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RESEARCH ARTICLE

Value of Glypican-1 Expression in Pleural Epithelioid Mesothelioma, Adenocarcinoma and Squamous Cell Carcinoma of the Lung

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Abstract

Background: Distinguishing between pleural epithelioid mesothelioma, lung adenocarcinoma, and poorly differentiated squamous cell carcinoma (SCC) is a challenge in some cases. A panel of markers has been recommended by the International Mesothelioma Interest Group (IMIG) guideline to differentiate epithelioid mesothelioma from lung adenocarcinoma and SCC. However, the use of novel highly specific immunohistochemical (IHC) markers is still required. **Objectives:** This study aimed to evaluate glypican-1 (GPC1) expression in epithelioid mesothelioma, lung adenocarcinoma, and SCC, correlating its expression with some known clinicopathological parameters to clarify its diagnostic and prognostic value. **Methods:** This study included seventy specimens designated as 20 cases of pleural epithelioid mesothelioma, 30 cases of lung adenocarcinoma, and 20 cases of lung SCC. GPC1 expression was evaluated using immunohistochemistry (IHC). The data was analyzed statistically by SPSS software 25. GPC1 expression was correlated to different clinicopathologic data using Chi-square test. The study was conducted according to local Ethical Committee regulations. **Results:** This study detected positive GPC1 reactivity in all cases (100%) of pleural mesothelioma and lung SCC, in which increased GPC1 expression was correlated to large-sized, high grade, advanced stage tumors, and the presence of lymph node metastasis (LNM). In contrast, GPC1 expression was absent in about 93% of lung adenocarcinoma cases, and only 2 cases exhibited weak focal expression. **Conclusion:** Our findings demonstrated that GPC1 expression is upregulated in advanced pleural mesothelioma and pulmonary SCC; tumors with high GPC1 expression exhibited more advanced biological behavior.

Keywords: Glypican-1- Mesothelioma- Lung adenocarcinoma- SCC- Prognostic biomarker

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Introduction

Lung carcinoma is ranked the 2nd most frequent malignancy and a major factor in cancer-related mortality globally, representing approximately 18% of all cancer deaths [1]. Lung carcinoma is the 5th most common type of cancer in Egypt. It affects males more than females, and most patients are diagnosed at the age of 60 or older. Smoking is the main risk factor for lung carcinoma [2].

Non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) are the main histologic subtypes of lung carcinoma. More than 80% of lung carcinoma are NSCLC. Histologically, NSCLC is categorized into three subtypes: lung adenocarcinoma, SCC, and large cell carcinoma. Adenocarcinoma accounts for about 40% of cases and is the most frequent subtype [3]. Based on the histologic and molecular status of the primary tumors, specific therapeutic strategies can be recommended. Consequently, it has become increasingly important to accurately discriminate between solid predominant lung adenocarcinoma and poorly differentiated SCC, as gene-targeted treatment requires the proper differentiation of these two histological subtypes [4].

Malignant pleural mesothelioma is a rare, highly

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aggressive neoplasm that arises from mesothelial cells that line the pleural cavity. It represents the most common primary pleural malignant tumor among Egyptians, accounting for more than 50% of cases. Exposure to asbestos is the main risk factor [5]. Three histologic subtypes are recognized: epithelioid, sarcomatoid, and biphasic variants. The majority, about 70%, of all histologic subtypes are epithelioid variants [6]. Epithelioid mesothelioma and lung adenocarcinoma share many similarities, and some peripheral lung carcinomas exhibit a pleurotropic growth pattern like mesothelioma. An accurate diagnosis of mesothelioma is required because it has a different prognosis and treatment [7].

GPC1 is a cell surface heparan sulfate proteoglycan, belongs to the six glypicans family. It is encoded by the GPC1 gene located at 2q37 [8]. It is involved in the signaling of growth factors such as transforming growth factor beta (TGF-β), fibroblast growth factor-2 (FGF-2), and vascular endothelial growth factor (VEGF) that regulate cell division and growth. It has three heparan sulfate chains and contains 588 amino acids in total [9]. It has been investigated as a possible target for cancer treatment in different neoplasms. Numerous studies have demonstrated the role of GPC1 in cancer cell growth, metastasis, and angiogenesis [10]. Previous studies reported its overexpression in various tumors, including pancreatic cancer, breast cancer, and glioma [11]. Studies evaluating the expression of GPC1 in pleural mesothelioma and lung carcinoma are insufficient and controversial. Further studies are required to fully understand its prognostic role and its potential value in distinguishing between pleural epithelioid mesothelioma, lung adenocarcinoma, and SCC.

Materials and Methods

Clinical data and specimens' collection

Seventy specimens, including 20 cases of pleural epithelioid mesothelioma, 30 cases of lung adenocarcinoma, and 20 cases of lung SCC, were included. After receiving approval from the Sohag University Ethical Committee (Registration number: Soh-Med-22-01-29), tissue blocks were obtained from the Pathology Laboratory of the Sohag University Hospitals and Sohag Oncology Center. Exclusion criteria included insufficient tissue for IHC, neoadjuvant chemotherapy or radiotherapy, and incomplete clinical data. Each block yielded two tissue sections stained with H&E and anti-human GPC1. The following parameters were re-assessed in the H&E stained sections: histologic type and tumor grade.

Immunohistochemical staining of GPC1

Serial sections from the tissue blocks were submitted for IHC. The staining process is based on the streptavidin-biotin immunoperoxidase complex procedure. 4 µm thick sections were placed in heated xylene to be deparaffinized. Descending levels of alcohol were used to rehydrate the tissue sections. Following a 10-minute incubation with 3% H_2O_2 to inhibit endogenous peroxidase activity, two rounds of washing in phosphate buffer solution (PBS) were performed. Using citrate buffer fluid at a concentration of 0.01 mmol/L for 20 minutes in the microwave at 650 W, antigen retrieval was accomplished. Sections were incubated with rabbit polyclonal anti-Glypican-1 antibody (1/100, ab217339, Abcam, UK) overnight at 4°C. After each step, tissue sections were washed in PBS. The slides were incubated for 10 minutes with goat serum secondary antibody, followed by streptavidin biotin. Diaminobenzidine (DAB) was used as a chromagen. Finally, tissue sections were counterstained using Harris' hematoxylin, then dehydrated, cleared, and mounted. Bronchial epithelium was used as an internal positive control. The negative controls were stained parallel to the positive controls but without the addition of the primary antibody.

Evaluation of GPC1 immunostaining

The evaluation of GPC1 immunostainig was based on the intensity and percentage of positive tumor cells. Membranous and cytoplasmic reactivity were detected within the tumor cells. The intensity of staining was scored as follows: (0= no stain, 1= weak, 2= moderate, and 3= strong). The percentage of positive cells was scored as follows: 0<5%, 1 (6–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%). The immunoreactive score (IRS) was calculated by multiplying intensity and percentage of positivity. Low expression was defined as a total IRS <4, while high expression was defined as a total score ≥4 [12].

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS, version 25) to perform the statistical analysis. Mean ± standard deviation (SD), and range were used for quantitative data. Frequency and percentage were used for qualitative data. The means of the two groups were compared using a student t-test. The expression rate between the categories was compared using the Chi-square test. If P value less than 0.05, it was regarded as statistically significant.

Results

Patients' characteristics

The current study included a total of 70 specimens: 20 cases of pleural Epithelioid mesothelioma, 30 cases of lung adenocarcinoma, and 20 cases of lung SCC. The clinical and histopathological characteristics of the studied cases were described in Table 1.

Immunohistochemical detection of GPC1

Membranous and cytoplasmic expression were observed within the neoplastic cells, and both patterns were considered positive. All cases of epithelioid mesothelioma and lung SCC showed positive reactivity. Epithelioid mesothelioma and lung SCC cases exhibited high GPC1 expression (score ≥4) in 16/20 (80%) and 17/20 (85%), respectively, while 4/20 (20%) and 3/20 (15%) of cases expressed low expression levels (score<4). In contrast, only 2/30 (6.7%) of lung adenocarcinoma cases revealed focal weak expression, and the remainder

Table 1. The Clinico-pathological Characteristics of the Studied Cases (N=70)

Variable	Mesothelioma (20 cases) N (%)	Lung Adenocarcinoma (30 cases) N (%)	Lung SCC (20 cases) N (%)
Age (Year)			
Range	43-77	55-75	60-75
Mean ± SD	58±8.6	63.4±5.4	67±4.7
Gender			
Male	14 (70)	15 (50)	13 (65)
Female	6 (30)	15 (50)	7 (35)
Smoking			
Smoker	11 (55)	17 (56.7)	14 (70)
Non-smoker	9 (45)	13 (43.3)	6 (30)
Tumor size (cm.)			
T1		4 (13.3)	3 (15)
T2	----	15 (50)	10 (50)
T3		11 (36.7)	7 (35)
Laterality			
Right side	13 (65)	20 (66.7)	15 (75)
Left side	7 (35)	10 (33.3)	5 (25)
Grade			
I	4 (20)	3 (10)	1 (5)
II	10 (50)	15 (50)	6 (30)
III	6 (30)	12 (40)	13 (65)
Stage			
I	2 (10)	3 (10)	2 (10)
II	10 (50)	13 (43.3)	10 (50)
III	8 (40)	11 (36.7)	6 (30)
IV	0 (0)	3 (10)	2 (10)
LNM			
Yes	9 (45)	17 (56.7)	13 (65)
No	11 (55)	13 (43.3)	7 (35)

of cases didn't show any expression (Figure 1).

Our findings revealed that GPC1 expression levels were significantly higher in pleural mesothelioma and lung SCC compared to its level in lung adenocarcinoma ($p<0.0001$) (Tables 2 and 3). On the other hand, there was no statistically significant difference in GPC1 expression between pleural mesothelioma and lung SCC ($p = 0.677$), Table 4.

Comparing the statistical results of the GPC1 immunostaining to the available cliniopathological data in epithelioid mesothelioma cases revealed increased expression levels in advanced, less differentiated tumors. The intensity of GPC1 immunostaining was noticed to be increased in higher tumor grades and stages ($p=0.008$) and ($p=0.007$), respectively. Additionally, GPC1 expression and LNM were shown to be statistically significantly correlated ($p=0.043$). However, statistical analysis of GPC1 expression in relation to patients' age, gender, smoking, and tumor laterality didn't reveal any statistically significant difference (Table 5).

Concerning lung SCC cases, GPC1 expression revealed a positive statistically significant correlation in relation to tumor size ($p= 0.021$), grade ($p= 0.045$), stage ($p= 0.005$), and LNM ($p= 0.01$). In addition, GPC1 expression was statistically analyzed in relation to the other studied clinicopathological characteristics, but no statistically significant correlations were found (Table 6).

Discussion

GPC1 regulates cell proliferation and differentiation. It has been reported to contribute to carcinogenesis, and its overexpression is associated with poor prognosis and chemoresistance in various types of human cancers. According to previous reports, GPC1 has been suggested as a potential therapeutic target in several neoplasms as it interacts with different growth factors such as TGF-β, FGF-2, and VEGF to regulate cell division and growth; furthermore, these growth factors are known to control tumor cell proliferation, angiogenesis, and metastasis [13, 14]. Several trials have developed antibody-based therapeutics that target GPC1 for the treatment of solid

Table 2. Comparison of GPC1 Expression in Pleural Mesothelioma Versus Lung Adenocarcinoma

Variable	GPC1 IHC Expression			P value
	Negative	Positive		
		Low N (%)	High N (%)	
Pleural mesothelioma	0	4 (20)	16 (80)	<0.0001**
Lung Adenocarcinoma	28 (93.3)	2 (6.7)	0	

Chi-square test was used; ** highly significant.

Table 3. Comparison of GPC1 Expression in Lung SCC Versus Lung Adenocarcinoma

Variable	GPC1 IHC Expression			P value
	Negative	Positive		
		Low N (%)	High N (%)	
Lung SCC	0	3 (15)	17 (85)	<0.0001**
Lung adenocarcinoma	28 (93.3)	2 (6.7)	0	

Chi-square test was used; ** highly significant.

Table 4. Comparison of GPC1 Expression in Pleural Mesothelioma Versus Lung SCC

Variable	GPC1 IHC Expression		P value
	Low N (%)	High N (%)	
Pleural mesothelioma	4 (20)	16 (80)	0.677
Lung SCC	3 (15)	17 (85)	(NS)

Chi-square test was used; NS, non-significant.

tumors such as oesophageal and pancreatic cancer [15, 16].

Few previous studies were conducted to evaluate GPC1 expression levels in pleural mesothelioma and lung carcinoma. In this study, we evaluated GPC1 expression and its applicability in distinguishing epithelioid mesothelioma from lung adenocarcinoma, and SCC correlated its expression with some known clinicopathological parameters.

GPC1 reactivity was observed in all cases of pleural epithelioid mesothelioma and lung SCC; high expression (score ≥4) was detected in 80% and 85% of cases, respectively. In contrast, only two cases of lung adenocarcinoma exhibited positive expression that was focal and weak. According to our findings, the GPC1 expression level was significantly higher in pleural epithelioid mesothelioma compared to its level in lung adenocarcinoma. These findings were in concordance with the findings of Amatya and his colleagues, who reported that GPC1 expression was detected in all epithelioid mesothelioma cases, and only 3 cases of pulmonary adenocarcinoma revealed focal weak expression. They described the value of GPC1 immunostaining to distinguish between epithelioid mesothelioma and lung adenocarcinoma, where GPC1 expression demonstrated 100% sensitivity, 97% specificity, and 98% accuracy. Therefore, they recommended using GPC1 as an additional positive marker for pleural epithelioid mesothelioma [17]. Meanwhile, our results differed significantly from those of Chiu and his colleagues, who reported positive GPC1 expression in all cases of pleural epithelioid mesothelioma as well as pulmonary adenocarcinoma and reported that GPC1 IHC can't distinguish between pleural mesothelioma and lung adenocarcinoma [18]. Moreover, Kai and his colleagues investigated the differential GPC1 expression in poorly differentiated SCC versus solid predominant adenocarcinoma of the lung and reported strong reactivity in all SCC cases, while weak positivity was observed only in two cases of adenocarcinoma. They hypothesized that GPC1 can help in distinguishing between poorly differentiated lung SCC and solid predominant adenocarcinoma, which was in agreement with our findings [19]. This variation in GPC1 expression levels makes it a promising target for future

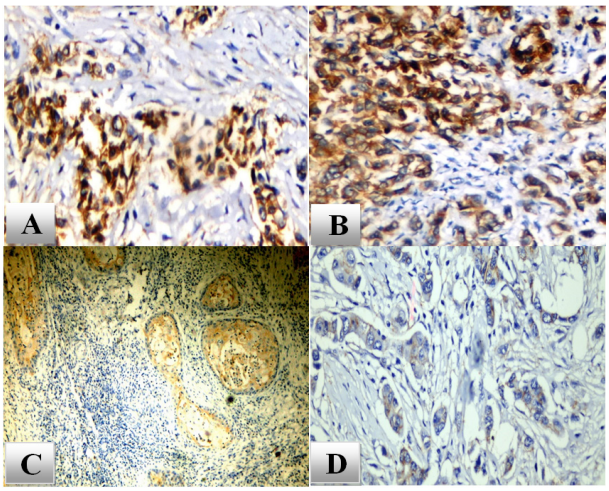

Figure 1. High GPC1 Expression in Pleural Epithelioid Mesothelioma (A&B), High GPC1 Expression in Lung SCC (C), Weak Focal GPC1 Expression in Lung Adenocarcinoma (D). X400.

Table 5. Statistical Analysis of GPC1 Expression in Relation to Clinicopathological Parameters in Cases of Epithelioid Mesothelioma (N=20)

Variable	No. of cases	GPC1 expression		
	(20)	High expression	Low expression	P value
		16 (80%) N (%)	4 (20%) N (%)	
Age (Year)				
Mean ±SD	-	59 ± 8.9	53.8 ± 6.6	0.284*
Gender				
Male	14	11(78.6)	3 (21.4)	0.807
Female	6	5 (83.3)	1 (16.7)	
Smoking				
Smoker	11	8 (72.7)	3 (27.3)	0.369
Non-smoker	9	8 (88.9)	1 (11.1)	
Laterality				
Right side	13	9 (69.2)	4 (30.8)	0.101
Left side	7	7 (100)	0	
Grade				
I	4	1 (25)	3 (75)	
II	10	9 (90)	1 (10)	0.008
III	6	6 (100)	0	
Stage				
I	2	0	2 (100)	0.007
II	10	8 (80)	2 (20)	
III	8	8 (100)	0	
LNM				
Yes	9	9 (100)	0	0.043
No	11	7 (63.6)	4 (36.4)	

P value was calculated by Chi-Square test. *P value was calculated by Independent Sample T-Test.

therapeutic approaches.

Several studies investigated GPC1 expression in various human cancers and correlated its expression with different clinical and histopathological features. To the best of our knowledge, no previous studies have discussed these correlations in either pleural mesothelioma or lung carcinoma. Analyzing the correlations between GPC1 expression and clinicopathological data in pleural mesothelioma and lung SCC cases, we found that GPC1 expression is significantly correlated with tumor grade and size. High GPC1 expression was more frequently observed in poorly differentiated tumors compared with well-differentiated tumors. Moreover, GPC1 expression was upregulated in larger tumors in lung SCC cases. These findings are in line with previous studies conducted on different neoplasms that reported higher levels of GPC1 expression in larger sizes and higher grades of pancreatic ductal adenocarcinoma [20] and breast carcinoma [21].

Additionally, there was an increase in GPC1 expression levels as the tumor became more advanced and invasive. There was a significantly higher frequency of GPC1 expression in advanced stages than in early stages. These findings are in agreement with a previous study by Chen and his colleagues, who observed higher levels of GPC1 immunoreactivity in advanced stages of hepatocellular carcinoma compared with early stages [12]. We observed that GPC1 expression was upregulated in association with the presence of nodal metastasis. This was in accordance with previous studies reporting that GPC1 plays a role in controlling cell migration [22]. In addition, GPC1 plays a key role in cancer progression and metastasis; GPC1 down-regulation has been noted to inhibit metastasis in pancreatic cancer cell lines [20]. On the other hand, no significant correlations were detected between GPC1 expression and other patients' characteristics, including age, sex, and smoking, as reported by previous studies [12].

In conclusion, our findings revealed that high GPC1 expression may be associated with more advanced biological behavior in pleural mesothelioma and lung SCC, so it may be a potentially valuable biomarker to predict the prognosis. GPC1 expression level was significantly lower in lung adenocarcinoma, which may help differentiate it from pleural epithelioid mesothelioma and poorly differentiated lung SCC. However, these findings must be interpreted with caution, and further large-scale prospective studies are recommended.

Limitations of the study

The sample size was not large enough, which in turn

Table 6. Statistical Analysis of GPC1 Expression in Relation to Clinicopathological Parameters in Cases of Lung SCC (N=20)

Variable	No. of cases	GPC1 expression		
		High expression	Low expression	P value
		17 (85%) N (%)	3 (15%) N (%)	
Age (Year)				
Mean ±SD	-	67.3 ±4.6	65.7 ± 6	0.596*
Gender				
Male	13	11 (84.6)	2 (15.4)	0.948
Female	7	6 (85.7)	1 (14.3)	
Smoking				
Smoker	14	12 (85.7)	2 (14.3)	0.891
Non-smoker	6	5 (83.3)	1 (16.7)	
Laterality				
Right side	15	12 (80)	3 (20)	0.278
Left side	5	5 (100)	0	
Size				
T1	3	1 (33.3)	2 (66.7)	0.021
T2	10	9 (90)	1 (10)	
T3	7	7 (100)	0	
Grade				
I	1	0	1 (100)	
II	6	5 (83.3)	1 (16.7)	0.045
III	13	12 (92.3)	1 (7.7)	
Stage				
I	2	0 (0)	2 (100)	
II	10	9 (90)	1 (10)	0.005
III	6	6 (100)	0	
IV	2	2 (100)	0	
LNM				
Yes	13	13 (100)	0	0.01
No	7	4 (57)	3 (43)	

P value was calculated by Pearson Chi-Square test. *P value was calculated by Independent Sample T-Test.

weakened the statistical power of the results.

Recommendations

Further large-scale prospective studies on GPC1 expression in pleural epithelioid mesothelioma, adenocarcinoma, SCC, and non-malignant lesions of the lung are recommended to obtain more accurate results. In addition, follow-up of patients is important to emphasize the correlation between GPC1 expression and patient survival and disease outcome.

Acknowledgements

Not applicable.

Abbreviations

GPC1, Glypican-1; H&E, Hematoxylin and eosin; HCC, Hepatocellular carcinoma; IHC, Immunohistochemistry/Immunohistochemical; IMIG, The International Mesothelioma Interest Group; IRS, Immunoreactive score; LNM, lymph node metastasis; NSCLC, Non-small cell lung cancer; PBS, Phosphate buffer solution; SCC, Squamous cell carcinoma; SCLC, Small-cell lung cancer.

Declarations

- Ethical approval and consent to participate: The study protocol was reviewed and approved by Ethical Committee of Sohag Faculty of Medicine.

Consent for publication

Not applicable.

Availability of data and material

All data and materials were available.

Competing interests

The authors declare that they have no conflict of interest.

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Authors Contribution

Noha ED Hassab El-Naby and Nagwa Abd EL-Sadek Ahmed carried out manuscript writing & design, figures analysis & manipulation and histopathological diagnosis with archival revision of paraffin blocks and slides. Mohsen Saber Mohammed Ahmed collected the clinical, demographic and radiological data.

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