



Case Report

Diffuse Non-Hodgkin Lymphoma of Extranodal Large Cells in a Young Patient with Symptoms of Splenic Infarction: Case Report

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Citation: Chazaro-Rocha E.F, Granados-Espinosa I.B, Zúñiga-Perea V, et al. (2021) Diffuse Non-Hodgkin Lymphoma of Extranodal Large Cells in a Young Patient with Symptoms of Splenic Infarction: Case Report. Ann Case Report 6: 659. DOI: 10.29011/2574-7754.100659

Received Date: 05 May, 2021; **Accepted Date:** 10 May, 2021; **Published Date:** 14 May, 2021

Abstract

Introduction: Diffuse large B-cell non-Hodgkin's lymphoma is the most frequent subtype of non-Hodgkin's lymphomas worldwide. It accounts for 30-40% of cases [1,2]. Splenic infarcts manifest with painful abdominal syndrome and B symptoms [3].

Material and Methods: The case of a 35-year-old man is discussed. The patient reports abdominal pain in the epigastrium with an intensity of 10/10, leukocytosis at 20,000, normal amylase and lipase; on USG pancreatitis is suspected. A CT scan showed splenic and hepatic abscess, free fluid and pleural effusion.

He presented splenic infarction. The histopathological study after splenectomy reported: infiltration by cells of atypical lymphoid appearance, immunohistochemistry: CD20 +, Cd3 -, CD15 -, CD 30 -. IPI 1 Ann Arbor I.

Treatment is started with R-CEOP x 6 cycles and the patient showed complete remission.

We looked for the association between non-Hodgkin's lymphoma of large B cells in young patients with splenic infarction, the frequency of abdominal pain and survival. The results were that, of 30,455 Ann Arbor stage I patients with large cell non-Hodgkin's lymphoma, 470 cases had spleen involvement (1.5%) [4], 613 patients had splenic involvement (6.3%) [5]; the most common manifestation was abdominal pain (30%) and survival was 48% at 100 months when limited to the spleen (HR=0.62,95% CI=0.53-0.86,p<0.01) [4].

Discussion: The treatment of choice is R-CHOP, and in case of spleen damage, splenectomy improves progression when combined with rituximab [6].

Introduction

Diffuse large B-cell non-Hodgkin's lymphoma is the most frequent subtype of non-Hodgkin's lymphoma in the world. It accounts for 30-40% of cases, depending on the geographic area [1,2]. It is more frequent in people > 60 years of age of the male gender. Approximately 33% of patients show an extranodal lymphoma. The most common affected areas are the gastrointestinal tract, the skin and soft tissues, bones and the urinary tract. The least common areas are the bone marrow, pleura, peritoneum, liver, and the central nervous system [7]. A total of 25,992 patients >20 years with a diagnosis of diffuse large cell non-Hodgkin's lymphoma were analyzed and found to have a 5-year survival of 50% [8].

The spleen is involved in non-Hodgkin's lymphomas, generally between 15-40%, with marginal zone, mantle and follicular lymphoma being more common. Diffuse large B-cell non-Hodgkin's lymphoma of the spleen is the rarest subtype. Splenectomy is the most important tool for making the diagnosis [5]. Splenic infarcts are even rarer as expressions of the disease, and they result from occlusion of branches of the splenic artery; they can result from septic emboli due to valvular involvement, vasculitis, myeloproliferative syndromes and lymphomas. They manifest with painful abdominal syndrome accompanied by B symptoms [3].

In the case of young patients aged 15-39, diffuse large B-cell non-Hodgkin's lymphoma (55-70%) and Burkitt's lymphoma are recognized as having the highest incidence. They are also the most aggressive types and mainly affect Waldeyer's ring and the abdomen. In early staging (stage I and II) diffuse large cell lymphoma is more prevalent than Burkitt lymphoma (stage III and IV) at the time of diagnosis. The treatment of diffuse large B-cell non-Hodgkin's lymphoma varies significantly depending on the age group. In adults, the treatment of choice are chemotherapy treatments with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and, although the disease improves, progression-free 60-80%, these treatments cause high toxicity. In the case of patients with extranodal large cell non-Hodgkin's lymphoma in the spleen, it is known that survival is superior if a splenectomy is performed [9-12].

Material and Methods

We searched for the association between large B-cell non-Hodgkin's lymphoma in young patients with abdominal pain syndrome and the presence of splenic infarction. There are only a few case reports and they require a complex diagnostic approach. The aim is to know the survival of these patients and the usefulness of splenectomy as a treatment.

The case of a 35-year-old male patient is discussed. He was admitted to the emergency department at 17.00 hours, approximately 6 hours after food intake, with general malaise, asthenia, adynamia, nausea and vomiting of gastrointestinal content on 5 occasions, accompanied by abdominal pain at the epigastric level with irradiation to the hypogastrium of oppressive type with an intensity of 10/10 in VAS scale, without aggravating or extenuating factors. Therefore, he went to the emergency department with the following vital signs: BP 100/50 mmHg, HR 120 bpm, RR 22 rpm, T 36°. Hydration therapy was started. A USG was requested, showing the presence of lithiasis and non-acute cholecystitis due to suspicion of acute pancreatitis. An inconclusive surgical evaluation was requested and the patient was admitted to the internal medicine department. After admission, the patient was admitted with 80% saturation. Clinically, data of pleural effusion were integrated. Physical examination revealed that the patient was neurologically intact, with spontaneous palpebral aperture, oriented verbal response, motor response, obeying orders, presence of ocher placement, dehydration of mucous membranes +++ Neck without jugular ingurgitation, presence of acanthosis nigricans, rhythmic heart sounds of good intensity. No murmurs, pulmonary fields without rales or wheezing, right hemithorax in pulmonary base with decreased vesicular murmur, decreased vocal vibrations, abdomen globose at the expense of adipose panniculus, painful on palpation in both superficial and deep epigastrium; there is no evidence of peritoneal irritation, but there is peristalsis. Extremities intact, capillary filling of 3 seconds; no edema. No palpable adenomegaly or organomegaly. Lab tests were requested and

found leukocytosis of 20,000 with deviation to the left, peripheral blood smear with 86 neutrophils and the presence of platelet aggregate, normal amylase and lipase. An abdominal radiography was performed with the presence of hydro-aerial levels. The simple and contrasted tomography of the abdomen showed the presence of probable splenic and hepatic abscess, septated free fluid in several retroperitoneal spaces that would be considered infected fluid and pleural effusion. The patient evolved with fever, weight loss, without improvement of abdominal pain, so it was decided to perform an exploratory laparotomy, which revealed 5000 cc of free serohematic fluid. The absence of abscesses and splenic infarction is noteworthy. Cytology of exudative characteristics was taken, reporting elevated figures of DHL 14.725, Glucose 1.0, Total Proteins 4.5, GASA 0. 51. Cytology: Hematic aspect, yellow color, negative coagulability, positive bacteria and a cross; no yeasts were observed, leukocytes 208-100% pyocytes, uncountable erythrocytes, negative BARR. The ultrasound of the liver and biliary tract is repeated post-surgery, and free fluid is reported in quantity with splenomegaly; the spleen shows lesions. Both a simple and contrasted tomography of the abdomen was repeated, showing collections and free fluid in retroperitoneal and mesenteric regions, adenomegaly, splenomegaly, posterior basal consolidation and scarce bilateral pleural effusion (Figures 1 and 2). TORCH profile, viral panel, rapid HIV test, C-reactive protein, rheumatoid factor, tumor markers and febrile reactions were negative. Since endocarditis was suspected as the main cause of splenic infarcts, blood cultures were performed without bacterial development, transthoracic echocardiogram without valvular lesions or vegetations with LVEF of 64%. Therefore, it was decided that the patient was a candidate for splenectomy. The corresponding prophylaxis with anti-pneumococcal vaccine was carried out and a second operation was performed. The pathology results: dark red color, opaque appearance and soft consistency; the cut is solid dark red with light yellow areas of irregular appearance that are distributed irregularly throughout the parenchyma; they are opaque and soft, red pulp with infiltration by cells of atypical lymphoid appearance, white pulp with depletion of Malpigi's corpuscles (lymphoid follicles) and perivascular cuffs with moderate lymphoid hyperplasia, zonal necrosis with chronic xanthomatous inflammation; a large number of lymphoid cells of abnormal appearance infiltrating sinusoids are observed; they present scant cytoplasm, large and hyperchromatic nuclei showing significant variation in the shape and arrangement of chromatin. An immunohistochemical test was performed, in which the diagnosis was non-Hodgkin large cell lymphoma immunophenotype: CD20 positive, Cd3 negative, CD15 negative, CD 30 negative. IPI score of 1 was calculated with Ann Arbor I staging of high low risk, BCEL-2 low risk for central nervous system infiltration; treatment with R-CEOP (rituximab, gemticitabine, etoposide, vincristine, prednisone) was initiated; 6 cycles were applied, and a complete remission was achieved.

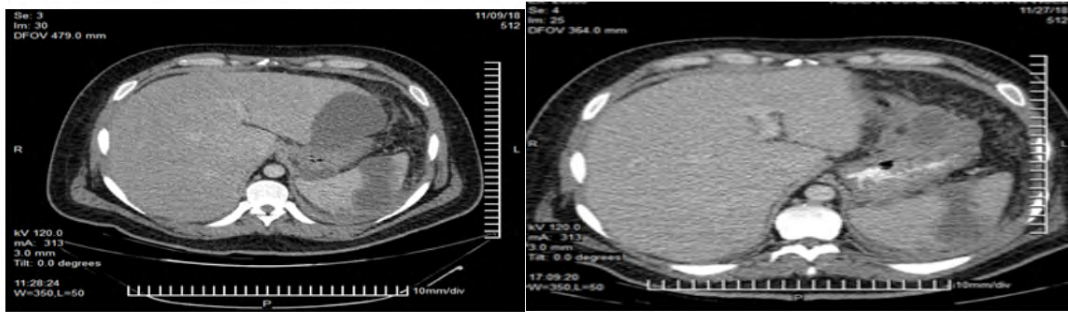


Figure 1: Simple and contrasted CT of the abdomen shows two hypodense lesions at the level of the left hepatic lobe and spleen of irregular contours (A). The following image shows bilateral pleural effusion. (B)

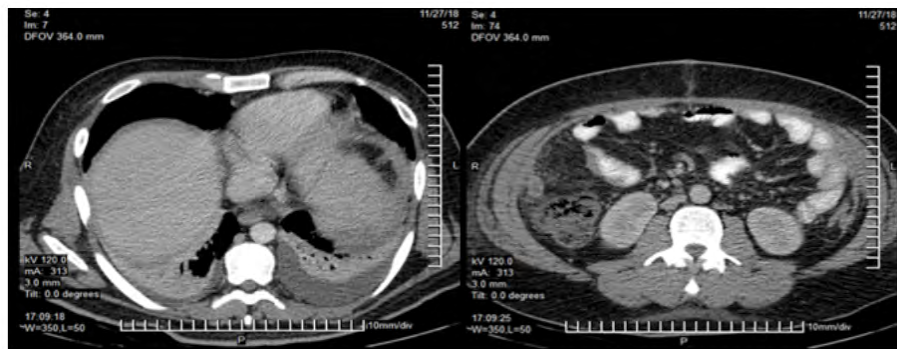


Figure 2: Simple and contrasted CT of the abdomen shows two hypodense lesions at the level of the left hepatic lobe and spleen of irregular contours (A). The following image shows bilateral pleural effusion. (B)

Discussion

Diffuse large cell non-hodgkin lymphoma (DLBCL) is reported in 30% of non-Hodgkin lymphomas. Up to 16 clinicopathologic entities have been reported. Diagnosis is based on morphology, immunohistochemistry, cytogenetics and molecular analysis. DLBCL is characterized by the expression of surface markers such as CD20, PAX5, transcription factors (OCT2) and CD79a. To differentiate it from other types such as plasmablastic lymphoma, anaplastic lymphoma must have negative results of CD138, CD38, Ki67, MYC, ALK, herpes virus 8, Epstein Barr virus. For staging, PET scan, the IPI scale as the prognostic standard and the search for high-risk translocations in MYC and BCL2 genes are recommended; in this case we do not have any of these tools [13,14].

Focus on splenic infarction

Splenic infarction is defined by CT as the presence of one or more of the following:

- Hypodense wedge-shaped lesion
- Multiple heterogeneous lesions with irregular enhancement

- Extensive or complete low attenuation lesions

The spleen is a hematopoietic organ that filters and removes aged blood products and aids immunity against encapsulated bacteria. Infarction occurs when blood flow to the spleen is compromised, causing tissue ischemia and eventual necrosis, which can be local or global depending on the occluded blood vessel. Irrigation is mainly from the splenic artery (branch emerging from the celiac trunk) and secondarily from the short gastric arteries (branch emerging from the left gastroepiploic artery).

Despite the arterial irrigation described, occlusion or infarction due to atherosclerosis is rare, as is the case with other organs. In this particular situation it is more commonly associated with hemoglobinopathies, mainly sickle cell anemia secondary to hypoxia-repetitive acidosis. Conditions with splenomegaly carry a risk of infarction such as primary myelofibrosis, Gaucher disease, malaria, AIDS, mycobacterium avium complex infections, acute myeloid leukemia and lymphomas. In terms of epidemiology, it has been reported at any age; however, people over 40 years of age are more prone. Its frequency increases over the years in relation to increased use of imaging studies, increased splenic embolizations and non-surgical management of atraumatic splenic

lesions. In a 2010 study of 26 patients, the most important features were described. The authors report that 21 patients had another underlying diagnosis [15].

Abdominal pain predominantly in the epigastrium and left hypochondrium is the most commonly described manifestation in patients with splenic infarction. The appearance of Kehr's sign is characterized by pain in the left shoulder in second place [16]. The presence of abdominal pain syndrome was associated with splenic damage, mainly splenic rupture. Even in cases in which extensive areas of infarction or rupture were reported, there was tachycardia, tachypnea, hypotension, and sometimes hypovolemic shock [16]. In the initial diagnostic approach, ultrasound or contrasted tomography is suggested if there is clinical suspicion [17]. In the clinical case presented, 3 main categories were ruled out: infectious, inflammatory and drug- or trauma-related conditions (Table 1).

More relevant characteristics of patients with splenic infarction (n=26)
Average age 52 years
50% STARTED WITH ABDOMINAL PAIN ON THE LEFT SIDE
36% PAIN ON PALPATION LEFT HYPOCHONDRUM
32% splenomegaly
31% NO SIGNS OR SYMPTOMS IN SPLEEN AREA
36% FEVER
32% NAUSEA AND VOMITING
36% FEVER
56% LEUKOCYTES
71% HIGH DHL

Table 1: Characteristics of patients with splenic infarction.

Association between NHL and splenic infarction

Regarding the association between large cell non-Hodgkin's lymphoma (DLBCL), in a study of 107,550 patients with DLBCL in the SEER database, out of 30,455 Ann Arbor stage I patients, only 470 cases had spleen involvement (1.5%) with a varied age range (17-93 years) [4]. There are different forms of spleen involvement: splenomegaly, abnormal cell infiltration, infarcts and areas of hemorrhage, and even together suggest splenic rupture unrelated to trauma. In the findings of this patient we found at least

3 of the elements that suggest that the patient was related to this mechanism; this regains importance in a review of 845 patients with non-traumatic splenic rupture between 1980-2008, and 6 major causes are defined: neoplastic (30.3%), infectious (27.3%), inflammatory, non-infectious, drug-related and idiopathic. Among the neoplastic causes, myeloid leukemia and lymphoma were reported as the most related to these afflictions [18]. Different authors report a low index of suspicion between splenic involvement and non-Hodgkin's lymphoma [19-21]. In another study of 613 patients with non-Hodgkin's lymphoma, 6.3% were associated with cases of splenic involvement [5]. In 2018 we report the case of a patient with follicular lymphoma that started with splenic rupture secondary to diffuse large cell lymphoma, which is why we emphasize the increase of diagnostic suspicion in patients with preexisting malignancy [22]. Fortunately, the patient did not have splenic rupture. The explanation for this patient's painful abdominal syndrome was splenic infarction and free fluid in the abdominal cavity at the expense of the underlying process.

Treatment and survival

As treatment according to stage I-II if the tumor mass does not exceed 7.5 cm, 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) followed by radiotherapy are recommended. If the tumor mass exceeds 7.5 cm, as with this patient, the guidelines recommend R-CHOP for 6 cycles. For stage III-IV, 2-4 cycles of R-CHOP are recommended, followed by 6 cycles and evaluation of response with PET; other first-line therapies with poor left ventricular function is RCEOP (Rituximab, cyclophosphamide, etoposide, vincristine, prednisone) [23]. In a retrospective study of 87 patients with diffuse large cell non-Hodgkin's lymphoma with spleen involvement, diagnosis was made with splenectomy, and survival improved. Most received CHOP chemotherapy in 92% and 82% received R-CHOP [6].

In another small study of 59 patients with primary spleen lymphoma, the median survival was 108 months in those who underwent splenectomy and 24 months in those who were not treated surgically. The drawback of this study was that patients did not have rituximab available [24]. In 2017, during a study of 107,550 patients with diffuse large B-cell lymphoma with 30,455 stage I, groups were divided to assess survival in patients treated with splenectomy and without splenectomy; lack of statistical significance was reported. Of note was the DLBCL group, which had lower survival compared to the group with other NHL limited to the spleen (27% vs. 48% at 100 months) (HR=0.62,95% CI=0.53-0.86,p<0.01) [4] (Table 2).

Author	Type of study	Frequency and/or etiology of splenic infarction	Treatment	Result	Complication
Jaroch 1986 [25]	Retrospective series 29 patients	29% hematologic neoplasia 38% cardioembolic 4% septic emboli	Splenectomy 9%	Mortality 13% in splenectomized patients versus 75% not splenectomized	Thrombosis Cardiovascular event
Goerg 1990 [26]	Retrospective series 23 patients	56% hematologic neoplasia 34% septic plungers	Splenectomy At 21%	Mortality 17%	Thrombosis and abscess
Okeef 1986 [27]	Case Series 96 autopsies	66% embolic 33% non embolic 5% hematologic Neoplasia.	Pre-death hemodynamic support	Mortality 100%	Thrombosis Cardiovascular event
Nores 1998 [28]	Retrospective series 59 patients	67% hematologic neoplasm 23% thrombosis 10% other causes	Splenectomy at 100%	Mortality 5%	Abscess and splenic rupture
Antopolski 2007 [29]	Retrospective series 48 patients	10% associated with neoplasia 10% septic plungers 22% hypercoagulation	Anticoagulation Did not perform splenectomy	No mortality reported	No complications
Brett 2020 [30]	Retrospective series	20% associated with neoplasia 6% lymphoma or leukemia 6% sickle cell anemia 25% embolic 17% septic shock	According to etiology	Mortality 29% associated with malignancy	Thrombosis Septic shock

Table 2: Experience in the Management of Splenic Infarction.

Diffuse large cell non-Hodgkin's lymphoma remains the most common in the age groups. It predominantly affects Waldeyer's ring and abdomen. Few cases report splenic infarction as the initial manifestation. The presentation may be indolent, but most commonly it debuts with painful abdominal syndrome and therefore the diagnostic approach is complex. Spleen involvement is frequently caused by endocarditis and neoplasms, mainly non-Hodgkin's lymphoma and leukemia. Diffuse large cell lymphoma is the least common. The treatment of choice is R-CHOP and, in case of spleen involvement, splenectomy improves the disease without progression, provided it is accompanied by rituximab.

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