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ORIGINAL ARTICLE

Value of Insulin-like Growth Factor II m-RNA-Binding Protein 3 (IMP3) Expression in Serous Ovarian Tumors: An immunohistochemical study

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ABSTRACT

Background: Ovarian cancer especially the epithelial type, is a major cause of female morbidity and mortality worldwide, so there is a great need for better diagnostic tools that can improve the histological diagnosis and predict the outcome by using immunohistochemical procedures.

Aim of the work: To evaluate the immunohistochemical expression of Insulin-like Growth Factor II m-RNA-binding Protein 3 (IMP3) in benign, borderline and malignant serous ovarian tumors and correlate this expression with some clinicopathological parameters.

Methods: This cross- sectional study was conducted retrospectively on 63 formalin fixed, paraffin embedded tissue blocks of serous ovarian tumors from pathology department, Zagazig University from 2016 to 2019. Immunohistochemical staining using anti- IMP3 antibodies was done using streptavidin-biotin immunoperoxidase technique. The relationship between the staining intensity and percentage of positively stained cells and clinicopathological factors were statistically analyzed.

Results: IMP3 expression was detected in all borderline and 91.4% of malignant cases, 12.5% of benign cases. IMP3 intensity and percentage of positive stained cells were correlated with higher tumor grades and stages (P <0.001). A significant correlation was found between IMP3 expression and patient's age (P <0.001).

Conclusions: IMP3 expression was increased from benign to borderline to malignant ovarian serous tumors, so it may have a role in carcinogenesis of ovarian serous tumors. IMP3 strong expression was expressed in higher stages and high grade serous carcinomas, so it can be used as bad predictive marker.

Keywords: IMP3; SBTs; ovarian serous carcinomas; immunohistochemistry

INTRODUCTION

Epithelial ovarian cancer is the second most common malignancy in female genital system. In Egypt, ovarian cancer is the fourth most common female cancer according to the National Population-Based Cancer Registry Program in Egypt (2008–2011) **[1]**.

The strongest risk factor for ovarian cancer is family history of ovarian or breast cancer. As women with history of having a first-degree relative with ovarian and breast cancers have 50% and 10% higher risk for ovarian cancer respectively**.** About 18% of epithelial ovarian cancers especially high-grade serous carcinomas, are caused by inherited mutations in the breast cancer genes 1 &2 (BRCA1 or BRCA2) **[2, 3]**. The incidence of ovarian cancer increases with age **[4].**

The WHO classified epithelial ovarian tumors into (serous, mucinous, endometrioid and others). The serous tumors are further subdivided into [benign, borderline and malignant]. Malignant serous tumors are either low-grade serous carcinoma (LGSC) or high-grade serous carcinoma (HGSC) **[5]**.

Insulin-like growth factor-II messenger RNA-binding protein family [IMPs] includes IMP1 and IMP2 and IMP3 **[6].**

IMP3 stabilizes mRNAs of many oncogenes such as (IGF2, MYC) enhancing their expression**.** It also has a role in regulating the expression of cell adhesion molecules e.g. CD 24, CD 44 and recently, it has been assumed that IMP3 can bind to mRNAs of many cyclins **[7]**.

Fetal ovarian follicles express strong IMP3 and weak IMP1 staining. Also, IMP3 may have a role in tubal or ovarian serous carcinogenesis **[8].**

There are contradictory results about the role of IMP3 in the prognosis of ovarian cancer**, Kobel et al [9]** proposed that IMP3 expression is a marker of bad prognosis in ovarian clear cell malignancies, however **Noske et al [10]** assumed that strong IMP3 expression was associated with better prognosis.

METHODS

Study design: This study was conducted retrospectively on 63 formalin fixed, paraffin embedded tissue blocks of serous ovarian tumors which were selected from archives of pathology department, Faculty of medicine, Zagazig University in the period from 2016 to 2019.

These cases were diagnosed histopathologically as: 16 cases of benign serous tumors, 13 cases of serous borderline tumors (SBTs) (2 micropapillary variant, 2 cases with microinvasion) and 34 cases of malignant serous tumors. Clinical data such as age, tumor size, surgical stage, uni and bilaterality were obtained from the patients files. Malignant tumors (34) were obtained by total abdominal hysterectomy with bilateral salpingoophorectomy with or without omentectomy and lymph node dissection, while unilateral ovarian oophrectomy or adenexectomy were done for benign and borderline cases. Other types of epithelial ovarian tumors and cases with insufficient tissue clinical data were excluded.

Four µm thick sections were cut from each paraffin block then stained with hematoxylin & eosin for histopathological examination.

The diagnosis and classification was performed according to the current World Health Organization (WHO) criteria **[11].** Malignant tumors were graded according to two tier grading system that is based on assessment of nuclear atypia and number of mitoses per 10 high power fields (HPFs) **[12]** and surgical staging was determined based on the criteria recommended by the International Federation of Gynecology and Obstetrics (FIGO**) [13].**

Immunohistochemistry:

Immunohistochemical reactions were performed using streptavidin- biotin immunoperoxidase system. **[14].** Paraffin sections 3-5 um from the paraffin sections were deparaffinized by incubating them in the oven at 56 ˚C for 15 minutes, and insertion in xylene for 30 minutes then the slides were rehydrated in descending grades of alcohol 95%, 85%, and then 75% for 5 minutes each and rinsed with distilled water for 5 minutes. Antigen retrieval was performed by boiling in sodium citrate buffer (0.01M, pH 6) for 15 minutes in microwave then incubated with hydrogen peroxide for 10 minutes to block endogenous peroxidase and then rinse with distilled water. Then the slides were incubated with the primary antibodies [mouse monoclonal antibodies against IMP3 overnight at 4˚C (E-2 (SC-365640), at dilution of (1:50), SANTA CRUZ, biotechnology, incS. The slides are rinsed with phosphate buffer saline (PBS) and then incubated with biotinylated secondary antibodies at for 30-60 min. This is followed by incubation with streptavidin-biotin-peroxidase complex. After 3 rinses with PBS, The slides were incubated with diaminobenzidine for 15 min. The slides were rinsed with H2O and counterstained with hematoxylin for 3 minutes. This was followed by washing in cold running water, then wash in distilled water. Sections were dehydrated in ascending grades of alcohol and cleared with xylene, then cover slipped and examined. Representive sections of tonsils served as positive controls for IMP3 antibody, and negative controls were performed by removing the primary antibody. Both Positive and negative controls reacted appropriately.

Immunohistochemical evaluation of MP3:

The IMP3 was scored semiquantitavely based on both staining intensity and percentage of positive cells (PP). IMP3 positivity was defined as dark brown cytoplasmic staining. Negative staining was defined as absent staining or staining of <5% of tumor cells. The staining intensity was recorded as: Negative, weak, moderate, and strong.

PP was defined as: (0), <25%; (1), 26-50%; (2), 51-75%; or (3), > 75% positive stained cells with IMP3. The intensity and the percentage of positive cells were recorded separately.

Ethical considerations:

This work has been carried out following the code of Ethics of The World Medical Association (Helsinki Declaration of 1975, as revised in (2000) for human studies. Institutional Review Board (IRB), Faculty of Medicine, Zagazig University has given approval.

Written informed consent was obtained from each participant.

St**atistical analysis**

Data collected throughout patient's files and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data, qualitative data was represented in number and percentage, quantitative data was represented by mean ± SD, the following tests were used to test differences for significance; Difference and association of qualitative variable by Chi square test X^2. Differences between quantitative independent groups by t test or Mann Whitney, paired by sign test. Chi-Square test X^2 was used to test the association

variables for categorical data. R→ spearman correlation: it evaluates the linear association between 2 quantitative variables (one is the independent var. X, and the other is the dependent var., Y). Value of "r" ranges from -1 to 1.

RESULTS

Histopathological results:

Out of 34 malignant serous tumors, 14 cases were stage I, 14 cases were stage III and 6 cases were stage IV. About 60 % of malignant cases aged between 50 to 49 years with median age of 52 years, while (84.6%) of borderline cases and f 62.5 % of benign cases ranged from (19-39) years with median age of 21 years with a high statistically significant difference between the age groups and serous categories as shown in **table [1].**

There was a high statistically significant difference between benign, borderline and malignant tumor according to bilaterality, consistency, tumor size, Papillae on inner& outer surface and Omental metastasis**.** (P < 0.001) **Table [2].**

Immunohistochemical results:

All ovarian serous tumors were examined for IMP3 by immunohistochemical analysis. The majority of serous carcinomas (94.1%) showed positive IMP3 expression, all borderline cases were positive for IMP3 in contrast to the majority of benign cases (87.5%) that were negative for IMP3.

A significant correlation was found between IMP3 expression and patient's age (P-value <0.001) as shown in **table [3].**

There was a high significant association between IMP3 expression and tumor stage (P < 0.001). Out of 14 stage III cases, 13 cases showed strong IMP3 staining. 5/6 of stage (IV) showed strong intensity. The P.P score was (3) in 100% of cases of Stages III & IV. In contrast to stage (I), 2 out of 14 cases were strongly positive and their P.P score were (0-2).**Table [4].**

There was a significant association between IMP3 intensity and P.P among the subtypes of serous tumors as (53%), (12.7%) and (23.5%) of serous carcinoma showed strong moderate and weak staining respectively and only 2 cases were negative. P.P >75% (score 3) in 59% of cases.

In contrast to the borderline cases, although 100% of cases were positive for IMP3 they showed variable staining intensity as (77%) of cases showed weak IMP3 immunostaining, (15.3%) showed moderate staining. The P.P score ranged from (1-2). Regarding cases with microinvasion, the microinvasive foci revealed moderate to strong IMP3 expression, their P.P ranged from (1-2). Regarding benign cases, (87.5%) of cases were completely negative for IMP3, the remaining cases revealed weak IMP3 immunostaining. **Table [5].**

The IMP3 expression showed a high significant correlation with the histological grade. Most LGSC cases (80%) showed weak to moderate staining, their P.P (1-2), in contrast to HGSC, IMP3 intensity was strong in 75% of cases. The P.P score was 3 in 83.3% of cases**. Table [6].**

Table (1): Relation between histopathological type of tumor and age:

Variable	Benign (n=16)		Borderline (n=13)		Malignant (n=34)		X^2	U	P value
Years	**N**	**%**	**N**	**%**	**N**	**%**			
19-39	10	62.5	11	84.6	2	5.9	34.91	103.2	**<0.001 (HS)**
40-49	2	12.5	2	15.4	6	17.6			
50-59	4	25.0	0	0.0	19	55.9			
>60	0	0.0	0.0	0.0	7	20.6			
Median age	21 y		21y		52 y				

X^2= Chi square test. U= mean. P-value < 0.001; highly significant.

Table (2): Gross characteristics of the studied histopathological types:

Variable	Benign (n=16)		Borderline (n=13)		Malignant (n=34)		F	P value	X^2
	N	**%**	**N**	**%**	**N**	**%**			
Bilaterality	0	0%	0	0%	20	58.8		**<0.001 (HS)**	24.99
Consistency									
-Cystic	12	75%	4	30.7%	1	3%		**<0.001 (HS)**	29.94
-Solid	0	0	3	23.1%	13	38.2%			
-mixed	4	25%	6	46.2%	20	58.8%			
Tumor size(cm)									
Mean± SD Range	9.06± 8.7 2-30		14.23± 5.7 5-22		18.82± 5.7 8-26		18.2	**<0.001 (HS)**	

Variable	Benign (n=16)		Borderline (n=13)		Malignant (n=34)		F	P value	X^2
	N	**%**	**N**	**%**	**N**	**%**			
Papillae on inner & outer surface	2	12.5 %	13	100%	12	35.2%		**<0.001 (HS)**	24.1

P-value < 0.001; highly significant. HS= highly significant.

Table (3): Relation between IMP3 intensity and age

Variable	Negative (n=16)		Weak (n=20)		Moderate (n=8)		Strong (n=19)		X^2	P value
Years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
19-39 N= (23)	12	52.2%	9	39.2%	2	8.7%	0	0.0 %	**53.39**	**<0.001 (HS)**
40-49 N= (10)	0	0.0	4	40%	5	50%	1	10%		
50-59 N =(23)	4	17.4%	7	30.4%	0	0.0	12	52.1%		
>60 N= (7)	0	0.0	0	0.0	0	0.0	7	100%		

Table (4): Relation between IMP expression and malignant tumor stages

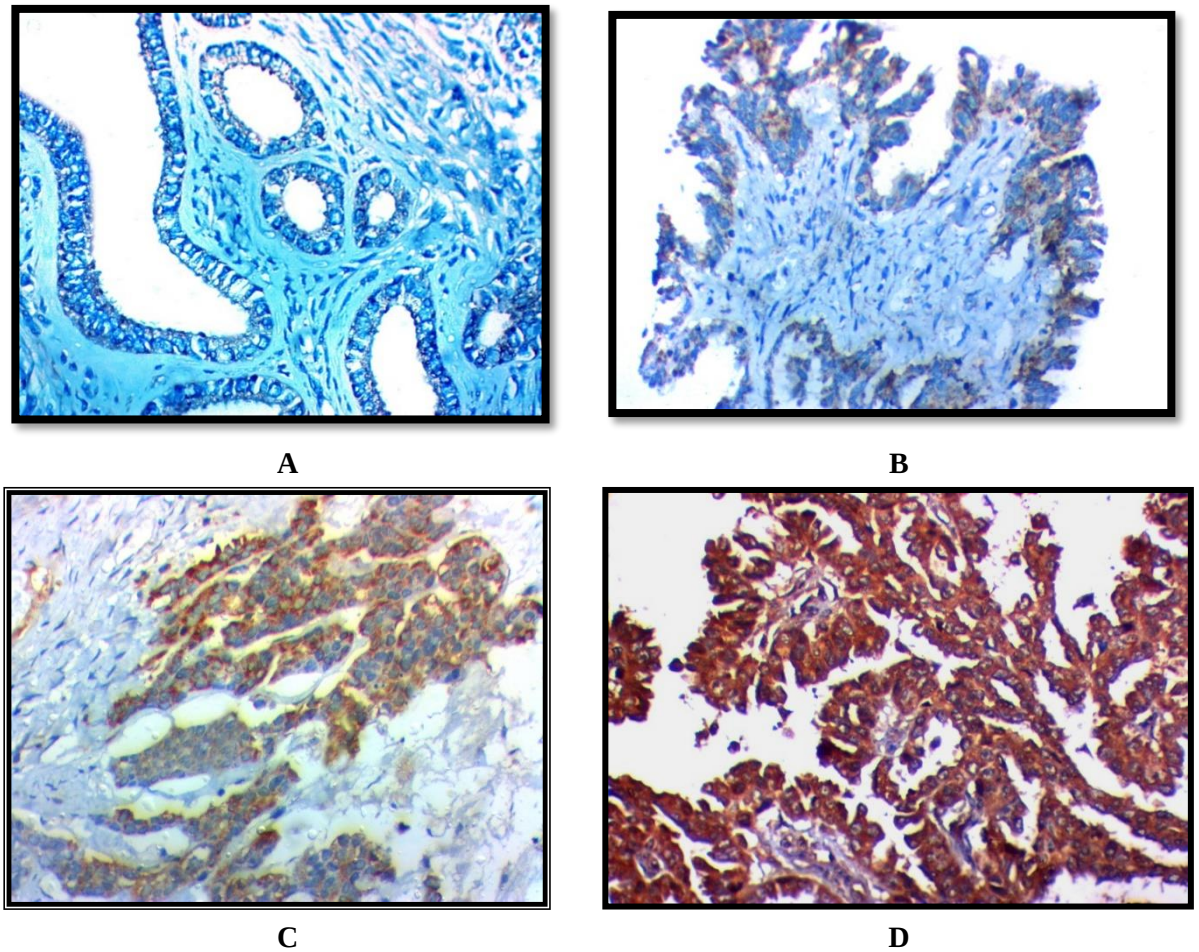
Variable	Negative		Weak		Moderate		Strong		X^2	P value
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Stage I(n=14)	2	14.3%	5	35.7%	5	35.7%	2	14.3%	20.2	<0.001 (HS)
Stage III (n=14)	0	0.0	0	0.0	1	7.2%	**13**	**92.8%**		
Stage IV(n=6)	0	0.0	1	16.6%	0	0.0	**5**	**83.4%**		
	Score (0) (<25%)		**Score (1) (26-50%)**		**Score (2) (51-75%)**		**Score (3) (>75%)**		**X^2**	**P value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Stage I (n=14)	2	14.2%	8	57.1%	4	28.6%	0	0.0	**24.86**	**<0.001 (HS)**
Stage III n=14)	0	0.0	0	0.0	0	0.0	14	100%		
Stage IV (n=6)	0	0.0	0	0.0	0	0.0	6	100%		

Table (5): Relation between IMP expression and different tumor subtypes:

Tumor entity	Negative		Weak		Moderate		Strong		X^2	P value
N= (63)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Benign (n=16)	14	87.5%	2	12.5%	0	.0%	0	0%	**69.3**	**<0.001 (HS)**
Borderline(n=13)	0	0%	10	77 %	2	15.3	1	7.7%		
Malignant(n=34)	2	5.9%	8	23.5%	6	17.6	18	53%		
	Score (0) (<25%)		**Score (1) (26-50%)**		**Score (2) (51-75%)**		**Score (3) (>75%)**		**X^2**	**P value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**78.84**	**<0.001 (HS)**
Benign (n=16)	15	93.7%	1	6.25%	0	0%	0	0%		
Borderline(n=13)	0	0%	9	69.2%	4	30.8 %	0	0%		
Malignant(n=34)	2	6%	8	23.5%	4	11.7 %	20	59%		

Table (6): Relation between IMP3 expression and tumor grades (for malignant cases):

Variable	Negative		Weak		Moderate		Strong		X^2	P-value
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Low grade (n=10)	2	20 %	6	60%	2	20%	0	0.0 %	20.35	<0.001 (HS)
High grade (n= 24)	0	0.0	2	8.3%	4	16.7%	18	75%		
	Score (0) (<25%)		**Score (1) (26-50%)**		**Score (2) (51-75%)**		**Score (3) (>75%)**		**X^2**	**P-value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Low grade (n=10)	2	14.2%	8	57.1%	4	28.6%	0	0.0		**<0.001 (HS)**
High grade (n= 24)	0	0.0	0	0.0	0	0.0	14	100%	**21.96**	



A **B**

C **D**

Fig. (1): Immunohistochemical expression of IMP3: A): serous cystadenoma showing negative IMP3 cytoplasmic staining & P.P score (0). (IHC X 400). **B):** Ovarian (SBT) (conventional type) showing weak IMP3 staining & P.P score (1). (IHC X200). **C):** low grade ovarian serous carcinoma showed moderate IMP3 staining intensity & (P.P score 2). (IHC X400). **D)**: A case of high grade papillary serous carcinoma showed **strong** IMP3 staining & (P.P score 3). (IHC X400).

DISCUSSION

Ovarian cancer is considered one of the most common cancers in the world and a major cause of female cancer related deaths. The epithelial subtype has been termed as the "silent killer", owing to its late presentation by non-gynecological and non-specific presentations **[15].**

IMP3 is a member of oncofetal RNA binding proteins concerned with RNA processing e.g. [localization, stabilization] that are expressed during embryonic life, playing an important role

in cell migration, metabolism and stem cells renewal. It is either absent or has a weak expression in adults being re-expressed in multiple tumors resuming its previous physiological function in neoplastic pattern **[16].** This study was concerned with the immunohistochemical expression of [IMP3] in serous epithelial ovarian tumors so as to clarify its role in diagnosis, pathogenesis and predictive implication in serous ovarian carcinomas specifically.

The current study showed that 60% of serous carcinoma cases were at stage III and IV at time of diagnosis. Similar results were reported by **Lindsey et al [17]** who had mentioned that 80% of serous carcinomas are diagnosed at stage III and IV reflecting the aggressive behavior of this cancer and also in accordance with the study of **Prat et al [13]** who reported that that most HGSCs tend to have late stages presentation.

In the current study, the positive IMP3 staining was detected in 91.4% of serous carcinomas, 100% of borderline tumors and 6.25% of benign cases. This finding demonstrated significant expression of IMP3 in serous carcinomas and borderline tumors compared with benign serous tumors. These results were in accordance with **Chiste´et al [18],** who positive IMP3 expression in (68%) serous ovarian carcinomas in contrast to <5% of the borderline tumors and showed agreement with little different ratio with **Noske et al [10]** who detected positive IMP3 staining in 47% of carcinomas in contrast to the epithelium of borderline tumors as well as benign tumors and normal ovaries that showed only weak or absent IMP3 expression. **Goodman et al [19]** demonstrated IMP3 expression in (64%) of serous carcinomas of the ovary, (12 %) of borderline serous tumors and (5%) of cystadenomas.

In the present study, there was a high significant correlation between IMP3 expression and tumor grade ($P < 0.001$) as strong expression and high IMP3 PP scores were detected in high grade cases. These results confirmed what the others have reported and showed for the first time the pattern of expression of IMP3 in LGSC as Imamura et al **[20]** who showed that IMP3 expression was frequently observed in HGSCs. but in contrast with Kobel et al **[21]** who had demonstrated the expression of IMP3 in only 50% of high-grade serous carcinomas.

As regards 13 cases of serous borderline tumors (SBTs), the strong intensity was detected in the conventional type but with microinvasive foci. Moreover, no significant correlation was found between IMP3 expression and subtypes of SBTs (micropapillary and microinvasion subtypes).

CONCLUSION

IMP3 immunohistochemical expression was increased from benign to borderline to malignant ovarian serous tumors, so it may has a role in carcinogenesis of ovarian serous neoplasia. IMP3 strong expression was correlated with higher stages and high grade serous carcinomas, so it can be used as bad predictive marker in malignant ovarian serous tumors.

Disclosure of potential conflicts of interest:

The authors report no conflicts of interest.

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