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RESEARCH ARTICLE

A CORRELATIVE STUDY ON BRONCHOALVEOLAR LAVAGE CYTOLOGY WITH HISTOPATHOLOGY IN PATIENTS WITH PULMONARY LESIONS

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ABSTRACT

This study was conducted with 132 brocho alveolar lavage (BAL) samples over the period of 2 years.The age group of patients ranged from 16 years to 80 years and the maximum numbers of cases were found in the age group of 51-60 years, comprising a total of 31.8% of the (42 cases) study population. Breathlessness and haemoptysis were present in equal number of cases (41 cases, 31.1%). Out of 132 BAL smears studied the diagnosis of malignancy was given in 36 (27.2%) cases, dysplasia in 20 (15.2%) cases and 52 (39.4%) cases were diagnosed as non neoplastic inflammatory lesions. The sample was inadequate to evaluate in 24 cases. Histopathological correlation was available for 45 cases in which 30 (66.7%) cases were diagnosed as malignant lesions, 5 (11.1%) cases were dysplastic and 10 (22.2%) cases were non neoplastic inflammatory lesions. Out of the total 132 BAL cases, 110 cases (83.3%) were males and 22 cases (16.7%) females (Fig 1). Male: Female ratio was 5:1. Out of the 45 biopsy samples studied 41 were males and 4 were females. Among the 30 cases, 22 cases were smokers and males. The remaining 6 males and 2 females were non smokers. Out of the 45 cases studied 30 cases (66.7%) were malignant lesions, 5 were dysplastic (11.1%) and 10 (22.2%) were non neoplastic lesions. Among males, there were 28 (68.3%) cases of malignant lesions, 5(12.3%) cases of dysplastic lesions and 8(19.5%) cases of inflammatory lesions). Among females, there were equal number of cases of malignant (2 cases) and non neoplastic lesions (2 cases). It is observed that there was no significant association between distribution of malignant lesion and sex of the patient. In the present study of 45 cases, the cytological diagnosis of malignancy was made in 19 cases, among them 18 cases were proved as malignancy in histopathology (True positive).

INTRODUCTION

The respiratory tract serves the dual purpose of supplying oxygen to and removing carbon dioxide from the circulating blood and is likely to develop all neoplastic and non-neoplastic diseases. Patients with diseases of the respiratory system generally present because of the symptoms, an abnormality on a chest radiograph or both. The diagnostic modalities available for assessing the patient with suspected or known respiratory system disease include imaging studies and techniques for acquiring biopsy specimens, some of which involve direct visualisation of parts of respiratory system. Bronchoscopy is one among such procedures which not only visualizes the respiratory system but also aids in obtaining the representative sampling material from the regions that are directly visualised and also from the more distal pulmonary parenchyma. Bronchoalveolar lavage (BAL) is one among several techniques which provides sequential access to well preserved cells to study the natural history of the disease process.[8] As an investigative tool BAL has enormous potential. It has been found useful in diagnosing opportunistic infections in the lung, bronchoalveolar hemorrhage and alveolar proteinosis. BAL has also been used to investigate the pathogenesis of such diverse lung conditions such as emphysema, ARDS, occupation lung disease, drug hypersensitivity reactions and asthma. The cytological examination of cells obtained by BAL has been useful in the diagnosis of primary bronchogenic cancer and the metastatic cancer to the lung in particular lymphangitic carcinomatosis. This study aims at studying the bronchoalveolar lavage samples obtained from the lungs in various pulmonary lesions and its histopathological correlation.

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Objective

- To evaluate the broncho alveolar lavage sample of patients presented with respiratory symptoms such as cough, fever, hemoptysis, breathlessness and weight loss.
- To study the abnormal smears and correlate the cytological finding with histopathological diagnosis
- To assess the usefulness of the cytological study in the diagnosis of pulmonary lesions.

Aim of study

- To evaluate the broncho alveolar lavage sample of patients presented with respiratory symptoms such as cough, fever, hemoptysis, breathlessness and weight loss.
- To study the abnormal smears and correlate the cytological finding with histopathological diagnosis
- To assess the usefulness of the cytological study in the diagnosis of pulmonary lesions.

MATERIALS AND METHODS

Study design: Cross sectional study.

The present study was carried out in the Department of Pathology, Madurai Medical College, Madurai, for a period of 2 years from July 2014 to June 2016. The cytological materials were obtained in the form of broncho alveolar lavage fluid using fibre optic bronchoscope, from the Department of Thoracic Medicine, Government Rajaji Hospital, Madurai. During this 2 year study period 132 BAL samples were collected. Details of the patients such as clinical history, personal history, and radiological investigations including details of bronchoscope findings if any were recorded.

Table 1. BAL Cellular patterns as an adjunct to diagnosis

Cellular	Diagnosis
Lymphocytic	Hypersensitivity pneumonitis
	Tuberculosis
	Sarcoidosis
	Beryliosis
	Malignant Infiltrates
	Drug induced pneumonitis
	HIV infection
Neutrophilic	Idiopathic pulmonary fibrosis
	Bacterial pneumonia
	Asbestosis
	Acute respiratory distress syndrome
	Wegener's Granulomatosis
Eosinophilic	Hyper eosinophilic syndrome
	Allergic broncho pulmonary aspergillosis
	Eosinophilic pneumonia
	Churg-Strauss syndrome
Mixed cellularity	Bronchiolitis obliterans organizing pneumonia (BOOP)
	Non specific interstitial pneumonia
	Inorganic dust disease

Cytology

The whole sample was taken in equal volumes in two clean glass test tubes and centrifuged for 5 minutes, at a speed of 2000 rpm. After centrifugation, the supernatant fluid was discarded and the sediments in the test tubes were pooled and smears were made on two clean grease free slides. One of the smears was air dried and stained with Giemsa's stain.[6] The other one was kept in coplin jar containing isopropyl alcohol for 10-15 minutes and stained with Haematoxylin and Eosin stain.

Histopathology

The histopathology specimens of lung biopsy were fixed in 10% neutral buffered formalin. The tissues were processed, paraffin blocked, 5 microns thin sections were cut and stained with Haematoxylin and Eosin. Special stains such as PAS were used as and when required. Immuno histochemical studies were done in relevant cases. The results of histopathological study of H and E stained sections and cytological study of BAL were entered in the proforma. Photomicrographs of the smears and sections were taken whenever needed. The information collected was recorded in a master Fig. The results of both procedures were compared.

Statistical analysis

'P' value analysis was used for statistical calculation to arrive at the conclusion. Sensitivity, specificity and accuracy were calculated using the following formulae and taking HPE findings as the Gold standard.

Screening Test results	Diagnosis	
	Diseased	Not Diseased
Positive	True positive TP	False positive FP
Negative	False negative FN	True negative TN

Sensitivity = TP/ (TP+FN) X 100
Specificity= TN/ (FP+TN) X 100
Accuracy = TP+TN/ (TP+FP+FN+TN) X 100

RESULTS AND DISCUSSION

Out of 132 BAL smears studied the diagnosis of malignancy was given in 36 (27.2%) cases, dysplasia in 20 (15.2%) cases and 52 (39.4%) cases were diagnosed as non neoplastic inflammatory lesions. The sample was inadequate to evaluate in 24 cases. Histopathological correlation was available for 45 cases in which 30 (66.7%) cases were diagnosed as malignant lesions, 5 (11.1%) cases were dysplastic and 10 (22.2%) cases were non neoplastic inflammatory lesions.

Sex Distribution

Out of the total 132 BAL cases, 110 cases (83.3%) were males and 22 cases (16.7%) females (Fig 1). Male : Female ratio was 5:1. Out of the 45 biopsy samples studied 41 were males and 4 were females.

Age incidence

The age group of patients ranged from 16 years to 80 years and the maximum numbers of cases were found in the age group of 51-60 years, comprising a total of 31.8% of the (42 cases) study population. The least number of cases were in the age group of 71-80 years among males comprising only 0.75% of the study population (Fig 2). Among females, no cases were found in the age groups of 11-20 years, and 61-80 years. The

youngest patient among males was 16 year old and the oldest patient was 72 year old. The youngest patient among females was 28 year old and the oldest patient was 60 year old.

fever. Among the 132 cases cough was the presenting symptom in 126 cases (95.5%). Fever was one among the presenting symptoms in 64 cases (48.5%).

Table 2. Diagnostic BAL findings

Sl.No.	BAL findings	Diagnosis
1	Pneumocystis carinii, fungi, cytomegalovirus transformed cells	Opportunistic infections
2	Milky effluent, periodic acid Schiff positive non cellular corpuscles, amorphous debris, foamy macrophages	Alveolar proteinosis
3	Hemosiderin laden macrophages, intra cytoplasmic fragments or red blood cells in macrophages, free red blood cells	Alveolar hemorrhage syndrome
4	Malignant cells of solid tumors, lymphoma, leukemia	Malignant infiltrates
5	Dust particles in macrophages, quantifying asbestos bodies	Dust exposure
6	Eosinophils greater than 25%	Eosinophilic lung disease
7	Positive lymphocyte transformation test to beryllium	Chronic beryllium disease
8	CD1 positive Langerhan's cells increased	Langerhans cell histiocytosis
9	Atypical hyper plastic type II Pneumocytes	Diffuse alveolar damage, drug toxicity

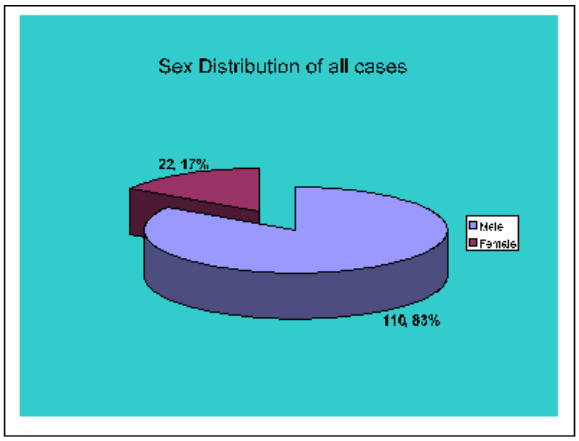

Fig. 1. Sex distribution of all cases

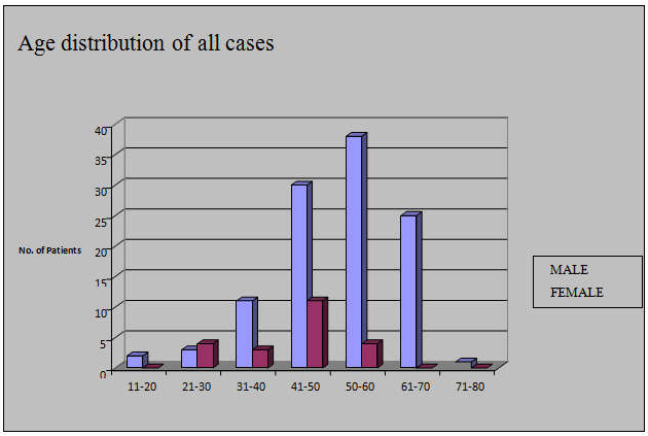

Fig. 2. Age distribution of all cases

The higher prevalence of respiratory diseases were in the age group of 51-60 years among males, and in the age group of 41-50 years among females. The highest prevalence respiratory diseases among males and females were (62.8%) in the age group of 41-60 years.

Mean age of cases (Lesion based)

The mean age for malignant lesions for males was 52.16 years, for females it was 50.75 years and the mean age for both sexes was 52 years. For dysplasia the mean age for males was 53.94 years for females was 46.75 years and the mean age for both sexes was 52.50 years. For inflammatory lesions the mean age for males was 51.93 years, for females 39.7 years and the mean age for both sexes was 49.54 years (Table 3 and Fig 3).

Smoking habit distribution

Significantly higher numbers of smokers (84 cases) were present among male population (Table 4). In total 63.6% of study population were smokers and 36.4 % were non- smokers. None of the female patients (22 cases) were smokers. Seventy six percent of the study population was smokers and the habit of smoking is a major risk factor for pulmonary diseases.

Clinical symptoms

Majority of the patients presented with clinical symptom (Fig 4) of cough followed by fever, breathlessness, haemoptysis and Breathlessness and haemoptysis were present in equal number of cases (41 cases, 31.1%). Weight loss was seen in 30 cases (22.7%).

Cytological diagnosis

Of the 132 cases, 108 cases had satisfactory smear. The diagnosis of malignancy was given in 36 cases, dysplasia in 20 cases, and 52 cases were diagnosed as non neoplastic inflammatory lesions. The sample was inadequate to evaluate in 24 cases (Fig 7). In our study, majority of BAL samples showed features of inflammatory smear, comprising 52 cases, followed by 36 cases of malignancy and 20 cases of dysplastic lesions.

Among the 52 inflammatory cases, one known case of pulmonary tuberculosis on treatment showed chronic inflammatory smears and collections of epitheloid cells. In the 36 malignant lesions diagnosed, 32 cases were males and 4 females. 16 males and 4 females were diagnosed as having dysplastic lesions. Among the 52 inflammatory lesions, 42 were males 10 were females. Out of these 132 samples, 45 cases had biopsy samples. Out of 45 smears studied, 11 cases (24.4%) were malignant lesions, 3cases (6.7%) were squamous cell carcinoma (Fig 5), 4 cases (11.1%) were adenocarcinoma ,one case of undifferentiated carcinoma(Fig 6) , 7 cases (15.6%) were dyaplastic and 15 cases (33.3%) were inflammatory smears. 4 cases had inadequate smears for evaluation.

Table. 3. Mean age of cases (lesion based)

	No. of Cases		
	Male	Female	Total
Malignancy	32	4	36
Dysplasia	16	4	20
Inflammatory	42	10	52
Inadequate	20	4	24

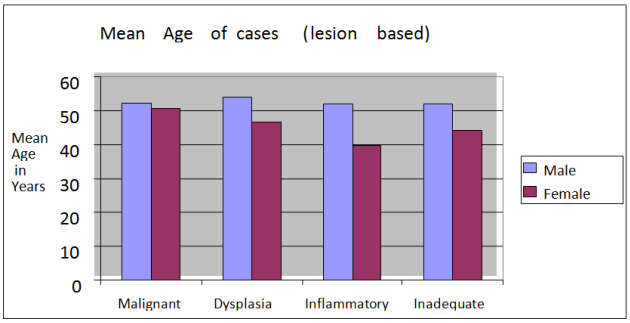

Fig. 3. Mean age of cases (lesion based)

Table 4. Smoking habit distribution of all cases

Habit	Male	Female	Total
Smoker	84(76.4%)	-	84(63.6%)
Non-Smoker	26(23.6%)	22(100%)	48(36.4%)
Total	110(100%)	22(100%)	132(100%)

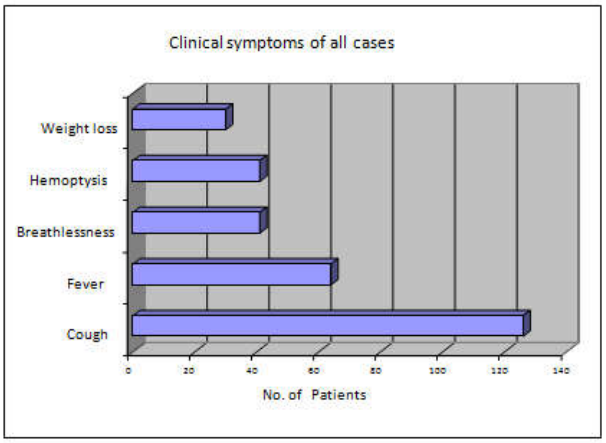

Fig. 4. Clinical symptoms of cases

Table 5. Histopathological diagnosis of biopsy

Sl.No	Lesion	No. of Cases		Total
		Male	Female	
1	Malignant	28(68.3%)	2(50%)	30(66.7%)
2	Dysplastic	5(12.3%)	-	5(11.1%)
3	Inflammatory	8(19.5%)	2(50%)	10(22.2%)
	Total	41(100%)	4(100%)	45(100%)

Table 6. Distribution of malignant lesions among smokers

	Non-Smokers	Smokers	Total
Male	6	22	28
Female	2	-	2
Total	8	22	30

Histopathological diagnosis

Out of the 45 cases studied 30 cases (66.7%) were malignant lesions, 5 were dysplastic (11.1%) and 10 (22.2%) were non neoplastic lesions.

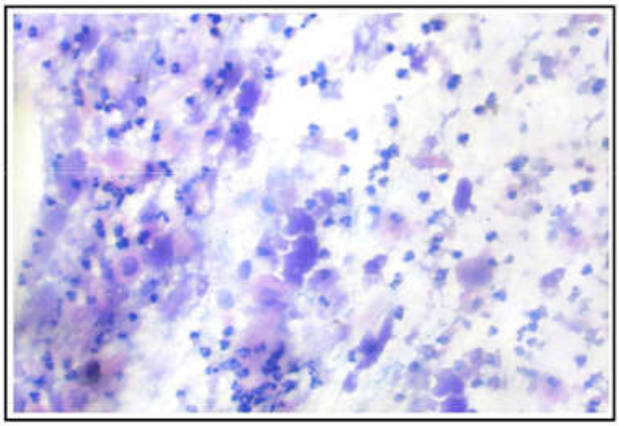

Fig 5: Squamous cell carcinoma: Degenerated squamoid cells are seen in inflammatory background Giemsa x400 (Cy 1492/07).

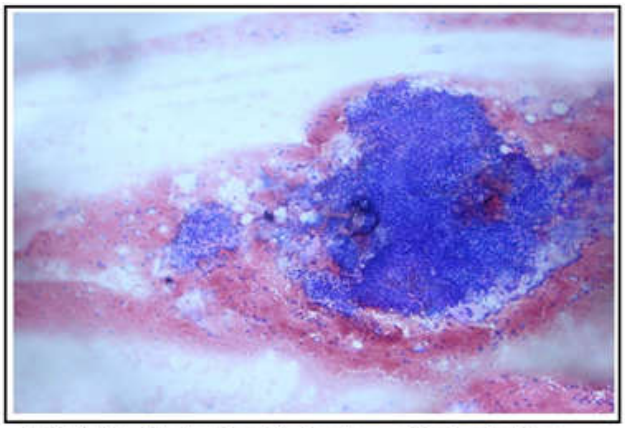

Fig 6. Undifferentiated carcinoma: Sheets and groups of malignant cells in a hemorrhagic background Giemsa x100 (Cy 4659/07).

Table 7. Distribution of malignant lesions on histopathology

Sl.No	Lesion	No. of Cases		Total
		Male	Female	
1	Squamous Cell Carcinoma	11(39.3%)	-	11(%36.7)
2	Adeno Carcinoma	7(25)	-	7(23.3%)
3	Bronchiolo alveolar Carcinoma	1(3.6%)	1(50%)	2(6.7%)
4	Poorly differentiated adeno carcinoma	3(10.7%)	-	3(10.0%)
5	Poorly differentiated carcinoma	2(7.1%)	-	2(6.7%)
5	Anaplastic carcinoma	3(10.7%)	-	3(10.0%)
6	Small cell carcinoma	1(3.6%)	-	1(3.3%)
7	Spindle cell sarcoma /? Sarcomatoid carcinoma	-	1(50%)	1(3.3%)
Total		28(100%)	2(100%)	30(100%)

Among males, there were 28 (68.3%) cases of malignant lesions, 5(12.3%) cases of dysplastic lesions and 8(19.5%) cases of inflammatory lesions (Table 5, Fig 8). Among females, there were equal number of cases of malignant (2 cases) and non neoplastic lesions (2 cases).

Distribution of malignant lesions in smokers

Histopathological correlation was available for 45 cases in which 30 cases were diagnosed as malignant lesions. Among the 30 cases, 22 cases were smokers and males. The remaining 6 males and 2 females were non smokers.

Table 8. Comparison of Cytological diagnosis of BAL with histopathological diagnosis

Cytological Diagnosis	Final Histopathological Diagnosis																						
	NSI		DYS		SCC		AC		BAC		PDAC		PDC		UDC		SmCC		Spindle cell tumour				Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M		F		
INF	6	2	1		2		2		1		1												15
Malignancy			1		3		3			1			1		2								11
SCC					3																		3
AC					1		1				2												4
UDC															1								1
DYS	2		2		1		1						1										7
IA			1		1												1				1		4
TOTAL	8	2	5	-	11	-	7	-	1	1	3	-	2	-	3	-	1	-	-		1		45

M – Male, F – Female, NSI – Non – Specific Inflammation, DYS – Dysplasia , SCC – Squamous cell carcinoma, AC – Adeno Carcinoma, BAC – Bronchiolo alveolar carcinoma, PDAC – Poorly Differentiated Adeno Carcinoma PDC – Poorly Differentiated Carcinoma, UDC – Undifferentiated Carcinoma, INF – Inflammation, IA – Inadequate

Table 9. Histopathological correlation of BAL Cases

Lesions	Total	C	NC
Malignant	30	18	12
Dysplastic	5	2	3
Inflammatory	10	8	2
Total	45	28	17

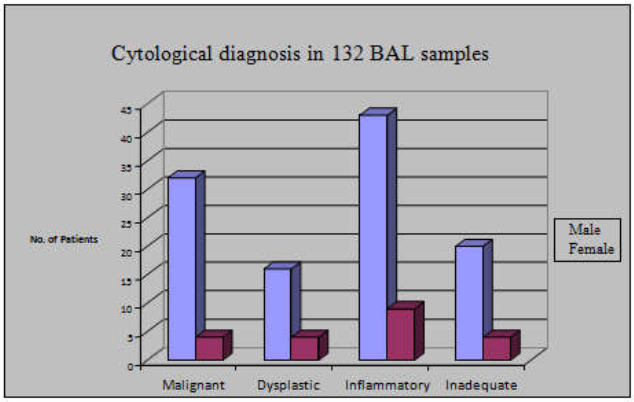

Fig. 7. Cytological diagnosis of BAL samples

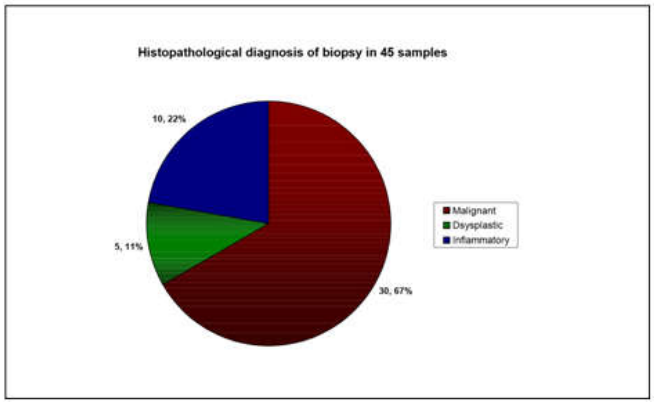

Fig. 8. Histopathological diagnosis of biopsy samples

It is observed (Table 6) that the malignant lesions of the lung were more common in smokers than non smokers.

Distribution of malignant lesions on histopathology

It is observed that there was no significant association between distribution of malignant lesion and sex of the patient. Out of the 30 cases of malignancy diagnosed in histopathology 28 were male and 2 were female (Table 7). Among males 11 cases were squamous cell carcinoma, 7 were adenocarcinoma, 3 cases of poorly differentiated adenocarcinoma, 2 cases of poorly differentiated carcinoma, 3 cases of anaplastic carcinoma, 1 case of bronchioloalveolar carcinoma and 1 case of small cell carcinoma was diagnosed.

Among females, 1 case of bronchiolo alveolar carcinoma and 1 case of spindle cell sarcoma/? Sarcomatoid carcinoma was reported. Immunohistochemistry study of the spindle cell tumour was done. This tumour was immunoreactive for vimentin and non reactive for markers such as cytokeratin, desmin and S-100. Based on the marker study, the tumour was diagnosed as high grade fibro sarcoma.

Histopathological correlation of BAL cases

Out of the 30 cases of malignancy diagnosed histopathologically, the corresponding BAL smears showed malignant cells in 18 cases. In the remaining 12 cases of malignancy, BAL did not correlate with histopathological diagnosis. Out of 12 smears 6 showed features of inflammatory lesions, 3 were dysplastic and 3 cases were inadequate for evaluation (Table 8 and 9). Out of the 5 cases diagnosed as dysplasia, 3 cases of BAL did not correlate with histopathological diagnosis of dysplasia. Out of them, 1 case was inadequate for evaluation, 1 case showed features of malignancy and 1 showed features of inflammatory lesion. Out of the 10 cases of inflammation diagnosed histopathologically, 8 cases of BAL showed inflammatory smears and 2 cases showed features of dysplasia.

Sensitivity and specificity

Malignant lesions

In the present study of 45 cases, the cytological diagnosis of malignancy was made in 19 cases, among them 18 cases were proved as malignancy in histopathology (True positive).

One case was falsely diagnosed as malignancy in cytology and showed features of dysplasia in histopathology (False positive). Malignancy was diagnosed in 12 cases histopathologically but the corresponding cytology did not show malignant cells (False negative). Neither cytology nor histopathology showed malignancy in 14 cases (True negative). The sensitivity of BAL cytology in diagnosing malignant lesions in our study is 60% while the specificity is 93.3%. The diagnostic accuracy is 71.1%. Bronchoalveolar lavage can address many lesions that are diffuse or peripherally situated. The goal of BAL is investigation of pathologic conditions situated beyond the range of bronchoscopic visualisation. Studies using BAL information for clinical correlation rest on the general concept that alveolar contents reflect parenchymal lung disease (86%). The present study was conducted to analyse the cellular elements recovered from BAL in patients with pulmonary lesions. Based on the cytomorphology of the cells in the BAL, cytodiagnosis was provided. The BAL cytodiagnosis was correlated in patients who underwent bronchoscopic biopsy.

Comparison of diagnostic accuracy for malignancy with other studies

In 1987, Linder J et al studied BAL fluid among 35 cases of biopsy proven lung carcinomas. However 4 cases had cells diagnostic of malignancy on cytologic preparation of BAL fluid. In 1992, Piruzynski M et al studied BAL fluid among 145 cases of biopsy proven lung carcinomas. Out of these 94 cases (64.8%) were found to have malignant disease of lung. The prospective study by de Gracia J et al, in 1993 BAL were diagnostic in revealing malignant cells in 24 cases out of 55 cases with biopsy proven malignancy. In a study by De beljek A et al in 1994, 61 patients were biopsy proven malignancies out of which 17 (27.9%) patients showed malignant cells in BAL fluid specimen. In 1998, after studying 30 patients with lung cancers Wongsurakiat P et al, reported that BAL was positive for malignant cells in 14 patients (46.7%). In the present study, 30 cases were diagnosed as malignant lesions in biopsy and corresponding BAL fluid samples examined show malignant cells in 18 cases (71.1%). In the present study the diagnostic accuracy was 71.1% and had a near correlation with the study of Pirozynski M and Linder J et al. In the study by Linder J et al, the biopsy diagnosis of patients studied by BAL showed 10 cases of squamous cell carcinoma, 15 cases of adenocarcinoma, 7 cases of large cell undifferentiated carcinoma and 3 cases of small cell undifferentiated carcinoma. Most of the patients with carcinoma in the study by Linder J et al were smokers and they had prominently neutrophils in the background of malignant cells. In the present study also male patients diagnosed as having malignancy showed neutrophils predominantly in the background of malignant cells.

Conclusion

In conclusion a correlative study of broncho alveolar lavage cytology and histopathological examination of pulmonary lesions revealed the overall sensitivity of 60%, specificity of 93.33%, and accuracy of 71.1%. The false negative and false positive cases in this study can be minimized by proper sampling, screening, and strictly adhering to adequacy criteria. The results are quite encouraging and BAL has a valuable role and is superior to other ancillary techniques of cytology in evaluating the pulmonary lesions, because of its safety, accuracy and minimal invasiveness. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. A short, paragraph summarizing the most important finding(s) of the research is required.

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