Familial gastric carcinoma

Fátima Carneiro
Xiaogang Wen
Raquel Seruca
Carla Oliveira

Abstract

Most cases of gastric cancer are sporadic and familial clustering is observed in about 10% of cases. Hereditary gastric cancer accounts for a very low percentage of cases (1–3%), encompassing: hereditary diffuse gastric cancer (HDGC) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Furthermore, gastric cancer can develop in the setting of other hereditary cancer syndromes such as Li–Fraumeni syndrome, Familial Adenomatous Polyposis, Peutz–Jeghers syndrome, Lynch syndrome, MUTYH-associated adenomatous polyposis, Juvenile Polyposis syndrome, and Cowden syndrome. HDGC is caused by alterations of the *CDH1* gene that encodes for e-cadherin and the model of development encompasses non-atrophic gastritis, *in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells and invasive carcinoma. GAPPS is characterized by proximal fundic gland polyposis, with areas of dysplasia or intestinal-type gastric cancer, without evidence of colorectal polyposis or other heritable gastrointestinal cancer syndromes. The genetic cause of GAPPS has not been identified yet.

Keywords *CDH1*; E-cadherin; familial gastric cancer; gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS); hereditary diffuse gastric cancer (HDGC); prophylactic gastrectomy

Introduction

Stomach cancer is the fifth most common cancer worldwide, with an estimated 952 000 new cases (7% of total cancer incidence) and 723 000 deaths (9% of total cancer mortality) in 2012.[1] According to Laurén's classification, two major GC types can be identified, diffuse (DGC) and intestinal (IGC), with distinct epidemiological, morphological and molecular features.

Most cases of gastric cancer are sporadic (90%), and familial clustering is observed in about 10% of cases. Hereditary gastric cancer accounts for a very low percentage of cases (1–3%), and two hereditary syndromes have been characterized: hereditary diffuse gastric cancer (HDGC) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).[1] Furthermore, gastric cancer can develop in the setting of other hereditary cancer syndromes such as Li–Fraumeni syndrome, Familial Adenomatous Polyposis, Peutz–Jeghers syndrome, Lynch syndrome, hereditary breast and ovarian cancer, MUTYH-associated adenomatous polyposis (MAP), juvenile polyposis syndrome, and Cowden syndrome. The life time risk of GC in these syndromes varies substantially between populations studied, but is generally low.

Fátima Carneiro *MD PhD Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP) Porto, Portugal; Medical Faculty of the University of Porto, Porto, Portugal; Centro Hospitalar São João, Porto, Portugal. Conflicts of interest: none.*

Xiaogang Wen *MD Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP) Porto, Portugal. Conflicts of interest: none.*

Raquel Seruca *MD PhD Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP) Porto, Portugal; Medical Faculty of the University of Porto, Porto, Portugal. Conflicts of interest: none.*

Carla Oliveira *PhD Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP) Porto, Portugal; Medical Faculty of the University of Porto, Porto, Portugal. Conflicts of interest: none.*

Hereditary diffuse gastric cancer (HDGC)

Definition

In 1998, Guilford et al. reported three Maori kindred with early-onset, multigenerational, diffuse gastric cancer, in which germline mutations of the gene encoding for E-cadherin (*CDH1*) were identified by genetic linkage analysis and mutation screening.[2] These findings led to the identification of a new inherited cancer syndrome designated as Hereditary Diffuse Gastric Cancer (HDGC) [MIM #137215].[2] Shortly afterward, families from other ethnicities were identified sharing similar features.

Diagnostic criteria

On the basis of clinical criteria, in 1999 the International Gastric Cancer Linkage Consortium (IGCLC) defined families with the HDGC syndrome as those fulfilling one of the following features.[3]

1. Two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before the age of 50;
2. Three or more cases of documented diffuse gastric cancer in first- or second- degree relatives, independent of age of onset.

According to the criteria of the IGCLC, families with aggregation of gastric cancer and an index case with diffuse gastric cancer, but not fulfilling the IGCLC criteria for HDGC, are coined as familial diffuse gastric cancer (FDGC).[3] The designation of familial gastric cancer (FGC) is used for cases with familial aggregation of gastric cancer in which the histopathology of the tumors is unknown. A family history of intestinal carcinoma can also be present and families with this type of aggregation are classified as having familial intestinal gastric cancer (FIGC).[3,4]

Full screening of the *CDH1* gene (genetic testing) is recommended in an individual fulfilling the HDGC criteria as defined above. The criteria for genetic testing were updated in 2010[5] and the updated recommendations include broadening of *CDH1* testing criteria such that histological confirmation of diffuse gastric carcinoma is only required for one family member, inclusion of individuals with diffuse gastric carcinoma before the age of 40 years without a family history, and inclusion of individuals and families with diagnoses of both diffuse gastric cancer and lobular breast cancer, with one case before the age of 50 years.[5]

From the above descriptions it is clear that the definition of HDGC is based mainly on clinical features (according to the IGCLC) while, according to the criteria adopted by the New Zealand group, the designation of HDGC should be restricted to cases in which *CDH1* gene germline mutations have been

identified.[2–6] The IGCLC definition for HDGC will be used in this chapter.[3,5]

Pathology

Macroscopy: macroscopic features differ in stomachs from asymptomatic *CDH1* mutation carriers submitted to prophylactic gastrectomy and index cases with HDGC. In the former, stomachs nearly always appear normal to the naked eye, there is no mass lesion, and slicing shows normal mucosal thickness.[7–9]

In some apparently normal stomachs, subtle pale areas are visible on standard white light endoscopy[10] and close inspection may show white patches that after formalin fixation correspond to intramucosal signet ring cell (diffuse) carcinoma.

Most index cases with HDGC present with advanced cancers that are indistinguishable from sporadic diffuse gastric cancer, often displaying features of linitis plastica, which can involve all topographic regions within the stomach.

Microscopy: systematic complete mapping of total gastrectomies from carriers of *CDH1* mutations show microscopic, usually multiple, *foci* of intramucosal (T1a) signet ring cell (diffuse) carcinoma in the majority of cases.[7–9,11–13]

Individual *foci* of intramucosal (T1a) signet ring cell (diffuse) carcinoma are small, ranging from 0.1 mm to 10 mm (Figure 1). These cells are small at the neck zone level and usually enlarge towards the surface of the gastric mucosa exhibiting the distinctive signet ring cell morphology. In North American and European families, microscopic *foci* of intramucosal carcinoma were not restricted to any topographic region in the stomach: *foci* were identified from cardia to pre-pyloric region, without evidence of antral clustering.[7,11,12]

In the series of cases reported by Rogers et al,[9] 70% of the total *foci* were localized in the proximal 1/3 of the stomach. In one study from the United States, the predilection for the proximal stomach, more specifically for oxyntic type mucosa was confirmed, estimating that 74% of cancer *foci* are clustered in the cardia and proximal fundus.[14] In another series from United Kingdom[13] the highest number of *foci* was observed in the fundus (44.7%) followed by the body (40.2%). In New Zealand Maori families, most early invasive carcinomas developed in the distal stomach and the body-antral transitional zone.[8] Reasons for the different anatomical localization of the cancer *foci* in the aforementioned studies remain to be clarified, although both background genetics and environmental factors are probable contributing factors.

As all regions of the gastric mucosa can be affected, pathological examination of the resected specimen should include confirmation of the presence of a complete cuff of proximal squamous esophageal mucosa and distal duodenal mucosa.

Two distinct types of intra-epithelial lesions were identified as precursors of the invasive cancers in *CDH1* mutation carriers[7]:

(1) *in situ* signet ring cell carcinoma, corresponding to the presence of signet ring cells within basal membrane, generally with hyperchromatic and depolarized nuclei (Figure 2), and

(2) pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae (Figure 3).

Confirmation of carcinoma *in situ* (Tis) and pagetoid spread of signet ring cells by an independent histopathologist with experience in this area is strongly recommended. Strictly following the criteria for the identification of these precursor lesions will diminish the risk of over-diagnosing nonspecific changes and will help to distinguish precursors (*in situ* carcinoma; pagetoid spread) and tiny *foci* of early intramucosal carcinoma from mimics of signet ring cells, including telescoped normal glands, hyperplastic changes with globoid cells, xanthomatous cells, neuroendocrine cell nests and clear/glassy cell change of mucous glands (Figure 4). The latter constitute a frequent cause of consultation cases. Distinctive features are: single row of cells with clear/glassy cell change (distinctive feature from pagetoid spread of signet ring cells, the latter characterized by two rows of cells; the clear/glassy cell change is due to the presence of basal cytoplasmic vacuoles (PAS negative) and a rim of normal cytoplasm (PAS positive) at the apical pole of the cells (Figure 3).

On the basis of the above-mentioned features, a model for the development of diffuse gastric cancer in germline *CDH1* deleterious mutation carriers was proposed,[4,7] encompassing the following lesions: mild non-atrophic gastritis, *in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells, and invasive carcinoma. E-cadherin immunoexpression was shown to be reduced or absent in early invasive gastric carcinomas (T1a) (Figure 1), contrasting with the normal membranous E-cadherin

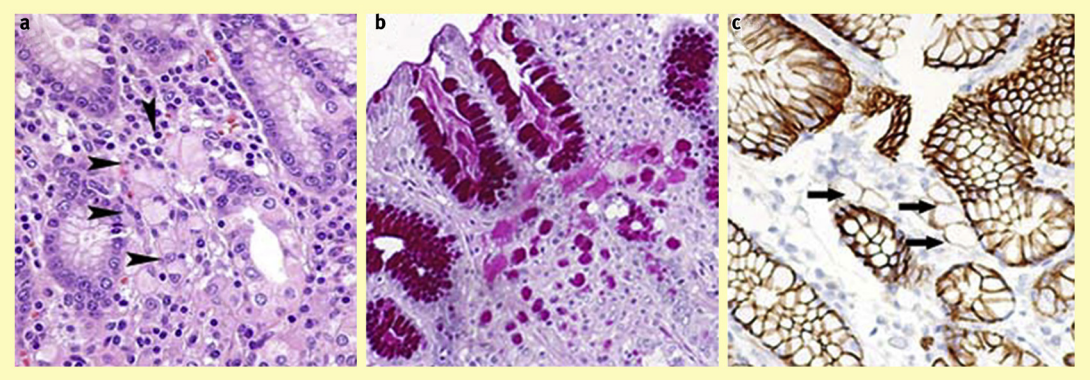

Figure 1 Intramucosal (T1a) signet ring cell (diffuse) carcinoma: (**a**) Neoplastic signet ring cells surrounded by arrow heads (H & E; original magnification 400×); (**b**) Neoplastic cells in the lamina propria highlighted by PAS staining; neoplastic cells closer to the surface of the mucosa are larger than those in deep areas, at the neck zone level (PAS; original magnification 400×); (**c**) Low or absent expression of E-cadherin in signet ring cells, in comparison with strong E-cadherin expression at the cell membrane of the normal glands (IHC; original magnification 600×).