Case Report

Spontaneous Remission of Diffuse Large B-Cell Lymphoma in a Patient with AIDS

Remissão espontânea de Linfoma Difuso de Grandes Células B em paciente com aids

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid hematologic neoplasm in adults living with HIV/AIDS. It is an aggressive disease, often with extranodal involvement, classically treated with chemotherapy. We report the case of a patient whose AIDS diagnosis was concomitant with an advanced lymphoma, requiring emergency intestinal resection due to an acute obstructive abdomen. Ten weeks postoperatively, spontaneous remission of the lymphoma was observed through positron emission tomography (PET/CT), a finding confirmed by a new surgical approach for intestinal transit reconstruction after six months and by a new PET/CT examination after one year. We attribute the phenomenon to immune reconstitution achieved through antiretroviral therapy and the associated use of ganciclovir for the treatment of cytomegalovirus infection.

Headings: Neoplasm Regression, Spontaneous; Lymphoma, Large B-Cell, Diffuse; Lymphoma, AIDS-Related; Antiretroviral Therapy, Highly Active; Case Report.

RESUMO

O linfoma difuso de grandes células B (LDGCB) é a neoplasia hematológica linfoide mais comum em pessoas adultas que vivem com HIV/aids. Trata-se de doença de curso agressivo, com frequente doença extranodal, classicamente tratada com quimioterapia. Relatamos o caso de um paciente cujo diagnóstico de aids foi concomitante ao de um linfoma avançado que implicou em uma ressecção intestinal de urgência devido a um quadro de abdome agudo obstrutivo. Decorridas 10 semanas de pós-operatório, entretanto, constatou-se a remissão espontânea do linfoma através de uma tomografia por emissão de pósitrons (PET/CT), informação ratificada por uma nova abordagem cirúrgica para reconstrução do trânsito intestinal após seis meses e por novo exame de PET/CT após um ano. Atribuímos o fenômeno à reconstituição imune alcançada pela terapia antirretroviral e ao uso associado de ganciclovir para tratamento de infecção por citomegalovírus.

Descritores: Regressão Neoplásica Espontânea; Linfoma difuso de grandes células B; Linfoma relacionado à aids; Terapia Antirretroviral de Alta Atividade; Relato de Caso.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a non-Hodgkin lymphoma characterized by the rapid and aggressive growth of abnormal B cells. Tumor cells tend to accumulate in lymph nodes but can also affect other organs such as the spleen, liver, and bone marrow. This lymphoma subtype is the most common among non-Hodgkin lymphomas, accounting for approximately 30% to 40% of cases diagnosed worldwide[1].

HIV infection represents a 10 to 20 times greater risk for the development of non-Hodgkin lymphomas, with DLBCL accounting for 35% to 50% of non-Hodgkin lymphomas in people living with HIV/AIDS (PLWHA), even those on highly active antiretroviral therapy (HAART)[2,3]. Although HIV does not directly infect lymphoma-transformed cells, several factors predispose to the development of AIDS-associated lymphomas, such as the disruption of immune surveillance for tumor antigens, the oncogenic function of some viral proteins, the dysregulation of cytokine secretion, the presence of a chronic inflammatory state, and co-infection with oncogenic viruses[2].

The present case reports an episode of spontaneous remission of DLBCL in a patient with AIDS without receiving the necessary chemotherapy, possibly as a consequence of immune reconstitution caused by HAART and the use of ganciclovir for the treatment of cytomegalovirus infection.

CASE REPORT

A 27-year-old businessman, native of São Carlos (São Paulo state, Brazil), reported dyspnea for one month, with dry cough, chills, and night sweats. Initially treated with azithromycin for five days, he evolved with partial improvement of symptoms but worsened after another five days when, in a new emergency room consultation, associated hypoxemia was found. He was in good general condition, non-cyanotic, non-icteric, afebrile, becoming eupneic on a nasal catheter at 2L/min with saturation of 93-96%. On physical examination, there were fine crackles in both lung bases, with no other changes. Among his personal history, the patient had been a smoker for seven years, using straw cigarettes (3 cigarettes/day) and electronic cigarettes, the latter of which he had not smoked for six months. He also reported recent exposure to gypsum dust and household insecticides. He related a weight loss of 15 kg in the last year and recurrent episodes of diarrhea, arthralgia, and myalgia, symptoms attributed to burnout and treated with pregabalin, without improvement. Influenza and COVID-19 infection was ruled out through rapid tests, but chest angiotomography performed to rule out pulmonary thromboembolism showed diffuse opacities in a ground-glass pattern, with occasional micronodules (Figure 1) - pneumocystosis was considered, among others. A rapid HIV test was requested, which was positive, later justified by a history of risky sexual behavior. Other noteworthy initial laboratory tests were serum hemoglobin of 12.1g/dL, hematocrit of 34.9%, leukocyte count of 6390/mm³ with only 1,050 lymphocytes/mm³, platelet count of 315,000/uL, creatinine 0.8 mg/dL, total serum protein 8.4 g/dL, albumin 3.3 g/dL, total bilirubin 0.4 mg/dL; serum lactate dehydrogenase (LDH) was 345 U/L (for a normal value of up to 190 U/L). Serologies for hepatitis A, B, and C and for syphilis were all negative, while for toxoplasmosis, IgG was reactive, but IgM was not. The patient was admitted and treated with intravenous sulfamethoxazole and trimethoprim plus prednisone, with an initial CD4 count of 34 cells/mm³ and a viral load (HIV-1) of 881,000 copies per mL.

Figure 1. Tomographic section showing pulmonary opacities in ground-glass, suggestive of pneumocystosis.

He was discharged with oral medication after 15 days, but returned after a week with fever for three days and non-pruritic red spots on the skin, in addition to a single episode of hematochezia. This time he was febrile and presented with an exanthema on the trunk and limbs, facial edema, aphthous ulcers on the lower lip, in addition to a whitish plaque in the oral cavity and oropharynx. New tests revealed hemoglobin of 9.6 g/dL, hematocrit of 28.2%, leukocytes of 7,000 cells/mm³ with 6,104 neutrophils, 168 eosinophils, and 497 lymphocytes, elevated transaminases (AST 1,029 U/L and ALT 1,753 U/L), without hydroelectrolytic disturbances or alterations in renal function. Readmitted with the hypothesis of drug hypersensitivity syndrome (DRESS), pneumocystosis treatment was replaced by clindamycin and primaquine, prednisone was maintained, and nystatin was added to treat oral candidiasis for five days. Given the improvement of the exanthema and facial edema, HAART was initiated with tenofovir, lamivudine, and dolutegravir on the second day of this readmission. The patient evolved, however, with abdominal pain, bloating, and postprandial vomiting

of food content, until a progressive cessation of feces and flatus elimination. This condition was initially interpreted as another drug reaction, but the distended abdomen began to show positive rebound tenderness in the right iliac fossa, which indicated a CT-scan revealing intestinal transit obstruction with distension of bowel loops upstream of a mass in the cecum (Figure 2). An emergency exploratory laparotomy was performed for acute obstructive abdomen; in the intraoperative inventory of the abdominal cavity, a tumor of neoplastic appearance was found in the cecum, which extended to the proximal third of the ascending colon. A right colectomy was performed with terminal ileostomy and closure of the transverse colon (Figure 3). Thirty-five lymph nodes were also resected, while 3 whitish and hardened lesions identified in the right hepatic lobe (suggestive of metastases) were not biopsied for technical reasons. The patient remained for 5 days on postoperative fasting and gastric drainage until the antiretrovirals could be reintroduced. Among other tests, polymerase chain reaction (PCR) for cytomegalovirus (CMV) DNA in plasma revealed a viral load greater than 20,000 IU/mL, and ganciclovir was prescribed for 21 days. The patient lost another 10kg during hospitalization but evolved satisfactorily to the point of being discharged on the 30th postoperative day. After just over two months at home, he had already recovered 30 kg of his original weight, and a new CD4 cell count was 324 cells/mm³, while the viral load reduced to 77 copies per mL.

The anatomopathological examination of the surgical specimen defined the diagnosis of DLBCL with involvement of 9 of the 35 resected lymph nodes (Figure 4). The immunophenotype was of the non-germinal center B-cell type, and there was immunohistochemical positivity for the EBER-1 transcript of the Epstein-Barr virus (EBV). It was decided to start chemotherapy with the classic regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) soon after a first positron emission tomography (PET/CT) for staging, which was performed 10 weeks after hospital discharge. This examination, however, did not identify the presence of any hypermetabolic tissue. Despite the result, the proposal for complementary treatment with R-CHOP was maintained, but it was refused by the patient. The intestinal transit was then reconstructed after six months, at which time an extensive lymph node block of the mesentery was resected. The histological study of these lymph nodes showed its general architecture preserved with the lymphoid follicles exhibiting prominent germinal centers (Figure 5A). Immunohistochemical tests revealed a mixed population of B (CD20+) and T

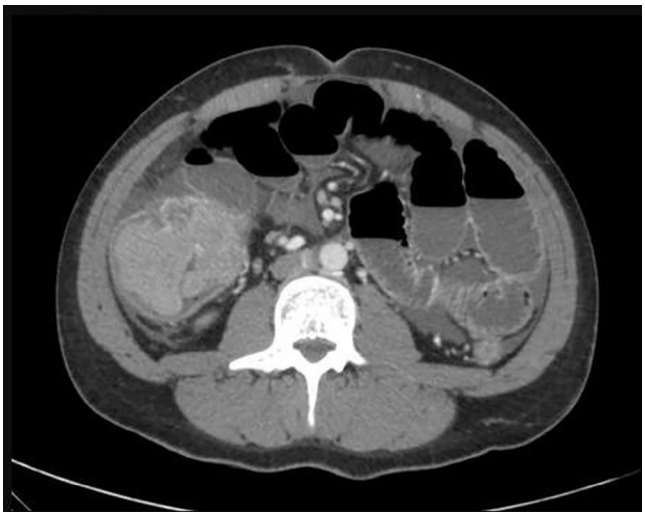

Figure 2. Tomographic section of the upper abdomen showing concentric parietal thickening with irregular contours in the cecum region involving the ileocecal valve, with diffuse distension of the upstream small bowel loops.

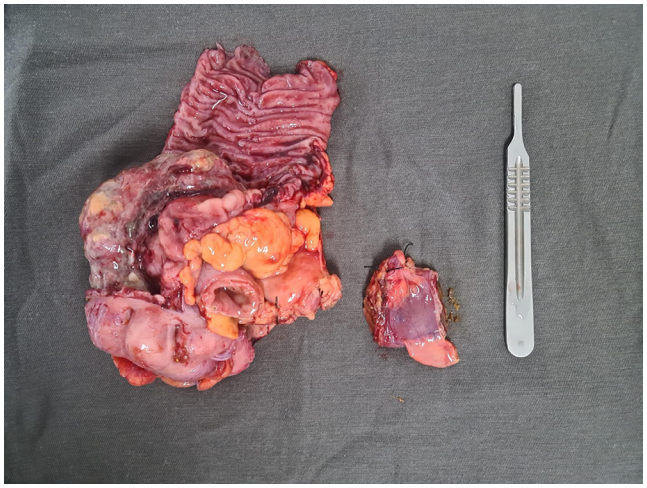

Figure 3. Macroscopic appearance of right colectomy with a large thickening of the cecum wall. The 35 resected lymph nodes are not individually represented in this image.

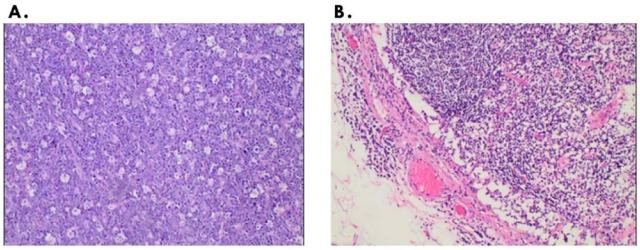

Figure 4. Histological sections of the colectomy products. A. Photomicrograph of diffuse large B-cell lymphoma (DLGCB) with a "starry sky" pattern. H.E. 200x. B. Photomicrograph of DLGCB affecting an abdominal lymph node with loss of normal architecture. Capsular infiltration, and adjacent adipose tissue infiltration can be observed. H.E. 200x. The immunohistochemical study revealed focal positivity for CD20 and high cellular proliferation index KI-67. There was positivity on in situ hybridization for the EBER-1 transcript of the Epstein-Barr virus.

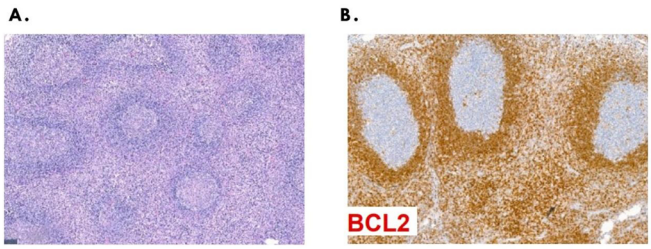

Figure 5. Histological sections of lymph nodes resected in the reoperation. A. Lymph node with general architecture preserved, while lymphoid follicles exhibiting prominent germinal centers are noted. B. The immunohistochemical study reveals a mixed population of B (CD20+) and T (CD3+) lymphocytes in the usual distribution, as well as positivity of the centrofollicular cells for CD10 and negativity for BCL2

(CD3+) lymphocytes in the usual distribution, positivity of the centrofollicular cells for CD10, and negativity for BCL2 (Figure 5B), without evidence of neoplasia. A new PET/CT performed after more than 11 months identified discreet glycolytic hypermetabolism with a maximum SUV of 6.7 in a dubious parietal thickening of the descending colon (Figure 6), without corresponding endoscopic findings on colonoscopy. The patient remains in outpatient follow-up with the infectious disease and onco-hematology teams without unequivocal evidence of disease for over 14 months.

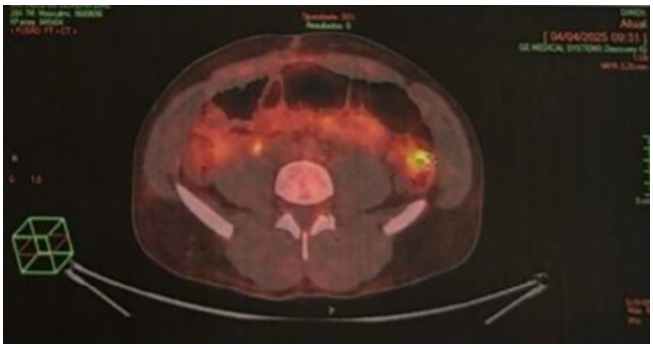

Figure 6. Positron emission tomographic section showing glycolytic hypermetabolism (SUV=6.7) in parietal thickening in the descending colon - colonoscopy was normal.

DISCUSSION

The most used and efficient treatment for DLGCB is the R-CHOP chemotherapy regimen[2]. Multiple variables must be taken into account concerning the therapeutic response, such as age and performance status of the patient, location and size of the mass, and extranodal involvement. Although rare, spontaneous remission of lymphomas in general, without the patient receiving chemotherapy, has been described in the literature[5,6]. Spontaneous remission specific to a DLGCB, on the other hand, is limited to cases reports and small series[6-8], which describe a variable time of 15 to 240 days between diagnosis and remission of the neoplasm, which was approximately 10 weeks in the case herein. Some hypotheses to explain this phenomenon are immunological mechanisms associated with the tumor and others induced in the patient by trauma, concomitant infection, or hormonal alterations[7-9]. In the context of PLWHA, it is very likely that these mechanisms are exacerbated by HAART[10-13], this being the main cause attributed to the remission of DLGCB in our patient, even more so given his excellent and rapid immune recovery and documented virological response after the introduction of HAART. It is also worth noting that, despite the higher incidence of these lymphomas in PLWHA, the response to chemotherapy with R-CHOP in these patients has been similar to that in those not infected with HIV, both groups reaching the same international prognostic indices when compared by age alone[3,4] - another fact that reinforces a possible protective role of HAART in this context.

There is a consensus that systemic therapy should be indicated even when eventual surgical resection has been complete[14] - after all, there are situations in which lymphoma patients benefit from surgical treatment, even in situations of more reserved prognosis[15]. However, this was not the case of our patient, as there was certainly not a complete surgical resection. In addition to the protective effect of HAART, another possible factor involved in the good evolution of our case may have been treatment with ganciclovir due to CMV infection. Although the antiviral has predominant activity against CMV, there is evidence that it may also act against other herpesviruses, including EBV[16]. EBV, in turn, appears to play an important role in the pathogenesis of DLGCB, since it is a virus with the ability to infect B cells and transform them into tumor cells[17,18]. In immunocompromised patients such as those infected with HIV, the ability of the immune system to control EBV replication may be reduced, thus contributing to malignant transformation of B cells[19]. The immunohistochemical positivity for the EBER-1 transcript in the surgical specimen of our case highlights the close relationship between EBV and neoplasia. The EBER-1 transcript (Epstein-Barr virus-encoded RNA 1) is a small non-coding RNA produced by EBV during latent infection. It is one of the most abundant RNAs in infected cells and is frequently used as a marker to identify EBV in tissues[20]. Bossolasco evaluated the evolution of 25 patients with AIDS and primary lymphoma of the central nervous system through the detection of EBV DNA by PCR in cerebrospinal fluid (CSF).

Eight of these patients were using ganciclovir to treat CMV co-infection and had a lower EBV load in CSF, achieving longer survival compared to those who did not receive this medication (median of 181 versus 72 days)[16]. This result suggests a potential complementary use of ganciclovir in this context, although more studies are still needed to elucidate its exact role in DLGCB.

Among the radiological methods, PET/CT stands out as an essential tool for demonstrating total remission of DLGCB by revealing or not revealing metabolic activity of any anatomical changes or masses suggestive of residual disease[6,11]. Performing this examination serially and sequentially in the oncological context of a spontaneous or drug-induced tumor remission becomes an imperative strategy given the possibility of recurrence, which can be early or late: Lim reported in 2017 a rare case of complete spontaneous remission of DLGCB in PLWHA for over five years[10]. In our case, the surprising finding of the first PET/CT was further confirmed by biopsies obtained in the reoperation for intestinal transit reconstruction, which ended up meaning a strategic opportunity to re-evaluate ("second look") and confirm the phenomenon of tumor remission. The suspicion of a possible recurrence based on the finding of the second PET/CT was ruled out through the colonoscopy, which was normal. Oncological surveillance, however, must continue.

CONCLUSION

Although spontaneous remission of DLGCB is rare, it is a phenomenon already described in other reports and offers us questions and learning opportunities regarding tumor biology and the possibility of new therapeutic options. This case also reinforces the relevance of HAART in PLWHA affected by lymphoproliferative diseases, in addition to suggesting a possible impact of controlling EBV replication on the prognosis of some of these diseases. The high risk of recurrence after remission of a high-grade lymphoma, however, requires rigorous clinical and radiological follow-up through serial PET/CTs and immunological control of the underlying disease.

"This case report deserved an official declaration of acknowledgement and ethical approval by its institution of origin and was peer-reviewed before publication, whilst the authors declare no fundings nor any conflicts of interest concerning this paper. It is noteworthy that case reports provide a valuable learning resource for the scientific community but should not be used in isolation to guide diagnostic or treatment choices in practical care or health policies.

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