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Immunohistochemical Study of Stathmin-1 as a Prognostic Factor in Non-Small Cell Lung Carcinoma

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Abstract:

Background: The cell cycle progression and cell motility mainly controlled by major microtubule-depolymerizing protein called Stathmin1 (also known as metablastin). Stathmin1 has been found to be up-regulated in some cancers and correlated with cell differentiation and proliferation.

Objectives: To Evaluate the role of immunohistochemical expression of stathmin1 in non-small lung carcinoma and its correlation to different prognostic factors or parameters.

Materials & Methods:
This retrospective study carried on 50 cases of -small lung carcinomas (surgical specimens of lung tumors embedded in formalin fixed paraffin). Applying the immunohistochemical techniques by using the primary antibodies to stathmin1. Statistical analysis was done and assessment of correlation with different clinical and pathological parameters was measured.

Results: The results revealed Fifty cases of Non-small lung carcinomas sub grouped as 42% adenocarcinoma, 44% squamous cell carcinoma, 10% adeno-squamous and 4% non-small lung carcinoma , 84 % were Stathmin-1 positive, but there is no statistically correlation between Stathmin-1 expression with age and patients' gender but Stathmin-1 expression correlated with parameters including type and grade of tumor. High expression was noted in poorly-differentiated tumors.

Conclusion: From these results we conclude that measurement of stathmin1 may be a beneficial prognostic biomarker for lung tumors, those poorly-differentiated tumors. Stathmin1 expression in non-small cell lung carcinoma significantly correlated with poor tumor differentiation and could be considered as independent prognostic factor

Keywords: Stathmin 1, immunohistochemistry, lung cancer.

Introduction:

Bronchogenic carcinoma is one the major killing cancers in the USA In 2001 it surpassed breast cancer to become the leading cause of cancer deaths in women. An estimated 160,300 Americans are expected to die from lung cancer in 2022, accounting for approximately one quarter of all cancer deaths (1). Long-term prognosis of pulmonary carcinoma remains disappointingly poor, with limited improvement having been made in recent years in long-term survival rates. The prognosis of lung carcinomas has been related to many factors like tumor stage, presence or absence of visceral pleural and lymphatic space invasion, Age, Gender, in research several Grading Biomarkers factors that may affect outcome. (2) The critical protein involved in microtubule polymerization and is necessary for survival of cancer cells is Stathmin 1 (STMN1), therefore, modulation of STMN1 can result in mitotic arrest, thereby exhibiting a critical role in microtubule dynamics (3) Microtubules are protein polymers comprising a/b tubulin heterodimers, which contribute to, and are essential for, the structure and functions of the cell. These functions include intracellular transport, cell motility, and polarity. (4) Tumor-derived cell lines with high stathmin-1 expression negatively influence the response to microtubule targeting drugs which concluded by several studies in vitro.(5) According to this fact STMN1 is extensively involved in signal transduction of malignant cells, so it can be for management tumor as a novel STMN1 down-modulator. By mechanism of novel STMN1 down-modulator action by which mediate antitumor activity involves microtubule polymerization, phase I clinical trial has recently been initiated to test the effect of STMN1 knockdown on

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cancer response. Chemotherapy modalities have broad clinical reach, commonly involving breast cancer, lung cancer, ovarian cancer, prostate cancer, sarcoma, and gastric cancer. (6)

Materials& Methods:

A retrospective study was done in Babylon training center for Pathology, Faculty of Medicine, Babylon University Ethical clearance approved from the scientific committee, College of Medicine, Babylon University. Fifty cases of Non-small cell lung carcinoma (NSCLC) included in this study group composed of formalin- fixed paraffin- embedded tissues blocks. We obtained two sections which were stained with Hematoxylin/ eosin (H and E) staining method and immunohistochemical polydetector plus horseradish peroxidase staining method using Primary antibody stathmin1 clone Bio SB2597, USA from each tissue block. The criterion for positive immunohistochemical staining depend on brown cytoplasmic staining & we utilized combined scoring system which depends on intensity of staining & percentage of area with positive cytoplasmic staining. Accordingly, our study groups were divided into 3 subgroups:

A. Less than 2: Low expression.
B. 3-4: Moderate expression
C. 5-6: High expression.

By using SPSS software version 24.0, Fisher's exact test and two-sided Chi-squared test, we calculated the relation between different Clinicopathological parameters and Stathmin1 IHC staining. Person's Chi-squared was used to determine the relationship between different categorical variables. P value less than (0.05) was considered statistically significant.

Results

Clinicopathological Features of fifty cases of Non-Small cell lung cancer were included in current study as illustrated in Table 1.

Table 1: The clinicopathological features of the presented cases with lung tumor

Parameter	Number	Percentage
Age(years)		
<60	18	36%
>60	32	64%
Gender		
Male	27	54%
Female	23	46%
Histological type		
Adenocarcinoma	21	42%
Squamous cell Carcinoma	22	44%
Adenosequamous carcinoma	5	10%
Non-small lung carcinoma (non otherwise specified)	2	4%
Grade		
Well differentiated	21	42%
Moderate differentiated	11	22%
Poor differentiated	18	36%

The positivity for Stathmin1 were detected as cytoplasmic staining in malignant cells and was scored according to percentage of cells with positive staining and intensity of staining into low, moderate and high (Fig 1). Accordingly, out of 50 cases involved in this study 42(84%) were positive for stathmin1 and 8(16%) was negative. Stathmin1 was expressed in all cases of adenocarcinoma 21(100%) and 18(81%) of squamous cell carcinoma, 2(40%) adenosequamous and 1(50%) of non-small cell lung cancer (NSCLC). According to above data there was significant relationship between type and IHC of STM1 (*P* value <0.05). Regarding the association of stathmin1 IHC with grade of tumors, it was positive with significant relationship between stathmin1 IHC expiration and the tumor grade (Table 2).

Table 2: The correlation of Stathmin 1 Immunohistochemical expression with Clinicopathological parameters in patients with Non -small cell lung carcinoma

Clinicopathological parameters	N (%)			P value
	positive	negative	Total	
Microscopic type				
Adenocarcinoma	21(100%)	0(0.0%)	21	0.03
Squamous cell carcinoma	18(81.8%)	4(18.2%)	22	
Adenosquamous	3(60%)	2(40%)	5	
NSCLC-NOS	0(0%)	2(100%)	2	
Grade				
Well	1(4.8%)	20(95.2%)	21	0.04
Moderate	1(9.1%)	10(90.9%)	11	
Poor	6(33.4%)	12(66.6%)	18	

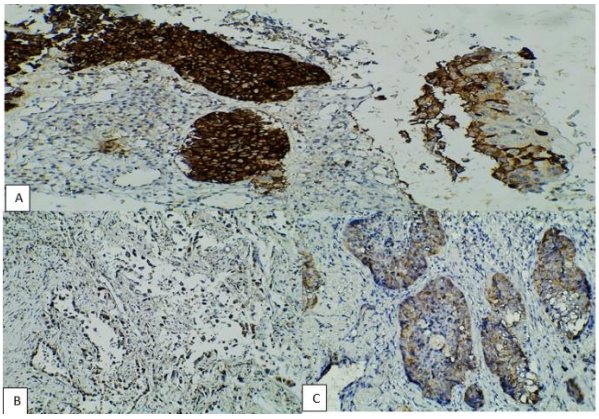

Figure 1. A: Cytoplasmic reactivity of stathmin1 in squamous cell carcinoma (100X).
B: cytoplasmic reactivity of stathmin1 in adenocarcinoma (100X).
C: cytoplasmic reactivity of stathmin1 in adenosequamous carcinoma (400X).

Discussion:

Morphology is still cornerstone in bronchogenic carcinoma classification. Cytology and small biopsy samples should be interpreted by morphology, whenever feasible. STMN1 expression in human cancer was reported to be invariably associated with increased local invasion, metastasis development, and poor prognosis, independently of the primary tumor

histology. (8, 9) This study presents a review of Fifty cases with Non-small cell lung carcinoma which was graded and evaluation for various clinical (age, gender, tumor type), histopathological grading and scoring parameters with Stathmin1 expression. We included 21 cases of adenocarcinoma and 22 of squamous cell carcinoma, 5 adenosquamous carcinoma and 2 cases of non-small cell lung cancer. Stathmin1 were expressed in all cases of adenocarcinoma 21(100%) and 18(81%) of sq. Cell carcinoma, 3(60%) adenosquamous and 0(0%) of non-small cell lung cancer. According to the above data, there was a significant relationship between type and IHC (*P* value <0.05). Similar this is study agreement was noted by comparing our results to other studies like Lin Yurong (2016)(10) and ong Biaoxne,et al. (2017) (11) with *P* values of 0.001 & 0.01, respectively. Regarding the association of stathmin1 IHC with grade of tumors, out of 21(42%) cases are well differentiated tumors, 20(95.2%) cases were positive Stathmin in moderate differentiated tumors, 10(90.9%) cases were positive and in poorly differentiated tumors and 12(66.6%) were positive with a significant relationship between STMN1 IHC expression and the tumor grade (*P* value 0.04). Similar positive association was observed by Shimizu et al. (2017) (12) in which he introduced a relatively large tissue samples which included 134 cases with well-differentiated and 169 cases with moderately differentiated and 54 cases poorly-differentiated with *P* value of 0.001(79). While Yurong (2016) (10), the total studied samples was approximate to the current study and same significant association (*P* value of 0.003). Biaoxne et al. (2017) (11) in their research depends on tissue samples of 48 patients with significant association between STM1 expression and the grade of the tumor (*P* value 0.06). In keeping with our study, several studies revealed no significant association between immunohistochemical expression of STMN1 & patient's age or gender (10,11,12) In this study, positive STMN1 immunohistochemical expression in high grade tumors suggest that STMN1 could be considered as an independent factor indicating poor prognosis especially that other studies have revealed its association with other poor prognostic factors like high microvessels density & vascular invasion, although their study involving patients with lung adenocarcinoma only.(12)

Study Limitations

The first limitation is that a sample of 50 cases, recruited in current study, is relatively small and immunohistochemical staining do not exhibit absolute sensitivity and specificity for NSCLC with evidence of false positive results and some cases need more than one marker to reach the definite diagnosis. The second limitation was the core of 0.2 cm as relative measures were used. The drawback of this small material not enough for extra markers and for more advanced tests. The third limitation is unavailability of matched resection specimens for the examined cases. Finally, the study was retrospective, therefore, no full information was available due to poor registration system, incomplete clinical data, unknown staging and improper preservation of samples.

Conclusion:

STMN1 protein expression was significantly expressed in non-small cell lung carcinoma & its expression was associated with poor prognostic factors like high tumor grade & worse tumor type.

Conflict of Interest

Authors have nothing to disclose and no commercial support.

Authors' Contributions:

Dr: Naddhema wetwet
Dr: Hadeel ali
Collecting biopsy of all case &do histopatholgial processing ,staining then sending for histopatholoical expert physician .
Dr:Ali Al baay
Collecting bronchogenic carcinoma cases
Dr: Muhammad Waheeb
Revision of all paper

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استخدام الصبغه المناعية (Stathmin 1) كعامل تنبؤي في سرطان الرئه ذو الخلايا غير الصغيره

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الخلاصة:

الخلفيه: Stathmin1 المعروف أيضًا باسم metablastin) هو بروتين رئيسي لإزالة البلمرة في الأنابيب الدقيقة ، يشارك في تقدم دورة الخلية وحركة الخلية. تم العثور على Stathmin1 في بعض أنواع السرطان ومرتبط بتمايز الخلايا وتكاثرها

Stathmin1 هو بروتين فسفوري خلوي رئيسي ينظم ديناميكيات الأنابيب الدقيقة ويرتبط بالأنماط الظاهرية الخبيثة في أنواع مختلفة من السرطان ، بما في ذلك سرطان الرئة ذو الخلايا غير الصغيرة.

المواد والأساليب :أجريت هذه الدراسة بأثر رجعي على عينات جراحية من الفورمالين مثبتة بالبارافين لأورام الرئة بتطبيق التقنيات الكيميائية الهيستولوجية المناعية باستخدام الأجسام المضادة الأولية لـ stathmin1 ، وإجراء التحليل الإحصائي وتقييم الارتباط مع المعايير السريرية والمرضية المختلفة المقاسة.

النتائج :خمسون حالة من سرطانات الرئة غير الصغيرة التي تحتوي على 42٪ سرطانة غدية ، و 44٪ سرطان الخلايا الحرشفيه، 10٪ سرطان غدي متماثل و 4٪ سرطان رئوي غير صغير ، 84٪ كانت إيجابية Stathmin-1 لا يوجد ارتباط كبير بين تعبير Stathmin-1 وعمر وجنس المرضى لكن تعبير Stathmin-1 كان مرتبطًا بمعلمات بما في ذلك نوع ودرجة الورم. لوحظ التعبير العالي في الأورام سيئة التمايز.

الاستنتاجات :قد يكون قياس مستوى ستاثمين 1 علامة بيولوجية تنبؤية مفيدة لأورام الرئة غير الصغيرة ، خاصة الأورام ضعيفة التمايز.

تعبير Stathmin1 في سرطان الرئة ذو الخلايا غير الصغيرة مرتبط بشكل كبير مع تمايز الورم الضعيف ويمكن اعتباره عاملاً تنبؤياً مستقلا.

الكلمات المفتاحية: Stathmin 1, المناعة السريرية, سرطان الرئة .