https://doi.org/10.22516/25007440.1252

Case report

Gastric Lymphoepithelioma-like Carcinoma: A Singular Case Challenging the Boundaries of Diagnosis and Treatment

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Citation:
Pacheco-Gaona JO, Mendoza-Orozco JE, Madariaga-Carocci CA. Gastric Lymphoepithelioma-like Carcinoma: A Singular Case Challenging the Boundaries of Diagnosis and Treatment. Revista. colomb. Gastroenterol. 2025;40(2):241-246. https://doi.org/10.22516/25007440.1252

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Received: 08/07/2024
Accepted: 12/04/2025

Abstract

Background: Lymphoepithelioma-like carcinoma is a rare presentation of gastric cancer, with an incidence of less than 4%. It has been associated with Epstein-Barr virus (EBV) in approximately 80% of cases. In the remaining cases, microsatellite instability has been documented, with loss of mismatch repair enzyme expression of the *hMLH-1* gene in 39% of cases. Chemotherapy is not standardized globally, and surgical management is considered first-line treatment. **Case Report:** We report the case of a 41-year-old male who presented with episodes of upper gastrointestinal bleeding, associated with a constitutional syndrome characterized by a 5-kg weight loss over the course of one month. An esophagogastroduodenoscopy revealed a Borrmann type III gastric adenocarcinoma. The patient underwent total gastrectomy, and the histological analysis revealed an infiltrating gastric carcinoma of the lymphoid stroma subtype, also known as lymphoepithelioma-like carcinoma. A notable finding was the reduced lymph node involvement, with only 2 of 25 lymph nodes affected. Immunohistochemistry was positive for CKAE1/AE3 and CAM5. The tumor was ultimately concluded to be a true lymphoepithelioma-like carcinoma, and Epstein-Barr virus positivity was confirmed using the EBER-ISH technique. **Conclusion:** Gastric lymphoepithelioma-like carcinoma is a rare entity with distinctive clinical and pathological features. Its strong association with Epstein-Barr virus highlights the need for a comprehensive diagnostic and therapeutic approach. This case underscores the importance of surgical management and immunohistochemical characterization to guide appropriate treatment.

Keywords

Epstein-Barr virus infections, gastric cancer, Epstein-Barr virus, microsatellite instability, immunohistochemistry.

INTRODUCTION

Gastric lymphoepithelioma-like carcinoma (LELC) is a rare subtype of gastric cancer characterized by undifferentiated carcinoma cells intermixed with a prominent lymphoplasmacytic infiltrate in the stroma. This type of cancer is strongly associated with Epstein-Barr virus (EBV) infection, though some cases test negative for EBV[(1)].

LELC accounts for approximately 1% to 4% of all gastric cancers. It is more frequently observed in men and often occurs in the upper regions of the stomach[(2)]. Clinically, it tends to exhibit less lymphatic spread and a better overall survival rate compared to other forms of gastric carcinoma, possibly due to the dense lymphoid stroma acting as an antimetastatic barrier[(1)].

Diagnosis is typically made via endoscopic biopsy and confirmed through histological examination, which reveals the characteristic lymphoid stroma and undifferentiated carcinoma cells[(1)]. Treatment approaches vary due to the disease's rarity, but successful outcomes have been reported with surgical resection and chemotherapy regimens such as tegafur, gimeracil, and oteracil plus oxaliplatin[(2)]. Despite

its aggressive histological appearance, the prognosis for gastric LELC patients is generally favorable, with many cases showing good outcomes post-treatment[3,4].

We present a clinical case of gastric lymphoepithelioma-like carcinoma (LELC). This diagnosis arose following a discrepancy in biopsy results and the patient's age, which fell outside the expected range for this tumor type. Additionally, multiple nodal involvement was identified, prompting exploration of further therapeutic options after surgical intervention. A pyrimidine inhibitor (capecitabine) was initiated as a chemotherapeutic agent in the context of adjuvant therapy.

CASE REPORT

A 41-year-old male patient presented with upper gastrointestinal bleeding in December 2019, accompanied by a 5 kg weight loss over one month, with no other associated symptoms. The patient underwent an upper gastrointestinal endoscopy (UGIE), which identified a gastric lesion described as a Borrmann type III fundic gastric adenocarcinoma. Initial pathological examination revealed a moderately differentiated infiltrating ulcerated adenocarcinoma. Staging studies via chest and abdominal computed tomography (CT) showed no metastatic lesions. Three months after symptom onset, a total gastrectomy was performed.

Pathological analysis of the gastric specimen described a lymphoepithelioma-like gastric carcinoma located in the gastric fundus, measuring 4 x 3 cm, with infiltration extending to the subserosa, along with lymphatic and perineural invasion but no vascular invasion (**Figure 1**). Surgical margins were tumor-free, and ectopic pancreatic tissue was noted as an incidental finding. Lymph node assessment revealed tumor involvement in 5 out of 25 lymph nodes without perinodal extension. The patient was evaluated by the clinical oncology service. Due to inconsistencies in the pathology results, a second review of both specimens was conducted. The final report confirmed that the gastric lesion identified in the UGIE was an infiltrating intestinal-type gastric adenocarcinoma with scant lymphocyte-rich stroma. The gastrectomy specimen confirmed an infiltrating gastric carcinoma of the lymphoepithelioma-like subtype, with the same size and infiltrative status as the previous report. The only difference was a reduction in nodal involvement, with 2 out of 25 lymph nodes affected by the neoplasm. Additional immunohistochemical studies

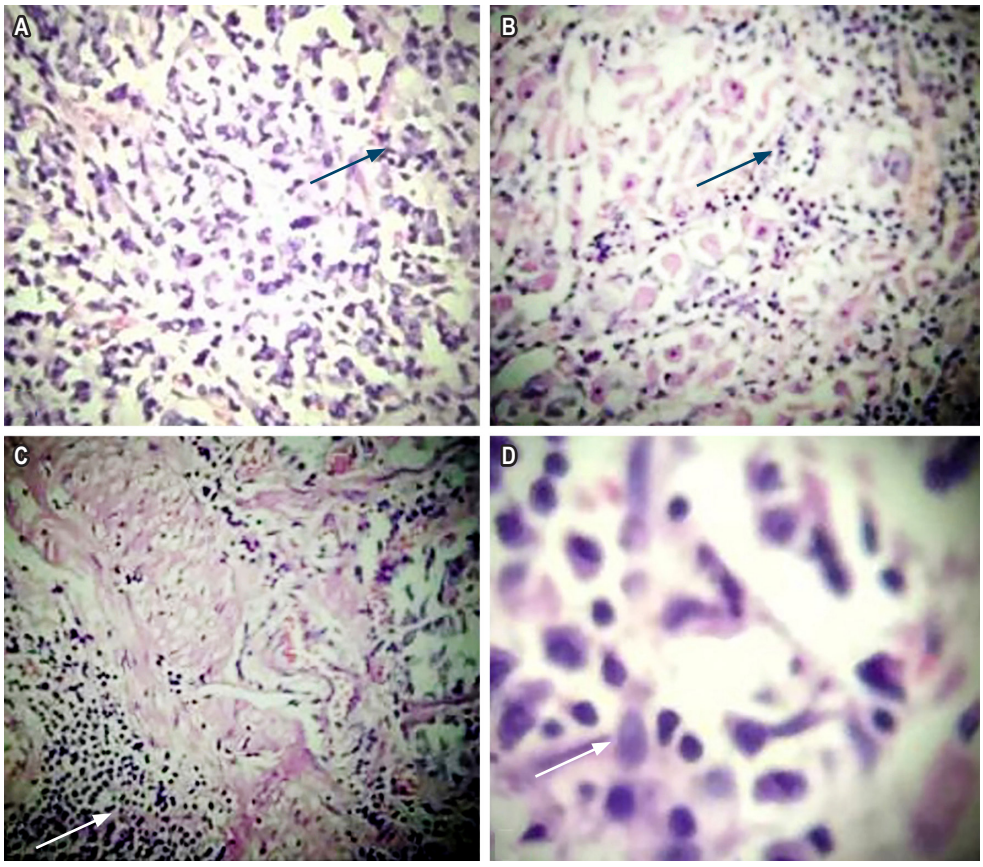

Figure 1. Gastrectomy specimen showing evidence of lymphoid infiltrate. Images property of the authors.

on one of the blocks showed positivity for CKAE1/AE3, CAM5.2, common leukocyte antigen, and CKAE1/AE (**Figure 2**). The pathology service corroborated these findings and concluded that the tumor was indeed a lymphoepithelioma-like carcinoma. EBV presence was confirmed via EBER-ISH testing.

The chemotherapy regimen consisted of six cycles of capecitabine. Over the next three years of imaging and endoscopic follow-up, the patient was considered to be in remission. However, in May 2022, the patient attended an oncology check-up reporting constitutional symptoms, including weight loss, night sweats, asthenia, and adynamia. Contrast-enhanced chest and abdominal CT scans revealed enlarged lymph nodes measuring 42 x 25 mm and 52 x 27 mm in the mesenteric root and retroperitoneum, suggesting metastatic involvement, along with hepatomegaly. A new biopsy and positron emission tomography (PET) scan were ordered to restage the disease.

DISCUSSION

Gastric cancer is one of the most frequent and deadliest neoplastic diseases worldwide, with an estimated annual prevalence of 934,000 cases. In the United States, approximately 27,600 stomach cancer cases are diagnosed each year (16,980 men and 10,620 women)[5], while in Colombia, it accounts for 9.5% of all diagnosed cancer cases[6].

The term *lymphoepithelioma-like gastric carcinoma*, also known as *lymphocyte-rich gastric carcinoma*, was introduced by Burke et al. upon observing this cellular distribution pattern in neoplastic gastric tissue[7]—a pattern previously described only in the nasopharynx by Regaud and Reverchon in 1921[8]. This tumor type is rare, constituting less than 4% of gastric cancers. Distinguishing this entity is clinically and prognostically significant, as it has distinct features affecting patient management and outcomes[9].

Chetty et al. describe lymphoepithelioma-like carcinoma as a neoplasm composed of small clusters of tumor cells with intratumoral lymphocyte infiltration[10]. In contrast, medullary carcinoma exhibits a syncytial histological pattern with peripheral lymphoid distribution, while conventional gastric carcinoma with lymphoid stroma is characterized by a glandular histological pattern and peripheral lymphoid distribution. This tumor type is more prevalent in males, suggesting a possible link to lifestyle and occupation. Although the average age of onset is around 60 years, it can occur in patients ranging from early adulthood to advanced age[11].

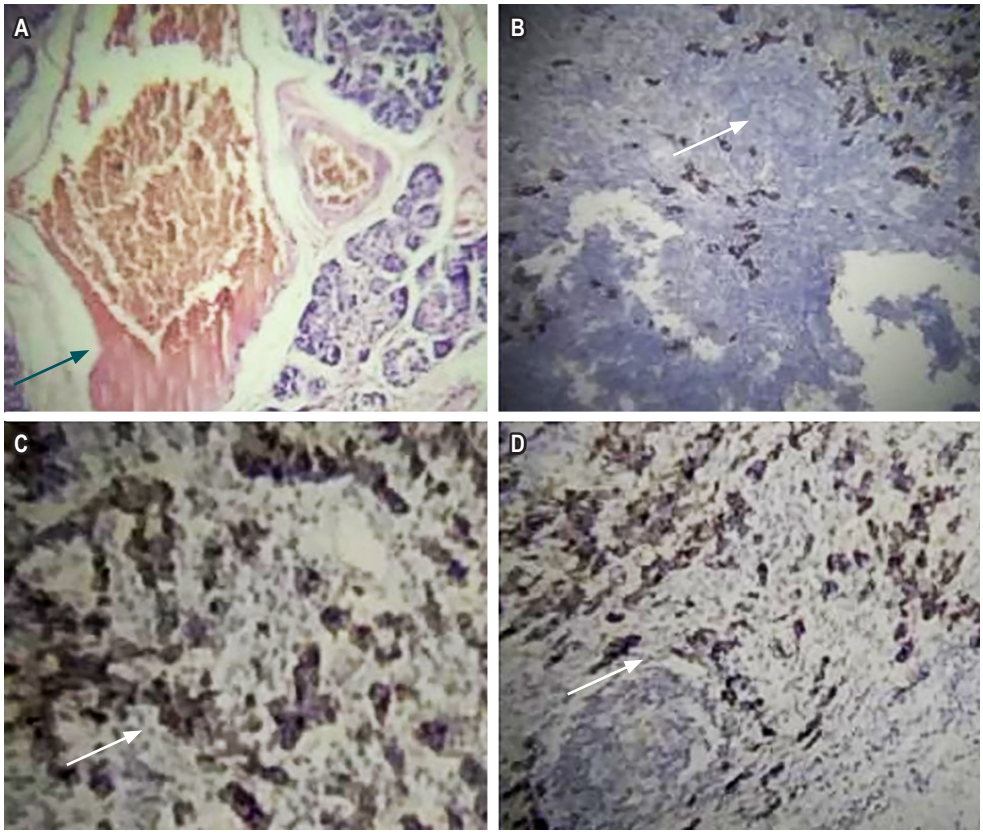

Figure 2. A. Subserosal involvement. **B.** Lymph node involvement. **C.** CAM5.2 immunohistochemistry. **D.** CKAE1/AE3 immunohistochemistry. Images property of the authors.

Several risk factors have been associated with this cancer, including consumption of salty or spicy foods, hot beverages, and exposure to wood dust or iron filings. However, these may be confounding factors, as the primary risk factor is its association with EBV[12–14]. *Helicobacter pylori* infection, a major risk factor for gastric adenocarcinoma, has also been studied but shows no correlation with this carcinoma type, suggesting distinct carcinogenic pathways[15].

Lymphoepithelioma-like carcinoma most frequently affects the proximal stomach but can occur in any gastric region or even elsewhere in the digestive tract[16]. It is characterized by dense, uniform stromal infiltration by T lymphocytes and plasma cells, alongside scattered adenocarcinoma cells. Two subtypes have been identified based on EBV presence (80%) and microsatellite instability (39%)[17].

Several hypotheses exist regarding EBV's oncogenic role. One widely accepted theory suggests that after primary infection, the virus remains latent in B lymphocytes via expression of the viral receptor CD21. EBV infection precedes clonal expansion of infected cells, inhibiting apoptosis and promoting cell proliferation, along with frequent chromosomal translocations. EBV detection in neoplastic tissue is typically performed using in situ hybridization (EBER-ISH) and polymerase chain reaction (PCR)[18].

Tumors with lymphoid stroma are generally smaller, exhibit less deep invasion, and have lower rates of nodal metastasis, contributing to a more favorable prognosis compared to typical gastric adenocarcinoma. The 5-year survival rate for lymphoepithelioma-like carcinoma is 83%–86% versus 46%–48% for conventional adenocarcinoma[19].

For diagnosis, UGIE is essential, particularly when identifying superficial depressed or ulcerated lesions in the upper stomach. The most sensitive diagnostic method is EBER1-2 in situ hybridization (EBER1-2 ISH) on biopsy specimens to confirm EBV[20].

Regarding therapeutic management, aggressive surgery can achieve radical cure, improving patient prognosis. Early-stage treatment—defined as cancer confined to the gastric mucosa or submucosa—has a 5-year survival rate exceeding 90%. Endoscopic mucosal resection and submucosal dissection are effective strategies at this stage. For advanced stages, though evidence is limited, DNA methylation inhibitors and immunotherapies (e.g., PD-1/PD-L1 blockade) have shown promising results in some studies[21].

This case underscores the importance of precise diagnosis and comprehensive management in lymphoepithelioma-like gastric carcinoma, highlighting the role of thorough pathological review and advanced techniques for accurate assessment.

CONCLUSION

This case emphasizes the need for rigorous diagnostic precision and multidisciplinary management in treating lymphoepithelioma-like gastric carcinoma. Exhaustive pathological specimen review and advanced techniques such as immunohistochemistry and EBER-ISH were crucial for confirming the diagnosis, which is vital for appropriate therapeutic intervention and patient prognosis.

Continuous follow-up and personalized treatment are essential to improving clinical outcomes in these patients. Early detection of recurrence and adaptive therapeutic strategies based on clinical progression and imaging findings enable better management of this rare and aggressive entity. This highlights the necessity for ongoing surveillance and an individualized therapeutic approach.

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