A tiny lesion arising within Barrett's esophagus

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CLINICAL CHALLENGE

A 72-year-old man underwent an esophagogastroduodenoscopy (EGD) for dyspepsia. His medical history was unremarkable and negative for cigarette or alcohol consumption, and he denied reflux-specific symptoms. Esophagoscopy showed a 16-cm long segment of flat salmon-colored mucosa, which raised suspicion for Barrett's esophagus (Prague class C14 M16). The *Z*-line and the esophagogastric junction were located at 26 cm and 42 cm from the incisor teeth, respectively. A 4-mm large, slightly elevated mucosal abnormality, 0-IIa in Paris classification, was identified at 34 cm from the incisors (Figure 1), and targeted biopsies were performed on that lesion, revealing a localization of mucin-producing carcinoma. Histological examination of random biopsies of the surrounding salmon-colored mucosa showed columnar epithelium with immune phenotype of gastric metaplasia mixed with complete intestinal metaplasia, with low-grade dysplasia.

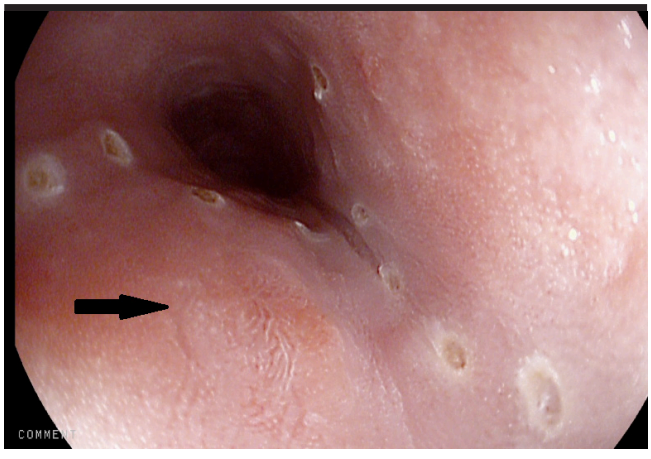

Figure 1. A 4mm large, slightly elevated mucosal abnormality, 0-IIa in Paris classification in a patient with ultra-long segment Barrett's esophagus.

Esophageal endoscopic ultrasound (EUS) excluded submucosal invasion, and thoracoabdominal computed tomography (CT) scan was negative for lymph node or distant metastases. The lesion was resected *en-bloc* by endoscopic submucosal dissection (ESD). An area of 18 × 14 mm diameter was gradually peeled off using a Dual knife (KD655Q, Olympus). No complications occurred during or after the procedure.

DIAGNOSIS

Pathological analysis showed a 4-mm large, poorly differentiated tumor infiltrating the lamina propria and consisting of mucin-secreting cells simultaneously immunoreactive to endocrine and exocrine markers, i.e., synaptophysin and cytokeratine CK 7 and CK AE1/AE3, with Ki67 70% (Figure 2). The final diagnosis was mixed neuroendocrine-non-neuroendocrine carcinoma (MiN-EN), amphicrine type, grade G3, pT1a; no lympho-vascular infiltration was seen. Excision margins were disease-free. At the three-month follow-up, EGD and a total body CT scan were both negative for neoplasia. Random biopsies from the esophageal salmon-colored mucosa confirmed the previous finding of columnar metaplasia (mixed gastric and complete intestinal phenotype) and low-grade dysplasia. Complete eradication of all remaining Barrett's epithelium was achieved by two sessions of radiofrequency ablation (Barrx™). Complete ablation was confirmed at 3 months by endoscopy with biopsies. The patient was followed for 18 months with endoscopy and CT scan, and no evidence of recurrent malignancy has been found.

Barrett's esophagus is a well-known premalignant condition of esophageal adenocarcinoma (1). Neoplasms with neuroendocrine differentiation arising from Barrett's mucosa are exceptional findings, and only two cases of mixed neuroendocrine non-neuroendocrine tumors have been reported in the available literature (2-5).

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MiNEN have been defined in 2017 by the World Health Organization as tumors in which a neuroendocrine component and a non-neuroendocrine component are present, accounting for at least 30% of the neoplasm (6). Previously termed mixed adenoneuroendocrine carcinomas (MANECs), MiNENs are very rare lesions of the gastrointestinal tract and can be morphologically classified into three entities: collision, composite, and amphicrine (7). Given the exceedingly low incidence of neuroendocrine neoplasms of the esophagus, little is known about their pathophysiology, clinical behavior, and management. To the best of our knowledge, a few cases of esophageal localization have been reported worldwide and only two cases have been described arising from Barrett's esophagus (4, 5, 8). One of them was removed endoscopically by ESD, whereas the other was treated by distal esophagectomy and proximal gastrectomy. Because of their extreme rareness and histologic heterogeneity, no clear recommendations can be made on optimal management strategies. Standard treatment for esophageal pure high-grade neuroendocrine tumors involves radical surgery; however, the prognosis of localized high-grade MiNENs is considered to be better than that of pure poorly differentiated neuroendocrine carcinomas (7). In our case, given the small dimension of the lesion and the need for a definitive histological diagnosis, an endoscopic excision was performed. Middle term follow-up showed no disease recurrence after ESD.

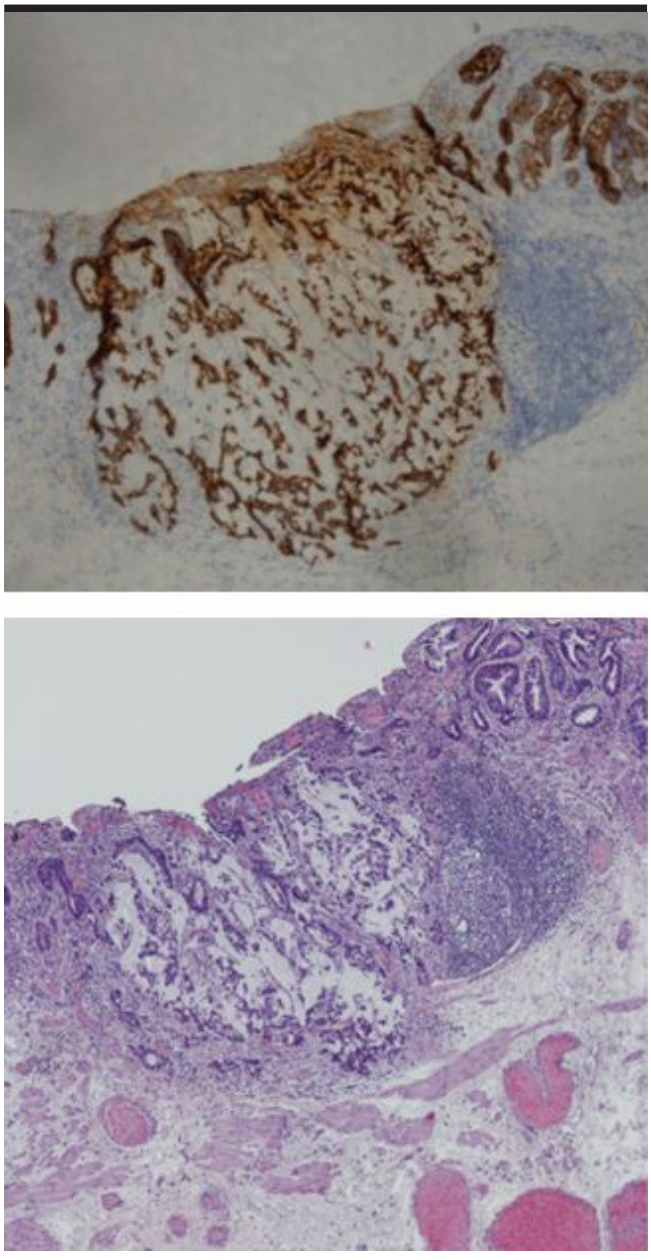

Figure 2. a, b. Histological features of mixed neuroendocrine-non-neuroendocrine carcinoma, amphicrine type. Immunohistochemistry staining showing co-expression of cytokeratine 7 (a, above) and synaptophysin (b, below) in the neoplastic cells.

Through this case, we aim to stress the importance of careful endoscopic evaluation in cases of ultra-long segment Barrett's esophagus. Moreover, we aim to present our management of such rare neoplasms given its early stage and small dimension. Nevertheless, as previously underlined, evidence on this topic is extremely scant, and further studies are needed to clarify the optimal treatment of MiNEN of the esophagus.

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

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