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Studying the Role of IMP3 and P53 in Detection of Dysplastic Changes in Barrett's Esophagus

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Abstract

Background: Barrett's esophagus (BE) is an acquired metaplastic lesion with unpredictable potential for esophageal adenocarcinoma (EAC). Searching for immunohistochemical markers for predicting progression in Barrett's esophagus is of increasing interest.

Aim of Study: The aim of this study is to detect early dysplastic changes in patients with BE for better management of diagnosed cases.

Material and Methods: This retrospective study was carried upon 28 endoscopic biopsies of BE; 6 cases of Barrett's esophagus without dysplasia, 12 cases were Barrett's esophagus with low grade dysplasia and 10 cases with high grade dysplasia. Cases were collected from archives of Pathology Department and Early Cancer Detection Unit (ECDU), Faculty of Medicine, Benha University during the years 2015-2020. IMP3 and P53 immunohistochemichal staining were performed and evaluated for each case.

Results: IMP3 was positive with high expression in 80% of high grade dysplasia cases which was a statistically significant relation between IMP3 expression and grade of dysplasia. P53 was a highly sensitive marker for early dysplastic changes, reporting 100% sensitivity to low grade dysplasia. P53 was also highly specific to high grade dysplasia (100%). IMP3 was found to be highly sensitive to high grade dysplastic changes (90%).

Conclusion: Combination of both markers could be helpful in detection of early dysplastic changes in Barrett's esophagus patients who are at risk of malignancy to start a strict follow-up procedures. Both markers together could be useful in detection ofhigh grade dysplasiaand rapid intervention to prevent malignant transformation.

Key Words: *Barrett's esophagus – Dysplasia – P53 – IMP3 – Immunohistochemistry.*

Introduction

IN Barrett's esophagus (BE) or Barrett's metaplasia, squamous epithelial lining of the esophagus is replaced in part bycolumnar epithelium due to the effect of chronic acid reflux [1]. In another definition, BE is a lesion in which the normal esophageal squamous epithelium is replaced by specialized intestinal one. It is considered the most important precursor lesion for esophageal adenocarcinoma [2].

Presence of Barrett's esophagus with high-grade dysplasia (HGD) is considered the best predictor for the development of esophageal adenocarcinoma. Six to sixty percent of HGD cases can progress to EAC each year [3]. However, large previous studies confirmed that patients who are diagnosed as BE with low grade dysplasia (LGD) have five times higher risk of development of EAC in comparison to those with non-dysplastic BE (ND-BE) [1]. Periodic upper gastrointestinal endoscopy is highly recommended for patients with low grade dysplastic changes, while, patients with HGD and EAC are subjected to more aggressive treatments such as endoscopic mucosal resection, ablation or even surgery [3].

Diagnosis of BE is depending on histopathologic examination of biopsies. An intra-observer and inter-observer variabilities in grading of dysplasia usually occur [3]. Therefore, accurate recognition of dysplasia in BE is essential because of its prognostic significance [4].

Insulin-like growth factor 3 (IMP3), is an oncofetal RNA-binding protein that controls the localization, translation, and stability of mRNAs. This oncofetal protein has high expression during embryogenesis, low expression in adult tissues and re-expression in malignancies [5]. It was reported to be highly expressed in many types of cancers such as gastric, pancreatic, colonic and urothelial cancers with valuable prognostic significance [6-9]. Another valuable marker is P53, which is a

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nuclear transcription factor that plays a crucial role in control of cell cycle, apoptosis and maintenance of genomic stability. Since more than 50% of human cancers carry loss of function mutations in P53 gene, it has been considered one of the classical type tumor suppressors [10].

Unfortunately, immunohistochemistry is not widely used for detection of dysplastic changes in BE patients because of overlapping expression pattern between reactive changes and low grade dysplasia [11]. There is a need for sensitive and specific immunohistochemical markers for early detection of dysplastic changes in BE patients. So, this work aims at studying the value of both IMP3 and P53 in patients with BE for better management of diagnosed cases.

Material and Methods

This uncontrolled retrospective study included 28 cases of Barrett's esophagus acquired by upper gastrointestinal tract endoscopy. Selected cases were collected from archives of Early Detection Cancer Unit (EDCU) and Pathology Department in Faculty of Medicine, Benha University during the period from June 2015 to December 2020. Grading of dysplasia was made according to Yin, et al., [2] and Odze [12]. Twelve cases were associated with low grade dysplasia (LGD) and 10 cases exhibited high grade dysplasia (HGD). Six cases of non-dysplastic BE (ND-BE) were also included. No cases indefinite for dysplasia were found during this period of time. Hematoxylin and Eosin sections were reviewed by two pathologists. Demographic data were retreived from the archived patients' files. Ethical approval from Research Ethics Committee, Faculty of Medicine, Benha University was obtained.

Immunohistochemichal study:

Four micron-tissue sections were prepared from paraffin blocks. P53 and IMP3 antigens were detected using streptavidin-biotin technique, following the manufacturer's instructions (Neomarker, LAB-VISION, USA, CA 94538-7310). Regarding IMP3, rabbit polyclonal antibody (Chongqing Biospes, Cat no. #YPA1463, China, dilution of 1:100) was incubated overnight at 4ºC. Fetal liver obtained from aborted fetus (16 weeks) was considered as positive control. P53 (Lab Vision, Thermoscientific, USA, cat No. # MA5-12557) dilution 1:100 was incubated for 60 minutes at room temperature, and invasive ductal breast carcinoma was considered as positive control. Citrate monohydrate buffer 10mmol/L (pH 6.0) was used for antigen retrieval thensections were heated for 15 minutes in the microwave. For visualization of the stained sections, diaminobenzidine (DAB) solution (0.02%) was used, and then the sections were counterstained by Hematoxylin. Finally, sections were dehydrated and mounted. A negative control was used for each marker, by neglecting the step of primary antibody.

Immunohistochemical interpretation:

Epithelial fragments were excluded during marker interpretation and evaluation of stained cells was limited only to intact metaplastic cells. Positive IMP3 expression was detected as cytoplasmic/membranous staining. A score for each case was calculated using intensity of staining and percent of positive stained cells referring to Burdelski, et al., [13]. Positive P53 staining was defined as strong nuclear staining (+3). Its expression was interpreted according to Strehl, et al., [10].

Statistical analysis: The collected data were analyzed by using SPSS version 16 software (Spss-Inc, Chicago, ILL Company). The association between markers of the study and case groups was done using Pearson correlation. Accepted level of significance was 0.05 ($p<0.05$ was considered significant. $p<0.01$ was considered as highly significant). ROC curves were constructed to assess the performance of both IMP3 and P53 in detection of patients with different grades of dysplasia, in addition to those without dysplasia.

Results

The age of patients in this study ranged between 13-64 years with mean age of 37.6 years. Twenty cases were males and 8 cases were females. Cases of the study were classified into 3 groups; ND, LGD and HGD according to histopathological diagnostic criteria. There were 12 (42.9%) cases of LGD and 10 (35.7%) cases of HGD in addition to 6 (21. 4%) cases of BE negative for dysplasia (ND).

Histopathological results:

In cases which were ND: The glandular epithelium was reactive showing surface maturation. Low nucleo/cytoplasmic ratio was detected with smooth nuclear contour. Nuclear polarity was maintained. Mild atypia was detected at basal layers of epithelium, in some cases (Fig. 1A). Low grade dysplasia was characterized histologically by preserved architecture. Nuclei were enlarged hyperchromatic. Nuclear polarity was maintained. No cribriform glands were detected (Fig. 2A). In cases of HGD, dysplastic changes found to be

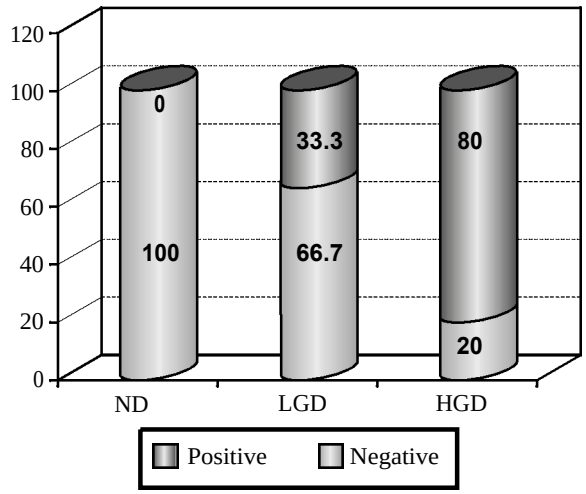
increased, but within intact glandular basement membrane. There were enlarged hyperchromatic pleomorphic nuclei, with irregular nuclear contour. Prominent nucleoli and abnormal mitotic figures were present. There was loss of polarity and cribriform glands could be seen (Fig. 3A).

Immunohistochemical results:

Cyto/membranous immunohistochemical expression of IMP3 represented a highly statistically significant relation (p<0.01) to grade of dysplasia. It was negative in all cases (100%) of BE without dysplasia (Fig. 1B) and in 8 cases (66.7%) of LGD (Fig. 2B). However, it was positive with high expression in 8 cases (80%) of HGD (Fig. 3B) (Graph 1).

ROC curves were constructed to assess the performance of both IMP3 and P53 in detection of patients with different grades of dysplasia, in addition to those without dysplasia. IMP3 was found to be highly sensitive to high grade dysplastic changes (90%); which are considered at high risk of malignant transformation (Table 3, Graph 2C).

P53 was found to be a highly sensitive marker for early dysplastic changes, reporting 100% sensitivity to LGD (Table 2, Graph 2B); in addition, P53 was highly specific to HGD (100%) (Table 3, Graph 2C).



Graph (1): Relation of IMP3 expression to grades of dysplasia in studied Barrett's esophagus cases.

ND : No dysplasia. LGD: Low grade dysplasia.
HGD: High grade dysplasia.

Table (1): Performance of P53 and IMP3 in detecting patients without dysplasiain studied cases.

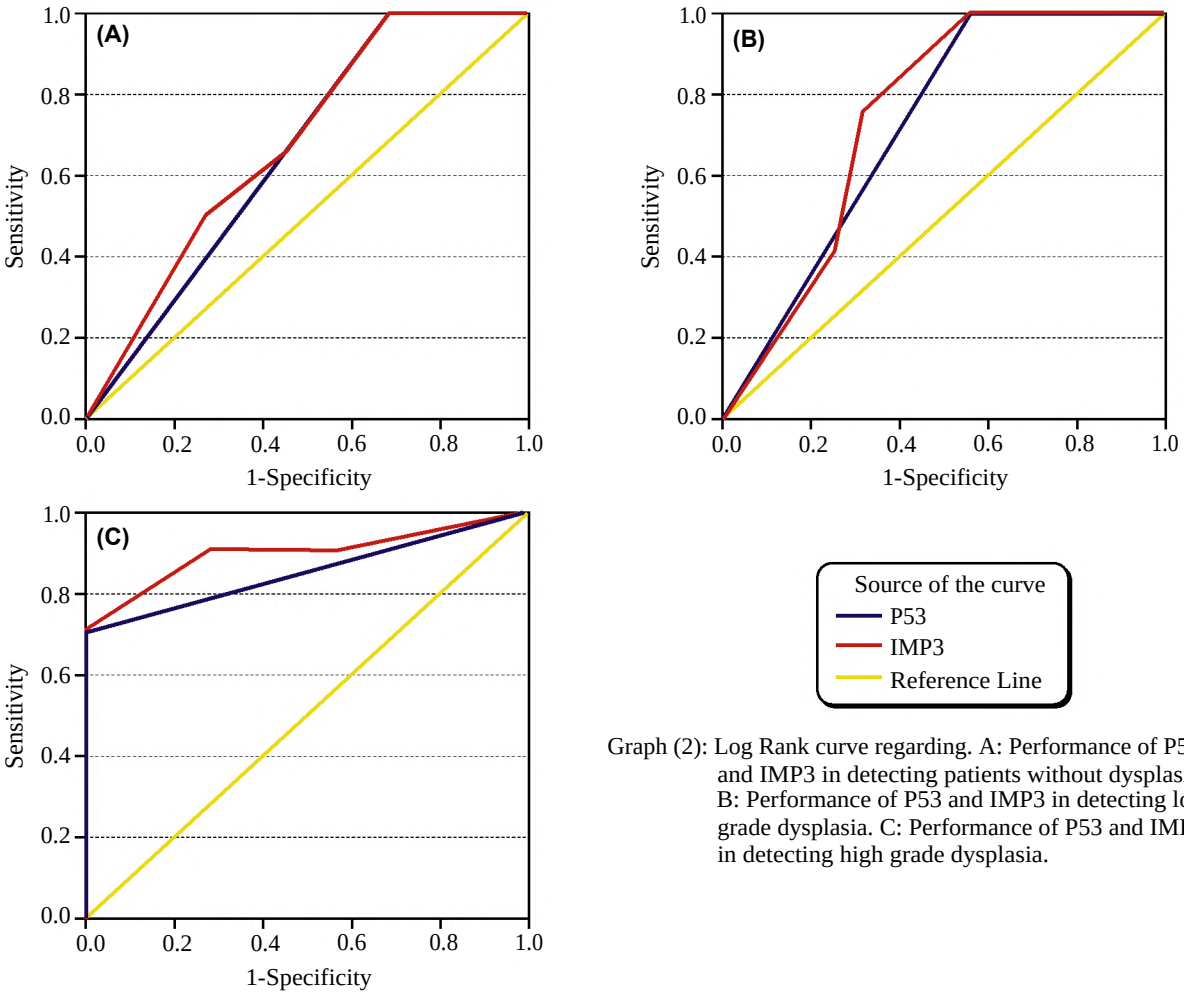
Variable	Sensitivity %	Specificity %	PPV%	NPV%	AUC	95% CI	*p*
P53 Negative vs. positive	100%	31.8%	28.6%	100%	0.659	0.44-0.874	0.24 (NS)
IMP3 Negative/weak positive vs. Moderate/strong positive	66.7%	54.5%	28.6%	85.7%	0.682	0.466-0.898	0.18 (NS)

Table (2): Performance of P53 and IMP3 in detecting low grade dysplasiain studied cases.

Variable	Sensitivity %	Specificity %	PPV%	NPV%	AUC	95% CI	*p*
P53 Negative vs. positive	100%	43.7%	57.1%	100%	0.719	0.53-0.908	0.051 (NS)
IMP3 Negative/weak positive vs. Moderate/strong positive	75%	68.7%	64.3%	78.6%	0.745	0.56-0.930	0.029 (NS)

Table (3): Performance of P53 and IMP3 in detecting high grade dysplasiain studied cases.

Variable	Sensitivity %	Specificity %	PPV%	NPV%	AUC	95% CI	*p*
P53 Positive vs. Negative	70%	100%	100%	85.7%	0.850	0.67-1.0	0.003 (S)
IMP3 Moderate/strong positive vs. Negative/weak positive	90%	72.2%	64.3%	92.6%	0.894	0.74-1.0	=0.001 (HS)



Graph (2): Log Rank curve regarding. A: Performance of P53 and IMP3 in detecting patients without dysplasia. B: Performance of P53 and IMP3 in detecting low grade dysplasia. C: Performance of P53 and IMP3 in detecting high grade dysplasia.

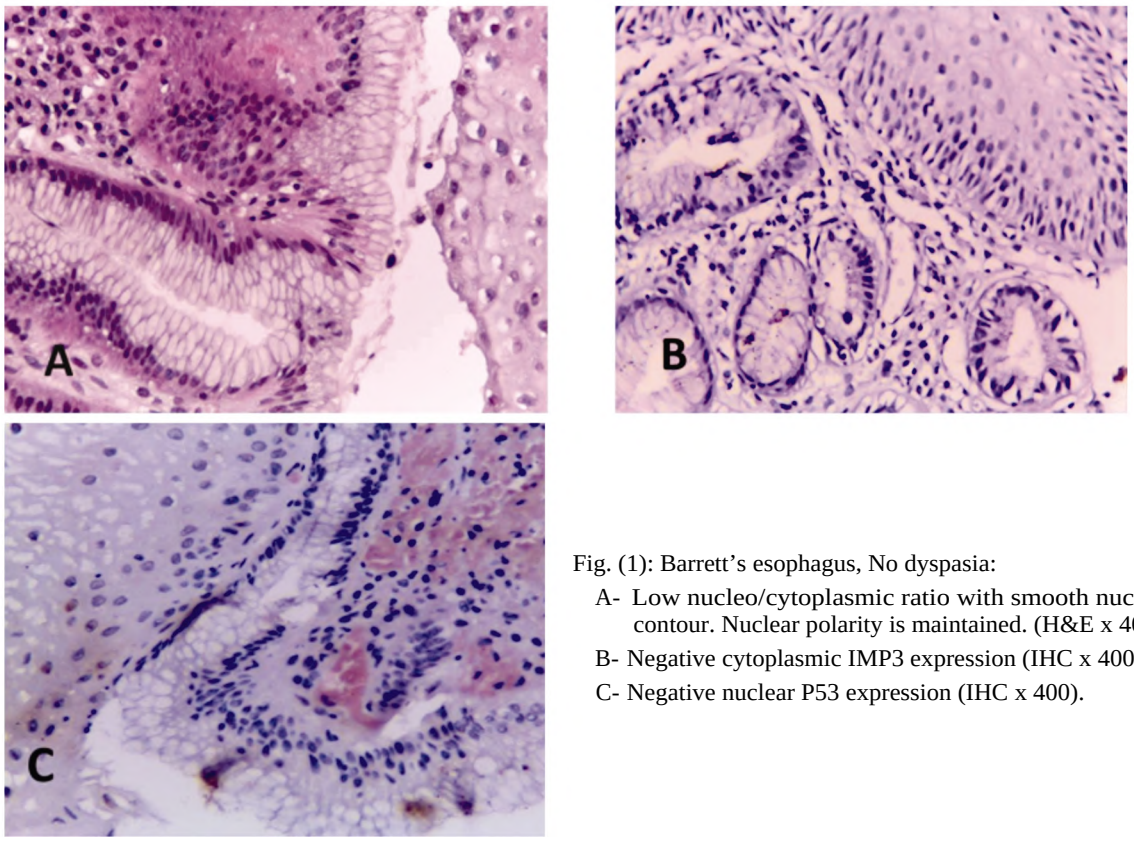


Fig. (1): Barrett's esophagus, No dyspasia:

A- Low nucleo/cytoplasmic ratio with smooth nuclear contour. Nuclear polarity is maintained. (H&E x 400).

B- Negative cytoplasmic IMP3 expression (IHC x 400).

C- Negative nuclear P53 expression (IHC x 400).

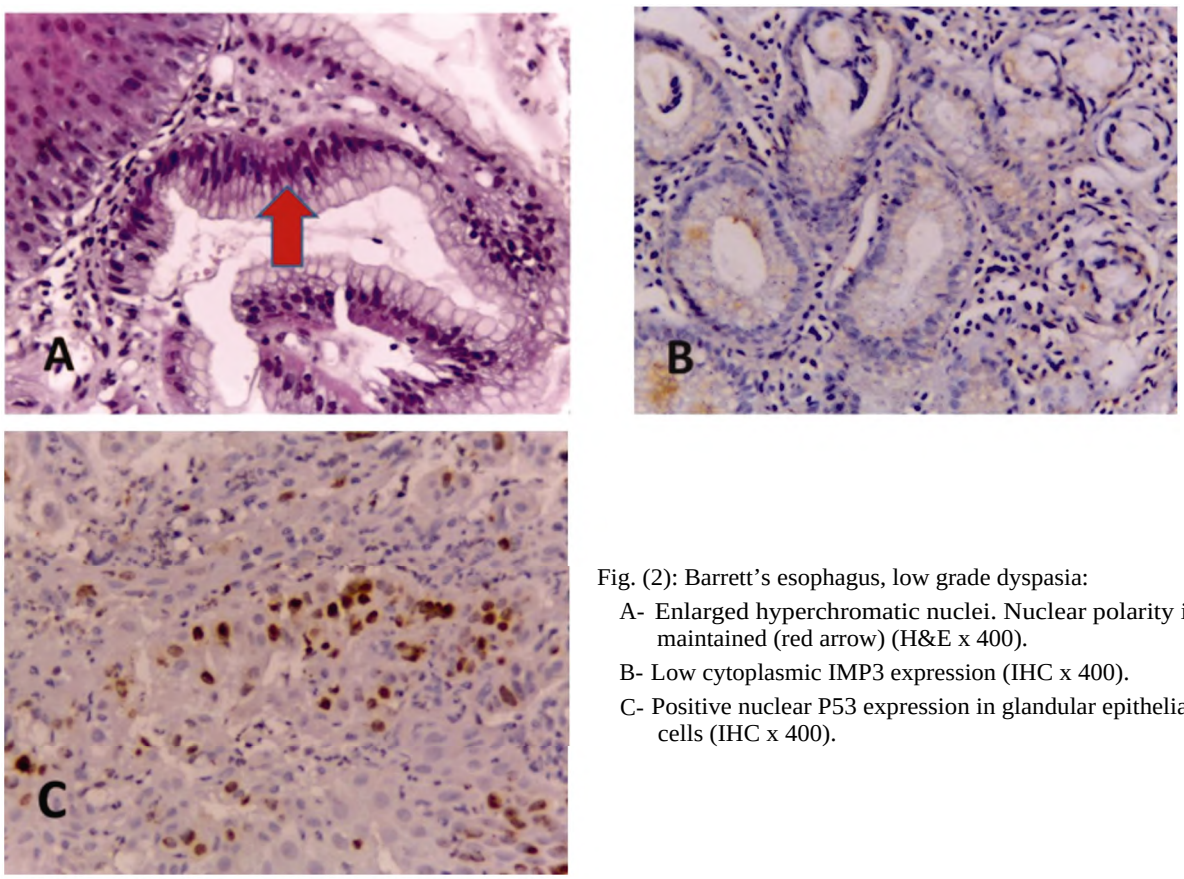


Fig. (2): Barrett's esophagus, low grade dyspasia:

A- Enlarged hyperchromatic nuclei. Nuclear polarity is maintained (red arrow) (H&E x 400).

B- Low cytoplasmic IMP3 expression (IHC x 400).

C- Positive nuclear P53 expression in glandular epithelial cells (IHC x 400).

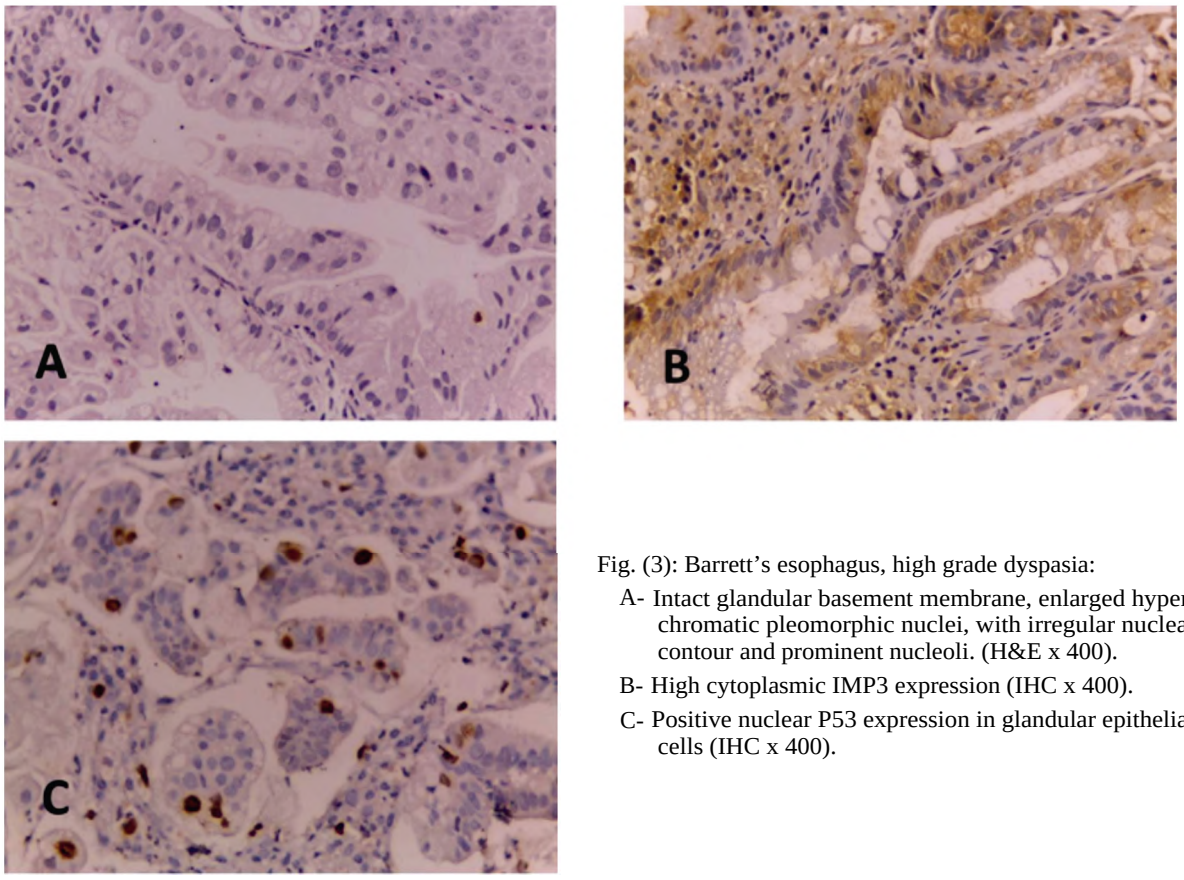


Fig. (3): Barrett's esophagus, high grade dyspasia:

A- Intact glandular basement membrane, enlarged hyper-chromatic pleomorphic nuclei, with irregular nuclear contour and prominent nucleoli. (H&E x 400).

B- High cytoplasmic IMP3 expression (IHC x 400).

C- Positive nuclear P53 expression in glandular epithelial cells (IHC x 400).

Discussion

Barrett's esophagus (BE) is the main precursor lesionfor esophageal adenocarcinoma which is a cancer with very poor prognosis. So, it is highly important to apply early and accurate diagnostic methods for BE, beside an accurate treatment guidelines [2]. Over-diagnosis to esophageal adenocarcinoma (EAC) occurs in nearly 40% of cases of BE with high grade dysplasia (HGD), this, of course, leads to possible mismanagement; even unnecessary esophagectomy [3]. However, clinical and histologic findings are not, alone, able to predict cases that may progress from low to higher grade of dysplasia or even after that to esophageal adenocarcinoma. In addition, no distinctimmunohistochemical markers are approved to predict this neoplastic progression [1]. This study was carried on different grades of dysplasia among Barrett's esophagus cases in addition to cases without dysplasiatrying to solve this issue and suggest a valuable marker that could early predict different dysplastic changes in BE.

In this study, IMP3 showed highly positive cyto-membranous expression (80%) among cases of HGD, while 100% of ND cases and 66.7% of low grade dysplasia (LGD) cases were negative.

This agreed with study done by Lu, et al. [14] on esophageal specimens and another study by Riener, et al. [15] on bile duct specimens. They reported strong positive IMP3 expression among HGD patients in comparison to negative results in most cases of LGD. In another study done by Daikuhara et al. [16] on small intestinal adenoma, higher immunohistochemical expression of IMP3 was associated with higher grade of dysplasia. Strehl, et al. [10] worked on gastric epithelium and found that IMP3 was completely negative among cases of LGD, while was strongly positive in 83% of HGD cases. Also Madkour, et al. [17], reported that IMP3 was expressed in 60% of LGD and in 90% of HGD in their work on BE and esophageal adenocarcinoma.

In this study, the negative expression of IMP3 in ND cases could be explained by the fact that IMP3 is an oncofetal protein which has high expression during embryogenesis and low expression in adult tissues.

According to this study, the significant relation between IMP3 expression and grade of dysplasia ($p<0.01$) could predict a possible role in development and progression of dysplastic changes in BE. This could be explained by the results of several in vitro studies which have suggested that IMP3 is synthesized de novo in cancer, where it act as an oncogene and promote malignancy through affecting cellular morphology, polarization, proliferation, migration, and differentiation [5].

In their work on Barrett's esophagus, Feng, et al. [18] reported that increase in IMP3 expression from BE towards EAC, suggests that IMP3 may play a role in the pathogenesis of EAC. Accordingly, they reported that IMP3 could be used in differentiation of dysplastic and neoplastic cases from Barrett's metaplasia and other reactive esophageal lesions. Though, it might be a helpful marker in evaluation of difficult surgical cases if routine light microscopy examination is not sufficient. In addition, according to Riener et al. [15], the IMP3 positivity in extrahepatic biliary epithelium showing HGD was a helpful tool and could be used in biliary brushing specimens.

In Strehl, et al. [10] work, IMP3 exhibited good sensitivity and specificity (70% and 96% respectively) when comparing inflammatory lesions and low grade dysplasia against high grade dysplasia in gastric specimens. They concluded that IMP3 is helpful in differentiation of LGD from HGD of gastric mucosa in routine pathological examination.

On contrary, in this work, Log rank curve for performance of IMP3 among HGD cases expressed high sensitivity (90%) but lower specificity (72.2%). This may be attributed to different size of sample and different clone of antibody used. However, still both works give good results about expression of IMP3 in dysplasia and support the idea that IMP3 is a good predictor of cases with high risk of malignant transformation.

In a good addition to this work, Alnasser et al. [19] and Madkour, et al. [17], concluded that patients with longer segment of BE should be subjected to a more intensive surveillance as there was a statistically significant relation between IMP3 immunoexpression and length of segment affected.

Nowadays, LGD is starting to be treated. Picking up these cases and marking who will benefit from treatment became a must. A reliable diagnostic marker should give information that will guide management of the patient. In cases of BE, a marker should identify dysplastic changes as a risk factor for EAC and detect type of dysplasia for monitoring follow-up and treatment [20].

In his study, Kaye [20] considered inflammatory cases with focal atypia as a diagnostic challenge, and P53 could be useful to overcome this problem. In this study, P53 expressed high sensitivity for detection of ND and LGD cases (100%), in spite

of low specificity (31.8% and 43.7% respectively). These results could give a good chance for early management, and hence, higher possible cure rates among LGD cases.

P53 expressed high specificity to cases of HGD (100%). This agreed with Kastelein, et al. **[21]** who reported 86% specificity towards malignancy in spite of low sensitivity (47%). The difference in reported sensitivity results between our work and Kastelein, et al. **[21]** may be due to different clone of antibody used and different staining protocols. However, considering the inter-observer variability in diagnosis, P53 is still useful and recommended in detection of dysplastic changes.

In this study, the decreasing sensitivity of P53 from ND cases (100%) towards HGD (70%) agreed with a previous study by Murray, et al. **[22]**, who reported that P53 had lower sensitivity to malignant progression. So, they suggested reporting positive P53 expression as strong nuclear staining rather than scattered nuclei.

Accordingly, the positive P53 staining pattern of expression in this study was expressed as the strong nuclear staining in more than 10% of glandular epithelium **[10]**. In a study by Younes, et al. **[23]**, aggregates of P53 positive cells could be considered to represent clonal expansion of cells with abnormal P53 and scattered P53 positive cells are considered negative expression because it may only represent physiological accumulation of P53. In dysplasia, they also reported that P53 expression in aggregates of cells and in multiple biopsies within the esophagus could be an indicator for the rising risk of malignancy.

Janmaat, et al. **[1]** and Keswani, et al. **[24]** reported that histological examination is not sufficient, alone, in diagnosis of dysplasia and P53 as a cheap and available marker besides its effectiveness, could be useful in overcoming this dilemma. In addition, using P53 could reduce overall costs of follow-up together with early detection of at-risk cases.

Finally, this work suggests that concomitant IMP3 and P53 immuno-staining could detect HGD cases because of high sensitivity of IMP3 plus the high specificity of P53 to these cases. This agreed with Strehl, et al. **[10]**, who reported that combination of both P53 and IMP3 could be helpful in differentiating reactive and neoplastic changes in gastric mucosa.

Conclusion: Positivity of P53 showed high sensitivity to detect low grade dysplasia in Barrett's esophagus. So, it could be considered an important indicator of early dysplastic changes and could be useful and recommended marker in detection of dysplastic changes. This could permit starting periodic and strict follow-up procedures for the patient. P53 was also highly specific to detect high grade dysplasia. IMP3 was highly sensitive to detect high grade dysplasia. Combination of both markers could be helpful in detection of high risk-cases that need rapid intervention to save the patient and prevent malignant transformation.

Conflicts of interest: There were no conflicts of interest.

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دراسة دور IMP3 و P53 فى إكتشاف تغيرات خلل التنسج فى مرئ باريت

مرئ باريت (BE) هو نوع من التحولا لمكتسب المصاحب لتوقع غير محدد لسرطان المرئ. إن البحث عن علامات كيميائية مناعية للتنبؤ بالتقدم فى مرئ باريت له أهمية متزايدة. الغرض من هذه الدراسة هو إكتشاف التغيرات المبكرة لخلل التنسج لدى مرضى مرئ باريت من أجل إدارة أفضل للحالات التى تم تشخيصها.

أجريت هذه الدراسة بأثر رجعى على ٢٨ خزعة بالمنظار من مرئ باريت، ٦ حالات بدون خلل التنسج ، و ١٢ حالة مع خلل التنسج منخفض الدرجة و ١٠ حالات مع خلل التنسج عالى الدرجة. تم جمع الحالات من أرشيف قسم علم الأمراض ووحدة الكشف المبكر عن السرطان بكلية الطب جامعة بنها خلال الأعوام ٢٠١٥–٢٠٢٠. تم إجراء وتقييم الصبغة المناعية IMP3 وP53 لكل حالة وكانت النتائج كالتالى:

كان IMP3 موجباً مع تعبير عالى فى ٨٠٪ من حالات خلل التنسج عالية الدرجة والتى كانت علاقة ذات دلالة إحصائية بين تعبير IMP3 ودرجة خلل التنسج. كان P53 علامة شديدة الحساسية للتغيرات المبكرة لخلل التنسج، حيث أبلغ عن حساسية بنسبة ١٠٠٪ لخلل التنسج منخفض الدرجة.كان P53 أيضاً شديد التحديد لخلل التنسج عالى الدرجة (١٠٠٪). وجد أن IMP3 حساس للغاية لتغيرات خلل التنسج عالية الدرجة (٩٠٪).

وقد خلصت الدراسة إلى أنه قد يكون الجمع بين كلا الدلالاتين المناعيتين مفيداً فى الكشف عن التغيرات المبكرة لخلل التنسج لدى مرضى مرئ باريت المعرضين لخطر الإصابة بأورام خبيثة لبدء إجراءات متابعة صارمة. يمكن أن تكون كلتا الدلالاتين مفيدتين فى الكشف عن خلل التنسج عالى الدرجة والتدخل السريع لمنع التحول الخبيث.