Primary Squamous Cell Carcinoma of the Stomach

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ABSTRACT: Squamous cell carcinoma (SCC) of the stomach is a rare entity. There are several theories regarding the development of this tumor, but its pathogenesis remains obscure. Fewer than 100 cases of primary SCC of the stomach have been published in the literature. Due to advanced stage at the time of diagnosis in most of these cases, the prognosis is generally poor. In the case presented here, endoscopy revealed a vegetative tumor in the stomach described as SCC by biopsy. Following curative surgery, adjuvant chemotherapy was administered; however, the patient died 3 years and 4 months after surgery after recurrence was diagnosed.

KEYWORDS: stomach, carcinoma, squamous cell carcinoma, tumor

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Introduction

The squamous cell carcinoma of the stomach is a very uncommon entity, with worldwide incidence of 0.04% to 0.07% of all gastric cancers,[1–5] with fewer than 100 cases reported in the literature to date. It occurs mostly in men, and the male to female ratio is 5 to 1.[5–7] It is more prevalent in the sixth decade of life,[4] and the most common tumor location is in the upper third of the stomach,[5] although 17-year-old patients have also been reported.[8] The pathogenesis of this tumor remains unknown; however, the presence of squamous metaplasia and positive history of smoking is often related to cases of squamous cell carcinoma of the stomach.[9,10] In addition, squamous cell carcinoma of the remnant stomach following gastrectomy is extremely rare and has been described in less than 5 reported cases.[11] The optimal treatment strategy is controversial and the prognosis is poor. Röring,[12] who described the first primary gastric squamous cell carcinoma case in 1895, hypothesized about basal cells in the gastric mucosa undergoing, transforming into squamous cells, and later turning into squamous cell carcinoma. Since then, not much has changed, although several theories have been proposed referred to this respect.[4,13,14]

Clinical Report

A 52-year-old woman, smoking 20 cigarettes per day (1 cigarette package) during the past 20 years, without any pertinent history, came for consultation due to several month history of intermittent abdominal pain accompanied by weight loss of 7 kg. Laboratory testing revealed moderate anemia, clinically well tolerated, and tumor markers elevated (carcinoembryonic antigen [CEA], 47 ng/mL and carbohydrate antigen [CA] 19-9, 196 U/mL), and on endoscopy, an excrescent neoplasm was seen in the fundus and lesser curvature of the stomach occupying half of the lumen, papilliform, ulcerated, and friable, which extends toward the cardia following the incisura. Biopsy reported findings suggestive of squamous cell carcinoma, so further studies were performed. Computed tomography (CT) revealed a large exophytic mass in the gastric fundus and body with infiltration of the adjacent fat and an adenopathic conglomeration at the level of the gastrohepatic ligament compressing the left lobe of the liver, at some points showing an absence of a plane of separation (Figure 1).

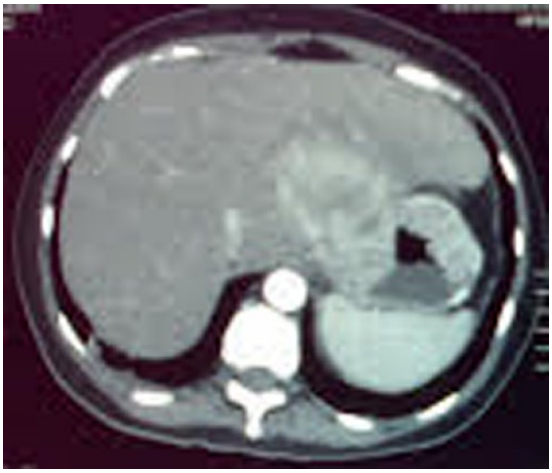

Figure 1. Computed tomography (CT) which reveals a large exophytic mass in the gastric fundus and body with infiltration of the adjacent fat and an adenopathic conglomeration at the level of the gastrohepatic ligament compressing the left lobe of the liver.

At surgery, an extensive gastric tumor was identified that infiltrated segments II, III, and IV of the liver. A total gastrectomy, greater and lesser omentectomy, splenectomy,

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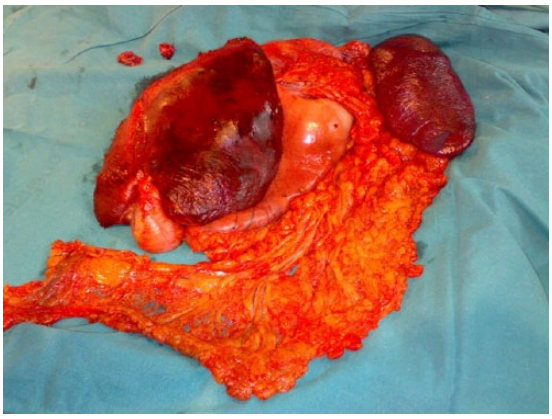

Figure 2. Extirpated sample that includes a total gastrectomy, greater and lesser omentectomy, splenectomy, cholecystectomy, and left hepatectomy.

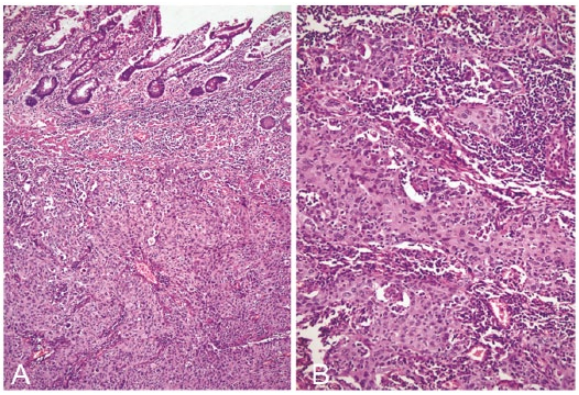

Figure 3. (A) Gastric mucosa substituted for a proliferation of keratinized cells that infiltrate the muscle layer (hematoxylin-eosin, original magnification ×10) and (B) the tumor nests composed of cells with ample eosinophilic cytoplasm with occasional keratinization (hematoxylin-eosin, original magnification ×20).

cholecystectomy and left hepatectomy, and reconstruction using a Roux-en-Y esophagojejunostomy were performed (Figure 2). The macroscopic histologic examination of the external surface of the stomach described an area of retraction of the serosa in the anterior surface and lesser curvature that corresponded to an excrescent tumor on opening the stomach, brownish in color with a papillary surface, measuring 10 cm × 8 cm; on the postero-superior surface of the stomach, another lesion measuring 7 cm × 6 cm × 5 cm was identified that infiltrated the liver tissue and protruded and ulcerated the mucosa. Both tumors were 0.5 cm apart from each other, and continuity with the esophageal mucosa could not be established for either of them, neither macroscopically nor microscopically. Microscopically, the presence of malignant epithelial proliferation was described which grew into a cord-like pattern with frequent images of dyskeratosis (Figure 3); there were anaplastic areas present with a high level of atypia and multinucleated giant cells with a lymphoid response and intense chronic gastritis with marked intestinal-type metaplasia.

Following surgery, the patient was evaluated by the Oncology Department to receive adjuvant treatment.

During 2 years, the patient was free of disease; this was verified by the normality of tumoral markers, CT scan, and magnetic resonance imaging (MRI) findings, which did not show recurrence, neither local nor metastatic. After 3 years of surgery, the patient presented with dysphagia and vomiting. Her physical examination revealed hypogastrium pain, without masses or visceromegaly, normal bowel sounds, blood count, and tumor markers (CEA and CA 19-9). Computed tomographic scan showed an 8.4 cm × 7.0 cm × 7.0 cm peripancreatic mass and 1.3 cm local lymph nodes due to recurrence. Endoscopy showed a normal esophageal motility and diameter, total gastrectomy, and an exophytic mass extending up to the blind end of the jejunal loop from the anastomosis that hinder emptying the efferent loop, supporting the diagnosis of anastomotic recurrence. Gastroscopy showed a big tumoral mass at the anastomotic level which covered almost the entire circumference and compressed the efferent loop. Biopsies were taken, and the diagnosis was confirmed. Treatment was initiated with reduced doses of docetaxel-cisplatin-5FU (TCF). Partial response after 3 cycles (mass of 5 cm × 4 cm and local lymph nodes <1 cm) was observed to be complete at the end of 6 cycles. The surgical resection of the recurrence was proposed, but the clinical worsening contraindicated the procedure. The patient died from sepsis due to intestinal necrosis and splanchnic ischemia, 3 years and 4 months after surgery.

Discussion

Many gastric tumors initially diagnosed as squamous cell carcinoma turn out to be, on close examination of the surgical sample, gastric adenosquamous cell carcinoma or esophageal squamous cell carcinoma with gastric extension. The diagnosis is established by applying the widely accepted criteria of Parks,[15] which excludes any case in which the tumor is located in the cardia and any tumor in which there is tumor extension with the esophageal mucosa. In addition, the presence of squamous cell cancer in any other site (uterus, lung, bronchi, pancreas, etc) must be ruled out. Our case meets the 3 criteria described above.

Prior to Parks, Boswell and Helwig[16] described 4 histopathologic criteria for diagnosis of squamous cell carcinoma, of which at least 1 must be present to make such a diagnosis: (1) keratinized cell masses forming keratin pearls, (2) mosaic cell arrangement, (3) intercellular bridges, and (4) high concentration of sulfhydryl and/or disulfide groups, indicating the presence of keratin or prekeratin. In our case, the presence of malignant epithelial proliferation that grows into a cord-like pattern was seen with frequent images of dyskeratosis (Figure 3); there was infiltration of the gastric serous membrane and liver tissue, none of the lymph nodes were metastasized, and the surgical borders were free of tumor infiltration (T4N0Mx).

Another classification[17] is the diagnostic criteria for primary squamous cell carcinoma of the stomach, by the Japanese

Gastric Cancer Association: (1) All the tumor cells are squamous cell carcinoma cells and any part does not contain gland cancer cells, and (2) there is sufficient evidence to show that squamous cell carcinoma originates in the gastric mucosa.

Despite standardization of the diagnostic criteria, the etiopathology continues to be unknown, although theories exist regarding the origin of squamous cell carcinoma of the stomach.[15,18,19] One hypothesis, the most likely in our opinion, is that proposed by Boswell and Helwig,[16] which suggests that squamous cell carcinoma of the stomach develops from a metaplastic squamous focus. The existence of this, though very rare, has been described around peptic ulcers,[16] following ingestion of a corrosive agent,[20] in one case of *linitis plastica* associated with congenital syphilis,[21] and during long-term chemotherapy treatment in a case of lymphocytic lymphoma.[22] The occurrence of induced squamous cell metaplasia has been documented by injecting the submucosa with pyrogallic acid in experimental animals. One recent case published in the literature[23] supports this hypothesis and relates the occurrence of squamous metaplasia with the process of chronic repair and inflammation associated with Mènètrier disease. In our case, once again, the histologic study was unable to identify cell metaplasia over which the squamous cell carcinoma had developed.

Mori et al[24] identified an adenomatous component during the detailed histologic study of 3 cases of squamous cell carcinoma of the stomach. This finding led them to the hypothesis that the precursor metaplastic squamous cell lesions would develop from an adenocarcinoma. However, it is difficult to accept that in pure squamous cell cancers, there are no histologic remains that suggest the previous existence of adenocarcinoma. Takita et al[25] proposed that Epstein-Barr virus (EBV) infection may be involved in the pathogenesis of certain cases of gastric squamous cell carcinoma. In the study of Hwang et al,[7] a liquid hybridization assay for human papillomavirus (HPV) infection and polymerase chain reactions for EBV infections were performed, which revealed the presence of EBV infection in surgical specimens of the tumor. However, no evidence of HPV or EBV infection was identified in the case of the same authors[7] when using DNA microarray for HPV infection and in situ hybridization for EBV infection. Other less-accepted hypotheses involve the growth of squamous cell tumors from undifferentiated stem cells mediated by still undetermined stimuli and the existence of nests of ectopic squamous epithelium.

Patients with gastric squamous cell carcinoma have variable clinical symptoms, such as abdominal pain, dysphagia, nausea and vomiting, melena or hematochezia, hematemesis, and weight loss, most of which are identical to those of other types of gastric tumors.[9] Raju et al[26] reported a case of a patient with squamous cell carcinoma of the stomach and hypercalcemia; in their opinion, malignant hypercalcemia is due to ectopic production of parathyroid hormone by the tumor; on the contrary, Chen et al[9] observed hypocalcemia in 9 of 56 patients and hypoalbuminemia in 9 patients and hypothesized that patients with hypocalcemia and hypoalbuminemia were related to inadequate intake and excessive consumption of the disease. Because of the limited number of cases, we did not find whether hypocalcemia and hypoalbuminemia were associated with prognosis or not. Needless to say, the development of sophisticated detection methods can contribute to setting up early diagnosis of gastric squamous cell carcinoma, which is most important to improve the prognosis of this tumor.

Immunohistochemistry represents an important complementary tool for the routine diagnosis of cancer and for the identification of the different histologic types and prognosis factors. Its purpose is to categorize patients to ensure appropriate and specific treatment, as well as to identify tumors at higher risk of recurrence and fatal outcomes. The essential immunohistochemistry panel recommended for the diagnosis and prognosis includes expression of several markers, such as CK5, CK7, CK20, TTF1, p63, chromogranin, synaptophysin, CEA, and CA 19-9.

Some immunohistochemistry studies have found strong straining for p63 and high-molecular-weight cytokeratin (CK5/6) with a specificity of 99% and a sensitivity of 98% for squamous cell carcinoma.[10,27] However, the association between serum CYFRA 21-1 level and the clinicopathologic features and prognosis in patients with gastric cancer was studied. In patients with primary gastric cancer, the serum CYFRA 21-1 titer was significantly higher than that of healthy controls, although it was not significantly higher than that of patients with benign gastrointestinal disorders.[28] CYFRA 21-1 is a reliable tumor marker for gastric cancer in predicting very advanced cases, recurrence of the disease, and overall poor prognosis. The study of tumor markers for gastric cancer is actually considered.[29]

The squamous cell carcinoma of the stomach has a locally aggressive behavior and a poor short-term prognosis, mostly due to late diagnosis and frequent lymphovascular serosal involvement.[6,7,30] In most of the cases, the disease is at an advanced stage at diagnosis, and hence, prognosis is poorer compared with other types of cancers of stomach[31]; however, Altshuler and Shada[13] disagreed. The overall survival rate of the patient is from 7 months to 8 years.[2,31] Adjuvant chemotherapy appears to improve survival rates, although there are insufficient data to support this statement,[2,4,5,9] so the role of adjuvant chemotherapy and also radiotherapy to long-term survival still cannot be justified[11]; only one previous study has demonstrated the efficacy of chemotherapy against the tumor.[32] In our case, surgical removal was complete, and at 2 years, after receiving 3 rounds of chemotherapy with cyclophosphamide and 5-fluorouracil, the patient was disease free. However, the patient died 3 years and 4 months after surgery from sepsis due to splanchnic ischemia and intestinal necrosis after recurrence was diagnosed. Neoadjuvant treatment was not indicated due

to lack of evidence for its beneficial effects in this type of tumor; this approach was supported by authors cited in this article.[9]

Author Contributions

RV acquired the data and wrote the paper. EC contributed to the pathologic study, and JAG-S and JAR-M designed the research, reviewed the current literature, analyzed and discussed the data, and revised the article. All authors approved the final version to be published.

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