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Original article

Significance of (IMP3) In Dysplasia- Adenocarcinoma Sequence in Barrett's Esophagus (Immunohistochemical Study)

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Abstract:

Background: Barrett's esophagus (BE) is the replacement of the squamous epithelium of the distal esophagus by a metaplastic columnar epithelium. It has been considered the most important precursor lesion for esophageal adenocarcinoma (EAC) through a series of genetic and epigenetic mutations. The oncofetal protein IMP3 is a member of a family of RNA-binding proteins that promotes tumor cell proliferation, adhesion, and invasion. **Aim**: The aim of this study was to evaluate IMP3 expression in BE and its associated pathological changes through the malignant progression. **Materials and Methods**: This retrospective study was done upon 51 different esophageal lesions designated as; 20 cases of EAC and 31 cases of BE. IMP3 immunostaining was done and assessed for each case. **Results:** IMP3 positivity was seen in 3/11 cases (27.5%) of BE-ND, 6/10 cases (60%) of BE-LGD, 9/10 cases (90%) of BE-HGD, and in all (100%) of EAC cases. IMP3 IHC expression was positively correlated with the different grades of BE (BE-ND, BE-LGD, and BE-HGD) and EAC cases ($P<0.01$). A positive significant statistical correlation was found between IMP3 expression and the BE segment length ($P<0.05$), the grading of EAC ($P<0.01$), tumor necrosis ($P<0.05$), and tumor infiltrating neutrophils ($P<0.01$) and a negative statistically significant correlation with lymphoplasmacytic infiltration in EAC ($P<0.01$). **Conclusions:** IMP3 can be a promising marker for risk stratification of BE cases, and may be a predictor of the poor prognosis in EAC cases specially when combined with other histopathological findings.

Keyword: Barrett's Esophagus, Esophageal Adenocarcinoma, IMP3.

Abbreviations: Barrett's esophagus (BE), Negative for dysplasia (ND), Low grade dysplasia (LGD), High grade dysplasia (HGD), Esophageal adenocarcinoma (EAC).

Introduction:

Barrett's esophagus (BE) is a common pre-neoplastic condition which is capable of progression to esophageal adenocarcinoma. The most accepted definition for BE is an endoscopic visualization of a change in the lining of the distal esophagus and histologic confirmation with columnar metaplasia (1). BE results from chronic long-standing gastroesophageal reflux disease (GERD). Approximately, 10-15% of patients who undergo endoscopy for evaluation of GERD symptoms are found to have Barrett's epithelium (2).

Barrett's esophagus (BE) has been identified as the single most important precursor lesion and risk factor for adenocarcinoma in the distal esophagus; through a series of genetic and epigenetic alterations. It undergoes the sequential progression to low-grade dysplasia (LGD), and high-grade dysplasia (HGD), up to esophageal adenocarcinoma (EAC) (3). The incidence rate of progression of BE patients with no dysplasia to HGD or invasive cancer equals 0.5-0.6%.

In contrast, the ratio of progression is increased in BE patients with LGD, being 9.1–13.4% per year (4 & 5).

Esophageal adenocarcinoma constitutes about 30% to 40% of primary esophageal cancers worldwide. There is an increased incidence of EAC in the United states of America (USA) over the past four decades (6).

Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is a member of the IMP family, consisting of IMP1-3, that plays an important role in RNA trafficking, stabilization and translation during embryogenesis. Although it is absent in human adult tissues, IMP3 is detected in high levels in various types of cancers including lung cancer, germ cell cancer, pancreatic cancer and gastric cancer (7,8, 9 & 10). IMP3 promotes tumor cell proliferation, migration, invasion, and aggressiveness (11).

The aim of this study was to evaluate the IHC expression of IMP3 in BE and its associated pathological changes to clarify

the role of IMP3 in the sequencing of BE to EAC.

Material and Methods:

This study was conducted retrospectively on 51 selected esophageal biopsies designated as 20 cases of EAC and 31 cases of BE (11 cases BE-ND, 10 cases of BE-LGD and 10 cases of BE-HGD) Six cases of chronic non-specific esophagitis were used as a control group. Cases were obtained through collection of archived formalin fixed, paraffin embedded blocks from Department of Pathology, Faculty of Medicine, Benha University, during the period from January 2015 to December 2018. Cases were selected on basis of availability of demographic data and clinicopathological data approved by ethical committee.

Hematoxylin and eosin-stained slides on all cases were reviewed by two observers simultaneously to confirm the diagnosis and to classify the lesions into one of the study categories. At this review, blocks were selected for immunohistochemistry (IHC).

BE cases were graded according to the dysplasia present into negative for dysplasia , BE-LGD, and BE-HGD (12). EAC cases were classified and graded as stated in the 2019 WHO classification (13). The remarkable histopathological features was noted such as the degree of lymphoplasmacytic and neutrophilic infiltration in BE and EAC cases by the application of the Updated Sydney system (USCS) into: absent, mild, moderate and severe (14), the grade of tumor , necrosis; by subjective scoring of necrosis in H&E stained sections into (score 1: absent confluent necrosis), (score 2; mild confluent area of tumor necrosis)(score 3; extensive confluent areas of necrosis), and grouped into Low grade: (scores 0 and 1) or High grade: (scores 2 and 3),(15) and presence of tumor ulceration (16).

The patients' demographic and endoscopic data were obtained from their original files, including patient's age, sex, smoking status and BE segment length which is grouped into (short segment: <3 cm in length) or (long segment: > 3 cm in length) (17).

Immunohistochemical study: Three-micron tissue sections were obtained from formalin-fixed, paraffin-embedded tissue blocks on coated slides. After xylene deparaffinization, the sections were rehydrated in descending grades of alcohol then in distilled water. Antigen retrieval was performed by using 10 mmol/L citrate monohydrate buffer (PH 6.0) and heated for 15 minutes in the microwave. The sections were then incubated in a blocking medium

(3% H2O2) for 15 minutes followed by washing with distilled water. The slides then were immunostained for IMP3 Rabbit polyclonal antibody **(*0.1mg/ml concentration, Chongqing, 400039, China*)** at a dilution of 1:100, at room temperature overnight. Immunodetection was executed using a standard labeled streptavidin-biotin system (***DakoCytomation, Denmark, A/S).*** Immune staining was performed based on manufacturer's instructions. Immunoreaction was visualized by adding DAB as a chromagen. Counterstaining of slides was performed with the Mayer hematoxylin.

Negative & positive controls:

Aborted fetal liver (16 weeks) was used as a positive control for IMP3. For negative controls, Omitting the primary antibody and replacing it with solution of BSA in phosphate-buffered saline (PBS).

Immunostaining evaluation:

The slides were evaluated for the presence or absence of IHC staining in studied esophageal biopsies; IMP3 expression was detected as cytoplasmic or membranous brownish coloration. Immunoreactivity was assessed by evaluating extent and intensity of the stained cells. In examined tissues, cytoplasmic staining was evaluated by staining intensity (0, 1+, 2+, and 3+), and the fraction of positive cells was scored for each tissue spot. A final score was done from these two parameters according to the following parameters: negative scores had a staining intensity of 0 and 1+ in ≤10% of epithelial cells; weak scores had a staining intensity of 1+ in >10% and ≤70% of epithelial cells or a staining intensity of 2+ in ≤30% of epithelial cells; moderate scores had a staining intensity of 1+ in >70% of epithelial cells, a staining intensity of 2+ in >30% and ≤70% of epithelial cells or a staining intensity of 3+ in ≤30% of epithelial cells; and strong scores had a staining intensity of 2+ in >70% of epithelial cells or a staining intensity of 3+ in >30% of epithelial cells. At least, weak IHC expression is required for the definition of IMP3-positivity of the cells. Expression of IMP3 was then correlated with histopathological data in studied BE and EAC cases.

Statistical analysis: Results were analyzed using SPSS (version 23) statistical package for Microsoft windows. The Pearson correlation coefficient was used for statistical analysis. P value <0.05 was considered statistically significant, and highly statistically significant when it was <0.01.

Results:

Clinico-pathological features of studied BE cases:

Mean age of the studied BE cases was (44.16). Twenty-three cases (74%) were male and 8 cases (26%) were females. Fifty five percent were smokers and 45% were non-smokers. Forty eight percent were short segment BE and fifty two percent were long segment BE. Non dysplastic BE represented 36%, LGD represented 32% and HGD represented 32% of BE cases.

A high significant statistical correlation was found between tumor grade and the histological subtypes of EAC ($P<0.01$). Also, a significant statistical correlation was found between tumor grade and Tumor infiltrating neutrophils (TINs) ($P<0.05$), and the lymphoplasmacytic infiltrate ($P<0.05$). No significant statistical correlation was found between histological subtypes of EAC and necrosis, Tumor infiltrating neutrophils (TINs) or the lymphoplasmacytic infiltrate ($P>0.05$). There was insignificant statistical correlation between tumor grade and necrosis ($P>0.05$).

Immunohistochemical results:

A highly significant correlation was found between IMP3 IHC expression and the different grades of BE and EAC cases. Regarding BE, a high significant statistical correlation between IMP3 expression and the segment length and grade of dysplasia in the studied cases. Both neutrophilic and lymphoplasmacytic infiltrate showed no statistically significant correlation with the IHC expression of IMP3. **Table (3) (Figure 1; a, b &c)**

IMP3 expression had a significant positive statistical correlation with tumor necrosis and a high significant statistical correlation with grading, neutrophilic and lymphoplasmacytic infiltration in the studied EAC cases. In contrast, there was no significant statistical correlation between the histological subtypes of EAC and the IHC expression of IMP3. **Table (4)** (**(Figure 2)**

Table1: Correlation between the grade of dysplasia and histopathological data of BE:

Grade of dysplasia	Segment Length			
	Short		**Long**	**P value**
BE-ND	63.5%		36.5%	<0.5*
BE-LGD	60%		40%	
BE-HGD	20%		80%	
	Neutrophilic infiltrate			
	Mild	**Moderate**	**Severe**	
BE-ND	27.2%	36.4%	36.4%	>0.5
BE-LGD	40%	20%	40%	
BE-HGD	40%	20%	40%	
	Lymphocytic infiltration			
	Mild	**Moderate**	**Severe**	
BE-ND	27%	46%	27%	>0.5
BE-LGD	30%	40%	30%	
BE-HGD	30%	40%	30%	

Table (2): Clinico-pathological features of studied EAC cases**:**

Variable		No=20 (100%)
Mean age		63.16
Gender	**Male**	12 (60%)
	Female	8 (40%)
Smoking	**Smoker**	14 (70%)
	Non-smoker	6 (30%)
Histological subtypes	**Tubular adenocarcinoma**	8 (40%)
	Papillary adenocarcinoma	2 (10%)
	Mucinous adenocarcinoma	4 (20%)
	Signet ring adenocarcinoma	6 (30%)
Necrosis	**High grade**	13 (65%)
	Low grade	7 (35)
Ulceration	**Present**	9 (45%)
	Absent	11 (55%)
Tumor grade	**Well differentiated**	6 (30%)
	Moderately differentiated	6 (30%)
	Poorly differentiated	8 (40%)

Table (3): Correlation between the Clinico-pathological variants of BE and IMP3 IHC expression

Clinico-pathological variants of BE		IMP3 expression				P value
		Negative	Weak	Moderate	Strong	
Segment length	**Short segment BE**	66.5%	27%	0%	6.5%	0.001**
	Long segment BE	19%	19%	25%	37%	
Grade of dysplasia	**BE-ND**	72.5%	27.5%	9%	0%	0.000**
	BE-LGD	40%	40%	20%	0%	
	BE-HGD	10%	0%	20%	70%	
Neutrophilic infiltrate	**Mild**	55%	18%	18%	9%	>0.05
	Moderate	37.5%	25%	12.5%	25%	
	Severe	33.5%	25%	8%	33.5%	
Lymphoplasmacytic infiltrate	**Mild**	44.5%	22%	11.5%	22%	>0.05
	Moderate	53.5%	15.5%	8%	23%	
	Severe	22.2%	33.4%	22.2%	22.2%	

Table (4): Correlation between IMP3 expression and clinicopathological variables of EAC.

Clinico-pathological variants of EAC			IMP3 IHC expression			P value
			Weak	Moderate	Strong	
Grading	**Well differentiated jdifferedifferentiated**		33.3%	50.0%	16.7%	0.003**
	Moderately differentiated		0%	16.7%	83.3%	
	Poorly differentiated		0%	12.5%	87.5%	
Histological subtypes	**Tubular adenocarcinoma**		25%	25%	50%	
	Papillary adenocarcinoma		0%	50%	50%	>0.05
	Mucinous adenocarcinoma		0%	25%	75.0%	
	Signet ring carcinoma		0%	16.7%	83.3%	
Necrosis	**Low grade**		15.5%	38.5%	46%	0.027*
	High grade		0%	0%	100%	
Neutrophilic infiltrate		**Mild**	33.5%	50%	16.5%	0.001**
		Moderate	0%	28.6%	71.4%	
		Severe	0%	0.0%	100.0%	
Lymphoplasmacytic infiltrate		**Mild**	0%	20%	80%	
		Moderate	0%	20%	80%	0.01**
		Severe	40%	40%	20.%	

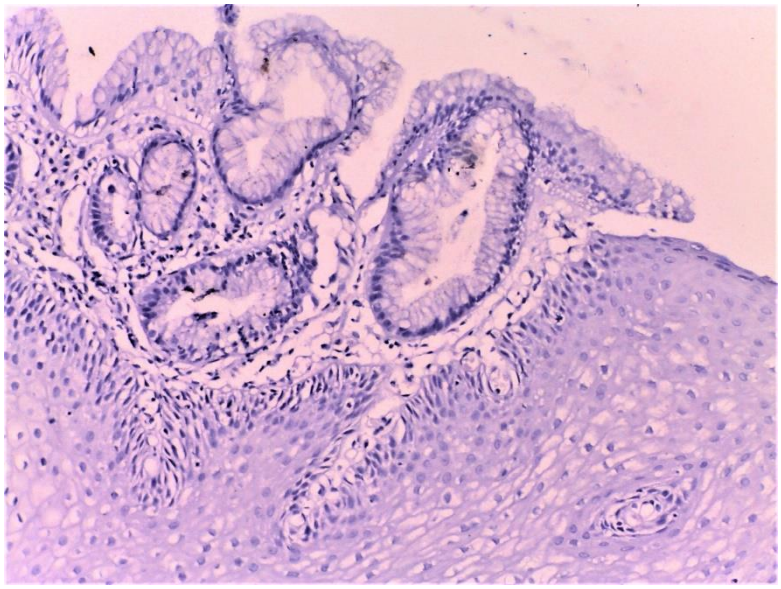

Fig. 1: Negative staining for IMP3 in BE-ND, X200

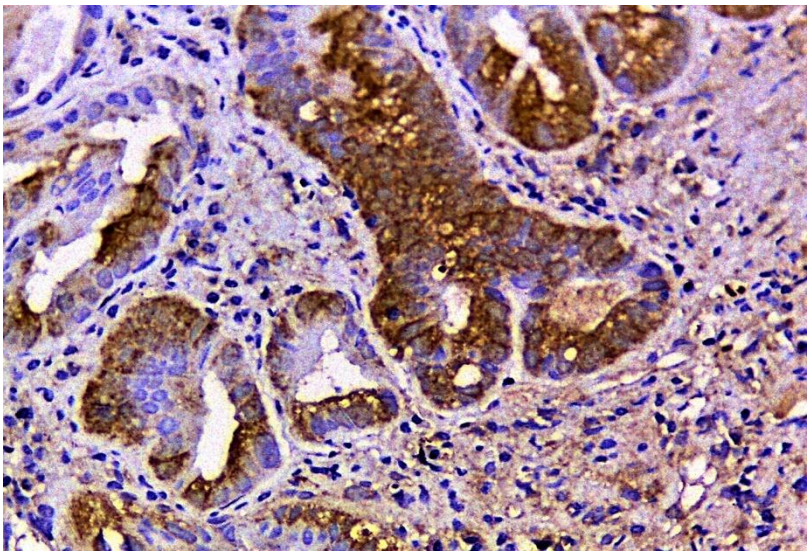

Fig. 1: Strong cytoplasmic staining in BE-HGD, X400

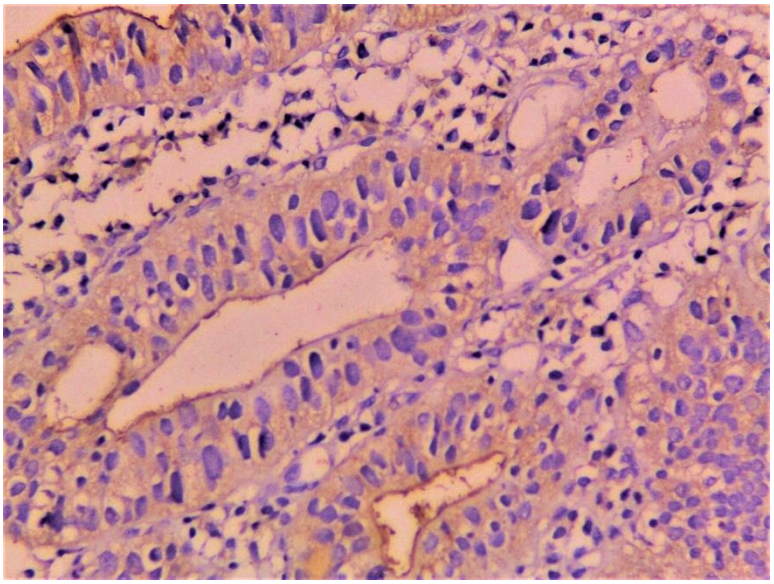

Fig.3: Weak cytoplasmic staning for IMP3 in well differentiated EAC, X400

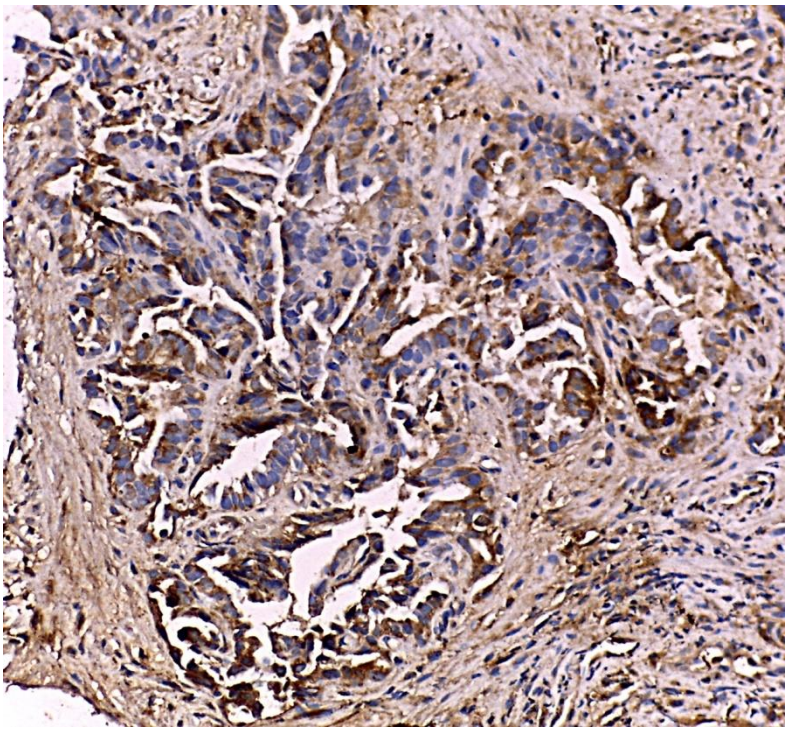

Fig. 4: moderate cytoplasmic staning for IMP3 in moderately differentiated EAC, X400

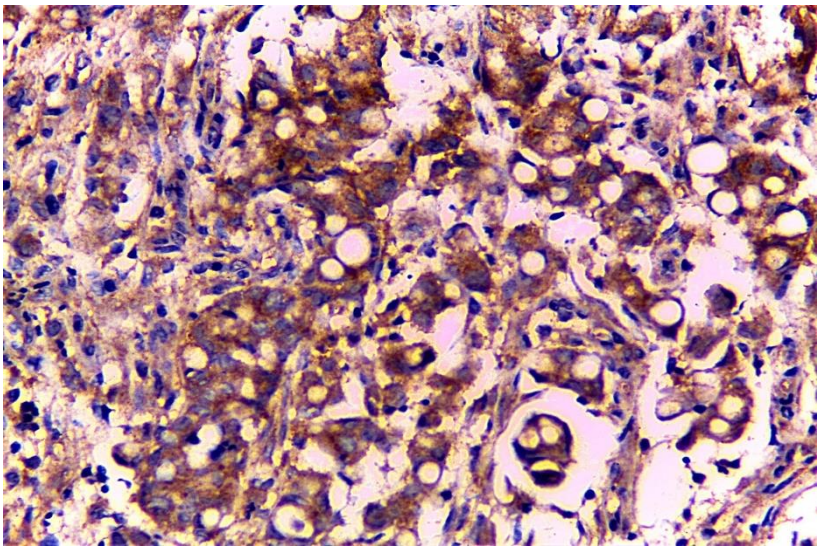

Fig. 5: Strong cytoplasmic and membranous staining in poorly differentiated signet ring adenocarcinoma, X400

Discussion:

BE is a major risk factor for esophageal adenocarcinoma (EAC), which has shown a dramatic increase in incidence over the past 50 years with a very poor prognosis (18).

This retrospective study was done on fifty-one cases of esophageal lesions including BE and EAC. IMP3 was immunohistochemically stained and evaluated for each case. Then its expression was correlated with different clinical and histopathological variables.

An obvious male predominance was found in both BE and EAC studied cases. This was in accordance with the finding proved recently in some studies (19, 20 & 21), on the esophagus. Researchers explained the male predominance in BE (22) by the gender related differences in the known risk factors of BE such as increased prevalence of tobacco use and alcohol consumption, being more common in in men. The male predominance in BE, being the strongest predisposing factor of EAC, can explain the emerging male predominance in EAC.

The current work revealed an increased prevalence of smoking in BE and EAC cases. This agreed to the work done 2018 (23) where it was found that current smokers have an increased risk of both BE and EAC, as compared to non-smokers. The role of smoking in BE and EAC through exposure to chemicals such as N-nitrosoamines **was explained before** (24) by the promotion of

GERD, and the continuous inflammatory effects of smoking promoting the cellular proliferation.

The present study showed a significant statistical correlation between the grade of dysplasia and segment length of the studied BE cases (P value<0.5). While no significant statistical correlation was found between the grade of dysplasia and the neutrophilic infiltrate in studied BE cases. In contrast, a high significant statistical correlation was found between the grading of EAC cases and tumor infiltrating neutrophils (TINs) (P value<0.01). In agreement with this, **Xiao et al., (2014)**(25) concluded that high neutrophil to lymphocyte ratio was associated with a poor tumor grade in hepatocellular carcinoma and **Tang et al., (2017)**(26) proved that neutrophilic count was significantly associated with high-grade bladder carcinoma. This can be explained by the carcinogenic role of neutrophils. It releases reactive oxygen species that causes genetic instability. Chemokines secreted from tumor cells themselves such as interleukin8 (IL8) recruit neutrophils to the site of tumorigenesis. Neutrophils also cause constitutive activation of the inflammatory signaling pathways leading to downstream activation of gene transcription and enzymatic activity that have a key role in tumor growth and survival. The IL-6/STAT3 signaling pathway is upregulated in esophageal cancer and several studies have correlated increased epithelial IL-6/STAT3 activity with cell proliferation and apoptotic resistance in BE and EAC (27).

In the current work, there was no significant statistical correlation between the lymphoplasmacytic infiltrate and the grade of dysplasia in studied BE cases (P>0.05). In contrast, we found a significant negative statistical correlation between the lymphoplasmacytic infiltrate and the grading of EAC cases (P value <0.05). This agreed to the result which proved previously (28) that high infiltration by CD8+ T lymphocytes is associated with favorable prognosis in esophageal cancer. In contrast to this, (29) it was found that higher tumor infiltrating lymphocytes are associated with higher histologic grades in breast carcinomas (29). It was suggested that the more poorly differentiated tumor cells recruit more tumor infiltrating lymphocytes from the circulation due to either the expression of pro-inflammatory factors or changes in their immunogenicity (30). This argument in results could be due to different tissues examined and different methods of lymphocytes evaluation.

In our study, tumor necrosis showed no statistically significant correlation with histopathological subtypes of EAC cases. Also, the correlation between necrosis score and grading of EAC cases was statistically insignificant (P value>0.05).

The insulin-like growth factor-II mRNA-binding protein 3 (IMP3) is an oncofetal protein that affects cellular proliferation, adhesion, and invasion of malignant neoplasms through the control of the translation or turnover of various candidate target genes, including IGF2, CD44, HMGA2, and MMP9. The IHC expression of IMP3 was detected in various neoplasms (31). So, we aimed to evaluate this protein expression in the pathological changes occurring in BE through its progression to adenocarcinoma.

There was complete negative IHC staining of IMP3 in chronic nonspecific esophagitis cases (control group). A significant statistical correlation was found between IHC expression of IMP3 and different grades of dysplasia in BE and esophageal adenocarcinoma (P value<0.01). IMP3 was expressed in 27.5% of BE-ND, 60% of BE-LGD and in 90% of BE-HGD. All esophageal adenocarcinoma cases (100%) showed IHC positivity of IMP3. Our finding were compatible with the results of other series in literature evaluating the expression of IMP3 in BE (32, 33, 34 & 35). Those results propose that IMP3 have a role in the tumorigenesis and progression from BE to EAC.

IMP3 is known to favor IGF2 translation, activating IGF signaling and promoting cell growth, proliferation, and resistance to ionic irradiation in different tumor types (36). It acts by synergizing with heterogeneous nuclear ribonucleoprotein M (HNRNPM) in the nucleus leading to an enhanced expression of cyclins and was also shown to promote the expression of HMGA2 (high-mobility group AT-hook 2) by preventing miRNA binding, leading to proliferation, migration and invasion of malignant cells (37).

The obvious upregulation of IMP3 expression in malignant lesions rather than benign and dysplastic cases in the current work and similar previous studies in other tissues, (38) (39) approved the fore mentioned oncogenic role in esophageal adenocarcinoma and other human malignancies and making it a promising biomarker for the differentiation between benign and malignant lesions in some doubtful cases specially when integrated with other clinicopathological parameters. Also, its different expression in high and

low dysplastic cases can help for risk stratification and close monitoring for low risk cases or be a guide for rapid intervention in high risk cases limiting the progression to invasive cancer.

In Barrett's esophagus cases, a significant statistical correlation was found between the IHC expression of IMP3 and the segment length (P value<0.01). Some previous result **was** is in line with our work (40). They concluded that the longer Barrett's was associated with increased risk of dysplastic and neoplastic progression. So, we can say that patients with longer Barrett's esophagus segment should undergo a more intense surveillance.

A highly significant statistical correlation was found between IMP3 expression of IMP3 and the grade of dysplasia (P <0.01). This result is compatible with others (41) in their study who reported that increased IMP3 IHC expression was associated with a higher degree of dysplasia in small intestinal adenomas.

A significant statistical correlation was found between IMP3 expression and the grading of esophageal adenocarcinoma cases (P <0.01). Against our result was the result of **lu et al., 2009**(42) who reported that no difference in IMP3 IHC expression between the grades of esophageal adenocarcinoma. We also argue with the result of **2018** (43) where it was claimed that there was no statistical difference in IMP3 expression between low and high grade leiomyosarcomas. This difference can be attributed to the different assessment and different tissue examined.

The current study showed a significant statistical correlation between IMP3 expression and the necrosis score in EACs. In agreement to this result, another (44) had found that IMP3 expression was correlated with necrosis in triple negative breast carcinomas. In a study done on 2017 it was concluded that a stronger IHC expression of IMP3 in cases of papillary biliary tumors associated with necrosis (39). But yet, not much research are found in literature about this issue

This study revealed a high significant statistical correlation between tumor infiltrating neutrophils and IMP3 IHC expression (p<0.01). Also, IMP3 expression showed a significant inverse correlation with the lymphoplasmacytic infiltration in EAC cases. But yet, no much research in literature explained the association between IMP3 expression and the neutrophilic or lymphoplasmacytic infiltrate. A wider cohort studies are needed to evaluate it.

Conclusion:

IMP3 is involved in the neoplastic progression of BE, and can be a potential diagnostic marker for dysplastic BE. Thus, it is considered a promising marker for the risk stratification of BE cases allowing a better surveillance and rapid intervention in the high risk groups. IMP3 may be a marker of poor prognosis in EAC. A wider cohort studies are needed to confirm the role of IMP3 in BE progression and esophageal carcinogenesis.

Histopathological findings such as neutrophilic and lymphoplasmacytic infiltration in EAC cases, could predict the prognosis as it correlates significantly with the degree of differentiation. But this still need confirmation in literature by further wider studies.

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