Non-Hodgkin Lymphoma Simulating Carcinoma of the Vulvar Region: Report of Two Cases

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Abstract

Two cases of primary non-Hodgkin lymphoma of the vulva are reported. The first one corresponded to an 82-year old woman who showed a 6-cm vulvar injury with a multinodular appearance, whose pathological diagnosis was diffuse large-cell lymphoma B, germinal center B-cell type. She received R-MiniCHOP treatment for three months with partial response. The patient did not return for clinical monitoring in the end.

The second case corresponded to a 35-year old woman showing an extensive vulvar ulcerated injury of 10 cm with pathological diagnosis of extranodal NK/T-cell lymphoma, nasal type with T-cell cytotoxic phenotype (EBER+), with CD56 expression and loss of CD8 expression. The T phenotype was determined by the study of genetic rearrangements for the T-cell receptor, which was monoclonal. The patient received the SMILE and GELOX treatments with low response and disease progression.

Differential diagnosis is discussed, and the literature is reviewed regarding non-Hodgkin's lymphomas of the female genital tract.

Keywords: Vulvar region; Diffuse large B-cell lymphoma; Extranodal NK/T-cell; Nasal type; Non-Hodgkin lymphoma; EBER

Introduction

Although on the last decades there has been a significant increase of the extranodal primary non-Hodgkin lymphoma (NHL) occurrence, there is not much reports of neoplasm in the female genital tract [1,2]. Up to 2015, 30 cases of primary vulvar NHL were described. By order of frequency; the first place was for the NHL of ovary (49%), then utero (29%), fallopian tube (11%), vagina (7%), and finally the one of vulva (4%) [3-11]. On this report, we show two cases of primary vulvar NHL that present signs and symptoms similar to vulva carcinomas, describing the clinical, pathological and immune phenotypic characteristics to help making a proper differential diagnosis. Since this pathology is quite rare, it is very important that gynecologists and pathologists include NHL in the diagnostic possibilities for patients presenting tumor mass in the female genital tract.

Histological and immune histochemical studies

The biopsies taken from the vulvar injuries were fixed in formalin, then placed on an automatic tissue processor (Leica ASP300S, Nussloch, Germany) and embedded in paraffin. Four 4-micron sections were cut from the tissue blocks and stained with Hematoxylin and Eosin (HE) for morphological assessment. Immunoperoxidase staining was performed in an automated Immunohistochemistry (IHC) equipment (Autostainer Link48, Dako, California, USA) using a detection system with polymers (EnVision Flex High pH, Carpinteria, California, USA). The following antibodies were used for the ICH reactions in the initial diagnostic biopsy: CD20, BCL2, BCL6, CD10, MUM1, C-MYC, CD3, CD4, CD8, CD56, CD30, ALK, Granzyme B (all Dako Flex, Carpinteria, California, USA) and TIA-1 (BioSB, Santa Barbara, California, USA). In addition, Epstein-Barr-virus-encoded RNA in situ hybridization was performed, EBER (HistosondaCenbimo, Lugo, Spain).

Molecular analysis

A Polymerase Chain Reaction (PCR) analysis was performed for the rearrangement of the
T-Cell Receptor (TCR) gamma chain, as described in the literature. Consensus primers were used for regions J gamma 1 and 2, J gamma P and J gamma P1 and P2 of the TCR gamma chain gene. The TCR products were analyzed in a capillary electrophoresis instrument (Genetic Analyzer 3500, Applied Biosystems, Carlsbad, California, USA).

Case Report 1

An 82-year old female patient from Lima came to the Gynecology Unit of Instituto Nacional de Enfermedades Neoplásicas (INEN) with a 2-month history progress, presenting a tumor in the vulvar region, in addition to oral intolerance, a 5-kg weight loss and night sweats. The patient was referred from another hospital with the clinical diagnosis of carcinoma. In the physical examination the patient was on ECOG 2, showing a 5 cm × 6 cm tumor of granulomatous, mameloned appearance, and bilateral inguinal adenopathies of up to 1.5 cm. An incisional surgical biopsy was performed, and during histologic exam a diffuse lymphoid neoplasia was noticed, composed by centroblasts-like large cells, with a lower component of immunoblasts-like cells, and a high level of mitosis. The tumor immunopheno type was CD20+, BCL-2+, CD10+, C-MYC+, BCL-6-, MUM1-, CD30-, Cyclin-D1-, and CD3-, with a proliferative index of around 90%, determined with Ki67 (Figure 2 and Figure 3). The diagnostic conclusion was Diffuse Large B-Cell Lymphoma (DLBCL), Germinal Centre B-cell-like (GCB) type, according to the origin cell (Hans algorithm), with C-MYC over expression. The bone marrow biopsy did not reveal neoplastic infiltration. The laboratory exams showed Hb 81.0 g/L, leukocytes 5.59 × 10^9/L (lymphocytes 16%, segmented 74%, basophils1%), DHL 918 IU, B2 microglobulin 3.63 mg/dL. She started treatment with Rituximab and MiniCHOP (R-MiniCHOP), with good tolerance to the Chemotherapy (CT). Later, the patient showed neoplastic engagement in the duodenum, thus it was categorized as Stage IV. She continued treatment for three months showing partial response, but then she was no longer seen for the follow-up.

Case Report 2

A 35-year old female patient from Lima with a year history progress came to the INEN for diagnoses and treatment, presenting a progressive-growth tumor in the vulvar region (Figure 4). She did not mention other symptoms and was referred from another healthcare center with the clinical diagnosis of carcinoma. In the physical examination the patient was on ECOG 2, showing a big new ulcerated formation of 10 cm in the vulva. A histological preparation was performed with H&E stain (Figure 5) taken from the initial...
hospital’s paraffin block, and IHC and TCR gene rearrangements studies were conducted. An extensive lymphoid neoplasm was noticed, of angiocentric and angiodestructive pattern, constituted by intermediate, pleomorphic cells, with extensive areas of fibrinoid necrosis. The immunophenotypic profile was CD45+, CD3+, CD56+, CD30+, TIA1+, GRANZYME-B+, CD4-, CD8-, CD20-, LMP1-, ALK-, with proliferative index of around 80%, determined with Ki-67 (Figure 6). EBER was positive and the TCR study showed a monoclonal peak in the gamma region. The diagnostic conclusion was primary extranodal NK/T-cell lymhoma, nasal type (ENKTL-NT) of the vulvar region. The laboratory exams revealed Hb 95 g/L, DHL 2531 UI, GGT: 207 UI, TGO 49 UI, TGP 95UI. In addition, reactivity for IgG EBV and HTLV1 was found. The bone marrow biopsy did not show neoplastic infiltration.

Analysis of LT-003 Sample

Clinical history: 587664
Diagnosis: extranodal T/NK lymphoma
Sample: Vulva
(Chart 1 and Chart 3)

Later, the patient received three CT cycles with the SMILE regimen and did not continue with the treatment for extramedical reasons. After six months, she comes in with clinical progression of the disease, thus she received CT with the GELOX regime.

Discussion

Primary lymphomas affecting the female genital tract are not common, but they often imply a diagnosis challenge if not suspected. The reported cases are individual, and the series are limited. Most of them lack of an IHC detailed analysis and molecular tests (very often unavailable for the diagnosis). Over time, many names have been used for this neoplasm; such as “reticulum cell sarcoma” or “lymphosarcoma”, which may have corresponded to DLBCL, according to the current classification [2], due to this NHL subtype’s high frequency in all the extranodal localizations [12]. Furthermore, few previous studies have described the therapeutic management and clinical follow-up of patients affected by this disease.

On this report, we reviewed two cases of vulvar neoplasm that were referred to our institution with the carcinoma diagnosis. After the proper morphological, immunophenotypic study, EBER determination, and TCR gene rearrangement (the last two for the second case), a diagnostic of two different NHL types was performed for both cases. The first one corresponded to DLBCL and the second one to ENKTL.

It is very likely that the female genital region’s NHL was sub-diagnosed for both the gynecologists (due to low incidence and unusual presentation) and pathologists, since they could have been confused with different malignancies or inflammatory injuries [4-9]. Having the current progress in the NHL’s biological and molecular knowledge may make the diagnosis less difficult.

In the series reported by Vang and Kosari [9,10] and other reports, DLBCL is described as the most frequent type of lymphoma in the female genital tract, regardless of the disease’s primary or secondary nature. Furthermore, the most frequent localization has
been reported to be ovary and utero [4-10].

Hodgkin’s Lymphoma (HL) of the female genital tract is very rare and has been associated with the infection by human immunodeficiency virus, and EBV’s infection [13], which shall be taken into consideration when assessing a biopsy.

For the primary ENKTL-NT diagnosis, the neoplasm’s morphological characteristics were taken into account, prevailing the hyperchromatic nuclei medium, pleomorphic cells, with angiocentric and angiodestructive pattern, and the cytotoxic T/NK cells (CD3+, TIA1+) immunophenotypic profile, which was confirmed with the EBV presence, that is a requirement to diagnose of this type of neoplasm. Finding the monoclonal gene rearrangement for gamma TCR qualifies this case on the cytotoxic T phenotype subgroup [14-16]. Interestingly, this type of neoplasm – being of cytotoxic T phenotype – showed expression loss of CD8 and expression of CD56, which has been described as T cell plasticity, and it is not clear if this has clinical implications [17]. The differential pathological diagnosis must be performed with the cutaneous primary lymphoma of gamma delta T cells. This entity is associated with mucous membranes and skin, and the clinical presentation with ulcerated areas and necrosis is predominant [1,2]. Usually, the injuries are generalized and mostly affect the extremities. Their phenotype is CD3+, CD56+, CD8-/+ and have gamma-delta TCR. They are not associated with EBV [2].

There are few publications regarding primary ENKTL-NT of female genital tract, and the reported cases had a bad response to CT and radiotherapy (RT) [18-21].

Other differential diagnosis of female genital tract NHL related to skin or mucous membranes include inflammatory conditions (lichenoid dermatitis, pseudolymphoma), different carcinomas (neuroendocrine carcinoma, Merkel cell carcinoma, squamous cell carcinoma or cutaneous adnexal carcinoma), HL, round cell sarcomas (extra skeletal Ewing’s sarcoma/primitive neuroectodermal tumor, rhabdomyosarcoma) and amelanotic melanoma.

It should be taken into consideration for the differential histological diagnosis that inflammatory processes are normally superficial, with a band-like, non-invasive infiltrate, and are composed by a polymorphous population of lymphocytes, plasma cells and histiocytes without atypia [1,2].

The poorly differentiated squamous carcinomas may present a diverse pattern, including discohesive appearance that could mimic DLBCL, however, the focal intercellular bridges, keratinization and the association with an in-situ component are key to the epithelial neoplasms diagnosis. On the other hand, the sclerosis that compartmentalizes the neoplastic lymphoid cells in the NHL may cause a false organoid or cohesive pattern giving the impression of a carcinoma. The IHC reactions and – when necessary – the molecular tests are extremely helpful for the diagnosis.

Most of the patients diagnosed with GCB-DLBCL respond positively to R-CHOP, meanwhile the same treatment seems to be less effective in ABC-DLBCL [22-25].

One of the treatments with better responses to primary ENKTL-NT is the SMILE therapy (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide), which was the treatment received by the second case patient. In some situations, this treatment may be complemented or intersperse with RT [20,21].

In conclusion, this report’s purpose is to highlight two unusual and extremely rare NHL cases in the female genital tract. Since they are quite infrequent on this localization, it is often a diagnosis challenge if this possibility is not considered. Gynecologists, oncologists, and pathologists should consider this disease in neoplasms of female genital tract for a proper therapeutic management. These cases should always be assessed by a multi-disciplinary team with specific experience on NHL assessment and management.

References
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