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Role of Gastrectomy in the Management of Gastric Pre-Malignancies - A Review of Current Literature and Illustrative Case Report

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Abbreviations

GC: Gastric Cancer; EGC: Early Gastric Cancer; SRCC: Signet Ring Cell Carcinoma; NSRC: Non-Signet Ring Cell; LN: Lymph Node

Background

Epidemiology

Gastric cancer has generally been subdivided histologically into intestinal and diffuse, with the intestinal type representing the majority of cases. The geographic variability in disease distribution is closely related to the regional prevalence of H. pylori. Despite its position as the third leading cause of cancer-related deaths, there has been a global decrease in the overall incidence of gastric cancer in recent decades [1]. However, this pattern is not reflected uniformly across gastric cancer subtypes. Review of epidemiologic data in low-incidence areas including the United States shows a relative increase in the proportion of diffuse gastric cancers, particularly in Signet Ring Cell Carcinoma (SRCC) [2]. These epidemiologic trends support an accumulating body of evidence that suggests that intestinal GC and diffuse GC are two distinct diseases with different clinical behavior. These characteristics have significant clinical implications that impact both diagnosis and management and therefore warrant increased attention in current medical literature.

Pathogenesis

It is currently believed that the pathogenesis of intestinal type GC is related to environmental risk factors such as *H. pylori* infection, food, and smoking status. In comparison, it appears that diffuse type GC has a much larger genetic component related to its development. A proposed model of carcinogenesis has been developed based on studies of hereditary diffuse cancers, which only represent 1-3% of total GCs [3]. Hereditary Diffuse Gastric Cancer (HDGC) is an autosomal dominant germline mutation of the CDH1 gene, which encodes E-cadherin, a cellular adhesion protein. Mutation carriers have a 70% lifetime risk for developing diffuse GC [3-5]. Gastric specimens from patients with HDGC are characterized by the presence of SRCC, suggesting a role for E-cadherin in the sequence of carcinogenesis. Further investigations have supported the suggestion of E-cadherin as a specific factor in SRCC. In cases of sporadic gastric cancer somatic loss of function mutations of the CDH-1 gene have been identified in patients with diffuse GC but not those with intestinal GC [3]. Immunohistologic studies have provided compelling evidence supporting the relationship between E-cadherin and SRCC and its utility as a diagnostic marker by demonstrating that in cases of GC with mixed histologic features changes in E-cadherin expression are only detected in the diffuse components [3].

Additional investigations of the molecular pathogenesis of SRCC have supported a genetic model of development. Malignant cells in SRCC have been found to show increased expression of TAZ protein, a known oncogene involved in the development of many cancers including non-small cell lung cancer, papillary thyroid cancer, colon cancer, and breast cancer [6]. High intracellular expression of TAZ is known to confer loss of differentiation and stem-cell characteristics in the development of poorly differentiated breast cancers, which supports the possibility that signet ring histology is indicative of neoplastic change [7].

Histopathology and Early Diagnosis

Early identification of DGC is very difficult as there are very few macroscopic changes in early stages and microscopic changes are subtle and subject to misinterpretation. Successful identification of a pre-neoplastic lesion or early SRCC requires close histologic analysis with careful review of both tissue architecture and cytology. A number of early neoplastic changes have been described throughout the literature and include: (1) tubule neck dysplasia, (2) SRCC in situ and (3) pagetoid spreading of signet ring cells [3-5,8].

Early histologic studies of gastric cancer suggest that intestinal and diffuse cancers originate from different anatomic regions of the gastric mucosa with the former developing from the surface epithelium and the latter from the tubular neck of gastric glands [8,9]. The tubular neck is situated at the junction between the gastric pit and the gastric gland and is an area of high proliferation [9]. Subtle architectural abnormalities of the tubule neck have been described in the literature as “tubule neck dysplasia” (TND). These changes have also been reported in association with atypical signet ring cells, and many authors have speculated that TND may be representative of early cellular changes ultimately leading to SRCC. Pagetoid spread has been considered a unique feature of HDGC [5], however sporadic cases of GC have been described in which foci of atypical tubule neck cells demonstrate upward and lateral spreading in clusters [9], suggesting that pagetoid spread may not be unique to HDGC,

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but rather a feature of SRCC in general. Signet ring cells have also been identified in varying number in cases of poorly-differentiated gastric cancer and have been observed to later transform into poorly differentiated cancers [10]. It is therefore reasonable to consider the possibility that these various histologic changes may represent a spectrum of changes that occur in the progression of the same pathologic process.

Detection methods

As previously described, early changes of diffuse GC are located in the gastric glandular neck which is located in the deeper tissues of the mucosa, below an intact surface epithelium. Macroscopic changes are often absent or subtle and missed on routine endoscopy [11]. Furthermore, the early histologic changes are easily mistaken for benign reactive processes such as inflammation or regeneration [12]. Investigations of improved diagnostic techniques have identified special endoscopic screening protocols and immunohistochemical stains with potential for improving earlier detection. This is an area in need of further research and investigation [6,13,14].

Case report

67 year old male was admitted to the hospital with complaints of melena, early satiety, abdominal pain and a 50 pounds weight loss over the course of one year. Patient has social history that includes 40 years of smoking as well as occasional alcohol intake. On EGD an antral mass was found and biopsy results revealed that most of the specimen consisted of benign gastric mucosa with ulceration and reactive changes. Multiple step sections showed small foci of adenocarcinoma with poorly differentiated signet ring cytoarchitectural features. MAK-6 immunostain highlighted the abnormal epithelial architecture and did not demonstrate any definite invasion of tumor into the submucosa. No evidence of *H. Pylori* was found. The surgical service performed a preoperative work up and found no evidence of metastasis and decision was made to proceed to the operating room.

Laparotomy was performed using a Chevron incision and a suspicious lesion was noted in segment 5 of the liver. Wedge biopsy of the lesion was performed using scalpel and hemostasis at the site of liver biopsy obtained using electrocautery. Frozen section of the wedge biopsy of liver lesion returned as granuloma. Celiac lymph nodes were sampled and sent to pathology. Greater curvature of the stomach was mobilized and short gastric vessels were taken with energy device. Using sharp dissection, lesser sac was accessed along the superior margin of transverse colon. Kocherization of duodenum was performed to enable distal transection at the Pyloro-Duodenal junction. To identify the site of preoperative biopsy and guide the proximal resection margin, an intraoperative gastroscopy was performed. Proximal transection was performed using gastrointestinal anastomosis (GIA) stapler 5 cm proximal to the superior margin of the gastric ulcer. Frozen section of the gastric margins was negative.

Final pathology demonstrated that the area of the previous biopsy showed marked submucosal edema and focal ulceration. Occasional scattered glands showed neutrophils and signet ring cells within the lumen. These glands also showed signet ring cells replacing the glandular mucosa. (See Figures 1-3) These glands were similar to those done at time of biopsy on initial EGD. Staining with Her2 was indeterminate. This is considered a neoplastic precursor lesion of diffuse types of gastric adenocarcinoma. All lymph nodes biopsied were benign with no evidence of malignancy. Postoperative surveillance included gastroscopy and computerized tomography (CT) scan which were negative for any local / regional recurrence.

Clinicopathology and Impact on Treatment

Retrospective studies comparing the clinic-pathologic features of SRC vs. NSRC cancer have yielded variable results (Table 1) [14-21]. The applicability of these studies has been questioned by Western authors as most were conducted in high prevalence geographic locations, which differ in population characteristics as well as screening practices and intervention strategies [22]. However, there is agreement between Eastern and Western authors that SRCC demonstrates unique behavior that often deviates from that of other GC subtypes. A 2009 case-control series identified SRC histology as a statistically significant negative prognostic indicator in patients with GC in addition to pTNM stage and tumor location. Through further analysis, the study concluded that SRC histology conferred a poor prognosis due to its invasive potential, increased rate of peritoneal carcinomatosis, and affinity for lymphatic tissue resulting in both higher frequency and greater extent of lymph node involvement [22].

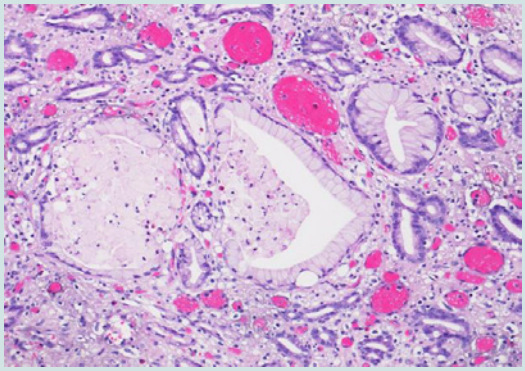

Figure 1: The gastric mucosa shows multifocal intramucosal signet-ring carcinoma cells confined within the gastric glands. In some glands, tumor cells about the non-neoplastic foveolar counterparts. No tumor cells are detected in the lamina propia or beneath the epithelial lining. Tumor cells are shed into the lumen, some underwent necrosis. Few eosinophils are present in the vicinity, the importance of which is unclear. *Helicobacter pylori* organisms are absent from this case (H&E, 20X).

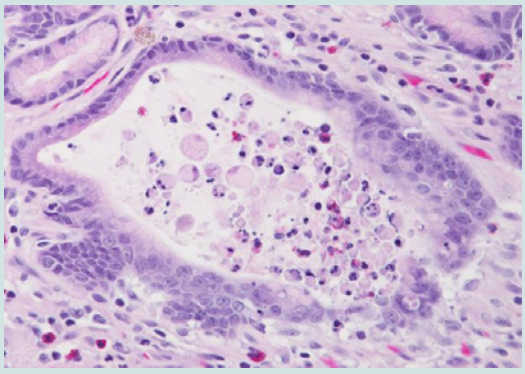

Figure 2: In other glands, tumor cells lack the signet-ring appearance and exhibit the usual features of nuclear pleomorphism, prominent nucleoli, accompanied by a loss of polarity (H&E, 40X).

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Table 1: Summary of studies that examined the prognostic significance signet ring cell histology in gastric cancer.

Study Reference (year)	Study Design	Sample Size and features	Prognosis according to stage		Other key findings
			Early	Advanced	
Kim et al. [14]	Retrospective	3702 patients 450 SRC (early, 185; advanced, 265)	N.S.	Worse prognosis	Advanced SRCs demonstrated more LN metastasis and deeper depth of invasion compared to advanced NSRCs
Otsuji et al. [15]	Retrospective	1498 patients 154 SRC (early, 94; advanced, 60)	Improved prognosis	N.S.	Increased peritoneal carinomatosis in advanced SRC
Yokota et al. [16]	Retrospective	683 patients 90 SRC (early, 41; advanced, 49)	N.S.	N.S.	Vascular invasion and tumor location were statistically significant prognostic factors
Hyung et al. [17]	Retrospective	933 patients with early GC (263 SRC)	Improved prognosis	(N/A)	Lower rate of LN metastasis overall no LN metastasis in tumors <1 cm Rate of LN metastasis did not increase with tumor size.
Kim et al. [18]	Retrospective	2358 patients 204 SRC; 94 early, 110 advanced	N.S.	N.S.	SRCs had a lower rate of LN metastasis in both early and advanced cancers vs. NSRCs
Kunisaki et al. [19]	Retrospective	1113 patients 174 SRC (early, 120; advanced, 54)	Improved prognosis	N.S.	Recommend gastrectomy with minimal lymph node dissection in patients with mucosal tumors <40 mm or submucosal tumors <20 mm
Jiang et al. [20]	Retrospective, mono-institutional	2315 patients 211 SRC (early, 54; advanced, 157)	Improved prognosis	N.S.	SRC histology is an independent predictive factor in survival rate in early gastric cancers only.
Li et al. [21]	Retrospective	4759 patients with advanced GC (662 SRC)	(N/A)	Worse prognosis	SRC histology identified as an independent risk factor for LN metastasis only. Statistically significant prognostic factors: depth of invasion, LN metastasis, hepatic/peritoneal metastasis, and surgical curability.

*GC: Gastric Cancer; SRC: Signet Ring Cell; NSRC: Non-Signet Ring Cell; N.S: No Significant Difference; N/A: Non-Applicable; LN: Lymph Node

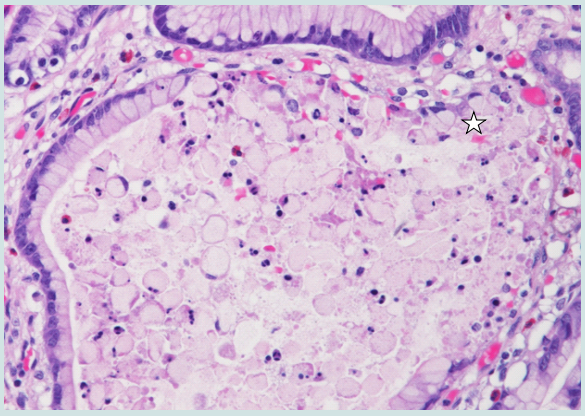

Figure 3: In this gland, the signet-ring carcinoma cells appear to have violated the basement membrane, thus suspicious for pagetoid spread or early invasion (H&E, 40X).

Many of these behaviors were supported by findings from previous studies [15,19,21], as well as subsequent literature identifying SRC or diffuse type histology as a positive predictive factor for lymph node involvement in EGC [21-23].

Endoscopic resection vs. primary surgery

In cases of intestinal GCs, pre-malignant lesions (neoplastic, non-invasive) that are identified as high-risk according to cytologic changes are treated with endoscopic resection. Early gastric cancer (EGC) is defined as an invasive malignancy that has not expanded beyond the submucosa, regardless of LN involvement [4]. In general, EGC has a significantly improved prognosis in comparison to advanced GC with 5YS reported as >90%. Studies of intervention strategies in EGC have suggested that patients meeting the following criteria are potential candidates for endoscopic resection: (1) tumor limited to the mucosa, (2) size <1-2 cm and (3) no histologic evidence of ulceration or lymphovascular involvement [24]. Studies on the risks for LN metastasis in early SRCand others comparing behaviors of different SRCCs have demonstrated that these criteria are unreliable in patients with SRC histology [25,26]. The strongest evidence comes from multiple studies identifying SRC histology as a risk factor for lymphatic involvement [21-23]. Overwhelmingly, recommendations for EGC and findings of signet ring cell histology are primary surgical treatment with gastrectomy and LN resection [21-24]. There is a general paucity of evidence regarding the use of perioperative chemotherapy. Large European clinical trials have proven the benefit of neoadjuvant chemotherapy in EGC, establishing it as the standard of care [27]. However, subsequent studies specifically investigating neoadjuvant therapy in early SRCC indicate that there is no survival benefit, and delaying surgery may in fact allow for disease progression [28]. Adjuvant chemotherapy following primary surgical resection is currently under investigation in a phase III RCT [29].

Future risk stratification

A final consideration in patient with SRC histology is evaluation of the need for referral to a genetic expert. Recently updated guidelines on HDGC have outlined criteria for initiating testing or considering familial testing patients with disease features suggestive of a hereditary syndrome (Table 2) [5]. In addition to gastric cancer, female HDGC mutation carriers have a 40% lifetime risk for developing lobular

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Table 2: Updated clinical criteria and recommendations for HDGC genetic testing.

Established criteria for genetic testing	Families in whom testing could be considered
- 2 GC cases regardless of age, at least one confirmed DGC - 1 case of DGC <40 - Personal or family history of DGC and LBC, one diagnosed <50	- Bilateral LBC or family history of 2 or more cases of LBC <50 - A personal or family history of cleft lip/palate in a patient with DGC - *In situ* signet ring cells and/or pagetoid spread of signet ring cells

*Criteria apply to 1st and 2nd degree relatives of patient in question

breast cancer [3-5]. Thus, genetic information may be important in future healthcare considerations and in determining appropriate screening practices for at-risk populations.

Conclusions

The recent changes in epidemiologic trends of diffuse gastric cancer make it a relevant topic warranting increased focus and attention. Based on the available literature, SRCC may be a potentially aggressive disease process and the finding of SRC histology therefore requires special consideration. If uncertain of the presence of change immunohistochemical evaluation may help establish a diagnosis. Patients with SRCC should be considered for immediate surgical intervention.

Potential Areas of Future Research

Molecular studies: biomarkers/targeted drug therapy.

Development of an SRC Specific treatment strategy.

Feasibility of less invasive surgical options.

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