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Endoscopic ultrasound and endoscopic ultrasound-guided fine needle aspiration in the diagnosis of diffuse gastrointestinal lesions with inconclusive endoscopic biopsies

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ABSTRACT

Background/Aims: Many gastrointestinal tumors appearing as diffuse circumferential malignancies, for example, diffuse signet ring adenocarcinoma and lymphoma, might primarily involve the submucosal layer and hence are difficult to diagnose because they frequently yield negative endoscopic biopsies. This main aim of this study was to evaluate the accuracy of endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) in the diagnosis of diffuse gastrointestinal lesions with inconclusive endoscopic biopsies.

Materials and Methods: This prospective study included 92 patients with diffuse or circumferential gastrointestinal lesions with non-conclusive biopsies that were taken during upper or lower endoscopy. EUS and EUS-FNA were performed on all patients with cytopathological examination.

Results: This study included 58 males (63%) and 34 females (37%) with a mean age of 54.2 years. Seventy-two cases (78.3%) were shown to have malignant lesions, and 20 cases (21.7%) were shown to be benign. EUS had a sensitivity of 94.4%, a specificity of 65%, a positive predictive value (PPV) of 90.7%, and a negative predictive value (NPV) of 45.1% with a $p<0.0001$ in diagnosing malignant lesions. EUS-FNA had a sensitivity of 83%, specificity of 100%, PPV of 100%, and NPV of 61.9% with a $p<0.0001$.

Conclusion: Endoscopic ultrasound with EUS-FNA is an accurate procedure in the diagnosis of endoscopic biopsy-negative diffuse or circumferential gastrointestinal lesions.

Keywords: Biopsy negative, endoscopic ultrasound, endoscopic ultrasound guided fine-needle aspiration, diffuse gastrointestinal lesions, lymphoma, adenocarcinoma

INTRODUCTION

Some gastrointestinal tumors appearing as diffuse circumferential malignancies, for example, diffuse signet ring adenocarcinoma and lymphoma, might primarily involve the submucosal layer (1). Although endoscopic forceps biopsy is the main procedure for obtaining tissues and reaching diagnosis in cases with gastrointestinal tumors, false-negative results are frequently observed, reaching up to 50% of cases (2).

Other methods might increase the positive yield of these lesions such as taking several biopsies from the same point, using large forceps, or snaring a protruding part of the lesion if possible. Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) is another method of tissue acquisition from these circumferential lesions, especially when conventional biopsy technique is inconclusive (3). Endoscopic ultrasound (EUS) is very useful for the assessment of regional anatomy with better delineation of the lesion allowing an assessment of the safest and most suitable site for needle introduc-

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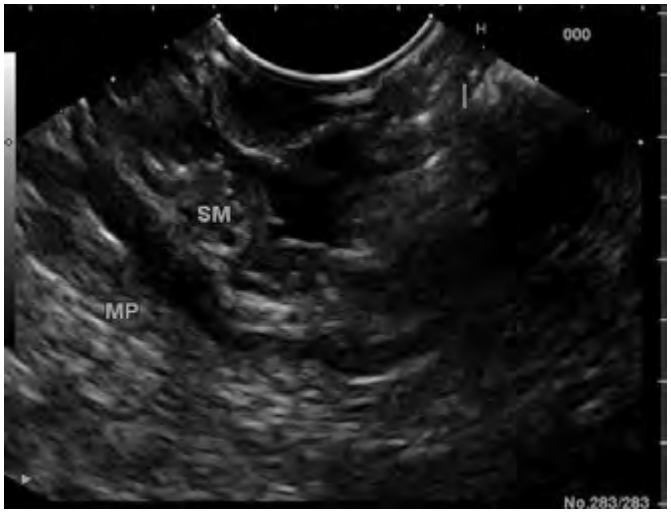

Figure 1. Marked circumferential thickening of the submucosal layer in a case with gastric lymphoma

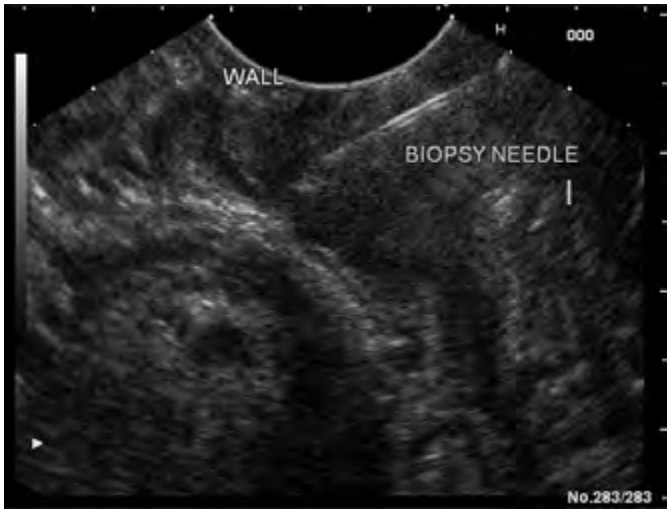

Figure 3. EUS-FNA of a case with gastric adenocarcinoma
EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration

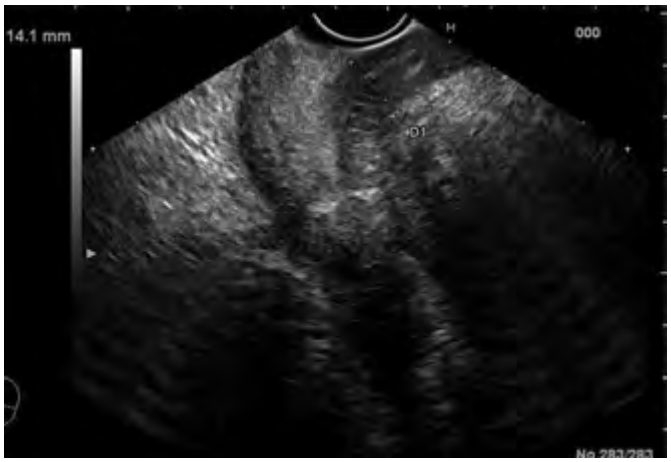

Figure 2. Diffuse thickening of all gastric wall layers in a case of gastric signet ring adenocarcinoma

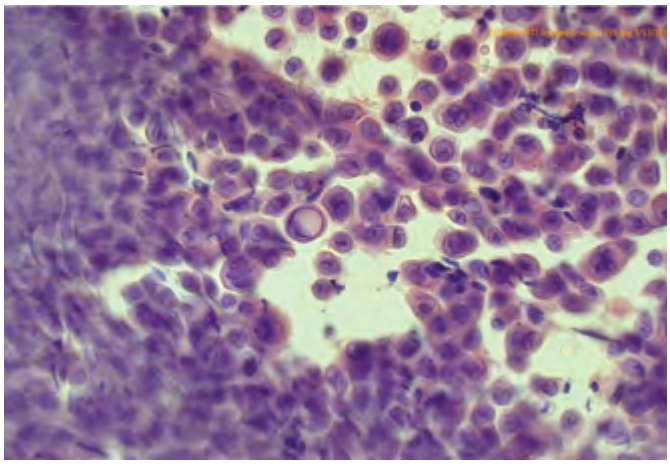

Figure 4. Cytopathological picture of a case with signet ring adenocarcinoma

tion to ensure adequate patient safety and care while avoiding unnecessary, costly, and potentially risky procedures and interventions (4).

This study aimed to evaluate the accuracy of EUS and EUS-FNA biopsy in the diagnosis of conventional endoscopic biopsy-negative diffuse or circumferential gastrointestinal lesions.

MATERIALS AND METHODS

Study Design and Population

This prospective study included 92 Egyptian patients from January 2012 to October 2016. Patients in the study included 58 (63%) males and 34 (37%) females. Their ages ranged from 25 to 77 years old with a mean (SD) of 54.2 (10.5) years.

Inclusion Criteria

Patients referred for EUS-FNA of endoscopically observed diffuse circumferential gastrointestinal lesions. These lesions had been previously biopsied by a biopsy-over-biopsy technique up to five biopsies from the same site in a trial to involve the deeper layer but the biopsy results proved to be inconclusive.

Exclusion Criteria

1. Patients who were unfit for anesthesia or had severe coagulopathy.

2. Final diagnosis was not settled such as in patients with no definite cytopathological diagnosis or patients who were lost to follow up.

Methodology

Endoscopic ultrasound was performed on all patients upon request of their consulting physicians, and informed consent was obtained after explaining the procedure to the patient. For confidentiality, their names were omitted and replaced by numerical codes. Patients who were candidates for EUS examination were appointed to the endoscopy unit on the day of the procedure where the following steps were taken.

Table 1. Variable presentations of the patients

Patients' presentation	Number	Percent %
Weight Loss	29	31.5
Dysphagia	26	28.3
Dyspepsia	16	17.4
Abdominal pain	6	6.5
Gastric outlet obstruction	6	6.5
Bleeding per rectum	4	4.3
Upper gastro-intestinal bleeding	1	1.1
Constipation	1	1.1
Persistent vomiting	1	1.1
Ascites	1	1.1
Obstructive jaundice	1	1.1
Total	92	100

Table 2. Site of the gastrointestinal tract lesions

Site of the lesions	Number	Percent %
Gastric antrum	18	19.6
Gastric fundus	16	17.4
Gastric body	5	5.4
Gastric fundus & body	7	7.6
Gastric body & antrum	5	5.4
Whole gastric wall	6	6.5
Duodenum	6	6.5
Upper esophagus	2	2.2
Middle esophagus	5	5.4
Distal esophagus	4	4.3
Gastro-esophageal junction	8	8.7
Gastro-jejunostomy	1	1.1
Recto-sigmoid	2	2.2
Ano-rectal	5	5.4
Colon	1	1.1
Anastomotic line	1	1.1
Total	92	100

- A thorough history and clinical examination was performed.
- All of the patients' data were recorded.
- EUS and EUS-FNA were performed in all cases by a single endosonographer.
- The procedure was done under deep sedation with intravenous Propofol. An EUS linear array machine was used (Pentax EG-3830UT and EG-3870UTK Echo-endoscope, HOYA Corporation, PENTAX Life care Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi EUB-7000 and Avius machines ultrasound unit (Hitachi Medical System, Tokyo, Japan).
- The target lesions were initially identified and their detailed endosonographic features were assessed, including location, thickness, and echotexture (echogenic or echopoor). Figure 1, 2 show the EUS features of gastric lymphoma and adenocarcinoma, respectively.
- EUS-FNA was carried out using a 22-gauge needle in 79 (85.9%) patients, a 19-gauge needle in 12 (13%) patients, and a 25-gauge needle in 1 (1.1%) patient passing through the esophageal, gastric, duodenal, or colonic walls (Echotip®; Wilson-Cook, Winston Salem, NC). Once guided into the target lesion, the stylet was removed and the needle was moved back and forth within the lesion while applying suction with a 10-mL syringe as shown in Figure 3. The number of passes ranged from one pass in 14 (15.2%) patients, 2 passes in 71 (77.2%) patients, 3 passes in 6 (6.5%) patients, and 4 passes in 1 (1.1%) patient.
- Alcohol (95%)-fixed slides and formaldehyde (Formalin) blocks were prepared immediately and sent for cytological and histological studies with hematoxylin and eosin (H&E) and immunohistochemistry (IHC) if needed.
- All patients were kept under observation for 6 hours for the detection of procedure-related complications, but no major complications were encountered.
- The patient's referring physician was contacted for further information on clinical monitoring, other diagnostic methods, and the final diagnosis.

Study Definitions

- **EUS diagnosis** suggestive of malignant or benign gastrointestinal lesions was based on the affected layers and its echotexture (4,5). It was considered benign if any or all of the innermost three layers were affected (mucosa, muscularis mucosa, or submucosa), while it was considered malignant if the deeper muscularis propria layer (4th layer) was involved. Also, heterogeneous lesions were suggestive of malignancy while homogenous lesions suggested a benign nature of the lesion (6,7).

- **EUS-FNA diagnosis** (benign or malignant) was based on the presence or absence of malignant cells in cytological examination of the slides or the cell block. Figure 4 shows the cytology of signet ring adenocarcinoma.

- **Final diagnosis** was reached by malignant EUS-FNA cytology for malignancy (due to its high specificity), malignant post-surgical histopathological examination, and follow-up of both benign lesions not indicated for biopsy and EUS-FNA benign cases for at least 12 months with no progression of the disease.

The protocol was approved by the ethics committee of Cairo University, and informed consent was obtained.

Table 3. Site of the gastrointestinal tract lesions

Final Diagnosis	Number	Percent %
Malignant lesions:	72	78.3
Gastric adenocarcinoma	39	42.4
Gastric lymphoma	13	14.1
Gastric signet ring adenocarcinoma	8	8.6
Rectal adenocarcinoma	3	3.3
Esophageal SCC	3	3.3
Esophageal adenocarcinoma	2	2.2
Distal sigmoid adenocarcinoma	2	2.2
Duodenal adenocarcinoma	1	1.1
Duodenal lymphoma	1	1.1
Benign lesions:	20	21.7
Gastritis	7	7.6
Hypertrophic pyloric stenosis	2	2.2
Duodenitis	2	2.2
Esophagitis	1	1.1
Esophagitis with low-grade dysplasia	1	1.1
Esophageal T.B.	1	1.1
Mild gastritis with low-grade dysplasia	1	1.1
Gastric sarcoidosis	1	1.1
Proctitis	1	1.1
Radiation proctitis	1	1.1
Eosinophilic gastro-enteritis	1	1.1
Achalasia	1	1.1
Total	92	100

Table 4. EUS features of the lesions

EUS features		Number	Percent %
Layer of origin	All Layers	69	75.0
	3rd Layer	17	18.5
	4th Layer	5	5.4
	5th Layer	1	1.1
Texture	Homogenous	50	54.3
	Heterogonous	42	45.7
Number of passes	1	14	15.2
	2	71	77.2
	3	6	6.5
	4	1	1.1
Needle size	19	12	13.0
	22	79	85.9
	25	1	1.1
EUS diagnosis	Benign	17	18.5
	Malignant	75	81.5
EUS-FNA	Benign	32	34.8
	Malignant	60	65.2
Total		92	100

EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 5. Comparing thickness measurement in both groups to the final diagnosis using the Mann-Whitney U-test

Thickness	Median	IQR	Mean Rank	p
Benign	1.1	0.45	27.88	0.002
Malignant	1.8	1.1	48.79	

IQR: inter-quartile range

Statistical Analysis

All patients' data were tabulated using Excel 2010. Data were processed by Statistical Package for Social Sciences version 20 (IBM Corp.; Armonk, NY, USA) for Windows. All qualitative data were analyzed by chi-square test or Fischer's exact test when appropriate. The chi-square test was used to calculate Pearson's chi-square and its p-value when both variables were quantitative. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The receiver operating characteristic (ROC) curve was used for calculating the area under the curve (AUC), sensitivity, and specificity for the tests used. Cut-off values were calculated. A $p>0.05$ was considered not significant, a p-value <0.05 was considered statistically significant, and a $p<0.001$ was considered highly significant.

RESULTS

The most common presentation of the patients was weight loss followed by dysphagia, dyspepsia, and abdominal pain (Table 1). Table 2 shows that 57 (60%) patients had their lesions located in the stomach, mainly in the antrum and fundus.

Table 3 shows the final diagnosis of the lesions where 20 (21.7%) patients proved to have benign lesions and 72 (78.3%) patients proved to have malignant lesions. The most common malignant lesions were gastric adenocarcinoma followed by gastric lymphoma and gastric signet ring carcinoma. Table 4 shows the EUS features of the lesions regarding texture, layer of origin, EUS diagnosis, and EUS-FNA. The lesions were significantly thicker in the malignant lesions (p=0.002) as shown in Table 5.

Table 6 shows the cross tabulation between EUS diagnosis, EUS-FNA, and final diagnosis using chi-square tests with p-value <0.0001. Table 7 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of wall thickness more than 1.1cm and EUS diagnosis and EUS-FNA in

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Table 6. Cross tabulation between EUS, EUS-FNA, and final diagnosis

		Final diagnosis				
		Benign	Malignant	Total	Chi-square	p
EUS-FNA	Benign	20	12	32 (34.8%)	47.2	<0.0001
	Malignant	0	60	60 (65.2%)		
EUS Diagnosis	Benign	13	4	17 (18.5%)	36.7	<0.0001
	Malignant	7	68	75 (81.5%)		
Total		20	72	100 %		

EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 7. PPV and NPV of different variables related to the final diagnosis

Variables	Sensitivity	Specificity	PPV	95% CI	NPV	95% CI
Thickness (>1.1 cm)	75.7%	72.2%	90.7%	78.7-97.2	45.1%	25.4-66.8
EUS diagnosis	94.4%	65%	90.7%	80.2-96.7	76.3%	45.6-95.5
EUS-FNA	83.3%	100%	100%	92.4-100	61.98%	40.6-80.4

PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 8. Univariate regression analysis between different variables and final diagnosis

Variables	Coefficient	Odds ratio	95% CI	p
Age	0.05	1.05	1.001-1.1	0.038
Gender	-0.16	0.8	0.3-2.3	0.75
Presentation	0.064	1.06	0.86-1.3	0.162
Site of lesion	-0.019	0.98	0.87-1.096	0.74
Layer of origin	-0.9	0.4	0.24-1.64	0.1103
Texture	1.5	4.4	1.36-14.6	0.007
Wall thickness	0.9	2.44	1.06-5.6	0.0109
EUS-FNA	23.5	17.5	0.84-0.96	<0.0001
EUS diagnosis	3.4	31.5	8-123.5	<0.0001

CI: confidence interval; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Table 9. Multivariate regression analysis between different variables and final diagnosis

Variable	Coefficient	Odds ratio	95% CI	p
Age	0.011	1.011	0.92 to 1.11	0.8323
Layer of origin	0.026	1.03	0.42 to 2.4	0.9542
Thickness	-0.23	0.8	0.27 to 2.4	0.6850
Texture	1.74	5.7	0.56 to 57.3	0.1403
EUS-FNA	2.4	6.6	0.5-40	0.9974
EUS diagnosis	2.47	12.02	1.03 to 140.7	0.0477

CI: confidence interval; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

relation to the final diagnosis. ROC analysis was used for determining the cut off value of >1.1cm of the wall thickness with a sensitivity and specificity of 75.5%and 72.2%, respectively.

Table 8 and 9 show the univariate and multivariate regression, respectively. Univariate regression showed that age, texture, thickness, EUS diagnosis, and EUS-FNA were significantly correlated with the final diagnosis. Multivariate regression showed that EUS diagnosis could be a possible predictor of malignancy in diffuse gastrointestinal lesions with an odds ratio of 12 and a p-value of 0.047.

DISCUSSION

Diffuse circumferential gastrointestinal malignancies, for example, diffuse signet ring adenocarcinoma and lymphoma, might primarily involve the submucosal layer. Although endoscopic forceps biopsy is the main procedure for obtaining tissues and reaching diagnosis in cases with gastrointestinal tumors, the false-negative result can reach up to 50% of cases. Possible reasons for this high false-negative rate include infiltrative and stenotic diseases as well as lesions in submucosal locations, such as lymphoma. Taking into consideration that "tissue is the issue" for accurate diagnosis of such lesions, alternative techniques for tissue sampling should be considered (2).

Although bite-on-bite biopsy was considered a useful technique for digging into the mass with conventional or jumbo biopsy forceps, the diagnostic yield was low, ranging from 17% to 38% (3).

This prospective study included 92 patients with diffuse or circumferential wall thickening or exaggerated gastric folds, occasionally associated with surface ulcerations and nodulations suggesting infiltrating malignant wall lesions such as adenocarcinoma or lymphoma. Endoscopic biopsies were inconclusive in all patients even after using the biopsy-over-biopsy technique.

This study also included rather rare specific benign lesions that produce significant increases in the wall thickness, including eosinophilic gastritis, achalasia of the cardia, hypertrophic pyloric stenosis, TB, and sarcoidosis.

Zhou et al. (8) studied 36 cases with flat gastric infiltrating tumors that had been diagnosed by EUS and compared conventional biopsy versus the bite-on-bite technique with or without endoscopic mucosal resection (EMR) to obtain submucosal tissue from the lesions. EUS was used to detect the appropriate biopsy sites. They concluded that this technique is superior to conventional endoscopic biopsy for reaching an accurate diagnosis for such lesions.

The use of EUS-FNA was shown to be valuable in the assessment of pancreatic masses and enlarged lymph nodes (9). However, only a few studies specifically evaluated the use of EUS-FNA in diffuse gastrointestinal tract lesions. Those studies as well as others that included pancreatic lesions and lymphadenopathies found that EUS-FNA was less valuable in the diagnosis of diffuse flat gastrointestinal tract lesions (10).

This study included 58 males (63%) and 34 females (37%) with a mean age of 54.2 years. All patients underwent EUS and EUS-FNA. The final diagnosis revealed 20 cases (21.7%) with benign lesions and 72 cases (78.3 %) with malignant lesions.

The mean wall thickness of malignant lesions was significantly higher than that of benign lesions, and at a cut off value > 1.1 the sensitivity was 75.7%, the specificity was 72.2%, the PPV was 90.7%, and the NPV was 76.3% with a $p<0.0001$. The minimal wall thickness of our cases (6 mm) was ultimately proven to be due to gastric wall adenocarcinoma. Thus, any wall thickening with negative endoscopic biopsies should be followed by EUS-FNA, especially in the presence of suspicious clinical or endoscopic findings.

Endosonographic characteristics of the lesion suggestive of a high risk of malignancy, such as lesions with heterogeneous echo-pattern and involvement of the deep muscularis propria layer (the 4th layer), were found to be strongly correlated with the final diagnosis with a sensitivity of 94.4%, a specificity of 65%, a PPV of 90.7%, and an NPV of 45.1% with a $p<0.0001$. This correlation was confirmed by many previous studies (11,12). False-negative cases that were encountered in this study (four cases) could be explained by the homogenous appearance of some lymphomas and cases with early adenocarcinoma that were limited to the innermost three layers and sparing the deeper muscularis propria layer. The false-positive cases (seven cases) could be explained by the involvement of the 4th layer (muscularis propria) by benign lesions such as hypertrophic pyloric stenosis, achalasia of the cardia, and eosinophilic gastroenteritis.

Taking into consideration that EUS diagnostic features are operator dependent, this emphasizes the importance of an efficient and well-trained endosonographer who can obtain an accurate diagnosis (9,12).

This study showed promising results for EUS-FNA in the biopsy negative diffuse gastrointestinal lesions with a very high PPV reaching 100%, an NPV of 61.98%, a sensitivity of 83%, and a specificity of 100% with a $p<0.0001$. Our current results go hand in hand with many previous studies (12-15).

In a study of 265 patients with gastrointestinal tract malignancies, Zargar et al. (13) found significantly higher diagnostic accuracy of EUS-FNA (94%) compared to endoscopic mucosal forceps biopsy (87%), and this was particularly true in the case of submucosal lesions and infiltrative malignancies. Furthermore, they found that EUS-FNA was diagnostic in 21 of 24 lesions that were negative on both brush cytology and mucosal forceps biopsy. This study and others concluded that EUS-FNA should be the diagnostic procedure of choice when standard methods, such as endoscopic mucosal forceps biopsy, fail to provide a definitive diagnosis (16-19).

In conclusion, our observations suggest that EUS-FNA is a very accurate and less invasive procedure with favorable sensitivity and specificity in the diagnosis of endoscopic biopsy-negative diffuse gastrointestinal lesions appearing as exaggerated gastric folds or as flat or circumferential lesions.

Ethics Committee Approval: Ethics committee approval was received for this study from Cairo University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.O.; Design - H.O., S.E., Supervision - H.O.; Resource - H.O., S.E.; Materials - H.O.; Data Collection and/or Processing - S.E., A.A.E.; Analysis and/or Interpretation - S.E.; Literature Search - M.S., R.E.M.; Writing - M.S., R.E.M.; Critical Reviews - E.E.G.

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