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Original Research Article

Bronchial Brushing Cytology in Evaluating Lung Cancer: Efficacy and Pitfalls

Prajwala Gupta[1], Manjari Kishore[2], Manju Kumari[3], Manju Kaushal[4], Minakshi Bhardwaj[4], Desh Deepak[5]

[1]Associate Professor, [2]Senior Resident, [3]Junior Resident, [4]Professor,
Department of Pathology, Post Graduate Institute of Medical Education and Research; Dr.Ram Manohar Lohia Hospital, New Delhi.
[5]Professor, Department of Respiratory Medicine, Post Graduate Institute of Medical Education and Research; Dr.Ram Manohar Lohia Hospital, New Delhi.

Corresponding Author: Manjari Kishore

ABSTRACT

Introduction: Lung cancer is one of the most common cause of mortality among cancer patients. A comprehensive clinicopathological approach is needed for labelling a correct diagnosis. Cytological diagnosis following fine needle aspiration (FNA) plays a pivotal role in diagnosis of lung cancer; especially in advanced stages and cases where biopsy may not be feasible. Besides, there is diagnostic role of exfoliative cytology by bronchial brushings which is a non-invasive procedure.
Aims & Objective: In the current 6-year-study, we study the role of bronchial brushing cytology in evaluation of lung cancer and its correlation with histopathology.
Materials & Methods: The present study is a retrospective study done in Department of Pathology for a period of 6 years (January 2012- December 2017). A total of 302 reported cases of bronchial brushing cytology were included. Categorisation was done based upon cytological diagnosis; however, immunocytochemistry was not done due to financial constraint. Histological correlation along with immunohistochemistry was done wherever available.
Results: Out of a total of 302 bronchial brushing cytology specimens, 208 were males and rest 94 females. The age of the patients ranged from 17-84 years with a mean age of 50.2 years. Histological findings were available in 152 cases. A total of 68 cases were reported as malignant on cytology; of which 36 cases had positive histological correlation and in rest 11 cases biopsy was inadequate. Eighty-four cases with negative cytological findings had similar histology (p value <0.05); however, 21 cases which were reported as negative on cytology had evidence of malignancy on histology. An attempt to classify the tumors into small cell lung carcinoma (SCLC) and non-small lung carcinoma (NSCLC) was done along with subclassification into adenocarcinoma and squamous cell carcinoma wherever possible. Diagnostic difficulty leading to misdiagnosis was noted in 5 cases. Few cases of pulmonary tuberculosis and occasional rare malignancies were also diagnosed on bronchial brushings while evaluating the patients clinically suspected for lung carcinoma.
Conclusion: Bronchial brushing cytology can play an excellent role in initial evaluation of lung cancer by giving an early diagnosis. Subclassification of lung tumors into SCLC or NSCLC can rarely be difficult on cytomorphology alone. In cases where biopsy is not feasible or histological findings are inadequate, bronchial brushing cytology is a reliable alternative for an early diagnosis and patient management.
Key words: Bronchial brushing, lung carcinoma, pulmonary tuberculosis, exfoliative cytology.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality. Presently, various cytologic diagnostic techniques are being used in the evaluation of suspected lung neoplasms. [1-5] Though the initial diagnosis of malignancy can be made based on clinico-radiological grounds, but the

definitive diagnosis needs cytological or histopathological examinations of the specimens from the respiratory tract. Cytological sampling is imperative as many lesions may not be feasible to biopsy. [3-6] Cytological diagnosis with ancillary techniques has been incorporated in the new World Health Organisation (WHO) classification of lung tumors. In the present study, we aim to evaluate the role of bronchial brushing cytology in diagnosis of lung cancer and correlate with the histopathological findings.

MATERIALS & METHODS

The present study is a retrospective study done in the Department of Pathology for a period of 6 years (January 2012-December 2017). A total of 302 reported cases of bronchial brushing cytology were included and correlated with the histopathology; wherever available. Rest of the respiratory cytological samples like sputum, bronchoalveolar lavage, bronchial washings, fine needle aspiration cytology was excluded from the study. The bronchial brushing samples were obtained by the pulmonologist in clinically and radiologically suspected cases of malignancy with the help of a flexible fiber-optic bronchoscope. Imprint smears were prepared from the bronchial brush and sent to cytology laboratory for further examination. Smears were fixed in 95% ethyl alcohol and air dried followed by staining with Papanicolaou and Giemsa stain; respectively. Ziehl-Neelsen staining for acid fast bacilli was also done wherever needed.

Cytological diagnosis on bronchial brushing smears were categorised into; 1) Unsatisfactory, 2) Negative for malignant cells, 3) Suspicious for malignant cells, 4) Positive for malignant cells, 5) Others. Unsatisfactory cases were those which had only haemorrhage and absence of bronchial epithelial cells. Suspicious cases reported on cytology were included in the malignant category for further statistical analysis. All cases with a specific diagnosis other than lung carcinoma were included in the "others" category. Positive malignant cases were segregated as non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). Further typing of NSCLC on cytomorphology as adenocarcinoma (AC) and squamous cell carcinoma (SCC) was not possible in all cases and immunocytochemistry was not applied due to financial constraint. Bronchial biopsy was done in feasible cases as per the clinicians' decision. Bronchial biopsy was fixed in 10% formalin for histopathological processing and subsequently stained with Hematoxylin & Eosin stain. Immunohistochemistry was applied wherever required, and final histological diagnosis was considered as the gold standard.

RESULTS

Out of the total 302 bronchial brushing cytology specimens, 208 were males and rest 94 were females; M:F=2.22:1. The age of the patients ranged from 17 to 84 years, with mean age of 50.2 years. None of the cases were unsatisfactory on bronchial brushing cytology. Out of the 302 cases, histological findings were present in 152 cases (152/302).

A total of 68 cases (68/ 302) were reported as malignant on bronchial brushings. The various diagnosis given on bronchial brushings were; 1) NSCLC favouring either squamous cell carcinoma, adenocarcinoma or poorly differentiated, 2) SCLC, 3) Large cell carcinoma (LGC), 4) Others [Table 1]. Figure 1A-D shows the classic feature of NSCLC, SCLC, AC & SCC on bronchial brushing cytology. Of all the 68 malignant cases, only 11 cases were in females and rest 57 cases were in males.

Three uncommon cases diagnosed on bronchial brushings were adenoid cystic carcinoma [Figure 2A] and primary B-cell Non-Hodgkin lymphoma [Figure 2B]; both located at the carinal end of trachea along with a case of bronchial carcinoid tumor [Figure 2C]. These cases had corresponding similar histological findings. 4 cases of

pulmonary tuberculosis with positive staining for acid fast bacilli on Ziehl-Neelsen stain were demonstrated on cytological examination [Figure 2D]. 2 cases showed evidence of fungal elements; suggestive of aspergillus.

Table 1: Cytological diagnosis of bronchial brushing smears (n=302).

Cytological reporting category	Total no. of cases (n=302)
Negative for malignant cells	222
Suspicious for malignant cells	04
Positive for malignant cells	64
Others	
Tuberculosis	04
Fungal (Aspergillosis)	01
Granulomatous	06
Carcinoid	01

Amongst the malignant cases reported on cytology (n=68), the histological findings were present in 47 cases (47/ 68). Bronchial biopsy was not done in 21 cases which were reported as malignant on cytology. Histopathology was available in a total of 152 cases for correlation of cytological diagnosis [Table 2]. Out of the cytologically diagnosed positive for malignant case, 11 cases were reported as inadequate/ negative on histopathological examination. 36 malignant cases (76.6%) on bronchial brushing cytology had corresponding malignant diagnosis. 21 cases which were reported as negative on cytology had evidence of malignancy on corresponding biopsy. Rest 84 cases (80.0%) with negative cytology had a statistically significant correlation ($p<0.05$) with the corresponding histological diagnosis of benign or negative for malignancy.

The sensitivity, specificity, positive predictive value and negative predictive values of bronchial brushing cytology for diagnosis of malignant cases were 63.2%, 88.42%, 76.6% & 80%, respectively.

Table 2: Correlation of Cytological diagnosis with the histopathology (n=152).

Cytological diagnosis (n=152)	Histological diagnosis (n=152)	
	Positive	Negative
Positive for malignancy (x=47)	36	11
Negative for malignancy (y=105)	21	84

Cytological subtyping of positive for malignancy cases (n=36) into NSCLC [Figure 1A] and SCLC [Figure 1B] was correlated with morphological types on histopathology [Table 3]. Amongst these 36 cases, positive morphological correlation was seen in 33 cases. Majority of the cases were NSCLC (n=32) and only 4 cases were of SCLC on histopathology diagnosis. Two cases reported as NSCLC on bronchial brushing smears were finally diagnosed as SCLC on histopathology. One case of SCLC reported on cytology had final diagnosis of NSCLC on biopsy.

Table 3: Morphological correlation of cytological diagnosis with histopathology in lung carcinoma (n=36).

Cytological Diagnosis (n=36)	Histological diagnosis (n=36)	
	NSCLC	SCLC
NSCLC (n= 33)	31	2
SCLC (n= 3)	1	2

An attempt was also made to subclassify the NSCLC into AC [Figure 1C] & SCC [Figure 1D]. However; amongst the cytological diagnosis of NSCLC, 1 case each of AC and SCC were subsequently reported as SCC and AC; respectively on bronchial biopsy.

Uncommon tumors reported on bronchial brushings were 1 case of typical carcinoid, 1 case of B-cell non-Hodgkin's lymphoma and 1 case of adenoid cystic carcinoma. All these cases had histological confirmation.

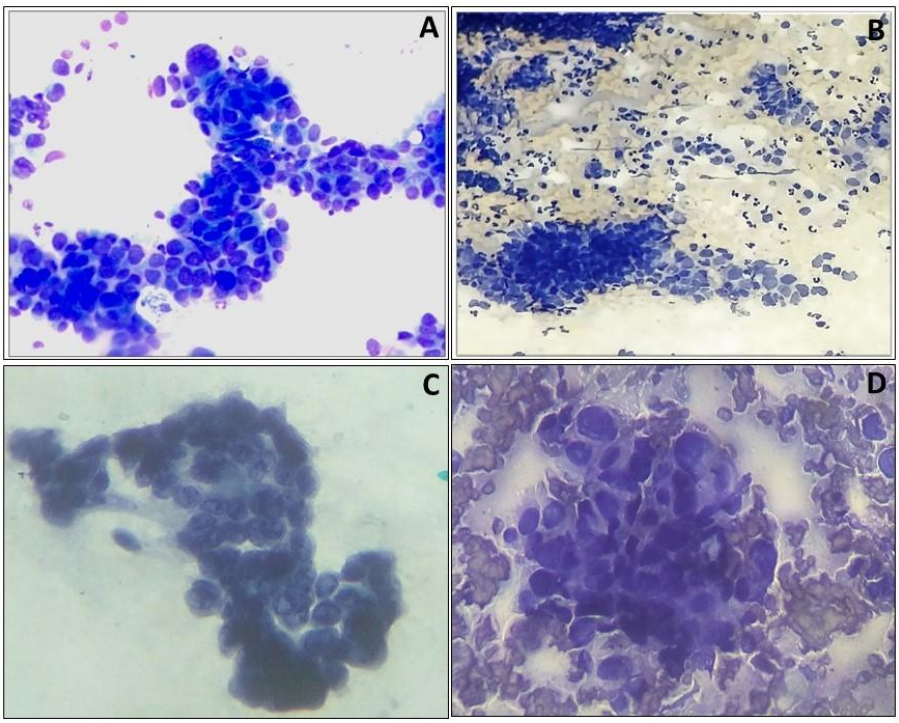

Figure 1A-D: A- Smear showing moderately sized atypical epithelial cells arranged in cluster and vague glandular pattern, favouring NSCLC [Giemsa, 200X]; B- Sheets of atypical cells showing crushing and nuclear molding, suggestive of SCLC [Pap, 100X]; C- Smear revealing atypical epithelial cells arranged predominantly in glandular pattern, favouring diagnosis of AC on cytology [Pap, 400X]; D- Loose cohesive cluster of atypical cells with moderate amount of cytoplasm and pleomorphic, hyperchromatic nuclei, suggestive of SCC on bronchial brushing cytology [Giemsa, 400X].

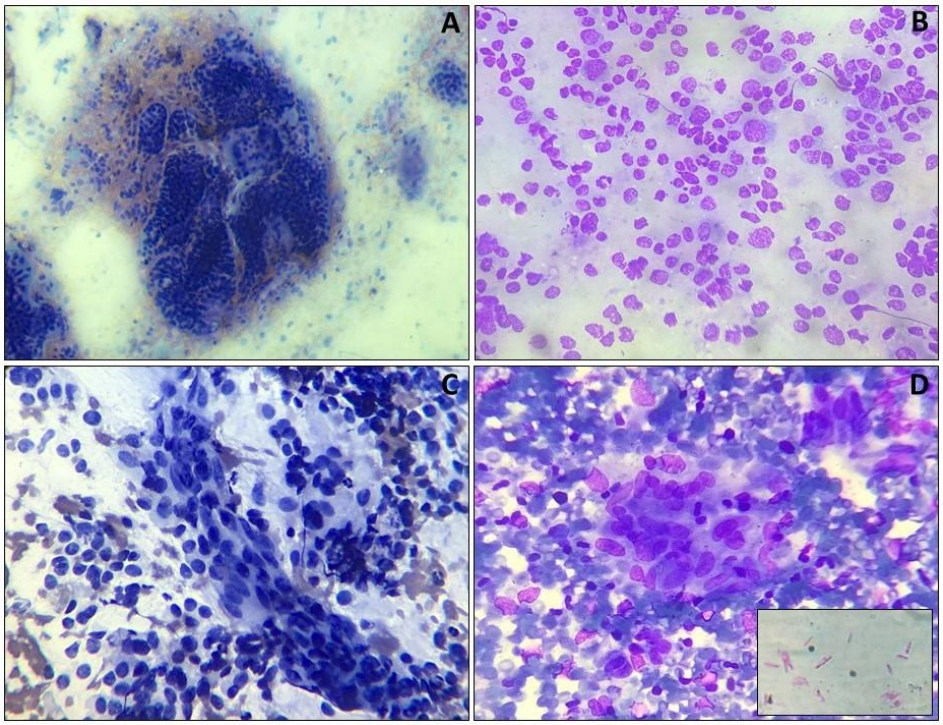

Figure 2A-D: A- Case of Adenoid cystic carcinoma revealing cup-shaped fragments of hyaline globules with mixture of small, uniform, basaloid cells with high nucleo-cytoplasmic ratios and metachromatic stroma [Pap, 200X]; B- Cellular smear revealing singly scattered atypical lymphoid cells; suggestive of Non-hodgkin lymphoma [Giemsa, 400X]; C- Monomorphic plasmacytoid tumor cells adhered around capillaries and show eccentrically placed nuclei with salt & pepper chromatin, suggestive of bronchial carcinoid tumor on cytology [Pap, 400X]; D- Epithelioid cell granuloma in bronchial brushing smear and inset shows many acid fast bacilli [Giemsa, 400X; inset- ZN stain, 1000x].

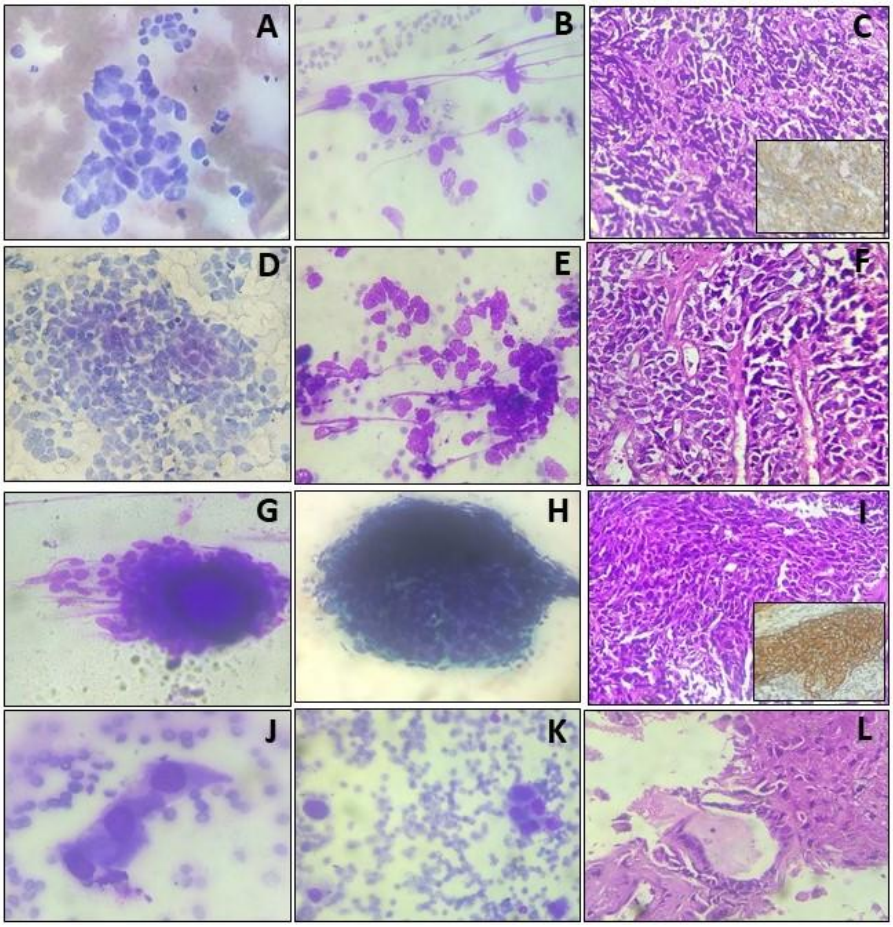

Figure 3: Figure 3A-C: NSCLC on cytology [3A, Pap, 200X] was finally proved to SCLC on cytological review showing crushing & nuclear molding [3B, Giemsa, 200X] and on histology & IHC [3C, H&E, 200X; Inset- Synaptophysin positivity, 200X]; **Figure 3D-F:** A case of SCLC on cytology [3D-Pap, 200X] was diagnosed as NSCLC on cytological review revealing vague glandular pattern [3E, Giemsa, 400X] and on histology [3F, H&E, 200X]. **Figure 3G-I:** A case diagnosed as AC on cytology [3G, Giemsa, 200X] was proved to be SCC on cytological review showing flattened cells with squamoid appearance at periphery of clusters [3H, Pap, 200X] and on histology with p63 positivity on IHC [3I, H&E, 200X; inset showing p63 positivity, 200X]; **Figure 3J-L:** A case of SCC on cytology [3J, Giemsa 200X & 100X respectively] was diagnosed as AC on cytological review showing occasional gland-like arrangement of tumor cells [3K, Giemsa, 100X] and on histology [3L, H&E, 200X].

DISCUSSION

Lung cancer is the most common cause of mortality in males. Recent studies have shown a rising trend in females as well. [1-3] Various diagnostic modalities available for an early diagnosis of lung malignancy are radiology, bronchoscopy, bronchial biopsy, exfoliative cytology and fine needle aspiration cytology. The combined use of the above techniques yields the best result. A clear distinction between NSCLC and SCLC is important as bears treatment implications. [3-7]

Though histopathological findings remain the gold standard for the diagnosis of type of lung malignancy; bronchial biopsy cannot be performed in all clinically suspected cases of lung malignancy especially if the tumor is in more peripheral location and in patients with risk of hemorrhage. In such cases, an alternative diagnostic modality is the cytopathological examination of bronchial brushings, washings or fine needle aspiration cytology, which helps in giving an early diagnosis. The recent WHO classification incorporates the importance of cytomorphology for diagnosing lung carcinoma with help of immunocytochemistry.

Fibreoptic bronchoscopy was introduced in 1968 as a diagnostic procedure, after which methods for obtaining satisfactory specimens for exfoliative cytology examination were implemented. [5-8] Our study evaluates the role of bronchial brushing cytology as a diagnostic modality in lung cancer.

In our study, male to female ratio was 2.22:1 in malignant cases diagnosed on cytology. Comparable results were noted in study by Gaur et al [9] & Arora et al. [10] The male predominance is attributed to higher prevalence of smoking, being the risk factor in lung cancers.

A study by Charles et al [11] reviewed 105 bronchoscopically acquired pulmonary cytology specimens of which 76 cases had histological diagnosis. Few other studies also noted similar results. [9-11] In our study, a total of 302 bronchial brushings cases were included of which 152 cases had histological follow up.

It is important to distinguish NSCLC from SCLC from clinical point of view as the subsequent management of the two differs. [12-17] The decisions to treat with chemotherapy versus other definitive treatment strategies may be based on cytological diagnosis with ancillary investigations in cases contraindicated for biopsy. In our study, biopsy was not available in 21 cases reported as malignant on cytology and the cytological diagnosis was the basis for guiding further treatment thereby highlighting the importance of cytology.

Certain cytomorphological clues point toward broadly categorizing lung carcinoma into NSCLC or SCLC. In SCLC there are cells with high nucleocytoplasmic ratios, scant delicate cytoplasm, nuclear molding, crush artifact, apoptotic bodies, diathesis, granular salt and pepper chromatin, inconspicuous nucleoli. [11-17] NSCLC; favouring SCC shows polygonal cells with orangeophilic cytoplasm and distinct cell borders, intercellular bridges, cell in cell arrangement, hyperkeratosis, spindle cells and hyperchromatic nucleus. NSCLC, favouring AC will show round to oval cells and arranged in 3-dimensional groups, gland formation and papillary fragments. [15-22] Cells show indistinct borders, intracytoplasmic mucin, foamy cytoplasm and vesicular opened up chromatin with prominent nucleoli or coarse chromatin.

In the current series, 33 cases of lung malignancies were diagnosed as NSCLC of which majority (31 cases) had positive histological correlation. Two of these 33 cases reported as NSCLC were found to be small cell lung carcinoma on histology. Bronchial brushing cytology smears in these two cases showed poorly differentiated cells in clusters, groups & singly scattered along with focal gland-like pattern. A diagnosis of poorly differentiated adenocarcinoma was considered initially with cells arranged in focal glandular pattern [Figure 3A]. But on review, crushing was noted in focal areas along with some evidence of nuclear overlapping & overcrowding along with nuclear molding [Figure 3B]. So, possibly lack of stippled chromatin in tumor cells on cytology led to the erroneous diagnosis of NSCLC. Histology was suggestive of SCLC and showed positive immunostaining for synaptophysin [Figure 3C]. A careful evaluation of smear is must to identify areas of crushing and cytological features like molding in absence of characteristic nuclear features.

Three cases of SCLC were reported in the present study; 1 case showed discordant histological findings with final diagnosis of NSCLC. In these smears, area of crushing was noted with some degenerative cells showing evidence of nuclear molding, which led to a wrong diagnosis of SCLC [Figure 3D]. However, on re-evaluation of the slides, foci of cells in glandular pattern were found [Figure 3E]. A final diagnosis of NSCLC was made on histology [Figure 3F]. Degenerative cellular changes may preclude a specific subtyping as was seen in this case.

Categorization of poorly differentiated NSCLC into SCC and AC is difficult on cytology and requires immunocytochemistry. [23-28] In our study 1 case each of AC and SCC were reported as SCC and AC on histology; respectively. A case diagnosed as adenocarcinoma on cytology showed mostly cohesive cluster of atypical cells, along with few singly scattered with few cells revealing mild to

moderate anisonucleosis and eccentric nuclei with granular chromatin [Figure 3G]. However, morphology was discernible at periphery of cluster. No marked pleomorphism or hyperchromasia was noted. However, on reviewing the smears again, focal areas showed flattening of the cells with squamoid appearance at the periphery of cohesive cell clusters [Figure 3H]. A final diagnosis of SCC was made based on histology and showed positive immunostaining for p63 [Figure 3I]. Hence, in cases with lack of single cells, a diagnosis of adenocarcinoma should be rendered with caution.

Similarly, a case diagnosed as SCC was finally proved to be adenocarcinoma on histology. Initially the diagnosis of SCC was given on cytology, as few atypical epithelial cells with dense cytoplasm and hyperchromatic nuclei was noted in occasional clusters and singly scattered [Figure 3J]. However, on reviewing the slide again, we could find single cell with eccentric nuclei with moderate to abundant cytoplasm with occasional gland-like pattern [Figure 3K]. Atypical epithelial cells with squamous metaplasia was mimicking as SCC in our case. In this case final diagnosis of AC was made on biopsy [Figure 3L].

Cytomorphology alone may not subtype NSCLC and the role of ancillary investigations like immunohistochemistry (IHC) on cell block is useful in distinguishing between AC and SCC in a small biopsy. AC of lung mostly shows expression of CK7, TTF-1 and E-Cadherin. SCC shows positivity for CK5/6, p63, 34βE12 and negativity for TTF-1 and CK7. [26-32] IHC for SCLS include CD56, chromogranin and synaptophysin. In cases of Large cell neuroendocrine carcinoma, the role of Ki67 is important in differentiating it from another neuroendocrine carcinoma. The 2011 IASLC/ATS/ERS in its guidelines for diagnosis of histological NSCLC subtypes in small biopsy and cytology samples has included an algorithm for appropriate use of mucin and immunohistochemical stains. Cytogenetics with application of Fluorescent in situ hybridisation (FISH) for EGFR mutation, ALK mutation, etc are promising in the diagnosis and prognosis of AC lung on cytological samples.

False positivity in diagnosis of lung malignancy on cytology can be attributed to due to chronic inflammatory cells, epithelioid cells, atypical histiocyte or squamous metaplasia. [30-32] The drawback of giving a false positive diagnosis on cytology has serious consequences for patients in which biopsy is not possible due to location of tumor or risk of haemorrhage.

It is also important to note the frequency of false negative cases on cytology. This could be due to superadded inflammation, non-representative sample, hypocellular smears or mucus production. [24-32] Other factors which contribute to false negative results are certain location of tumor or technical error in sample collection. We noted 21 cases which were negative on cytology but were found to be malignant on histology. In our cases possible non-representative area cytological sampling as normal benign bronchial epithelial were seen but lacked the representative tumor area.

Primary tracheal tumors are rare and comprise of about 0.1% of respiratory tract neoplasms and less than 1% of all malignancies. [24,32] In our study, a single rare case of adenoid cystic carcinoma was noted in trachea at the level of carina.

We also noted a case of primary B-cell Non-Hodgkin lymphoma with granulomatous lesion in a young female at the level of tracheal carinal level and diagnosed on bronchial brushings. It is an extremely rare neoplasm with an incidence of 0.5-1% of primary pulmonary malignancies. [29-32] It is important to correctly identify these tumors for appropriate therapeutic and prognostic implications.

One case of typical carcinoid tumor was reported on bronchial brushing smears. Few cases have been reported in literature

on diagnosis of carcinoid on bronchial brushings. FNAC or biopsy have better cellular yield in carcinoid; however, carries risk of torrential haemorrhage.

In our study few non-neoplastic cases were noted like pulmonary tuberculosis, aspergillosis and granulomatous lesions. Raiza et al [30] reported similar non-neoplastic lesions on cytology. These cases reveal the importance of bronchial brushings in diagnosis of clinically non-neoplastic lesions mimicking malignancy.

To conclude, bronchial brushing cytology has an excellent role in diagnosing lung cancer with subsequent morphological typing. It also helps exclude infectious lung lesions which mimic malignancy on radiology. In cases where biopsy is not feasible, bronchial brushing cytology is quite safe; however, requires expertise of pulmonologist and warrants careful evaluation of cytological smears.

Ethics statement by all authors:

This study was conducted with approval from the clinical department and as per the directives of Institutional Review Board. The corresponding author takes responsibility to maintain relevant documentation in this respect.

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