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Immunohistochemistry comparison of Napsin A and CK7 expression in primary lung adenocarcinoma

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Abstract
Background: Lung cancer is the most common cancer worldwide and the leading cause of cancer-related death. Lung carcinomas are broadly divided into small cell carcinoma and non-small cell lung carcinoma (NSCLC). Non-small cell lung cancer accounts for 80% of lung cancers and lung adenocarcinoma is one of the main types of NSCLC. Here we studied the significance of the commonly used lung adenocarcinoma diagnostic markers, including TTF-1, Napsin A and CK7, in the diagnosis of lung adenocarcinoma using immunohistochemical (IHC) analysis.
Aim: To evaluate and compare the significance of IHC markers, CK 7 and Napsin A in diagnosis of lung adenocarcinoma as far as specificity and reliability are concerned.
Material and Methods: This study was conducted over a period of 5 years, from 2018 to 2022 which included all cases diagnosed as lung carcinoma on tissue biopsies and later subjected for IHC using relevant markers like CK7, TTF-1, Napsin-A, CK5/6, p63, Synaptophysin and Chromogranin A. 47 cases of lung adenocarcinoma were selected from the retrospective database of lung cancer.
Results: Among the 47 cases of lung adenocarcinoma. IHC was done on 41 cases (87.23%). Immunocytochemistry (ICC) was done on 6 cases (12.8%). Lung adenocarcinoma IHC markers study shows CK 7 positive and Napsin-A negative in 21 cases (51.2%). CK 7 negative and Napsin-A positive only in 1 case (2.4%). Both are positive in 16 cases (39.0%) and both were negative in 3 cases (7.3%). ICC was studied in total 6 cases which show CK 7 positivity in 4 cases (66.7%). Only 2 case of ICC show Napsin-A positivity (33.3%).
Conclusion: As far as IHC is concerned CK 7 is more reliable and specific than Napsin-A in diagnosis of primary lung adenocarcinoma.

Keywords: Adenocarcinoma, Immunohistochemistry, Immunocytochemistry, Lung carcinoma, Napsin A, Cytokeratin 7

Introduction
Lung cancer is a major public health problem. It is the most common cancer worldwide and the leading cause of cancer-related mortality, accounting for 1.76 million cancer deaths per year. It is almost twice more common in males than in females [1].
In India, the incidence of lung cancer is lower than that in the west. It is the second most common cancer in males, while in females, it is ranked 6th. The mortality rate is ranked 4th after breast, cervix, and lip-oral cavity cancer [2].
It is a challenge for a pathologist to accurately diagnose and classify lung cancer in small biopsies. However, appropriate use of immunohistochemistry (IHC) assists in precise histological classification, which serves as the foundation for choosing additional molecular testing and treatment planning [3]. Immunochemistry is indicated in four settings, namely (a) to help establish malignancy (b) to determine cell lineage (c) to ascertain the primary site of tumor origin, and (d) for prognostic and therapeutic assessment with a few adaptations and precautions, most of the principles that govern the application of IHC to surgical specimens can also be applied to cytopathology.
Immunochemistry can be done on whole tissue specimens, fine needle aspiration smears, cytospins of fluids, or cell blocks. Cell blocks are the more optimal specimen on which ICC should be performed [4].
The precursor lesion for adenocarcinoma is thought to be atypical adenomatous hyperplasia (AAH), which is also found peripherally [5].

AAH is defined as a proliferation of atypical type II pneumocytes with gaps between the cells and is ≤ 0.5 cm. It is evident that AAH represents the premalignant stage of nonmucinous bronchioloalveolar carcinoma (BAC), another peripherally located lesion. Due to a 100% disease-free survival rate following complete resection of these preinvasive lesions, the term BAC will be withdrawn from the new proposed classification of lung adenocarcinoma and replaced by adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) (6). Both AIS and MIA are classified as having a size of 3 cm or less and a lepidic growth pattern, however MIA has an invasive component that measures 0.5 cm or less in the largest dimension of each focus. Both lesions are usually nonmucinous. In addition to AIS and MIA, other new terms that are used to describe BAC depending on the morphology include lepidic predominant adenocarcinoma (nonmucinous), invasive mucinous adenocarcinoma (formerly mucinous BAC) and adenocarcinoma predominantly invasive with some nonmucinous lepidic components [6]. IHC has been used to show that that some adenocarcinomas actually arise centrally, and that these centrally derived tumors do not derive from AAH. On the other hand, immunohistochemical and EGFR mutational patterns in peripherally derived adenocarcinomas are similar to those in AAH [7]. These peripherally derived adenocarcinomas resemble terminal respiratory epithelial cells in terms of their cellular appearance (type II pneumocytes, Clara cells and non-ciliated bronchiolar cells). Goblet cell hyperplasia, reactive or atypical bronchial epithelial cells, granular cell tumors, and hamartomas must be distinguished from adenocarcinoma [8].

TTF-1 is now widely used to identify adenocarcinomas of pulmonary origin, with a sensitivity of 75-94% and a specificity of 100% [9]. CK7 is also useful in identifying adenocarcinomas of pulmonary origin. Typically, an adenocarcinoma of pulmonary origin will stain positive for CK7 but negative for CK20 [9-11]. As was previously mentioned, CK20 is used to distinguish adenocarcinomas from those of the gastrointestinal tract or the urothelium since it is not expressed in the epithelium of the respiratory airways [12-14]. As previously mentioned, Napsin A can also be utilised to identify primary lung cancer. For instance, Napsin A has been utilised to distinguish primary pulmonary adenocarcinomas from adenocarcinomas from other organs [15-16].

Aim

To evaluate and compare the significance of IHC markers, CK 7 and Napsin A in diagnosis of lung adenocarcinoma as far as specificity and reliability are concerned.

Material and Methods

In this retrospective study, a total of 47 cases diagnosed with lung adenocarcinoma has been studied at our institute for a duration of 5 years, from 2018 to 2022. The detailed clinical history such as patient's age, habits like smoking or chewing tobacco, disease stage, histopathological findings, treatment offered and disease status was retrieved. All the 47 cases of these primary lung adenocarcinomas were first reported on Haematoxylin and Eosin sections and were later subjected for IHC using markers like CK7, TTF-1, Napsin-A, CK 5/6 and p63.

Immunohistochemical localization was performed on formalin fixed paraffin embedded (FFPE) tissue blocks containing primary tumor evaluated by Hematoxylin and Eosin (H & E) staining in our pathology department, M.P. Shah Medical college.

Inclusion criteria

All cases having histopathological morphology of primary non-small cell carcinoma.

Exclusion criteria

Inadequate biopsy material for performing IHC panel for lung.

Result

A total of 47 cases of lung adenocarcinoma was studied. The overall male-to-female (M: F) ratio was 3.0:1.0, and the age ranged from 33 to 90 years with a mean of 60.9 ± 11 years. The mean age for males and females was 61.6 and 59.1 years respectively. The age group of 51-70 years comprise of 65.9% of the total patients. The age and gender distribution of lung carcinomas are shown in Table 1.

Table 1: Distribution according to age

Age range	Total cases	percentage
30-40	03	06.4%
40-50	04	08.5%
50-60	14	29.8%
60-70	17	36.1%
70-80	06	12.8%
80-90	03	06.4%
Total	47	100%

In our study the maximum number of patients were in the age group of 51 to 70 years which comprise of 65.9% of the total patients. 6.4% of the patients were in the age group of 30 to 40 years, 8.5% of the patients were in the age group of 40 to 50 years, 12.8% of the patients were in the age group of 70 to 80 years and 6.4% 0f the patients were in the age group of 80 to 90 years.

Table 2: Distribution according to Expression of markers in IHC study of lung adenocarcinoma:

Immunohistochemical profile	CK 7	Napsin A
Positive	37 (90%)	17 (41.5%)
Negative	04 (9.8%)	24 (58.5%)
Total	41	41

In our study CK 7 was positive in 90% of the cases and negative in 9.8% of the cases. Napsin-A was positive in 41.5% of the cases and negative in 58.5% of the cases.

Table 3: Comparative study of IHC markers CK 7 and Napsin-An in Adenocarcinoma of lung

Immunohistochemical profile	Total	Percentage
CK 7 positive and napsin A negative	21	51.21%
CK 7 negative Napsin A positive	01	02.43%
CK 7 and Napsin A (both) Positive	16	39.02%
CK 7 and Napsin A (both) Negative	03	07.31%
Total	41	100%

Among the 47 cases of lung adenocarcinoma. IHC was done on 41 cases (87.23%). Immunocytochemistry (ICC) was done on 6 cases (12.77%). Lung adenocarcinoma IHC markers study shows CK 7 positive and Napsin-A negative in 21 cases (51.2%). CK 7 negative and Napsin-A positive

only in 1 case (2.4%). Both are positive in 16 cases (39.0%) and both were negative in 3 cases (7.3%). Markers were perform TTF-1, CK 7, Napsin A, CK 5/6, p63.

Table 4: Comparative study of ICC markers CK 7 and Napsin-A in Adenocarcinoma of lung

Immunohistochemical profile	Total	Percentage
CK 7 positive and Napsin A negative	04	66.67%
CK 7 positive and napsin A negative	O4	66.7%
Napsin A positive and CK 7 negative	02	33.3%
Total	06	100%

Out of 47 cases diagnosed with adenocarcinoma of lung, ICC was done in 06 cases due to Patients non-cooperative to take biopsy, so immunocytochemistry study was performed in 6 cases. In our study CK 7 was positive in 66.67% of the cases and Napsin-A was positive in 33.33% of total cases.

Discussion

In our study, CK 7 expression was observed in 87.2% of the total 47 cases (90% positive on IHC and 66.7% positive in ICC) of lung adenocarcinoma. Similar findings were also observed in the study of Gurda *et al* [17] in which CK 7 was positive in 93% and in the study of Alekhya M. *et al* [18], CK 7 was positive in 95% of the cases.

Napsin-A expression was observed in 40.4% of the total 47 cases (41.5% positive on IHC and 33.3% positive in ICC) of lung adenocarcinoma. Similar findings were also observed in the study of Stoll *et al* [19] in which Napsin-A was positive in 57.1% of the cases.

Comparative study showing positivity of IHC markers in Adenocarcinoma

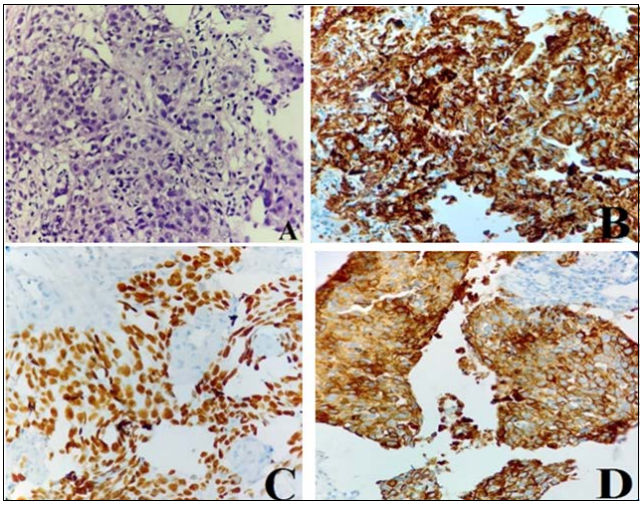

Fig 1: IHC markers in Adenocarcinoma; A): H&E 40X; B): Napsin-A positive; C): TTF-1 positive; D): CK7 positive

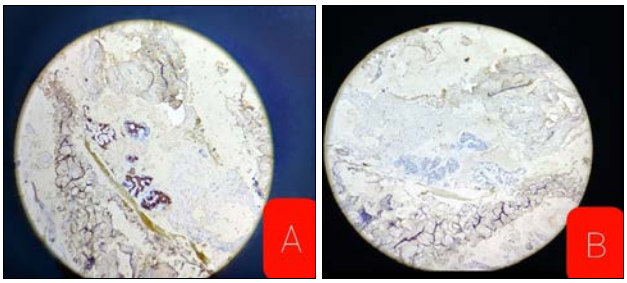

Fig 2: IHC markers in Adenocarcinoma; H&E 40X; A): CK7 positive B): Napsin-A negative

Conclusion

Understanding the basic histology of the respiratory airways as well as their cell structure and composition has led to further understanding the possible cell line origins of primary lung neoplasms. Using immunochemistry techniques, primary lung carcinoma can now be distinguished from a metastatic carcinoma. In our study CK 7 expression has been observed to be more reliable and specific than Napsin-A in diagnosis of primary lung adenocarcinoma. However, further studies are required to consolidate the role of immunochemistry in guiding targeted therapy in lung cancer and determining prognosis.

Conflict of Interest

Not available

Financial Support

Not available

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