Polypoid Nodule Scar after Gastric Endoscopic Submucosal Dissection: Not So Uncommon after Resection of Neoplasms Located in the Antrum

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To the editor,

We read with great interest the study recently published in this Journal by Kim et al. [1], addressing the healing process of gastric mucosal defect after endoscopic submucosal dissection (ESD). The authors reported a single-center large series of 2,096 cases that underwent gastric ESD, with a polypoid nodule scar noted in 48 patients (2.7% incidence) over a total of 1,757 cases that underwent endoscopic follow-up. Univariate analysis demonstrated that the protruded-type scar was found more often in the antrum, anterior wall, and greater curvature ($p < 0.001$). Moreover, the occurrence of protruded-type scar presented a positive correlation with the absence of *Helicobacter pylori* infection, ESD specimens of small size, lower fibrosis in the submucosal layer, and less frequent need for hot biopsy or endoclipping during ESD. The authors concluded that the healing type of mucosal ulceration after ESD seemed to be influenced by the location, specimen size, and presence of *H. pylori* infection.

First of all, we would like to congratulate this group of researchers for conducting an interesting study over a large population that add some important clinical information concerning the healing process of gastric ESD procedures. Nevertheless, we cannot agree with this au-

thor's statement: "no study has investigated the mucosal healing type after ESD" [1]. Therefore, we would like to share with the authors and readers the main findings of our researches about this topic. For many years, our group has been interested in studying the healing process of ESD defect. After successful ESD, the endoscopist expects to find in follow-up a consolidated and homogeneous whitish scar, often with converging folds, which was named as "flat scar" by Kim et al. [1]. Interestingly, over time, we also have observed in our clinical practice the development of anomalous and bizarre postoperative scars with a relatively large and protruded polypoid nodular neoformation in a subset of patients after curative ESD, particularly for lesions located in the antrum. In 2016, we first described this entity and named this condition as polypoid nodule scar (PNS) [2]. In this same period, in order to better understand the incidence of this phenomenon, we reviewed retrospectively the occurrence of PNS in 2 ESD referral centers, one from Japan and the other from Brazil [3]. A total of 14 PNS cases were collected among 403 patients who underwent gastric ESD, with an incidence rate of 3.47%, similar to the incidence rate reported by Kim et al. [1]. Biopsy samples were always taken, and histological assessment revealed in all

cases regenerative and hyperplastic tissue, without recurrent tumor or dysplasia. All lesions were originally located in the distal stomach (antrum 13, angle 1). These patients were followed up on an annual basis, and no malignant recurrence in the ESD scar was identified (the mean follow-up duration was 45 months). We concluded that PNS was a benign condition, most likely related to an anomalous over-regeneration of epithelium that developed mainly in lesions located in the antrum. The reason why we defined this specific condition of post-ESD scar as PNS is because it obviates any clinical concern and interventions for recurrence when we find this endoscopic appearance in the scar. We determined the following criteria to characterize PNS and differentiate it from tumor recurrence: (1) successful en bloc ESD procedure with R0 and curative resection confirmed histologically; (2) post-operative endoscopic examination with identification of a polypoid nodule scar at the ESD site; and (3) biopsies of the PNS with hyperplastic or regenerative tissue, reviewed by an experienced gastrointestinal pathologist.

After these studies, we conducted a large multicenter study to validate the occurrence and clinical relevance of PNS, with the participation of 5 high-volume ESD centers [4]. We collected data from 2,275 patients who had undergone gastric ESD and endoscopic follow-up control. We encountered 28 patients (18 men and 10 women) who developed PNS. Looking at a larger population, the incidence rate of PNS dropped to 1.2%, and it ranged from 0.15 to 11.4% between centers. Likewise, all patients who developed PNS in this multicenter study had primary neoplastic lesions located in the distal stomach. When we extracted only operations performed in the distal stomach ($n = 912$), the incidence rate of PNS increased to 3.1%. After a mean follow-up of 43 months (range 6–192 months), no malignant recurrence was identified in this population. Of note, in 5 patients (17.8%), PNS disappeared after a mean of 18 months. Our observations allowed us to conclude that PNS occurs after ESD in the distal stomach in approximately 3% of patients, and although its appearance seems concerning, if all criteria utilized to characterize PNS are respected (particularly R0 and curative resection with biopsies negative for tumor cells), tumor recurrence appears to be highly unlikely, and PNS should be viewed as a benign alteration that does not require any type of intervention, other than endoscopic surveillance.

In our study, we attempted to correlate the learning curve and ESD experience with the occurrence of PNS, but this association was not confirmed. Different from the observations of Kim et al. [1], *H. pylori* infection did

not seem to be involved in PNS development in our multicenter study [4], as half of the patients were positive and the other half were negative. Likewise, the influence of proton pump inhibitors (PPIs) and acid antagonists on the appearance of PNS remains poorly understood. In our multicenter study, we attempted to investigate this correlation. However, we noticed that in all centers, PPI was routinely administered after ESD, although with some variation in the regimen and doses, as well as treatment duration and combination with other drugs such as sucralfate or rebamipide. PPI induces a potent gastric acid secretion inhibition by increasing cyclooxygenase-2 expression and prostaglandin E synthases, which may theoretically lead to the expression of several growth factors, ultimately stimulating an accelerated mucosal repair and overgrowth of regenerated mucosa. Notably, tumor size was not correlated with PNS in our multicenter study, as we encountered PNS after removal of tumors of different sizes, such as smaller than 10 mm or larger than 50 mm. In contrast to Kim et al.'s [1] findings, none of the 5 centers that participated in our study had encountered PNS after ESD in the proximal stomach, such as the body, fundus, or cardia. We were surprised that 12.5% of protruded-type scars documented by Kim et al. [1] occurred for lesions located in the gastric body. These findings differ substantially from ours, and it is important to check carefully if all criteria needed to characterize PNS were respected in those patients with lesions in the proximal stomach. It is noteworthy that 1 case of polypoid type scar among the 48 individuals in their series developed recurrent tumor (2.08%). In our view, this particular case may not fulfill all criteria to characterize PNS because although tumor resection was reported as complete, follow-up endoscopic biopsy revealed tumor recurrence and not hyperplastic or regenerative changes.

In conclusion, the study by Kim et al. [1] adds important scientific evidence for the occurrence of protruded and hypertrophic scars after ESD that may look concerning to the patient and family doctor. It confirms that such anomalous scars occur predominantly when ESD is carried out in antral lesions, and its incidence rate is not so negligible. Although the exact mechanism that leads to PNS formation remains to be elucidated, we speculate that gastric peristalsis and/or bile reflux or submucosal layer thickness in the antrum may enhance development of PNS. Other authors also interestingly postulated about a possible association between PNS and inflammatory fibroid polyps (Vanek's tumor) that typically occur in the antrum and are composed of non-neoplastic cellular proliferations including fibroblasts, blood vessels, and in-

inflammatory cells [5]. Despite the lack of understanding, it remains of paramount importance to clearly differentiate PNS from tumor recurrence, in order to avoid unnecessary redo ESD or salvage surgery.

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Author Contributions

Vitor Arantes: conception, design, data collection and/or processing, analysis and interpretation, literature review, and writing. Noriya Uedo: supervision and critical review.

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