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Original Research Article

Lung cancer immunophenotypic profile: a tertiary health care institute's experience with new WHO classification

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ABSTRACT

Background: Lung cancer is one of the most common cancers accounting for 13% of all new cancer cases and 19% of cancer related deaths all over world. In India it constitutes 6.9% of all new cancer cases and 9.3% of all cancer related deaths in both sexes. The new 2015 WHO Classification recommends to apply immunohistochemistry, when possible, for small biopsies/cytology, and also for resected specimens.
Methods: An observational study with 113 cases between January 2017 to January 2019 received in the department of pathology. Morphological and immunohistochemical examination was done in each case.
Results: Based on morphology and immunohistochemistry cases were classified as adenocarcinoma, squamous cell carcinoma, adeno-squamous carcinoma, small cell carcinoma, and large cell carcinoma in accordance with 2015 WHO classification.
Conclusions: Classification and staging of lung cancer at the time of diagnosis is the most important predictor of survival in the era of specific targeted therapy. Immunohistochemistry is proved to be an invaluable tool for definite categorization of lung cancer cases.

Keywords: Lung cancer, Immunohistochemistry, WHO

INTRODUCTION

Lung cancer is one of the most common cancers accounting for 13% of all new cancer cases and 19% of cancer related deaths all over world.[1] In India it constitutes 6.9% of all new cancer cases and 9.3% of all cancer related deaths in both sexes. it is the commonest cancer in men with the highest reported incidence from Mizoram in both males and females.[2] Cancer lung occurs most often between ages of 40 and 70 years, only 2% of lung cancers appear before age of 40 years.[3]

The new 2015 WHO Classification recommends to apply immunohistochemistry, when possible, for small biopsies/cytology, and also for resected specimens.[4,5] Immunohistochemical markers are a highly effective ancillary tool for definite histological categorization of lung cancer. Most tumors can be classified using a single adenocarcinoma marker (example- TTF-1 or mucin) and a single squamous marker (example- p40 or p63). For neuroendocrine differentiation chromogranin, synaptophysin and CD56 are widely used.

The key question is that "What percentage of cases need immunohistochemistry for definite subtyping of lung cancer?". Main objective of the study is the Immunohistochemical characterization of lung carcinomas based on WHO 2015 classification and to share our experience in a tertiary health care centre. We found that to classify lung cancers according to WHO 2015

classification, a minimum panel of three immunohistochemical markers is able to classify majority of cases.

METHODS

This was an observational study, conducted in Department of Pathology, Safdarjang Hospital, New Delhi, India. A total of 113 Tru-cut biopsies of lung cancer were studied reported in last two years duration.

Inclusion criteria

Clinico-radiologically and bronchoscopy suspected cases of lung cancer. Fresh cases without prior radiotherapy or chemotherapy.

Exclusion criteria

Patients on chemotherapy were excluded from the study. Patients unable to undergo Tru-cut biopsy procedure.

Morphological and immunohistochemical examination was done in each case. A basic immunohistochemistry (IHC) panel of p63, MUC-1, TTF-1 was put on all cases. An extended panel comprising NSE and synaptophysin or chromogranin was used in those cases where all the basic panel markers were negative. The cases were then classified as per the WHO 2015 classification. Immunohistochemical stain scoring was based on the cytoplasmic, nuclear and/or membrane staining intensity as following: 0 - no staining or faint staining intensity in <10% of tumor cells; 1+ = faint staining in >10% of tumor cells; 2+ = moderate staining; 3+ = strong staining. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

A definite histomorphological typing could be done in 50 cases (44.2%) (Table 1).

Table 1: Distribution of 50 cases (44.25%) where morphologically tumours could be classified.

	SCC	Adenocarcinoma	Adenosquamous	Small cell carcinoma
No. of cases	18	20	8	4

Whereas no definite histomorphological pattern (Figure 1) was seen in 63 cases (55.8%) and thus were classified using IHC as per the WHO 2015 classification of lung carcinomas. 62 cases (Table 2) could be classified further with the help of IHC while 1 case (0.88%) remained inconclusive even after application of extended IHC panel.

Table 2: Distribution of 62 (54.87%) cases where morphology was not contributory.

	NSCLC favour ADC	NSCLC favour SQCC	NSCLC possibly adenosquamous carcinoma	NSCLC with neuroendocrine differentiation
p63 -ve, TTF-1 +ve	11	-	-	-
p63 -ve, MUC-1 +ve	10	-	-	-
p63 +ve, MUC-1 –ve	-	21	-	-
p63 –ve, MUC-1 –ve, Synaptophysin +ve, NSE +ve	-	-	-	4
p63 +ve, MUC-1 +ve	-	-	16	-

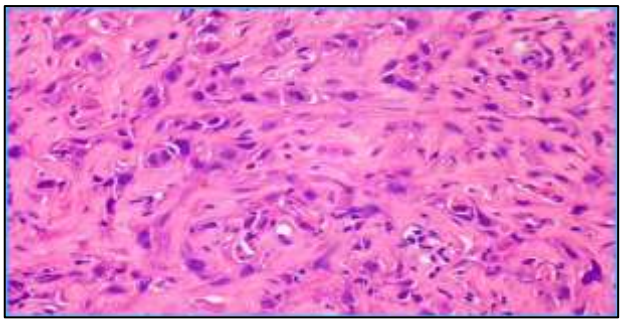

Figure 1: Morphologically inconclusive, H and E (400x).

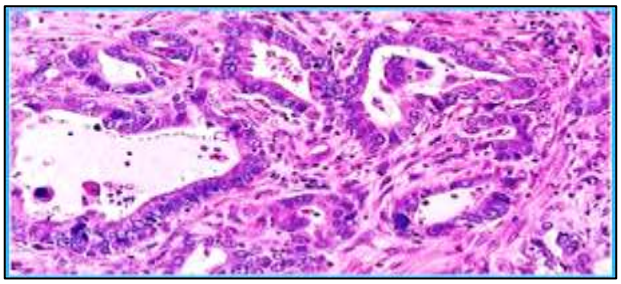

Figure 2: Adenocarcinoma showing glandular formations, H and E (400x).

Figure 3: MUC-1positive: NSCLC favour adenocarcinoma.

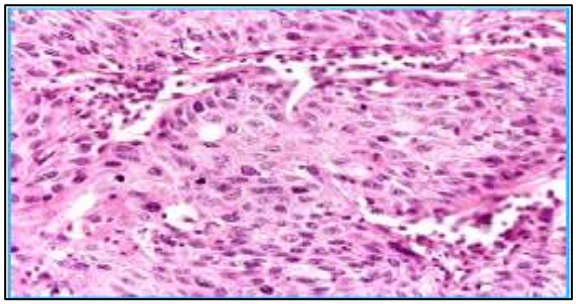

Figure 4: Squamous cell carcinoma showing tumor cells arranged in sheets, H&E(400x).

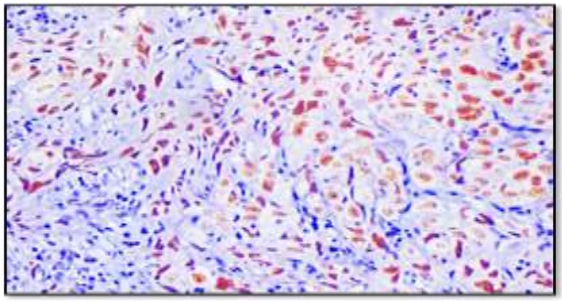

Figure 5: p63 positive NSLC favour SCC.

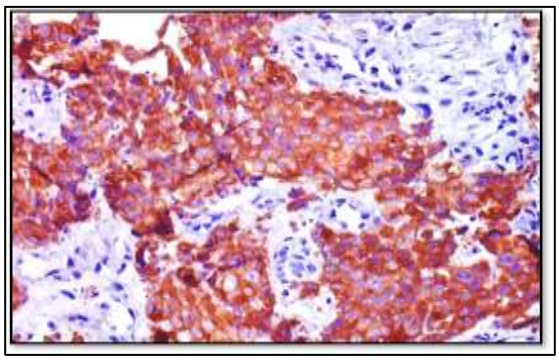

Figure 6: Synaptophysin positive: NSCLC with NE differentiation.

Morphologically classified tumors were also confirmed with IHC. Of these 113 cases, adenocarcinoma (Including NSCLC favour ADC) (Figure 2, 3) accounts to 36.3% (41 cases), followed by squamous cell carcinoma (including NSLC favour SCC; 34.5%) (Figure 4, 5), adenosquamous carcinoma (including NSCLC possibly adenoquamous carcinoma; 21.2%), NSCLC with neuroendocrine differentiation (3.5%), (Figure 6) and small cell carcinoma (3.5%).

DISCUSSION

Classification and staging of lung cancer at the time of diagnosis has been the most important predictor of survival in the era of specific targeted therapy. Approximately 60% of new cases are already at advanced clinical stage at initial diagnosis.[4] Main pitfall in classifying lung tumours especially non-small cell lung cancers is small specimen with poorly differentiated areas and low specimen cellularity.[6] The previous 1967, 1981 and 1999 WHO classifications addressed lung cancer classification based mainly on resection specimens.[7-9] Inclusion of cytology was done for the first time in 2004 WHO classification.[10-12] Recently 2015 WHO classification is given, proposing new criterias for classification of lung cancers on small biopsies/cytology.[13] when a tumour does not reflect classic morphologic criteria of glandular or squamous features, a limited stain workup must be performed in order to classify them further. The use of only one marker for adenocarcinoma and another squamous marker is suggested. From a practical perspective, probably the most accepted antibody pair is that formed by TTF-1 for adenocarcinoma and P63 for squamous tumors. Tumors staining for adenocarcinoma markers are termed as NSCLC-favor adenocarcinoma (Figure 3), While tumors positive for squamous markers are classified as NSCLC-favor squamous-cell carcinoma (Figure 5). Tumors that can not be further classified in spite of these methods remain diagnosed as NSCLC-not otherwise specified (NOS). The concept of large-cell carcinoma is restricted to resection specimens, where the tumor is completely sampled excluding a differentiated pattern. In our study, approximately 55.8% cases were inconclusive on morphology. For definite subtyping, a basic panel of p63, MUC-1 and/ or TTF-1 was used; one marker for squamous morpholgy and other two for glandular. Maximum cases found were of adenocarcinoma followed by squamous cell carcinoma and adenosquamous carcinoma. Enough number of cases showing both squamous and glandular morphology (21.2%) were found. 1 case (0.88%) remained inconclusive even after application of extended IHC profile which was labelled as NSCLC-NOS.

CONCLUSION

Classification and staging of lung cancer at the time of diagnosis is the most important predictor of survival in the era of specific targeted therapy. Approximately 44% of the cases could be diagnosed based purely on histomorphology. However for classifying rest of the cases IHC was important. A basic panel of minimum three IHC markers including p63, MUC-1 and TTF-1 is adequate for categorizing majority of morphollogically inconclusive cases except the neuroendocrine variant where an extended panel is required. Immunohistochemistry is

proved to be an invaluable tool for definite categorization of lung cancer cases.

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Ethical approval: The study was approved by the institutional ethics committee

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