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Early stage primary gastric diffuse large B-cell lymphoma in a young HIV-positive patient

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ABSTRACT

HIV infection is known to be associated with the development of a wide range of neoplasia. About 25 to 40% of HIV-positive patients will present some kind of malignancy in the course of the disease; among them 10% are non-Hodgkin lymphomas (NHL) and 20% of these are represented by the diffuse large B-cell lymphoma. HIV-positive patients have a relative risk of 110 times higher to develop neoplasia, than the non-infected population. The gastrointestinal (GI) tract is the most frequent extranodal site of involvement. However, the primary GI lymphoma is rare. The authors present a case of a 31-year-old male patient with a 16-year history of HIV infection, who deliberately withdrew the Highly Active Antiretroviral Therapy (HAART) regimen and was hospitalized because of a respiratory infection. Because of a long-term complaint of dyspepsia, an upper gastrointestinal endoscopy was performed disclosing a large elevated and ulcerated gastric lesion, which biopsy revealed a diffuse large B-cell lymphoma. Clinical, imaging and laboratory tests showed an early stage diagnosis: Lugano stage I. Although not frequent, the authors alert to considering this neoplasia in all HIV-positive patients with dyspeptic symptoms.

Keywords
Lymphoma, Large B-Cell, Diffuse; Stomach Neoplasms; Lymphoma, AIDS-Related; Acquired Immunodeficiency Syndrome.

CASE REPORT

A 31-year-old male patient, with the history of HIV infection diagnosed 16 years ago, sought medical care complaining of high-grade fever, diaphoresis, and cough with few whitish sputum during the last 20 days. He referred 20 kg of weight loss during the last 8 months associated with intermittent epigastric pain and dysphagia. He deliberately withdrew the HAART regimen and the medical follow-up during the last three years. After hospitalization, he was initially treated with antibiotics, with favorable outcome, but still referred worsening of the epigastric pain and dysphagia. Initial laboratory work up revealed a normal total blood cell count, as well as renal and liver function tests, electrolytes and lactate dehydrogenase. CD4 cell count was 261 cells/mm^3 and viral load was 163,597 copies/mL. The upper gastrointestinal endoscopy showed a 20 cm-length narrowing of distal esophagus, recovered by a healing pattern mucosa. At the posterior wall of the antrum an ulcer measuring 4 cm at its longest axis, with elevated and

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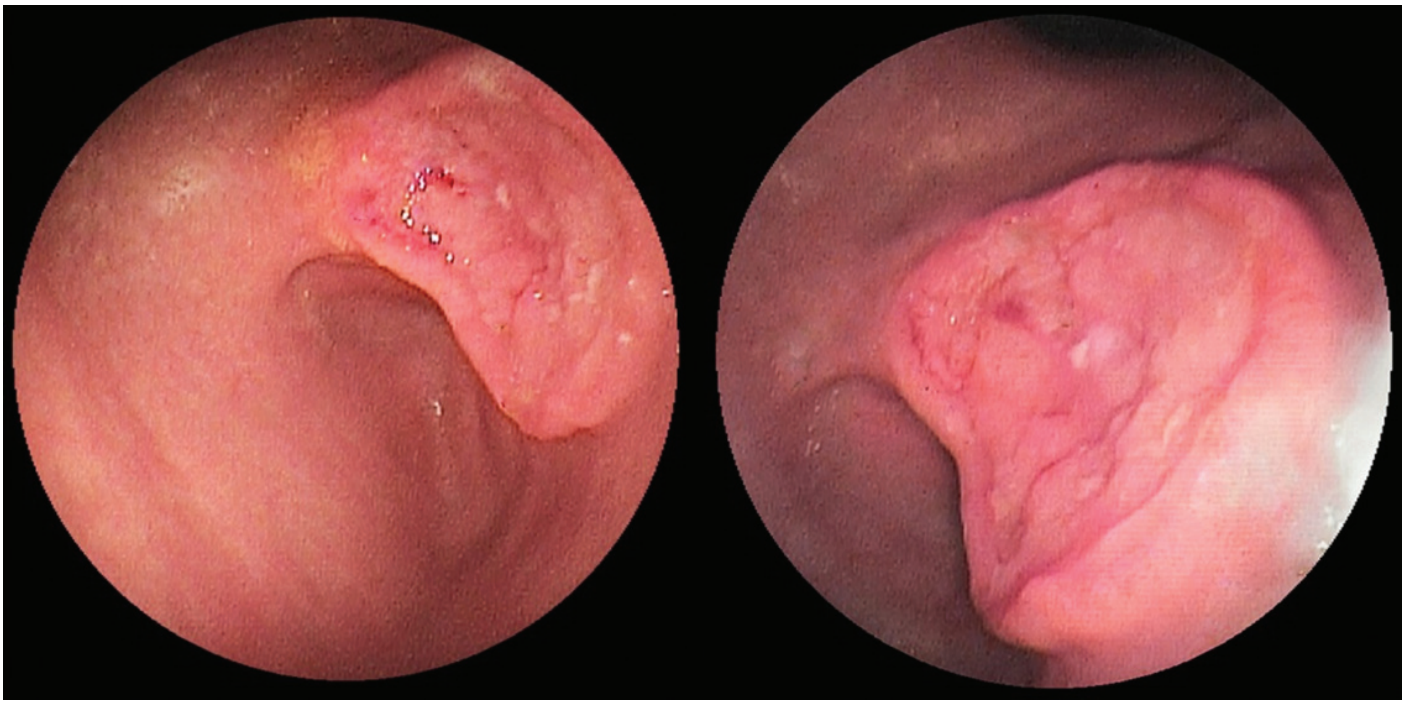

Figure 1. Endoscopic view of the gastric antrum, showing in its posterior wall a well-delimitated ulcerated lesion, with elevated borders, granular and clean wound bed.

well-circumscribed borders and clean wound bed was found (Figure 1).

Biopsies were performed from the esophageal and gastric lesions. Pathologic examination of the esophagus revealed unspecific chronic esophagitis with *Candida sp*. Gastric biopsies revealed a high-grade, poorly-differentiated neoplasia, with atypical poorly cohesive cells in a solid pattern, mitotic figures and conspicuous nucleoli. *Helicobacter pylori* was not detected (Giemsa stain). Immunohistochemistry showed diffuse and strong staining for CD20+ and Bcl-6; and negative staining for CD30 and MUM-1. Proliferation index was 80-90% as accessed by Ki67. Immunostainings for keratins (AE1-AE3), Epstein-Barr virus (EBV), Bcl-2 and cyclin-D1 were negative. *In situ* hybridization for EBV was negative. The morphology accompanied by the immunohistochemical panel handled the diagnosis of diffuse large B-cell lymphoma (DLBCL) (Figure 2).

Thoracic and abdominal computed tomography ruled out lymph node involvement, except in the mediastinum where some lymph nodes measuring up to 1.0 cm were present. Spleen and liver were normal. Bone marrow biopsy showed normal cellularity and absence of lymphomatous invasion. Therefore clinically the patient was considered as Stage I. HAART was restarted and the patient was referred to the oncology center.

DISCUSSION

HIV infected patients are at increased risk of developing malignancies.[1-3] Lymphoma is frequently observed among immunosuppressive diseases such as AIDS. They usually present with extranodal involvement with diffuse aggressive histology, B-cell lineage derivation (95% of cases), in association with EBV, clinically aggressive courses, involving younger patients and presenting in advanced stage at the time of diagnosis.[4-6] Up to 80% of the HIV-associated NHL arise systemically.[5,7]

In the beginning of AIDS epidemics a dramatic increase in the incidence of Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and cervical cancer was observed, therefore these tumors were classified as AIDS-defining cancers. Regarding the gastrointestinal (GI) involvement in the first decade of epidemics, Danzig et al. found 32% of GI neoplasia mainly represented by silent KS and symptomatic NHL.[8]

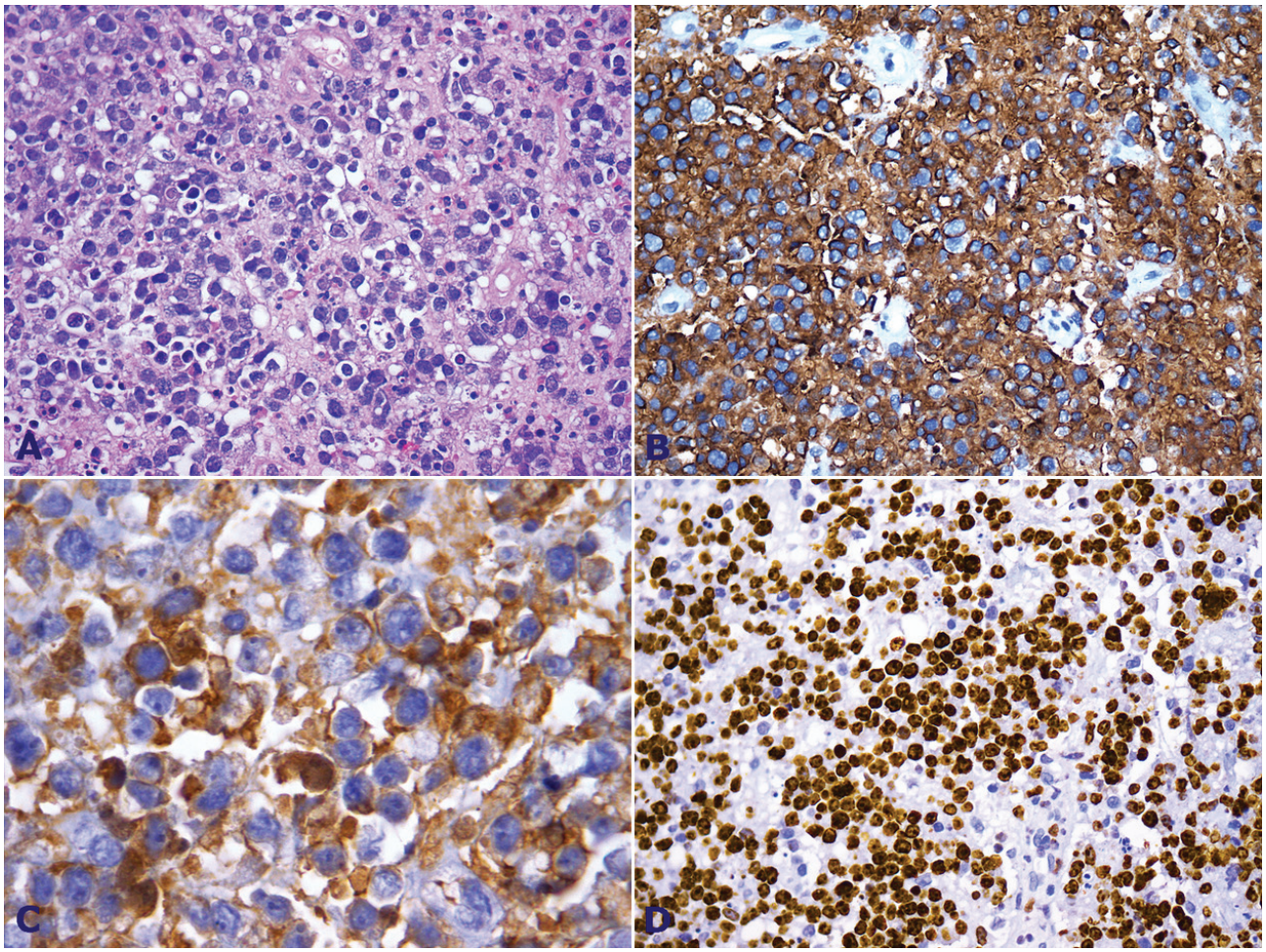

Figure 2. A - Photomicrography of gastric biopsy showing large lymphoid cells exhibiting prominent nucleoli and basophilic cytoplasm in a diffuse growing pattern. (H&E, 400x); **B** - Immunohistochemistry showing diffuse staining for CD20 (400x); **C** - Focal immunostaining for CD30 (1000x); **D** - High proliferation index (80-90%) as accessed by Ki67 (400x).

With the advent of HAART the incidence of KS and NHL decreased, but they were replaced by other malignancies (non-defining AIDS tumors).[9]

The GI tract is the main site for extranodal AIDS-related NHL localization followed by the central nervous system involvement.[6,10] In this setting GI involvement can be primary or secondary; the latter taking part of a disseminated disease. Dawson's criteria[11] are used for the diagnosis definition of primary GI lymphoma, and include: 1 – absence of peripheral palpable lymph nodes; 2 – normal plain chest radiography; 3 – normal white blood cell count; 4 – predominant lesion confined to the GI tract; 5 – absence of liver and spleen involvement; 6- absence of lymphadenopathy on computerized tomography; 7 – absence of bone marrow involvement. Another definition of primary GI NHL was stated by Lewin et al., which criteria require GI symptoms or predominant lesions confined to the GI tract.[12,13] According to these authors, our patient fulfilled all the criteria for the diagnosis of primary gastric lymphoma.

GI primary lymphomas are rare, showing an incidence of 0,8-1,2 cases per 100.000 persons per year.[12,14] This entity represents up to 1% to 4% of the tumors of small intestine, stomach and colon,[10] while the secondary involvement of GI occurs in up to 10% of patients.[15] The stomach is the most frequent involved organ with 68%-75% of cases, followed by small intestine (9%), ileocecal region (7%) and rectum (2%).[12]

Primary gastric lymphoma represents 3% of all gastric malignancies and 10% of all lymphomas.[12] HIV-associated NHLs are related to long-term severe immunosuppression, low CD4 count (generally less than 100 cells/mm^3), high viral load, increased age and previous AIDS defining condition.[6] Gastric lymphomas

are more frequent among males between 50 and 60 years of age.[12]

Epigastric pain, nausea and/or vomiting, anorexia usually represents clinical features associated to gastric lymphoma, but weight loss, early satiety and occult gastrointestinal bleeding are also frequently present. B symptoms are present in 12% of cases. Symptoms may vary from days to years, until the diagnosis is achieved.[12] Diagnosis may be made by endoscopy and imaging work up, always confirmed by histological examination. On endoscopy, gastric lymphoma may appear as a polypoid lesion, tumoral mass, erythematous mucosa, nodules or gastric ulcer, like the presentation found in our patient.[16-18] Our patient's endoscopic lesion was very suspicious of malignancy, due to the infiltrated, elevated and well circumscribed border with a clean ulcer bed. Peptic ulcer is usually more shallow and recovered by fibrinous debris. Endoscopic ultrasound may be helpful in determining the depth of gastric wall invasion as well as the presence of perigastric lymphatic nodes.[19] The endoscopic ultrasound does not have enough accuracy to differentiate benign from malignant involvement, however when associated with biopsy the accuracy raises to 90%.[20]

After making the diagnosis, staging constitutes the next step for treatment planning. The Lugano Staging System[21] (Table 1) is a modification of the original Ann Arbor staging system designed for the staging of primary gastointestinal lymphomas. Following the Lugano criteria, our patient presented the stage I.

The majority of gastric lymphomas is represented by MALT lymphomas (38%-48%) and DLBCL (45%-59%); the remaining cases are mantle cell lymphoma (1%), follicular lymphoma (0.5%-2%) and peripheral T-cell lymphoma (1.5%-4%).[4,12] However, among the HIV-infected patients, the histological distribution is somewhat different. In this setting Burkitt lymphoma and DLBCL are the most representative, followed by primary effusion lymphoma, plasmablastic lymphoma (normally confined to the oral cavity) and in a small number, the classic Hodgkin lymphomas.[6,22,23]

DLBCL is a heterogeneous group of tumors that are characterized by large B-cells exhibiting prominent nucleoli, basophilic cytoplasm, a diffuse growing pattern and high proliferation index. Involved lymph nodes lose their normal architecture by the invasive atypical lymphoid cells, which are large cells resembling centroblasts or immunoblasts.[24] Immunohistochemistry is characterized by the expression of CD19, CD20, CD22 and CD79a, as well as CD45.[25]

The pathogenesis of HIV-related lymphomas is multifactorial, besides the inherent HIV-induced immunosuppression; chronic antigenic stimulation, genetic abnormalities, cytokine deregulation and the role of EBV as well as HHV-8 also take part.[22,26-28]

The differential diagnosis include infectious mononucleosis, melanoma, carcinomas, Burkitt lymphoma, and T-cell anaplastic lymphoma.[29,30]

Although primary gastric DLCL has, currently, a better prognosis[31] with rituximab added to cyclophosphamide, doxorubicin, vincristine and

Table 1. Lugano Staging System[21] – Staging of primary gastrointestinal lymphoma

Stage	Extent of lymphoma
I	Confined to GI tract (single primary, or multiple non-contiguous lesions)
II	Extending into abdomen from primary GI site
	II_1 = local nodal involvement
	II_2 = distant nodal involvement
IIE	Penetration of serosa to involve adjacent organ or tissues
	Specify site of involvement, e.g. IIE (pancreas)
	If both nodal involvement and involvement of adjacent organs, denote stage using both a subscript (1 or 2) and E, e.g. II_1 E (pancreas)
IV	Disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement

prednisone, or with surgery plus chemotherapy and radiotherapy,[32] the prognosis of NHL in HIV-positive patients is not as much favorable. Rezende et al.,[33] studying 243 HIV-positive patients submitted to upper gastrointestinal endoscopy found 6 cases of primary gastric NHL which showed a median survival time after diagnosis of 185 days.

HIV-related primary gastric lymphoma predominates in long-term infected male patients, what is observed in this report. Our case calls attention to the age of the patient, the early stage at diagnosis (since the majority of cases present in advanced stages) in the presence of a reasonable elevated count of CD4 and viral load of 163,597 copies, what is atypical according to the literature.

Due to the relative frequency of GI involvement by lymphomas in AIDS patients, we call attention to the suspicion for this diagnosis in every HIV/AIDS patient presenting some or all of the following symptoms: non-apparent cause for epigastric pain, weight loss, B symptoms and signs suggestive of GI bleeding. Despite the advances in diagnostic methods and therapeutics, the occurrence of GI NHL has been associated to a shorter survival of the HIV-positive patients.

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