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Managing esophageal strictures following endoscopic resection of superficial neoplastic lesions

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Esophagectomy has been the traditional treatment with curative intent of superficial neoplastic lesions of the esophagus. The high morbidity and mortality rates associated with surgery conditioned therapeutic decisions for these patients. The evolution and development of endoscopy has made it feasible to resect these lesions with three significant benefits: minimal invasion, reduced complications, and effective cancer treatment.

Endoscopic submucosal dissection (ESD) is ideal for en-bloc resection of larger superficial lesions of the esophagus. The European Society of Gastrointestinal Endoscopy (1) and the *Sociedad Española de Endoscopias Digestivas* (2) recommend ESD as first option for superficial squamous cell carcinoma of the esophagus and visible

lesions on Barrett's esophagus. This recommendation is based upon the en-bloc resection (83-100 %/81-100 %), complete resection (78-100 %/38.5-97 %), and local recurrence (0-2.6 %/0 %) rates obtained, respectively. Furthermore, complications during ESD are minor as compared to those of surgery, and most may be solved endoscopically.

Esophageal stricture risk from endoscopic resection is partly favored by the organ's small caliber. In different series, after ESD this risk goes up to 7-18 % (3), versus 5.4 % with esophagectomy (4). The resulting dysphagia reduces quality of life considerably, and patients require multiple endoscopic balloon dilation (EBD) sessions (5). Associated factors may increase this risk — mucosal or submucosal resections involving more than 75 % of the esophageal circumference (70-80 % of strictures), lesions larger than 3 cm, histologic depth (deep submucosal involvement), and perforations during ESD (6,7). In circumferential ESD strictures usually develop in 100 % of cases (8), with many of them being refractory to therapy.

Initial stricture treatment after ESD includes EBD with variable periodicity (radially expanding balloon in increments of 3 mm), a simple procedure that requires multiple sessions and entails an inevitable risk for perforation (1 % of patients) (9). No clear protocols are available in this respect but early dysphagia dictates dilation therapy onset or early endoscopy for patients undergoing wide resections. On the other hand, mechanisms are available that may prevent this complication: early EBD, fully covered metal stents, biodegradable stents, local steroid injections, polyglycolic acid sheets, autologous oral mucosal epithelial cell transplants, and systemic steroids (10,11). While the level of evidence is insufficient, therapy with steroids, primarily locally injected triamcinolone (a potent, long-acting glucocorticoid), is a most commonly used strategy for preventing esophageal stricture; after extensive resection, it reduces — and at times precludes — the need for EBD as a result of inflammation inhibition and reduced development of fibrous connective tissue. Hashimoto et al. (12) and Hanaoka et al. (13) showed that endoscopic injection with steroids had significantly reduced stricture rate (19.0 %, 4/21) versus a control group (75.0 %, 15/20), as well as the need for EBD (median: 1.7; rango: 0-15) versus a control group (median: 6.6; range: 0-20). In their prospective, randomized trial no injection-associated side effects or

complications arose, such as delayed perforation or mediastinal abscess. Short, fine (25G) needles are recommended for endoscopic injection in an attempt to reduce perforation risk at the ulcerated mucosa brought about by ESD (4). Triamcinolone is diluted in saline to a solution of 5 mg/mL, which is then uniformly injected into the residual submucosal tissue at the ulcer's bottom, in increments of 0.5 to 1.0 mL (20 to 40 punctures). Initial injections are placed in the ulcer margins; then linear injections are placed from the distal to the proximal side of the ulcer bed.

In complete circumferential resections systemic/oral steroids may provide more benefit than local treatment. Thus, Yamaguchi N et al. (14) used systemic steroids after ESD: prednisolone PO 30 mg every 24 hours starting on the second day, and gradual dose reduction until discontinuation. Stricture rate at 3 months was lower in the group with steroid therapy (5.2 %, 1/19) than in the group receiving dilation alone (31.8 %, 7/22). The average number of EBD sessions required was 15.6 in the control group and 1.7 in the oral steroids group; furthermore, 32.7 (20-48) dilation sessions on average were required in the control group whereas the group with steroid therapy required significantly fewer sessions: 0.7 (0-2).

In the study by Hanaoka et al., refractory strictures were associated with a number of factors including circumferential ESD (91 %, 11/12), ESD involving more than 75 % of the luminal circumference (31 %, 18/58), and use of ESD at the upper or cervical esophagus (likely associated with luminal diameter in the upper esophagus) (15).

Management of dilation-refractory strictures represents an endoscopic challenge (16). Today, placement of self-expandable covered metal stents is most widely used for treatment. Ham et al. (17) published a systematic review of 172 patients with refractory strictures with a technical success rate of 98 %, a clinical success rate of 45 %, and an early migration rate of 31 % (a major drawback requiring reintervention). Biodegradable esophageal stents represent another treatment option. In studies, efficacy is temporary for most patients, who will require newer stents to remain free of dysphagia. Also, their use has been associated with substantial complications such as retrosternal pain and vomiting (18). Incisional therapy is another procedure used for refractory strictures that has proven effective: cuts are made with a needle-knife, followed by EBD. Muto et al. (19), in their study, reported significantly higher response

rates versus EBD at 6 months (65.3 % *vs*. 19.8 %, p < 0.005) and 12 months (61.5 % *vs*. 19.8 %, p < 0.005) of follow-up, with no serious adverse events in any of their subjects. Interestingly, Gallego et al. (20) recently reported a similar case in this journal. In cases refractory to these treatments, surgery usually represents the only feasible option despite a high rate of complications.

In this issue of *Revista Española de Enfermedades Digestivas* (REED), Pérez-Cuadrado Robles et al. (21) discuss the risk factors for symptomatic strictures following endoscopic esophageal resections with ESD. They report a retrospective study in a large, consecutive series of patients. Lesions on Barrett's esophagus predominate in the study with a mean size of 50 mm, and 95 % were resected en bloc. Lesions on Barrett's esophagus involving more than 75 % of the organ's circumference also predominate (58.6 %/32 %). Oral steroids were administered for prevention in cases of full circumferential resection. Local steroids were not systematically administered. A total of 83 (20.1 %) patients developed symptomatic strictures after ESD, and the clinical success rate of EBD was 84.7 %, with a refractory stricture rate of 15.3 % (high when compared to other series). Refractory stricture-associated risk factors found to be statistically significant included: ESD for proximal and for squamous esophageal lesions, recurring strictures, and complications during the procedure. Circumferential resections required a higher number of EBDs but were not associated with refractory strictures, in contrast with other studies, probably due to systematic oral steroid use after ESD, although such data were not analyzed.

The presence of symptomatic strictures and the need for dilation in patients undergoing endoscopic resection for large superficial lesions of the esophagus have increased and will continue to increase in the next few years as a consequence of the techniques performed at endoscopy units. We must be prepared and analyze each lesion's characteristics and the treatments received in order to establish preventive measures. In this regard further studies and, desirably, newer techniques are required to reduce the rate of refractory strictures.

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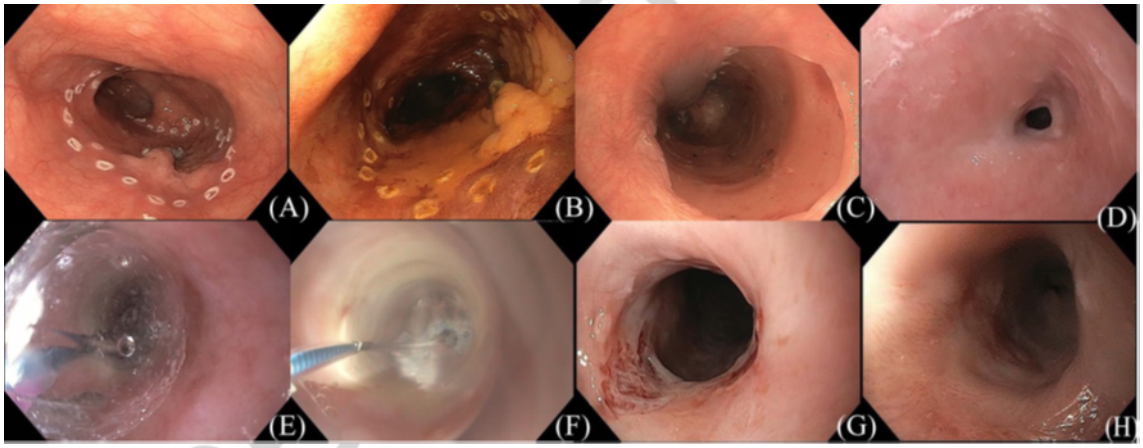

Fig. 1. Esophageal lesion treated with ESD where esophageal stricture subsequently developed, which required EBD (22).