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Current Concepts in Gastric Signet Ring Cell Carcinoma

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Abstract

Background: Classified as "diffuse" by the Lauren's classification gastric signet ring cell carcinoma is an adenocarcinoma with distinct features which separates it from other types of gastric cancer. Affecting mainly young female patients, gastric SRC is mainly due to the loss of E-cadherin and CDH1+. In this review we look into the pathogenesis, clinical features, diagnosis, treatment, and prognosis of gastric SRC.

Materials and Methods: We reviewed the literature published until September 2014 to identify studies of gastric SRC. Studies were identified by using the Medline and PubMed databases using the terms "gastric signet ring cell carcinoma", "gastric signet ring cell cancer", "signet ring cell cancer", "signet ring cell carcinoma". Researches on esophageal SRC, intestinal SRC were excluded in our study.

Results: A down-regulation of epithelial cadherin is essential for the initiation, and progression of gastric signet ring cell cancer cells. Once gastric cells lose E-cadherin, they have an increase in motility due to epithelial-mesenchymal transition. A strong correlation in the mutation of Snail, Slug, and Twist as well as an activation of the phosphatidylinositol 3 kinase (PI3K)/AKT axis, Wnt/β-catenin signaling pathway, and transforming growth factor β have been found to be associated with the pathogenesis of gastric signet ring cell cancer. Diagnosis relies mainly on histological findings. While surgical treatment includes resection and lymphadenectomy with retrieval of at least 15 lymph nodes, few patients respond well to chemotherapeutic regimens.

Conclusion: Despite recent advances, more patients are being diagnosed with advanced gastric SRC. Understanding the pathogenenis of gastric signet ring cell cancer is critical in the treatment and improving the prognosis of patients.

Keywords: Gastric carcinoma, Signet ring cell carcinoma, Prognosis

Introduction

According to WHO, gastric cancer is microscopically classified into 4 types: tubular, papillary, mucinous and poorly cohesive (including signet ring cell carcinoma) [1]. Any cell type that amounts to more than 50% of the total determines the histology of the tumor [2]. Therefore gastric signet ring cell carcinoma (SRC) is defined as an adenocarcinoma in which the majority (>50%) consists of isolated or small groups of malignant noncohesive cells containing intracytoplasmic mucin [3].

Classified as "diffuse" by the Lauren's classification gastric SRC has distinct features which separates it from other types of gastric cancer [4]. Affecting mainly young female patients, gastric SRC is mainly due to the loss of E-cadherin and CDH1+ [5]. In this review we look into the pathogenesis, clinical features, diagnosis, treatment, and prognosis of gastric SRC.

Materials and Methods

We reviewed the literature published until September 2014 to identify studies of gastric SRC. Studies were identified by using the Medline and PubMed databases using the terms "gastric signet ring cell carcinoma", "gastric signet ring cell cancer", "signet ring cell cancer", "signet ring cell carcinoma". Researches on esophageal SRC, intestinal SRC were excluded in our study.

Etiology and pathogenesis

A down-regulation of epithelial cadherin (E-cadherin) is essential for the initiation, and progression of gastric signet ring cell cancer

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cells [6]. Encoded by the CDH1 gene [7], E-cadherin plays a vital role in epithelial tissue cell-to-cell adhesion [8]. It is yet unclear as to how a CDH1 mutation leads to diffuse gastric cancer. One hypothesis is that the gastric epithelium is more prone to damage caused by genetic and epigenetic damage [9]. The latter might be caused by an increase in carcinogen exposure, hypoxia [10], long-standing inflammation [11], or even Helicobacter pylori infection [12]. The other possibility could be due to an intrinsically high cellular turnover, tissue remodelling and repair [13]. Proteolytic enzymes are also believed to play a role in the down-regulation of CDH1 gene. Mechanisms such as gene mutation, degradation by matrix metalloproteinases have also been found to be responsible for the down-regulation of E-cadherin in diffuse gastric cancer [14].

Once gastric cells lose E-cadherin, they have an increase in migration and are hence able to transgress into the basement membrane as well as invade into the surroundings [15]. This is a fundamental characteristic of cancer cells which are known to be able to detach themselves from the primary tumor, elude apoptosis, invade and metastasize to other parts of the host. Changes in E-cadherin are believed to be linked with epithelial-mesenchymal transition (EMT) [16]. Under physiological circumstances, EMT is an essential process necessary for normal embryonic development, wound healing, and fibrotic disease [17,18]. However, unwanted activation of EMT in the gastric mucosa has been shown to result into genesis, invasion and metastasis [19]. This is mainly achieved by having epithelial cells lose their adhesive properties, then arranging cytoskeletal components in such a way that they are rendered more motile, and eventually redesigning the extracellular matrix so as to facilitate invasion [20]. During EMT, E-cadherin transforms into neuronal-cadherin (N-cadherin) [21]. N-cadherin is an invasion promoter. Once epithelial cells begin to express N-cadherin, a cascade of molecular changes occurs making the cells more motile and invasive.

Till now, three types of EMT have been discovered [22]. Associated with the normal embryonic development, type I EMT is fundamental during the development of organs such as the heart and musculoskeletal system [23,24]. Type II is necessary during wound mending and tissue repair_ after an injury, epithelial cells are transformed into inflammation-induced fibroblasts to assist in healing [22]. Type III EMT is present during tumor initiation and invasion; it allows cancer cells to metastasize and promote carcinoma progression [20]. This type may also be associated with chemoresistance and the formation of stem cell phenotypes [25]

In these phenotypes EMT-induced cancer stem cell is believed to be responsible for the aggressiveness of gastric SRC. Recent studies have shown that not all cells have the ability to be cancerous. It is only the subgroup of cancer stem cells that can actually initiate, extensively proliferate, self-renew and differentiate into heterogeneous tumorigenic cancer cells [26]. Gastric cancer cells expressing CD44 have been shown to express cancer stem cell properties. These cells have the power to not only initiate tumorigenesis but also act as reservoir for defense against treatment [27]. Recent studies have shown CD44 to be substantially significant with the expression of EMT-activating transcription factors hence showing that gastric cancer stem cells may be associated with EMT [28].

Aside from initiating tumorigenesis, EMT has an essential role in tumor progression. The latter is done by bestowing gastric SRC cells with migratory and invasive properties which induce stem cells properties, contribute in immunosuppression and eventually prevent both apoptosis and senescence. Tumor invasion consists of multiple biological processes which enable tumor cells to move from the primary neoplasm to the underlying stroma. Known processes include the loss of cellular adherence, separation of cells from the extracellular matrix, proteolytic breakdown of the stroma, and the motility to actively push a tumor cell through the stroma [29]. Next is tumor metastasis. The multistep process is as follows: local invasion, intravasion, transport, extravasation and colonization.

Transcription factors such as Snail, Slug, Twist have been found to be strongly correlated with the cadherins switch in gastric signet ring cell gastric cancer. Snail is a member of the Snail superfamily of zinc finger transcription factors [30]. Being able to attach DNA to its carboxyterminal zinc fingers, Snail has been characterized as a transcriptional repressor [31]. Like EMT, Snail has an essential function in embryonic development [32]. It is also responsible for neural differentiation, cell division and survival [33]. An overexpression of Snail has been found to correlate with a down-regulation of E-cadherin [34]. Snail has an essential role in mediating the normal physiological function of NF-κB. Recent studies have shown that up-regulation of snail mediated through nuclear factor-κB (NF-κB) contributes to the loss of E-cadherin. NF-κB is involved in the control of cell growth. Mutation in NF-κB hence allows the cells to evade apoptotic death. As observed by Hu et al, an inhibition of NF-κB has been shown to result in an overexpression of E-cadherin and a underexpression of snail. Using a time-dependent method, they concluded that a loss of E-cadherin may be mediated through the NF-κB-induced snail upregulation [35]. Another mechanism that has been proposed for Snail degradation is the binding and phosphorylation of GSK3. While phosphorylation leads to ubiquination phoshorylation results in protein subcellular localization alteration [36].

Slug (Snail2) is another member of the Snail superfamily [30]. Under physiological circumstances, the transcription factor is present in the neural crest and mesodermal cells [37]. In tumorigenesis, Slug has been found to repress and transcript the E-cadherin gene by binding to the E-box elements of the proximal E-cadherin promoter [38,39]. Slug's expression in diffuse gastric cancer has been found to be positively correlated to lymph node metastasis and an advanced TNM stage. This implies that Slug has a role in both the promotion and invasion of gastric signet ring cell cancer [40]. Further studies still need to be performed to determine the exact mechanism as to how Slug contributes to E-cadherin down-regulation.

Twist, a major gene responsible for the regulation of EMT is mainly located in the placenta, the embryonic mesoderm, and in adult undifferentiated tissue which originated from the mesoderm. During embryonic development, Twist functions mainly in the induction of cell migration and in the formation of

tissue morphogenesis [41]. While the exact pathway of how Twist promotes gastric signet ring cell cancer is unknown, Lopez et al found that an up-regulation of Twist activates the AKT pathway. This results into the down-regulation of E-cadherin along with the activation of EMT and COX-2 inhibitor [42]. In gastric cancer, the latter has the ability to induce the expression of proangiogenic factors, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase [43].

Few signal pathways have been shown to express a correlation between EMT and gastric SRC. Activation of the phosphatidylinositol 3 kinase (PI3K)/AKT axis [44], Wnt/β-catenin signaling pathway [45], and transforming growth factor β (TGF-β) [46], have all been shown to play a critical role in gastric SRC initiation and progression. Gastric cancer cells depend on the PI3K/AKT pathway activation for attachment and spreading. PI3K phosphorylates PIP2 into PIP3. When PIP3 binds the the PH domain AKT is activated [47]. Since PI3K/AKT is positive regulators of GSK3β activity, an up-regulation in the PI3K/AKT pathway leads to EMT through Snail mediated CDH1 repression [48].

The extent of a cytoplasm's β-catenin phosphorylation and degradation leads to the stimulation of the Wnt/β-catenin signal. β-catenin binding to E-cadherin and actin results in a down-regulation of the Wnt signal. Again, GSK3β plays an essential role in this pathway [49]. Activation of the Wnt signal is only possible when GSK3β phosphorylates β-catenin. Dephosphorylation of the latter eventually leads to an accumulation of β-catenin in the plasma. Since this excess of β-catenin can move freely into the nuclei of gastric cells increase in the expression of Snail, Slug and Twist is observed, ultimately activating EMT. Moreover, Wnt activation is also made possible when snail reaches for the β-catenin in the N-terminal region of the Wnt signal [50].

Generation of EMT is also made possible through TGF-β. Briefly, TGF-βinduces the TGF-β receptor type II (TβR- II), which phosphorylates TGF-β receptor type (TβR- I) [51]. EMT is further improved when this stimulated TβRI kinase phosphorylates Smad2/3 to merge with Smad4 for nucleus translocation [52]. According to a study by Ono et al, protein-bound polysaccharide can inactivate Smad2 signaling to directly inhibit the TGF-β pathway in GC [53]. Thus, the inhibition of the TGF-β pathway is a potential treatment for GC.

However, only a down-regulation of E-cadherin is insufficient for the development of gastric SRC. There needs to be at least 2 hits for the disease to happen. Histone mutations have been implemented to play a role in the epigenetic regulatory mechanism [54]. Recent studies have shown the second hit is most likely due to hypermethylation [55]. More than 50% of patients suffering from gastric signet ring cell cancer have been observed to express hypermethylation. As observed by Humar et al, each and every of the gastric signet ring cancer cells had an obvious regular pattern, implying the malignant cells are independent and of monoclonal origin [56]. Hypermethylation of histone proteins at specific residues plays a critical role in determining whether a gene expression is active or silent. Zeste homolog 2 (EZH2) is a transcriptional repressor that has a crucial function in maintaining the homeostasis between gene expression and repression. Since E-cadherin has been shown to be suppressed through the regulatory action of EZH2 on histone H3 methylation in gastric cancer cells [57] we believe further research is needed to find out whether EZH2 plays a role in the second hit in gastric SRC.

Several triggers have been hypothesized for the second CDH1 hit. These triggers include hypoxia, inflammation, Helicobacter pylori infection. It should be noted that at the time of diagnosis most patients do not have an active Helicobacter pylori infection; this suggests that either this pathogen is not a major trigger for the CDH1 hit or that transient episodes of Helicobacter pylori infection or gastritis are enough to induce methylation.

Diagnosis

Diagnosing a patient with gastric signet ring cell carcinoma is solely based on the histological diagnosis >50% of the cells are isolated or small groups of malignant noncohesive cells containing intracytoplasmic mucin [1]. Typically, young and or female patients present with the disease [58]. Till now, there is no definite reason as to why females are more predisposed to gastric signet ring cell cancer. Researchers believe sex hormones affect the SRC histology for pregnancy and delivery have been shown to accelerate carcinogenesis. A recent immunohistochemical analysis showed that more than 80.0% of SRC expressed estrogen receptors require estrogen for growth and infiltration [59]. However, conflict exists on this hypothesis. Lindblad et al observed a reduced risk of gastric cancer in a male cohort treated with estrogen, supporting the hypothesis that the female hormone may play a preventive role in gastric cancer [60].

Gastroesophageal reflux, dyspepsia, epigastric pain, upper gastrointestinal hemorrhage, vomiting, unwanted weight loss were the most common clinical manifestations leading to endoscopic examination with biopsy. At the time of diagnosis, most patients present at an advanced stage with metastasis to lymph nodes [61], peritoneum [62], ovary, uterine cervix [63].

Histological examination is essential in diagnosing the endoscopic biopsy. However, the usual immunohistochemical stain can fail to diagnose whether the patient has gastric SRC. It is hence essential for the pathologist to suspect gastric SRC and use the Alcacian blue [64] or Genta stain [65] which has better sensitivity in diagnosis

Treatment and prognosis

Surgical resection with lymphadenectomy is the treatment of choice for gastric SRC. The type of surgical procedure will depend on the tumor location. For cancers found in the proximal or in the middle third of the stomach a total gastrectomy is recommended as the probability for recurrence to occur to the gastric stump is substantially decreased. A subtotal gastrectomy with negative margin is appropriate for patients diagnosed with a distal gastric cancer. In order to avoid recurrence a luminal margin of 5-6 cm with frozen-section analysis is recommended. For both promixal and distal gastric cancers, the surgical procedure should include retrieval of at least 15 lymph nodes [66].

The pT stage of gastric SRC is strongly correlated to whether there is metastasis to the splenic hilum lymph nodes. Unless a patient has a suspected enlarged hilar node or has metastasis

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to the spleen, the latter should be preserved. However for an advanced proximal gastric tumor (pylorus and upper body) even when the above 2 recommendations are not met, a splenectomy is advised. This is because the risk of residual disease in the splenic hilum nodes is about 15-20%. However, preoperatively and perioperatively diagnosing a patient with advanced gastric cancer is not an easy task_ not only does preoperative diagnosis by CT scan or endoscopic ultrasound lack in accuracy but also an intraoperative macroscopic diagnosis is far from possible.

Nowadays, different continents use different guidelines in the non-surgical treatment of gastric cancer. For example, Europeans favor perioperative chemotherapy, Americans adjuvant chemoradiotherapy, while Asians have found better survival in using adjuvant chemotherapy. However, till today there has been no evaluation of the sensitivity of gastric SRC towards chemotherapeutic drugs. Few retrospective studies have observed chemotherapeutic resistance, especially observed during neoadjuvant treatment. In a phase II study by Rougier et al., the effect of 5-fluorouracil and cisplatin was investigated on 30 patients diagnosed with locally advanced gastric adenocarcinomas. While a 56% response rate was observed in the overall population, only 16% of gastric SRC patients were susceptible to the regimen [67]. The same results were observed by Takiuchi et al. (83.3% versus 22.2%) [68].

Recently, Messager et al. investigated the effects of perioperative chemotherapy using an epirubicin-cisplatinum-5-Fluorouracil (ECF) regimen. 171 gastric SRC patients were given the ECF treatment while 753 patients were not. The authors observed an overall median survival of 14.0 months and a 3-year survival rate of only 11.7%. Patients who had received preoperative ECF did not show any survival benefits over those who did not. Among the 171 patients that had used perioperative chemotherapy, adjuvant chemotherapy was given to 106 patients (64.8%). These patients did not observe any cytotoxic effect of chemotherapy. There was no downstaging in lymph nodes, no decrease in the risk of recurrence, no improvement in the R0 resection rate and no eradication of micrometastases [69].

Cytoreductive surgery and hyperthermic intaperitoneal chemotherapy have been considered in the treatment of gastric SRC with peritoneal metastasis. Patients diagnosed with a peritoneal metastasis have found a better response rate when an intraperitoneal approach was considered. This increase in efficacy is not only due to the positive gradient of chemotherapy maintained by the peritoneal plasma but also due to hyperthermia. A temperature of 42-43°C enhances both the effects of antimoral drugs (oxaliplatin, mitomycin C, doxorubicin, cisplatin, paclitaxel, irinotecan) as well as increases the chemosensibility of neoplastic cells. Care should however be taken not to exceed 43°C to avoid the risk of bowel perforation [70]. In a randomized controlled trial by Yonemura et al, advanced gastric cancer patients with a peritoneal metastasis observed a 61% 5-year survival rate when treated with both hyperthermic intraperitoneal chemotherapy and surgery. However, gastric SRC patients observed only a median overall survival time of 8-14 months, despite a complete cytoreduction in 72% [71].

In advanced gastric SRC, the presence of signet ring cells is in itself an indicator of poor prognosis. This is mainly because at the time of diagnosis there is already metastasis to lymph nodes and to the peritoneum [72]. Even after a radical resection and an aggressive chemotherapeutic treatment, up to half the patients are found to have recurrence [73]. In the literature 5 factors have been found to determine whether there will be peritoneal carcinomatosis recurrence: the presence of a linitis plastica, tumor invasion to and beyond the peritoneal serosa, positive lymph nodes, a tumor of gastric origin, and chemoresistance [74-78]. Strikingly if the SRC is of gastric origin the patient is at a higher risk of having the primary tumor evolving into a the peritoneum [79]. This characteristic is not so often observed in esophageal or junctional tumors. One possible reason could be since the intra-abdominal location of the stomach is already covered by a peritoneal surface metastasis is facilitated.

On the other hand early gastric SRC has a good prognosis. Patients are younger, are found to have less lymph node involvement, and no metastasis to the peritoneum [80]. Unlike the advanced stage, the presence of signet ring cells is not a prognostic factor in early gastric SRC. In fact independent predictors of poor prognosis were incomplete tumor resection, age>60 years, malnutrition [81]. Patients who have a very early gastric cancer (less than 3 cm in size, without ulceration, and with no metastasis to lymph nodes and to the peritoneum) can be considered ideal candidates for endoscopic mucosal resection (EMR) and endoscopic submucosal resection (ESR) [82]. We however do not advise to stick only to an endoscopic resection. This is because at the time of presentation patients are already at an advanced stage of the disease and would require a total gastrectomy. Also, since patients are positive for a CDH1 mutation, a preventive radical total gastrectomy with extensive lymphadenectomy is indicated. Hence, even if the patient has performed an endoscopic resection, we advise to perform an explorative laparoscopy as well as a preventive total gastrectomy if the patient has a mutation in the CDH1 gene.

Since there is an obvious chemoresistance observed among gastric SRC patients, targeted molecular therapy is an interesting option to counteract cancer progression. Targeting EMT would selectively target tumor cells who have started to develop motility. Owing to the central role Snail has in EMT focusing on this transcription factor either though the use of small interfering RNA (siRNA) or through the use of chemical inhibitors would eventually offer a better prognosis for advanced staged patients.

Conclusion

Despite recent advances, more patients are being diagnosed with gastric SRC. Downregulation of E-cadherin. EMT and transcription factors such as Snail, Slug, Twist, as well as hypermethylation are believed to play a role in the pathogenesis. The patient is usually a young female presenting with GERD, abdominal pain and weight loss. Unfortunately, most patients are already at an advanced stage of the disease at the time of diagnosis. Surgical treatment includes resection and lymphadenectomy with retrieval of at least 15 lymph nodes. Depending on the tumor location, a subtotal gastrectomy or total gastrectomy is performed. There is controversy on whether a chemotherapeutic regimen should be used. Most patients do not respond well to chemotherapy, and the survival benefit is only increased by a few months. While a patients with early gastric SRC have a good prognosis, patients in a more advances stage do not. Therefore, once the disease has attacked a person, the rest of the family should be screened.

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