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Clinical Case Study

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Diagnosis of MALT Lymphoma from Surveillance Endoscopy of a Patient with a *CDH1* Gene Germline Mutation

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Keywords
CDH1 protein · Stomach neoplasms · *Helicobacter pylori* · Marginal zone B-cell lymphoma

Abstract
Carriers of the mutated *CDH1* gene have an increased risk of developing early-onset signet-ring cell (diffuse) gastric cancer. We present a case of a young patient with a confirmed mutation of the *CDH1* gene, who was diagnosed with a gastric marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma) from surveillance endoscopy. He underwent *Helicobacter pylori* eradication treatment and was subsequently submitted to a total prophylactic gastrectomy. The surgical specimen only revealed foci of signet-ring cell carcinoma (SRCC) in situ without lymphoma signs. We highlight here the occurrence of other pathology in high-risk patients as well as its possible influence on the decision to perform gastrectomy.

Diagnóstico de um linfoma MALT numa endoscopia de vigilância de um doente com mutação germinativa do gene CDH1

Palavras Chave
Proteína CDH1 humana · Neoplasia gástrica · Helicobacter pylori · Linfoma de células B da zona marginal

Resumo
A mutação do gene CDH1 determina um risco aumentado de desenvolvimento precoce de cancro gástrico de células em anel de sinete (tipo difuso). Apresentamos um caso de um doente jovem portador de uma mutação no gene CDH1 que foi diagnosticado com linfoma de MALT gástrico numa endoscopia de vigilância. O doente foi submetido a terapêutica de erradicação da *Helicobacter pylori* e subsequentemente realizou uma gastrectomia total profilática. A avaliação histológica da peça cirúrgica identificou focos de carcinoma in situ de células de anel em sinete, sem evidência de linfoma. O nosso objetivo é salientar a ocorrência de outras patologias em doentes de alto risco assim como a sua possível influência na decisão cirúrgica.

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Introduction

Mutations in the *CDH1* gene cause deregulation of the E-cadherin tumor-suppressing mechanism, thereby conferring a cumulative risk of developing signet-ring cell (diffuse) gastric cancer in carriers, of up to 70% by the age of 80 years and a mean age at diagnosis of 38 years [1]. Considering that patients often show multiple foci at an early age and the high mortality related to diffuse gastric cancer, prophylactic total gastrectomy (PTG) is recommended at a young age (20–30 years), regardless of endoscopic findings [2, 3].

In *CDH1* mutation carriers, an index high-quality endoscopy according to the Cambridge protocol [4], with additional targeted biopsies of any visible lesion, should be performed to search for macroscopic and microscopic tumors and exclude heterotopic gastric mucosa or others lesions that may alter the extent of the resection or therapeutic approach [5].

In those not fit for surgery (due to comorbidities) or who choose to postpone PTG, an annual high-quality surveillance endoscopy is advised to help the decision-making process if microscopic foci of signet-ring cells are detected [6].

Marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma) is the most common type of marginal zone lymphoma, representing 5–8% of all B-cell lymphomas. The gastrointestinal (GI) tract is frequently affected, particularly the stomach [7].

We report the case of a 23-year-old male with a known mutation of the *CDH1* gene, under a surveillance program for gastric cancer, who received a diagnosis of MALT lymphoma. We also report the subsequent management.

Case Report

This patient was referred to our institute due to a family history of hereditary diffuse gastric cancer (HDGC). The presence of the mutated gene was confirmed, and he was advised to have a PTG.

He was submitted to a surveillance endoscopy with biopsies according to the Cambridge protocol that showed a chronic gastritis with *Helicobacter pylori*. At this point, the patient consented to the surgery, so it was decided not to eradicate the *H. pylori*. By patient's decision, the surgery was postponed and an upper GI endoscopy was scheduled. No visible lesions were detected (Fig. 1), but histology of the corpus-antrum transition revealed signs of inflammatory infiltrate, and lymphoid follicles with alterations suggestive of extranodal MALT lymphoma, with a score of 4 according to the classification of Wotherspoon et al. [8] (Fig. 2). The immunohistochemistry study revealed CD20+, CD3–, Bcl2+, focal CD21+, CD10–, and signs suggesting the production of κ light chains (Fig. 3).

The patient was informed of this result and prescribed the bismuth quadruple therapy eradication treatment. He also underwent a thoraco-abdomino-pelvic computed tomography scan that showed no further involvement (stage I). Given these findings, the patient consented to undergo PTG. *H. pylori* fecal antigen was negative, confirming eradication.

The surgery was performed without complications and there was no evidence of intraabdominal metastases or involvement of the 26 isolated ganglia. The histologic examination of the specimen identified 2 foci of signet-ring cell carcinoma (SRCC) in situ in the body region, without invasion of the lamina propria (Fig. 4). There were no signs of MALT lymphoma. He was proposed to undergo surveillance at a multidisciplinary meeting.

Discussion

Due to the poor prognosis associated with diffuse gastric cancer (DGC) and the high probability of *CDH1* mutations carriers to develop it, the best risk reduction strategy is PTG.

Only 10% of the patients who develop symptomatic invasive DGC have a potentially curable disease and, even in this group, the 5-year survival rate does not exceed 30% [6].

However, surgery has significant implications for quality of life and nutritional status, so the timing should be individualized, with some patients deciding to postpone the procedure [9].

In this setting, gastroscopy performed by experienced endoscopists has an important role in this risk group's surveillance [10]. Annual endoscopy following the Cambridge protocol (5 random biopsies from 6 different anatomic sites) is advised for to optimize diagnosis, due to the small size of the foci of signet-ring cells that can only be recognized by microscopy. White-light exam is recommended, since other endoscopic modalities have not been proven to confer any additional benefit. Gastrectomy may be necessary when macroscopic or microscopic disease is found [11]. Despite all efforts, gastroscopy with random biopsies has low sensitivity to detect SRCC [12].

During the previous year, our patient had produced negative endoscopic and histological findings. Although there is no proven association between *H. pylori* infection and HDGC, testing via gastric biopsy is recommended, because they frequently coexist and may play a role in inducing DGC [13]. Additionally, *H. pylori* is a class I carcinogen, and its treatment and confirmation of eradica-

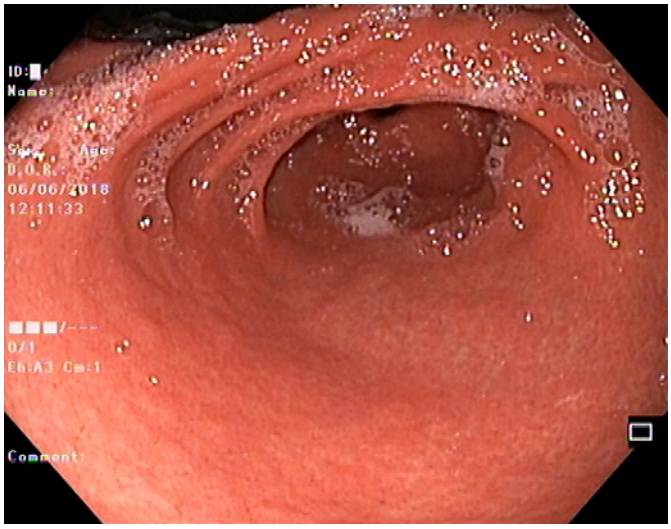

Fig. 1. Endoscopic image of corpus-antrum transition with normal mucosal and no lesion identified.

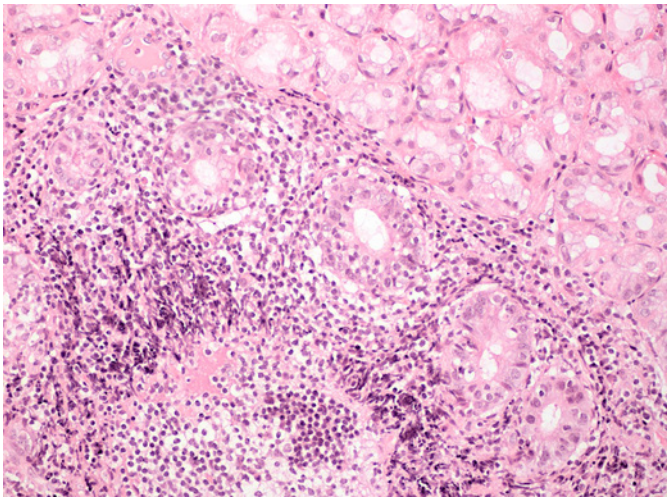

Fig. 2. Extranodal marginal zone B-cell lymphoma (MALT) in corpus-antrum transition. HE.

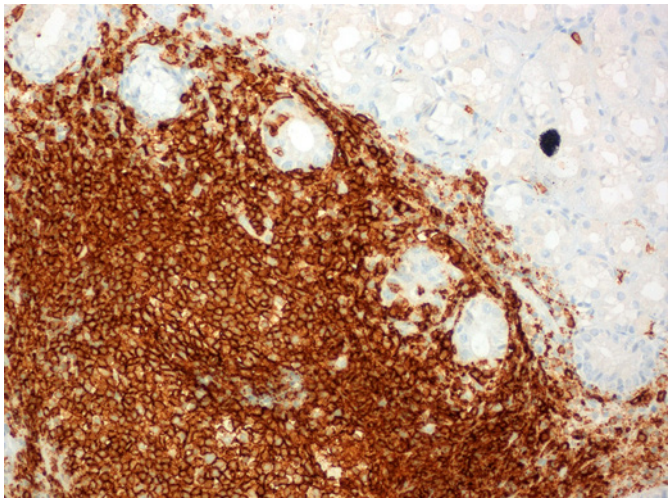

Fig. 3. Immunohistochemistry study revealing CD20+ in corpus-antrum transition: extranodal marginal zone B-cell lymphoma (MALT).

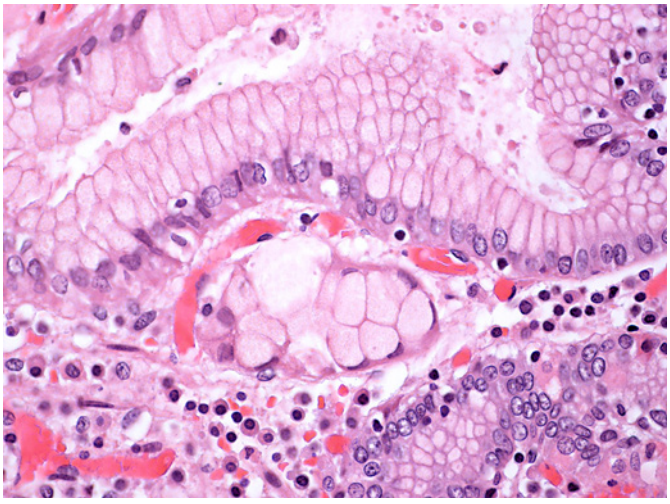

Fig. 4. Focus of signet-ring cell carcinoma in situ in the corpus region (surgical specimen). HE.

tion are advised for those who test positive [6, 14]. In this specific case, it was decided not to eradicate the *H. pylori* because PTG was already planned in the short term. Despite initially accepting surgery, subsequent postponement resulted in endoscopic surveillance and active *H. pylori* infection through this period.

H. pylori is associated with gastric MALT lymphoma in >90% of the cases and its eradication should be the only initial therapy for a localized *H. pylori*-positive lymphoma as well as being considered in *H. pylori*-negative patients with a false-negative test or infection by other *Helicobacter* spp. It results in lymphoma regression and

long-term clinical control in the majority of patients [7, 15].

MALT lymphomas typically have an indolent course and tend to be self-limited if the *H. pylori* infection stimulus is no longer present [7]. In our patient, a PTG was already planned and the timing of surgery was dictated by the diagnosis of gastric MALT lymphoma. The surgical specimen revealed only foci of SRCC; no lymphoma was identified, which showed the response to the *H. pylori* eradication treatment.

Reports of advanced DGC in patients with multiple negative surveillance exams are frequent because the endoscopic detection of SRCC foci is poor [11, 16]. After surgery, multiple foci of intramucosal (T1a) SRCC are found in 45–60% of patients with negative endoscopic evaluations [6, 17, 18].

Our literature review found some clinical reports of coexisting diagnoses of gastric MALT lymphoma and sporadic DGC, but none reporting gastric MALT lymphoma in *CDH1* mutation patients [19–21]. This can be explained by the low prevalence/underdiagnosis of HDGC and the prophylactic/curative gastrectomy early in life which reduces the chance of this kind of lymphoma developing.

To our knowledge, this is the first report of a patient with a known mutation of the *CDH1* gene diagnosed with a gastric MALT lymphoma while undergoing endoscopic surveillance. Despite having a higher risk of developing neoplasia (and this is the primary screening focus), these patients should also be screened for otherwise-common pathologies, the presence of which may determine different treatment strategies.

Statement of Ethics

The subject gave his written informed consent to publish (including publication of images). This study did not require approval from the appropriate ethics committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.P. collected the data, wrote the manuscript, and is the guarantor of the article. A.L.C., A.R., and R.D. wrote and revised the manuscript. C.B. and M.D.-R. revised and approved the final version.

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