Review Article

Hereditary Diffuse Gastric Cancer

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Introduction

Gastric Cancer (GC) is the 5th most common cancer in the world, accounting for 5.7% of all new cancers, affecting one million people annually [1]. It is the third leading cause of death by cancer (DC), accounting for 8.2% (DC), or 782,000 deaths in 2018. The cumulative risk of death from GC, from birth to 74 years, is 1.36 % for males and 0.57% for females. Its incidence and mortality are highly variable, and will depend on the region in the world analyzed and its culture [2]. GC have been associated with diet and / or infection with *Helicobacter pylori* bacteria. It's more prevalent in men, and is more common in developed nations. The incidence of the GC is higher in Central and East Asia, and Latino America, but has been declining for the past 50 years, possibly due to the prevention and eradication of Helicobacter pylori bacteria. Ninety five percent of GC are adenocarcinomas, followed by primary gastric lymphomas. Survival of patients with GC at 5 years of diagnosis is 31% in the United States, this is because they are usually diagnosed at advanced stages. The majority of GC's, are sporadic, but there is a hereditary tendency, as has been identified in several groups of families with GC (10%), and in about 1 to 3% of the families with Hereditary Diffuse Gastric Cancer Syndrome (HDGCS).

Classification of gastric adenocarcinomas

Gastric adenocarcinomas are classified according to, their anatomical location in the stomach, histologically and finally clinically [3]. Due to their anatomical location, they can be classified as gastric cardia or gastric noncardia. Cancers of the gastric cardia arise in the region close to the esophagogastric junction and share the epidemiological characteristics of esophageal adenocarcinomas. The cause of this type of cancer is not clear, they have characteristics of adenocarcinoma of esophagus and is associated with gastroesophageal reflux. The Gastric Non-cardia related GC, are associated *Helicobacter pylori* bacteria and atrophic gastritis [4]. Sometimes the anatomical definition of the region of the cardia has been difficult to identify, which is why the International Gastric Cancer Association separated cancers into type I, type II and type III, representing tumors in the distal esophagus, in the cardia and distal stomach to the cardia, respectively [5]

being very difficult to define the anatomical location , of the cardia, the American's Cancer Adjunct Committee, simplified the classification based on the location of the epicenter of the lesion, or the presence or absence of involvement of the gastroesophageal junction [6]. Classified as esophageal cancer, if its epicenter is in the lower third of the esophagus or Gastro-Esophageal Junction (GEJ) or within 5 cm proximal to the stomach (ie cardia) with the mass of the tumor extending to GEJ, or distal esophagus. If the epicenter is more than 5 cm from the GEJ, or less, but does not extend to the GEJ, it's classified as gastric cancer. Histologically we can classify them into two groups, according to the Lauren criteria established in 1965, as diffuse (poorly differentiated) or intestinal (well differentiated) [7]. These two subtypes of GC's differ in their clinical and molecular characteristics, including histogenesis, cell differentiation, epidemiology, etiology, carcinogenesis, biological behavior, and prognosis. Clinically we can classify them depending on the invasiveness at the time of diagnosis, in Early, limited to the mucosa, or Advanced, involving mucosa, submucosa with or without metastases to lymph nodes.

Stage and Grades

According to the American Joint Committee, the stage system in Gastric Cancer (GC) was defined according to 1. Involvement of the gastric wall by cancer (Stage T), 2. Lymph nodes (Stage N), 3 distant metastases (Stage M). In the gastric wall, GC is considered stage T1 (invasion of the mucosa or muscular tissues would be T1a: if the submucosa is involved it would be T1b), T2 (Invasion of the muscularis propia), T3 (invasion of the subserosa), T4 (penetration to serosa-T4a; invasion of nearby structures T4b). The Classification by the lymph nodes involved by the tumor is based on the number of metastatic nodes. N-0 - No involved nodes, N1-metastasis in 1 or 2 regional lymph nodes, N2-metastasis to 3-6 regional lymph nodes, N3- metastasis in 7-15 regional lymph nodes-N3a; or in 16 or more regional nodes N3b. Finally, the M stages are classified as M0- no distant metastasis, M1, presence of distant metastases [8].

There are several types of hereditary gastric cancer:

Gastric Adenocarcinoma and Proximal Stomach Polyposis Syndrome (GAPSPS)

Familial Gastric Intestinal Carcinoma Syndrome (FGICS)

Gastric cancer in other hereditary syndromes

Hereditary Diffuse Gastric Cancer Syndrome (HDGCS)

Gastric adenocarcinoma and proximal stomach polyposis Syndrome (GAPSPS)

This condition has been recognized as a variant of Familial Adenomatous Polyposis, with a gastric phenotype that distinguishes it. Inherited as autosomal dominant and fundic gland polyposis, with areas of dysplasia or intestinal gastric cancer, restricted to the proximal stomach without evidence of colorectal cancers duodenal polyposis or other inherited cancer syndromes. Nine families have been described in the literature so far. The syndrome is characterized by its incomplete genetic penetration, with several elderly carriers of the condition, without endoscopic changes. Multiple polyps, more than 100, less than 10mm in diameter, carpet the area of the body and the fundus of the stomach. The esophagus, antrum, pylorus, and duodenum are usually not involved. The age of development of these cancers varies greatly and can range from 23 to 75 years (mean age 50 years). The histopathology can range from fundic gland polyps, with areas of dysplasia, hyperplastic polyps, adenomatous polyps and mixed. The genetic alteration identified is a point mutation in the germ cells, in the area of the promoter gene 1B of APC (Adenomatous Polyposis Coli). Genetic analysis for this mutation in patients who have the inherited characteristics of this syndrome, GAPSPS, are available. It is important to exclude that they do not have another polyposis syndrome or are using proton pump inhibitors.

Familial Intestinal Gastric Cancer Syndrome (FIGCS)

There is a hereditary tendency to develop intestinal-type gastric cancer in groups of relatives. So far there is no genetic test available for identification, and we do not know the cause [9,10].

Gastric cancer in other hereditary syndromes

There are several inherited syndromes associated with gastric cancer , FAP (germ cell mutations in the APC gene), MUTYH-associated polyposis, Lynch syndromes , Type 1 and type 2 (germ line mutations due to mismatch repair genes), Li-Fraumelli syndrome (germ line mutations in TP53), Puest-Jeghers syndrome (germ line mutations in STK11), Juvenile polyposis syndrome (germ line mutations of SMAD4 / BMPRI1A), hereditary breast and ovarian cancer syndrome (BRACA1 / BRACA2 germ line mutations) and Cowden syndrome (PTEN germ line mutations).

Hereditary Diffuse Gastric Cancer Syndrome (HDGCS)

HDGCS is a difficult condition to treat due to its aggressiveness and difficulty in establishing an early diagnosis. This is so because it has the peculiarity of developing under the mucosa, making early endoscopic and clinical identification very difficult. At the time of detection, 90% of patients are already in advanced stages, which carries a poor prognosis. This is inherited as autosomical dominant. The risk of diffuse gastric cancer in these patients at 80 years of age is 67% for men, and 83% for women, with an average age of 38 years [12]. HDGCS global incidence is estimated at 5 to 10 per 100,000 births (33). Lobular breast cancer has been associated with this condition, and the lifetime risk of developing lobular breast cancer is 39%, average age at diagnosis is 53 years.

Type of inheritance in HDGCS and the identification of the CDH1 gene

In 1994, at the annual meeting of the American Gastro-enterological Association , Kutz [11] reported the presence of 8 members of related families, who developed GC at an early age (between, 31 to 65 years) for 4 generations, the pedigree showed an autosomal dominant inheritance. In 1998, Guilford presented, a group of indigenous relatives (Maori), in New Zealand, with multiple cases of high grade poorly differentiated diffuse gastric cancer [13]. The genealogy showed that the diffuse gastric cancer, followed an autosomal dominant inheritance, and was able to identify a mutation, which inactivated (truncating mutations) E-cadherin / CDH1 in germ cells, located on chromosome 16q22.1. In 1999, 6 more families with diffuse gastric cancer were reported, with mutations in CDH1. The inheritance determined in these families by the pedigree analysis, was autosomal dominant, and observed in 90% of the cases. The CDH1 mutation, was identified in 30-40% of the patients.

Germ line alterations in HDGCS

The HDGCS, develops from a mutation in the germ lines of the CDH1 gene. This mutation is located on chromosome 16q22.1, in the CDH1 gene, a tumor suppressor gene, which codes for epithelial cadherin (E-cadherin). The coding sequence of E-cadhrein produces a 27 amino acid activation peptide (exon 1-2), a 154 amino acid precursor peptide and a mature protein made of 728 amino acids. The mature protein has 3 mayor domains, the biggest domain, extracellular (exons 4-13), a smaller transmenbranal domain (exons 13-14) and cytoplasmic domain (exons 14-16) [14]. As in almost all cancers where there are mutations in the genes, and are inherited as autosomal dominant, only one allele of E-cadherin is mutated in the germ line, and most of the genetic changes lead to "cutting" the protein produced. There are 14 known truncating producing mutations throughout the gene [12]. The E-cadherin is an integral transmenbranal glycoprotein, calcium dependent, controlling the adhesive properties between epithelial cells, as well as the suppression of malignant invasive cells, metastasis development, and cell proliferation. The E-cadherin plays an important role in the transduction, gene expression, cell differentiation and motility [13]. The mutation in E-cadherin is

associated with an increase in the activity of the Epidermal Growth Factor Receptor (EGFR) in addition to increasing the recruitment of downstream signals in Ras transduction and activation. Activation of the EGFR by mutations in the E-cadherin in the extracellular area, explains the increased motility in the cells of cancer present in this area [14]. 80% of pathological mutations are truncating mutations, the rest are missense mutations. Although deletions and methylation of the CDH1 gene promoter have been identified in germ cells in about 5%. Other mechanisms described are monoallelic germ cells with down-regulation mutations (allelic imbalance), which has been found in 37% of families with HDGCS. In some families, with HDGC, and CDH1 negative, frame-shift mutations in PALB2 have been observed [15]. Other mutations present in patients with HDGCS, have been described in hereditary cancer syndromes, such as BRCA2, TP53, STK11, SDHB, PRSS1, ATM, MSR1, INSR, FBXO24 YDOT1L, MAP3K6, MYD88 and CTNNA1. Of these mutations, MAP3K6 and CTNNA1 have been the most commonly found associated with HDGCS. Interestingly only 16% of families with HDGCS have no genetic abnormalities in their germ cells [16].

Histopathology of CGDH

In patients with CDH1 gene mutation, in its early stages, histological changes are characterized by multiple foci of diffuse carcinoma with signet ring cells, invasive (T1a) in the superficial gastric mucosa, without metastasis to nodules. Different family groups with CGDH and the CDH1 mutation, show a great variation in the number of T1a foci observed in stomach biopsies, systematically taken, in different areas of the stomach. They can range from a T1a foci to multiple foci. The specific location of these T1a foci, in the stomach, could not be determined, since some studies show a location in the proximal stomach and others in the transitional zone / distal stomach. This is possibly due to genetic susceptibility or environmental factors. Two precursors to signet ring cell carcinomas have been recognized in families with HDGC, the first, a pagetoid growth of signet ring cells, below the intact epithelium, but within the basement membrane, and the second In situ type signet ring cell carcinoma, the presence of signet ring cells within the basement membrane, replacing normal epithelial cells with hyperchromatic and depolarized nuclei.

Criteria to consider the molecular genetic test of CDH1 in patients with gastric or diffuse cancer , first established by the "International Gastric Cancer Linkage Consortium (IGCLC) " in 1999, the modification of Brooks-Wilson 2004 [9], the modification of the IGCLC in 2020 in Wanaka, New Zealand (33)

Family Criteria

1. Two or more gastric cancer patients at any age, and one with diffuse gastric cancer.

2. More than one case with CGDH, at any age, and one or more cases of lobular breast cancer aged less than 70 years in different members of the family.

3. One or more cases with lobular breast cancer in relatives, under 50 years of age.

Individual Criteria

1. HDGCS, age under 50 years

2. HDGCS, at any age in individuals ethnic of Maori

3. HDGCS, at any age, in individuals with a personal or family history (first degree relative) of cleft lip or palate.

4. History of HDGCS and lobular breast cancer, both diagnosed before age 70.

5. Bilateral lobular breast cancer diagnosed before age 70 years.

6. Gastric ring cells "" in situ "" or pagetoid extension of gastric tissue signet ring cellsin People under 50 years of age.

Prognosis

Among the factors that have been associated with poor prognosis of this condition are, submucosal invasion at the time of diagnosis, the diameter of the tumor more than 3.0-3.5cm, presence of vascular invasion, involvement of lymphatic nodules, shape of the lesions if they are undermined or ulcerated, undifferentiated or poorly differentiated histology, which are independent risk factors for the development of metastases to the nodules.

Factors that may affect the growth of the tumor

Apart from germ line mutations, the cell growth of cancer is affected by several factors. These include the microenvironment around the tumor, stromal cells (in the non- cancerous compartment), and the immune response in the area where the malignancy is developing. Tumor cells can cause fibroblast stimulation, releasing substances that stimulate cell replication, which in some cases offer resistance to chemotherapy, and stimulate immunosuppression, thus preventing the elimination of malignant cells. In addition, affecting the cells that regulate the vascular and immune development of the tumor [17].

Genetic diagnosis

The genetic test used in the index patient with CGDH is the identification of the mutation in the CDH1 gene. All 16 coding exons and their associated introns must be amplified, followed by direct DNA sequence analysis. Once the mutation has been identified, family members at risk can be offered a more specific test, using DNA sequence analysis, mutated in the CDH1 region, identified in the proband.

Recommendations to the patient identified with HDGC

Once a patient is diagnosed with CDH1 mutations, and meets the diagnostic criteria of HDGC (see Diagnostic criteria for CGD H, of the IGCLC in Wanaka 2020)*,* in genetic counseling is imperative. The Genetic counselor should discussed the only available preventive alternative, prophylactic total gastrectomy, with asymptomatic patients between the age of 16 to 40 years old [18,19]. For patients who choose endoscopic follow-up, the recommendation is to have an annual endoscopy, following the Cambridge protocol [20], taking into account the low probability that this technique has, in early detection of diffuse gastric cancer. Fujita showed, that in order to have a detection ratio of 90% [18], 1768 biopsies will needed to be taken, to detect a single focus of cancer. In addition, the healing and scarring changes, caused by previous prophylactic biopsies, will make identifying a lesion more difficult. A recent study by Kumar [19], showed that endosonography in patients with HDGC, offered no advantage in early diagnosis of diffuse gastric cancer, when compare with the use of white light panendoscopy (endoscopic sensitivity was 45 %). Due to its submucosal development, the endoscopic diagnosis is extremely difficult. Endoscopic ultrasound [19], High Resolution Endoscopy, Chromoendoscopy [21], Narrow Band Imaging, Autoflorescence Imaging/Magnification Endoscopy, none of this tecniques have been capable of making an early diagnosis before metastasis of the tumor [22].

Screening for colon cancer in patients with HDGC

There is limited evidence on the association of HDGCS and colon cancer. It is speculated that patients with HDGC and the CDH1 variation, with close relatives with colon cancer, especially if these tumors have signet ring cells and / or mucinous characteristics, may have a predisposition to develop this malignancy. In this group of patients, it is recommended to begin screening colonoscopy at age 40 or 10 years before the relative identified with colon cancer. Then repeat the colonoscopy every 3-5 years [18].

Recommendations to direct relatives of the patient identified with HDGC

1. Genetic counseling and detecting the presence of CDH1 mutations, in all relatives who meet the diagnostic criteria for HDGC.

2. Those with the positive E-cadherin test, genetic counseling should be provided pre and post test. Genetic counseling should be done by an experienced genetic counselor in HDGCS.

Surveillance in female patients with HDGC

Due to the high risk of lobular breast cancer, in women with HDGCS, calculated to be from 39% to 53% until the age of 80 years, it's recommended, breast exam every 6 months and annual mammography. A better alternative is the use of MRI, since it is more effective in the diagnosis of lobular breast cancer than mammography [23].

New techniques in the evaluation process for CGDH patients.

Endodrill 1A (BIBB Instruments Lund, Sweden):

This is a new instrument developed by Region S Kant, Sweden, which uses a drill style movement within a rigid metal coverage, allowing deeper sampling, including the submucosa. Presented by R. Skantin his study "" Endodrill vs. conventional biopsy, evaluation of diagnostic capacity in diffuse gastric cancer "", Clinical Trails.gov, ends December 2019 [24,25].

Double bite technique:

"Biopsy Technique for Endoscopic Surveillance of Hereditary Diffuse Gastric Cancer ", Study carried out by Dr. Massimiliano di Pietro, University of Cambridge [21], in patients with HDGCS. The technique consists of taking a biopsy, reposition the forceps, and take another biopsy from the same site. The biopsies were taken at "suspicious areas", 5 random biopsies of the 6 segments in the stomach (pre pylorus, antrum, transitional zone, body, fundus and cardia).

Confocal Endoscopic Microscopy (CEM): For detection of early stage gastric cancer in subjects with HDGCS:

In a protocol of investigation, that begin in August 28, 2018 - ended October 24, 2019: Sponsor - National Cancer Institute (NCI): Responsible party: National Institutes of Health Clinical Center. An endoscope was advanced into the stomach, patient injected with fluorescein (for better image contrast) , the microscope (Cellvizio (R) 100 microscope) advanced through the endoscope biopsy channel , generating "" optical biopsies "", real-time microscopic images of the tissue being evaluated, looking for foci of intra mucosal signet ring cell carcinoma ("" signet ring cell "") [26,27].

Liquid Biopsy Technique

One of the new techniques described to detect mutated DNA/RNA, **is** to take blood samples to identify circulating DNA (ctDNA) produced by malignant tumors in the body and used as measures of prevention and prognosis [28-34]. Although this technique is beginning to be used in gastric and colon cancer in advanced stages, perhaps eventually it can be used preventively in the identification of HDGCS in their early stages.

Conclusions

As we have seen the HDGC is an aggressive condition, caused by a mutation in the CDH1 / E-cadherin, which in turn causes the development of a submucosal malignancy. This submucosal growth makes its early diagnosis difficult using

the endoscopic techniques available at this time. Prophylactic gastrectomy in patients with syndrome HDGC, is the only effective prophylactic technique available to prevent the development of the diffuse gastric cancer diffuse in these patients. It still remains the only preventive alternative in patients with HDGC between 18 and 40 years of age. Given the drastic changes in the life styles of the patient, associated with this surgery, and that not all patients with the mutation will develop cancer, another alternative would be annual endoscopies, following the protocol of Cambridge. Knowing these endoscopic techniques will not help us to detect changes in its early stages. By previous studies, we have known that new techniques such as white light panendoscopy, Endoscopic ultrasound, High Resolution Endoscopy, Chromoendoscopy, Narrow Band Imaging, Autoflorescence Imaging/Magnification aren't effective in early diagnosis. Perhaps the new endoscopies techniques "in vivo"" cytology evaluation of gastric mucosa, liquid biospies, will help in the early diagnosis of patients with HDGC.

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