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Name of Journal: *World Journal of Gastrointestinal Endoscopy*

ESPS Manuscript NO: 25734

Manuscript Type: ORIGINAL ARTICLE

RESPONSE TO REVIEWERS

Name of journal: World Journal of Gastrointestinal Endoscopy

ESPS manuscript NO: 25734

Title: Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection

First of all we would like to thank the Editor and the reviewers for their fruitful comments and suggestions. We attempted to answer all comments and add the correspondent alteration to the manuscript text. Please see bellow all answers concerning each reviewer observations.

1- Reviewer's code: 00502831

COMMENTS TO AUTHORS

The authors described a series of cases with aberrant polypoid nodular scar (PNS) developed after gastric ESD. The authors concluded that PNS should be viewed as a benign alteration that does not require any type of intervention, other than endoscopic surveillance. This study is interesting and is the first report about a series of cases with PNS. But I have some questions as bellow. #1. Why were there many of PNS on the antrum of the stomach? #2. There was lack of findings of submucosal component of PNS in this article. So the authors should present the histology or ultrasonic endoscopic findings of PNS. #3. Are there same phenomenon such as PNS after EMR? #4. How is the relationship between H. pylori and PNS? #5. What is the point of differential diagnosis between submucosal recurrence and PNS? #6 What is the feature of patients with PNS after ESD except for antrum?

RESPONSE

#1. Why were there many of PNS on the antrum of the stomach?

This is a very important observation and unique aspect of this entity. In our series PNS occurred only after ESD performed for antral (including incisure) lesions. We did not notice PNS after ESD in the body, fundus or cardia. Likewise we did not observe this finding after esophageal or colorectal ESD. The reason for this phenomenon is unclear. We postulate that the frequent gastric peristalsis may enhance development of PNS in the antrum. Moreover, submucosa layer in the antrum is thicker than the other part of

the stomach; therefore inflammatory or regenerative reaction in the submucosa can be more obvious and cause more elevation in the antrum than in the corpus or fundus. We added this hypothesis to the Discussion (4th paragraph).

#2. There was lack of findings of submucosal component of PNS in this article. So the authors should present the histology or ultrasonic endoscopic findings of PNS.

Thank you for this interesting comment. We have not performed ESD/EMR for PNS so we could only provide histological image of biopsy samples. Biopsies were taken from the nodular part of the scar and histological assessment showed a similar pattern in all cases characterized by hyperplastic regenerative mucosa on the fibrotic tissue in the submucosa, without any signs residual or recurrent dysplasia or tumor. Moreover, we have not performed EUS for cases with PNS in this study, since we do not associate PNS to SM invasion. Most likely EUS will be unhelpful to clinical management, just showing hypoechoic tissue growth in mucosa and submucosa. Our solid conviction about benign behavior of PNS is based on a curative endoscopic resection confirmed after histological assessment of the specimen as described in the manuscript, as well as the follow-up of our cases, some of them are 3 years follow-up currently (illustrative case - Figure 2). In old days, some patients with PNS after peptic ulcer received surgical resection because it was not possible to rule out malignancy (Reference number 10 Ito, et al.). Histological finding of the surgical specimen of PNS at ulcer scar was consistent with our biopsy findings: hyperplastic regenerative mucosa on the fibrotic tissue in the submucosa. We suspect (and mentioned it in Discussion) that endoscopists around the world, unfamiliar with this entity, could be indicating unnecessary EMR or ESD to manage PNS. We added this comment about histology to Results (1st paragraph).

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#3. Is there same phenomenon such as PNS after EMR?

We did not look specifically at our data from patients that underwent EMR. In our old experience, PNS was observed after EMR as well (unpublished observation). EMR currently is performed seldom in both centers, only for small and benign lesions under 10 mm. As we described in Discussion, PNS may occur after healing of peptic ulcers, therefore it is fair to assume that it may occur after EMR. We added this comment to Discussion (paragraph 4).

#4. How is the relationship between H. pylori and PNS?

Thank you for bringing this important aspect to our attention. We did not compare the incidence between H. pylori negative and positive patients. We searched the H pylori status of all patients included in this series. A total of 8 patients were H pylori positive and 6 were negative. Positive patients underwent eradication therapy before or after ESD. We added Hp status to Table 1. We suspect there is no association between development of PNS and H. pylori infection. We added data to Results and also to Discussion (paragraph 4)

#5. What is the point of differential diagnosis between submucosal recurrence and PNS?

Because PNS is composed of granulation tissue or regenerative mucosa, surface structure is irregular, whereas surface of the submucosal recurrence tends to be smooth because it is covered with normal gastric mucosa. We postulate that dye based (chromoendoscopy)

or equipment based (NBI or FICE) image enhanced endoscopy facilitates the differential diagnosis. We added this comment to Discussion 5th Paragraph.

#6 What is the feature of patients with PNS after ESD except for antrum?

In our experience, we have noticed PNS only for lesions in the antrum.

2- Reviewer's code: 00045997

COMMENTS TO AUTHORS

In this retrospective study, Arantes and colleagues assessed clinical relevance of aberrant polypoid nodule scar, a novel finding in the gastrointestinal region, after endoscopic submucosal dissection. Although this study has been well conducted in Japan and Brazil, major revision of manuscript is needed before it can be accepted for publication. The authors should clarify/correct the points listed below.

Major

1. As for incidence of PNS, there is a big difference between the two centers (13.3% and 1.7%). Authors should discuss why this happened.

Center 1 (Brazil) presented 8 cases out of 60 cases. In this center 37 lesions were located in the antrum and 23 were located in the corpus/fundus/cardia. Center 2 (Japan) presented 6 cases out of 343. In this center lesions were located more in the corpus (n=185) than in the antrum (n=158). There was also a difference in ESD knives, setting of electrosurgical unit and operators. Moreover, because this was a retrospective study, the incidence may be underestimated because of unavailability of the endoscopic images. A prospective large-scale multicenter study enrolling multiple ESD centers is needed to assess the true incidence of PNS. We plan to start this study in the near future. We added this data to Results, including Table 1 and also to Discussion (paragraph 6).

2. Authors described that PNS frequently occurred in the antrum rather than other parts in the stomach. They should show the incidence of PNS in each part individually and discuss why the antrum tends to harbor this lesion.

In first center, PNS occurred in 8 out of 37 (21%) antral lesions and 0 of 23 (0%) lesions in proximal stomach.

In the second center, PNS occurred in 6 of 158 (3.8%) antral lesions and 0 of 185 (0%) corpus lesions.

We added Table 1 with these data as requested.

The second comment: "reason why antrum tends to harbor the lesion": please refer to

response to reviewer 1, first comment.

3. Is there any relationship between incidence of PNS and tumor size which mean the size of resected area?

Table 2 demonstrates that there was a wide variation in the size of the lesions. It is noteworthy that two lesions were only 8 mm in size; therefore we suspect the location is more associated with development of PNS, not the size of the lesion. We added this comment to Discussion.

Minor 1. In Figure legends, numbering of Figure 2 is wrong.

This was corrected. Thank you for pointing out this error.

3 - Reviewer's code: 01467363

COMMENTS TO AUTHORS

I think it is appropriate to allow the reviewers to compare the contents of reference No. 4: "Arantes V, Uedo N, Pedrosa MS. Polypoid nodule scar after endoscopic submucosal dissection in the gastric antrum. Rev Gastroenterol Mex. In Press." before the final evaluation/decision of the article in WJGE

Thank you for your interest in our previous report. We added a copy of our case report as a supplemental file. We described this interesting finding, PNS, in this case and thereafter conducted case series to explore characteristic of PNS in a larger number of patients from two different centers. This case report is accepted for publication at Rev Gastroenterol Mex. We are expecting it to be published in the next couple of months. Please be aware that the images utilized in this report are from a different case than the images utilized in the case series.

4- Reviewer's code: 02445518

COMMENTS TO AUTHORS

The study : Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection From Arantes, is an interesting and particular study about the follow up of patients treated with ESD. It describes an aberrant scar condition that must be differentiated by recurrence and this can be considered a problematic suspect for the endoscopist. The study can be published after minor changes:

Authors may remove from results that all patients were submitted to esd procedure and en bloc R0 resection because this are the inclusion criteria just presented in methods.

We agree with the Reviewer. Thank you for pointing out redundant information. We removed the sentence from Results as suggested

Authors must add more information about their PNS. The different observed scar characteristics could be better described on a table and presented in relation to size, time of diagnosis from ESD and variations during follow up or information about eventual treatment.

The endoscopic and histological features of PNS are similar among all cases as you can notice on the images of the two illustrative cases included in the manuscript. In all cases PNS was already present in the first endoscopic control usually performed between 6 and 12 months of the ESD procedure. Currently we are observing this cases prospectively in order to assess changes in size or surface structure, but we still do not have firm data about it. No patient in this series received any endoscopic or surgical treatment, other then endoscopic annual surveillance. The information about lesion size, histological characteristics, *H. pylori* infection, medical therapy and number of years in follow-up was depicted in Table 2.

In discussion can be add eventual skills on how to differentiate PNS from other lesions.

Thank you for important observation. We think it could be difficult to differentiate neoplastic recurrence and PNS by endoscopic finding only because PNS is consisted of granulation tissue or regenerative mucosa, and surface structure and vasculature are as irregular as those of intramucosal carcinoma. Therefore, information of R0 resection at ESD is very important as well as histological assessment of biopsy samples. To distinguish PNS from submucosal recurrence would be easier because surface structure of PNS is irregular, but that of submucosal recurrence is regular because it is covered with normal gastric mucosa. It is possible that dye based (chromoendoscopy) or equipment based (NBI or FICE, etc.) image enhanced endoscopy facilitate differential diagnosis. Please refer to response number 5 to Reviewer 1 and please note comments added to Discussion paragraph 5

5- Reviewer's code: 01429208

COMMENTS TO AUTHORS

The author investigated cases with aberrant polypoid nodule after endoscopic submucosal dissection (ESD) in two academic institutions. However, ESD cases (60 vs. 343) and the prevalence of enrolled cases (13.3% vs. 1.7%) are a big difference in both institutions. That mean the difference in experience between the two institutions is one of important factors. Also, the prevalent lesion was antrum. The author didn't describe the distribution of location enrolled total ESD cases. In case of one center enrolled 8 cases, there's a possibility that all ESD cases are located in antrum. Therefore, this study has many confounding factors to generalize.

Thank you for your important comment. The lesion location was different between the two institutions and it might influence the incidence of PNS. Moreover, one institution used needle type knife for ESD and another institution used IT knife for ESD. Such

difference in devices or settings of electrosurgical unit may cause variation in incidence of PNS. Further large-scale prospective study may clarify pathogenesis and incidence of PNS.

Please refer to response to questions 1 and 2 from Reviewer 2. We added to results the total number of ESD cases as well as the specific incidence of PNS from each center (Table 1 was added with these data). We also added to Discussion comments about possible explanations for the difference in incidence of PNS between the 2 centers.