video-assisted thoracoscopic lung surgery (VATS) under general anesthesia. The invasive nature and morbidity of open lung biopsy causes hesitation among patients and are reasons for SLB being done rarely in DPLD. But SLB has definite role in DPLD especially if BLB is contraindicated or is unsuccessful in arriving at the diagnosis. In patients with contraindications for bronchoscopy (Table 3) option of SLB should be discussed. For example Miliary sarcoidosis with severe hypoxemia on mechanical ventilation, should be taken up for surgical lung biopsy as the risks of BLB are higher and with specific diagnosis appropriate treatment can be instituted which may be life-saving.

Overall SLB has high yield over 95 % but carries average mortality of 1-3%, median mortality 4-6% at 30 days which may be as high as 28% in acute exacerbation of IPF and morbidity of 5–20% in various series.¹² At present, with greater emphasis on cosmesis and minimal access surgery, VATS lung biopsy is the preferred method wherever available. VATS lung biopsy has less morbidity, shorter hospital stay and lesser costs.

CLINICIAN-RADIOLOGIST-PATHOLOGIST INTERACTION

In every case of DPLD, the clinician must take into account various factors as presentation of illness (acute, subacute or chronic), radiological pattern and clinical background

to arrive at the diagnosis. The chest radiographs may be normal in 10% of DPLD especially in early phase of illness. High resolution CT chest is imaging of choice in DPLD and shows extent and patterns of involvement to narrow down the differential diagnosis and site of lung biopsy.¹² Biopsy samples must be taken from sites of maximum ground glass opacity, nodularity or interstitial fibrosis. Also biopsy must be taken from relatively normal looking adjacent lungs.

Relevant clinical and epidemiological data must be provided to the pathologist at the time of lung biopsy to help them in analysis. These should include age, gender, duration of illness, occupational exposure (silicosis, asbestosis), recreational exposure (eg bird keepers), immune status of the patient, prior drug use (amiodarone, chemotherapy), radiological picture and clinical diagnosis suspected (eg Connective tissue disease ILD etc).

Bronchoscopic lung biopsies clinch the diagnosis in a few DPLD as in Sarcoidosis, Organizing pneumonia, pulmonary alveolar proteinosis, Eosinophilic pneumonias and hypersensitivity pneumonitis. More often BLB shows abnormal patterns which may be seen in several diseases which cause diffuse involvement of the lungs.¹⁴ This pattern based diagnostic approach needs close coordination between the clinician, pathologist and radiologist for arriving at the correct diagnosis.

Histopathological patterns on BLB can be broadly of following types¹⁴

1. Cellular Interstitial pneumonias (acute)
2. Fibrotic interstitial pneumonia (chronic)
3. Granulomatous lesions: Sarcoidosis, Tuberculosis
4. Eosinophilic pneumonias
5. Organizing pneumonia
6. Specific diagnosis: malignancy/alveolar proteinosis/alveolar hemorrhage
7. Normal lung tissue
8. Inadequate lung biopsy (less than 20 alveoli in the lung biopsy)

In the succeeding paragraphs a few cases of DPLD seen at our centre are discussed with histopathological photomicrographs to make the reader aware of the dilemma faced by the pulmonary physician and pathologists.

Usual Interstitial Pneumonia (UIP)

Histopathological pattern seen in idiopathic pulmonary fibrosis (IPF). There is sub-pleural interstitial fibrosis with loss of lung architecture with or without honey combing. Key pathologic features of UIP are spatial and temporal heterogeneity of the lesions and presence of fibroblastic foci (FF) of varying ages interspersed with normal areas (Figure 3). UIP pattern may be seen in other diseases as Chronic hypersensitivity pneumonitis, Pneumoconiosis, Rheumatoid arthritis ILD and Amiodarone induced lung

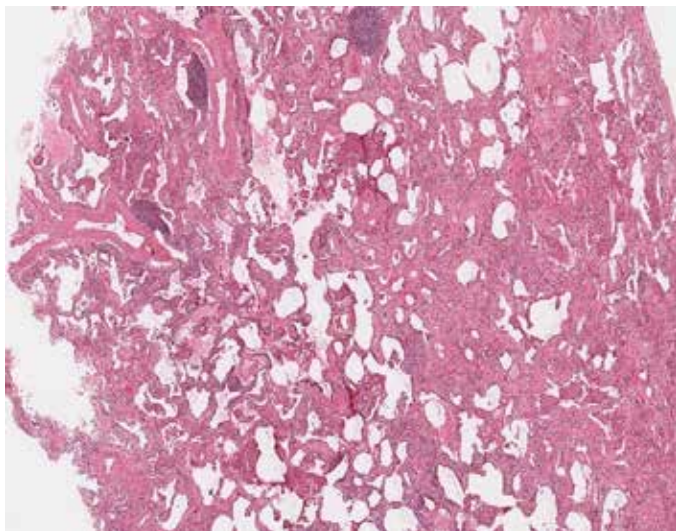


Fig. 4: Nonspecific Interstitial pneumonia

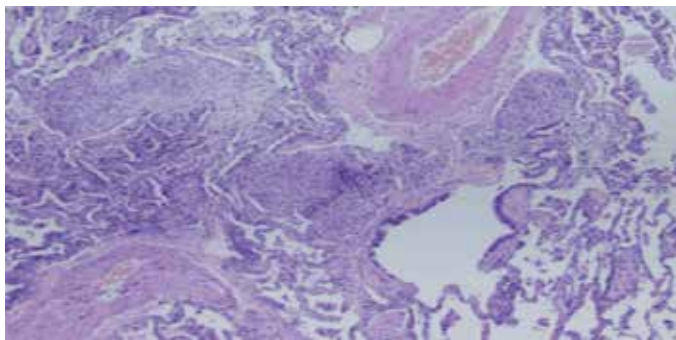


Fig. 5: Organizing pneumonia pattern in case of drug induced ILD

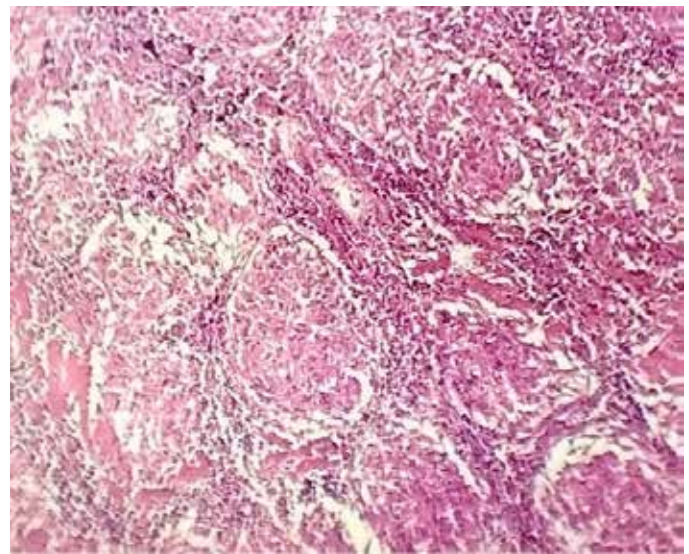


Fig. 6: Pulmonary sarcoidosis

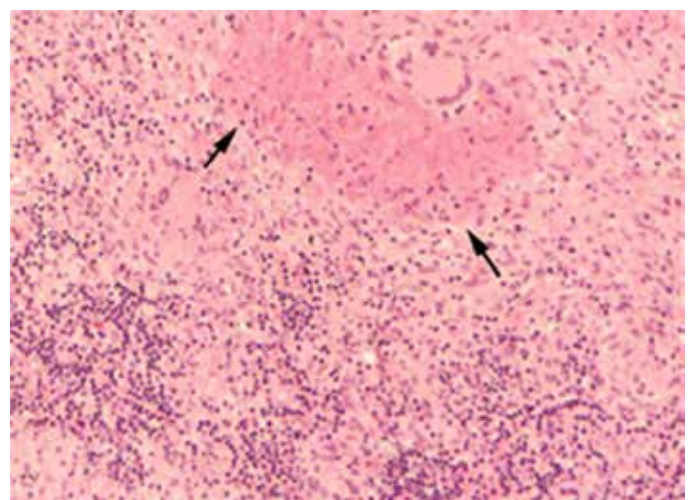


Fig. 7: Tubercular Granuloma

fibrosis. These alternative causes of UIP must be excluded by in depth history and relevant investigations as they have much better prognosis than IPF.

Nonspecific Interstitial Pneumonia (NSIP)

Idiopathic NSIP now a distinct entity, has diffuse and temporally homogenous interstitial inflammation with or without fibrosis (Figure 4). Two patterns of NSIP are seen. Cellular NSIP, when chronic inflammatory cells predominate in the alveoli and interstitium. Fibrotic NSIP when fibrosis involves the lung diffusely. Unlike UIP, fibroblastic foci and honeycombing are rare findings and disease is homogeneous in lungs. NSIP may be caused by connective tissue diseases or drugs and relevant investigations are required to be done. Most patients with idiopathic NSIP have a good response to treatment with glucocorticoids. The 5 year mortality rate is estimated to be 10 to 15 percent as compared to IPF which has mortality of 75-80% at 5 years.

Organizing Pneumonias (OP)

Earlier called as bronchiolitis obliterans organizing pneumonia (BOOP). If no secondary cause is found, cryptogenic organizing pneumonia is diagnosed. Secondary causes of OP include viral infections, mycoplasma pneumonia, drug reaction (Figure 5), connective tissue disease and post bone marrow transplantation. Numerous buds of granulation tissue are

seen within alveoli which may extend to alveolar ducts and small airways. Later on these can be replaced by fibrotic changes. The cases with OP show good steroid response if initiated early in the illness.

Granulomatous Lesions

Tuberculosis and Sarcoidosis are the common DPLD with this pattern. The lesions in Sarcoidosis are peribronchovascular and peri-lymphatic in distribution hence yield of BLB is good. There are non-caseating compact granulomas with or without fibrosis. Sarcoid granulomas (Figure 6) are generally non-necrotic and are naked without inflammatory cellular ring around the lesions. Tubercular lesions favour the upper lobes in lungs and may show cavity or miliary pattern. TB granulomas have caseation necrosis and may show acid fast bacilli on ZN stain (Figure 7). Other Granulomatous lesions in lungs include fungal infections, Hypersensitivity pneumonitis, Granulomatosis with polyangiitis (Wegener's) Churg-Strauss syndrome and Hodgkin's lymphomas.

Eosinophilic Pneumonias

Variety of diseases can cause EP. Tropical pulmonary eosinophilia is a common DPLD associated with filarial

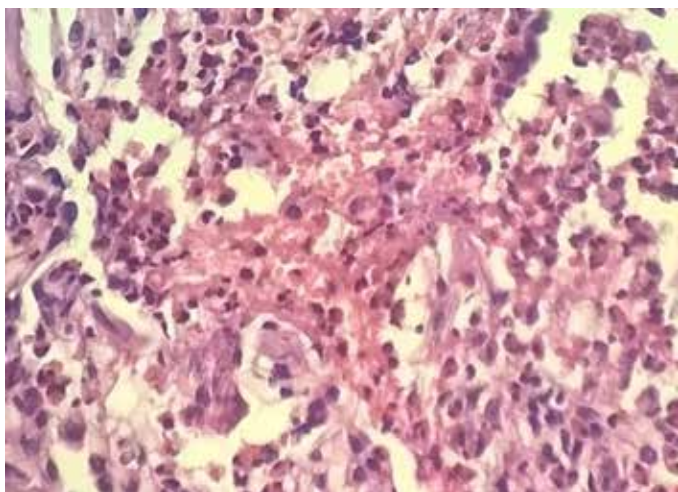


Fig. 8: Tropical pulmonary eosinophilia

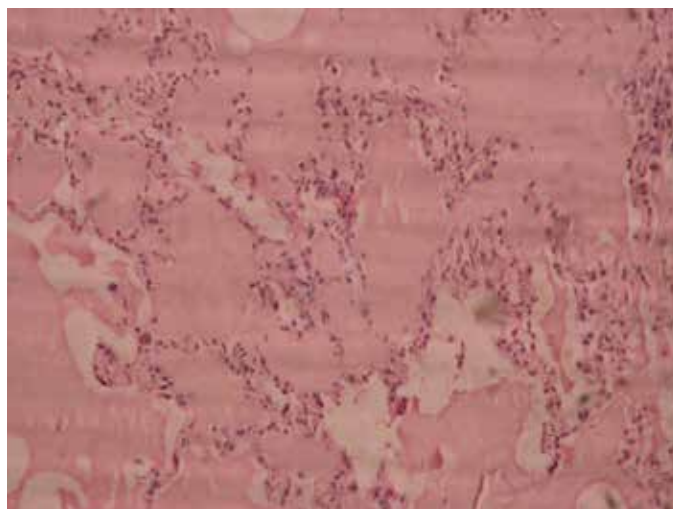


Fig. 9: Pulmonary alveolar proteinosis

infection and is characterized by peripheral blood eosinophilia and BAL eosinophilia > 25 %. It is seen in residents of coastal India and Eastern states of India. BLB (Figure 8) shows intense eosinophilic infiltration of interstitium with other chronic inflammatory cells. They recover with treatment with Diethylcarbamazine over 4-6 weeks. If left untreated it results in significant residual fibrosis and loss of lung functions.

Pulmonary Alveolar Proteinosis

Rare DPLD which results from defective surfactant metabolism in alveoli due to anti GMCSF antibodies. HRCT chest shows crazy pavement pattern which is a combination of diffuse ground glass opacity superimposed on smooth interlobular septal thickening. BAL shows amorphous pink appearance with PAS positive material. The BLB is usually diagnostic, showing alveoli filled with acellular pink surfactant material which is PAS positive. There is complete absence of alveolar inflammation in PAP (Figure 9).

CONCLUSIONS

Flexible bronchoscopy is an important tool for making early diagnosis of DPLD. Bronchoalveolar fluid analysis is useful in establishing diagnosis of infections in immune compromised hosts with DPLD. Bronchoscopic lung biopsy has a high yield in DPLD such as Sarcoidosis, hypersensitivity pneumonitis, organizing pneumonias, eosinophilic pneumonias and pulmonary alveolar proteinosis. Small samples of BLB make it unpopular with pathologist in diseases like Idiopathic pulmonary fibrosis and Nonspecific interstitial pneumonia and surgical lung biopsy is considered gold standard at present. Bronchoscopic cryobiopsy may overcome these limitations and needs to be compared with SLB in randomized trials.

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