Original Article

Retrospective study of correlation between cytological and histopathological diagnosis of lung lesions

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Abstract

Background: The diagnostic modalities available for respiratory system include imaging studies and techniques that acquire biopsy specimens along with direct visualization of the respiratory system. Bronchoalveolar lavage [BAL] is one among several techniques with enormous potential and BAL cytology has been useful in the diagnosis of pulmonary neoplasms. **Aims and Objectives:** This study was conducted to find out the diagnostic accuracy of the cytology specimens obtained through BAL in detecting malignancy. Materials and Methods: This is a retrospective study of 132 cases with BAL samples and 45 biopsy samples in tertiary care hospital over a period of 2 years. **Result:** In our study the sensitivity of diagnosing malignant lesions by BAL cytology is 60% while the specificity is 93.3%. The diagnostic accuracy is 71.1%.Conclusion: BAL cytology is a valuable tool in the diagnosis of pulmonary lesions.
Key Words: Bronchoscopy, Broncho Alveolar Lavage (BAL), Histopathology, Inflammatory, Dysplasia and Malignant.

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INTRODUCTION

The respiratory tract can be categorized into upper and lower compartments. The upper airway extends from the sinonasal area to the larynx. The lower respiratory tract extends from the trachea to the lungs and this is the major focus of diagnostic cytopathology. Johnston and Frable (1845) stated that Exfoliative cytology was first used to study cells of the respiratory tract [1]. Linder J. revealed its ability to diagnose malignancy as early as 1919[2], but it was not until 1950s and 1960s, that it was developed into a valuable diagnostic modality. Rigid bronchoscopic biopsy was the standard method of obtaining specimens for definitive diagnosis of lung malignancies until the advent of flexible fibreoptic bronchoscopy in 1960`s. In 1965 BAL was introduced initially as a therapeutic procedure to clear the alveolar spaces of accumulated secretions blocking gaseous exchange, for example in alveolar proteinosis and bronchial asthma[3]. Subsequently in 1984, the technique has been used for diagnostic purposes primarily in suspected pneumocystis carinii pneumonia, replacing open lung biopsy and in 1987 in the diagnosis of interstitial lung disease and later for the diagnosis of lung tumors[4]. The cytological appearance of the common lung malignancies vary in different types of specimen. Both cytological and histological material samples taken by fibreoptic bronchoscopy are best examined together before final reports are issued. Such correlation enhances sensitivity of diagnosis, optimizes tumour typing and may prevent confusion if material with different appearances is present in biopsy and cytological samples[5]. A 100% predictive value of malignant diagnosis is the aim of our study, because cytological diagnosis is to be used for definite management decisions[6,7].

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MATERIALS AND METHODS

This is a retrospective study of 132 cases with BAL samples and 45 biopsy samples in tertiary care hospital over a period of 2 years. Personal history, clinical history and history of previous chemotherapy or radiotherapy were obtained from the records. The cytological materials from the Broncho Alveolar Lavage (BAL) were obtained using fiber optic bronchoscope.

Cytology

The sample was taken in two clean glass test tubes in equal volumes and centrifuged for 5 minutes. After discarding the supernatant fluid, smears were made on two glass slides using the sediments in the tubes. One of the smears was air dried and stained with Giemsa's stain. The other slide was kept in coplin jar containing isopropyl alcohol for 10 to 15 minutes and stained with Hematoxylin and Eosin stain.

Histopathology

The histopathology specimens of lung biopsy were fixed in 10% neutral buffered formalin. The tissues were processed; thin 5 micron sections were cut and stained with Hematoxylin and Eosin. Special stains such as PAS and Immunohistochemistry were used as and when required.

OBSERVATIONS AND RESULTS

In this study bronchoscopy was performed using flexible fiber optic bronchoscope followed by broncho alveolar lavage for 132 patients and bronchoscopic biopsy for 45 patients. Out of the 132 BAL samples, 110 were from males and 22 from females, with the male to female ratio of 5:1. Out of the 45 biopsy samples studied 41 were males and 4 were females. The prevalence of pulmonary lesions were common in males. In our study, age group of pateints range from 16 years to 72 years. We received the samples of male patients from the age group of 11-80 years and female patients in the 21- 60 years age group. It is observed that the higher prevalence of respiratory disease were in the age group of 51-60 years among males and in the age group of 41-50 years among females. In the present study the mean age group of malignant lesions in males was 52.16 years, for females was 50.75 years. [Table 1]

Table 1: Age Distribution of all cases

Age Group (in years)	No. of Cases		Total
	Male	Female	
11-20	2 (1.8%)	-	2(1.5%)
21-30	3(2.7%)	4(18.2%)	7(5.3%)
31-40	11(10%)	3(13.6%)	14(10.6%)
41-50	30(27.2%)	11(50%)	41(31.0%)
51-60	38(34.5%)	4(18.2%)	42(31.8%)
61-70	25(22.7%)	-	25(18.9%)
71-80	1(0.9)	-	1(0.75%)
Total	**110(99.8%)**	**22(100%)**	**132(99.9%)**

In the present study out of 110 males 84 (76.4%) were smokers and 26 (23.6%) were non smokers. All 22 females were non smokers. The smoker to non smoker ratio was 1.8:1. It was observed that 63.6% of the study population were smokers and smoking is a major risk factor for pulmonary diseases. Out of the 132 BAL samples 52 cases were diagnosed as non-neoplastic inflammatory lesions,20 cases as dysplasia,36 cases as malignant lesions and 24 samples were inadequate for evaluation. In this study majority of the BAL samples were inflammatory smears. Among the 52 inflammatory smears one known case of pulmonary tuberculosis on treatment showed inflammatory smears with collection of epithelioid cells. [Table 2]

Table 2: Cytological diagnosis in 132 BAL samples

Sl. No	Lesion	No. of Cases		Total cases
		Male	Female	
1	Malignant	32(29%)	4(18.2%)	36(27.2%)
2	Dysplasia	16(14.5%)	4(18.2%)	20(15.2%)
3	Inflammatory	42(38.2%)	10(45.4%)	52(39.4%)
4	Inadequate	20(18.2%)	4(18.2%)	24(18.2%)
	Total	**110(100%)**	**22(100%)**	**132(100%)**

Out of 132 cases with BAL samples, we received biopsy samples for 45 cases. The corresponding 45 BAL samples studied show malignant lesions in 11 cases, squamous cell carcinoma in 3 cases, adenocarcinoma in 4 cases and undifferentiated carcinoma in 1 case. 7 cases were dysplastic and 15 cases were inflammatory smears.4 cases had inadequate smears for evaluation. Histopathological examination of 45 biopsy samples showed malignancy in 30 cases, dysplasia in 5 cases and inflammatory lesions in 10 cases. Out of the 30 cases of malignancy diagnosed on histopathological examination, 11were squamous cell carcinoma, 7were adenocarcinoma, 2 were lepidic carcinoma, 3 cases of poorly differentiated adenocarcinoma, 2 cases of poorly differentiated carcinoma, 3 cases of anaplastic carcinoma, 1 case of small cell carcinoma and 1 case was spindle cell sarcoma/sarcomatoid carcinoma. [Table 3]

Table 3: 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	Lepedic 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%)**

Correlation of cytological diagnosis of BAL samples with histopathological diagnosis: Histopathological examination of 45 biopsy samples showed malignancy in 30 cases. The corresponding BAL smears showed malignant cells in 18 cases. Remaining 12 BAL smears did not correlate with the histopathological diagnosis. Out of the 12 smears 6 showed inflammatory lesions, 3 were dysplastic and 3 were inadequate for evaluation. Dysplasia was diagnosed in five biopsy samples. The corresponding BAL smears showed similar dysplastic cells in two cases, one case showed features of malignancy, one showed features of inflammatory lesion, and one case was inadequate for evaluation. Inflammatory lesion was diagnosed in ten biopsy samples, correlated with corresponding eight BAL samples. The other two BAL samples showed features of dysplasia. [Table 4 and 5].

Table 4: Histopathological Correlation of BAL Cases

Lesions	Total	Correlted	Not Correlated
Malignant	30	18	12
Dysplastic	5	2	3
Inflammatory	10	8	2
Total	**45**	**28**	**17**

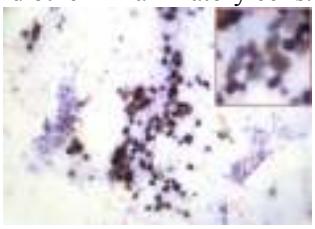
Table 5: Comparison of Cytological diagnosis of BAL with histopathological diagnosis

Cytological diagnosis	Final Histopathological Diagnosis																						Total
	NSI		DYS		SCC		AC		LC		PDAC		PDC		UDC		SmCC		Spindle cell tumour				
	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
PDAC															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, LC – Lepedic Carcinoma, PDAC – Poorly Differentiated Adeno Carcinoma, PDC – Poorly Differentiated Carcinoma, UDC – Undifferentiated Carcinoma, INF – Inflammation, IA – Inadequate.

DISCUSSION

Bronchoalveoiar lavage can address many lesions that are peripherally situated and diffuse. The goal of BAL is to diagnose pathologic conditions that are situated beyond the range of bronchosopic visualisation. The purpose of our study is to analyse the cellular elements recovered from BAL in patients with pulmonary lesions. Based on cytomorphology, cytodiagnosis was provided and correlated with histopathological diagnosis in patients who underwent bronchoscopic biopsy. For the purpose of study 132 BAL samples and 45 biopsy samples were studied. In our study the common cellular components of the respiratory cytology samples are squamous cells, bronchial epithelial cells, goblet cells, reserve cells, macrophages and other inflammatory cells. [Figure -1]



Figiure 1: BAL smear specimen adequacy showing Benign epithelial cells and macrophages > 10 / Highpower field. (Geimsa stain, 10x) Inset: shows macrophages (40x)

The commonest malignant lesion in our study was squamous cell carcinoma. Cytological diagnosis of squamous cell carcinoma was based on the identification on abnormal squamous cells with malignant nuclear criteria, including nuclear enlargement, dense hyperchromasia, angularity and irregular chromatin distribution. Squamous dysplasia is cytologically graded based on nuclear morphology, amount of cytoplasm and nuclear cytoplasmic ratio, the higher the ratio, the less differentiated the cell is and higher the grade of dysplasia. Histologically squamous call carcinoma is characterized by the presence of keratinisation and intercellular bridges. Keratinization takes the form of squamous pearls or individual cells with markedly eosinophilic dense cytoplasm[8]. [Figure 2 A and B]

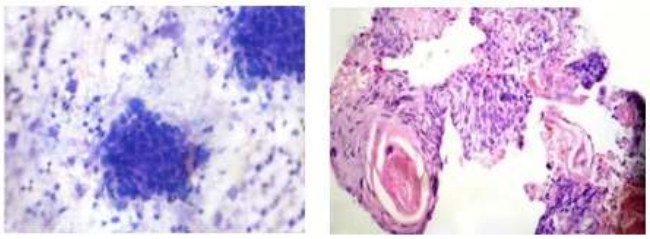


Figure 2 A: BAL smear shows malignant squamous cells in small fragments with hyperchromatic nuclei (Geimsa stain, 40x) **B:** Corresponding smear the Histopathological findings of Squamous cell carcinoma [Grade I]: Islands of malignant squamous cells with keratinisation and squamous pearl.(H and E stain,10x)

Adenocarcinoma is a malignant epithelial tumour with glandular differentiation or mucin production by the tumour cells. Adenocarcinoma appear in cytologic material as single cells and cell groups consist of ball like clusters, papillary fragments, loose clusters or true acini with central lumina. The cytoplasm is homogenous to extremely vacuolated, round to oval enlarged nuclei and finely granular chromatin. Central macronucleoli is a prominent feature of adenocarcinoma of acinar type. The two morphologic signs of glandular differentiation, often found together are formation of tubules or papillae and secretion of mucin were taken as clues foradenocarcinoma[8]. [Figure - 3]

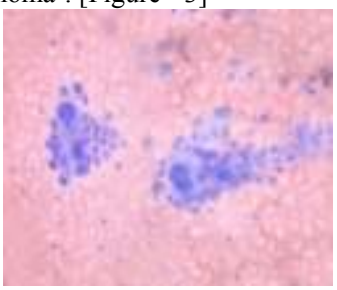


Figure 3: BAL smear showing loose clusters of acini malignant cells with pleomorphic nuclei in the mucinous background (Geimsa stain, 40x)

In our study Small cell carcinoma was diagnosed cytologically by elongated groupings of small dissociating tumour cells with scant cytoplasm, irregular moulded nuclei, coarsely stippled chromatin and inconspicuous nucleoli. [Figure 4]. Histopathologically it was identified by the growth patterns which included solid sheets, streams, ribbons, rosettes and pseudo rosettes or tubules and ductules. Nuclear moulding in cytological smears was taken as a clue for small cell carcinoma along with degenerative changes[9].

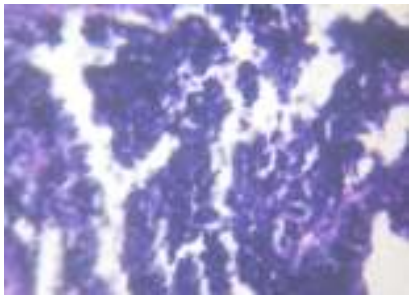


Figure 4: BAL Smear studied shows Small cell carcinoma: Round to fusiform malignant cells, scant cytoplasm, nuclei finely granular and hyperchromatic with absent or inconspicuous nucleoli. (HandE stain,40x).

Large cell undifferentiated carcinoma cells are pleomorphic malignant epithelial cells without definite evidence of either squamous or glandular differentiation. This tumour is composed of solid sheets of relatively uniform large tumour cells. This neoplasm exfoliates large numbers of diagnostic cells that appear in respiratory specimens both as large single cells and syncytial groups. Cytoplasm is usually cyanophilic and varies from granular to foamy with ill defined outlines. Nuclei round to lobulated with irregularly dispersed, intensely staining chromatin. Nucleoli may be large and vary in number from cell to cell. No evidence of keratinization is seen, and insufficient cytoplasmic differentiation is seen to warrant a diagnosis of adenocarcinoma [Figure 5]. In metastatic carcinoma, detailed clinical history, histopathological examination and immunohistochemistry was done to arrive at the diagnosis [10, 11].

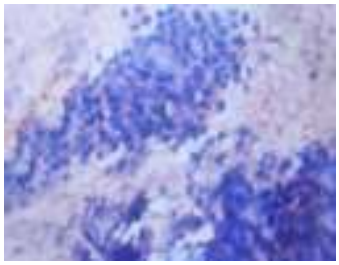


Figure 5: Microscopically BAL cytology shows undifferentiated carcinoma: Sheets and clumps of malignant cells with pleomorphic nuclei. (Geimsa stain, 40x)

Primary pulmonary sarcomas are very uncommon and few are intra bronchial origin. Those that arise in the lung seldom erode the bronchial wall and they do not exfoliate easily. The most common are leiomyosarcoma, malignant fibrous histiocytoma and fibro sarcoma, but precise classification of tumor type by cytology is difficult[12]. Further it should be emphasized that malignant spindle cells in sputum or a bronchial aspirate are much more likely to be derived from a spindle cell or sarcomatoid carcinoma. It is quite possible for a sarcoma of lung to be misinterpreted as spindle cell carcinoma. Conversely a mistaken diagnosis of sarcoma may be due to exfoliated cells of a primary or metastatic spindle cell carcinoma in lung[13]. In our study among females, one case of bronchoalveolar carcinoma and one case of spindle cell sarcoma/? sarcomatoid carcinoma was reported. Immunohistochemistry study of the spindle cell tumor was done. This tumor was immunoreactive for vimentin (focally positive) and non reactive for markers such as cytokeratin, desmin and S-100. Based on the marker study, the diagnosis was high grade fibro sarcoma. [Figure 6 and 7].

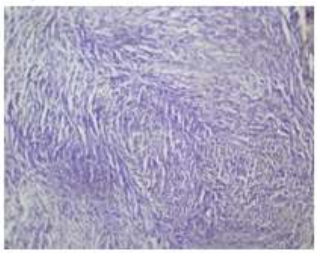


Figure 6

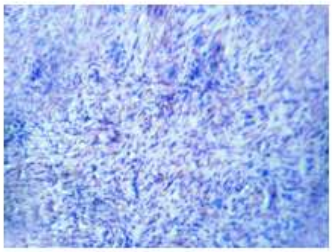


Figure 7

Figure 6: Spindle cell sarcoma: Spindle shaped tumour cells arranged in fascicles. (H and E stain,10x)

Figure 7: Immunohistochemical study Tumor cells are focal positive with vimentin. (IHC vimentin, 10x)

In all the 45 biopsy samples studied, 30 cases were diagnosed as malignant lesions of which 28 were males and 2 were females. The male to female ratio was 14:1.Faludi *et al* in their study found that the male to female ratio was 6.22:1[14], whereas study by Naziz Bhat *et al* showed male to female ratio as 5.72:1[15] and study by Bodh *et al* at 3013 showed male to female ratio of 3.35:1[16]. Smoking and environmental pollution were the main etiological factors for lung cancer. Among the 30 malignant casess diagnosed, 22 were smokers and 8 were non smokers. The smoker to nonsmoker ratio in malignant lesions was 2.75:1.This correlates well with the study of Gupta D *et al*[17] and Rajasekaran *et al*[18]. The most common type of lung cancer diagnosed in biopsy was squamous cell carcinoma (36.7%). This correlates well with the study by Bodh *et al*[16] in which the squamous cell carcinoma was the most common subtype (38.7%). Khan *et al* also found in their study squamous cell carcinoma as the most common type of lung cancer (77.3%)[19]. In our study adenocarcinoma was the second most common subtype which is in contrast with western literature where incidence of adenocarcinoma was more than squamous cell carcinoma. When comparing the diagnostic accuracy of BAL for malignancy with other studies, Linder J *et al* in 1987 studied BAL fluid for 35 cases of biopsy proven lung carcinomas and only 24 cases had cells diagnostic of malignancy on cytologic preparation of BAL fluid[20]. In 1992, piruzynski M *et al* studied BAL fluid of 145 biopsy proved lung carcinoma cases. Malignant cells were present in 94 BAL samples (64.8%)[21] The prospective study by de Gracia J *et al* in 1993 showed 43.6% diagnostic accuracy of BAL in diagnosing malignant lesions[22]. In 1994, study by De beljek A *et al* showed diagnostic accuracy of 27.9%[23]. They studied 61 BAL samples of patients with biopsy proved malignancy, out of which 17 samples showed malignant cells. In 1998 Wongsurakiat P *et al*, studied BAL samples of 30 patients with lung cancers, and reported that BAL was positive for malignant cells in 14 patients[24]. In our study the diagnostic accuracy was 71.1%.and had a correlation with the study of Pirozynski M and Linder J *et al*. Among the 45 biopsy samples 5 cases were diagnosed as dysplasia with the corresponding 5 BAL samples showed correlation as dysplastic cells in 2 cases. The remaining 3 BAL samples showed inadequate smear in one case, inflammatory smear in one case and malignant cells in one case. Our study reveals only one false positive case. False positive is mainly due to misinterpretation of smears due to cellular changes in chronic inflammatory disorders, squamous metaplasia and alveolar cell polymorphism in lung fibrosis. In our study false positive diagnosis was due to misinterpretation of dysplastic cells as malignancy. If suspicious cells are present in cytology samples, instead of over reporting it is better to correlate with clinical, radiological/ bronchoscopic findings and to repeat biopsy if necessary. Studies have shown that increasing the number of attempts at obtaining BAL sampling can improve it's sensitivity, specificity and diagnostic accuracy[25,26]. Since our study was based on single BAL sample, studying more number of samples in suspicious cases will give better results.

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%. By proper sampling, screening, and strictly adhering to adequacy criteria, the false negative and false positive cases in this study can be minimized. 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.

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