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Original Research Article

ROLE OF IMMUNOHISTOCHEMICAL MARKERS IN THE DIAGNOSIS OF PRIMARY AND METASTATIC CARCINOMA OF THE LUNG: A RETROSPECTIVE STUDY

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Abstract

Background: Transthoracic radio-imaging (mostly CT scan) guided needle aspiration and biopsy technique through fine bore needle/cannula have developed over time as an important method of sampling in lung mass lesion as a diagnostic modality, a daycare procedure, giving the advantage of lesser invasiveness offering really minimum possible complications. **Objective:** Our study aimed to evaluate the diagnostic yield of cytology and biopsy techniques. Also to see the role of ImmunohistoChemistry as well as Immuno CytoChemistry in diagnosing lung lesions. Needle size was considered on the characteristics and location of the lung lesion. **Materials and Methods:** A total of 48 FNA cases were enrolled clinically and radiologically over a period of one year. The immunostaining pattern of NAPSIN A, P 63, TTF-1, and CK 7 was correlated with the cyto/histopathological diagnosis of the tumor. **Results:** In primary SqCCs, P63 has (85% -sensitivity,70%-specificity,85% -PPV, and 70%-NPV) from Histology findings Vs P63 has (70%-sensitivity, 91.7%-specificity,87.5% -PPV,78.6%-NPV) from cytology findings. sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Napsin, TTF-1, CK-7 was (20%,66.7%,33.3%,50%, Vs 25%,87.5%,62.5%,58.3% Vs 5%,95.8%,50%,54.8%-cytology) (5%,54%,8%,57%, Vs 15%,54%,8%,57%, Vs 4.76%,82.16,16.67%,48.72%-Histology).PPV of TTF-1, Napsin A, and CK7 in Adenocarcinoma are (23.1%,100%,50% Vs 41.7%,91.7%, and 80%) (cytology and Histology) in the primary Adenocarcinoma. The sensitivity and specificity of TTF-1, Napsin A, and CK7 are (17.6%,52.9%,17.6% and, 63%,100%, 92.6%) Vs (26.3%,57.9%, 21.1%, and 72%,96%,96%). **Conclusion:** Our study showed that TTF-1 and NAPSIN A tend to have variable sensitivity and specificity in primary and metastatic adenocarcinoma of the lung. Therefore, the combined use of TTF-1, Napsin A, and CK7 could be considered in problematic cases.

INTRODUCTION

Lung cancer accounts for over 1.3 million deaths across the world.[1,2] Primary lung carcinomas have been classified into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). The latter include adenocarcinoma (50-70%), squamous cell carcinoma (20-30%), and other subtypes.

Immuno cyto/histo chemistry is based on a primary antigen-antibody reaction and a secondary antibody-enzyme complex that interacts with a chromogen for a microscopically visible color reaction.

Immuno cyto/histo chemistry is often used for accurately diagnosing malignancies and in the workup of an undifferentiated carcinoma, usually to exclude melanoma, and lymphoma, which can mimic highly pleomorphic epithelial tumors.

The range of markers used to evaluate large cell cancer are cytokeratin antibodies such as AE1/3, CAM 5.2, and pan-cytokeratin are used. Lymphoid neoplasm includes Leukocyte common antigen

(LCA), CD 30, B and T cell markers CEA, MOC 31, B 72.3, LeuM1, Bg8, and BerEP4, etc. For small cell cancer, pan-cytokeratin, synaptophysin, chromogranin, CD 56, TTF 1, CK 7, CK 20, CD 99, S 100, desmin, WT 1, LCA, myogenin, and TLE.

Unusual clinical circumstances or radiographic imaging particularly in a younger patient or a nonsmoker should prompt consideration of a broad immunohistochemical workup as well as molecular tests for characteristic cytogenetic abnormalities for tumors such as a poorly differentiated synovial sarcoma, desmoplastic small round cell tumor, Ewing's sarcoma and rhabdomyosarcoma.

The use of immunohistochemistry has not eliminated the challenges of distinguishing a primary lung carcinoma from metastatic disease. There are only limited instances in which immunohistochemical stains are useful in differentiating a pulmonary primary from a metastatic tumor.

The need for a more precise classification of poorly differentiated non-small cell carcinoma into squamous or non-squamous histology has further expanded the use of immunohistochemistry within pulmonary pathology.

MATERIALS AND METHODS

Study Population and study area

We retrieved data from 48 patients diagnosed with carcinoma lung between January 01, 2019, to December 31, 2019, from lab registers of the Department of Pathology, M P Shah Govt. Medical College, Jamnagar using the term SCC or SqCC or Adeno or NSCLC and obtained immuno histochemistry markers namely P63, TTF, CK-7, and Napsin. The search of the register yielded 48 cases among which half of them had carcinoma right lung and half had carcinoma left lung. The data we obtained was unlinked and unanonymous with the protection of the privacy of patients.

Inclusion Criteria

All patients (visiting OPD and Admitted patients-Respiratory Medicine Department) suspected of having lung malignancy – lesion located at the periphery of the lung field

Exclusion Criteria

1. Those who were not willing to participate
2. Patients with Central lesions on the lung field
3. Patients not suspected of malignancy

Study duration: One Year (1st January 2019 to 31st December 2019)

Sample Size: Universal sampling

Method

CT-guided FNAC and biopsy were performed under complete aseptic conditions and without complications with informed written consent. After obtaining the material from FNAC/B, immediately smears were prepared and fixed in methanol/formalin. The biopsy material obtained was transferred to a fixing solution (10% neutral buffered formalin)

The FNAC smears after proper fixation were stained by Hematoxylin & Eosin (H & E) stain, MGG, and PAP stain. Biopsy specimens after fixation were processed by his techniques, and the tissue blocks were sectioned by H & E stain, MGG, and PAP stain. The diagnosis was made using a microscopic examination. This diagnosis was further confirmed by performing Immunocytochemistry/ Immunohistochemistry study using antigen retrieval technique and DAB reagent.

The study was approved by the institutional ethical committee of M P Shah Government Medical College, Jamnagar, Gujarat.

Statistical Analysis

We correlated immunohistochemical markers with different types of carcinoma lung. Any missing data due to loss of tumor cells or if immunohistochemical markers were not performed were excluded from the analysis. Statistical analysis was carried out using Microsoft Excel for Windows 10. A P-value equal to or less than 0.05 ($P \leq 0.05$) was considered a statistically significant result. The specificity, sensitivity, and Positive predictive value (PPV) were calculated according to the final cytological observations.

RESULTS

Table 1: Clinico-social characteristics of the patient. (n=48)

Characteristic	Type of carcinoma		Acellular (n=6)(%)
	Primary (n=41) (%)	Metastatic(n=1)(%)	
Mean Age ± SD	61.58 ± 9.2		65.6 ± 8.7
Median Age	65		65
Range	45 -75		62-70
Sex			
Male	38(92.6)	1(100)	5(83)
Female	3(7.2)	-	1(17)
Cytology			
Types of Carcinoma (cytology)	**Primary (n=41) (%)**	**Metastatic(n=1) (%)**	**Acellular (n=6)**
Squamous cell	20 (49)	1 (100)	
Adenocarcinoma	16(39)		
Small cell carcinoma	5(12)		
Side of Lung			

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Right	20(49)	0	4(67)
Left	21(51)	1	2(33)
Histology (N=48)			
Type of carcinoma (Histology)	**Primary (n=44) (%)**	**Metastatic (n=0)**	**Acellular (n=4) (%)**
Mean Age ± SD	61.58 ± 9.2		65.6 ± 8.7
Median Age	65		65
Range	45 -75		62-70
Sex			
Male	40(91)		4(100)
Female	4(9)		-
Type of carcinoma (Histology)	**Primary (n=44) (%)**	**Metastatic (n=0)**	**Acellular (n=4) (%)**
Squamous cell	20(45)	-	
Adenocarcinoma	19(43)	-	
Small cell carcinoma	3(7)	-	
NSCLC	2(4.5)	-	
Side of lung			
Right	22(50)	-	2(50)
Left	22(50)	-	2(50)

Table 2: Immunohistochemical patterns in primary and metastatic Carcinoma (cytology)

Types of carcinoma	Immunohistochemical markers			
	P63+/-	CK-7+/-	Napsin +/-	TTF+/-
Primary cancer (n=44)				
Adeno (n=17)	4/13	2/15	9/8	3/14
Squamous(n=20)	14/6	1/19	4/16	5/15
Small cell Carcinoma (n=5)	2/3	0/5	0/5	4/1
NSCLC(n=2)	0/2	1/1	0/2	1/1
Metastatic(n=1)				
Adeno	-	-	-	-
Squamous(n=1)	1/0	1/0	0/1	1/0

Table 3: Immunohistochemical patterns in primary Cancer (Histology)

Types of carcinoma				
	P63+/-	CK-7+/-	Napsin +/-	TTF+/-
Adeno (n=19)	16/3	4/15	11/8	5/14
Squamous(n=20)	17/3	0/20	1/19	3/17
Small cell Carcinoma (n=3)	1/2	0/3	0/3	3/0
NSCLC(n=2)	1/1	1/1	0/2	1/1

Table 4: Sensitivity, Specificity, PPV, and NPV of individual markers in primary carcinomas (cytology)

Markers to correctly predict a squamous histotype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
P63	23.5	40.7	20	45.8
Napsin	52.9	100	100	77.1
TTF-1	17.6	63	23.1	54.8
CK-7	11.8	92.6	50	62.5
Markers to correctly predict an adenocarcinoma histotype				
P63	70	91.7	87.5	78.6
Napsin	20	66.7	33.3	50
TTF-1	25	87.5	62.5	58.5
CK-7	5	95.8	50	54.8

Table No.5 Sensitivity, Specificity, PPV, and NPV of individual markers in primary carcinomas (Histology)

Markers to correctly predict an Adeno Carcinoma histotype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
P63	84.2	32	48.5	72.7
Napsin	57.9	96	91.7	75
TTF-1	26.3	72	41.7	56.3
CK-7	21.1	96	80	61.5
Markers to correctly predict a Squamous histo-type				
P63	85	70	85	70
Napsin	5	54	8	57
TTF-1	15	88	50	56
CK-7	4.76	82.61	16.67	48.72

PPV- positive Predictive Value, NPV- Negative Predictive Value

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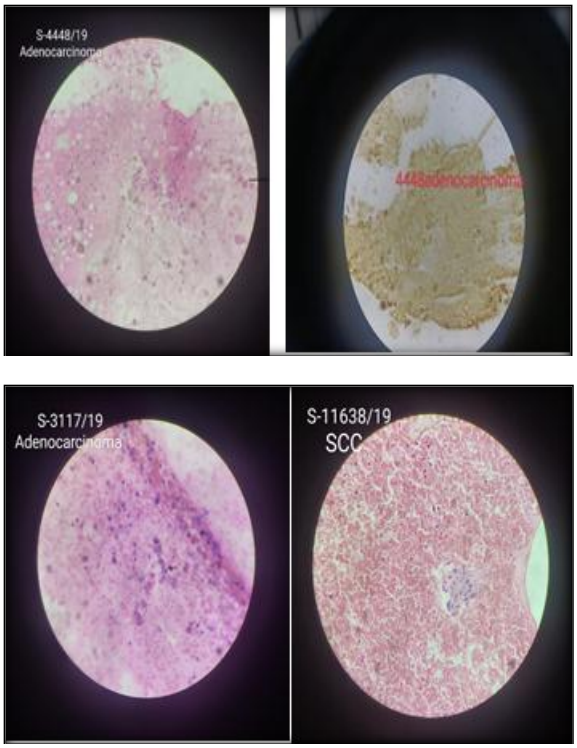

Figure 1: Histology showing SCC and Adenocarcinoma

DISCUSSION

After attrition because of inadequate biopsy material, 44 resection specimens initially diagnosed as NSCLC-NOS on small sample biopsy in histology and 41 in cytology were included in this study. Table 1 summarizes the distribution of the final diagnosis after resection of both histology and cytology. Squamous cell carcinoma was the dominant type, accounting for just more than half of the cases; one-quarter of cases were adenocarcinoma

The ability, in numerical terms, of the four selected markers, P63, Napsin, TTF-1, and Ck-7, to correctly predict a squamous histotype is summarized in Table 5

Individual staining patterns of P63, Napsin, TTF-1, CK-7 in SqCCs

The cytological features of SqCCs include pleomorphic large tumor cells with hyperchromatic nuclei, opaque or "hard" cytoplasm, intracytoplasmic processes, or other features characteristic of squamous differentiation

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of P63 in primary and metastatic SqCC are summarized in Tables 4 and 5. In primary SqCCs, P63 has (85% -sensitivity,70%-specificity,85% -PPV, and 70%-NPV) from Histology findings Vs P63 has (70%-sensitivity, 91.7%-specificity,87.5% -PPV,78.6%-NPV) from cytology findings when it is compared to previous studies however, showed that in SqCC P40, P63, and CK5/6 had a sensitivity of 80.5%, 90.0%, and 93.5% and a specificity of 80.0%, 89.6%, and 80.0%, respectively.[12] More than 50% of Primary SqCC were positive for p63(16/3 Vs14/6) both from Histology and cytology findings (Table-2 and 3)

In SqCCs, we also found that TTF-1 and Napsin A could stain entrapped bronchial epithelial cells and alveolar macrophages rather than tumor cells. In this circumstance, tumor cells were considered negative for TTF-1 and Napsin, so sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Napsin, TTF-1, CK-7 was (20%,66.7%,33.3%,50%,\ Vs 25%,87.5%,62.5%,58.3% Vs 5%,95.8%,50%,54.8%-cytology)
(5%,54%,8%,57%, Vs 15%,54%,8%,57%, Vs 4.76%,82.16,16.67%,48.72%-Histology)

In SqCCs, P63 and CK5/6 have commonly used markers. The Human TP63 gene is located on chromosome 3q-29, and the expression of the gene produces the full-length protein P63 and the truncated protein P40.[13,15].P63 can be detected in benign bronchial stem cells and in neoplastic cells with evidence of squamous differentiation.[16] CK5/6 is a high molecular weight cytokeratin and is expressed in neoplasms of epithelial origin, including SqCC, mesothelial carcinoma, and urothelial carcinoma.[17] p63 and CK5/6 have been used in the diagnosis of lung SqCC(14,15,18,19).and CK7 has a specificity of 95.8% Vs 82.61%(cytology vs histology). However, our study only had a few cases of SqCC. A further study with larger numbers is necessary to draw a conclusion. Staining patterns of TTF-1, Napsin A, and CK7 in ADCs. The cytological features of ADCs include clusters of tumor cells with prominent nucleoli, predominate or overt mucin production, vacuolated cytoplasm, acinar formation, and other features characteristic of glandular differentiation (Figure). The immunostaining patterns of TTF-1, Napsin A, and CK7 in ADCs are shown in Table-2 and 3. PPV of TTF-1, Napsin A, and CK7 in ADCs are (23.1%,100%,50% Vs 41.7%,91.7%, and 80%) (cytology and Histology) in primary ADCs. The sensitivity and specificity of TTF-1, Napsin A, and CK7 are (17.6%,52.9%,17.6% and, 63%,100%, 92.6%) Vs (26.3%,57.9%, 21.1%, and 72%,96%,96%). Napsin A had a better specificity for the primary lung ADCs. Whereas, CK7 showed a suboptimal specificity for lung ADCs.

CK7, TTF-1, and Napsin A are the most commonly used primary lung ADC markers in daily practice. Although CK7 has been used for decades to identify lung ADCs, its suboptimal sensitivity and specificity are well known.[15,18,20] TTF-1 is a nuclear transcription factor that is expressed in epithelial cells of the lung and thyroid. In the lung, it regulates the expression of genes involved in the production of surfactants. The sensitivity and specificity of TTF-1 in the identification of lung origin vary and range from 75% to over 95%.[14,18,21,22] However, TTF-1 is also immunoreactive in several other

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tumors, such as thyroid neoplasms, breast adenocarcinoma, gastrointestinal carcinomas, small cell lung carcinoma (SCLC), carcinoid and, possibly but controversially.[23] primary lung squamous cell carcinoma.[29-32] Napsin A is a relatively new marker for primary lung ADCs.[24] it is a 35-kilodalton protein that is expressed in type II pneumocytes, alveolar macrophages, and renal tubular cells.[24] Functionally, it is an aspartic protease involved in the posttranslational modification of surfactant protein B (SP-B) in type II pneumocytes.[25] The expression of Napsin A has been shown to be transcriptionally regulated by TTF-1.[26] Previous studies using surgically resected specimens indicated that Napsin A has better sensitivity and specificity than TTF-1 in well to moderately differentiated lung ADCs.[28] Therefore, it has been used with TTF-1 together in the differential diagnosis of lung adenocarcinomas.[27] Napsin A may be particularly useful in poorly differentiated ADCs, which may lose TTF-1 expression.[16,19]

Taken together, all three markers revealed similar sensitivities in primary lung ADCs; Napsin A showed the best and TTF-1 showed the worst specificity. Interestingly, we found that the addition of Napsin A to routine practice coincided with an increase in the diagnosis of ADC subtypes from 14% to 36% and a concurrent decrease in NOS (otherwise not further classified) subtypes from 24% to 9% among NSCLC. This observation of improved subclassification of NSCLC with the use of Napsin A has also been reported elsewhere.[22,23,36,48] All studies, however, should also address limitations of Napsin A including (a) Napsin A is positive in some cases of SCLC and lung carcinoid.[33], (b) Napsin A is positive in some cases of renal cell carcinomas.[28] and (c) Napsin A also stains pulmonary macrophages.[23], which need to be distinguished morphologically from tumor cells. With these caveats in mind, we show that Napsin A exhibits strong specificity for ADCs of the lung origin.

CONCLUSION

The 2011 IASLC/ATS/ERS lung adenocarcinoma classification recommends using a single adenocarcinoma marker (TTF-1 or Napsin A) and a single squamous marker for NSCLC classification in small biopsy or cytology specimen in the absence of definitive glandular or squamous morphology to reserve tissue. Our study showed that TTF-1 and Napsin A tend to have variable sensitivity and specificity in primary and metastatic adenocarcinoma of the lung. Therefore, the combined use of TTF-1, Napsin A, and CK7 could be considered in problematic cases.

In summary, the FNA-based sampling could present a unique set of diagnostic challenges, such as a small number of tumor cells, the obscuring effect of tumor necrosis, the need to assess samples from different areas/ multiple needles passes on a single slide, and difficulty in quantifying the degree or extent of IHC staining. We evaluated the most commonly used five IHC markers, including TTF-1, Napsin A, CK7, P63, and CK5/6 in the subclassification of NSCLC. Based on our findings, we propose an algorithmic approach utilizing a panel of IHC markers for the subclassification of NSCLC. Our step-wise approach allows prioritization of markers if the amount of tissue or resources are limited to optimally conserve tissue for future molecular testing of the lung carcinoma. This subclassification approach has the potential benefit to improve IHC diagnostic utilization. A further prospective study using an independently collected cohort is necessary to validate our approach

Limitation of the study: smaller sample size and less number of metastatic lung cancer, so we cannot able to compare the use of markers between primary and secondary lung cancers.

Conflicts of interest: No conflict of interest

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