Inherited CDH1 pathogenic variant: is there a place for surveillance of esophageal gastric inlet patch?

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Introduction

Inherited CDH1 pathogenic variants cause Hereditary Diffuse Gastric Cancer (HDGC) syndrome, a disease with very poor prognosis.[1] Carriers of such variants present an estimated lifetime risk of gastric signet ring cell carcinoma (SRCC) of 70% in men and 56% in women, by the age of 80 years old.[2] Although risk reduction gastrectomy is the indicated procedure for disease prevention in pre-symptomatic mutation carriers, some carriers opt for delaying surgery and undergo regular endoscopic surveillance. When using a strict endoscopic surveillance protocol (focal visible lesion and random biopsy sampling), SRCC detection rate yield is approximately 60% in CDH1 mutation carriers.[3]

In this letter, we wish to call the attention to cervical esophageal gastric inlet patches (GIPs). GIPs are comprised of islands of heterotopic gastric columnar epithelium in the cervical esophagus and may represent a novel and unacknowledged target area for theoretical development of SRCC in CDH1 mutation carriers. GIPs have a reported endoscopic prevalence of 0.18–14.5%.[4] Interestingly, when very rarely esophageal adenocarcinomas occur in the proximal esophagus, they are associated with those GIPs.[5] For instance, Orosey *et al.* recently reported a case of SRCC occurring in the cervical esophagus from a GIP; however, germline CDH1 mutation testing was not mentioned in that study.[5]

In a recently published *CDH1* mutation carrier's series, GIPs were reported at upper GI endoscopy in 50% of the cases, all confirmed histologically.[6] When performing risk-reduction total gastrectomy in *CDH1* mutation carriers, the proximal resection line must be in the distal squamous esophagus to guarantee that all at-risk gastric tissue is removed.[7] It is also recommended to be confirmed in the intra-operative time (by frozen section or examination of the opened resection specimen), and can be guided by the use of on-table endoscopy to mark the squamo-columnar junction.[6,7]

Despite these precautions, we still leave in place gastric tissue at theoretical risk of cancerization in cervical esophagus of almost half patients.[6] Surprisingly, to the best of our knowledge, no GIP-related SRCC have been reported to date in CDH1 mutation carriers.

Even if endoscopic ablation of GIPs (by argon plasma coagulation or radio frequency ablation) has been reported as a safe and effective technique in benign indications,[8–10] there is currently insufficient evidence supporting systematic preventive endoscopic GIPs resection or ablation in *CDH1* mutation carriers.

Considering this, even if GIP's cancerization risk remains currently speculative for CDH1 mutation carriers, while waiting for more data and applying a precautionary principle concept, we advise that systematic GIPs screening be undertaken during upper GI endoscopy, as well as careful histological examination of GIP biopsies for gastric tissue confirmation and to exclude small foci of SRCC. In cases of histologically confirmed esophageal GIP, we discuss endoscopic surveillance of this ectopic

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gastric tissue, which may present a theoretically greater risk of SRCC development.

Conflict of interest statement

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