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Immunohistochemical Expression of Annexin A2 in Endometrial Carcinoma

Marwa M. Dawoud, Moshira M. Abd El-Wahed,
Ilaf M.A. Gaber, Marwa M. Serag El-Dien
Pathology Department, Faculty of Medicine, Menofia University, Egypt
Corresponding Author: Ilaf Mohamed Abdelhafiz Gaber,Telephone: +201061873456, E-mail: Eilaf.m.Jaber@icloud.com

ABSTRACT

Background: Endometrial carcinoma (EC) is second common gynecological cancer worldwide. It represents 2.83% of female genital malignancy and 72.37% of uterine corpus malignancy according to Egyptian National Cancer Institute (NCI). Distinction between endometrial atypical hyperplasia (EAH) and EC has been controversial, with clinical impact.

Objective: Investigate immunohistochemical expression of Annexin A2 (ANXA2) in EC versus endometrial proliferative lesions and correlation with available clinicopathological parameters.

Materials and Methods: This retrospective study included formalin-fixed, paraffin-embedded blocks of 66 specimens of endometrial tissue divided into four groups: EC, EAH, endometrial hyperplasia (EH) without atypia and proliferative endometrium. Immunohistochemical staining by ANXA2 antibody was done. Evaluation by semi-quantitative scores followed by correlation of results with clinicopathological data was applied.

Results: Annexin A2 was positive in all cases without significant variations between groups. Analysis using ROC curve revealed that immunohistochemical expression of ANXA2 has weak power in differentiating type I- EC from EAH. Correlation between ANXA2 expression and clinicopathological parameters in type I- EC showed a significant negative association between ANXA2 immuno-reactivity score (IRS) and maximum tumor dimension (P=0.03). On other hand, in type II- EC, there was a significant positive linear correlation between ANXA2 H-score and both maximum tumor dimension (P= 0.02) and apoptotic count (P=0.008).

Conclusion: Annexin A2 is essential for development of endometrial tissue beside carrying good features in type I- EC by its association with small tumor size. In type II- EC, ANXA2 has two opposing effects; increased tumor maximum dimension and apoptosis. Net result is in favor of increase tumor burden.

Keywords: Annexin A2, Endometrial carcinoma, endometrial hyperplasia, Immunohistochemistry.

INTRODUCTION

Endometrial carcinoma (EC) is the second most common gynecological cancer worldwide[(1)], the fourth common cancer among women in United States and the sixth leading cause of mortality according to American Cancer Society surveillance [(2)]. In Egypt, cancers of uterine corpus represent 1.3% of all new cancer cases. World age-standardized incidence and death rates are 8.7 and 1.8 per 100.000 person-years, respectively [(3)].

Endometrial carcinoma represents 22.83% of female genital system malignancy and 72.37% of primary uterine corpus malignancy according to Egyptian National Cancer Institute (NCI) [(4)].

Endometrial epithelial tumors and precursor lesions were classified into endometrial hyperplasia (EH) without atypia, endometrial atypical hyperplasia (EAH) and EC [(1)]. Since 1980 till now; Bokhman's 2-tiered classification model of EC is used by both pathologists and clinicians. It divides EC into type I which accounts for 85% of cases and type II. This classification is according to clinical, demographic, and endocrine characteristics [(5–7)].

We noticed that distinction between EAH and grade I- endometrioid endometrial carcinoma (EEC) has been always a matter of controversy. Thus, search for new biological markers aiding in this differential diagnosis was warranted. Annexin A2 also known as P36, is a 36 kDa protein, located on chromosome 15q22.2 [(8)]. Annexin A2 presents in endothelial cells, monocytes, macrophages and most cancer cells [(9,10)]. It has a great role in variable types of malignancies such as breast cancer, pancreatic ductal adenocarcinoma, renal cell carcinoma, hepatocellular carcinoma, colorectal carcinoma, acute promyelocytic leukemia, prostate cancer, and head and neck cancer. Annexin A2 is considered as potential diagnostic/prognostic marker for prediction of tumor malignancy, metastatic recurrence, tumor invasion, and patient survival [(10)]. Many studies reported significant changes in the level of ANXA2 expression in different body tumors. Only very few studies addressed ANXA2 immunohistochemical expression in EC suggesting its diagnostic and prognostic values [(11)].

The purpose of our study is to evaluate immunohistochemical expression of ANXA2 in EC versus other endometrial proliferative lesions and its correlation with the available clinicopathological parameters in carcinoma cases.

MATERIALS AND METHODS

This retrospective study involved formalin-fixed, paraffin-embedded blocks of 66 tissue specimens. These randomly selected cases included proliferative endometrium, EH without atypia, EAH, type I, and II- EC. Data of involved cases were taken

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from Pathology Department database, Tanta Cancer Center, Egypt in the period from 2015 to 2019. Hematoxylin-Eosin stained sections were examined for confirmation of diagnosis and re-evaluation of histological type, grade, T and N stage of EC. Histologic type of tumors were classified according to WHO classification 2020 [(1)] and as type I and II according to Bokhman's 2-tiered classification model [(5–7)].

According to International Federation of Gynecology and Obstetrics (FIGO) grading system, histologic grade of EC was either GI, GII or GIII based on solid areas percentage. Tumors of GI and II were considered "low grade" and GIII tumors were considered "high grade" [(12)]. Staging of the tumors was done according to the joint 2010 of FIGO classification system [(13,14)].

Immunohistochemistry:

Immunohistochemical stain was done using a standard streptavidin–peroxidase method. Annexin A2 primary antibody was used. It is a mouse monoclonal antibody. Concentrated 1.0 ml was diluted at 1:500 (sc-28385, SANTA CRUZ BIOTECHNOLOGY, USA. Antigen retrieval was carried out using citrate buffer, pH 6.0. Each run included a positive and negative control slides. Positive control of ANXA2 was human liver tissue.

Immunostaining Interpretation:

A code number was assigned to each of the 66 histological samples, and ANXA2 staining was assessed blindly as the pathologist didn't know any pathological data about the slide being investigated. Each sample was microscopically scanned; initially with a low-power magnification, then with a high-power magnification. Each case was assessed for ANXA2 immuno-expression in the whole tumor tissues.

ANXA2 expression was evaluated by the following methods:

1) **ANXA2 staining status:** we considered tumors positive if any percentage of malignant cells showed membranous and/or cytoplasmic brown staining [(15)].
2) **Percentage of positivity:** positive malignant cells percentage was evaluated as a continuous value (Mean, Median, (SD) Standard Deviation, and Range).
3) **Scoring methods depending on both ANXA2 stain intensity and percentage of positivity:**

a) **H-score system:**

Histological scores ranged from zero (no immunoreaction) to 300 (maximum immunoreaction) by applying the formula: Histoscore = 1 X (% of malignant cells showing weak staining) + 2 X (% of malignant cells showing moderate staining) + 3 X (% of malignant cells showing strong staining) [(16)].

b) **ANXA2 immunoreactivity score (IRS):**

Intensity of ANXA2 staining was scored as zero (no staining), 1 (weak), 2 (moderate), and 3 (strong). Percentage scores were assigned as 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%). Each tumor sample scores were multiplied to give a final IRS of (0–12), then we categorized tumors finally as negative (−); score 0, low expression (+); score ≤ 4, moderate expression (++); score 5–8 and high expression (+++); score ≥ 9. The cutoff value which was optimum identified: IRS ≤ 4 "low expression", and IRS ≥ 5 "high expression" [(15)].

4) **Stromal ANXA2 expression:**

Annexin A2 expression in stromal fibroblasts was assessed. Stromal ANXA2 expression was considered positive if any percentage of stromal fibroblasts showed cytoplasmic and/or membranous brown staining [(17)].

Ethical approval:

An informed consent routinely was taken from patients for proposed research and publications. Additionally, **it was approved from Ethical Committee of Faculty of Medicine, Menofia University assuring confidentiality of patients' data.**

Statistical methods

Using IBM SPSS software package version 21, all studied data were analyzed. The descriptive statistics used here were mean, SD, median, and range. Analytic statistics includes Kruskal Wallis and F-test (ANOVA), were used to compare between more than two groups containing quantitative variables. Mann Whitney was used to compare between two groups containing quantitative variables. Monte Carlo Exact test was used for comparison between qualitative data. ROC curve used to evaluate diagnostic validity of ANXA2 percentage of positivity, H score, and IRS. Spearman correlation, used for non-parametric quantitative variables to compare more than two studied groups. P-value of < 0.05 was considered statistically significant.

RESULTS

This study included 66 cases. Most of cases were received as total abdominal hysterectomy (TAH) (50/66, 75.7%) specimens, while D and C specimens constituted 21.3% (14/66) and subtotal hysterectomy constituted 3% (2/66) of studied cases. Type I (EEC and mucinous adenocarcinoma) constituted about three fourths and type II (clear, serous, and mixed adenocarcinoma) represented 25.6% of EC cases. Low grade (GI and GII) carcinoma cases represented 69.2% of EC cases. T stage was available for EC cases excised as TAH specimens (31/39).

Eighty percent of them were stage T1a and T1b at time of diagnosis. N stage was available for 7 carcinoma cases, only one of them was positive (stage N1a). The clinicopathological data of the cases are shown in table 1.

Table (1): Clinicopathological data of studied cases (n=66)

		Proliferative endometrium (n=7)	EH without atypia (n=9)	EAH (n=11)	EC (n=39)	
Type of specimen	TAH (n=50)	3 (42.9%)	7 (77.8%)	9 (81.8%)	31 (79.5%)	
	D and C (n=14)	2 (28.6%)	2 (22.2%)	2 (18.2%)	8 (20.5%)	
	Subtotal hysterectomy (n=2)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Age	Mean ± SD.	40.6 ± 11.18	54.4 ± 8.17	55.7 ± 10.37	59.5 ± 9.72	
	Min. – Max.	26 – 55	42 - 65	34 - 70	36 – 82	
	Median	42	55	56	58	
Age groups	< 60 (n=42)	7 (100.0%)	6 (66.7%)	8 (72.7%)	21 (53.8%)	
	≥ 60 (n=24)	0 (0.0%)	3 (33.3%)	3 (27.3%)	18 (46.2%)	
Menopausal status	Premenopausal (n=22)	6 (85.7%)	4 (44.4%)	4 (36.4%)	8 (20.5%)	
	Postmenopausal (n=44)	1 (14.3%)	5 (55.6%)	7 (63.6%)	31 (79.5%)	
Maximum dimension of the tumor (cm)	Mean ± SD.				5.6 ± 3.26	
	Min. – Max.				1 – 14	
	Median				5	
Histological types	EEC				26	66.70%
	Clear cell carcinoma				6	15.40%
	Mucinous adenocarcinoma				3	7.70%
	Serous adenocarcinoma				2	5.10%
	Mixed cell adenocarcinoma				2	5.10%
Behavior	Type I				29	74.40%
	Type II				10	25.60%
Grade	GI				14	35.90%
	GII				13	33.30%
	GIII				12	30.80%
Grade	Low				27	69.20%
	High				12	30.80%
T stage (n=31)	T1a				14	45.20%
	T1b				11	35.50%
	T2				1	3.20%
	T3a				2	6.40%
	T3b				3	9.70%
T stage groups (n=31)	T1a				14	45.20%
	T1b				11	35.50%
	T2, T3a, and T3b				6	19.30%
N stage (n=7)	NX				24	77.40%
	N0				6	19.40%
	NIA				1	3.20%
	Necrosis					
	+ ve				12	30.80%
	- ve				27	69.20%
Mitotic count /10HPF	Mean ± SD.				2.5 ± 2.27	
	Min. – Max.				0 – 8	
	Median				2	
Apoptotic count /10HPF	Mean ± SD.				3.9 ± 4.98	
	Min. – Max.				0 – 20	
	Median				2	
Lympho-vascular invasion (n=31)	Positive				14	45.20%
	Negative				17	54.80%
Adjacent tissue (n=19)	Atrophy				1	5.30%
	Endometritis				9	47.40%
	EAH				8	42.40%
	EH				1	5.30%

EH=Endometrial Hyperplasia **EAH**= Endometrial Atypical Hyperplasia **EC**= Endometrial Carcinoma
D and C=Dilatation and Curettage **TAH**=Total Abdominal Hysterectomy **Min**=Minimum
SD=Standard Deviation, **Max**=Maximum ,**EEC**= Endometrioid Endometrial Carcinoma, **HPF**=High Power Field

Expression of ANXA2 in all cases (n=66):

All studied cases were positive for ANXA2. No significant difference was observed statistically between groups of studied cases regarding percentage of positivity, H score or IRS (Table 2).

Table (2): Comparison between studied groups regarding Annexin expression

	Proliferative endometrium (n=7)	EH (n=9)	EAH (n=11)	EC		Test of significance	P
				Type I (n=29)	Type II (n=10)		
Percentage of positivity							
Mean ± SD.	70.0 ± 32.15	68.9 ± 34.26	74.6 ± 26.12	72.6 ± 25.41	74.0 ± 19.41	**K=** 0.236	= 0.994
Min. – Max.	30 – 100	15 - 100	20 – 100	20 - 100	50 – 95		
Median	90	90	75	80	82.5		
H. Score							
Mean ± SD.	171.4 ± 118.73	159.4 ± 97.61	139.1 ± 81.91	155.2 ± 67.47	151.5 ± 65.45	**k=** 0.191	P= 0.942
Min. – Max.	45 – 285	25 - 280	45 – 295	20 - 250	70 – 260		
Median	220	205	110	165	132.5		
Annexin IRS							
Mean ± SD.	7.1 ± 5.01	7.0 ± 4.53	6.0 ± 3.66	7.3 ± 3.65	7.6 ± 3.53	**K=** 1.354	P= .852
Min. – Max.	2 – 12	1 - 12	2 – 12	1 - 12	3 – 12		
Median	8	8	6	8	7		
Annexin IRS groups							
Low	3 (42.9%)	3 (33.3%)	5 (45.5%)	9 (31.0%)	3 (30.0%)	**MC=** 1.041	P= .907
High	4 (57.1%)	6 (66.7%)	6 (54.5%)	20 (69.0%)	7 (70.0%)		
Stromal Annexin expression						**MC=** 6.238	P= .192
+ ve	3 (42.9%)	8 (88.9%)	4 (36.4%)	16 (55.2%)	6 (60.0%)		
- ve	4 (57.1%)	1 (11.1%)	7 (63.6%)	13 (44.8%)	4 (40.0%)		

%= Percentage by columns **EH=**Endometrial Hyperplasia without atypia
EAH= Endometrial Atypical Hyperplasia **EC**=Endometrial Carcinoma
P= P-value **SD**=Standard Deviation, **Min**=Minimum, **Max**=Maximum
IRS=Immuno-Reactivity Score **K**= Kruskal Wallis test **MC**= Monte Carlo Exact test

Diagnostic validity of ANXA2 expression:

Using ROC curve for testing the diagnostic validity of ANXA2 expression in the differentiation between EAH and type I- EC revealed its insignificance. Regarding percentage of positivity, H score, and IRS, P. value = 0.8, 0.5, and 0.3, respectively.

Relation between ANXA2 expression and available clinicopathological variables:

In type I- EC cases, high ANXA2 IRS was significantly associated with smaller tumor maximum dimension (median=4 cm), compared to low ANXA2 IRS (median=8.5 cm) (P=0.03) (Figure 1).

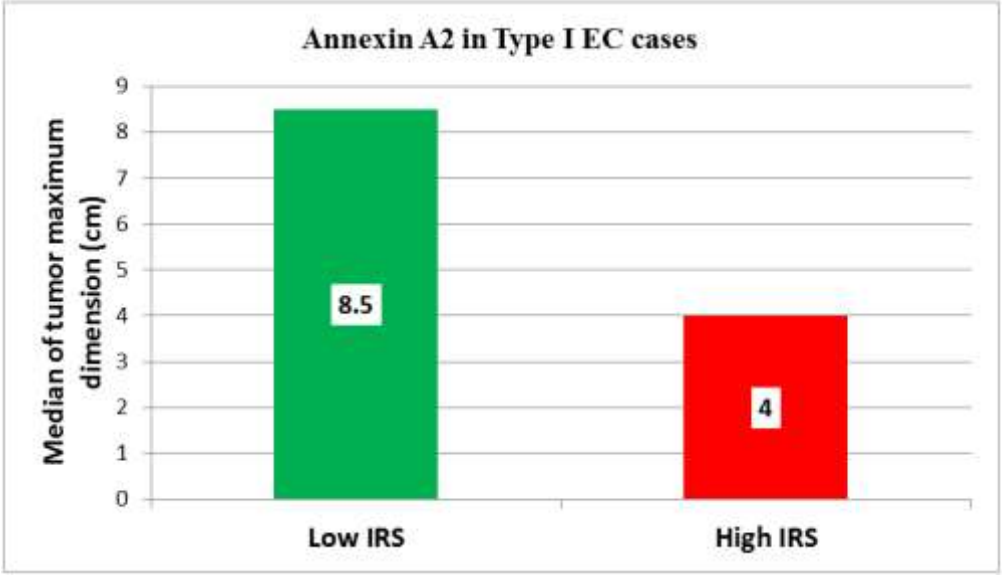

Figure (1): In type I EC: the higher ANXA2 IRS, the smaller the tumor maximum dimension (P=0.03)

Whereas, ANXA2 H-score in type II- EC showed significant positive linear correlation with tumor maximum dimension (Figure 2) and with apoptotic count (Figure 3 and Plate 1).

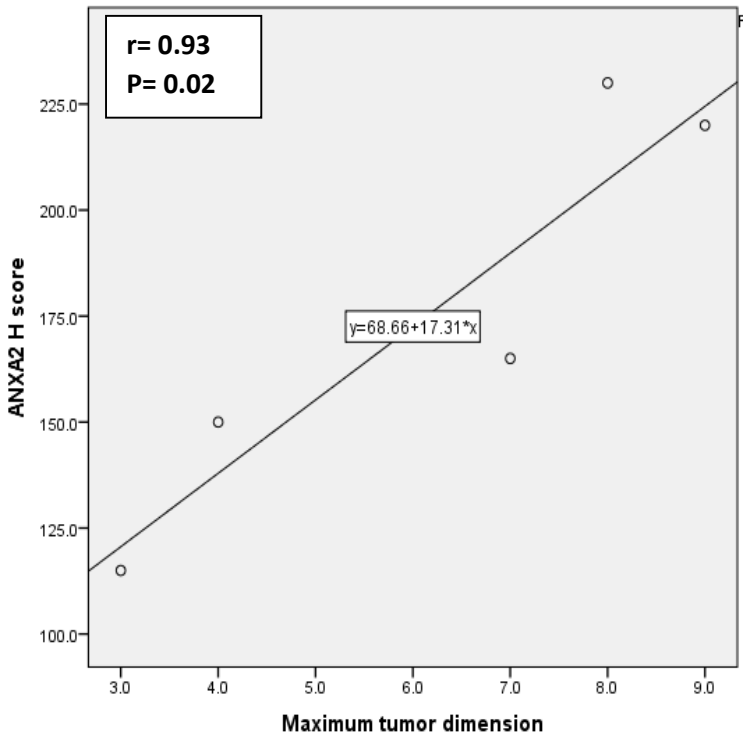

Figure (2): Positive linear correlation between ANXA2 H score in type II EC and maximum tumor dimension

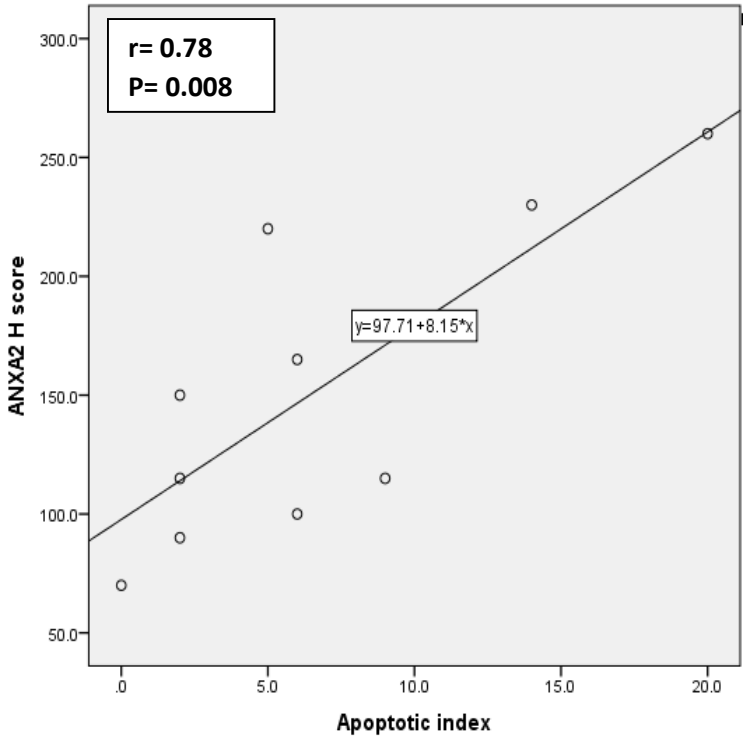

Figure (3): Positive linear correlation between ANXA2 H score in type II EC and apoptotic count

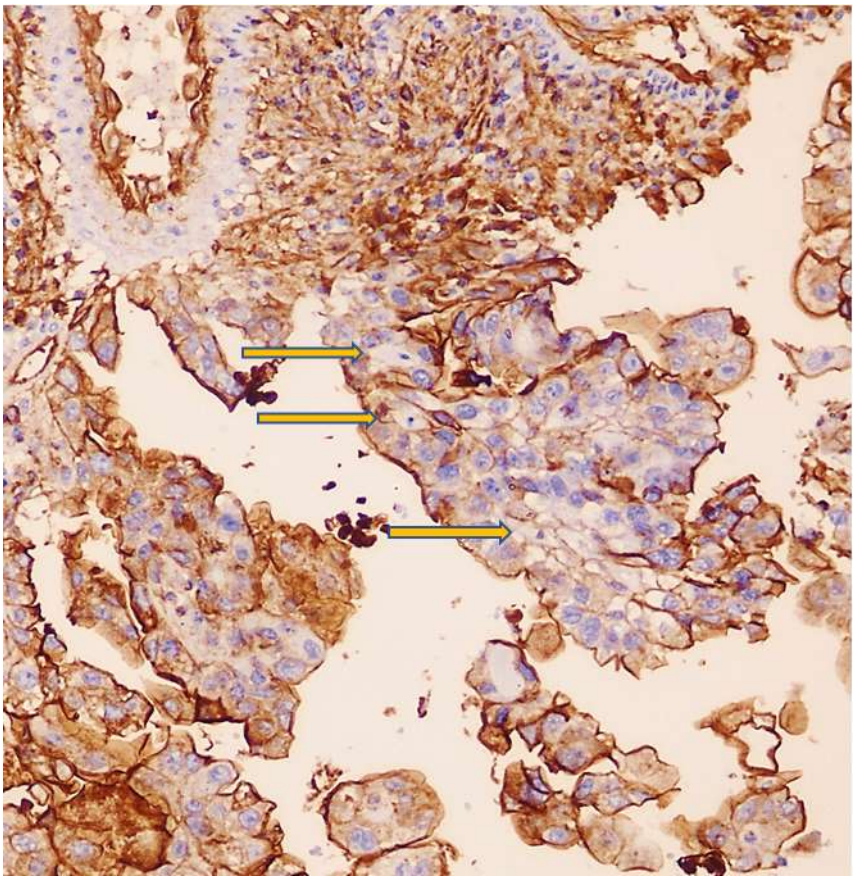

Plate (1): Clear cell adenocarcinoma showing high expression of ANXA2 (IRS=12) and apoptotic bodies (yellow arrows) (IHC X 200)

DISCUSSION

This study showed positive ANXA2 expression in all studied cases. Furthermore, ANXA2 median percentage of positivity, H-score, and IRS were nearly the same in both malignant and non-malignant groups with no statistically significant difference. Annexin A2 percentage of positivity, H score, and IRS were unable to differentiate between EAH and type I-EC. These results contrast those observed by **Deng *et al.*** [11] who reported that ANXA2 positivity increased significantly from normal endometrium to atypical hyperplasia with the highest level appears in EC cases. The possible rationale for this controversy is the difference in number of studied cases, type of used primary antibody, and it`s used concentration.

Annexin A2 expression in all groups of our study might be due to that ANXA2 was identified as mostly significant altered estrogen-responsive proteins. Moreover, functional analysis demonstrated that estrogen could remarkably up-regulate ANXA2 in endometrial cells [18]. Strong ANXA2 expression in endometrial glands and luminal epithelium suggesting that the endometrial epithelium is where ANXA2 performs its main function [19].

Regarding correlation between ANXA2 expression and clinicopathological parameters in the current study, higher ANXA2 IRS in type I- EC, was associated with smaller tumor maximum dimension (P=0.03). This is against result noted in colorectal carcinoma (CRC) [20]. These controversial findings may be due to studying variable types of malignancy with variable grade and stage. Most of our type I- EC cases (88.9%) were of low grade and stage (50% T1a), while in **Emoto *et al.*** [20] study, 55% of CRC cases were of stage II or above and 45% were of high grade. Additionally it was spotted in the results of this study that, ANXA2 score was a little bit higher in proliferative endometrium than EAH and type I- EC groups.

In contrast, in type II- EC cases, ANXA2 H-score showed strong positive linear correlation with maximum tumor dimension (P=0.02). This is agreed with previous studies applied in gastric and laryngeal carcinoma [21,22]. No such results were observed in previous studies concerned with ANXA2 expression in EC.

The relation between apoptotic count and ANXA2 expression in EC hasn't been investigated in previous studies but in this study we found that ANXA2 H-score in type II- EC showed positive linear correlated with apoptotic count (P=0.008). This finding is agreed with previous studies which reported that ANXA2 promotes apoptosis, and Annexin A2 receptor activates apoptosis and autophagy [23,24]. On the other hand, previous studies found that knockdown of ANXA2 significantly increase cell apoptosis [15] and

overexpression of ANXA2 increases the anti-apoptotic protein IL-6 secretion [25]. This could be explained by presence of many apoptosis pathways, which are regulated by several pro- and ant apoptotic proteins, inter-observer variations in counting apoptosis and difference in malignant tissue.

It is puzzling to some extent that our results revealed significant association between ANXA2 expression and both large tumor size and increase apoptotic count in type II- EC. It is expected that, increase apoptotic count is associated with small tumor size, which is against our results. This could be explained by that tumor size (including its greatest dimension) is the final result of multi-factorial equation formed of some factors. Apoptotic count is one but not the only one of them. The equation also includes mitotic rate, blood supply, availability of growth factors, toxic metabolites accumulation, intercellular inhibitory communication, cell senescence, immune system, and genome instability/mutation. Several factors affect tumor growth, sustainment of proliferative signals, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, activation of invasion and metastasis, energy metabolism, evasion of immune destruction, genome instability and mutation, and tumor-promoting inflammation [26,27].

In the current study, we noticed that most of EC cases showed high IRS (69.2%). Non-malignant cases did not show any preference. However, these differences between expression rates were not significant. No such results have been reported previously between EC and non-malignant endometrial lesions regarding ANXA2 expression. On the other hand, in ovary, malignant ovarian tumors displayed the highest positive ANXA2 expression and significantly higher than borderline and benign cases [28].

This study couldn't differentiate between type I (29/39) and type II- EC (10/39) either by percentage of ANXA2 positivity, H score or IRS and this is agreed with **Deng *et al.*** [11] who found no significant difference in ANXA2 expression was detected among different pathological tumor types and also agreed with **Zhuang *et al.*** [28] who reported that the positive expression rates of ANXA2 in ovarian cystadenocarcinoma types showed noticeable difference but with no statistical significance.

In the current study, there was no significant association between the stage of EC cases and neither ANXA2 percentage of positivity, H score nor IRS. This is in agreement with two previous studies in both endometrial and ovarian carcinoma [11,28]. **Deng *et al*.** [11] evaluated ANXA2 expression by two methods, negative/positive (if any percentage of cells showed expression, as in our study) and low/high (depending on cut off value). While positivity didn't show significant association with stage, high ANXA2 showed this relation. This controversy may denotes that, the difference in results between previous studies and ours, may be due to difference in immunostaining interpretation method.

CONCLUSION

ANXA2 may be essential for development of endometrial tissue, so it exists near equally in normal, benign and malignant endometrial lesions. Immunohistochemical staining of ANXA2 is a poor diagnostic test in differentiating EAH from type I- EC. ANXA2 may carry good features in type I- EC in the form of its association with small tumor size. In type II- EC, ANXA2 has two opposing effects, enlarges tumor size and promotes apoptosis. The end result of both of them is in favor of the bad feature which is increase tumor burden.

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