ORIGINAL ARTICLE

Dynamin-2 and Angiopoietin-like protein 2 as novel prognostic markers in papillary thyroid carcinoma

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common histological type of thyroid cancer. Fortunately, most PTC patients have favorable outcomes, but about 20% of patients,have distant metastases. Therefore, the exploration of new biomarkers to know new characteristics of PTC should be updated.

The aim of our study is to evaluate the possible role of Dynamin-2 and Angiopoietin-like protein 2 (Anglp2) as novel prognostic markers for papillary thyroid carcinoma.

Material and Methods: In our study, we investigated the expression of DNM2 and Anglp2 in 60 cases of PTC . The clinical significance of the markers was evaluated by assessing correlation with the clinicopathological parameters.

Results: High DNM2 expression PTC was significantly associated with advanced tumor stage, lymph node metastasis, recurrence and death (p<0.002,0.018, <0.001, <0.001respectivelly).High expression levels of Anglp2 in PTC were significantly associated with advanced tumor stage, , recurrence and death (p <0.004, ,p= 0.004,p=0.003 respectively).

Conclusions: DNM2 and Anglp2 were independent PTC markers indicating more likely recurrence and poor prognosis. Expression may help to select the high-risk patients for adjuvant targeted therapy.

Keywords: Papillary-thyroid-carcinoma, DNM2, Anglp2, Immunohistochemistry, Prognosis.

INTRODUCTION

Thyroid carcinoma (TC) is the most common endocrine malignancy , with 298, 000 cases diagnosed globally, representing 2.1% of all new cancer cases worldwide. The morbidity of TC has increased worldwide during the past decades [1,2]. Histological subtypes of TC can be classified into papillary TC (PTC), follicular TC, medullary TC, poorly differentiated TC, and Hurthle cell and anaplastic TC [3].

Papillary carcinoma of the thyroid gland (PTC) is the commonest among thyroid gland malignancies, representing more than 85%. Papillary thyroid carcinoma (PTC) is well known for its favorable prognosis with a 10-year survival rate around 90% . However, up to 20% of PTC will show local recurrences, invasion, multiple lymph node and distant metastasis, indicating that PTC comprises a heterogeneous group of tumors resulting in various clinical prognosis and the lack of effective therapies [4] . Mechanisms

regarding response to therapeutic agents remain unclear.Therefore, the exploration of new biomarkers and the knowledge of new characteristics of PTC should be continuously updated for evaluating prognosis and response to therapy .

Endocytosis is a physiological process which is modified in cancer[5]. Clathrin-mediated endocytosis (CME) reported to influence tumor progression via promoting recycling and endocytosis of membrane receptors such as epidermal growth factor receptor (EGFR) [6]. Dynamin 2 is a GTPase molecule that has been implicated in cancer progression owing to its roles in endocytosis, morphogenesis, actomyosin contractions, focal adhesion maturation and epithelial-mesenchymal transition (EMT)[7]. Dynamins (DNMs) gather around the necks of clathrin-coated pits that can facilitate DNM tumorigenesis function [8].

DNM have been identified to be responsible for motility, invasion, and metastasis in several cancers such as pancreatic, prostatic cancers [9,10]. However, their mechanism in PTC progression remains unclear.

Angiopoietin-like protein2 (Anglp2) is a secreted glycoprotein belonging to the angiopoietin (ANGPTL) family which involved in angiogenesis, glucose and lipid metabolism [11]. Several studies concluded that the role of Anglp2 in different solid tumors was not only to act as a trigger of carcinogenesis but also to promote tumor angiogenesis, lymphangiogenesis, and metastasis. (12,13,14). However, whether ANGPTL2 plays a role in metastasis and recurrence of PTC, remains undeinvestigated.

MATERIAL AND METHODS

Patients and tissue samples

Patients and tissue samples

In our study, a total of 60 consecutive patients, the inception cohort, was diagnosed with TC and underwent radical surgical resection in the surgery department during the period from 2015 to 2018. Formalin-fixed-paraffin-embedded tissue specimens were obtained from Pathology department of the same institute .The validation cohort was selected from the primary cohort, consisting of 60 patients who (1) had systemic follow-ups, (2) received no adjuvant therapy before tumor recurrence, and (3) were diagnosed with PTC. The validation cohort comprised 16 male patients and 44 female patients. The average follow up time was 60.8 months and the median follow-up was 44 months. The pathological stage of PTC was classified with 7th tumor-nodes-metastases (TNM) American Joint Committee on Cancer staging system. Written informed consent was obtained from all participants,The study was approved by the ethics committee of Faculty of medicine,Zagazig University. The Code of Ethics of the World Medical Association (Declaration of Helsiniki) for studies involving humans

Preoperative evaluation

All patients included in the study underwent physical examination, thyroid hormonal profile and high-resolution ultrasonography (US) of the neck. Fine needle aspiration cytology (FNAC) was performed in any suspicious nodules. Tc99m pertechnetate thyroid scan was done only in patients with hyperthyroidism, manifested as high or normal serum free T3 , free T4 and low serum TSH (<0.4 mIU/L).

Postoperative evaluation:

All patients were referred to Nuclear Medicine Units NCI, or Mansora University Hospitals to Undergo RAI-131 scan and /or Ablation dose routinely after total thyroidectomy according to the risk stratification of the patient (intermediate and high-risk patients).

Serum Thyroglobulin (Tg) ,Anti-Tg antibodies, (Thyroid Stimulating Hormone) TSH measurements and neck ultrasound (US) were used in for postoperative evaluation every 6–12 months for all patients

initially and also for high risk patients during the entire follow up period. for low and intermediate-risk patients who showed excellent response to treatment, Tg measurements were repeated every 12–24 months.

At any risk level, thyroid hormone withdrawal prior to RAI imaging or therapy was done .

Disease-free status was defined as: no Evidence of Disease (NED) and included the following features: no clinical evidence of tumor, no imaging evidence of disease by RAI -131imaging and/or neck US, and low serum Tg levels during TSH suppression (Tg < 0.2 ng/mL) or after stimulation (Tg < 1 ng/mL) in the absence of interfering antibodies.

Recurrent disease was defined as clinical, biochemical or structural evidence of disease found one year after surgery or later in a patient considered disease-free after primary treatment.

Histopathology

 Representative paraffin-embedded sections of PTC were constructed. Hematoxylin and eosin staining of slides was carried out to select the staining area of all samples.

Immunohistochemistry

Immunohistochemical staining was carried out using the polymer envision technique [15]. The used primary antibodies; anti-DNM2 (ab3457) Anglp2 antibody (ab199133), as well as the detection kit (UltraVision Detection System Anti-polyvalent, HRP/DAB, Ready-To-Use) were purchased from the Thermo Scientific Lab..

Assessment of the immunohistochemistry

Dynamin 2 scoring

Dynamin 2 immunoexpression is detected in the cytoplasm of tumor cells. The intensity of staining was graded as (0, negative; 1+, weak; 2+, moderate; and 3+, strong) . The positive tumor cells as follows: < 25 % as 1, 25 %-50 % as 2, 51 %-75 % as 3, and > 75 %

as 4. Dynamin 2 expression in more than 50% was scored as high expression [13].

Anglp2 scoring

Anglp2 immunoexpression is detected in the nucleus and cytoplasm . The score representing the percentage of the positive tumor cells was assigned as follows:: (1) 0–25% , (2) 25–50% , (3) 50–75% and (4) >75% [14]. Expression of Anglp2 in more than 50% was considerd high expression

Statistical analysis :.

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using chi square test and Fisher exact test when appropriate. For comparing two groups regarding ordinal categorical data, chi square for trend test was used. Phi correlation coefficient was used to assess the strength and direction of association between two dichotomous categorical variables. Survival analysis and Kaplan Meire plot was used to measure the fraction of subjects living for a certain amount of time after treatment and for analyzing the expected duration of time until one event occurs, either death or recurrence. The OS time was defined as the time between operation and the death time or last follow-up, and the DFS time was defined as the time from operation to recurrence confirmed by imaging examination such as ultrasound. The level statistical significance was set at 5% ($P<0.05$).

RESULTS

Patients' characteristics

The majority of patients (56.7 %) were above 45 years at the initial diagnosis. Among the studied cases, 93.3% of the cases were PTC while 6.7% were Follicular variant. Stage II was the predominant among the cases (38.3%). Bilaterality, multifocal lesion and extrathyroid involvement were noted in 40%,

60% and 66.7% cases respectively. During the follow-up duration , 20 patients (33.3%) died. The clinicopathological features of the patients were presented in Table 1.

Association between Anglp2, Dynamin immunoexpression and the clinicopathological features and outcome

High Anglp2 was expressed in 65% of the cases where PTC cases showed the highest rate of expression Figure(4).There were statistically significant association between high expression with tumor stage, recurrence and death (p <0.004, 0.004 and 0.003 respectively. Association of Anglp2

expression with various clinicopathological characteristics is summarized in Table 2 High Dynamin presented in 70% of patients where PTC showed the highest rate of expression, Figure (2).There were statistically significant association between Dynamin expression with stage, nodal metastasis, recurrence and death (p <0.002, p=0.018, p<0.001 and p<0.001respectivelly). Association of Dynamin expression with various clinicopathological characteristics is summarized in Table 2 . There is significant positive correlation between Anglp2 and Dynamin levels p <0.001 (table 3)

Table (1) Baseline characteristics of the studied patients:

Parameter	N=60	%
Age:		
≤ 45 years	26	43.3
>45 years	34	56.7
Pathological type:		
PTC	56	93.3
Follicular variant	4	6.7
Staging:		
I	8	13.3
II	23	38.3
III	18	30
IV	11	18.3
Extra-thyroid extension:		
No	20	33.3
Yes	40	66.7
Multifocality:		
No	24	40
Yes	36	60
Bilaterality:		
No	36	60
Yes	24	40
Lymph node metastasis:		
Negative	37	61.7
Positive	23	38.3
Recurrence:		
No	25	41.7
Yes	35	58.3
Death:		
No	40	66.7
Yes	20	33.3
Anglp2 :		
No	21	35

Parameter	N=60	%
Yes	39	65
Dynamin2:		
No	18	30
Yes	42	70

Table (2) Relation between Anglp2, Dynamin and both baseline characteristics and outcome of the studied patients:

Parameters	Total N=60	Anglp2 low N=21 (%)	high N=39 (%)	p	Dynamin low N=18(%)	high N=42(%)	p
Age:							
≤ 45 years	26	9 (34.6)	17 (65.4)	0.956‡	6 (23.1)	20 (76.9)	0.306‡
>45 years	34	12 (35.3)	22 (64.7)		12 (35.3)	22 (64.7)	
Pathological type:							
PTC	56	19 (33.9)	37 (66.1)	0.606‡	16 (28.6)	40 (71.4)	0.366‡
Follicular variant	4	2 (50)	2 (50)		2 (50.0)	2 (50.0)	
Staging:							
I	8	6 (75.0)	2 (25.0)		5 (62.5)	3 (37.5)	
II	23	10 (43.5)	13 (56.5)	<0.004¥*	9 (39.1)	14 (60.9)	<0.002¥
III	18	3 (16.7)	15 (83.3)		4 (22.2)	14 (77.8)	*
IV	11	2 (18.2)	9 (81.8)		0 (0)	11 (100)	
Extrathyroid extension							
No	20	6 (30.0)	14 (70.0)	0.556‡	5 (25.0)	15 (75.0)	0.550‡
Yes	40	15 (37.5)	25 (62.5)		13 (32.5)	27 (67.5)	
Multifocality:							
No	24	8 (33.3)	16 (66.7)	0.825‡	8 (33.3)	16 (66.7)	0.645‡
Yes	36	13 (36.1)	23 (63.9)		10 (27.8)	26 (72.2)	
Bilaterality:							
No	37	15 (40.5)	22 (59.5)	0.254‡	15 (40.5)	22 (59.5)	0.024*‡
Yes	23	6 (26.1)	17 (73.9)		3 (13.0)	20 (87.0)	
Lymph node metastasis:							
Negative	23	11 (47.8)	12 (52.2)	0.101‡	11 (47.8)	12 (52.2)	0.018‡*
Positive	37	10 (27.0)	27 (73.0)		7 (18.9)	30 (81.1)	
Recurrence:							
No	24	17 (70.8)	7 (29.2)	0.004*‡	15 (62.5)	9 (37.5)	<0.001
Yes	36	4 (11.1)	32 (88.9)		3 (8.3)	33 (91.7)	*‡
Death:							
No	36	18 (50.0)	18 (50.0)	0.003*‡	18 (50.0)	18 (50.0)	<0.001
Yes	24	3 (12.5)	21 (87.5)		0 (12.5)	24 (100.0)	*‡

‡Chi square test *p<0.005 is statistically significant   ¥Chi square for trend test

Table (3) Correlation between Anglp2 and Dynamin among the studied patients:

	Anglp2		Dynamin2	
	Phi	**p**	**Phi**	**p**
Anglp2			0.663	<0.001*
Dynamin	0.663	<0.001*		

*p<0.05 is statistically significant

Table (4): Kaplan– Meier survival curves illustrating overall survival time differences in patients as regard markers expressions

		Total N	N of Events	Censored		Survival time, Months		P
				N	%	Mean		
						Estimate ±SD	95% CI	
Dynamin	Negative	18	0	18	100.0%			<0.001*
	Positive	42	24	18	42.9%	29.17±1.14	26.93 – 31.42	
Anglp2	Negative	21	3	18	85.7%	34.07±1.07	31.97-36.18	0.001*
	Positive	39	21	18	46.2%	30.6±1.6	23.33-29.17	
Overall		60	24	36	60.0%	29.17±1.14	26.93 – 31.42	

*p<0.05 is statistically significant
There is statistically significant association between OS and expression of either Dynamin2 or Anglp2. Neither of patients with negative Dynamin2 had died during follow up period. Patients with negative Anglp2 had significantly higher OS.

Table (5): Kaplan– Meier survival curves illustrating disease free survival time differences in patients as regard markers expressions

		Total N	N of Events	Censored		Survival time, Months		P
				N	%	Mean		
						Estimate ±SD	95% CI	
Dynamin	Negative	18	3	15	83.3%	30.37±0.94	28.54—32.2	<0.001*
	Positive	42	33	9	21.4%	19.0 ±1.24	16.56 – 21.43	
Anglp2	Negative	21	4	17	81.0%	29.17±1.35	26.52-31.82	<0.001*
	Positive	39	32	7	17.9%	18.87±1.27	16.39-21.36	
Overall		60	36	24	40.0%	22.58±1.14	20.34 – 24.82	

p<0.05 is statistically significant
There is statistically significant association between OS and expression of either Dynamin or Anglp2.. Patients with negative Anglp2 and Dynamin had significantly higher DFS.
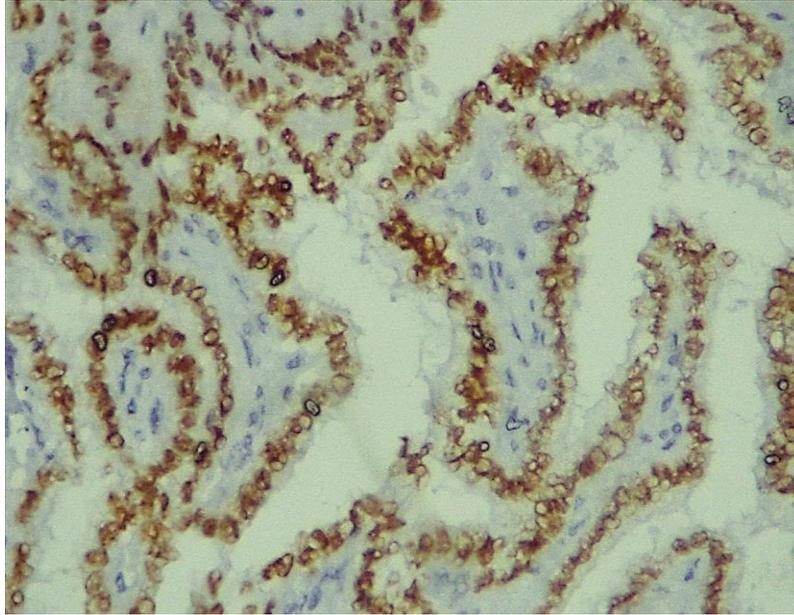
Figure1 . Papillary thyroid carcinoma , moderate Dynamin2 immunoexpressionX400
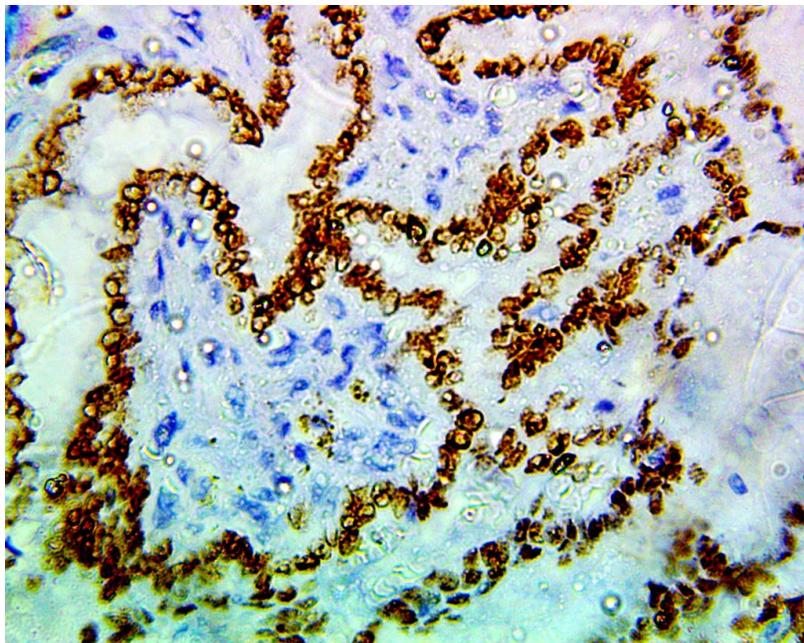

Figure2 . Papillary thyroid carcinoma , strong Dynamin2 immunoexpressionX400
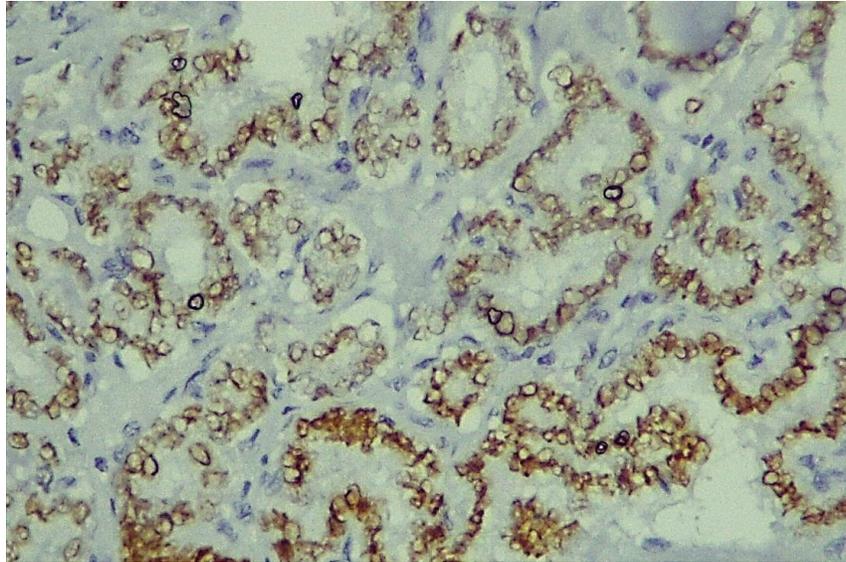
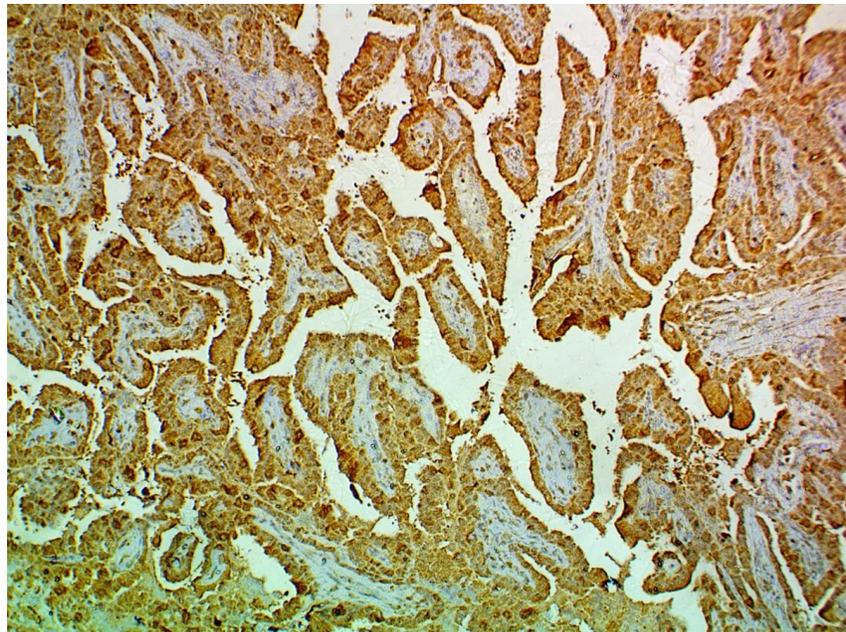Figure 3 . Papillary thyroid carcinoma , weak Dynamin2 immunoexpressionX400

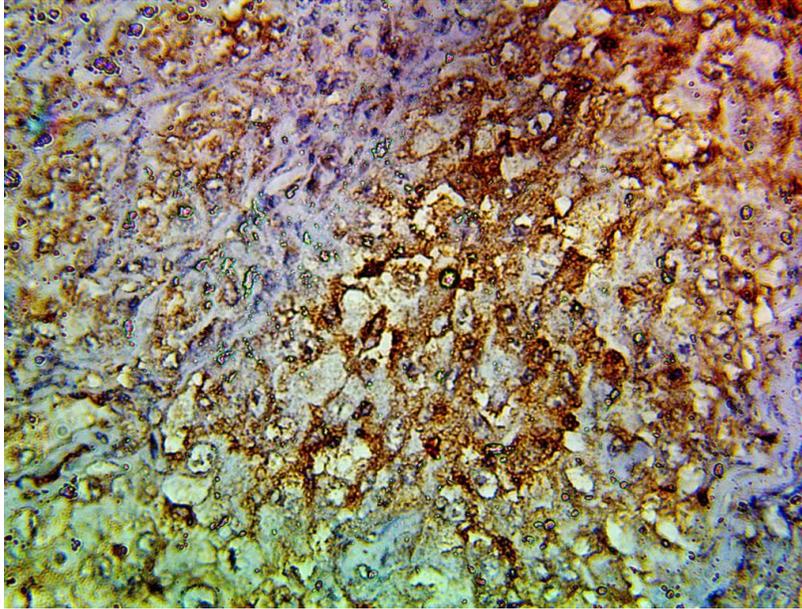Figure 4 . Papillary thyroid carcinoma , strong Anglp2 immunoexpressionX400

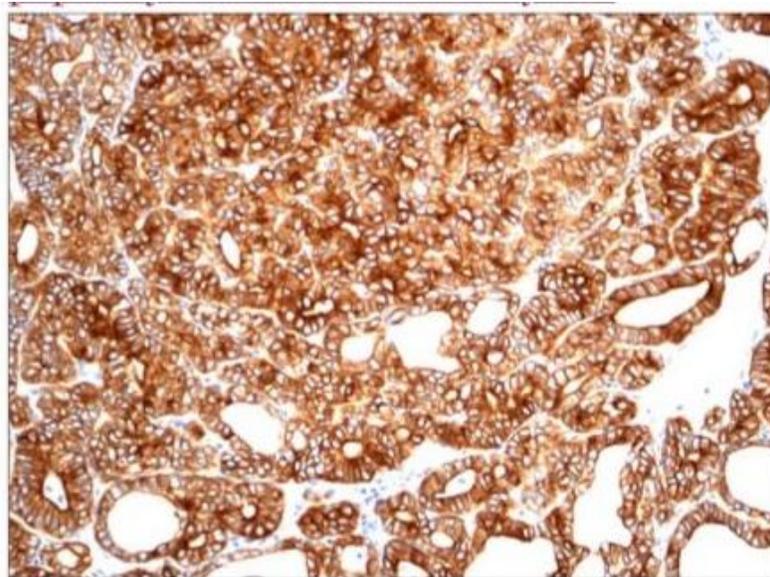Figure 5 . Follicular variant of papillary thyroid carcinoma ,moderate Anglp2 immunoexpressionX400

Figure 6 : Follicular variant of papillary thyroid carcinoma ,strong Anglp2x400
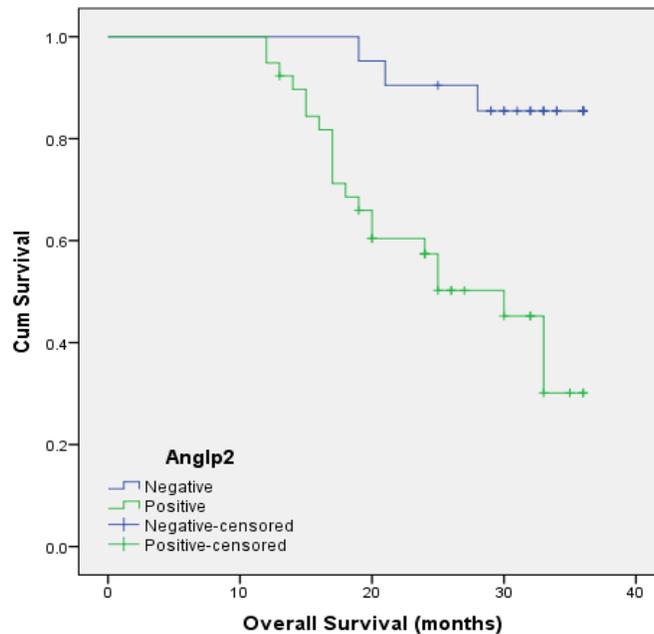
Figure (7) Kaplan Meier plot showing relation between overall survival and Anglp2 (median survival in positive Anglp2 was 26.25 month versus 34.07 month in Anglp2 negative) (p<0.05)

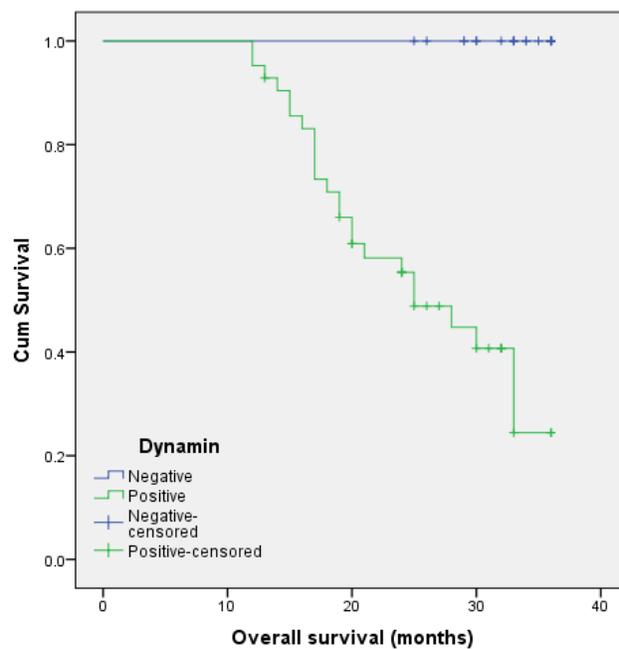
Figure (8) Kaplan Meier plot showing relation between overall survival and Dynamin (no patient with Dynamin positive died during follow up) (p>0.05)

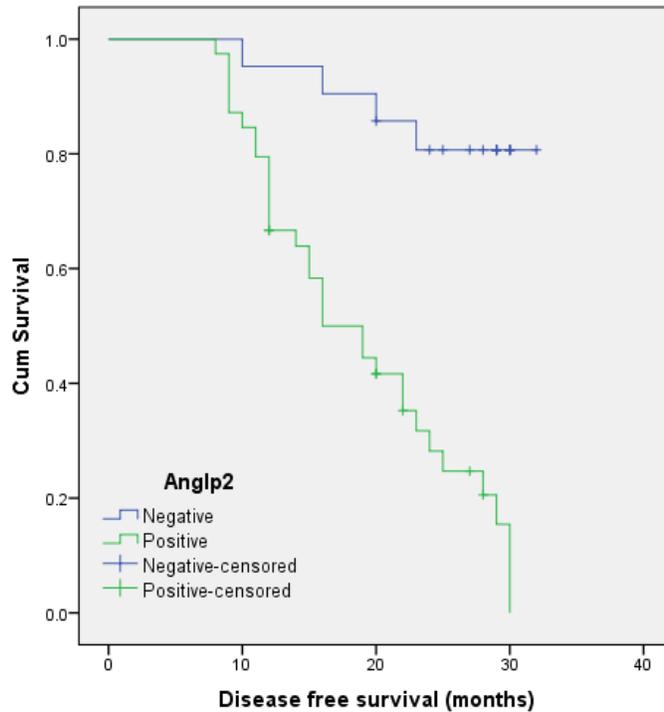**Figure (9) Kaplan Meier plot showing relation between DFS and Anglp2 (median survival in positive Anglp2 was 18.87 month versus 29.17 month in Anglp2 negative) (p<0.05)**
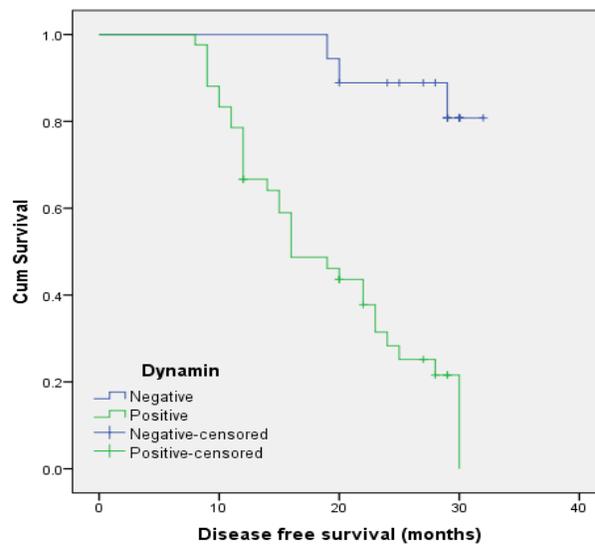

Figure (10) Kaplan Meier plot showing relation between DFS and Dynamin (median survival in positive Dynamin was 19.0 month versus 30.37 month in Dynamin negative) (p<0.05)

DISCUSSION

Tumor proliferation, metastasis, and invasion are key factors in cancer-related death. Although most patients with papillary thyroid carcinoma (PTC) have good prognosis, around 20% of have a high rate of recurrence, metastasis and mortality rate even after the routine treatment.So, understanding the carcinogenesis process of PTC will help in recognizing new targets that can prohibit the PTC progression.

We found that dynamin 2 expression in 63.8% of the studied case which was significantly correlated with tumor stage, lymph node metastasis, bilaterality, extrathyroid involvements , recurrence and death, confirming the past observation of the essential role of dynamin 2 expression in tumor progression through endocytosis of membrane molecules. Similar to our data, Ren et al. [16] reported that in 112 patients with PTC low and high DNM2 expressions were accounted for 75% and 25% respectively. High DNM2 expression was significantly associated with recurrence (P=0.014) and poor prognosis (P=0.004).

various studies have shown that, increasing the expression of dynamin 2 molecule increases the motility as well as metastatic capacity of cancer cells confirming the role of dynamin 2 in cancer cells' movement.

The results on the role of dynamin 2 in PTC were matched with that in other cancers. Eppinga et al.,[17] showed that 81 of 85 % of the patients had the increased dynamin 2 expression in pancreatic tumor tissues compared to normal tissues . Xu et al.,[18] also reported that dynamin 2 expression significantly increased during the stages of prostate cancer . It has been reported that dynamin 2 expression was association with more aggressive tumor behavior and more advanced disease in the patients with breast cancer [19]. Therefore, dynamin 2 molecule could be considered as an indicator of disease progression and aggressiveness. Near results

were reported in other studies [20],[21]. In addition to the function of DNM2 in regulating endocytosis, DNM2 can contribute to invadopodia formation via its GTPase function in bladder cancer [22].

Our results help to select high-risk patients for adjuvant therapy after surgery by detecting expression of dynamin2. Moreover, our findings that DNM2 led to increased recurrence and poor prognosis has great value for clinical application. Dynamin 2 inhibitor , as dynasore, has good cell permeability and specificity [23] that could be a viable drug for PTC .

.Angptl2 is an important marker that is involved in carcinogenesis and tumor development.[24] Anglp2 is present mainly in adipose tissue, explaining the risk of obesity on thyroid carcinogenesis [25]

In the current study, positive Anglp2 expression was detected in 50% of the studied cases. There is statistically significant relation between Anglp2 , tumor stage, recurrence and death. These findings confirmed that ANGPTL2 accelerate PTC progression and tumor growth.our results was in agreement with Yang et al., [26] who evaluated 36 patients with PTC and found that Anglp2 was higher in thyroid cancer tissue than adjacent normal thyroid tissue and increased in the advanced stage of PTC tumor Several research evidences have showed that Anglp2 was upregulated in various human tumor tissues and correlated with tumor size and severity [27],[28]. All these studies are consistent with our findings. Contrary to our report, Kikuchi et al. reported Anglp2as a putative tumor suppressor in ovarian cancer[29].

CONCLUSION

In summary, this study demonstrated that Dynamin2 and Anglp2 participated in PTC cell proliferation, metastasis, and invasion, which suggested the possibility of these markers to be new therapeutic target for treatment of PTC patients.

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