Original Article

Role of a Pattern-based Approach in Interpretation of Transbronchoscopic Lung Biopsy and Its Clinical Implications

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ABSTRACT

Background. Transbronchial lung biopsy (TBLB) is commonly performed for confirming the tissue diagnosis of diffuse parenchymal lung diseases (DPLDs). There is an urgent need to establish guidelines for interpretation of TBLB in order to improve its diagnostic utility.

Methods. We retrospectively studied 916 consecutive patients (494 males; mean age 49 years) who underwent TBLB over a 5-year period (July 2005 to July 2010) at Vallabhbhai Patel Chest Institute.

Results. In 615 (67.1%) procedures, material obtained during TBLB was adequate for histopathology interpretation. Pathological features evaluated in each case were: alveolar architecture, inflammatory infiltrate, interstitial fibrosis, atypical cells, pigment deposition, honey-comb change and fibroblast foci. The cases were categorised on the basis of histopathology into six patterns: (1) adequate biopsy without a specific diagnostic abnormality (n=137, 22.3%); (2) acute pneumonitis (n=29, 4.7%); (3) neoplasia (n=109, 17.7%); (4) chronic interstitial inflammation with or without fibrosis (n=138, 22.4%); (5) granulomatous inflammation, (n=186, 30.2%); and (6) other specific causes (n=16, 2.6%). Definitive diagnosis could be made after correlation of TBLB histopathology with clinical and radiological features in 55.3% cases.

Conclusions. TBLB appears to be an important diagnostic tool for the diagnosis of DPLDs. The use of a pattern-based approach to TBLB adds to its diagnostic yield and can be helpful in cases where open lung biopsy is not available.
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Key words: TBLB, Diffuse lung disease, Histopathological patterns.

INTRODUCTION

Transbronchial lung biopsy (TBLB) is often employed in the diagnosis of diffuse parenchymal lung diseases (DPLDs). Due to the high morbidity associated with and the non-availability of open lung biopsy (OLB) in many centres, high resolution computed tomography (HRCT) followed by TBLB continue to remain the mainstay of diagnosis of DPLDs. The small size of TBLB specimen makes it a "histopathologist's nightmare", leading to difficulty in categorisation within the spectrum of DPLDs. Therefore, TBLB is considered by some as an 'ailing gold standard' and is utilised only to exclude diseases, such as, sarcoidosis, lymphangitis carcinomatosis, infection, etc. There is a need for systematic categorisation of the histopathological patterns identified on TBLB for increasing the diagnostic yield and their rigorous correlation with clinical and radiological features for confirming the diagnosis accurately. The present study was undertaken to evaluate the histopathological patterns identified on TBLB and the clinical usefulness of TBLB in the diagnosis of patients with DPLDs presenting to a tertiary care pulmonary centre in North India.

MATERIAL AND METHODS

We retrospectively analysed records of 916 patients who underwent TBLB at the Vallabhbhai Patel Chest Institute over a 5-year period from July 2005 to July 2010. All specimens were stained with haematoxylin-eosin stain; special stains for reticulin and collagen; Gomori silver methenamine; and Masson Trichrome stains. Periodic acid-Schiff stain, Gomori silver methenamine stain, Gram's stain, Ziehl-Neelsen stain (Z-N) were done to rule out infection. Treatment history was obtained to rule out drug-toxicity.

The number of pieces of alveolated lung parenchyma and bronchial wall were recorded. The

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TBLB was considered to be adequately alveolated if more than 20 alveoli were seen. Pathologic features evaluated in each adequate biopsy were: alveolar architecture, inflammatory infiltrate, granulomatous inflammation, atypical cells, interstitial fibrosis, fibroblast foci, vasculopathy, pigment deposition, and honey-comb change. The adequate biopsies were further categorised on the basis of the histo-pathological patterns into six patterns (Figure 1): adequate biopsy without a specific diagnostic abnormality (pattern 1); acute pneumonitis (pattern 2); neoplasia (pattern 3); chronic interstitial inflammation with or without fibrosis (pattern 4); granulomatous inflammation (pattern 5); and other specific causes (pattern 6).

The cases with chronic interstitial inflammation with or without fibrosis (pattern 4) were further categorised into non-specific interstitial pneumonitis (NSIP), desquamative interstitial pneumonitis (DIP), lipoid interstitial pneumonia (LIP), usual interstitial pneumonia (UIP)-like patterns on the basis of pathological features, which included the anatomic compartment of involvement, the nature of cellular infiltrates, distortion of alveolar architecture, presence of fibroblastic foci and fibrosis and microscopic honey-combing. History of occupational exposure and polarisation for identifying dusts/ birefringent particles was obtained in all cases. All the cases were then correlated clinically and radiologically to assess the relevance of the pathological diagnosis offered on TBLB.

In cases with granulomatous inflammation (pattern 5), the granulomas were categorised on the basis of their location (subepithelial or interstitial), presence or absence of; necrosis, multinucleated giant cells (Langhans', foreign body type), intracytoplasmic inclusions (Schaumann body, crystals), acid-fast bacilli (AFB) and reticulin staining patterns.

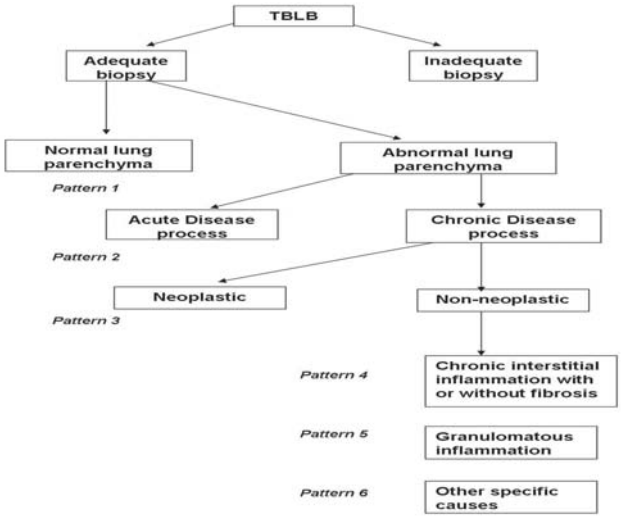

Figure 1. Pattern-based categorisation on transbronchial lung biopsy. (*Based on reference 1*)

RESULTS

Nine hundred and sixteen patients underwent TBLB (494 males; mean age 49 years range 13 to 83 years). An average of four TBLB samples (range 2-6) were obtained from each patient. On gross examination, biopsy size varied from 0.1cm to 0.3cm. The size of the biopsy was not found to correlate with the alveolar content. In general, the larger biopsy specimens were found to be more likely to contain diagnostic tissue. In patients with suspected sarcoidosis, endo-bronchial biopsy samples were additionally obtained. Satisfactory specimens enabling tissue diagnosis were obtained in 615 (67.1%) cases. These biopsies were further categorised on the basis of the histopathological critera[1] into six patterns (Table 1): granulomatous inflammation (pattern 5) (n=186, 30.2%) was the most common followed by interstitial pneumonitis with or without fibrosis (pattern 4) (n=138, 22.4%) and neoplasia (pattern 3) (n=109, 17.7%). Definitive diagnosis could be made on correlation of TBLB histopathology with clinical and radiological features in 55.3% cases. In 301 (32.9%) biopsies, TBLB tissue was inadequate and the condition remained undiagnosed after TBLB.

Table 1. Pattern based categorisation of histopathological diagnosis on TBLB (n=615)

Pattern	Histopathological Diagnosis	No. (%)
1	Normal lung parenchyma	137 (22.3)
2	Acute pneumonitis	29 (4.7)
3	Neoplasia	109 (17.7)
4	Chronic interstitial inflammation with or without fibrosis	138 (22.4)
5	Granulomatous inflammation	186 (30.2)
6	Other specific causes	16 (2.6)

TBLB=Transbronchial lung biopsy

In the cases with acute lung injury (pattern 2), the presence or absence of hyaline membranes, nature of cellular infiltrates, foci of organising pneumonia (loose fibroblastic proliferation with scattered inflammatory cells and minimal collagen deposition within the interstitium and focally in the alveolar spaces) and type II epithelial cell hyperplasia were noted (Figures 2A and 2B). Clinical correlation revealed non-resolving pneumonia with consolidation; lung opacities with or without cavity formation; and reticulo-nodular opacities suggestive of interstitial lung disease (ILD) to be the three most common clinical-radiological presentations. One case each of actinomycetes and botryomycetes and two cases of nocardiosis were identified. A diagnosis of eosinophilic pneumonia, a histopathologic subtype of acute lung injury, characterised by the triad of reactive type II hyperplasia, eosinophils in alveolar spaces accompanied by densely eosinophilic macrophages and variable amount of fibrin[2,3] was

made in 4% cases. In one case with bronchial asthma, the presence of eosinophilic pneumonitis with vasculitis was suggestive of Churg-Strauss syndrome.

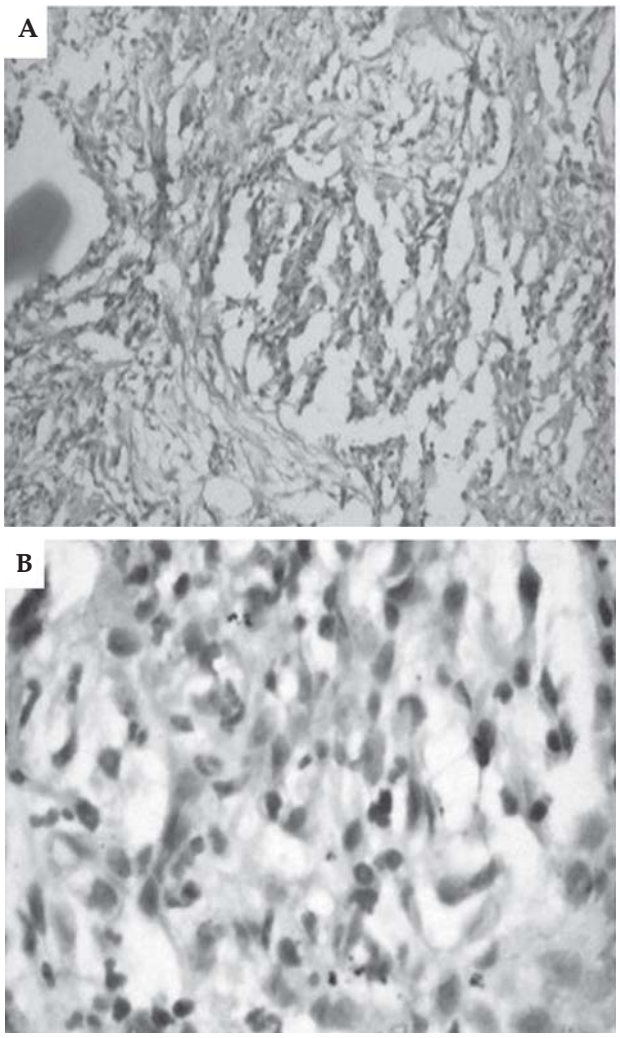

Figure 2. Acute pneumonitis (*Pattern 2*). Photomicrograph showing (A) acute neutrophilic parenchymal infiltrate leading to loss of alveolar architecture (Haematoxylin and eosin×40); and (B) high power view of the same (Haematoxylin and eosin×400).

Neoplasias (pattern 3) were clinically suspected and sampled by TBLB in 143 cases (15.6%). In 109 of these 143 cases (76.2%), the neoplastic tissue was adequately sampled and the diagnosis of carcinoma was confirmed (Table 2).

Table 2. Neoplasia (n=109) identified by TBLB

Type of Neoplasia	No. (%)
Squamous cell carcinoma	66 (60.5)
Adenocarcinoma	14 (12.8)
Small cell carcinoma	14 (12.8)
Large cell undifferentiated carcinoma	11 (10.1)
Carcinoid tumour	02 (1.8)
Lymphangitis carcinomatosa	02 (1.8)

TBLB=Transbronchial lung biopsy

Squamous cell carcinomas were the most common tumours and accounted for 66 cases (60.5%) (Figures 3A, 3B and 3C). Small-cell carcinoma lung (n=14, 12.8%); adenocarcinoma (n=14, 12.8%); large cell undifferentiated carcinoma (n=11, 10.1%); 2 cases (1.8%) each of carcinoid

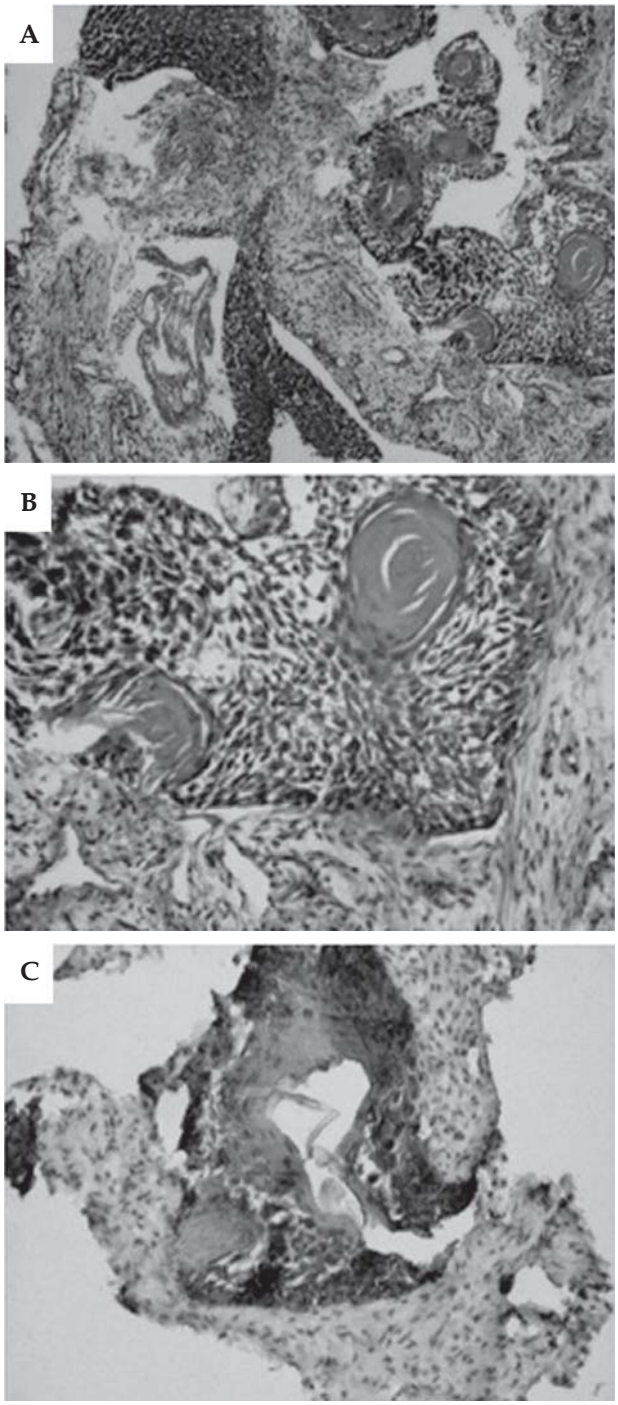

Figure 3. Neoplasia (*Pattern 3*). Photomicrograph showing (A) well-differentiated squamous cell carcinoma (Haematoxylin and eosin×40); (B) high power view of the same (Haematoxylin and eosin×200); and (C) pancytokeratin positivity on immunohistochemistry in the same specimen (IHC×100).

tumour and lymphangitis carcinomatosa were indentified. Out of 143 cases, TBLB was inadequate in 34 (23.8%) for opinion due to following causes: (a) superficial biopsy taken because of increased vascularity and bleeding tendency; (b) mass lesion obstructing passage of bronchoscope; and (c) sampling of the periphery of the lesion showing pneumonitis with or without overlying epithelial dysplasia and/or carcinoma *in-situ*.

Among the cases of chronic interstitial inflammation with or without fibrosis (22.4%, pattern 4) (Figures 4A, 4B, 4C, 4D, 4E and 4F), NSIP-like pattern with and without fibrosis was the most common seen in 110 (79.7%) of the 138 cases.

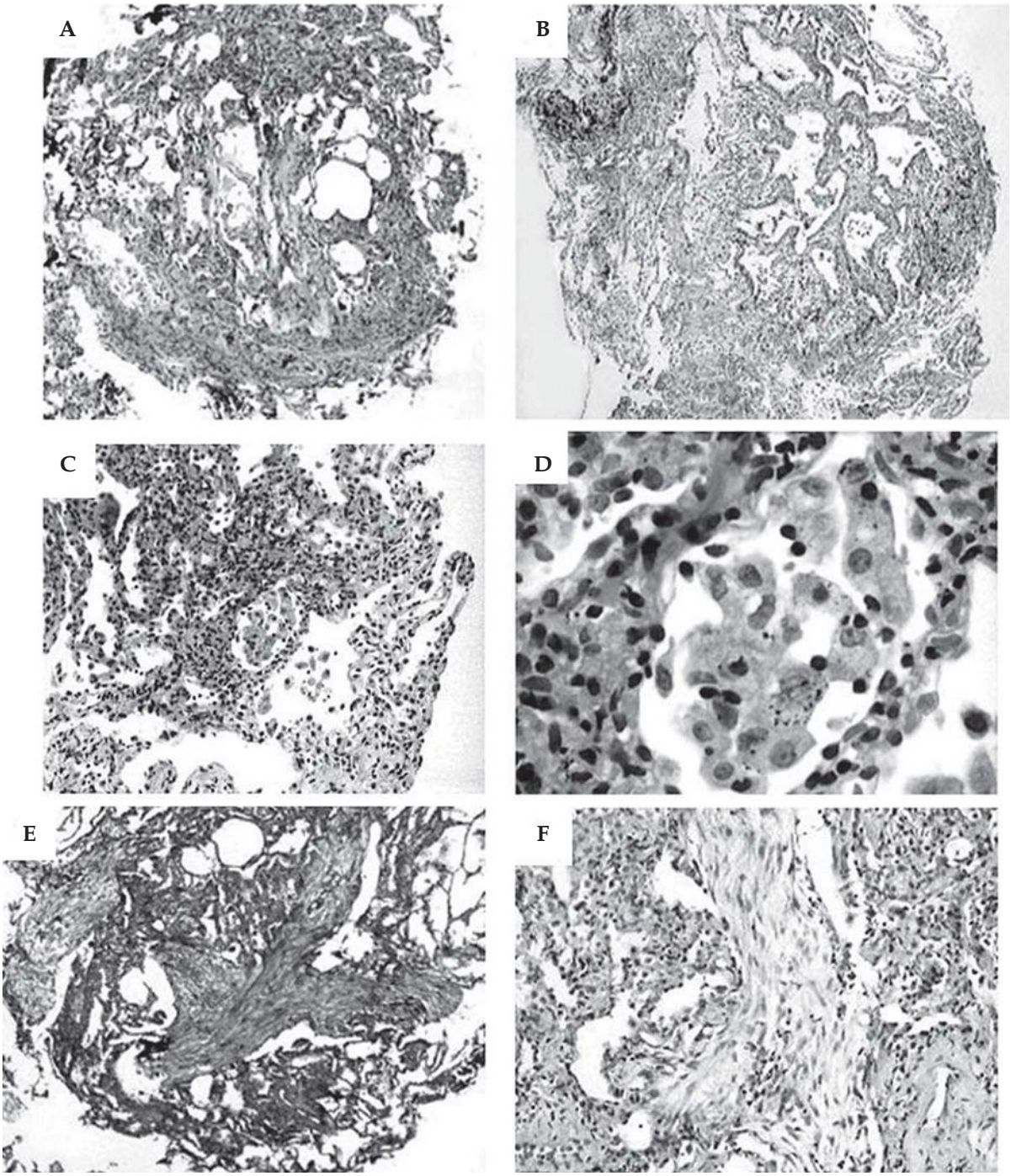

Figure 4. Chronic interstitial inflammation with or without fibrosis (*Pattern 4*). Photomicrograph showing (A) chronic interstitial inflammation with fibrosis and microscopic honey-combing (Haematoxylin and eosin×40); (B) chronic interstitial inflammation without fibrosis (Haematoxylin and eosin×40); (C) DIP-like pattern without fibrosis (Haematoxylin and eosin×40); (D) high power view of the same (Haematoxylin and eosin×400); (E) intra-alveolar organising pneumonia suggestive of cryptogenic organising pneumonia-like pattern; (Masson Trichrome stain×40); and (F) high power view of the same (Haematoxylin and eosin×400).

On correlation (Table 3) the final diagnosis offered included ILD associated with collagen vascular diseases, tuberculosis fibrocavitary lesions, pneumoconiosis, post-radiation fibrosis and idiopathic interstitial pneumonias. DIP-like pattern, seen in 18 of the 138 (13.0%) cases was next most common pattern and was seen in ILD associated with smokers. Distortion of alveolar architecture with microscopic honey-combing and presence of fibroblastic foci were the criteria used to differentiate UIP-like pattern from fibrosing NSIP and was seen in seven of the 138 (5.2%) cases. These correlated with honey-combing and fibrosis on computed tomography. In three (2.2%) cases with rheumatoid arthritis associated lung disease, interstitial infiltration and widening by lymphocytic infiltrate was seen and categorised as LIP-like pattern. Even though the diagnosis offered by TBLB histopathology alone were not conclusive, the exclusion of the infectious and neoplastic pathologies in these cases, in the absence of OLB, was very helpful in further management of these patients, especially in light of clinical and radiological features and pulmonary function tests.

Table 3. Clinical-radiological-pathological correlation of cases showing interstitial inflammation with or without fibrosis on TBLB (Pattern 4, n=138)

Histopathological Features	Clinical Diagnosis	No. (%)
NSIP pattern	Tuberculosis, collagen vascular diseases, sarcoidosis, pneumoconiosis, post-radiation fibrosis, idiopathic ILD	110 (79.7)
DIP pattern	ILD associated with smokers	18 (13.0)
UIP pattern	Tuberculosis, collagen vascular diseases, pneumoconiosis, IPF	07 (5.2)
LIP pattern	Rheumatoid arthritis associated lung disease	03 (2.2)

TBLB=Transbronchial lung biopsy; NSIP=Non-specific interstitial pneumonitis; ILD=Interstitial lung disease; DIP=Desquamative interstitial pneumonia; UIP=Usual interstitial pneumonia; IPF=Idiopathic pulmonary fibrosis; LIP=Lipoid interstitial pneumonia

Granulomatous inflammation (pattern 5) was seen in 186 (30.3%) cases. Using the histopathological criteria and correlating with clinical and radiological features, bronchoalveolar lavage fluid analysis and AFB culture, the diagnosis of tuberculosis was confirmed (Figures 5A and 5B) in 121 (65.1%) cases (Table 4). Submucosal non-necrotising granulomas occurring within sclerotic fibrosis, with multi-nucleated giant cells showing the typical conchoidal (Schaumann) body (Figures 5C and 5D), diagnostic of sarcoidosis were seen in 46 (24.7%) cases. In 19 (10.2%) cases a definitive diagnosis could not be obtained after bronchoscopy and these subjects were referred for surgical biopsy or were empirically started on antituberculosis treatment.

Other specific causes (pattern 6) identified on TBLB accounted for 16 cases (2.6%). These included 3 cases with diffuse alveolar haemorrhage, which were confirmed by the Perl's Prussian blue stain. Pulmonary vasculitis, characterised by damage to the vessel wall and accompanied by fibrin deposition was seen in two cases. Four cases primarily showed features of pulmonary artery hypertension which were low grade lesions: grade 1 (muscular hypertrophy) and grade 2 (mild intimal proliferation).[4] One case each with pulmonary alveolar proteinosis, alveolar microlithiasis (Figures 6A and 6B) and pulmonary lymphangioleio-myomatosis were identified on TBLB. A rigorous clinical-radiological-pathological correlation was important in coming to a definitive diagnosis in these cases.

An adequate lung parenchymal biopsy without a specific diagnostic abnormality (pattern 1) (Figures 7A and 7B) was identified in 137 (22.3%) cases. These were the cases with radiological abnormalities but had no abnormalities seen in the lung biopsies, signifying them to be a result of either 'minimal change disease' or 'sampling error'. In 301 (32.9%) procedures, tissue was considered inadequate for opinion since it comprised of superficial epithelium only and/or alveolar tissue with less than 20 alveoli. Analysis of these cases revealed various factors predisposing to these failures and included lack of patient co-operation, excessive coughing, bleeding leading to termination of the procedure. These cases were then referred for OLB and/or clinical-radiological correlation.

DISCUSSION

The DPLDs comprise of a wide spectrum of over 200 diseases.[5] Many of these diseases have similar clinical presentations with widespread shadowing on the chest radiograph and increasing shortness of breath. Occasionally the radiographic appearances are sufficiently characteristic to enable a specific diagnosis, for example, sarcoidosis, pulmonary eosinophilia, some occupational lung diseases, etc. However, in most patients, chest radiographic patterns are not specific. The final diagnosis can be made from clinical-radiological correlation in about 50% of cases only.[6] Surgical OLB, considered to be the *gold standard* for the diagnosis of DPLDs, however, is associated with greater morbidity and cost. Moreover, OLB is not available in most centres in the developing countries, such as, India. This has lead to a slow but steady increase in the number of TBLBs

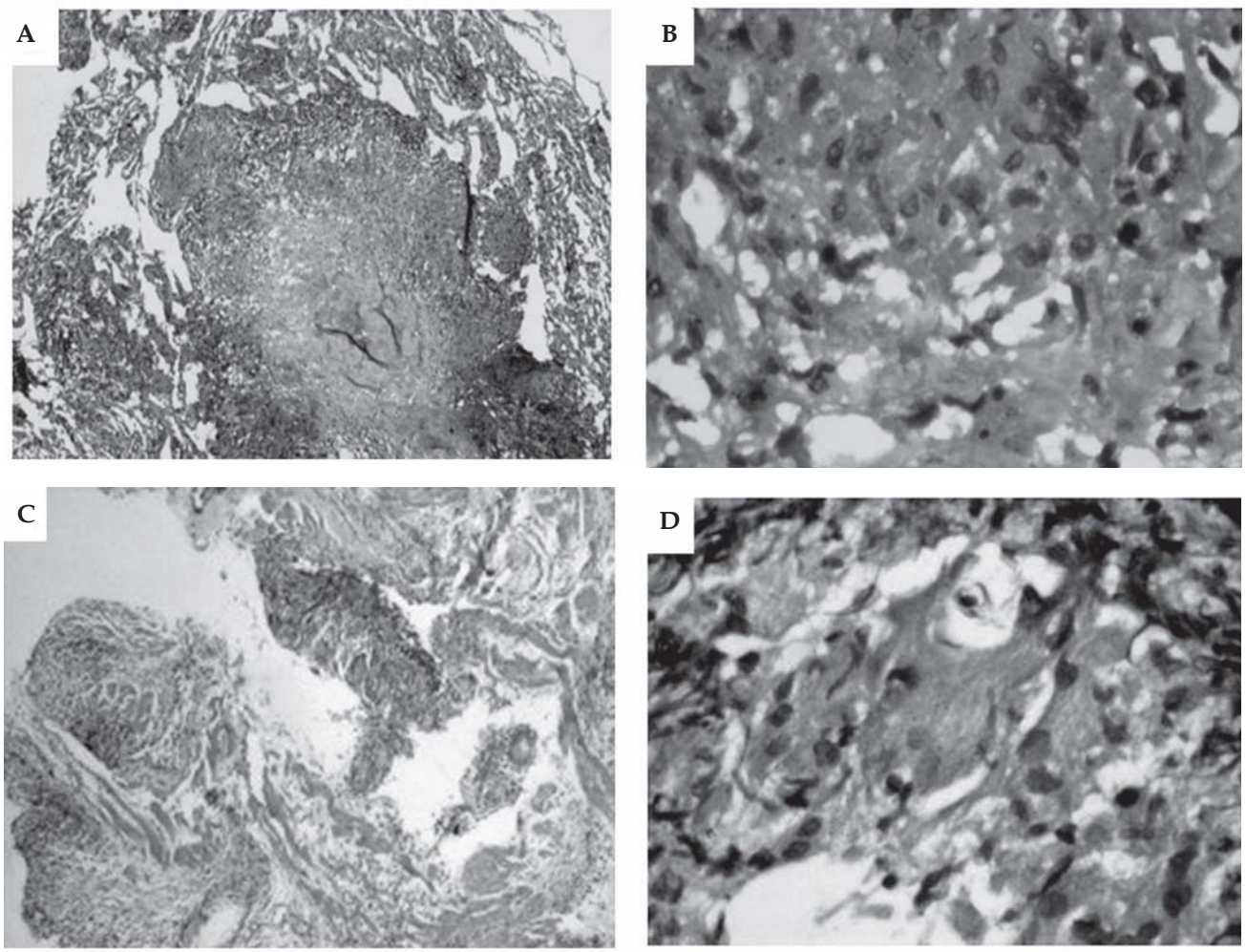

Figure 5. Granulomatous inflammation (*Pattern* 5). Photomicrograph showing (A) coalescing epithelioid cell granulomas with central area of caseation necrosis (Haematoxylin and eosin×40); (B) high power view of the same (Haematoxylin and eosin×400); (C) single discrete subepithelial non-caseating granuloma showing multinucleated giant cells with calcified lamellated intracytoplasmic Schaumann body (Haematoxylin and eosin×40); and (D) high power view of the same (Haematoxylin and eosin×400).

Table 4. Histopathological criteria used for categorisation of granulomatous inflammation in TBLB into tuberculosis and sarcoidosis

Histopathological Criteria Used	Tuberculosis	Sarcoidosis
Necrotising granulomas	+	-/+
Submucosal non-necrotising granulomas occurring within sclerotic fibrosis	-	+
Langhans type of multinucleated giant cells	+	-/+
Multinucleated giant cells showing the typical conchoidal (Schaumann) body	-/+	+/-
Reticulin stain positive	Within granulomas	Surrounding granuloma
Acid-fast bacilli stain	+	-

+=Present; -=Absent

being performed worldwide. Today the most common lung tissue samples seen by pathologists in India and worldwide[1] are those derived using flexible fibreoptic bronchoscopy (FOB).

The usefulness of TBLB for diffuse interstitial pneumonias was first addressed by Andersen in 1978.[7] He stressed on "the importance of an interested and experienced pathologist willing to glean every information from these tiny bits of tissue.[7]" Poletti *et al*[8] reported high diagnostic yield of TBLB of 67% and subdivided the results of morphologic features into three groups: (i) specific morphologic diagnosis (29%); (ii) histopathologic changes consistent with the clinical pattern (38%); and (iii) non-specific lesions (33%). With the use of the FOB and multiple biopsy samples, TBLB has been found to achieve a high diagnostic yield in DPLDs with centrilobular accentuation, such as granulomatous and metastatic

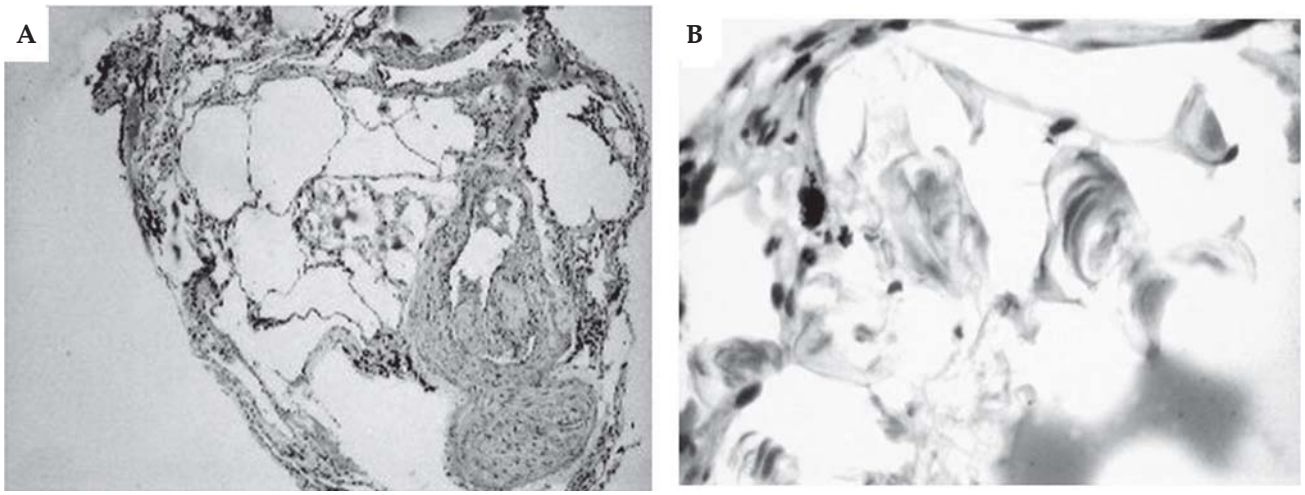

Figure 6. Other specific causes (*Pattern* 6). Photomicrograph showing (A) pulmonary alveolar microlithiasis (Haematoxylin and eosin×40); and (B) high power view of the same (Haematoxylin and eosin×400).

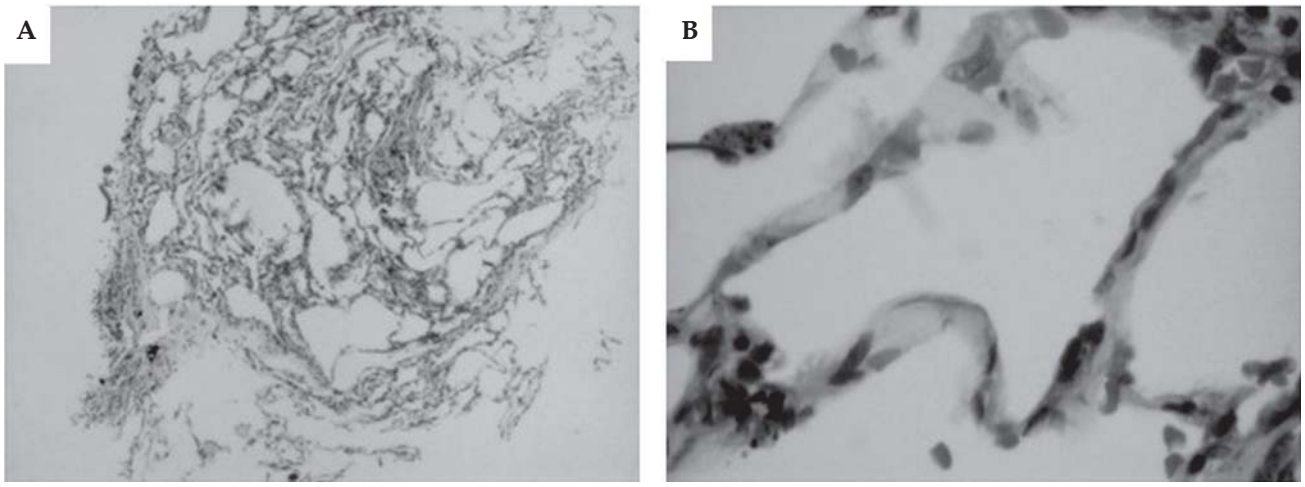

Figure 7. Normal lung parenchyma (*Pattern* 1). Photomicrograph showing (A) normal lung parenchyma (Haematoxylin and eosin×40); and (B) high power view of the same (Haematoxylin and eosin×400).

diseases.[9-13] However, over the broad spectrum of DPLDs, the diagnostic information was found to vary from 38% to 79%.[9-11,14-17]

In 2002, the American Thoracic Society/European Respiratory Society statement on idiopathic interstitial pneumonias[18] defined a set of histologic patterns that provided the basis for a final clinico-radiologic-pathologic diagnosis. Because the histologic patterns seen by pathologists usually allowed for better separation of these entities than the imaging patterns seen by radiologists, the histologic patterns provided the primary basis for the various categories of idiopathic interstitial pneumonia (IIP) and served as the foundation for the classification. It was recommended that the term *pattern* be added to the IIP designations when referring to the lung biopsy pathologic pattern, to distinguish it from the clinico-radiologic-pathologic diagnosis (e.g., NSIP, DIP, or LIP pattern).

Kitachi *et al*[19] observed that there was no straightforward consensus of pulmonary pathologists, even on OLB diagnosis of DPLDs and introduced a quantitative diagnostic method in order to systematise the assessment of histopathology of fibrotic interstitial lung lesions. They assessed the alveolar-aeration ratio, the normal alveolar-wall ratio, number and size of lymphoid follicles, number and maximum size of fibrocystic lesions/ honey-combing, number of fibroblastic foci, number of granulation tissue formations in terminal air spaces per field, abruptness of transition to fibrosis, smooth muscle proliferation score. The histopathologic summary was then correlated with radiology (CT findings of consolidation, ground-glass opacity, etc.,) and clinical course (acute, subacute and chronic process). A similar quantitative assessment of histopathological features needs to be done on TBLB also.

Berbescu *et al*[20] reported that, characteristic histologic features of UIP, a combination of patchwork fibrosis, fibroblast foci, and microscopic honey-combing, could be identified on TBLB specimens. This has lead to renewed interest in role of TBLB in diffuse interstitial lung diseases.[21] TBLB has also been found to be clinically useful in the diagnosis of 75% cases of DPLDs;[21] in the 25% of TBLBs that were clinically unhelpful, there was failure of the procedure to obtain an adequate quantity of lung parenchyma for a meaningful histological analysis. Leslie *et al*[1] have elaborated the most common diagnostic entities and histopathologic patterns seen in TBLB in the setting of diffuse or multifocal lung disease. These included, acute lung injury, eosinophilic pneumonia, diffuse alveolar haemorrhage, chronic cellular infiltrates with or without fibrosis, organising pneumonia, alveolar proteinosis, sarcoidosis, Wegener's granulomatosis, intravenous drug abuse related microangiopathy, Langerhans cell histiocytosis and lymphangio-leiomyomatosis. These were further categorised on the basis of histopathological pattern of lesion into five patterns: (i) acute or subacute injury; (ii) chronic interstitial inflammation with or without fibrosis; (iii) granulomatous inflammation; (iv) vascular diseases (e.g., vasculitis, diffuse alveolar haemorrhage, intravenous drug abuse microangiopathy; and (v) alveolar filling processes (alveolar proteinosis, etc.).

In the present study, we retrospectively analysed the TBLB submitted over 5-year period and used the systematic pattern-based approach described by Leslie *et al*[1] to categorise the histopathological features into six histopathological patterns. The three most common diagnostic patterns in our study were granulomatous inflammation, chronic interstitial pneumonitis and carcinoma lung. In 32.9% procedures, no lung parenchyma was obtained. This was similar to the earlier observations where the problem of inadequate lung tissue from TBLB was observed in up to 20% of patients.[22] The pattern-based categorisation added the much needed guidelines to interpretation of TBLB histopathology and provided clarity to clinicians when submitted for correlation with clinical and radiological features.

TBLB showing chronic interstitial pneumonitis, with or without fibrosis was the second commonest finding in our series and the most difficult to interpret. Review of existing literature revealed that previously this finding was considered to be only helpful in supporting a clinical impression of DPLDs or reported as non-diagnostic since the TBLB specimens were generally considered to be too small and non-representative to determine the relative degree of cellularity and fibrosis. [14,15,23] In the present series too, a confirmatory diagnosis could be given in these cases only after they were correlated clinically and radiologically to assess the relevance of the pathological diagnosis offered on TBLB. Distortion of alveolar architecture with microscopic honey-combing and the presence of fibroblastic foci were the criteria used to differentiate UIP pattern from fibrosing NSIP and these were seen to correlate with honey-combing and fibrosis on CT.

Serious questions on the use of TBLB for the diagnosis of UIP have also been raised,[24] especially since TBLB samples are insufficient to determine temporal heterogeneity, a critical histologic hallmark. The identification of 'concordant pattern of UIP', in which all lobes showed UIP and there is no evidence of intra-patient variation and 'discordant UIP pattern' in which intra-patient variation with lung lobes showing a mixture of UIP and NSIP is present[25] has further compounded the problem of pattern-based diagnosis by TBLB in these two conditions. Therefore, the current assumption is that there is no *gold standard* for the diagnosis of DPLDs, and clinical, radiologic, and histopathologic evaluation by OLB, have emerged as the *silver standard*.[18]

Interstitial lung diseases appear to be under-reported from India. The lack of recognition and inadequate availability of diagnostic facilities, like HRCT are thought to be some of the main reasons for this.[26] Previously, Ahluwalia *et al*[27] have assessed the role of TBLB in ILD and concluded that FOB and TBLB are safe and useful adjuncts to the diagnosis of ILD. The correlation of TBLB histological features with spirometric indices has also been reported in sarcoidosis by Gupta *et al*.[28]

TBLB for the diagnosis of lung disease has come a long way from the time these specimens were first obtained via a rigid bronchoscope.[7,29] Then, sampling was a problem and the specimens were often too small to enable a definitive diagnosis.[14,15] With the use of the FOB, advanced radiological guidance and increasing user expertise the diagnostic yield has increased considerably. However, two crucial questions remain. First is the problem of "sampling error", namely, divergent histopathologic diagnoses in two or more biopsy sites.[30] This is likely, to be minimised by using HRCT to select multiple biopsy sites representative of the full range of morphologic appearances.[31] A second crucial consideration is "inter-observer variation" between histopathologists. In a recent study[32] very significant observer variation was quantified, and the observer agreement was found to be barely clinically acceptable. This is likely to be a result of intermediate histopathologic appearances between two entities in a significant proportion of cases. It is especially because of this scenario that the systematic categorisation of histopathological features seen on TBLB using the pattern-based approach is advocated. These when correlated with clinical and imaging data can be the key determinants of a final consensus diagnosis of DPLDs, especially in patients from developing

countries such as India, with high burden of chronic respiratory diseases, who are unable to undergo surgical lung biopsy.

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