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Original Article

Pathology Section

Significance of Immunohistochemistry Testing in the Diagnosis and Subtyping of Lung Carcinomas- A Retrospective Study from a Tertiary Care Centre in Southern Rajasthan

PREETI AGRAWAL[1], KAVITA GUPTA[2], PAWAN NIKHRA[3], MALA JAIN[4], MEGHA PANDEY[5], ASHISH PANDEY[6]

ABSTRACT

Introduction: In the present era, the classification of lung carcinoma is not confined to Small Cell Lung Carcinoma (SCLC) and Non Small Cell Lung Carcinoma (NSCLC). Precise subtyping of lung carcinoma has a direct impact on patient management and prognosis. Further molecular study helps in identifying adenocarcinoma receptors, such as Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK), which are useful in targeted therapy.

Aim: To assess the role of Immunohistochemistry (IHC) in accurate diagnosis and subtyping of lung carcinoma and to analyse the prevalence of EGFR mutations and ALK rearrangement in lung adenocarcinoma.

Materials and Methods: A retrospective hospital-based, observational study was conducted at the Department of Pathology of American International Institute of Medical Sciences, Udaipur, Rajasthan from January 2020 to August 2021. Total of 105 cases of guided core needle biopsies from lung and bronchoscopic biopsies were included. IHC markers were applied based on histopathological diagnosis from a panel of p63, Cytokeratin 7 (CK7), AE1/AE3, Thyroid Transcription Factor (TTF1), Napsin A, p40, synaptophysin, chromogranin, CD56 and Ki67. Adenocarcinoma cases were further analysed for EGFR mutations and ALK rearrangements. Data was tabulated and analysed statistically using Microsoft excel to determine the percentage frequency distribution of cases.

Results: Among 105, there were 88 males and 17 females and the mean age of the population was 60.57 years. The most prevalent subtype of lung malignancy was squamous cell carcinoma (44.7%) followed by adenocarcinoma (29.5%). The diagnostic accuracy of squamous cell carcinomas and adenocarcinomas on morphology was 93.1% and 84.6%, respectively and for small cell carcinoma it was 100%. Amongst 28 cases of adenocarcinoma, EGFR mutation was found in 46.42% cases whereas ALK mutation was found only in 21.42% cases.

Conclusion: The study highlights the importance of IHC, and a substantial prevalence of EGFR mutations was found in patients with lung carcinoma.

Keywords: Adenocarcinoma, Bronchoscopic, Small cell carcinoma, Synaptophysin

INTRODUCTION

Lung carcinoma is a significant public health issue. It is the second most common cancer worldwide and most common cause of cancer related death according to World Health Organisation (WHO). Every year, it results in 1.76 million cancer-related deaths [1]. Lung cancer is less common in India than in the west. It is the second most prevalent cancer in men and the sixth most frequent cancer in women [2].

The WHO 2015 classification of lung tumours provides a new classification for small biopsies, emphasising the importance of accurate subclassification of lung cancers and the critical role of IHC markers [3]. Primary lung carcinoma have been categorised into SCLC and NSCLC. NSCLC accounts for over 80% of lung cancer cases. The most prevalent histological forms of NSCLC are adenocarcinoma (50-70%) and Squamous Cell Carcinoma (SCC) (20-30%).

The majority of lung cancer patients are detected late in the course of disease, where small biopsies remain the gold standard method for reliable diagnosis [4]. Application of IHC aids in correct histological categorisation, guides in deciding on additional molecular tests and therapy options [4,5]. Molecular studies of lung cancers has led to the development of targeted therapies [6,7].

The introduction of IHC has proven to have a beneficial role in the areas of diagnostic dilemmas because of morphological variability of lung cancers [8]. IHC confirms the diagnosis in morphologically diagnosed cases as well as contributes in diagnosing poorly differentiated neoplasms where morphology alone is insufficient [9].

Several biomarkers for NSCLC have emerged, including EGFR mutations, ALK gene alterations, c-ros oncogene 1 (ROS1) rearrangements, BRAF V600E point mutations, and *PD-L1* expression levels [10]. EGFR mutations and ALK rearrangements predict response to targeted therapies such as EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) [11-14].

The aim of the present study was to assess the role of IHC in accurate diagnosis and subtyping of lung carcinoma and also to analyse the prevalence of EGFR mutations and *ALK* rearrangement in lung adenocarcinoma cases in Southern Rajasthan population.

MATERIALS AND METHODS

A hospital-based, retrospective study was conducted at the Department of Pathology of American International Institute of Medical Sciences, Udaipur, Rajasthan, India from January 2020 to August 2021. Evaluation of data obtained was done in

October 2021. Ethical clearance was obtained from the Institutional Ethics Committee.

Inclusion and Exclusion criteria: Cases of lung carcinoma diagnosed by core needle or bronchoscopic biopsies from January 2020 to August 2021 were included in the study. Cases with insufficient biopsy material and predominantly necrotic tissue were excluded.

Study Procedure

Clinical data such as age, sex, and clinical features were collected from Medical Records Department. Paraffin-embedded, 4 µm-thick sections of the tumours were stained by Haematoxylin and Eosin (H&E) stain and were studied. All the blocks were reanalysed and subtyped as per the diagnostic criteria given in WHO 2015 classification of lung tumours [3]. IHC was done judiciously depending on the H&E morphology and included monoclonal antibodies for CK7, TTF1, p63, AE1/AE3, Napsin A, p40, synaptophysin, CD56, Ki67 and polyclonal chromogranin. Cases which were negative for the above lung markers were sent to other laboratory for extensive IHC panel to arrive at a diagnosis, as researchers had limited panel of IHC markers at the institute. Confirmed cases of adenocarcinoma were also sent to other laboratory for EGFR and ALK mutation analysed by Real Time Polymerase Chain Reaction (ARMS RT-PCR).

STATISTICAL ANALYSIS

Data was tabulated and analysed statistically using Microsoft excel to determine the percentage and frequency distribution of cases.

RESULTS

There were 105 patient records that were studied. Majority of lung carcinomas were seen in elderly with a peak incidence in the sixth decade followed by fifth decade. Median age at presentation of the cases was 60.5 years (range 27-85 years) [Table/Fig-1]. Male preponderance was seen in lung carcinomas of all age groups. There were 88 males and 17 females in this study with a male to female ratio of 5.1:1.

The most prevalent subtype of lung malignancies was SCC (44.7%) followed by adenocarcinoma (29.5%) [Table/Fig-2].

Age range (in years)	Number of cases	Percentage
21-30	01	0.9%
31-40	06	5.7%
41-50	14	13.3%
31-60	23	21.9%
61-70	40	38.1%
71-80	18	17.1%
81-90	03	2.8%

[Table/Fig-1]: Age distribution of lung malignancies (N=105).

Diagnosis	Frequency	Percentage
Squamous cell carcinoma	47	44.7%
Adenocarcinoma	31	29.5%
Small cell carcinoma	10	9.5%
Adenosquamous carcinoma	04	3.8%
Non small cell carcinoma, NOS	02	1.9%
Sarcomatoid carcinoma	02	1.9%
Large cell neuroendocrine carcinoma	01	0.9%
Synovial monophasic sarcoma	01	0.9%
High-grade Non Hodgkin lymphoma	01	0.9%
Metastatic carcinoma	06	5.7%

[Table/Fig-2]: Frequency of various histological subtypes of lung malignancies in this study.
• N=105; NOS (not otherwise specified)

Apart from the common lung carcinomas, there were two cases of sarcomatoid carcinoma, one case of synovial monophasic sarcoma, one of high-grade Non Hodgkin's lymphoma (NHL), and six cases of metastatic carcinoma. All these cases were diagnosed morphologically as NSCLC due to epithelioid morphology, poor differentiation and crushing artefacts in some limiting morphological assessment. These cases were finally reclassified following extensive panel of IHC and subtyped [Table/Fig-3]. Thus, in cases with poorly differentiated morphology, IHC is of paramount importance to arrive at a final diagnosis. IHC also helped in confirming the diagnosis of morphologically diagnosed cases.

The SCC cases were positive for p40 (44/47,93.6%), and p63 (42/47,89.3%) IHC markers. Thyroid transcription factor (TTF1) (26/31, 83.8%), Napsin A (24/31, 77.4%) and CK7 (27/31, 87.1%) were expressed in adenocarcinoma cases. Four cases of adenosquamous carcinoma were positive for p40, TTF1, Napsin A and CK7. Synaptophysin and Ki67 expression were found to be 100% in small cell carcinoma, while chromogranin and CD56 were positive in 70% of cases. One case of large cell neuroendocrine carcinoma showed positive staining for synaptophysin, CD56, AE1/AE3, and Ki67.

Two cases of sarcomatoid carcinoma showed positivity for TLE1 and negativity for p40, TTF1, calretinin, S100, CD34, and desmin. One case was diagnosed as synovial monophasic sarcoma based on positive expression for TLE1, CK7, BCL2 and negative expression for p40, TTF1, S100, CD34, and desmin. One case was diagnosed as high-grade NHL with positivity for CD45, CD3, CD20, CD23, CD10, BCL6, and ALK and negativity for p40, TTF1 and TLE1. Total 6 cases of metastatic carcinomas were confirmed with the help of IHC. The primary sites of origin for these cases were breast (2/6), kidney (1/6), cervix (2/6) and prostate (1/6) [Table/Fig-4].

Histopathology diagnosis was compared to final diagnosis obtained after performing IHC. All 10 cases of SCLC were identified accurately on morphology, so as single case of large cell neuroendocrine carcinoma [Table/Fig-5]. The diagnostic accuracy of SCC and adenocarcinomas on morphology was 93.1% and 84.6%, respectively [Table/Fig-6]. The diagnostic pitfalls of histopathology were in the poorly differentiated cases, which showed no clear differentiation of adenocarcinoma, squamous cell carcinoma, or neuroendocrine pattern. All these cases were finally diagnosed by IHC and reclassified. Out of 11 cases of poorly differentiated carcinomas on morphology, five were diagnosed as adenocarcinomas and four were squamous cell carcinomas (4, 36.3%) [Table/Fig-7]. Two cases were negative for TTF1, Napsin A, p63 and p40, were classified as non small cell carcinomas, NOS (not otherwise specified) (2, 18.2%). Other 10 cases which were negative for most of the lung markers, were subjected to extensive IHC panel and subsequently subtyped. Two were sarcomatoid carcinoma, one synovial monophasic sarcoma, one high-grade NHL and six metastatic carcinomas.

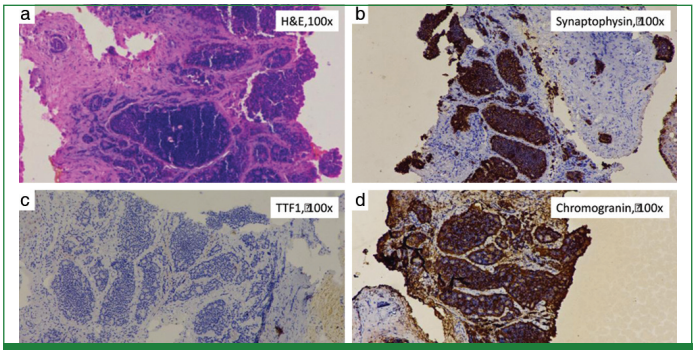
The EGFR mutation and ALK rearrangement analysis was performed on 28 out of 31 confirmed cases of adenocarcinoma by RT-PCR. It could not be performed on rest three cases as the tumour tissue got depleted following extensive IHC panel. Amongst 28 cases of adenocarcinoma, EGFR mutation was found in 46.42% cases whereas ALK mutation was found only in 21.42% cases and the expression was mutually exclusive [Table/Fig-8].

IHC	SCC (n=47)	Adenocarcinoma (n=31)	Adenosquamous (n=4)	Small cell carcinoma (n=10)	Non small cell carcinoma, NOS (n=2)	Large cell neuroendocrine carcinoma (n=1)	Others (n=4) (excluding 6 cases of metastasis)
TTF1	2 (4.6%)	26 (83.8%)	4 (100%)	7 (70%)	0	0	0
P40	44 (93.6%)	2 (7.6%)	4 (100%)	1 (10%)	0	0	0
P63	42 (89.3%)	3 (11.5%)	0	0	0	0	0
Synaptophysin	1 (2.32%)	1 (3.8%)	0	10 (100%)	1 (50%)	1 (100%)	0
Napsin A	0	24 (77.4%)	3 (75%)	1 (10%)	0	0	0
CD56	0	1 (3.8%)	0	7 (70%)	0	1 (100%)	0
Chromogranin	0	1 (3.8%)	0	7 (70%)	0	0	0
CK7	1 (2.3%)	27 (87.1%)	3 (75%)	0	1 (50%)	0	0
Ki67	0	2 (7.6%)	3 (75%)	10 (100%)	2 (100%)	1 (100%)	0

[Table/Fig-3]: Immunohistochemical profile of different histological types of lung carcinomas.

Metastasis (n=6)	Breast (n=2)	Prostate (n=1)	Kidney (n=1)	Cervix (n=2)
p40	N	N	N	N
TTF1	N	N	N	N
NKX3.1	-	P	-	-
GATA3	P	-	-	-
CK20	N	-	-	-
AMACR	-	P	-	-
Vimentin	-	-	P	-
p16	-	N	-	P
p63	-	-	-	P

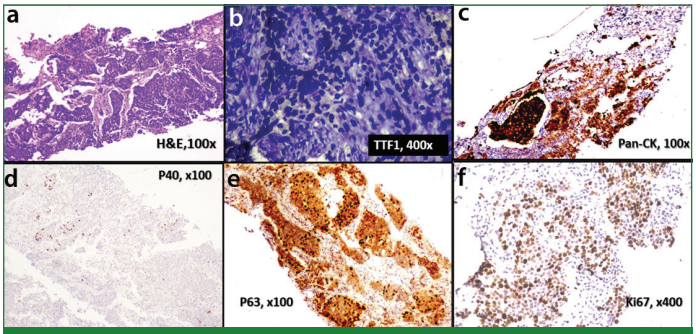
[Table/Fig-4]: IHC profile for lung metastatic tumours (N=6).
N: Negative; P: Positive



[Table/Fig-5]: Photomicrograph shows a case diagnosed as small cell carcinoma on H&E (a, x100) and confirmed as same following IHC. The tumour cells were positive for Synaptophysin (b, x100), Chromogranin (d, x100) and negative for TTF-1 (c, x100).

Histology diagnosis	SCC	Adenocarcinoma	Adeno squamous carcinoma	Small cell carcinoma	Large cell neuroendocrine carcinoma	Non small cell carcinoma, NOS	Others	Diagnostic accuracy (%)
SCC	40	2	0	1	0	0	0	92.1
Adenocarcinoma	2	22	0	2	0	0	0	84.6
Adenocarcinoma	1	1	2	0	0	0	0	50
Small cell carcinoma	0	0	0	10	0	0	0	100
Large cell neuroendocrine carcinoma	0	0	0	0	1	0	0	100
Poorly differentiated carcinoma	4	5	0	0	0	2	10	0

[Table/Fig-6]: Comparison of diagnostic accuracy of lung tumours based on initial histopathological diagnosis and IHC.



[Table/Fig-7]: Photomicrograph shows a case diagnosed as poorly differentiated carcinoma on H&E (x100) and as squamous cell carcinoma following IHC. The tumour cells were positive for Pan-CK (C, x100), P63 (E, x100), focal positive for P40 (D, x100) and negative for TTF-1 (B,x400).

Adenocarcinoma (n=28)	Positive	Negative
EGFR	13 (46.42%)	15 (53.57%)
ALK	6 (21.42%)	22 (78.75%)

[Table/Fig-8]: EGFR and ALK profile in adenocarcinoma cases.

DISCUSSION

Accurate classification of lung tumours along with molecular profiling lays the foundation stone for effective treatment protocols. IHC testing is widely available technique now-a-days. If performed by trained technician, it gives accurate and meaningful results and is cost-effective in comparison to other techniques. The median age in the present study was 60.5 years which was slightly higher as compared to other studies [Table/Fig-9] [15-19]. The gender ratio was 5.1:1 which was also higher as compared to other studies with predominance of male patients. This study has shown higher number of SCC cases than adenocarcinoma cases which was concordant with the findings of Dey A et al., and Singh N et al., [Table/Fig-9] [16,18].

The frequency of expression of TTF1(26/31,83.8%) and Napsin A (24/31,77.4%) in adenocarcinomas in this study were almost comparable with studies by Mallick D et al., (both TTF1 and Napsin A-92%), Bhatti V et al., (TTF1-85.4% and Napsin A-92%) and Mukhopadhyay S et al., (TTF1-80% and Napsin A-58%) [19-21].

The diagnostic accuracy for SCC (92.1%) and adenocarcinomas (84.6%) with classical histomorphological features is significant. However, for poorly differentiated carcinomas, IHC needs to be applied to accurately subclassify these cases. IHC panel should be applied in conjuncture with morphology in a step-wise manner for optimal use of tissue and reagents. Initially, a panel consisting of p40, TTF1, p63, CK7 and Napsin A was applied to differentiate between SCC and adenocarcinoma. In cases of tumours showing neuroendocrine morphology, synaptophysin, chromogranin and CD56 was performed. However, for poorly differentiated carcinomas, tumours with dual morphology and metastatic carcinomas, many IHC markers were used to arrive at a diagnosis.

Authors	Duration of study (yrs)	No. of cases	Median age (yrs)	Male to female ratio	SCC (%)	Adenocarcinoma (%)	Small cell carcinoma (%)	Others (including all other lung cancer subtypes) (%)
Malik PS et al., [15]	3	434	55	4.6:1	25.1	41.0	14.8	19.1
Dey A et al., [16]	4	607	47.4	4.1:1	35.1	30.8	16.5	17.6
Noronha V et al., [17]	1	489	56	3.5:1	24.1	40.3	8.0	27.6
Singh N et al., [18]	1.5	250	57.9	4.4:1	34.8	26.0	18.4	20.8
Mallick D et al., [19]	3	83	58	2.5:1	28.2	38.1	7.9	25.8
Present study	1.5	105	60.5	5.1:1	40.9	24.7	9.5	34.2

[Table/Fig-9]: Comparison of different studies with present studies [15-19].

Squamous cell carcinoma cases showed significant positivity for p40 (93.6%) and p63 (89.3%) in the present study. Mallick D et al., showed 82% positivity for p40 while Stojsic J et al., showed absolute positivity (100%) for CK5/6 and p63 in squamous cell carcinomas [19,22].

Apart from primary lung malignancies, lung is a frequent target of metastasis. IHC not only helps in identifying metastatic diseases, it also guides in diagnosing the primary site of origin when its unknown. In the present study, there were six cases of metastatic carcinoma from various sites of primary tumours such as breast, cervix, kidney and prostate.

The EGFR is a transmembrane glycoprotein receptor which has a role in activation of cytoplasmic tyrosine kinase domain. This in turn elicits downstream signalling pathways that leads to cell proliferation and tumourigenesis [11]. ALK is also a tyrosine kinase activator and is oncogenic driver of lung adenocarcinoma [13]. In this study, EGFR and ALK mutation was found in 46.4%, and 21.42% respectively. Shankar S et al., found EGFR mutation in 89% of cases of lung adenocarcinoma [23].

In the present study, it is found that histomorphological features, as well as IHC, plays a crucial role in the exact categorisation of lung carcinomas. In the era of chemotherapy and targeted therapy, it is crucial to accurately subtype every case of lung carcinoma. Characterisation of histologic type of lung cancer plays an increasingly pivotal role in the multidisciplinary approach in the diagnosis and management of lung cancer. Recognising the biological diversity of lung cancer, a comprehensive and accurate tumour classification has been developed, which is important for treatment and prognosis. Between 30 and 50% of cancers can currently be prevented by avoiding risk factors and implementing existing evidence-based prevention strategies [24]. In future a larger study can be done with follow-up of patients and determination of overall survival and progression free survival associated with different subtypes of lung carcinoma.

Limitation(s)

Being a retrospective study, the follow-up findings of the patients could not be studied, and hence the prognosis remained unknown.

CONCLUSION(S)

The proposed panel of IHC markers can help in accurate classification of lung carcinoma. The p40, p63, TTF-1 and Napsin A are useful immunohistochemical markers for distinguishing SCC from the adenocarcinoma in biopsy specimens, whereas EGFR and ALK can be used for therapeutic purposes in adenocarcinoma cases. In this era of targeted therapy, an accurate diagnosis of lung cancer is crucial as these drugs are less toxic than generic chemotherapeutic agents. Also they are more effective as they inhibit mutation driven genetic alteration.

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PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.
2. Associate Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.
3. Associate Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.
4. Assistant Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.
5. Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.
6. Associate Professor, Department of Pathology, American International Institute of Medical Sciences, Udaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mala Jain,
T/5, New Santosh Nagar, Tekari Madari, Gayariawas,
Udaipur-313002, Rajasthan, India.
E-mail: drjain.mala@gmail.com

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