REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Is prophylactic gastrectomy indicated for healthy carriers of CDH1 gene mutations associated with hereditary diffuse gastric cancer?

Authors:
Vicente Munitiz Ruiz, Pilar Jimeno, David Ruiz de Angulo, Ángeles Ortiz, Luisa F. Martínez de Haro, Miguel Marín, Pedro Cascales, Gema Ruiz García, Eduardo Ortiz Ruiz, Pascual Parrilla

DOI: 10.17235/reed.2018.5831/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
Munitiz Ruiz Vicente, Jimeno Pilar, Ruiz de Angulo David, Ortiz Ángeles, Martínez de Haro Luisa F., Marín Miguel, Cascales Pedro, Ruiz García Gema, Ortiz Ruiz Eduardo, Parrilla Pascual. Is prophylactic gastrectomy indicated for healthy carriers of CDH1 gene mutations associated with hereditary diffuse gastric cancer?. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5831/2018.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 5831 inglés

Is prophylactic gastrectomy indicated for healthy carriers of CDH1 gene mutations associated with hereditary diffuse gastric cancer?

Vicente Munitiz[1], Pilar Jimeno[1], David Ruiz-de-Angulo[1], Ángeles Ortiz[1], Luisa F. Martínez-de-Haro[1], Miguel Marín[2], Pedro Cascales[1], Gema Ruiz-García[3], Eduardo Ortiz-Ruiz[3] and Pascual Parrilla[1]

Services of [1]General Surgery, [2]Medical Oncology and [3]Pathology. Hospital Clínico Universitario Virgen de la Arrixaca. IMIB. Murcia, Spain

Received: 22/07/2018

Accepted: 26/08/2018

Correspondence: Vicente Munitiz. Service of General Surgery. Hospital Clínico Unviersitario Virgen de la Arrixaca. Ctra. Madrid-Cartagena, s/n. 30120 El Palmar, Murcia. Spain

e-mail: vmunitiz@yahoo.es

ABSTRACT

Introduction: hereditary diffuse gastric cancer (HDGC) is a recently reported hereditary cancer syndrome. Patients with suspected HDGC must be under surveillance via endoscopy and multiple biopsies. As an alternative, some studies suggest prophylactic gastrectomy (PG) for disease carriers. The goal of this article was to report our experience with a CDH1 mutation positive family who underwent PG.

Patients and methods: the index case was a 34-year-old female diagnosed with diffuse gastric adenocarcinoma and massive carcinomatosis. There was a family history of gastric adenocarcinoma in seven family members. A genetic study identified the c.1577G>A mutation, in exon 11 of the CDH1 gene via sequencing analysis.

Results: this mutation was also present in other six family members, who subsequently underwent prophylactic gastrectomy. The pathology study of resected gastric segments revealed multiple microscopic foci of adenocarcinoma in five of these

individuals. These foci were not detected in the multiple endoscopies performed before surgery.

Conclusions: we recommend prophylactic gastrectomy for CDH1 mutation carriers even in the absence of lesions during endoscopic screening.

Key words: Hereditary diffuse gastric cancer. Gastrectomy. E-cadherin.

INTRODUCTION

Hereditary diffuse gastric cancer (HDGC) is a recently reported hereditary cancer syndrome and represents 1-3% of gastric adenocarcinoma cases (1). It was initially described in 1998 by Guilford et al. among members of a Maori family in New Zealand; an inactivating germline mutation was identified in the CDH1 gene. This gene codes for E-cadherin (2), which is located on the short arm of chromosome 16. This mutation induces cell disruption, facilitating infiltration into adjacent tissues. Currently, over 100 germline mutations have been identified in this gene, small insertions being the most common. The inheritance pattern is autosomal dominant with incomplete penetrance and a cumulative risk with age.

Suggested clinical criteria to suspect HDGC include (3,4):

– Two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, at least one diagnosed before 50 years of age.

– Three or more familial cases, regardless of the age at presentation.

– Patients younger than 40 years of age diagnosed with DGC, regardless of family history.

– Patients diagnosed with DGC (one case diagnosed before 50 years of age) and lobular breast carcinoma.

The estimated risk for gastric cancer at age 80 years in family members with HDGC is 70% for males and 56% for females (4). Furthermore, age at disease onset is lower (37 years) when compared to non-familial gastric cancer (5). In females, this mutation also increases the risk of lobular breast carcinoma by up to 40% (3,4). Interestingly, these mutations are less common in countries such as Japan and Korea, where gastric cancer rates are the highest (3).

This increased rate of gastric cancer requires effective prevention approaches, which remains the most important issue in the management of these families. According to updated clinical guidelines (4), patients with suspected HDGC must be monitored by a multidisciplinary team including endoscopists, surgeons and pathologists experienced in this syndrome. However, no studies have shown the usefulness of the various imaging tests for monitoring these patients. These include upper digestive endoscopy with multiple biopsy sampling, high-definition endoscopy, chromoendoscopy, endoscopic ultrasound, abdominal computed tomography and positron emission tomography (6). As an alternative, some studies suggest prophylactic gastrectomy for mutation carriers, despite the risks and sequelae of this surgery (6,7).

The goal of the present article was to report our experience with a CDH1 mutation-carrying family whose members underwent a prophylactic total gastrectomy.

PATIENTS AND METHODS

The index or proband case (no. 1) was a 34-year-old female with stage-IV diffuse gastric ADC (signet ring cell), with surgically unresectable peritoneal spread. The patient received multiple lines of chemotherapy and died two years after diagnosis. Analysis of the family tree (Fig. 1) identified seven family members who had died from gastric cancer from 29 to 52 years of age (cases 2-8) within the previous three generations.

Given that three first-degree relatives had been diagnosed with gastric adenocarcinoma at a relatively early age, the presence of hereditary diffuse gastric cancer syndrome was suspected. To this end, the patient underwent genetic tests including sequencing of CDH1. The analysis identified the c1577G>A mutation in exon 11 of the CDH1 gene, which substitutes guanine (G) for an adenine (A) at position 1577. This change, which had not been previously described (8,9), results in a premature stop codon and leads to a truncated CDH1 protein (pTrp56). Thus, a diagnosis of hereditary gastric cancer was confirmed and a mutational study was recommended to the rest of the family members.

RESULTS

The previously mentioned mutation was identified in the father of the index case (no. 9, 56 years old), brother (no. 10, 31 years old), paternal aunt (no. 11, 53 years old) and female cousin (no. 12, 27 years old). Monitoring was performed via chromoendoscopy and biopsy sampling every three months, which revealed no macroscopic or histological changes in three of the four subjects. Endoscopy identified an intramucosal signet ring cell carcinoma in one subject (no. 12). Genetic testing was performed in the children of case number 5 from a different branch of the family. Two cases were positive, a 43-year-old male (no. 13) and a 56-year-old female (no. 14), both with standard chromoendoscopy. Prophylactic gastrectomy was offered and all subjects agreed.

All six individuals (Table 1) underwent a total gastrectomy with D1 lymphadenectomy and Roux-en-Y reconstruction using a CEEA # 25 stapler. Radiographic monitoring with an oral contrast medium was performed on the fourth postoperative day to rule out any leaks. All patients were discharged with good general status and oral diet tolerance after a mean hospital stay of seven days. No early or late complications occurred.

The pathology reports identified multiple intramucosal foci of signet ring cell carcinoma in five patients (nos. 10, 11, 12, 13 and 14) (Fig. 2A), with loss of E-cadherin immunohistochemical expression (Fig. 2B), no evidence of regional lymph node involvement (stage pT1aN0) and free margins. The gastrectomy specimen from the probands' father (no. 9) had mild chronic superficial gastritis and extensive intestinal metaplasia, both complete and incomplete, with low-grade dysplasia.

Furthermore, patient no. 11 was diagnosed with carcinoma in her left breast and a multidisciplinary committee decided to perform a bilateral subcutaneous mastectomy with a left-side sentinel lymph node biopsy (negative with OSNA) and bilateral breast implant placement. The pathology report identified an infiltrating lobular carcinoma of the classic variant that was 1.5 cm in size (pT1c pN0 M0) and stage IA, with a luminal phenotype A. The patient completed the adjuvant therapy regimen with tamoxifen.

DISCUSSION

Hereditary diffuse gastric cancer (HDGC) is a rare autosomal dominant disease associated with CDH1 gene mutations in around 40% of affected families. Histologically, it is an invasive, diffuse, poorly differentiated, signet ring cell adenocarcinoma with impaired or absent E-cadherin expression. This protein belongs to the cadherin superfamily. The function of this protein is cell development and differentiation, the establishment of intercellular connections on cell surfaces and structure maintenance in epithelial tissues (6,8).

Genetic counseling is key for the assessment of HDGC. This should be performed in affected family members when a suspicion arises based on the above criteria. In our series, this was performed in a 34-year-old patient after studying her family tree. CDH1 sequencing found a previously undescribed mutation that was deemed pathological as it resulted in a premature stop codon and a truncated protein (p.Trp526) involved in the development of hereditary diffuse gastric carcinoma. Finding a pathological mutation in an affected proband means that all first-degree relatives should be studied. This assessment yielded positive results in six of nine family members.

The International Gastric Cancer Linkage Consortium (IGCLC) consensus recommends prophylactic gastrectomy, regardless of endoscopic findings, in the presence of HDGC and CDH1 gene mutations (4,6,10-13). This indication is based on multiple studies, which found that all carriers that underwent prophylactic gastrectomy had microscopic foci of diffuse gastric cancer in their surgical specimens while no mucosal lesions were identified by endoscopy. This was also the case in five of our family members. In this respect, different studies have shown the high prevalence and multifocality rate of this disease at the time of prophylactic surgery. Hebbard et al. (12) reported 23 patients who underwent prophylactic surgery, only two of whom had positive biopsies preoperatively. However, 22 patients had carcinoma foci identified via a pathology study. In the study by Strong et al. (13) that included 41 patients, 85% (35 patients) had microscopic carcinoma foci, whereas only one subject had a positive preoperative biopsy. From all the above, endoscopic monitoring is now questioned as a proper strategy for these patients, even following the advent of chromoendoscopy (4,14). Shaw et al. (15) reported that only 6% of carcinoma foci larger than 4 mm were identified preoperatively.

In line with other studies, we believe that the decision to carry out a total gastrectomy requires a multidisciplinary assessment on an individual patient basis. Surgery must also be performed by experienced surgical teams with a low postoperative mortality rate. Gastrectomy timing may vary widely according to age and physical and psychological status, as physical and digestive sequelae should not be underestimated (4,16). The present IGCL consensus suggests that surgery be performed between the second and third decade of life, as the risk for HDGC before ten years of age is lower than 1% but rises to 4% by the age of 30.

With regard to prognosis, there was no long-term data of survival. However, data (17) from patients without familial disease who underwent gastrectomy for early-stage signet ring cell gastric cancer indicate that it is around 90% at ten years. This figure may be extrapolated to patients with HDGC with neoplastic foci found in gastrectomy specimens that are confined to the mucosa.

To conclude, in our experience, and based on the literature, we recommend prophylactic gastrectomy for CDH1 gene mutation carriers even in the absence of malignant lesions detected by endoscopic screening with gastric mapping.

REFERENCES

1. Caldas C, Carneiro F, Lynch HT, et al. Familial gastric cancer: overview and guidelines for management. J Med Genet 1999;36:873-80.

2. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392:402-5. DOI: 10.1038/32918

3. Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001;121:1348-53. DOI: 10.1053/gast.2001.29611

4. Van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015;52(6):361-74. DOI: 10.1136/jmedgenet-2015-103094

5. Lee HE, Smyrk TC, Zhang L. Histologic and immunohistochemical differences between hereditary and sporadic diffuse gastric carcinoma. Hum Pathol 2018;74:64-72. DOI: 10.1016/j.humpath.2017.12.023

6. Norton JA, Ham CM, Van Dam J, et al. CDH1 truncating mutations in the E-cadherin gene: an indication for total gastrectomy to treat hereditary diffuse gastric cancer. Ann Surg 2007;245(6):873-9. DOI: 10.1097/01.sla.0000254370.29893.e4

7. Herraiz M, Valenti V, Sola J, et al. Hereditary diffuse gastric cancer: strategies to reduce tumoral risk. Rev Esp Enferm Dig 2012;104(6):326-9.

8. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol 2015;1(1):23-32.

9. Leiden Open Variation Database. CDH1 gen homepage. Available from: https://databases.lovd.nl/shared/genes/CDH1

10. Blair VR. Familial gastric cancer: genetics, diagnosis, and management. Surg Oncol Clin N Am 2012;21(1):35-56. DOI: 10.1016/j.soc.2011.09.003

11. Huntsman DG, Carneiro F, Lewis FR, et al. Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. N Engl J Med 2001;344:1904-9. DOI: 10.1056/NEJM200106213442504

12. Hebbard PC, Macmillan A, Huntsman D, et al. Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): the Newfoundland experience with 23 patients. Ann Surg Oncol 2009;16(7):1890-5. DOI: 10.1245/s10434-009-0471-z

13. Strong VE, Gholami S, Shah MA, et al. Total gastrectomy for hereditary diffuse gastric cancer at a single center. Postsurgical outcomes in 41 patients. Ann Surg 2017;266(6):1006-12. DOI: 10.1097/SLA.0000000000002030

14. Hüneburg R, Marwitz T, Van Heteren P, et al. Chromoendoscopy in combination with random biopsies does not improve detection of gastric cancer foci in CDH1 mutation positive patients. Endosc Int Open 2016;4(12):E1305-10. DOI: 10.1055/s-0042-112582

15. Shaw D, Blair V, Framp A, et al. Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? Gut 2005;54(4):461-8. DOI: 10.1136/gut.2004.049171

16. Van der Kaaij RT, Van Kessel JP, Van Dieren JM, et al. Outcomes after prophylactic gastrectomy for hereditary diffuse gastric cancer. Br J Surg 2018;105(2):e176-82. DOI: 10.1002/bjs.10754

17. Fang C, Shi J, Sun Q, et al. Risk factors of lymph node metastasis in early gastric carcinomas diagnosed by WHO criteria in 379 Chinese patients. J Dig Dis 2016;17(8):526-37. DOI: 10.1111/1751-2980.12385

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Table 1. Description of cases undergoing prophylactic gastrectomy

Patient	*Age*	*Sex*	*Pathology pre-surgery*	*Pathology post-surgery*
9	57	Male	Antral chronic gastritis. Enteroid metaplasia and foci of mild dysplasia	Superficial chronic gastritis, extensive metaplasia with mild dysplasia
10	32	Male	Normal. No inflammatory features, metaplasia, or dysplasia	5 foci of intramucosal ADC
11	26	Female	Small intramucosal foci of diffuse signet ring cell ADC (pT1a)	17 foci of intramucosal ADC
12	53	Female	Normal. No inflammatory features, metaplasia, or dysplasia	6 foci of intramucosal ADC
13	43	Male	Normal. Absence of metaplasia or dysplasia	4 foci of intramucosal ADC
14	45	Female	Normal. Absence of metaplasia or dysplasia	18 foci of intramucosal ADC

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

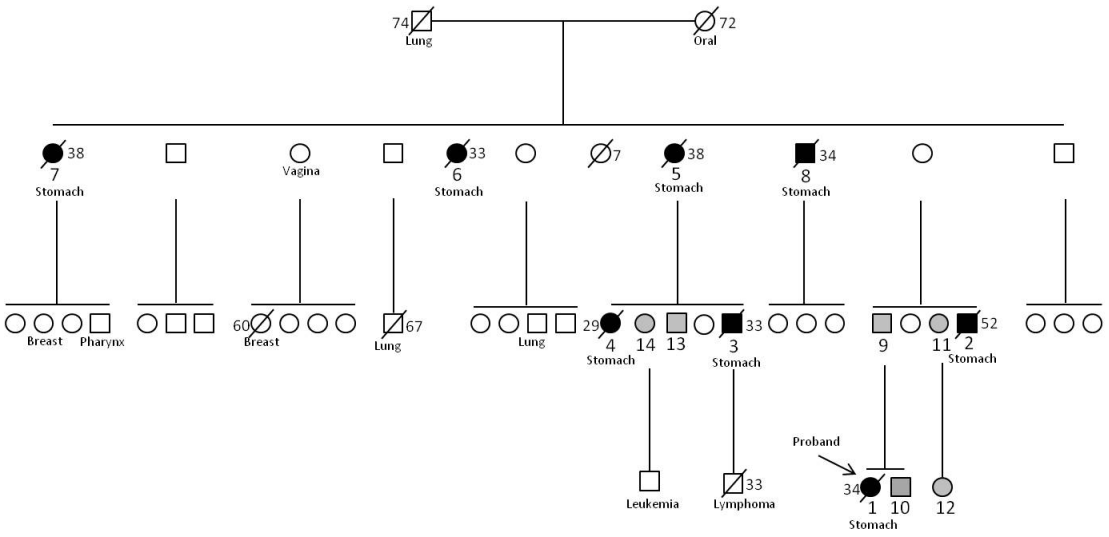

Figure 1. HDGC family tree (4 generations). In bold, the patients died due to gastric cancer. In gray the patients with prophylactic gastrectomy. Patients diagnosed with other tumors are also indicated. The oblique line indicates that the patient has died due to the disease (age).

Fig. 1. Family tree (four generations) of the HDGC family. In bold are the patients who died due to gastric cancer. In gray are the patients with a prophylactic gastrectomy. Patients diagnosed with other tumors are also indicated. The oblique line indicates that the patient died due to the disease (age).

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

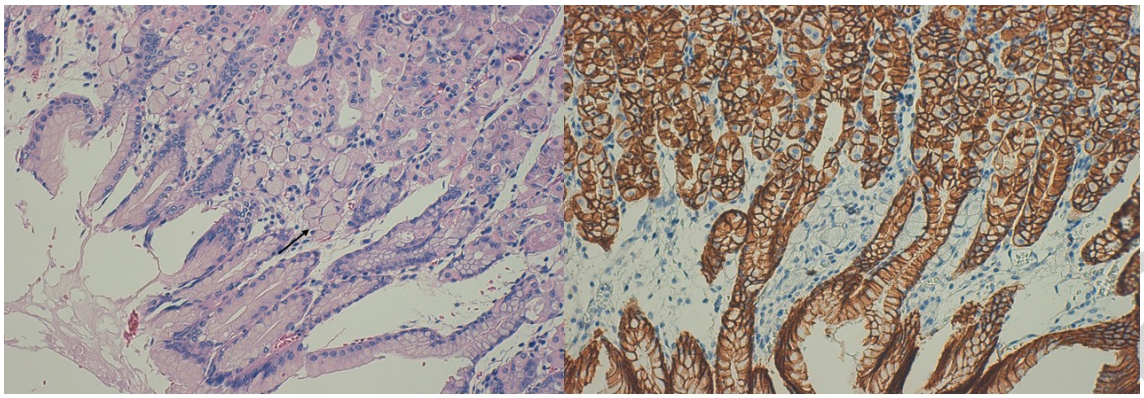

Imagen 2. (a) Hematoxilina-Eosina con un foco intramucoso de adenocarcinoma en células en anillo de sello (flecha).
(b) Tinción inmunohistoquímica con pérdida para E-cadherina.

Fig. 2. A. Hematoxylin-eosin with an intramucosal focus of signet ring cell adenocarcinoma (arrow). B. Immunohistochemical staining with loss of E-cadherin.