Splenic diffuse large B-cell lymphoma. Case report

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Abstract

Lymphomas are defined as a solid tumor of the lymphoid tissue, of malignant biological behavior, and with great diversity of clinical and histological forms. It originates in lymph nodes in 35% of cases or in the lymphoid tissue of the parenchyma of the original organ in 65% of cases. Lymphomas are classified into two major groups: Hodgkin's disease and non-Hodgkin's lymphomas (NHL). The spleen may be involved in a wide variety of lymphomas; in some cases they infiltrated said organ as part of a broad diffusion of a base node other particular lymphoma. Splenectomy with liver biopsy and biopsy of the para-aortic lymph node is the treatment of choice for splenic lymphoma. In patients with low-grade NHL confined to the spleen, complete remission of the associated haematological abnormality may reach approximately seven months after splenectomy. Postoperative adjuvant therapy depends on the clinical stage of the disease.

Key words: B-cell lymphoma. Reed-Stenberg cells. Ann Arbor classification. Splenectomy. Symptoms B.

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Introduction

Lymphomas are defined as solid tumors of the lymphoid tissue that have a malignant biological behavior and a diversity of clinical and histological forms. This type of neoplasm originates in lymph nodes in 35% of cases or in parenchymal lymphoid tissue of the original organ in 65% of cases. Lymphomas are classified in two large groups: Hodgkin's Lymphoma (HL) and non-Hodgkin Lymphoma (NHL); this division was established according to the presence or not of very characteristic cells, the "Reed-Stenberg cells"¹⁻⁵.

NHLs are a group of more than 30 neoplasms originating in B or T cells. It is a highly heterogeneous group of multiple lymphoproliferative disorders, with large differences at the clinical level, in biological and histologic behavior and long term prognosis. NHLs constitute the third type of neoplasms with the highest growth after melanoma and lung cancer. The spleen is involved in 30-40% cases of NHL, and primary lymphoma of the spleen (PLS) is a rare condition with an incidence lower than 1%; most lymphomas of the spleen are of the B-cell type¹⁻⁵.

Age older than 60 years, occupational exposure to toxic agents and exposure to infectious agents such as HIV and *Helicobacter pylori* increases NHL incidence. Predisposing factors for its development are: genetic factors, congenital or acquired immunodeficiency, chronic pharmacological immunosuppression and autoimmune-type factors (Sjören's disease, thyroiditis, celiac disease), among others².

Epidemiology

Lymphoma affects more than one million people in all the world. Every year, its incidence increases by 3%, and it currently accounts for 5% of all types of cancer diagnosed in one year in the USA¹. Mean age at primary spleen lymphoma (PSL) presentation is 36 years, with a range of between 22 and 48 years of age. It is more common in women at a female:male ratio of 4:1. Recent works associate hepatitis B virus and the presence of B-cell NHL in between 22% and 37% of cases^{1,6,11,13}. Currently, it constitutes the fifth cause of cancer-related death in the world³. In Mexico, in 2003, it was the third cause of cancer-related death in males (7.83%) among the registered neoplasms, after skin and prostate cancer. In women, it was the sixth cause of cancer (3.97%) out of total cancer cases in this gender². NHL incidence in 2012 in Mexico was 4,632 cases, which equals 3.1%, and mortality by its cause was

2,558 cases, which equals 2.3%. It is more common in females, with 2,546 cases, in comparison with 2,086 cases in males^{13,16}.

Classification

Something very important to understand any classification is knowing the basic differences between that which defines a low grade and a high grade lymphoma since, although in the World Health Organization (WHO) last classification this difference is not specified, conceptually, knowing the different types of lymphoma is helpful. The Revised European American Lymphoma (REAL) classification is the one that best marks these differences, and among low grade or indolent NHL, it includes^{1,3}:

- B-cell lymphomas^{1,3}:
 - Lymphocytic lymphoma/Chronic lymphatic leukemia
 - Lymphoplasmocytic lymphoma
 - Follicular lymphoma (FL)
 - Nodal and extranodal marginal zone lymphomas (MZL)
 - Splenic marginal zone lymphoma
- T-cell lymphoma^{1,3}:
 - Mycosis fungoides
- In turn, the WHO classification recognizes three types of MZL^{1,3}:
 - Mucosa-associated MZL (or MALT type)
 - Primary nodal MZL
 - Primary splenic MZL

Primary splenic NHL is an infrequent pathology. It has a lower than 1% incidence; however, splenic involvement in patients with NHL ranges from 50% to 60%. Owing to its low frequency, diagnosis of this condition is difficult to be established. In this entity, mean age at presentation is 48 years, and it is more common in women than in men at a 4:1 ratio¹⁷⁻¹⁹.

Primary splenic MZL is a rare condition that accounts for less than 1% of all lymphoid neoplasms; hilar lymph nodes are usually involved, but peripheral lymphadenopathy is quite uncommon^{1,3}.

Types of lymphoma that infiltrate the spleen

The spleen can be compromised by a wide variety of lymphomas. In some cases, they infiltrate as part of a wide diffusion of a primary node or another particular lymphoma. In spite of many years of research into the origins and characteristics of lymphomas favoring the spleen, the participation of the oldest type described to

preferably involve this site, hairy-cell lymphoma, remains a mystery. Lymphoma and splenic B-cell marginal zone, its most recently described variants, have been widely investigated, but their actual relationship with splenic marginal zone normal B-cells remains controversial^{4,15}.

Hairy cell leukemia

The most cytologically and histologically distinctive splenic lymphoma, hairy cell leukemia (HCL), was first described in 1972. It is a rare malignancy, since it accounts for less than 2% of NHLs and it doesn't show a tendency towards an increased frequency. It is still poorly known, in spite of more than 25 years of research; its cell of origin remains a mystery. Its characteristic cytology is observed in peripheral blood smear, with cells that have structures resembling hairs that extend radially from its membrane. In the spleen, they are often present in a massive form, and patients present with spleen-related symptoms. However, growth of this lymphoma is indolent, and most patients are likely to have a long prodromal period prior to seeking medical attention. HCL is unique in the degree of destruction it causes to the underlying splenic architecture⁴.

Neoplastic cells typical immunophenotype in HCL, demonstrable in spleen sections fixed by means of immunohistochemistry techniques, is⁴:

- CD25 and CD123 expression in most cases.
- Cyclin D1 nuclear expression in more than 50% of cases (although generally weak and/or heterogeneous).
- CD10 expression in up to 20% of cases⁴.

Follicular lymphoma

Follicular lymphoma is a subtype of low-grade B cell lymphoma that is known as the prototype of indolent lymphoma. It accounts for 20% of NHLs and 70% of indolent lymphomas. It is recognized by the presence of white pulp nodular growths composed of a relatively pure population of small, chopped-up lymphocytes; this cells very often also infiltrate the red pulp. Their proposed normal counterparts are centrocytes within lymph node secondary lymphoid follicle germinal centers (GC). Patients are often asymptomatic, in spite of the presence of disseminated disease at diagnosis, frequently at multiple lymph node groups, the spleen and the liver. It is composed of follicular structures, such as tumor cell-centrocyte compounds that express CD10 and BCL2 protein. BCL2 protein expression is a consequence of the t(14;18) and (q32;q21) chromosomal translocation,

where the BCL2 locus is under the control of promoter IgH. It occurs not only as the nodal type, but also as extranodal lesions, including the splenic one. Pure extranodal presentation are infrequent (9% of cases). Follicular lymphomas that compromise the spleen can exhibit one of two histologic patterns^{9,10,12}.

The first model consists of very closely aggregated neoplastic follicles, often enlarged, which alter splenic architecture and frequently show neoplastic B-cell interfollicular proliferation. This pattern resembles typical examples of nodal FL. In contrast, the second pattern consists of disperse neoplastic GCs with an entirely intrafollicular growth pattern and general splenic architecture preservation. Interestingly, neither pattern is associated with clinical stage or spleen weight differences^{10,12}.

Hepatosplenic T-cell lymphoma

This is an aggressive systemic lymphoma that generally occurs in young men, sometimes in the setting of chronic immune deterioration, with cytopenias and hepatosplenomegaly. Bone marrow and liver infiltration is typically intrasinusoidal, whereas in the spleen, white pulp structures atrophy accompanies infiltration. Cells are of small or medium size, except at last phases of the disease, when a leukemic phase and blastic transformation are typically notorious⁴.

Clinical presentation

PSL clinical presentation can be variable. Symptoms are generally unspecific, and it includes abdominal pain, weight loss, fever and splenomegaly; however, sometimes it can occur asymptotically^{20,21}.

This tumor has a wide spectrum of clinical manifestations such as: left upper quadrant abdominal pain, constitutional symptoms, weight loss, fever, paleness, night sweats, anorexia, asthenia and adynamia^{6,11}, as well as infiltrative syndromes (adenopathies, splenomegaly, hepatomegaly). However, exceptionally it can be asymptomatic².

In most lymphomas, patients generally have painless cervical, axillary or inguinal progressively-growing adenopathies (of more than 3-weeks' evolution, with or without B symptoms and with no evidence of associated infectious process). However, 20% of cases can have extranodal presentation, with the most common being the digestive presentation. There can be B symptoms: fever, sweating or weight loss, as well as gastrointestinal, skin, upper airway, tonsillar, brain, thyroid and bone symptoms².

On splenic lymphoma physical examination, splenomegaly and absence of peripheral adenopathies are found. Most common laboratory anomalies include anemia, thrombocytopenia or leukopenia. However, it can manifest itself with pancytopenia, bicytopenia or monocytopenia, but it can start with leukocytosis in 40% of cases^{6,11}.

Diagnostic workup

For diagnosis, a biopsy that is representative of the tumor area has to be performed or a review of available material must be carried out, as long as it is adequate for histopathological diagnosis, ideally by an experienced pathologist; and subsequently, immunochemistry study. Fine needle aspiration biopsy (FNAB) is not adequate to establish lymphoma initial diagnosis, as well as for correct classification. Therefore, a biopsy of the compromised lymph node, organ or tissue has to be obtained in order to establish an accurate diagnosis².

Laboratory tests that should be performed are: a complete blood count that includes adequate morphological characterization in order to identify lymphoma cells, globular sedimentation rate, blood chemistry screen, liver function tests, lactate dehydrogenase, alkaline phosphatase, beta-2 microglobulin, serum electrolytes and urinalysis, as well as bone marrow aspiration or bone biopsy (uni- or bilaterally) in selected cases of immunophenotype and genetic study².

Most common PSL-associated laboratory anomalies include anemia, thrombocytopenia or leukopenia. However, there may be no alterations¹⁷.

Imaging tests required for diagnosis are: chest X-ray, computed tomography (CT) of the abdomen and pelvis or neck or facial skull in selected cases, as well as positron emission tomography combined with CT (PET-CT), which can be requested in case of doubt at early stages, and it is also useful to assess treatment response². With regard to spleen lymphoma diagnosis, ultrasound and CT are the modalities of choice. Four helical CT radiological patterns have been described for lymphoma⁸:

- Homogeneous splenomegaly.
- Miliary pattern constituted of multiple 1-5-mm nodules.
- Diverse masses of different sizes ranging from 2 to 10 cm.
- Single mass of 7 to 14 cm in diameter with or without central hypodensity.

In case of suspicion or risk of infiltration to the central nervous system, performing lumbar puncture, cytochemistry with lactate dehydrogenase (LDH), cytology and

flow cytometry is recommended, in addition to brain CT or magnetic resonance².

This lymphoma is difficult to diagnose at early stages owing to its low incidence and unspecific symptoms. Prognosis for this type of patients is related to the stage (Ann Arbor classification) and the type of cells involved. Splenic lymphoma cases are more numerous in NHL, although they are often highly heterogeneous with regard to clinical and histological evaluation. Most common histologic subtypes are low grade lymphocytic lymphoma and intermediate grade lymphoma⁷.

The international prognostic index is useful in diffuse large cell lymphoma, but it is not adequate using it in other lymphoma variables. This index evaluates the age, stage according to Ann Arbor classification, performance status (ECOG), LDH, and extranodal infiltration sites. The international prognostic index for FL evaluates the age, stage according to Ann Arbor classification, performance status (ECOG), hemoglobin and number of lymph node sites².

Treatment

Splenectomy with liver biopsy and para-aortic lymph node chain biopsy is the treatment of choice for splenic lymphoma. In patients with low-grade NHL confined to the spleen, complete remission of the associated hematologic alteration can be reached at approximately 7 months of splenectomy. Postoperative adjuvant therapy depends on clinical stage of the disease¹⁴.

Therefore, treatment in patients with stage I-II indolent lymphomas with no bulky disease and without risk factors is locoregional radiotherapy or observation in selected cases. In patients with stage I-II non-bulky disease and with risk factors: chemotherapy with or without immunotherapy, or chemotherapy plus radiotherapy². In patients with stage III-IV bulky disease: R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone) or R-CVP (rituximab-cyclophosphamide, vincristine, prednisone) or R-FMD (rituximab-fludarabine, mitoxantrone, dexamethasone) or rituximab monotherapy (in selected cases)².

Treatment in aggressive lymphomas will depend on the stage. In stage I-II with no bulky disease and with or without risk factors: R-CHOP x 3 cycles plus locoregional radiotherapy (30-36 Gy) or R-CHOP x 6-8 cycles if radiotherapy is contraindicated or unavailable. For stage I-II with bulky disease: R-CHOP x 6-8 cycles plus locoregional radiotherapy (30-36 Gy)².

Survival and relapse

One-year relative survival rate (percentage of patients who survive at least one year once cancer is detected, excluding those who die due to other diseases) of patients with NHL is of up to 79%. Relative survival rates at 5 and 10 years are 63% and 51%, respectively². Relapse rate is constant in time, even in patients with treatment complete response. No treatment combination has managed to be curative. Mean survival of patients with advanced FL is 10 to 14 years¹⁴.

Case presentation

This is the case of a female patient with family and hereditary history of siblings with pancreatic and prostatic cancer. She was active smoker, and had a history of moderately differentiated large cell lineage, clear cell variant of squamous cell cancer at the malar region.

She was evaluated by the Department of Surgical Oncology, where she was referred to by the Department of General Surgery for presenting with a 2-month history of mild to moderately intense pain at left hypochondrium irradiating as left sided girdling pain, accompanied with nausea with no vomiting and general malaise, and exacerbated by active movement, in addition to hyporexia, loss of 8 kg of weight in two months, intermittent constipation, in addition to having been bedridden owing to left hypochondrium trauma and incapacitating lumbar pain. In view of all this, plain and contrasted abdominal and pelvic CT was practiced, where images consistent with a splenic tumor of 13 x 10 x 10 cm in diameter, with apparent infiltration to surrounding tissues, were observed (Figs. 1 and 2), with abscessed hematoma associated with previous trauma in the zone being ruled out, in addition to reporting vertebral column and left coxofemoral region osteodegenerative changes, with no presence of intra-abdominal lymph node activity. This prompted referral to the Oncology Department. On physical examination the patient was found in anatalgic posture, with good skin and integument coloration, good mucosal hydration, neck free of regional adenopathies, uncompromised cardiorespiratory function, axillary regions with no adenopathies, flat abdomen, with left hypochondrium and ipsilateral lumbar zone pain with deep palpation, with the presence of a spleen-dependent, fixed, slightly painful, hard in consistency tumor with ill-defined borders being palpated, and no data consistent with peritoneal irritation or abdominal distension or inguinal adenopathy being found. Limbs were hypotrophic for

Figure 1. Abdominal CT axial and coronal section where a 13 x 10 x 10-cm diameter tumor, with apparent infiltration to adjacent tissues and with no data consistent with intra-abdominal lymph node activity, is observed.

Figure 2. Pelvic CT axial and coronal section where a 13 x 10 x 10-cm diameter tumor with apparent infiltration to adjacent tissues and no data consistent with intra-abdominal lymph node activity is observed.

the patient's age, with no presence of edema and with adequate capillary refill.

In view of this, she was admitted to the department in order to complete the diagnostic workup and for surgical preparation for exploratory laparotomy. Chest X-ray and laboratory tests showed no anomalies, and LDH was normal. The electrocardiogram showed no alterations, with assessment to determine cardiovascular risk without surgical contraindication.

The patient underwent exploratory laparotomy where, as trans-surgical finding, a 15 x 10 x 8 cm tumor with irregular borders, hard consistency and highly vascularized was found at the splenic upper pole, with infiltration to the splenic hilum and pancreatic tail; therefore, the patient underwent splenectomy and distal pancreatectomy, with the specimen being sent for histopathological study (Fig. 3). Postsurgical period was uneventful, with adequate clinical evolution and tolerance to the oral route, without abdominal pain or fever. She was discharged home for follow-up as outpatient of the Department of Surgical Oncology.

The histopathology report referred, with regard to the splenectomy product: diffuse and massive infiltration by large cell, poorly differentiated malignant neoplasm of diffuse pattern, extensively necrosed (30% necrosis) (Fig. 4), pancreatic parenchyma is identified with infiltration (Fig. 5). The immunohistochemistry report referred: CD intensely positive status, 100%; CD20 intensely positive status, 100% (Fig. 6); bcl-2 intensely positive status, 100% (Fig. 7); MUM-1 intensely positive status, 100%; PAX-5 moderately positive status, 50%; Ki67 intensely positive status, 90%; ckae1/ae3 negative status; HMB-45 negative status; Cyclin d-1 negative status; CD3 negative status. The following conclusion was established: splenectomy product with diffuse and massive infiltration by diffuse large B-cell lymphoma, immunoblastic morphologic variant, post-GC in origin by immunohistochemistry.

The patient was subsequently assessed by the Hematology Department, where PET-CT studies were requested in order to rule out other sites of tumor activity and for pertinent staging.

Discussion

Lymphomas are a clonal proliferation of lymphocytes. These tumors originate in lymph nodes in 35% of cases or in the lymphoid tissue of the compromised organ parenchyma in 65% of cases. Lymphomas are classified in two large groups: HL and NHL. NHLs are a group of more than 30 neoplasms originating in B or T lymphocytes. These tumors can affect any organ of the lymphoid tissue: lymph nodes, the spleen, gastrointestinal tract, bone marrow and the skin¹⁷.

From 50 to 60% of patients with NHL have splenic involvement; however, splenic primary tumors have an incidence lower than 1%, which makes for diagnosis difficult to be established owing to the low frequency of

Figure 3. Splenectomy product section macroscopic photograph. Note the presence of multiple, whitish grey-colored neoplastic nodules, with areas of necrosis and hemorrhage.

Figure 4. Microscopic photograph where neoplasm with extensive necrosis (upper part) infiltrating most part of the organ is observed (10x, hematoxylin and eosin).

this condition¹⁷. PSL clinical presentation can be variable. Symptoms are generally unspecific and include abdominal pain, weight loss, fever and splenomegaly; however, sometimes it can occur asymptomatic.

Most common PSL-associated laboratory anomalies include anemia, thrombocytopenia or leukopenia. However, there may be no anomalies, as it occurred in our case. Imaging methods play an essential role in PSL diagnosis, with ultrasound and tomography being the studies of choice. CT radiological patterns consistent with PSL have been described: homogeneous splenomegaly, multiple nodules of between 1 and

Figure 5. Microphotograph detail, with presence of malignant neoplasm with intense atypia and pleomorphism; note the important mitotic activity (arrows) (40x, hematoxylin and eosin).

Figure 6. Detail of immunochemistry for CD20, intense in 100% of neoplastic cells (10x, immunohistochemistry).

5 mm, several masses of different sizes ranging from 2 to 10 cm and a single mass of 7 to 14 cm in diameter, with or without central hypodensity, with the latter being the presentation in our case, where it had an average of 14 cm in diameter¹⁷.

Therefore, establishing an accurate diagnosis will always represent a huge challenge for the oncologist or hematologist owing to the low frequency of this pathology, with the diagnosis being established in many occasions with the support of imaging studies.

Figure 7. Immunohistochemistry image with positivity for bcl-2, intense in 100% of neoplastic cells (10x, immunohistochemistry).

Conclusion

It is essential always bearing in mind the possibility that any splenic tumor might be due to a lymphoma with an uncommon localization, together with an absence of adenopathies documented on physical examination; and also that the treatment of choice will generally be of the surgical type, either with an open or a laparoscopic approach, as long as the neoplasm is limited to this organ, and that this will allow for definitive histopathological diagnosis of the specimen to be obtained. Therefore, adjuvant treatment with chemotherapy or radiotherapy is rarely administered in this type of lymphoma, just as it occurred in our case, where there was no need for any other type of management.

Conflict of interests

The authors declare not having any conflict of interests.

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