Interstitial Pneumonias: Histopathologic Re-evaluation of 25 Cases

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Abstract

Study Objectives: To assess the major difficulties in applying the updated classification on idiopathic interstitial pneumonia patterns and to define the minor features of each category in our patient population.

Design: Retrospective study on cases who have been diagnosed as interstitial pneumonia/fibrosis.

Setting: Our study group comprised 18 thoracoscopic or open lung wedge biopsy specimens,1 lobectomy specimen, and 6 consultation cases.

Interventions: According to the revised criteria on the histologic pattern analysis we subclassified cases into usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), bronchiolitis obliterans organizing pneumonia (BOOP), respiratory bronchiolitis associated lung disease (RB-ILD), and nonspesific interstitial pneumonia (NSIP) patterns. In all of these pattern groups we determined the minor histological features. In addition, we tried to ascertain if there is any difference in the fibroblastic foci between BOOP, NSIP, and UIP in terms of new capillary formation.

Results: The distribution of cases according to histologic pattern analysis was as follows: NSIP- cellular= 3, NSIP-fibrosing= 5, AIP= 2, BOOP= 4, UIP= 8, and RB-ILD=3.

Conclusions: Our study revealed that, with a systematic approach to the lung biopsy, vast majority of the idiopathic interstitial pneumonia (IIP) cases could be classified into patterns with prognostic implications.

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Key words: *Interstitial lung disease, Interstitial pneumonia, Histology.*

Liebow, in 1975, classified idiopathic interstitial pneumonias (IIP) according to the histopathologic patterns (1). Since then, there have been considerable change in the understanding of interstitial lung diseases that led to a significant change in this classification system (2-5). Recently, Katzenstein and coworkers have suggested a classification that included not only chronic interstitial pneumonia (usual interstitial pneumonia - UIP and desquamative interstitial pneumonia - DIP), but also acute interstitial pneumonia (AIP) and nonspesific interstitial pneumonia (NSIP) (3). Travis (6) and Colby (2) have agreed upon Katzenstein's classification but also have accepted bronchiolitis obliterans organizing pneumonia (BOOP) as a pattern of IIP.

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In routine practice, to diagnose a patient as interstitial pneumonia /fibrosis does not solve the problem of both the clinician and the patient, because this term includes diverse conditions which have different prognostic implications (3,4,7-11). In this study, we reviewed our files and examined the cases that were previously diagnosed as IP and classified our cases according to the advised system (3,6) (table -1). Our aims were

1) to determine the major reason of the discrepancy (if there is one) of the two diagnosis,

2) to define the minor features in each category in our patient population,

3) to assess the major difficulties in applying this system. In addition, we tried to ascertain if there is any difference in the fibroblastic foci between BOOP, NSIP, and UIP in terms of new capillary formation and if this could be used as a feature in the differential diagnosis in these patterns of IPs.

Table 1. Classification of Histologic Patterns in Idiopathic Interstitial Pneumonia (6)

Desquamative Interstitial Pneumonia (DIP)
Respiratuar Bronchiolitis Associated Interstitial Lung Disease (RB-ILD)
Bronchiolitis Obliterans Organizing Pneumonia (BOOP)
Diffuse Alveolar Damage (DAD)/Acute Interstitial Pneumonia (AIP)
Nonspecific Interstitial Pneumonia (NSIP)
Cellular Pattern / Fibrosing Pattern

Material and Methods

We retrieved the cases who were diagnosed as interstitial fibrosis (n=18), interstitial pneumonia (n=7), DIP (n=2), UIP (n=8), BOOP (n=7), diffuse alveolar damage (DAD) (n=2), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (n=2), nonspesific changes in the interstitial compartment (n=6), and organizing pneumonia (n=6) from the archives of Marmara University School of Medicine, between 1990 and 2000. We maintained the clinical data from the patients' files. We excluded all transbronchial biopsies (n=32), 4 cases in which the major pathology was bronchitis and 2 cases with prominent interstitial eosinofilic infiltration. Our study group comprised 18 thoracoscopic or open lung biopsy specimens,1 lobectomy specimen, and 6 consultation cases.

The following criteria, as briefly outlined in table-2, was used in classifying these cases (3,4,6). UIP pattern: Patchy involvement of the lung with temporally

Table 2. Histopathological features of idiopathic interstitial pneumonia patterns (4,6,9,13)

	Type of Pulmonary Lesion						
	DAD/AIP	**BOOP**	**DIP**	**RB-ILD**	**UIP**	**NSIP-C**	**NSIP-F**
Distribution of lesions	diffuse	Patchy	diffuse	patchy	patchy	diffuse	diffuse
		Bronchioler		bronchioler	subpleural		
Uniformity of lesions	uniform	Uniform	uniform	uniform	nonuniform	uniform	uniform
Nature of fibrosis	interstitial	Luminal	interstitial	interstitial	interstitial	interstitial	interstitial
	none	Fibroblastic	collagen	collagen	collagen	none	variable
BOOP-pattern	+/-	+	-	-	-/+	+	-/+
Loss of architecture	yes	No	no	no	yes	no	no
Honeycombing	no	No	no	yes	yes	no	focal
DIP-pattern	no	No	yes	yes	yes	yes	yes
Hyaline membranes	yes	No	no	no	yes	no	no
Fibroblastic foci	no	No	no	no	diffuse	no	focal
interstitial inflam.	-/+	-/+	+	-/+	+	++	+

Table 3. Idiopathic Interstitial Pneumonia – 25 Case

Case	Age (yr)	Sex	Smoker	Specimen	Previous diagnosis	Pattern
1	62	K	Yes	Consultation	Interstitial pneumonia	NSIP-cellular
2	57	E	?	Consultation	Interstitial pneumonia	NSIP-cellular
3	51	E	No	Wedge biopsy	BOOP	NSIP-cellular
4	49	K	No	Wedge biopsy	UIP	NSIP-fibrosing
5	74	E	?	Wedge biopsy	UIP	NSIP-fibrosing
6	55	E	?	Wedge biopsy	Interstitial fibrosis	NSIP-fibrosing
7	62	K	Yes	Consultation	NSIP-fibrosing	NSIP-fibrosing
8	59	E	Yes	Consultation	NSIP-fibrosing	NSIP-fibrosing
9	62	E	No	Wedge biopsy	DIP	UIP
10	58	E	?	Wedge biopsy	BOOP	UIP
11	53	K	?	Wedge biopsy	Interstitial fibrosis	UIP
12	65	E	?	Wedge biopsy	UIP	UIP
13	43	E	?	Wedge biopsy	UIP	UIP
14	61	E	Yes	Wedge biopsy	UIP	UIP
15	55	K	Yes	Wedge biopsy	UIP	UIP
16	51	E	Yes	Consultation	UIP	UIP
17	46	K	?	Wedge biopsy	Interstitial pneumonia	BOOP
18	61	K	No	Wedge biopsy	BOOP	BOOP
19	74	E	Yes	Wedge biopsy	BOOP	BOOP
20	68	K	Yes	Wedge biopsy	BOOP	BOOP
21	44	E	Yes	Wedge biopsy	DIP	RB-ILD
22	58	E	Yes	Lobectomy	Interstitial fibrosis	RB-ILD
23	78	E	Yes	Consultation	RB-ILD	RB-ILD
24	73	K	?	Wedge biopsy	DAD/AIP	DAD/AIP
25	69	E	?	Wedge biopsy	DAD/AIP	DAD/AIP

heterogeneous or variegated appearance, that is alternating zones of inflammation, fibrosis, honeycombing, and normal lung. Subpleural distribution, diffuse fibroblastic foci, and prominent honeycombing were accepted as features that favor UIP over NSIP with fibrosis. DIP pattern: Diffuse involvement of the lung with prominent alveolar macrophage accumulation within alveolar sacs with little inflammation and collagen fibrosis within the interstitial compartment. RB-ILD pattern: Patchy involvement of the lung with similar histomorphologic findings as DIP but with bronchiolocentric distribution. BOOP pattern: Patchy bronchiolocentric involvement of the lung with prominent intraluminal plugs within airspaces with little interstitial fibrosis and foamy macrophage accumulation within distal alveolar sacs.

DAD (AIP) pattern: Diffuse, temporally homogeneous involvement of the lung with some architectural derangement that mainly affects interstitium with moderate inflammatory cell infiltration and with fibroblastic proliferation but not collagen fibrosis. Hyaline membranes were used as a feature that favors DAD over NSIP cellular pattern. NSIP-cellular pattern: Diffuse, temporally homogeneous involvement of the lung with marked or moderate interstitial inflammation without any fibrosis and architectural destruction. NSIP-cellular pattern: Diffuse, temporally homogeneous appearance with none or mild interstitial inflammation but with fibrous thickening of alveolar septa. Within each group, we also evaluated minor histologic features.

Table 4. Distribution of minor histological features according to the interstitial pneumonia pattern (data is given in percentages)

	Type of Pulmonary Lesion					
	DAD/AIP	BOOP	RB-ILD	UIP	NSIP-C	NSIP-F
Alveolar cellularity						
Macrophages	0	0	100	100	100	40
Giant cells	O	0	0	0	33.3	20
Fibrin	100	0	0	37.5	66.7	20
Interstitial cellularity						
Hyaline membranes	100	0	0	37.5	33.3	0
Lymphoid aggregates	0	50	33.3	37.5	100	40
Fibrosis						
Fibroblastic plugs	0	100	0	37.5	33.3	60
Fibroblastic foci	50	0	0	100	0	20
Dense septal fibrosis	0	50	33.3	100	0	80
Honeycomb fibrosis	0	0	0	62.5	0	20
Smooth muscle proliferation	0	0	0	75	0	60
Epithelial changes						
Cuboidal hyperplasia	100	75	33.3	87.5	100	100
Bronchiolar metaplasia	0	0	0	75	33.3	40
Squamous metaplasia	0	0	0	25	0	20
Airway changes						
Inflammation	100	100	66.7	0	66.7	0
Dense fibrosis	0	0	0	25	33.3	60
Vascular changes						
Medial/intimal thickening	0	0	0	87.5	0	80
Pleural changes						
Pleuritis	100	0	0	87.5	33.3	60
Fibrosis	0	0	0	62.5	33.3	60
Fat	0	0	0	12.5	33.3	0

Utilizing streptavidin-biotin-alkaline phosphatase system, immunohistochemistry (IHC) was performed in the cases with BOOP, NSIP-fibrosing, and UIP patterns with antibody raised against factor VIII. IHC evaluation was made at high power by counting the number of capillaries at 4 different fields. Due to the fact that each group is composed of small numbers of cases, we preferred to sentence our observations rather than performing statistical analysis.

Results

The distribution of 25 cases according to the pattern analysis was as follows: 8 case as UIP, 8 case as NSIP (3 case with cellular and 5 case with fibrosing pattern), 4 case as BOOP, 3 case as RB-ILD, and 2 case as AIP/DAD. The age, sex, smoking history, the type of specimen analyzed, previous diagnosis, and the pattern analysis of each case is given in table-2. Pattern analysis revealed 3 cases with NSIP-cellular pattern in which the previous diagnosis were idiopathic pneumonia in 2 cases (case 1 and 2) and BOOP in 1 case (case 3). Two cases with initial diagnosis of UIP (case 4 and 5) and 1 case with an initial diagnosis of interstitial fibrosis (case 6) were accepted as cases with NSIP- fibrosing pattern. Two cases, who were initially diagnosed as DIP, were cases with UIP-pattern (case 9) and RB-ILD pattern (case 21). UIP pattern was recognized in two cases previously diagnosed as BOOP (case 10) and interstitial fibrosis (case 11). Two cases who had been signed out as interstitial fibrosis and interstitial pneumonia showed RB-ILD pattern (case 22) and BOOP pattern (case 17), respectively.

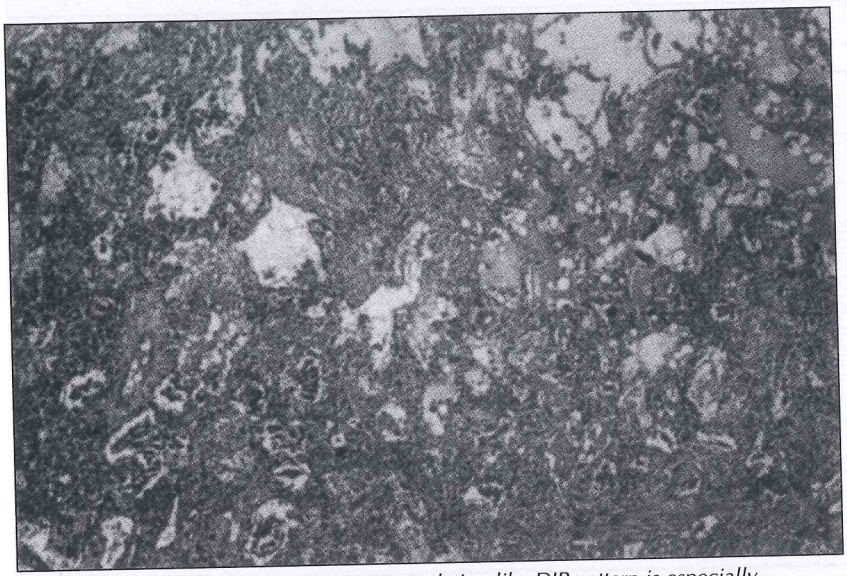

Figure 1. *Intraalveolar machrophage accumulation like DIP pattern is especially prominent in this example of UIP. Although many alveoli contain machrophages, there is a uniform, variegated appearance which favor the diagnosis of UIP; Hematoxylin-Eosin, X100.*

Within each group, minor histological features are summarized in table 3 (Figures 1–5).

Immunohistochemically detected new capillary formations showed no prominent differences between cases with UIP and NSIP-fibrosing pattern, but the values were higher in cases with BOOP pattern (figure 6).

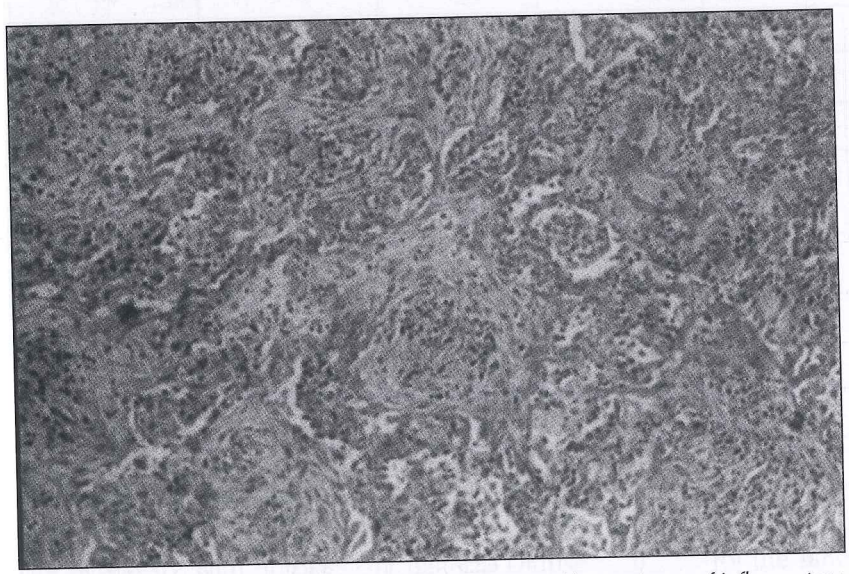

Figure 2. *In this example of NSIP, the alveoli are thickened by a mixture of inflammatory cells and collagen type fibrosis which appear uniform throughout the biopsy; Hematoxylin-Eosin, X40.*

Discussion

Interstitial lung disease is the forth most common disease of the lungs, following chronic obstructive lung disease, asthma, and lung cancer(12). Under the heading of interstitial lung disease, there are diverse etiologies that lead to similar histologic patterns(2). These patterns are the main determinants of the clinical outcome of the patients and are also important in the differential diagnosis, mainly from other diseases that also affect interstitial compartment of the lungs(3,6,10,11).

Recently, well defined criteria in the diagnosis of patterns has been established(3). According to these criteria

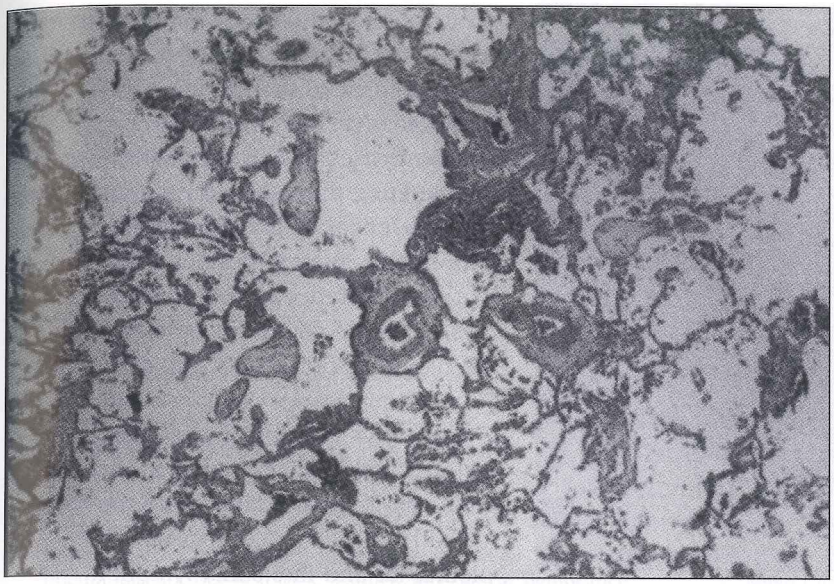

Figure 3. Patchy involvement with intraluminal fibroblastic plugs are characteristics of this case with BOOP; Hematoxylin-Eosin, X40.

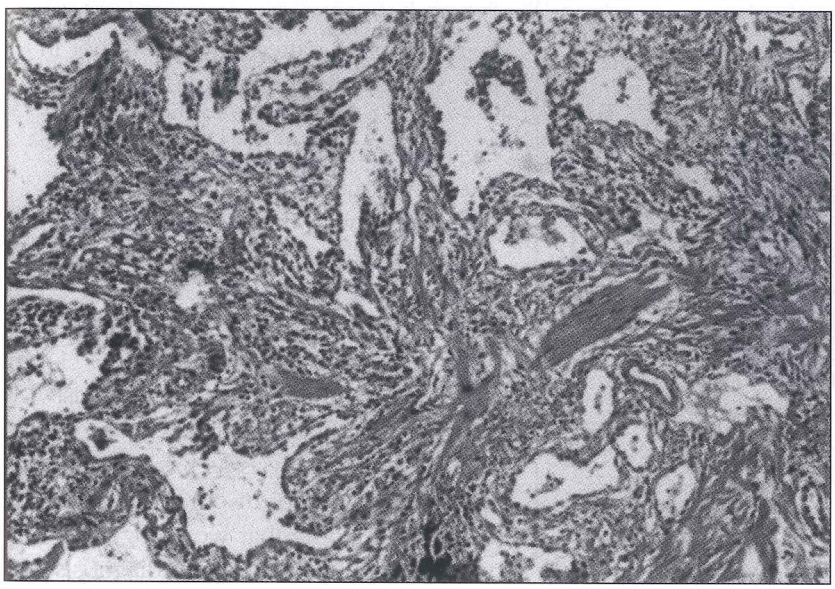

Figure 4. Smooth muscle hyperplasia in a case with UIP; Hematoxylin-Eosin, X200.

we re-evaluated 25 case with IIP without clinical and radiological knowledge and tried to determine the applicability of this classification. In the re-evaluation of the cases, systematic approach to the lung biopsy led us to the diagnosis of the pattern in most of the cases. In the evaluation of the cases; 1) the distribution of the pathologic process a) whether it is patchy or diffuse and b) whether it has preferential distribution (subpleural, bronchiolocentric, not specific), 2) the uniformity of the features, whether it shows temporal homogenity or temporal heterogenity (that is the changes appear to have occurred over a single relatively narrow life span or reflects features that have occurred at different times during the course of disease, respectively) and 3) the nature of fibrosis a) whether it is intraluminal or interstitial and b) whether it is a fibroblastic proliferation or a collagenous fibrosis were the questions that we tried to answer in this systematic approach to diagnose individual pattern(12). Based on our observations, to discriminate AIP from NSIP-cellular pattern and UIP from NSIP-fibrosing pattern were the main difficulties among the differential diagnosis of IIP patterns. Both AIP and NSIP-cellular pattern are diffuse, temporally homogeneous and the nature of fibrosis in both of these diseases is fibroblastic proliferation(3,13). Travis et al suggested that, thrombosis, hyaline membranes, and architectural derangement are the features that favor the diagnosis of AIP(6). Among our NSIP-cellular pattern cases, one of the cases revealed hyaline membranes that were incorporated in the interstitial space. Thrombosis and architectural derangement were evident in only one case with DAD-pattern limiting the utility of these features in the differential diagnosis. In our cases, the severity of interstitial inflammation was more pronounced and lymphoid aggregates were common in NSIP-cellular pattern implicating that these two features could be of help in the differential diagnosis. However, we believe that in the differentiation of AIP from NSIP-cellular pattern, there must be considerable clinical input in order to reach to the definite diagnosis. To differentiate these two patterns are important because in AIP the mortality rate is 68 % in contrary to NSIP-cellular pattern in which the given 10 year survival rate is 100 %(6,14,15). To differentiate UIP from NSIP-fibrosing pattern has also prognostic implications due to the fact that 5- and 10- year survival rates differ substantially being 90% and 35 % for NSIP-fibrosing pattern compared with 43 % and 15 % for UIP(6). As mentioned in the literature, the distinction between these patterns may be difficult(6,13). Altough diffuse fibroblastic foci, patchy subpleural distribution, and temporal heterogenity are the features that favor UIP(6,13), we think that the most helpul criteria is temporal heterogenity with honeycomb fibrosis in the differentiation of UIP from

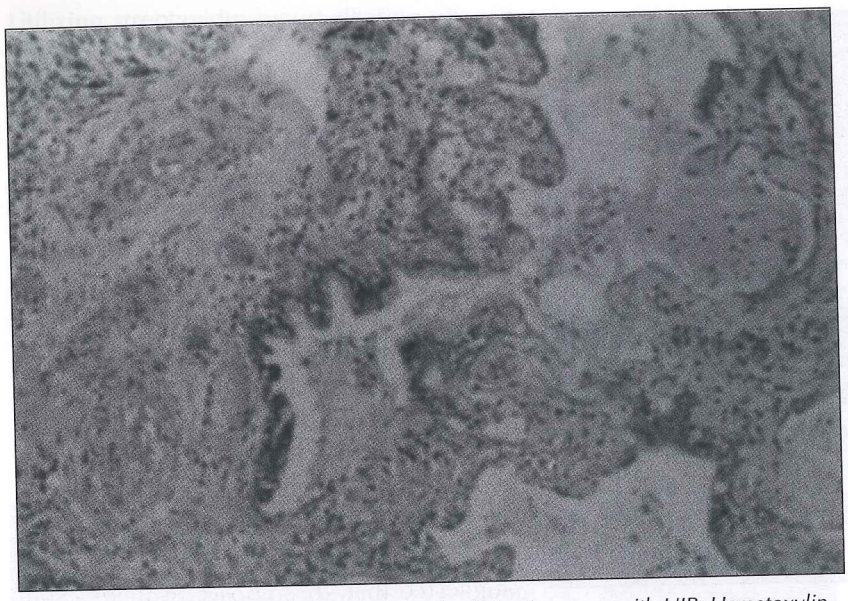

Figure 5. *Bronchioler metaplasia in the alveoler lining in a case with UIP; Hematoxylin-Eosin, X200.*

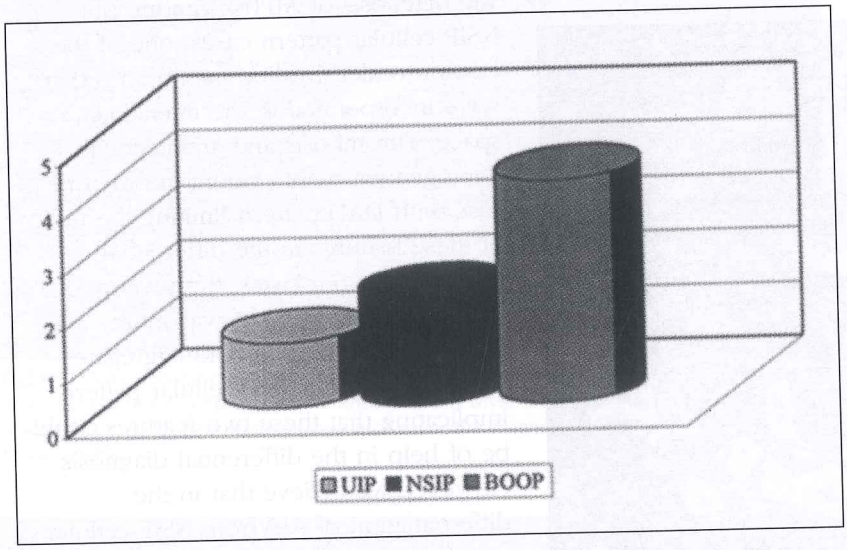

Figure 6. *Comparative values of new capillary formation in fibroblastic foci and fibroblastic plugs of cases with UIP, NSIP, and BOOP patterns.*

NSIP-fibrosing pattern because rare patchy involvement and focal fibroblastic proliferation can also be seen in cases with NSIP-fibrosing pattern(3,4). However, lung biopsy interpretation must be done in conjunction with clinical and radiographic data due to the fact that some NSIP-fibrosing pattern may represent poorly sampled cases of UIP(6). That is, biopsies that show NSIP-fibrosing pattern in patients with clinical and radiologic features suggestive of UIP probably should be regarded as UIP (6).

In a recent study by Lappi-Blanco, the nature of fibroblastic proliferations, in terms of new capillary formations, were found to be different in BOOP and in UIP(16). It has been thought that this reflects the different clinical course of these two patterns of IIPs. We detected similar findings in cases of UIP and BOOP, however there was no difference between cases of UIP and NSIP patterns thus limiting the use of this parameter in the differential diagnosis of the cases with these patterns. Besides it shows us that the difference in the prognosis of these patterns could not be explained by the nature of fibroblastic proliferation.

Our findings of minor histological features within each pattern group are generally in concordance with the values found by Travis et al(6), except that, pleural fat and interstitial lymphoid aggregates were found to be rare in UIP and NSIP-fibrosing pattern groups in our study. Besides, in our study group, BOOP pattern was more common in NSIP-fibrosing pattern group but not in the NSIP-cellular pattern group.

Five cases initially diagnosed as interstitial pneumonia/fibrosis could be categorized with the defined criteria. Interstitial pneumonia/fibrosis is a general term used for all of these patterns(17). However, different patterns have different courses of disease(7-11). In this aspect, the role of the pathologist must be to subclassify the case according to the pattern analysis as has been done in our study group. In our study the most surprising finding that we recognized was in the cases with initial diagnosis of BOOP and DIP. BOOP and DIP patterns can be a component of UIP and also NSIP (13). We think that in signing out these cases the histologic features other than intraluminal plugs have been ignored or unrecognized. We classified 2 cases with initial diagnosis of UIP as NSIP due to the uniformity and temporal heterogenity and 1 case with initial diagnosis of DIP as RB-ILD due to the patchy involvement. Considering that NSIP- fibrosing pattern and RB-ILD have better prognosis than UIP and DIP respectively, it is clear that pattern analysis is the main step in the correct diagnosis of individual IIPs(8,9,11,18).

We conclude that, in order to have accurate diagnosis that is essential to determine prognosis and

appropriate therapeutic intervention for a given patient, pathologic diagnosis of the pattern in conjunction with clinical and radiological findings is mandotory. We believe that, with a systematic approach to the lung biopsy, vast majority of the IIP cases could be classified into patterns with prognostic implications.

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