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TITLE: A rare case of primary squamous cell carcinoma of the stomach and literature review

ABSTRACT

Introduction
Given that stomach is lined by glandular epithelium, the most common type of gastric malignancy is adenocarcinoma, which accounts for more than 90% of primary gastric carcinomas. Primary squamous cell carcinoma of the stomach is an extremely rare entity with an incidence of 0.04% to 0.07% among all gastric carcinomas. In this study, we report a case of a 66-year old man and review the literature about this uncommon disease.

Case Report
A 66-year old man presented to our outpatient department and complained about epigastric pain. Gastroscopy found a protruding mass (about 3.0cmx4.0cm) with central ulceration on the greater curvature of the middle gastric body. He was finally diagnosed with primary squamous cell carcinoma of the stomach based on pathological examination of biopsies. The patient declined further examination and therapy, lost to follow-up after discharge.

Conclusion
Primary squamous cell carcinoma of the stomach is an extremely rare entity. This type of tumor is aggressive and prone to metastasize to lymph nodes and liver, it is critical to make a correct diagnosis at early stage and place the patients on appropriate management.

Keywords: primary squamous cell carcinoma of the stomach, gastric carcinoma, adenocarcinoma, squamous metaplasia
TITLE: A rare case of primary squamous cell carcinoma of the stomach and literature review

INTRODUCTION
The most common type of gastric malignancy is adenocarcinoma and primary squamous cell carcinoma of the stomach is extremely rare\[1, 2\]. The pathogenesis is still not well understood for the latter. It exhibits non-specific symptoms such as epigastric pain etc. The prognosis is poor since it is usually diagnosed at an advanced stage and prone to metastasize to lymph nodes and liver. No general consensus on the management of this disease is available. This study presents a case of a 66-year-old man who presented as epigastric pain and protruding mass on the gastric body. Epidemiological characteristics, hypotheses regarding pathogenesis, available diagnostic criteria, management and prognosis are also discussed based on literature review.

CASE REPORT
A 66-year-old man presented to our outpatient department with a complaint of epigastric pain for four months. He denied any other symptoms like dysphagia, haematemesis, and melena. His past medical history was unremarkable. Mild tenderness was elicited on the epigastric area. Other systems were normal on physical examination. No data of laboratory tests was available. An upper gastrointestinal endoscopy was performed, which revealed a protruding mass (about 3.0cmx4.0cm) with central ulceration on the greater curvature of the middle gastric body. The mass was friable and covered by yellow greasy fur [Figure 1]. Endoscopic observation was normal for the esophagus, gastroesophageal junction and cardia. Multiple endoscopic biopsies were taken for histopathological examination, identifying a moderately differentiated squamous cell carcinoma with keratinized cell masses and keratin pearl formation under haematoxylin-eosin staining [Figure 2]. No evidence of adenocarcinoma was found. Finally, a diagnosis of primary squamous cell carcinoma (SCC) of the stomach was confirmed. Unfortunately, the patient declined further examination and therapy, lost to follow-up after discharge.
DISCUSSION

It is well known that the stomach is lined by glandular epithelium, the most common type of gastric malignancy is adenocarcinoma, which accounts for more than 90% of primary gastric carcinomas [1, 2]. Primary SCC of the stomach is an extremely rare entity with an incidence of 0.04% to 0.07% among all gastric carcinomas [3]. It was first described by Rörig et al in 1895 and less than 100 cases have been reported in the English literature [3]. There is a male predominance in the incidence of primary gastric SCC, with a male/female ratio of 5:1[4]. The peak incidence is in the sixth decade of life, however, a case as young as 17 years old has been reported by Schwab et al.[3, 5]. Wakabayashi et al reviewed 56 cases based on Japanese literature and reported a median age of 64.7±1.7, the ratio of male/female was 3.7(44/12) [6]. A retrospective analysis included 21 patients diagnosed in china reported a higher median age of 67 years old, a male/female ratio of 6:1[7]. The most common location of tumor is the upper third of the stomach (57.1%, 66.7%) [6, 7]. The common clinical manifestations were identical with other type of gastric tumors, included abdominal pain, nausea, vomiting, melena, haematemesis, and weight loss [4, 7]. Symptoms of paraneoplastic syndrome like hypercalcaemia and leukocytosis also have been reported [8, 9]. In addition, there was a patient of SCC of the stomach that presented as a huge retroperitoneal tumor revealed by CT scan and showed no significant results on endoscopic examination [10]. Here we reported a 66-year old male patient with primary SCC of the stomach, who presented with upper abdominal pain, in line with the epidemiology characteristics of this uncommon disease.

The pathogenesis of primary SCC of the stomach are still not well understood and various theories regarding its histogenesis have been proposed, including (1) the presence of nests of ectopic squamous cells in gastric mucosa; (2) squamous metaplasia of the gastric mucosa before malignant transformation; (3) squamous differentiation in a preexisting adenocarcinoma; (4) totipotential stem cells in the gastric mucosa which is capable of differentiating into any cell type[1, 11]. Islands of squamous epithelium have been identified in the gastric mucosa of individuals without SCC, supporting the theory that the primary SCC of the stomach may arise from ectopic squamous cells [12, 13, 14]. Squamous metaplasia may occur in the
Corrosive acid burns, infection with syphilis, chemotherapy for lymphocytic lymphoma, chronic inflammation and foveolar hyperplasia in Menetrier’s disease were also reported to be associated with squamous metaplasia of the stomach, which was further followed by development of squamous cell carcinoma [15, 16, 17, 18]. In addition to squamous metaplasia, SCC was also reported to arise in the context of chronic atrophic gastritis with intestinal metaplasia [3, 17]. Another theory suggested SCC may origin from the overgrowth of a squamous epithelium element in a primary adenocarcinoma, since the reexamination of previously diagnosed pure squamous cell carcinoma revealed components of adenocarcinoma [3, 19]. Mori et al. proposed the hypothesis that multipotential stem cells first turn into adenocarcinoma, followed by the occurrence of squamous metaplasia, which finally turn into SCC [19].

Besides the above etiological theories, some other risk factors have also been suggested for the pathogenesis of primary gastric SCC. Takita et al proposed that Epstein-Barr virus (EBV) infection may play a role in the development of gastric SCC given that the evidence of EBV infection was witnessed in surgical specimens of the tumor [20]. However, in situ hybridization of other patients failed to confirm evidence of EBV infection [9, 21]. The long-term use of cyclophosphamide has ever been suggested as a risk factor for the development of gastric SCC in patients with multiple myeloma and lupus erythematosus [22]. In addition, Chen et al reported that 61.9% of patients with gastric SCC had a long history of smoking [7]. It is well known that smoking plays an important role in the pathogenesis of squamous carcinoma of lung and esophagus. Taken together with Chen’s finding, it is suggested that smoking may be a risk factor for this disease.

Although primary gastric SCC is very rare, some diagnostic criteria have been suggested for it. According to the Japanese Classification of Gastric Carcinoma, the diagnostic criteria of primary SCC of the stomach include: (1) all tumor cells are SCC cells, without components of adenocarcinoma in any sections (2) there is distinct evidence that SCC arises directly from the gastric mucosa [3, 23]. To exclude SCC that extended from esophageal carcinoma and other primary sources, Parks proposed three diagnostic criteria: (1) the tumor should not be located in the cardia; (2) the tumor must not extend into the esophagus; (3) there must be no evidence of
SCC in any other part of the body [1, 3]. The histopathological criteria for primary SCC of the stomach were identified by Boswell and Helwig as followings: (1) keratinized cell masses with typical keratin pearls formation; (2) a mosaic pattern of cell arrangement with sharp borders; (3) the presence of intercellular bridges; (4) high concentrations of sulphhydryl or disulphide bonds which indicates the presence of keratin [14]. Immunohistochemistry analysis for indicators of squamous cell carcinoma (p63 and CK5/6), is widely performed to confirm the diagnosis, with a high specificity of 99% and a sensitivity of 98% [7, 24]. CK7, the indicator for adenocarcinoma, is negative in pure squamous cell carcinoma [3].

As our case is concerned, the tumor was located in the greater curvature of the middle gastric body. The possibility of involvement of cardia and esophagus was ruled out through endoscopic examination. No evidence of tumors in any other organs including skin was observed on physical examination. Thoracic computed tomography was carried out to exclude tumors originating from lung. Histologically, the tumor showed moderately differentiated squamous cell carcinoma without glandular components. Above all, our case meets the diagnostic criteria of primary SCC of the stomach.

Due to the rarity of primary SCC of the stomach, there is no general consensus on the management of this disease. Radical surgical resection remains the mainstay of the treatment for localized disease. Surgery to achieve R0 (no residual tumor) resection can substantially improve outcome. A retrospective analysis reported that patients could achieve a median survival time of 46 months in surgery group and 4.5 months in non-surgery group [7]. For advanced-stage SCC of the stomach, survival after surgical resection is poor and adjuvant chemotherapy may improve the prognosis [6]. Combined postoperative radiotherapy and chemotherapy with aggressive surgical resection have been reported to result in a recurrence-free survival time of 5 years [25]. However, no standard chemotherapy regimen has been established. The most commonly used chemotherapy regimens were based on 5-Fluorouracil [7]. Intrahepatic administration with 5-fluorouracil plus mitomycin was reported to obtain complete response in metastatic SCC in liver [4]. A patient on FP chemotherapy (5-fluorouracil plus cisplatin) after surgery has survived at least 45 months [7]. Amazing effectiveness of neoadjuvant chemotherapy with low-dose FP
was first demonstrated by Marubashi et al. in a 70-year old male patient [26]. Neoadjuvant chemotherapy with carboplatin and paclitaxel followed by successful surgical resection was also reported to improve a clinical outcome [27]. It is difficult to predict the prognosis of primary SCC of the stomach. Generally speaking, its prognosis is better than gastric adenocarcinoma [7]. An overall survival time ranging from 7 months to 8 years has been reported by Gao et al [4]. but it has also been reported that a patient died within 3 months of admission in Turkey [11]. However, primary gastric SCC is usually diagnosed at an advanced stage. Its marked local infiltration and distant metastasis often means a poor outcome [6]. Given that this uncommon tumor is aggressive and prone to metastasize to lymph nodes and liver, it is critical to make a correct diagnosis at early stage and place the patients on appropriate management.

CONCLUSION
Primary squamous cell carcinoma of the stomach is an extremely rare entity which has a peak incidence in the sixth decade of life and non-specific symptoms identical with other type of gastric tumors. It is usually diagnosed at an advanced stage and the outcome turns out to be poor. So prompt diagnosis and appropriate management are critical since it is aggressive and prone to metastasize to lymph nodes and liver.

CONFLICT OF INTEREST
There is no conflict of interest.

AUTHOR’S CONTRIBUTIONS
Xu Chen
Group 1- Finishing the gastroscopy examination and took the biopsies for pathological examination,
Group 2- Drafting the article
Group 3- Final approval of the version to be published
Chengxin Luo
Group 2- Drafting the article;
Group 3- Final approval of the version to be published

Hu Zhang

Group 1- Substantial contributions to conception and design;
Group 2- Revising it critically for important intellectual content;
Group 3- Final approval of the version to be published

REFERENCES


FIGURE LEGENDS

Figure 1: An upper gastrointestinal endoscopy revealed a protruding mass (about 3.0cmx4.0cm) with central ulceration on the greater curvature of the middle gastric body. The mass was covered by yellow greasy fur.

Figure 2: Histopathological examination of biospies taken under endoscopy identified a moderately differentiated squamous cell carcinoma with keratinized cell masses and keratin pearl formation under haematoxylin-eosin staining.
FIGURES

Figure 1: An upper gastrointestinal endoscopy revealed a protruding mass (about 3.0cmx4.0cm) with central ulceration on the greater curvature of the middle gastric body. The mass was covered by yellow greasy fur.
Figure 2: Histopathological examination of biopsies taken under endoscopy identified a moderately differentiated squamous cell carcinoma with keratinized cell masses and keratin pearl formation under haematoxylin-eosin staining.