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Lymphoepithelioma-like Gastric Carcinoma (LELGC): A Case Report and Review of Literature

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Abstract
Lymphoepithelioma-like gastric carcinoma (LELGC), is a rare type of gastric cancer characterized by a carcinoma with intense stromal lymphocytic infiltration. It is one of the histological patterns observed in patients with Epstein-Barr virus (EBV)-associated gastric carcinoma. According to the World Health Organisation classification of tumors of digestive sysytem 2010, LELGC is a rare type of tubular carcinoma. Although this entity is hard to be recognized in the biopsy specimens, pathologists and clinicians should acknowledge this subset of gastric cancer because it generally has a better prognosis than other forms of EBV-associated gastric carcinomas and conventional gastric carcinomas. This might be due to the fact that the patient's inflammatory response may prevent the spread of tumor through the gastric wall and to the lymph nodes or remote organs.(21) In order to gain a detailed understanding of this rare disease, we reviewed the literature and report here a recent case of epithelioid gastric cancer in a 60 year old male patient presented in our Emergency Department.
Keywords: Lymphoepithelioma-like Gastric Carcinoma, gastric cancer , Ebstein-Barr virus, prognosis

Introduction

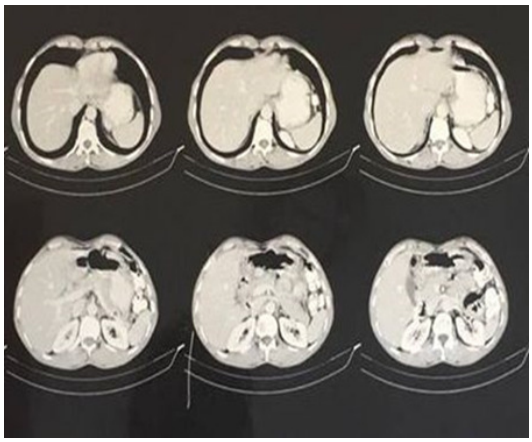
Gastric cancer is the fourth most common cancer diagnosed and the second leading cause of cancer-related death worldwide. In Europe (2012), the highest World age-standardised Open (AS) mortality rates for stomach cancer are in Belarus for men and Albania for women.The highest mortality rates are in Eastern Asia , Japan, Korea and the lowest in Northern America (World cancer research institute 2008).(1,2)

Gastric cancer is first described in hieroglyphs and papyruses in Ancient Egypt. The first statistical analysis of the incidence and mortality of gastric cancer was done in Verona, Italy, 1760-1809, according to which gastric cancer was the most common and deadly cancer. Overall, gastric cancer incidence and mortality have fallen dramatically over the past 70 years.(2) It continues to be one of the most important malignant diseases with a wide range of geographic, ethnic and socio-economic distribution. Lymphoepithelioma-like carcinoma (LLC) of the stomach is a rare and peculiar type of gastric carcinoma that was first described by Watanabe et al in 1976 as gastric carcinoma with a lymphoid stroma.(3) The reports in the literature with the synonyms undifferentiated carcinoma with lymphoid stroma, gastric Lymphoepithelioma-like carcinoma, or medullary carcinoma all describe carcinomas with similar morphology.(4,8) Lymphoepithelioma orginally described in nasopharynx. (3,4)

Case presentation

SH.B. a 60 year old male patient was admitted at the Emergency Department of “Nene Tereza” University and Hospital Center, Tirana, complaining of epigastric pain and gastro-duodenal hemorrhage. For several months, the patient complained of epigastric pain, loss of apetite, rectal bleeding and weight loss. The laboratory findings appeared altered, with hgb = 8.8 g/dl , HCT=28%, WBC= 14.5 x 10^9 cells/l (normal range, 4.0–10.0×109 cells/l). Stool/occult blood test-positive. Liver and kidney functions normal. After performing the laboratory and imaging examinations was diagnosed neoplastic lesion on the greater curvature wall of the gastric body.

A contrast-enhanced computed tomography (CT) scan of the abdomen was conducted, indicating solid focal thickening of the mucosa at the greater curvature wall of the gastric body towards the antrum, infiltrating up to 1.4 cm. 2 small surrounding lymph nodes correlated with Echo. With discrete loco-regional lymphadenopathy. Without evidence of solid hepatic, pulmonary or pelvic lesions.



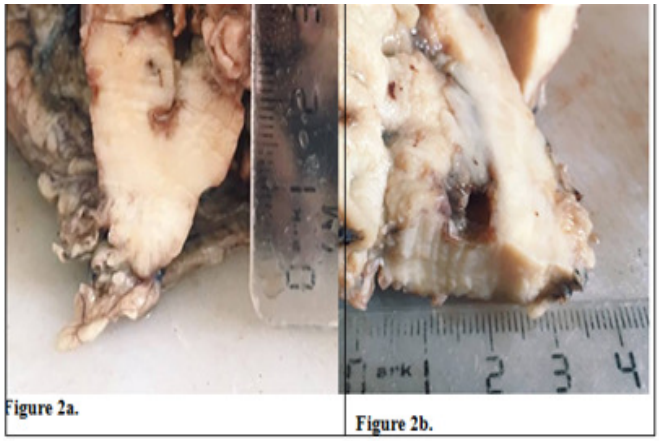


Figure 1. Contrast-enhanced computed tomography scan indicating solid focal thickening of the mucosa at the greater curvature wall of the gastric body.

Figure 2 a,b : The gross examination of the gastrectomy specimen revealed a tumor measuring 3×1.8×1 cm with a sizeable ulcer on the greater curvature of the gastric body.

In the surgical procedure the peritoneal cavity was opened.Ventricular neoformation ulcer-vegetative was evidenced at the major curvature .Without evidence of penetrating serosis. Loco-regional lymphadenopathy. No metastasis detected at distance. The gross examination of the gastrectomy specimen revealed a patelliform tumor measuring 3.0x1.8x1 cm with depression and central ulcer at the greater curvature wall , demarcated by the surrounding gastric mucosa. In the transverse sections is noticed thickening of the gastric wall and infiltration by a colour beige lesion that infiltrates the gastric muscular layer and reaches subserosa. In the examination for lymphnodes 19 lymphnodes were found in the subserosal tissue and omentum .

In the histological examination it was noted a malignant neoplasm of epithelial origin, organised in sheets and nests of round to polygonal cells with poorly defined cell borders within a dense lymphocytic background with diffuse pattern or organized in follicles with germinal centers. The epithelial tumor cells are mainly organized in small, irregular groups and rarely in larger solid groups. No vascular or lymphatic invasion was observed. The tumor infiltrates up to the subserozal tissue. None of the 19 dissected lymph nodes showed metastasis.

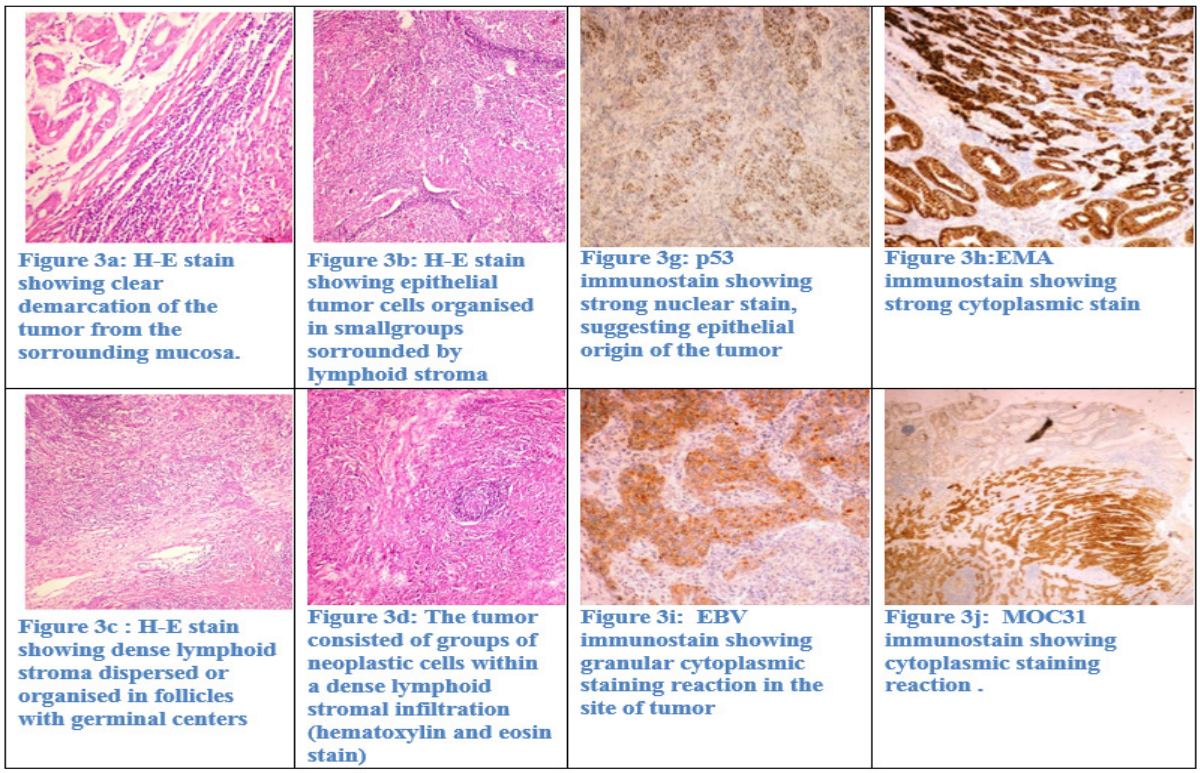


Figure 3: Hematoxylin-eosin staining of biopsy specimens (a,b, c, d) and Immunohistochemical staining (g, i, h, j).

The tumor cells showed positive stain for p53, EMA , EBV, Moc 31, and negative immunoreactivity was noticed for CK7, CEA , CK20. The association with EBV is based on the uniform expression of EBV in all tumor cells while absent in normal epithelium, dysplastic lesions.[30] p53 showed strong and diffuse positivity in the tumor cells, suggestive of P53 mutations.

Discussion

The lymphoid stroma in lymphoepithelioma-like gastric carcinomas can be so pronounced that the lesion can be mistaken for an intense reactive lymphoid infiltrate only or even a lymphoma, justifying its designation as a lymphoepithelioma-like carcinoma. However, careful search for atypical epithelial cells intimately intermixed with the lymphoid cells will allow for the correct diagnosis to be made. In the event that cancer cells are scarce, special stains will be of help. The demonstration of cytoplasmic mucin in the large epithelioid cells favors carcinoma over reactive macrophages. Differential diagnosis often is made with : poorly differentiated adenocarcinoma, metastasis from naso-pharyngeal carcinoma, lymphoma (Large B-Cell Lymphoma), neuroendocrine tumor, GIST, malignant melanoma or medullary carcinoma.

Histopathologic analysis findings such as: The presence of small solid groups of neoplastic epithelial cell without glanduloid organization, dense lymphocitic stroma sparsed or organised in follicles with germinating centers, accompanying the lesion, clear demarcation of the lesion from the sorroundig mucosa in the macroscopic examination, lack of displastic changes in the sorrounding gastric mucosa, positive immunoreactivity for EBV in the site of tumor, p53 diffusely and strongly overexpressed in the tumor cells, suggestive of P53 mutations. and positivity stain for EMA, suggest the diagnosis:"Lymphoepithelioma-like gastric carcinoma" (T3N0M0 according to TNM, Stage IIA) WHO classification of tumors 2010 [28]

LELGCs are defined as tumors which possess histologic similarity to nasopharyngeal carcinoma .[29] LELGC of the stomach is a rare type of gastric carcinoma that was first described by Watanabe et al as gastric carcinoma with a lymphoid stroma.[3] The stroma consists of CD8- or CD4-positive T lymphocytes, and CD68-positive macrophages, in a ratio of 2:1:1 and EBV infection is observed only in a very limited number of these infiltrating lymphocytes .[16] There are different reports in the literature with the synonyms undifferentiated carcinoma with lymphoid stroma, gastric Lymphoepithelioma-like carcinoma, or medullary carcinoma all describe carcinomas with similar morphology.[4,8,31] LELGC is also known as EBV-associated gastric carcinoma. An etiologic association with EBV is based on the uniform expression of EBV in all tumor cells while absent in normal epithelium, dysplastic lesions and lymphoid cells.[30] The mechanism by which EBV contributes to carcinogenesis in gastric mucosa is still unknown . EBV-positive gastric LLC has been confirmed to be composed of a monoclonal proliferation of a single EBV-infected progenitor cell.[16]This has strongly suggested that EBV infects the gastric mucosa before neoplastic transformation and is involved in the early stage of gastric carcinogenesis .In a study of 365 cases of gastric neoplasia removed surgically in 1989, 6 of them were diagnosed as LELGC.The histologic criteria proposed by Hamazaki for distinguishing this carcinoma were intercellular edema and lymphoid cell in- filtration of the tumor parenchyme; lymphoid feature of the tumor stroma; uniformity in distribution of these elements within the tumor. Since the number of cases diagnosed with LELGC was too small to provide a base for this special category, this criteria were not precise enough to be adopted universally for the identification of this tumor, anyway they are important because they help the pathologists for the accurate differential diagnoses. In a study conducted in Korea 2005 -2012 in a group of 18 patients diagnosed with LELGC Tak et al [26] compared the clinical characteristics and prognostic factors between gastric LELGC and gastric adenocarcinoma, and found that postoperative recurrence or metastasis tended to occur less frequently in gastric LELGC compared with poorly-differentiated gastric adenocarcinoma. Among prognostic factors, only the number of lymph node metastases exhibited a significant difference, with gastric LELGC being associated with a smaller number of lymph node metastases. The disease-free and overall survival rates of gastric LELGC were higher compared with those of poorly-differentiated gastric adenocarcinoma.

Conclusions

Lymphoepithelioma-like gastric carcinoma is a rare subtype of gastric carcinoma with a better survival rate than other gastric cancers.[21] Clinically 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. The diagnosis of lymphoepithelioma-like gastric carcinomas should mainly rest on the characteristic morphology and demonstration of EBV using different techniques. By using EBV-encoded RNA in situ hybridization, which is now considered to be the most sensitive method for detecting EBV in paraffin-embedded tissues, viral RNA can be demonstrated easily. It is considered to be the gold standart in the diagnosis of LELGC. In spite, pathologists and clinicians should acknowledge this subset of gastric cancer because it generally has a better prognosis than other forms of EBV-associated gastric carcinomas and conventional gastric carcinomas. Pathologists and

clinicians should take into consideration this subset of gastric cancer to make an accurate diagnosis and select the appropriate treatment.

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