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CASE REPORT

Lymphoepithelioma-like gastric carcinoma: A case report and review of the literature

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Author contributions: All authors contributed to the acquisition of data; Wang ZH and Yuan Z designed the research; Wang ZH was the physician in charge and participated in endoscopic treatment; Zhao JJ made the histopathologic and immunohistochemistry diagnosis, and provided the pathologic images; Wang ZH and Yuan Z performed the research and data analysis; Yuan Z wrote the manuscript; Wang ZH and Yuan Z revised the manuscript.

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Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

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Abstract

Lymphoepithelioma-like gastric carcinoma is a rare type of gastric cancer characterized by a carcinoma with intense stromal lymphocytic infiltration. Although lymphocytic infiltration is closely associated with Epstein-Barr virus (EBV) infection, concomitant occurrence with differentiated adenocarcinoma is relatively rare. The clinical manifestations of lymphoepithelioma-like gastric carcinoma (including EBV-positive and -negative forms) are similar to those of gastric cancer, and the diagnosis is based on pathologic, histologic, and immunohistochemical findings. This report describes the case of a 55-year-old female patient who presented with a 10-year history of recurrent and worsening abdominal pain and melena that had been occurring for 2 mo. An ulcerative lesion was detected in the stomach by endoscopic examination, which raised suspicion of early gastric cancer. A subsequent preoperative endoscopic biopsy showed adenocarcinoma, but the postoperative pathologic, histologic, and immunohistochemical analyses of the resected specimen revealed a final diagnosis of lymphoepithelioma-like gastric carcinoma.

Key words: Epstein-Barr virus; Lymphoepithelioma-like carcinoma; Stomach neoplasms

Core tip: Lymphoepithelioma-like gastric carcinoma is a rare subtype of gastric carcinoma with a better survival rate than other gastric cancers. It is similar

to gastric cancer, with no obvious early symptoms. Lymphoepithelioma-like gastric carcinoma is difficult to discern from biopsy specimens because of the stromal lymphocyte infiltrates. As preoperative diagnosis is difficult and it is easily misdiagnosed, cases are usually diagnosed pathologically after tumor surgery. In order to gain a detailed understanding of this rare disease, we reviewed the literature and report here on a recent case of epithelioid gastric cancer in our hospital.

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INTRODUCTION

Gastric cancer is the second leading cause of cancer mortality in the world[1]. Lymphoepithelioma-like gastric carcinoma (LELGC), first described by Watanabe *et al*[2] in 1976 as gastric carcinoma with a lymphoid stroma, is an uncommon subtype of gastric carcinoma (GC), which has a better survival rate than other GCs. LELGC comprises approximately 4% of all GCs[3,4], and its simultaneous occurrence with differentiated adenocarcinoma is relatively rare. Lymphoepithelial carcinoma[5], a type of undifferentiated nasopharyngeal carcinoma[6] with lymphoid stroma and non-keratinizing squamous cells, has distinguishing clinical, epidemiologic, and etiologic features. Lymphoepithelioma-like carcinomas (LELCs) are well known to occur in the nasopharynx. In comparison, LELGCs, which histologically resemble lymphoepithelioma[7], are not found in the nasopharynx but in various organs such as the stomach, lungs[8], tonsils, esophagus[9], salivary glands[10], thymus, cervix[11], and skin[12]. LELGCs tend to lack continuous sheets of cancer cells, but rather consist of small clusters and aggregates of cancer cells that are broken up by large numbers of intratumoral lymphocytes[7]. In order to acquire better insight into this rare disease, we review the literature here and report on a recent case of epithelioid gastric cancer in a patient from our hospital.

CASE REPORT

A 55-year-old woman was admitted to our hospital with a 10-year history of persistent abdominal pain, acid regurgitation, and heartburn. Two months prior to admittance to the hospital she had visited the emergency room with complaint of dizziness, fainting spells, cold sweat, amaurosis fugax, and melena. The patient had a history of multiple leiomyoma resection and use of nonsteroidal anti-inflammatory drugs. On admission, she was pale with normotensive blood pressure (105/68 mmHg), normal cardiac rhythm (85 beats/min) and ventilation rate (16 breaths/min).

The patient was then transferred to the gastroenterology ward and underwent a physical examination, which was unremarkable except for her pale appearance. Laboratory results revealed decreased hemoglobin (66 g/L) and hematocrit (0.208) levels, but an elevated urea nitrogen level (9.74 mmol/L). Meanwhile, no abnormal findings were detected by the chest radiograph or CT. However, gastroscopic examination revealed that the patient had a typical ulcerative lesion (malignancy could not be excluded) close to the gastric antrum, with an advanced damaged area of 3.0 cm × 3.5 cm (Figure 1A). A subsequent biopsy analysis revealed inflammatory changes. After the standard treatment of blood transfusion, acid suppression and protection of the gastric mucosa, the patient's symptoms improved and she was discharged from the hospital. As the possibility of GC was not completely eliminated, the patient was asked to continue the drug treatment and return one month later. The follow-up endoscopy showed that the ulcer remained unhealed (Figure 1B), while the biopsy revealed no malignancy. Accordingly, the drug treatment was combined with *Helicobacter pylori* eradication therapy for another month. Histologic typing at this time revealed an adenocarcinoma.

The patient was transferred to our general surgery unit for surgical treatment. In view of the patient's general condition, laparoscopic-assisted radical gastrectomy was performed under general anesthesia. Intrasurgical observation revealed that the tumor situated in the antrum had not invaded the serosa. Thus, groups of 1-8 lymph nodes were cleared, and the tumor was treated by distal subtotal gastrectomy. After providing continuous decompression, active antibiotics (cefotaxime sodium), acid-base balance fluid, rehydration, and other supportive treatment, the further postoperative course was uneventful and the patient recovered well.

Postoperative pathologic analyses (Figure 2) showed that the tumor was composed of epithelial cell nests surrounded by large numbers of lymphocyte plasma cells, which was consistent with lymphoepithelial carcinoma with deep myometrial invasion (tumor size was about 5.5 cm × 4.0 cm × 1.0 cm). Analysis of the upper and lower margins revealed no cancer tissue. Additionally, no lymph node metastasis was found in the regional lymph nodes. Furthermore, immunohistochemical analysis (Figure 3) indicated that the tumor cells were intensely positive for Ckpan and negative for CD3 and CD20. On the other hand, no expression of chromogranin, synaptophysin, or neuron-specific enolase was observed.

The patient did not receive any adjuvant chemotherapy or radiotherapy postoperatively, and she remains well without further evidence of the disease.

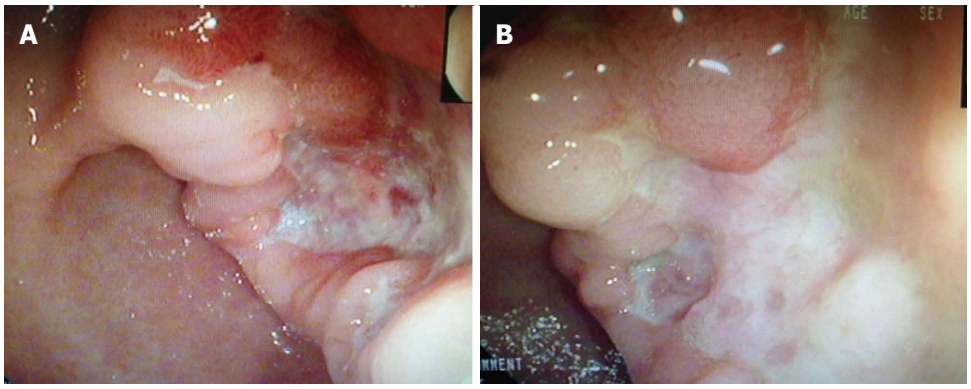

Figure 1 Endoscopic findings. A: The patient had a typical ulcerative lesion close to the gastric antrum; B: Follow-up endoscopy showed that the ulcer remained unhealed.

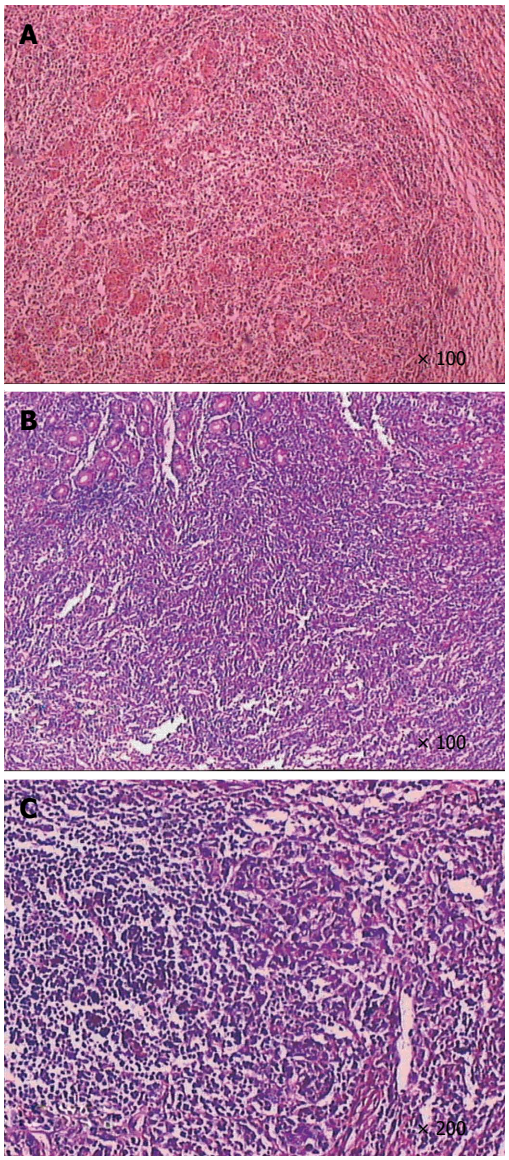

Figure 2 Hematoxylin-eosin staining of biopsy specimens indicated lymphoepithelioma-like gastric carcinoma.

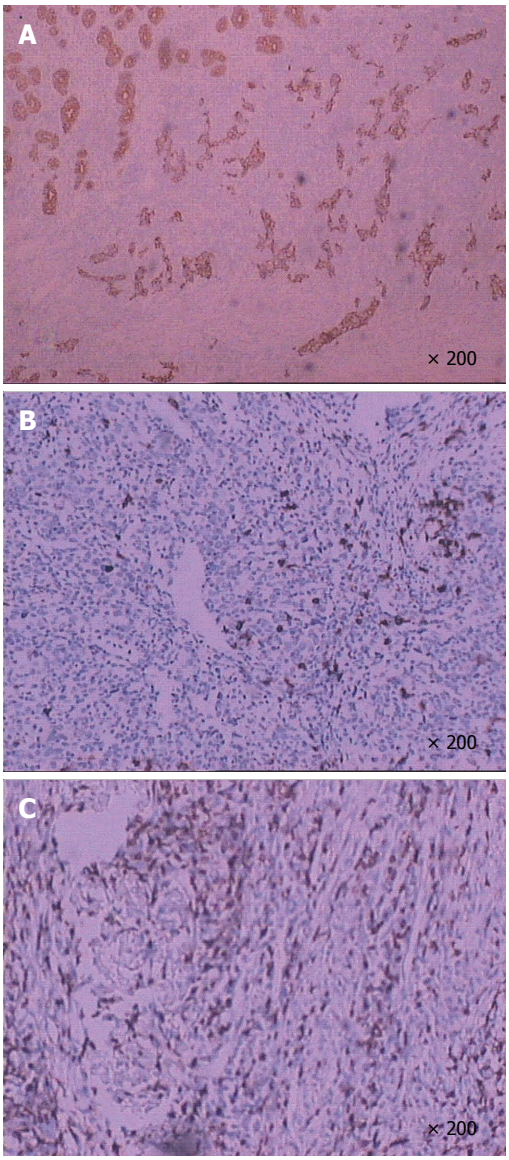

Figure 3 Immunohistochemical staining. The tumor was positive for Ckpan (A), and negative for CD3 (B) and CD20 (C).

DISCUSSION

LELGC is a type of GC with distinctive clinicopathologic features, including stromal, intense lymphocytic infiltration. EBV is believed to be a possible factor in the etiology of lymphoepithelioma-like tumors[13]. The worldwide prevalence of EBV infection among GCs has been reported as 8.29% for gastric adenocarcinoma, 7.08% for the intestinal type and 9.82% for the diffuse type[14]. EBV was the first virus found in human neoplastic cells, the Burkitt's lymphoma cell line, in 1964[15], and subsequent studies have identified the virus in a variety of malignant neoplasms. Two subsets of gastric cancer, namely EBV-positive and microsatellite instability-high cancers, have been linked with a lymphocyte-rich phenotype[16]. Additionally, EBV infection is reported to be associated with a majority of the nasopharyngeal carcinomas and a few of the LELCs[17]. Specifically, more than 90% of LELGCs occurring in areas other than the foregut were reported to be EBV-positive[18]. EBV-associated LELGC occurs more frequently in men[19]. As most cases of gastric cancer, the disease is usually prevalent among the elderly, and although some reports have indicated that tumors occur in younger patients[18,20], a meta-analysis did not confirm these reports[21]. In addition, while it has been shown in LELGC that only EBV-infected progenitor cells exhibit monoclonal proliferation, the exact mechanism whereby EBV contributes to gastric mucosa carcinogenesis, though a hot topic in cancer research, is still uncertain. Our patient refused to do EBV testing because of personal economic reasons.

LELGC is similar to GC in various aspects, such as no obvious early symptoms and occasional abdominal pain as the disease progresses. Additionally, there may be aggravated abdominal pain, loss of appetite, fatigue, weight loss, *etc*. The occurrence of LELCs with epithelioid granulomas has rarely been reported[22]. Hence, most radiologists are not familiar with these tumors. In the present case, imaging analysis revealed no lymph node or distant organ metastasis. This is because the spread of the tumors through the gastric wall may have been prevented by abundant lymphocytic and granulomatous reactions[22,23]. Because preoperative diagnosis of LELGC is difficult, most cases are diagnosed pathologically after tumor surgery, even if endoscopic biopsy is performed[24]. Indeed, a definitive diagnosis of LELGC could not be established in the present case from the sample obtained from endoscopic biopsy, as this disease is pathologically characterized by prominent lymphocytic infiltration, which often obscures the neoplastic epithelial component. Furthermore, small LELGCs are easily and frequently missed by endoscopic ultrasound fine-needle aspiration. Endoscopic mucosal resection is recommended for diagnosis and potential curative resection of gastric submucosal lesions[25]. In our case, despite thrice performing endoscopic biopsy, we were initially unable to make an accurate diagnosis.

Histopathologic analysis findings from our case were similar to those found in all previously reported cases, including characteristics such as a syncytial growth pattern, round-to-large vesicular nuclei, and prominent nucleoli. The nests of epithelial tumor cells were associated with an intense and accentuated lymphoid infiltrate[26]. Accurate diagnosis was aided by immunohistochemical staining for a panel of epithelial markers and common leukocyte antigens. Generally, immunohistochemical staining shows nests that are positive for cytokeratin, carcinoembryonic antigen, and epithelial membrane antigen, suggesting epithelial origin, and the interstitial lymphoid tissue, or T lymphocyte clones. In the present report, the immunohistochemical profile of the neoplastic cells showed strong positivity for cytokeratin.

In a previous study, the rate of 12-year disease-free survival in patients with LELC was reported to be approximately 95%[27], suggesting that the extensive lymphocytic infiltration contributes to a low risk of tumor spread and a better prognosis. In fact, a lower rate of lymph node involvement has been found in LELC, especially during its early stage within the submucosa[28]. Accordingly, a lymphadenectomy did not seem necessary in our case. Surgical resection of LELGC and adjuvant short-term chemotherapy offered a good prognosis. Homogeneous LELCs have a significantly better prognosis than other types of stomach cancer. Indeed, the 5-year survival rate is significantly higher than that of non-lymphoid epithelioma gastric cancer and there have been reports of a 5-year survival of 59%[28,29], reaching 62% for the pure type[30].

In summary, LELCs of the stomach are rare neoplasms, thought to be associated with EBV infection. Diagnosis is based on pathologic, histologic, and immunohistochemical analyses. LELGC is difficult to identify in biopsy specimens due to the stromal lymphocyte infiltrates. This tumor type generally has a better prognosis than other forms of EBV-associated GCs and conventional GCs[28].

COMMENTS

Case characteristics

A 55-year-old female patient, whose preoperative endoscopic biopsy showed adenocarcinoma, was finally diagnosed with lymphoepithelioma-like gastric carcinoma (LELGC) according to findings of postoperative pathology and immunohistochemistry of the resected specimen.

Clinical diagnosis

LELGC had no obvious early symptoms, and gastroscopy revealed a typical ulcerative lesion.

Differential diagnosis

Lymphoepithelial carcinoma discovered in nasopharynx, which histologically resembles lymphoepithelioma-like carcinoma (LELCs).

Laboratory diagnosis

A decreased level of hemoglobin (66 g/L) and hematocrit (0.208), and increased

urea nitrogen (9.74 mmol/L).

Imaging diagnosis
The CT appearance of LELCs with epithelioid granulomas has not been reported previously.

Pathological diagnosis
LELCs are pathologically characterized by a pronounced lymphocytic infiltrate, which often obscures the neoplastic epithelial component.

Treatment
Surgical resection of LELGC and adjuvant short-term chemotherapy has a good prognosis. The patient refused to receive any adjuvant chemotherapy or radiotherapy postoperatively, but did accept and receive oral proton pump inhibitor conservative treatment.

Related reports
There are a few cases of LELGC reported in the literature.

Term explanation
Immunohistochemical staining is widely used in the diagnosis of abnormal cells, such as those found in cancerous tumors. Specific molecular markers are characteristic of particular cellular events, such as proliferation or cell death (apoptosis).

Experiences and lessons
This case report represents the diagnosis and therapeutic strategy for LELGC, and patients with non-healing ulcers on standard treatment should be evaluated for possible malignant tumors using immunohistochemical analyses for differential diagnosis when necessary.

Peer-review
The authors performed a good literature review. Although this condition is not that rare, it deserves further recognition.

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