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REVIEW ARTICLE

Hereditary diffuse gastric cancer: how to look for and how to manage it

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Abstract
With a current molecular revolution, hereditary gastric cancer represents a small group of patients that require a special multidisciplinary treatment. Surgeons being a member of the multidisciplinary teams are an important part of the diagnosis, treatment and follow-up of these patients. The prophylactic nature of the gastrectomy with all different problems associated with this procedure need to be widely discussed with patients. We present a review of how to look for and how to manage a hereditary diffuse-type gastric cancer.

Keywords Hereditary · E-cadherin · CDH-1 · Stomach cancer · Molecular

Hereditary gastric cancer

Gastric cancer (GC) is still one of the most common cancers worldwide [1]. Even though its incidence decreased in the last years, still it is the third highest cancer-related cause of death after lung cancer and liver cancer [2]. The vast majority of GCs are of sporadic origin, but about 10% of the cases represent familial background. The environment factors are well-known and infection of Helicobacter Pylori and Epstein Barr Virus (EBV) is only an example of such a factors. The real hereditary GC occurs in about 1–3% of cases [3]. The main 3 syndromes are represented by hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC) [3].

GC is also related to hereditary cancer syndromes. An example of such a group is Lynch syndrome. It is caused by a mutation in one of mismatch repair (MMR) genes. The other syndromes that play an important role in familial GC are Li-Fraumeni syndrome, Peutz-Jeghers, hereditary breast and ovarian cancer, MUTYH-associated adenomatous polyposis and juvenile polyposis syndrome and PTEN hamartoma tumor syndrome (Cowden syndrome) [4].

It is seen from the analysis of 75 families with CDH1 mutation that the cumulative risk of diffuse-type GC by age of 80 is 70% for men and 56% for women. Additionally, lobular breast cancer in females with this CDH1 mutation is about 42% by age of 80 years [4]. It is also underlined that no other cancers showed significantly increased the incidence of occurrence [5].

For many years, it has been suggested that family history of GC may be responsible for less aggressive GC as we compare it with sporadic one. However, the new data by van der Post et al. showed that survival of patients with CDH1 mutation is poor and presented 4% of 5 years survival compared with 13% of patients without that mutation [6, 7].

The HDGC should be taken into consideration in patients presenting specific familial cancer history. According to the International Gastric Cancer Consortium and the publication of the group, the established criteria are for 1st and 2nd-degree relatives [4]:

- 2 GC cases regardless of age, at least one confirmed diffuse GC
- One case of diffuse GC < 40
- Personal or family history of diffuse GC and lobular breast cancer, one diagnosed < 50

Additionally for families in whom testing could be considered:

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- Bilateral lobular breast cancer or family history of 2 or more cases of lobular breast cancer < 50
- A personal or family history of cleft lip/palate in patients with diffuse gastric cancer
- In situ signet ring cells and/or pagetoid spread of signet ring cells

These new criteria were established as a consensus of experts and to simplify the way we should treat these patients. Using the criteria proposed in 1999, the detection rate of CDH1 mutation was 25–50%, and with criteria formed in 2010, it has decreased to 10–18% in low GC incidence countries [5, 8–11]. The genetical analysis should be made on the basis of three-generation family tree. All genetical tests need to be confirmed by signing the special content and then discussed by a full multidisciplinary team (MDT). The genetical analysis might be offered even for 16–18-year-old patients as some case reports showed also diffused GC in patients younger than 18 [12].

MSI and GC

MSI is a new molecular subtype of gastric cancer and from clinical point of view is characterized by female gender, older age, Lauren intestinal histotype, no lymph node involvement, mid/lower gastric location, TNM stage I/II [13].

The link between familial background and GC characterized by MSI has been found by Keller et al. [14]. They found that in patients with positive history of familial GC in 1st and 2nd relatives, the incidence of MSI occurred in 46%. In the paper by Leite et al., the incidence of familial history and MSI GC was found in 24% of cases [15]. Younger age and a higher rate of females were found. In a paper by Polom et al. on sporadic GC, MSI was found in 22.1% and in familial background GC, MSI was found in 28% of cases [16]. The results of familial GC and its link to MSI has been described by many authors but probably because of a small group of patients and different methods used for MSI detection the results are inconclusive [17–21]. The publications by Predazzani et al. and Kanemitsu et al. showed a link between MSI and familial history of GC [19, 22]. The contrary results showing no link between MSI and familial history of GC were published by Bernini et al. [21] and Polom et al. [16]. One of the explanations might be the age of patients analyzed in the different studies. In the majority, MSI is linked with older age and younger patients represent only a small group of MSI GC patients [23]. In the publication by Arai et al., no patients with MSI were aged 51–64 or below [24]. Currently, an interesting publication by Therklidsen et al. has been published on the 1624 Lynch syndrome mutation carriers from Danish hereditary non-polyposis colorectal cancer register [25]. They showed the incidence of 30 extra-colorectal neoplasms in this group of patients. For gastric cancer, in Lynch syndrome, the peak incidence rate was after the age of 70. Maybe following these results, we should focus more on the elderly MSI gastric cancer patients to find a familial background associated with Lynch syndrome.

Prophylactic gastrectomy

The group from Utrecht University in the publication by Haverkamp et al. presented their experience in prophylactic laparoscopic total gastrectomy with jejunal pouch reconstruction in patients presenting CDH1 mutation [26]. They reported a group of 11 patients with a median age of 40 (22–61). They found multiple foci of intramucosal diffuse signet ring cell cancer in 9 of 11 cases (82%). In all cases, radical resection was performed. The laparoscopic approach seems to be interesting, but the authors showed 2 cases with anastomotic leakage (2nd and 3rd case so probably related with a learning curve) and a complication rate of 55% with no mortality in 60 days. The median length of stay in hospital was 10 days. D1 lymphadenectomy was performed, and all patients presented N0 status.

The Canadian experience presented by Hebbard et al. reported 23 patients who underwent prophylactic gastrectomy [27]. Only 2 of them had a positive gastroscopic biopsy for a cancer occurrence. After operation, 22 of 23 on the final standardized pathological examination revealed diffuse cancer of signet ring cell characteristic, so almost all of them were not detected by standard gastroscopy before the operation. Also, this group showed 6 patients with major complications and 14 with minor ones.

The largest cohort was published by Memorial Sloan Kettering team in a publication by Strong et al. on 41 patients [28]. They performed 25 open and 16 minimally invasive operations with 27% presenting complications and 1 (2.5%) postoperative mortality. In 85% of cases in final pathological examination, 1 or more demonstrated intramucosal signet ring cell cancer with only 1 patient being diagnosed by preoperative biopsy. They also reported data about the weight loss of median 4.7 kg (15% of preoperative weight) with a stabilization of the weight after 6–12 months. Patients reported postoperative outcomes were collected from 20 patients. All patients who fulfilled the questionnaire returned to work. In 40% of cases, the overall outcome was reported to be as expected and in 45% better than expected. The results were similar with other patients who underwent total gastrectomy because of GC without the mutation.

A publication by van der Kaaij et al. presenting Dutch people's experience about morbidity after prophylactic gastrectomy in a group of 26 patients points out that we

should present these data to our patients [29]. In the first year after the operation, re-laparotomy was performed in 5 of 26 patients (adhesiolysis in 2 patients, jejunostomy-related complications in 3 patients). In the first year, 6 patients were readmitted to hospital because of nutritional or psychosocial support with 2 reoperations included in that group. The authors showed that the patients mean weight loss was 15%. In the follow-up after 1 year versus 3 months after surgery, the main complaints were bile reflux—15 versus 11 patients, and dumping syndrome 11 versus 7 patients. 15 of 19 patients who studied or worked before surgery returned to full work activity after 1 year. These data should point out the importance of still high risk of morbidity and functional problems of patients treated with prophylactic gastrectomy.

The Italian experience from Milan published by Feroce et al. described experience of two families. A 32-year-old patient in the first family was diagnosed with N+ diffused GC [30]. The sister was found to have GC as well based on CDH1 mutation and the father was also a carrier of mutation but after the gastroscopy with multiple biopsies refused prophylactic gastrectomy. The second family was diagnosed starting with 36-year-old patient presenting lobular breast cancer with a strong family history of this type of breast cancer. After confirmation of CDH1 mutation, she underwent prophylactic gastrectomy with final pathology revealing diffuse GC. The brother also had the mutation in the gastroscopy which revealed signet ring cell GC and underwent gastrectomy; the uncle also with positive genetical test refused gastroscopy.

The group from Bonn, Germany in a publication by Pantelis et al. reported their experience of prophylactic gastrectomy in a group of 9 patients where 8 of them presented CDH1 mutation and 1 presented SMAD4 mutation [31]. D2 lymphadenectomy was performed in 4 of 9 patients and proven multifocal signet ring cell cancer has been found in 6 of 9 (67%) patients. It is important to note that only one patient presented preoperative confirmation of cancer. No lymph node metastases have been found in the pathological examination.

An interesting publication by Hallowell et al. analyzed different factors that affect the decision making of a patient with HDGC [32]. The factors presented by them were: receiving a positive mutation test result, or positive biopsy result, perceptions of cancer burden, subjective risk perceptions, experiences and perceptions of the different risk management options and individuals' stage in the life course. It is clear that multidisciplinary decision making is crucial in this group of patients, but currently, many groups of patients are also active especially in social media and this aspect should also be taken into consideration especially that they collaborate with centers of excellence and support the families together with their own example [33].

With prophylactic gastrectomy, we should also analyze the fact that this operation is associated with severe postoperative syndromes. In a paper by Worster et al., the authors checked the quality of life of patients who underwent prophylactic gastrectomy using EORTC quality of life questionnaire (QLQ C30 and QLQ STO22) [34]. Importantly at baseline, they have not found any difference in mental health depending on the CDH1 mutation and treatment preferences. The physical activity decreases and then came back to the baseline before operation. The mental functioning decreased in the first month but recovered by 3–9 months. The patients presented specific symptoms such as diarrhea (70%), fatigue (63%), discomfort during eating (81%), reflux (63%), eating restriction (45%), and body image (44%) that remained after surgery. In previous publication, it was well-documented that in patients with cancer gastrectomy the comorbidity is up to 100% with symptoms like diarrhea, dumping syndrome, and loss of about 10–20% of body weight as compared with the time before cancer [35].

Gastroduodenoscopy protocol

First, it is important to underline again that all endoscopic procedures should be performed in specialized centers after multidisciplinary team (MDT) qualification. The optimal frequency of endoscopy is not set yet. As more biopsies are taken, we have to remember about the higher risk of bleeding after multiple biopsies so all anticoagulants if possible should be stopped before the examination. Careful inspection together with inflation/deflation (for linitis plastic confirmation) is mandatory. Before the biopsy, the mucosa should be washed carefully. The biopsies should be taken randomly. All even small foci should be examined and a biopsy should be taken. The examination should be performed with the additional help of endoscopic ultrasonography. A test for H. pylori infection should be performed even if this infection is not common in this type of gastric cancer.

The random biopsies should be taken from all the mucosa of the stomach with a special attention to all small foci as well as pale areas. According to Cambridge protocol in total minimum 30 biopsies should be collected with a minimal number of 5 biopsies from each of following areas: pre-pyloric area, antrum, transitional zones, body, fundus, cardia [36]. Taking more biopsies as reported by Fujita et al. is not feasible [37]. New visualization techniques, especially with chromoendoscopy, fluorescent techniques, and others, are awaited and their use in the HDGC should be carefully investigated.

Colon cancer and breast cancer surveillance

Few cases about colorectal cancer and appendiceal signet ring cell carcinomas in the hereditary diffused gastric cancer mutation carriers are reported [38–40] but still no high-quality evidence of higher risk of colorectal cancer incidence were found. Because of that, no specific endoscopic surveillance is recommended. For families with proven colorectal cancer history enhanced colonoscopy starting from 40 years should be planned with 3–5 years intervals.

For breast cancer, the link of HDGC with the lobular type of breast cancer was reported by Pharoah et al. [41]. The situation is complex because some families present no increased risk of breast cancer and some are at a higher risk of this type of cancer. Some genotype–phenotype link probably plays a more important role. Importantly, screening mammography is not a good tool for lobular breast cancer as the sensitivity is about 34–92% [42]. For this group of patients, MRI is recommended. Annual MRI starting at the age of 30 should be performed. Presence of breast cancer specialist in MDT meetings for these patients is mandatory. Dedicated trials for breast and colorectal cancers surveillance are awaited.

Gastrectomy and mastectomy—surgical point of view

Prophylactic gastrectomy should be strongly recommended for germline CDH1 mutation carriers. The best time for prophylactic gastrectomy is unknown. Oncological awareness from one side and quality of life after the operation from the second side are the main factors associated with the decision about prophylactic gastrectomy. For the majority of patients, prophylactic gastrectomy already reveals some invasive or at least in situ signet ring cell carcinoma. Currently, 20–30 year-old-patients is recommended for the operation. In case of prophylactic operation in the majority of patients T1N0 status of the disease is found and together with the data from signet ring cells GC studies an early stage of this histological type is associated with better prognosis [43]. In contrast, HDGC patients with signet ring cell pathology and advanced stage of the disease present poor outcome in less than 10% of patients presenting that it is a curable disease.

The recommended operation is total gastrectomy with Roux-en-Y type of anastomosis. The proximal and distal margins should be evaluated with pathologically intraoperative examination for confirmation of complete removal of gastric mucosa. Additionally, searching for Meckel diverticulum is recommended because sometimes gastric mucosa is present in this structure.

Extension of lymphadenectomy is debated. Some advocates for D1 lymphadenectomy as the majority of prophylactic patients present T1N0 stage of the disease. However, we stand on the position that in specialized centers D2 lymphadenectomy should be performed as in T1a intramucosal cancer the incidence of metastases into the lymph nodes is about 2–5% and even up to 6% in undifferentiated or diffuse histotype [44–46]. In case of T1b cancers, the incidence of lymph node metastases rises up to 17–28% of cases [45, 46].

The formation of the jejunal pouch is still under discussion. Currently, prospective trials showed not fully convincing results about this entity [47]. We recommend the reconstruction that a surgeon is most familiar with.

In the age of minimally invasive approach, laparoscopic and/or robotic prophylactic gastrectomy should be recommended as the advantages of these techniques are important especially for the group of young patients [26].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not involve any studies with animals.

Informed consent For this type of study formal consent is not required.

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