



ROLE OF TTF-1 IN THE DIAGNOSIS OF LUNG CARCINOMAS WITH HISTOPATHOLOGICAL CORRELATION

Pathology

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ABSTRACT

Introduction: Lung cancer is the most commonly diagnosed cancer worldwide. It is also the number-one cause of cancer-related death in the Western world. Lung cancer remains the leading cause of cancer mortality for both men and women. Lung Cancer occurs most often between ages 40 and 70 years, with a peak incidence in the 50s or 60s. **Purpose:** To evaluate the role of TTF-1 (Thyroid Transcription Factor-1) in the diagnosis of Lung Carcinomas with histopathological correlation. **Materials and Methods:** The study was done in the Department of Pathology, Government General and Chest Hospital, Erragadda, Hyderabad, Telangana, India over a period of 30 months. The data collected was subjected to statistical tabulations and analysis was done. **Results:** A total of 30 biopsies of histopathologically diagnosed Lung carcinoma cases were reviewed during the 30 month retrospective study period. The cases included Adenocarcinoma(n=10), Squamous Cell carcinoma (n=10), Small cell carcinoma(n=6), Poorly Differentiated carcinoma(n=4). TTF-1 was observed in 70% of Adenocarcinomas, 25% of poorly differentiated carcinomas, 16.67% of Small cell carcinomas while all the squamous cell carcinomas were immune-negative for TTF-1. **Conclusions:** This study concludes that TTF-1 is reasonably sensitive and strongly specific for pulmonary adenocarcinomas.

KEYWORDS

TTF-1, Lung carcinoma, Adenocarcinoma, Squamous Cell Carcinoma

INTRODUCTION

In the 19th century, lung cancer was an unusual tumor; so much so that single case reports of the rare cancer were published in the scientific literature of the day. Things have changed. Lung cancer is now the most commonly diagnosed cancer worldwide.^[1,2]

It is also the number-one cause of cancer-related death in the Western world. Lung cancer remains the leading cause of cancer mortality for both men and women in the United States. Lung Cancer occurs most often between ages 40 and 70 years, with a peak incidence in the 50s or 60s. Only 2% of all cases appear before the age of 40. Global lung cancer incidence and mortality rates in men are 34.92 and 31.43 and in women 11.05 and 9.53 respectively.^[3]

Adenocarcinoma is the most common form of lung cancer in women (47%). Its incidence is highly correlated with cigarette smoking, and about 10% of long-term smokers will eventually be diagnosed with lung cancer.

Thyroid transcription factor 1 (TTF-1), also known as NK2 homeobox 1 (NKX2-1), is a protein which in humans is encoded by the NKX2-1 gene.^{[8][9]} TTF-1 is a 38-kilodalton nuclear protein and is a member of the Nkx2 homeo-domain transcription factor family, was originally characterized as a promoter of thyroid-specific transcription of the thyro-globulin and thyroperoxidase genes.^{[9][10]} TTF-1 was subsequently detected in the fetal lung as well as within certain areas of the diencephalon. It has been implicated in the normal growth and development of the lung, and the disruption of the TTF-1 locus leads to neonatal death with pulmonary hypoplasia.^[26] It regulates the transcription of genes specific for thyroid, lung and diencephalon.^{[12][13]} Because of its restrictive expression, TTF-1 is a useful immunohistochemical marker in the diagnosis of tumors of thyroid or lung origin.^[15]

MATERIALS AND METHODS

The study was done in the Upgraded Department of Pathology, Government General and Chest Hospital Erragadda, Hyderabad. This study was done retrospectively with the collection of biopsy material for over a period of two and a half years i.e., 30 months with a total number of 30 cases. The common symptoms of presentation were: Cough, Weight loss, Dyspnea, Hemoptysis, Chest pain, Hoarseness of voice. Based on the investigative work-up and also depending upon the location of the tumor, the biopsy material was then procured. The biopsy material required for the histopathological examination was obtained from these patients using Fiber optic Bronchoscopy. Hematoxylin-eosin stained slides of all cases were reviewed and histopathological diagnoses were made. Immunostaining with immunohistochemical marker TTF-1 (Clone 8G7G3/1) was done. Appropriate positive and negative controls were used for each

antibody. Thyroid follicular cells were taken for positive control and the primary antibody was omitted in the negative controls.

Statistical Methods: The data collected was subjected to descriptive statistical tabulation

RESULTS

Following the histopathological diagnosis and Immunohistochemistry, the results were analyzed for significance. The relationship between TTF-1 expression and the Histopathological types were analysed. A total of 30 biopsies of histopathologically diagnosed Lung carcinoma cases were reviewed during the 30 month retrospective study period. The cases included Adenocarcinoma(n=10), Squamous Cell carcinoma (n=10), Small cell carcinoma(n=6), Poorly Differentiated carcinoma(n=4). TTF-1 was observed in 70% of Adenocarcinomas, 25% of poorly differentiated carcinomas, 16.67% of Small cell carcinomas while all the squamous cell carcinomas were immune-negative for TTF-1. This result signifies the value of TTF-1 as immunohistochemical marker by giving a statistically significant p-value (0.006). TTF-1 is hence the marker of choice in lung carcinomas.

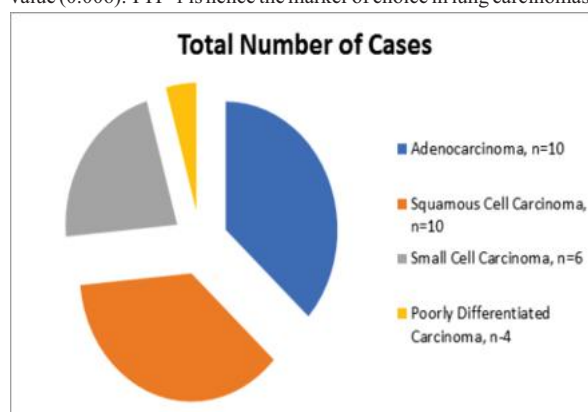


Figure 1: Total Number of Cases and the Histopathological Diagnoses

Table 1

Histopathological Diagnosis	Number of Cases	TTF-1 Positivity	TTF-1 Negativity
Adenocarcinoma	10	7(70%)	3
Squamous Cell Carcinoma	10	0	10
Small Cell Carcinoma	6	1(16.67)	5
Poorly Differentiated Carcinoma	4	1(25%)	3
Total Cases	30	9	21

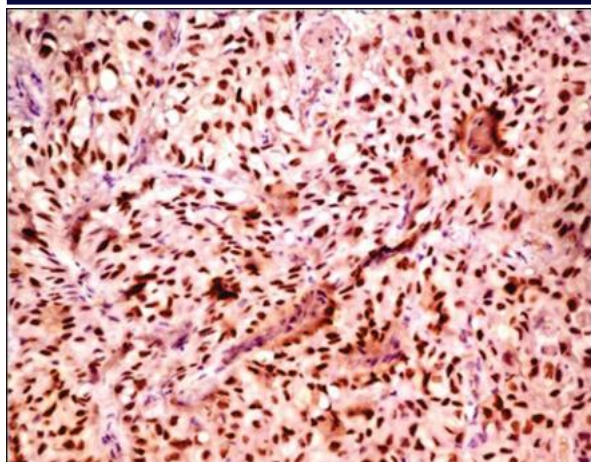


Figure 2: Adenocarcinoma Showing Strong Nuclear Immunopositivity for TTF-1

DISCUSSION

Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer death worldwide. Evaluation of pulmonary and pleural neoplasms requires determination of histopathologic type and differentiation, as well as assessment of probable site of origin.

Although this process is currently based primarily on histopathologic features, immunohistochemistry (IHC) can provide valuable information in several settings. Thyroid transcription factor 1 (TTF-1), also known as NK2 homeobox 1 (NKX2-1), is a protein which in humans is encoded by the NKX2-1 gene.^{[8] [9]} TTF-1 is a 38-kilodalton nuclear protein and is a member of the Nkx2 homeo-domain transcription factor family, was originally characterized as a promoter of thyroid-specific transcription of the thyroglobulin and thyroperoxidase genes.^{[9] [10]}

TTF-1 was subsequently detected in the fetal lung as well as within certain areas of the diencephalon. It has been implicated in the normal growth and development of the lung, and the disruption of the TTF-1 locus leads to neonatal death with pulmonary hypoplasia. It regulates the transcription of genes specific for thyroid, lung and diencephalon.^{[12] [13]}

In normal lung tissues, TTF-1 has been observed primarily in the nuclei of alveolar cells, particularly type II pneumocytes, non-ciliated bronchiolar cells (Clara cells), and basal cells.^[14] Because of its restrictive expression, TTF-1 is a useful immunohistochemical marker in the diagnosis of tumors of thyroid or lung origin.^[15]

Staining for TTF-1 is nuclear. By virtue of its tissue-specific expression in tumors of lung and thyroid, TTF-1 has recently been used as a marker for the diagnosis of primary and metastatic lung cancer, especially for identification of the lung as the primary site of metastatic adenocarcinomas. TTF-1 has limited value in differentiating pulmonary from extrapulmonary squamous cell carcinomas, since most pulmonary squamous cell carcinomas are immunonegative.

Table 2: Comparison with Other Studies Have Revealed Consistent Results on TTF-1 Expression.

Histopathological Diagnosis	Na-Hye Myong (2003)	Andres Matoso and Kamaljeet Singh et al (2010)	Our Study (2012)
Adenocarcinoma	19/25 (76%)	121/185 (65.4%)	7/10 (70%)
Squamous Cell Carcinoma	0/30 (0%)	01/97 (1.0%)	0/10 (0%)
Small Cell Carcinoma	14/16 (88%)	04/23 (17.4%)	1/5 (16.6%)
Poorly Differentiated Carcinoma	1/2 (50%)	07/22 (31.8%)	1/4 (25%)
Adenocarcinoma Vs Squamous Cell Carcinoma (P-value for significance)	<0.0001 Extremely significant	<0.001 Very significant	<0.0031 Very significant
P-value for significance	<0.001	<0.001	<0.006

CONCLUSIONS

Lack of Thyroid Transcription Factor (TTF-1) positivity in squamous cell carcinomas suggests that TTF-1 is not involved in the differentiation of squamous cells. Thyroid Transcription Factor (TTF-1) is a reasonably sensitive and highly specific diagnostic marker for pulmonary adenocarcinomas

REFERENCES

1. Haiman CA, Stram DO, Wilkens LR, et al: Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006; 354:333-342.
2. Coleman MP, Esteve J, Damiecki P, et al: Trends in Cancer Incidence and Mortality. Lyon, France, International Agency for Research on Cancer, 1993.
3. GLOBOCAN 2000. Cancer incidence, mortality and prevalence worldwide.
4. Metzger RJ, Klein OD, Martin GR, Krasnow MA: The branching programme of mouse lung development. *Nature* 2008; 453:745-750
5. Grays Anatomy for Students, 2nd edition. Churchill Livingstone Elsevier Publication
6. Wheater's Functional Histology: a text and color atlas, 5th edition. Churchill Livingstone Elsevier Publication
7. Textbook of Human Histology, Inderbir Singh, 3rd edition.
8. Lau SK, Luthringer DJ, Eisen RN (2002). "Thyroid transcription factor-1: a review." *Appl. Immunohistochem. Mol. Morphol.* 10 (2): 97-102. doi:10.1097/00022744-200206000-00001. PMID 12051643.
9. Guazzi S, Price M, De Felice M, et al. (1990). "Thyroid nuclear factor 1 (TTF-1) contains a homeodomain and displays a novel DNA binding specificity." *EMBO J.* 9 (11): 3631-9. PMC 552115. PMID 1976511. //www.ncbi.nlm.nih.gov/pmc/articles/PMC552115/.
10. Gehring WJ. Homeo boxes in the study of development. *Science* 1987;236:1245-1252.
11. Murray and Nadel's Textbook of Respiratory Medicine, 5th edition. Saunders Elsevier Publication
12. Lazzaro D, Price M, De Felice M and DiLauro R. The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the fetal brain. *Development* 1991;113:1093-1104.
13. Kimura S, Hara Y, Pineau T, Fernandez-Salguero P, Fox CH, Ward JM and Gonzalez FJ. The T/ebp null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. *Genes Dev* 1996; 10:60-69.
14. Nakamura N, Miyagi E, Murata S, Kawaoi A and Katoh R. Expression of thyroid transcription factor-1 in normal and neoplastic lung tissues. *Mod Pathol* 2002;15:1058-1067
15. Ordóñez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol.* 2000 Mar;7(2): 123-7.
16. Review Article Immunohistochemistry for Assessment of Pulmonary and Pleural Neoplasms: A Review and Update by Dongfeng Tan and Dani S. Zander *Int J Clin Exp Pathol* (2008) 1, 19-31
17. Na-Hye Myong, in 2003 at the Department of Pathology, Dankook University College of Medicine, Cheonan, Korea. *Journal of Korean Med Sciences* 2003; 18: 494-500.
18. Andres Matoso and Kamaljeet Singh et al in 2010 at the Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Brown Medical School, Providence, RI, USA and published in *Appl Immunohistochem Mol Morphol.* 2010 March; 18(2): 142-149.