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Case Report

J Med Cases. 2022;13(1):36-39

Lymphoepithelioma-Like Gastric Carcinoma and Gastric Involvement of Chronic Lymphocytic Leukemia: Two Rare Identities Coexisting in One Patient

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Abstract

Lymphoepithelioma-like gastric carcinoma (LELGC) constitutes 1-4% of all gastric carcinomas and gastrointestinal involvement in leukemia can be present in up to 25%, being more common in acute than chronic leukemia, affecting most frequently the stomach, ileum, and proximal colon. LELGC is usually associated with a better prognosis than other gastric carcinomas, generally presenting with low T and N stages. The reports of chronic lymphocytic leukemia (CLL) involving infiltration of the gastrointestinal tract are relatively rare in the literature, and the estimated incidence ranges from 5.7% to 25%. We present the case of a 77-year-old female, on surveillance by a known CLL that was diagnosed with gastric carcinoma on an esophagogastroduodenoscopy (EGD) performed for epigastric pain. A subtotal gastrectomy was performed and the surgical specimen revealed simultaneous involvement of the stomach by LELGC and CLL. To the best of our knowledge, this is the first reported case of a LELGC and CLL simultaneously involving the stomach.

Keywords: Lymphoepithelioma-like; Medullary; Chronic; Lymphocytic; Leukemia; Gastric; Stomach; Carcinoma

Introduction

Firstly described by Watanabe et al in 1976, lymphoepithelioma-like gastric carcinoma (LELGC), also known as medullary carcinoma, is an undifferentiated type of carcinoma, characterized by an intense inflammatory infiltrate. In up to 80% of the cases, it is associated with Epstein-Barr virus (EBV), identified by *in situ* hybridization [1, 2]. The treatment of LELGC follows the same recommendations as other types of gastric carcinoma.

Chronic lymphocytic leukemia (CLL) accounts for approximately 25% of adult leukemias in the western world. The reports of CLL cases involving infiltration of the gastrointestinal tract are relatively rare in the literature, and the estimated incidence ranges from 5.7% to 25% in patients with CLL [3-5].

We describe the case of a woman with known CCL that was diagnosed with a gastric adenocarcinoma and proposed for radical gastrectomy. The surgical specimen revealed the simultaneously presence of medullary carcinoma (or LELGC) and CCL.

To the best of our knowledge, this is the first reported case of a LELGC and CLL simultaneously involving the stomach.

Case Report

Investigations

We report the case of a 77-year-old female, who was diagnosed with CLL in March of 2018, staged as a Rai I (intermediate risk). In the first few years of diagnosis, the patient was under a watch-and-wait strategy, but she had recently developed CLL symptoms (fatigue), and was then classified as a Rai I with active disease. As so, she was proposed to start therapy for CLL with ibrutinib.

Diagnosis

In the process of starting CLL therapy, the patient complaint of recurrent epigastric pain and the hematologist ordered an esophagogastroduodenoscopy (EGD). Aside from the fatigue and epigastric pain, the patient did not have any other symptoms. The EGD identified the presence of a large ulcerated lesion with high edges involving the entire anterior hemi-circumference of the distal antrum. The ECG biopsy revealed the presence of gastric adenocarcinoma. In this setting, a cervico-

Manuscript submitted November 9, 2021, accepted January 6, 2022
Published online January 17, 2022

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doi: https://doi.org/10.14740/jmc3846

thoraco-abdominopelvic computed tomography (CT) was performed, revealing multiple cervical adenopathies in submaxillary location and in all cervical chains, internal mammary chains, mediastinal and hilar adenopathies, probably due to CCL status. It was also present a vegetative gastric lesion of the anterior wall, without extraparietal invasion and adenopathies in the gastro-hepatic ligament. There were no signs of pulmonary, hepatic or any other site metastatic involvement. Tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and CA 72-4 were normal.

At this point, the patient had two distinct malignancies: CCL and gastric adenocarcinoma. The clinical case was discussed in the multidisciplinary team consultation, and the patient was proposed to surgery.

Treatment

A radical subtotal gastrectomy and D2 lymphadenectomy with Roux-en-Y reconstruction was performed.

The postoperative period was complicated by a chylous fistula that was conservatively treated; the patient was discharged on the eighth postoperative day, and was regularly observed in the General Surgery Consultation. The fistula closed spontaneously on the third week.

Follow-up and outcomes

Histopathological examination of the surgical specimen revealed a 6.5-cm medullary carcinoma of the gastric antrum, infiltrating the muscularis propria, without lymphovascular or perineural invasion and the simultaneous presence of a diffuse gastric involvement at the level of subserosa and serosa by a continuity solution of CLL, which was also present in 18 out of 24 lymph nodes. Surgical resection margins were tumor-free. Lymphoproliferative disease cells showed strong and diffuse expression for cluster of differentiation (CD)20, CD5 and Bcl2.The gastric carcinoma was classified as a pT2 N0 M0, according to the TNM staging system.

The clinical case was discussed in the multidisciplinary team consultation and it was decided to maintain surveillance of the gastric carcinoma, and start treatment for the CCL.

Discussion

In the case that we present, the patient had two different types on malignancy: LELGC (also known as medullary carcinoma) and CLL. As so, we address both entities briefly.

LELGC is a rare type of gastric cancer characterized by lymphocytic infiltration of the tumor stroma [6]. According to the World Health Organization classification of tumors of the digestive system, LELGC is a type of tubular carcinoma [7]. LELGC constitutes 1-4% of all gastric carcinomas, and it is considered to predominantly affect males and having a better prognosis than other types of gastric carcinoma [8]. LELGC is categorized into two subtypes: EBV-positive carcinoma and microsatellite instability (MSI)-high carcinoma. Over 80% of LELGC is EBV-positive [6]. This subtype is associated with recurrent mutations in the *PIK3CA*, DNA hypermethylation, amplification of JAK2 and overexpression of PD-L1 and PD-L2, and is associated with a better prognosis, since the PD-1/PD-L1 complex may be a therapeutic target [9]. On the other hand, the prevalence of MSI-high LELGC is 7-39%, depending on geographical location [6]. MSI-high status may result from defective function of DNA mismatch repair enzymes, including MutL homolog 1 or MutS homolog 2, but rarely MutS homolog 6 [8]. In our patient, unlike most known cases of LELGC, it was associated with microsatellite instability carcinoma.

The clinical symptoms of LELGC are similar to other types of gastric carcinoma, and include abdominal pain, anorexia and weight loss, among other symptoms [8]. Park et al in 2015 studied a population of 4,282 patients who underwent gastrectomy to treat gastric cancer, 46 of which had LELGC, and concluded that LELGC usually presents in lower T-stages (predominantly T1-2) and has a lower frequency of lymph node metastasis, confirming previous studies [10]. The management of LELGC is similar to the other types of gastric carcinoma.

While under the surveillance on the hemato-oncology department, our patient presented with recurrent epigastralgia, so an EGD was ordered, revealing an ulcerated lesion with high edges located in the distal antrum, and the biopsy confirmed the presence of gastric carcinoma. In this case, since the patient was 77 years old and had an active CLL disease that fulfilled therapeutic indication, the decision of the multidisciplinary team consultation was not proposed for perioperative chemotherapy, and instead, propose primary gastrectomy.

The surgery specimen revealed a LELGC/medullary carcinoma, classified as a pT2 N0 according to the TNM staging system. In this case, there was also gastric involvement by the known CLL. In the literature it is reported that gastrointestinal involvement in leukemia can be present in up to 25% [4, 5], being more common in acute than chronic leukemia, affecting most frequently the stomach, ileum and proximal colon [4], and is more prevalent in men [5]. CLL gastric involvement may present itself as leukemic infiltration in the form of nodules, thickened folds, or ulcers [4].

CLL is characterized by the progressive accumulation of monoclonal lymphocytes in peripheral blood, bone marrow, and lymphoid tissues [11]. CLL is the most common leukemia in western countries [12], and typically affects older adults, with a median age at diagnosis of approximately 70 years [13]. It is a heterogeneous disease with certain subsets of patients having survival rates without treatment that are similar to the normal population [14]. The diagnosis of CLL is established by the following two criteria [15]: presence of $\geq 5 \times 10^9$/L monoclonal B lymphocytes in the peripheral blood (confirmed by demonstrating light chain restriction using flow cytometry) and leukemia cells found in the blood smear, which are characteristically small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin (larger, atypical lymphocytes or prolymphocytes may be seen but must not exceed 55%). CLL cells coexpress the B-cell surface antigens CD19 and CD20 together with CD5, CD23,

Table 1. Progression Criteria of CLL, Defined by the iwCLL (International Workshop on Chronic Lymphocytic Leukemia)

Progressive bone marrow failure with the development or aggravation of anemia and/or thrombocytopenia
Massive or progressive or symptomatic splenomegaly
Significantly enlarged or symptomatic or progressive lymphadenopathies
Progressive lymphocytosis
Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapies
Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine)
The presence of constitutive symptoms, one or more of the following signs or symptoms related to the disease: unintentional weight loss of 10% or more in the previous 6 months, significant fatigue (ECOG PS 2 or worse; inability to perform usual activities), fever over 38.0 °C for 2 weeks or more without signs of infection, and night sweats lasting more than a month with no sign of infection

CLL: chronic lymphocytic leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status.

CD43 and CD200 [15]. CLL should be classified according to Binet or Rai classification system [14]. The standard treatment of patients with early asymptomatic disease is a watch-and-wait strategy [15]. Patients with intermediate (stage I and II) and high-risk (stage III and IV) disease, according to the modified Rai classification, or at Binet stage B or C, usually benefit from the initiation of treatment, but some of these patients may be monitored without therapy until they have evidence for progressive or symptomatic disease [15]. The progression criteria have been defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) (Table 1) [16].

Before treatment, del(17p), *TP53* mutations and *IGHV* status should be assessed, as well as imaging (CT scans of neck, chest, abdomen and pelvis or magnetic resonance imaging (MRI)) [15]. In this case, our patient was being monitored in the hemato-oncology department. She was staged initially as a Rai I (intermediate risk), and was previously under a watch-and-wait strategy. She had recently developed significant fatigue, so she was in the process of beginning treatment; the *TP53* assessement by fluorescence *in situ* hybridization (FISH) was negative, and the *IGHV* mutational status was also negative; at this point, the patient was proposed for ibrutinib (Bruton tyrosine kinase inhibitors).

After the diagnosis of gastric carcinoma on EGD, the process of beginning ibrutinib was stopped, and the patient was proposed for surgery, since the treatment of the gastric carcinoma had precedence to the beginning of CLL treatment.

The histopathological examination of the surgical specimen revealed a medullary carcinoma/LELGC plus a diffuse gastric involvement of CLL, also involving the lymph nodes. The gastric carcinoma was staged as staged as IB (according to TNM staging classification). As so, in the multidisciplinary team consultation it was decided to propose surveillance for the gastric cancer and to start ibrutinib for CLL. The patient is currently under ibrutinib and maintains surveillance for the gastric cancer.

Conclusions

It is difficult to distinguish gastric LELGC from other types of gastric carcinoma with an endoscopic biopsy, as the stromal lymphocytic infiltration is dense, so the diagnosis of LELGC is usually established after the histopathological examination. LELGC is associated with a better prognosis than other gastric carcinomas, as it usually is characterized by low T and N stages. The gastrointestinal involvement by CLL is relatively rare, but it can range up to 25% of the cases.

There are no guidelines to treat these coexisting entities, so the multidisciplinary team consultation is crucial to establish a clear plan. In this case, since the gastric carcinoma was staged as an IB, according to TNM staging classification, the patient was proposed for surveillance and the decision to start ibrutinib was considered a safe treatment option.

Acknowledgments

We appreciate the contributions of all surgeons.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Consent was provided for the publication of necessary data.

Author Contributions

Narcisa Guimaraes: corresponding and first author, conceptualization and study design, data acquisition, analysis and interpretation, article drafting and critical revision of the work for important intellectual content. Ines Bolais Monica, Simone Oliveira, Daniela Pato Pais, Sara Andrade and Ines Bertao Colaco: data analysis and interpretation, critical revision of the work for important intellectual content, and final approval of the manuscript to be published. Carlos Vila Nova, Vera Vieira,

Nuno Azenha, Joao Fonseca Pinho, Fatima Guedes, Lucilia Conceicao and Jose Valente Cecilio: revising it critically for important intellectual content, final approval of the version to be published.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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