

[ORIGINAL ARTICLE]

Multiple White and Flat Elevated Lesions Observed in the Stomach: A Prospective Study of Clinical Characteristics and Risk Factors

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Abstract:

Objective Multiple white and flat elevated lesions (MWFLs) observed in the stomach have only been presented in abstracts at academic conferences over the last decade; therefore, relatively little is known about these lesions. Our aim was to prospectively clarify the clinical characteristics of MWFLs, to identify their risk factors and to retrospectively evaluate the clinical progression of these lesions.

Methods A prospective analysis of clinical characteristics and risk factors was conducted in participants who underwent esophagogastroduodenoscopic screening at our hospital. A retrospective analysis of the medical chart of patients identified as having MWFLs was conducted to describe the clinical progression of these lesions.

Results The prevalence rate of MWFLs was 10.4% (80/767), with the following risk factors identified on a logistic regression analysis: use of proton pump inhibitors [odds ratio (OR), 3.51; 95% confidence interval (CI), 1.92-6.43], female sex (OR, 1.92; 95% CI, 1.19-3.12) and a 1-year increase in age (OR, 1.05; 95% CI, 1.02-1.08). Among the 70 cases with MWFLs observed over a mean duration of 2.3 years, no progression of MWFLs was detected in 67 cases (96%). Among the 3 remaining cases, progression was mild, with none of the lesions progressing to malignancy.

Conclusion The use of proton pump inhibitors (PPIs), female sex, and age are risk factors for MWFLs. We believe that endoscopists should recognize these lesions.

Key words: esophagogastroduodenoscopy, multiple white and flat elevated lesions

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Introduction

Multiple white and flat elevated lesions (MWFLs) observed in the stomach were first reported by Kawaguchi et al. in 2007, with multiple cases subsequently described by Haruma et al. (1-3) Although these lesions are also known as Haruma and Kawaguchi lesions, they are classified as MWFLs according to the Kyoto classification of gastritis and are different from intestinal metaplasia and adenoma (4).

MWFLs are pathologically characterized by a hyperplasia of the foveolar epithelium, in which inflammatory cell infiltration is extremely low (1-5). Although the mechanism un-

derlying the development of MWFLs is unknown, an association with hypergastrinemia has been speculated (2, 3, 5). With regard to risk factors, it has been observed that many patients with MWFLs use proton pump inhibitors (PPIs) (1-3, 5, 6). However, the prevalence rate of MWFLs among PPI users has not been confirmed. Thus, the risk factors of MWFLs are still not well understood. In addition, the clinical course of MWFLs is unknown.

Therefore, our aim in this study was to prospectively clarify the clinical characteristics and risk factors of MWFLs. The secondary objective was to retrospectively analyze the progression of MWFLs.

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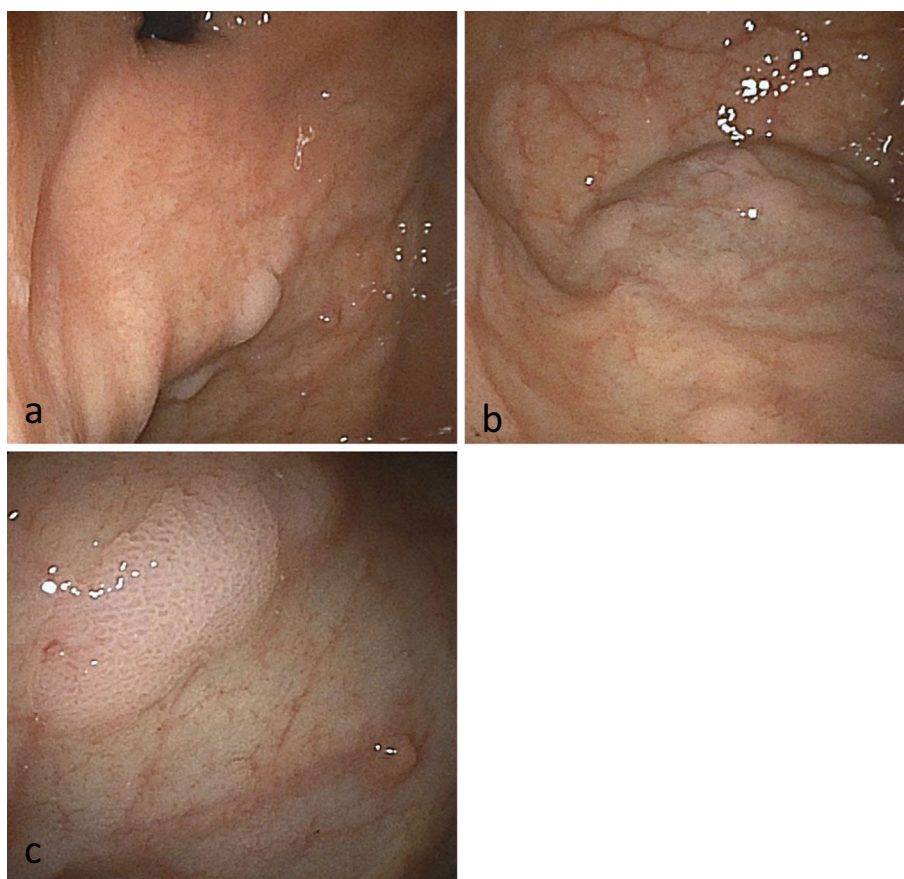


Figure 1. Typical multiple white and flat elevated lesions (MWFLs). MWFLs were identified in the fornix (a-c). The mucosal pattern is visible in (c).

Materials and Methods

Study method and participants

The clinical characteristics and risk factors for MWFLs were prospectively investigated in consecutive participants who underwent esophagogastroduodenoscopic screening by a single endoscopist at the health screening center of Kameda Medical Center, between August 2013 and October 2014. Participants in whom the history of *Helicobacter pylori* (*H.pylori*) eradication and prescription use could not be confirmed were excluded. Participants with a history of gastrectomy were also excluded. For participants who had undergone screening more than once during the research period, only the data from the last screening were used in the analysis. The present study was approved by the Institutional Review Board at the Kameda Medical Center.

Screening procedures

All screening procedures were performed using an EG-580 NW, EG-590 WR (FUJIFILM, Tokyo, Japan) or a GIF-PQ 260 (Olympus, Tokyo, Japan) endoscope, without magnification. The endoscopist performing the screenings had more than 5 years of continual endoscopic experience, with about 5,000 esophagogastroduodenoscopy examinations per-

formed.

The following features were deemed to be characteristic of MWFLs for the diagnosis: whitish and flat elevated lesions, usually observed in the upper part of the stomach, and occasionally in the middle part, with a tubular or round mucosal pattern visible on close inspection; and a clear margin observable for large lesions (Fig. 1). For diminutive lesions, non-magnified image enhancement, using either flexible spectral imaging color enhancement (FICE) or narrow-band imaging (NBI), improved the visibility of the margin and of the mucosal pattern (Fig. 2). Although the term ‘multiple’ is included in the name of these lesions, the number of lesions identified was not included in the diagnostic definition, as some cases do not have multiple lesions. As MWFLs are frequently overlooked, we performed a careful examination with white light, and if a lesion was suspected, image enhancement (FICE or NBI) was performed.

Outcomes and statistical analyses

To evaluate the clinical characteristics, we compared the following demographic and background clinical factors between participants with and without MWFLs: age, sex, *H. pylori* infection status (three groups: no infection, current infection, previous infection), use of PPI, and the degree of gastric mucosal atrophy (Kimura-Takemoto classification). The status of *H. pylori* infection was determined from endo-

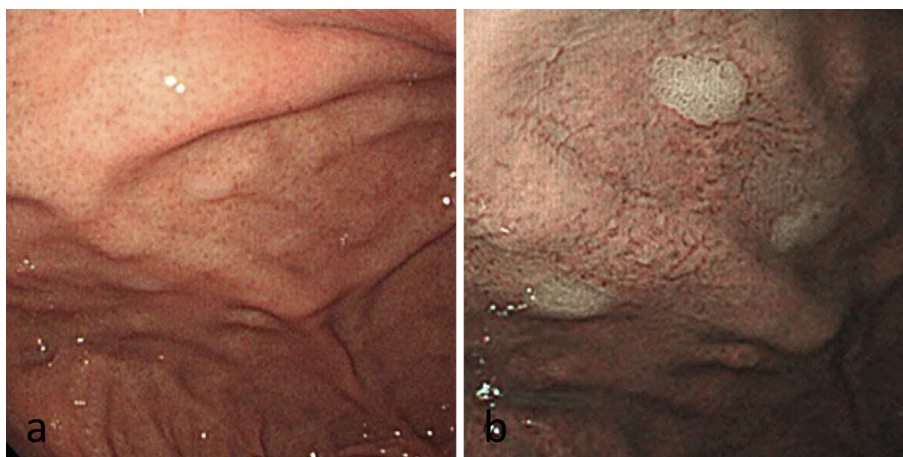


Figure 2. Diminutive multiple white and flat elevated lesions (MWFLs), which are difficult to differentiate, become more visible using narrow-band imaging.

scopic findings and from patient interviews regarding their history of *H. pylori* eradication, carried out by the endoscopist. Between-group differences in measured variables were evaluated using Fisher's exact test and Student's *t*-test, as appropriate for the dataset.

We also calculated the prevalence of MWFLs and the associated 95% confidence interval (CI) for overall lesions, multiple lesions (≥ 5 lesions; Fig. 1), and a few lesions (< 5 lesions; Fig. 2). These prevalence rates (and their associated 95% CIs) were calculated separately by sex, age, *H. pylori* infection status, use of PPI, and degree of gastric mucosal atrophy. Between-group differences in the prevalence of MWFLs for each measured variable were evaluated using Fisher's exact test. A Bonferroni correction was applied for comparisons between ≥ 3 groups. The effect of age on the prevalence of MWFLs was evaluated using a Cochran-Armitage test for trend. A logistic regression analysis was used to identify risk factors for MWFLs, controlling for the following explanatory variables: age, sex, *H. pylori* infection status, and use of PPI.

All statistical analyses were performed using EZR (ver 1.27; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A *p* value < 0.05 was considered to be statistically significant.

Secondary retrospective study

In patients with identified MWFLs, the progression of the lesions was retrospectively evaluated through a review of esophagogastroduodenoscopic findings in their medical chart, with an end date of April 2017. Progression of MWFLs was defined by an obvious increase in the size of the lesion and/or an increase in the number of lesions. In addition, we also analyzed the change in MWFLs among patients in whom PPI administration was discontinued.

Results

A total of 767 participants met our eligibility criteria. The relevant demographic and clinical variables between patients with and without MWFLs are shown in Table 1, with significant between-group differences in the distribution of sex, age, and use of PPI. The overall prevalence rate of MWFLs in our study group was 10.4% (80/767), with a prevalence rate of multiple lesions of 2.7% (21/767) and a rate of a few lesions of 7.7% (59/767) (Table 2). The prevalence rate of MWFLs, and the associated 95% CI, calculated by sex, *H. pylori* infection status, use of PPI, and degree of gastric mucosal atrophy, is shown in Table 2. The prevalence of MWFLs was higher among females than males ($p=0.04$) and increased with age (Fig. 3, *p* for trend < 0.001). No effect of *H. pylori* infection status was identified, with the prevalence rate being low in the currently infected group but with no significant difference between the three groups ($p=0.20$). The prevalence of MWFLs was significantly greater among PPI users than non-users ($p<0.001$). The degree of gastric mucosal atrophy was comparable among the 4 groups ($p=0.47$).

The results of our logistic regression analysis are summarized in Table 3. The following independent risk factors for MWFLs were identified: use of PPI [odds ratio (OR), 3.51; 95% CI, 1.92-6.43], female sex (OR, 1.92; 95% CI, 1.19-3.12), and a 1-year increase in age (OR, 1.05; 95% CI, 1.02-1.08). Although current *H. pylori* infection was not retained as a significant risk factor, it did exert a suppressive effect on MWFLs (OR, 0.40; 95% CI, 0.16-1.03, $p=0.058$).

In our retrospective analysis of the medical course of the 70 patients with MWFLs over a mean duration of observation of 2.3 years (minimum, 1.0 year; maximum, 3.1 years), MWFLs did not progress in 67 cases (96%), with the progression being mild in the 3 remaining cases; no cases of marked progression nor of progression to malignancy were noted. Two of the three patients with mild progression were

Table 1. Comparison of Demographic and Clinical Background between Patients *with* and *without* MWFLs.

Characteristics	Total	MWFLs		p value
		Present	Absent	
Numbers	767	80	687	
Sex-number. (%)				
male	440 (57)	37 (46)	403 (59)	p=0.042
Age-years				
mean (SD)	60 (10)	64 (9)	60 (10)	<0.001
Estimated <i>H. pylori</i> infection status-number. (%)				p=0.20
no infection	360 (47)	36 (45)	324 (47)	
current infection	99 (13)	6 (7.5)	93 (14)	
previous infection	308 (40)	38 (48)	270 (39)	
use of PPI-number. (%)				<0.001
PPI	76 (10)	20 (25)	56 (8.2)	
no use	691 (90)	60 (75)	631 (92)	
Kimura-Takemoto classification (degree of gastric mucosal atrophy)-number. (%)				p=0.47
no atrophy	335 (44)	31 (39)	304 (44)	
C1-C2 (mild atrophy)	139 (18)	12 (15)	127 (18)	
C3-O1 (moderate atrophy)	171 (22)	22 (28)	149 (22)	
O2-O3 (severe atrophy)	122 (16)	15 (19)	107 (16)	

MWFLs: multiple white and flat elevated lesions

PPI: proton pump inhibitor

Table 2. The Prevalence of MWFLs and the 95% Confidence Interval of the Prevalence.

	The prevalence % (number)	95% confidence interval
Overall	10.4 (80/767)	8.4-12.8
multiple lesions	2.7 (21/767)	1.7-4.2
a few lesions	7.7 (59/767)	5.9-9.8
Sex		
male	8.4 (37/440)	6.0-11.4
female	13.1 (43/327)	9.7-17.3
Estimated <i>H. pylori</i> infection status		
no infection	10.0 (36/360)	7.1-13.6
current infection	6.1 (6/99)	2.3-12.7
previous infection	12.3 (38/308)	8.9-16.5
use of PPI		
PPI	26.3 (20/76)	16.9-37.7
no use	8.7 (58/669)	6.6-11.1
Kimura-Takemoto classification (degree of gastric mucosal atrophy)		
no atrophy	9.3 (31/335)	6.4-12.9
C1-C2 (mild atrophy)	8.6 (12/139)	4.5-14.6
C3-O1 (moderate atrophy)	12.9 (22/171)	8.2-18.8
O2-O3 (severe atrophy)	12.3 (15/122)	7.0-19.5

MWFLs: multiple white and flat elevated lesions

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patients in whom PPI administration was initiated during the period (Fig. 4), while the third patient was using a PPI over the period from the initial to the follow-up endoscopies.

In our retrospective analysis, a total of 54 patients with MWFLs were not using PPIs at the time of the first endoscopy. Of these, 52 patients with MWFLs were able to confirm whether they had used PPIs during the follow-up period. Only 6 patients reported that they had started PPI treatment; the remaining 46 patients reported that they had not. Of the 6 patients for whom PPI treatment was initiated, a

mild progression was observed in 2 (2/6, 33%). No progression was observed among those who did not start PPI treatment (0/46; $p=0.01$, Fisher's exact test).

The change in MWFLs after PPI discontinuation could only be evaluated in two patients in whom PPI use was discontinued during the period of observation. No change in MWFLs were observable on an assessment of the images for these two patients.

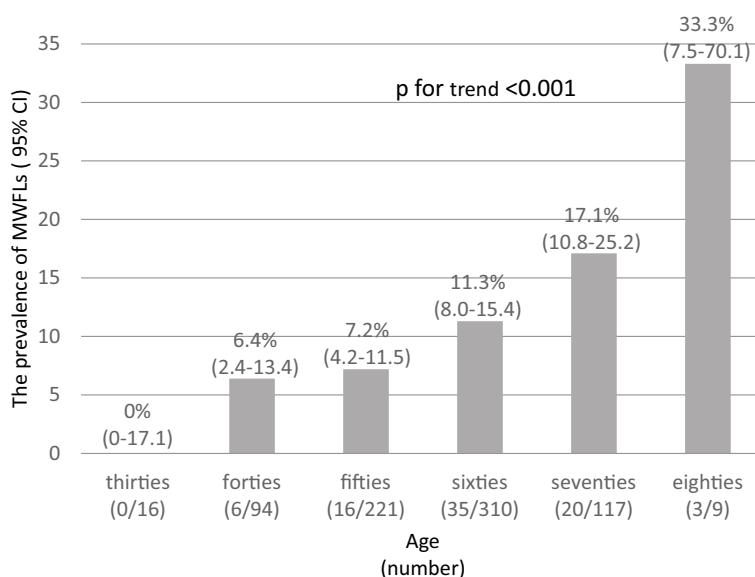


Figure 3. Increase in the prevalence (95% confidence interval) of multiple white and flat elevated lesions (MWFLs) as a function of increasing age.

Table 3. Risk Factors for MWFLs Identified by Logistic Regression Analysis.

	odds ratio	95%CI	p value
Sex (female)	1.92	1.19-3.12	0.008
Aging (+1)	1.05	1.02-1.08	0.001
no <i>H. pylori</i> infection	1	-	-
current infection	0.40	0.16-1.03	0.058
previous infection	1.08	0.65-1.80	0.77
use of PPI	3.51	1.92-6.43	<0.001

MWFLs: multiple white and flat elevated lesions

PPI: proton pump inhibitor

Discussion

We identified the use of PPI, a female sex, and age as independent risk factors for MWFLs, with current *H. pylori* infection exerting a suppressive effect on MWFLs. Our findings are in agreement with those of Murao et al., who reported that 71.8% of patients with MWFLs were PPI or H2 blocker users (5). In addition, there was no significant increase in the prevalence of MWFL among H2 blocker users in our study (data not shown). Maruyama et al. reported a clearer observation of MWFLs after *H. pylori* eradication than before it (7). We similarly identified a low trend in the prevalence of MWFLs among patients with a current *H. pylori* infection, with the rate of MWFLs being higher among patients with a previous *H. pylori* infection. Oono et al. also reported a 4:15 male:female prevalence of MWFLs (6), with our findings of a higher prevalence among women than men supporting this finding. A novel finding of our study was the increased prevalence of MWFLs as a function of increasing age. These findings suggest that the prevalence of MWFLs may increase with the increased use of PPIs, even

in countries where the population is continuing to age and/or *H. pylori* eradication has increased. Therefore, we believe that endoscopists should recognize these lesions.

Our prevalence rate of 10.4% was higher than the 1.2% prevalence previously reported (6). Differences in the demographic and clinical characteristics of the study populations, as well as differences in methodology, may have contributed to the differences in the prevalence rate. At our institution, we pursue the aggressive eradication of *H. pylori* infection, and many individuals undergo repeated esophagogastroduodenoscopic screening. Therefore, few of our patients were likely to have a current *H. pylori* infection, which exerts a suppressive effect on MWFLs. This might explain our high prevalence rate of MWFLs. Our use of close inspection or image enhancement to identify diminutive MWFLs may also explain our high prevalence rate of MWFLs. As these diminutive lesions are difficult to identify, they may not have been detected in the previous retrospective study. The prospective design of our study enabled us to better detect these diminutive lesions.

Although the mechanism underlying the development of MWFLs has not been elucidated, the possibility of an association with gastrin has been reported. In a previous study, hypergastrinemia was reported in 32% of patients with MWFLs (3, 5). Furthermore, among patients treated with PPIs, the gastrin levels were significantly higher in patients with MWFL than in those without MWFLs (2). Since it has been reported that PPI administration increases the gastrin level (8) and that gastrin exerts an epithelial mucosal cell proliferation effect (9), there is a possibility that PPIs may facilitate the development of MWFLs via an effect on gastrin. Since the gastrin level increases with age (10), the increase in MWFLs due to aging in the present study may be in response to the effect of gastrin. However, it is known that gastrin levels are lower in women than men (10); there-

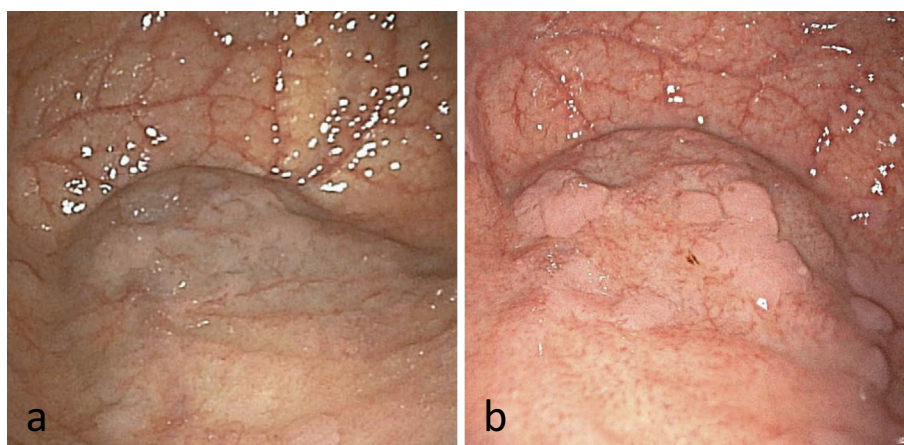


Figure 4. The most impressive case of mild progression in a patient in whom PPI treatment was initiated during the period of observation. From the first endoscopic image (a) to the follow-up endoscopic image (b), an increase in the thickness of the lesion was observable.

fore, factors other than gastrin must account for the increased prevalence of MWFLs in women compared with men. Given the low prevalence of MWFLs in patients with current *H. pylori* infection, it is possible that these lesions are more likely to develop in normal mucosa. Estrogen, as a sex-specific hormone in women, decreases gastric acid secretion (11) and has a protective effect on the mucosa (12). It is therefore possible that the lower risk of damage to the gastric mucosa in women than in men might increase the likelihood of MWFLs developing in women.

In our retrospective analysis of the medical course of MWFLs, we did not identify any cases of aggressive progression of the lesions, with none of the lesions progressing to malignancy. The use of PPIs has previously been associated with an increased prevalence of gastric fundic gland polyps (13), with some of these polyps growing extremely large (14). However, in our study, although the use of PPIs increased the prevalence of MWFLs, we did not identify any cases in which the lesions grew extremely large by the effect of PPIs. This absence of a marked progression in size and number of lesions, with no progression to malignancy, underlines the good clinical prognosis that can be expected for MWFLs. In addition, there were a significantly greater number of cases of mild progression in patients who initiated PPI than in those who did not. However, it is important to recognize that our follow-up period was relatively short and that our study group was limited in size. Therefore, a further evaluation of the prognosis of MWFLs is needed. Regarding the effect of PPI discontinuation, the MWFLs was unchanged, but this result is based on only a few cases and a retrospective judgment of non-close images of the lesions.

Several limitations associated with the present study warrant mention. First, we did not conduct a pathological assessment of MWFLs. These lesions are clinically diagnosed based on a characteristic distribution of lesions and a distinctive mucosal pattern, but the possibility of contamination with only a few other lesions cannot be denied. Second, we

did not perform standardized testing for *H. pylori* infection, with the infection status being based on endoscopic findings and interviews. Recent evidence supports the diagnosis of *H. pylori* infection based on an endoscopic examination (15). However, the differentiation of current infection from previous *H. pylori* infection is difficult by endoscopic imaging alone (16). Given that the endoscopist who conducted the screenings in our study was accustomed to making endoscopic diagnoses of *H. pylori* infection and performed a detailed interview of patients regarding their history of *H. pylori* eradication, we are confident in our estimation of the *H. pylori* infection status. Third, we did not clarify the duration, dosage, or type of PPI used. Therefore, we were unable to determine whether or not the risk for MWFLs increased as a function of an increased duration of PPI use and could not evaluate possible dose- and type-specific effects. Fourth, this study was conducted to investigate the examination performed by a single endoscopist at single center. In the future, it would be desirable to conduct the investigation at multiple centers. The strength of our study lies in our careful prospective evaluation of MWFLs, including diminutive lesions that are often overlooked or ignored. Based on our findings, future research on MWFLs is warranted to more clearly determine the clinical course over long-term follow-up.

In summary, we performed a prospective study to investigate the clinical characteristics and risk factors of MWFLs. We identified the use of PPIs, female sex, and age as risk factors. We believe that endoscopists should recognize these lesions.

The authors state that they have no Conflict of Interest (COI).

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