Oral and Cutaneous Lymphomas other than Mycosis Fungoides and Sézary Syndrome in a Mexican Cohort: Recategorization and Evaluation of International Geographical Disparities

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Abstract

Background: Nonmycosis fungoides/Sézary syndrome (non-MF/SS) primary cutaneous lymphomas (PCL) are currently categorized under the 2005-World Health Organization/European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for PCL. These differ in behavior from secondary cutaneous lymphomas (SCL) and to lymphomas limited to the oral cavity (primary oral lymphomas [POL]) both categorized under the 2016-WHO classification for lymphoid neoplasms. Aims: This study aims to report the first series of non-MF/SS PCL, SCL, and POL in a Mexican cohort, examine the applicability of current classification systems and compare our findings with those from foreign cohorts. Materials and Methods: Eighteen non-MF/SS PCL, four SCL, and two POL with available tissue for morphology and immunophenotypic assessment were reclassified according to the 2005-WHO/EORTC and 2016-WHO classifications. Results: Non-MF/SS PCLs were primarily of T-cell origin (61%) where CD30+ lymphoproliferative disorders predominated, followed by Epstein-Barr virus-induced lymphomas, and peripheral T-cell lymphomas, not otherwise specified. Primary cutaneous B-cell lymphomas (BCL) were primarily of follicle center cell origin followed by postgerminal lymphomas of the diffuse large BCL variety. Conclusions: Most non-MF/SS PCL, SCL, and POL can be adequately categorized according to the 2005-WHO/EORTC and 2016-WHO classification systems, even when dealing with clinically atypical cases. The relative frequencies in our cohort hold closer similarities to Asian registries than from those of Europe/USA, supporting the concept of individual and/or racial susceptibility, and the notion of geographical variances in the rate of lymphomas. In particular, such disparity may arise from viral-induced lymphomas which might show partial geographical restriction.

Key Words: Primary cutaneous lymphomas, primary oral lymphomas, secondary cutaneous lymphomas

Introduction

Classification of lymphomas, particularly of primary cutaneous lymphomas (PCL), has dramatically evolved over the last decades due to advances in the characterization of their clinical, morphological, immunophenotypic, and molecular features.[1-4] PCL are lymphomas occurring solely in the skin after a complete staging evaluation has ruled out extracutaneous involvement, differing in biological behavior from systemic lymphomas with secondary cutaneous dissemination (secondary cutaneous lymphomas [SCL]).[4] The 2005-World Health Organization/European Organization for the Treatment and Research of Cancer (WHO/EORTC) classification for PCL includes 13 specific entities, subcategorized into those of indolent, intermediate, or aggressive clinical behavior.[4-5] These
comprise a heterogeneous group of clonal neoplasms with protean manifestations, arising from skin-homing T-/natural killer (NK)-, B- or precursor-lymphocytes which albeit their rarity, represent the second most common form of extranodal lymphomas (19%), following those of the gastrointestinal tract. Their reported incidence among European countries is 1:100,000 persons/year, whereas recent studies in the USA suggest an incidence as high as 10.7:100,000 persons/year, with increased prevalence among non-Hispanic whites.\(^\text{[7-10]}\)

In contrast to nodal lymphomas, where B-cell lymphomas (BCL) outnumber T-cell lymphomas (TCL), PCL are mainly derived from T-cells (65%–80%) with primary cutaneous-BCL (PC-BCL) in the minority (20%–29%). Among well-defined PC-TCL, mycosis fungoides/Sezary syndrome (MF/SS) and CD30+ lymphoproliferative disorders (lymphomatoid papulosis [LyP] and anaplastic large cell lymphoma [ALCL]) embody most cases; 55% of PC-BCL fall under the indolent category (follicle center BCL and marginal zone lymphoma), and approximately 40% represent intermediate lymphomas of the diffuse large BCL (DLBCL) variant.\(^\text{[7-10]}\) Oral cavity lymphomas are scarcer than PCL, with scant reports and lack of consensus regarding a specific classification for primary oral lymphomas (POL).\(^\text{[11-19]}\)

The incidence and clinical-histopathological features of non-MF/SS PCL and POL in Latin America, and particularly Mexico, is largely unknown. In this paper, we reviewed oral and cutaneous lymphomas (primary and secondary) other than MF/SS, which presented to our institution over a 24-year period and recategorized them according to the 2005-WHO/EORTC\(^\text{[4,5]}\) and 2016-WHO classifications.\(^\text{[20]}\) To the best of our knowledge, this paper represents the first Mexican series from a single referral center using such classification systems. Finally, we compare our findings to those deriving from foreign cohorts and analyze gross geographical differences.

**Materials and Methods**

Skin and oral biopsies diagnosed as oral or non-MF/SS cutaneous lymphoma over a 24-year period (1988–2012) were retrieved from the pathology archive of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, after approval by the Institutional Committee for Medical Ethics. Only cases with sufficient tissue available for adequate assessment of morphological and immunophenotypic features were included in the study. Clinical information was obtained through medical records and phone interviews when necessary for data confirmation. Formalin-fixed paraffin-embedded tissue (FFPET) sections were stained with hematoxylin and eosin. Immunophenotyping with a comprehensive panel of stains was performed under standard procedures on FFPET, using commercially purchased primary antibodies according to the diagnostic possibilities for each case, concurring with the 2005-WHO/EORTC and the 2016-WHO classification criteria.\(^\text{[4,5,20]}\) In situ hybridization (ISH) for Epstein–Barr virus (EBV) encoding region (EBER) and kappa/lambda immunoglobulin light chains were performed when deemed necessary in a case-by-case basis. Skin lymphomas were typified as PCL if no lymph node or visceral involvement was present at diagnosis, after performing a complete staging evaluation (physical examination, head to pelvis computed tomography, and bone marrow biopsy). The same staging criteria were used to designate POL.

**Results**

Seventy-eight non-MF/SS oral and cutaneous lymphomas were identified. Twenty-four (30%) fulfilled inclusion criteria for proper recategorization; of these, 18 (75%) were skin-limited (PCL), 4 (16%) represented SCL [Tables 1 and 2], and 2 (8%) POL [Table 3].

**Non-mycosis fungoides/Sézary syndrome**

Non-MF/SS PC-TCL outnumbered PC-BCL (11 cases, 61% vs. 7, 39%). Non-MF/SS PC-TCL were categorized as follows: three CD30+ lymphoproliferative disorders (two LyP and one PC-ALCL), one subcutaneous panniculitis-like TCL (SPLTCL), two PC-NK/TCL, one hydroa vacciniforme-like lymphoproliferative disorder (HVLLPD), one aggressive epidermotropic CD8+ TCL (PC-AECD8+ TCL), one gamma/delta TCL (PC-GD-TCL), and two peripheral TCL, not otherwise specified (PC-PTCL-NOS). PC-BCL were primarily of follicle center cell origin: four cases (57%) of follicle center lymphoma (PC-FCL), three cases (43%) of PC-DLBCL further subdivided into two of leg type variety and one EBV+ DLBCL NOS.

**Clinical features**

Non-MF/SS PC-PCL occurred in 12 males and 6 females. Age range at diagnosis was 19–67 years (mean 44 years), similar in all subgroups of non-MF/SS PCL. These arose primarily in a single anatomic region (13/18, 72%) such as trunk (4/13), extremities (4/13), head (3/13), or genital skin (2/13). Two regions were involved in 4/18 cases (22%): trunk and extremities (2), trunk and head (1), and head and extremities (1). Only one case, corresponding to HVLLPD, presented with skin lesions extending to all body segments (except palms and soles), accentuated on sun-exposed areas. Most non-MF/SS PCL had more than one clinical morphology (12/18, 66%) as red or red-violaceous nodules (11) and/or infiltrated plaques (8), commonly developing secondary ulceration (6). Less frequent morphologies were recurring “waxing and waning” papules (in two patients with LyP), facial edema, hemorrhagic vesicles, small crustated
Hernández-Salazar, et al.: Oral and cutaneous lymphomas in a Mexican cohort

Table 1: Clinical and immunohistochemical features of non-mycosis fungoides/Sézary syndrome primary cutaneous lymphomas

| Diagnosis          | Sex, age (years) | Topography                      | Morphology                                                                 | Immunophenotype (positive/negative)       |
|--------------------|------------------|---------------------------------|----------------------------------------------------------------------------|-------------------------------------------|
| LyP (Type A)       | Female, 20       | Upper extremities               | Waxing and waning papules, small nodules and scars                         | CD30+, CD4+, CD25+, CD8−                   |
| LyP (Type D)       | Male, 31         | Chest                           | Waxing and waning small nodules*                                           | CD30+, CD3+, CD8+, CD25+, CD7−            |
| ALC (ELD)          | Male, 61         | Lower extremity                 | Nodules, some ulcerated                                                   | CD30+, CD3−, CD4+, CD8−, CD20−, ALK−      |
| LPLP               | Male, 44         | Face and trunk                  | Subcutaneous nodules                                                       | CD3+, CD8+, TIA-1+, ßF1+, CD5+, CD2+, CD43+, CD4− |
| NK/TCL             | Male, 43         | Nose and nasogenial folds       | Firm, ulcerated, erythematous plaque                                       | CD3+, CD56+, CD8+, TIA-1+, perforin+, EBER+, CD4−, CD8−, LMP-1−, granzyme B−, CD20− |
| NK/TCL             | Female, 51       | Vulvar, perianal and auricular   | Firm, ulcerated plaques                                                    | CD3+, CD56+, TIA-1+, perforin+, EBER+, CD4−, CD8−, LMP-1−, granzyme B−, CD20− |
| HVLLPD             | Male, 19         | Generalized (except acral skin from extremities) | Facial edema, hemorrhagic vesicles, small crusted ulcers, varioliform scars | CD56+, CD8+, EBER+                         |
| AEC8+TCL           | Male, 44         | Head and extremities            | Flaccid bullae and large crusted ulcers                                   | CD45RA+, CD3+, CD8+, TIA-1+, granzyme B+, perforin+, ßF1+, CD7−, CD45RO−, CD2−, CD5−, CD7− |
| GDTCL              | Male, 24         | Penis and scrotum               | Firm, ulcerated plaques                                                    | GM1+, CD4−, CD8+, EBER−                   |
| PTCL-NOS           | Female, 26       | Upper extremities               | Dark-red infiltrated plaques                                               | CD3+, CD4+, CD8+, CD5+, CD7+, CD20−, CD19−, CD22− |
| PTCL-NOS           | Male, 55         | Trunk and extremities           | Erythematous infiltrated plaques and papules                              | CD3+, CD4+, CD8+, CD3+, CD5+, CD7+, CD20−, CD19−, CD22− |
| MALT               | Female, 65       | Soft palate                     | Nodular, ulcerated tumor                                                   | CD19+, CD20+, CD22+, CD79a+, BCL2+, MUM-1+, CD10−, CD5−, CD138− |
| PTCL-NOS           | Male, 67         | Oral mucosa and upper lip       | Firm, subcutaneous nodules                                                 | CD19+, CD20+, CD22+, CD79a+, BCL2+, MUM-1+, CD10−, CD5−, CD138− |
| EBV+DLBCL-NOS      | Female, 66       | Trunk and lower extremities     | Ulcers                                                                     | CD20+, MUM-1+, EBER+, BCL6−, CD10−        |

LyP: Lymphomatoid papulosis, PC: Primary cutaneous, ALC: Anaplastic large cell lymphoma, ELD: Extensive limb disease, SPTCL: Subcutaneous panniculitis-like T-cell lymphoma, NK/TCL: Natural killer/T-cell lymphoma, HVLLPD: Hydroa vacciniforme-like lymphoproliferative disorder, AEC8+TCL: Aggressive epidermotropic CD8+T-cell lymphoma, GDTCL: Gamma-delta T-cell lymphoma, PTCL: Peripheral T-cell lymphoma, NOS: Not otherwise specified, FCBCL: Follicle center B-cell lymphoma, DLBCL: Diffuse large B-cell lymphoma, LT: Leg type, EBV+: Epstein-Barr virus positive, EBER: In situ hybridization for Epstein-Barr virus encoding region, PCBCL: Primary cutaneous B-cell lymphoma, PCTCL: Primary cutaneous T-cell lymphoma, Non-MF/SS: Nonmycosis fungoides/Sézary syndrome

Table 2: Clinical and immunohistochemical features of lymphomas from the oral cavity

| Diagnosis          | Sex, age (years) | Topography                      | Morphology                                                                 | Immunophenotype (positive/negative)       |
|--------------------|------------------|---------------------------------|----------------------------------------------------------------------------|-------------------------------------------|
| MALT               | Female, 65       | Soft palate                     | Nodular, ulcerated tumor                                                   | CD19+, CD20+, CD79a+, CD138+, BCL2+, BCL6−, CD10− |
| PTCL-NOS           | Male, 67         | Oral mucosa and upper lip       | Erythematous infiltrated plaques and nodules                              | CD3+, CD4+, CD8+, CD5+, CD7+, CD20−, CD19−, CD22−, CD30− |

MALT: Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, PTCL: Peripheral T-cell lymphoma, NOS: Not otherwise specified
Histopathologic and immunohistochemical features
Primary cutaneous CD30+ lymphoproliferative disorders
Both LyP cases showed a perivascular wedge-shaped dermal infiltrate with scant to moderate epitheliotropism (epidermotropism and folliculotropism). Clusters of large atypical lymphocytes were evident amidst a background of inflammatory cells (small lymphocytes, eosinophils, and few neutrophils). Large lymphocytes comprised <30% of the infiltrate and displayed CD30 expression, both co-expressed CD3 and CD25, one was CD4+ and the other CD8+ [Figure 1]. On morphological and immunophenotypical correlation, the former case would best fit with LyP Type A, the latter with LyP Type D.

The infiltrate of PC-ALCL consisted of diffuse sheets of large pleomorphic cells extending through the dermis and into the subcutis without a significant inflammatory infiltrate. Large CD30+ cells comprised over 75% of the infiltrate, and displayed an activated Th2 CD4+ immunophenotype, without anaplastic lymphoma kinase-1 or EMA (Epithelial Membrane Antigen) expression [Figure 2].

Subcutaneous panniculitis-like T-cell lymphoma
SPLTCL was characterized by a lobular panniculitic-like infiltrate of variably sized mononuclear cells, with pronounced atypia particularly among lymphocytes surrounding individual fat cells (adipocyte rimming). Neoplastic cells displayed a cytotoxic T-cell immunophenotype with expression of CD8, TIA-1, and a high Ki-67 proliferation index, especially around individual fat cells. Furthermore, an \( \alpha/\beta^+ \) phenotype was confirmed by \( \beta F1 \) immunoreactivity. Features common to lupus panniculitis (lymphoid follicles, dermal-epidermal interface alteration, or hyalinization of fat cells) were absent [Figure 3].

Primary cutaneous aggressive cytotoxic lymphomas
PC-GD-TCL showed diffuse infiltrates occupying not only the subcutaneous tissue (as in SPLTCL) but involving dermis and epidermis (with marked epidermotropism). Dermal necrosis and angioinvasion were conspicuous. Mononuclear cells were medium-large, showed extensive karyorrhexis, and profound adipocyte rimming without hemophagocytosis. Neoplastic cells were EBER and CD4- but expressed CD8, CD3, CD56, and TIA-1. A \( \gamma/\delta^+ \) phenotype was confirmed by GM1 immunoreactivity and negativity for \( \beta F1 \).

Infiltrates in both PC-NK/TCL revealed a diffuse pandermal proliferation of lymphocytes with partial subcutaneous involvement, prominent angiocentricity, focal angiodestruction, and scant epidermotropism. Neoplastic cells were variable in size, pleomorphic, and expressed of CD3ε, CD2, CD56, cytotoxic proteins (TIA-1, granzyme B, and perforin), and EBV clonal integration (EBER+) [Figure 4].

PC-AEC8+ TCL was characterized by a superficial and deep dermal, angiocentric, and angiodestructive lymphoid proliferation with marked epidermotropism and focal adnexal destruction. Neoplastic cells were pleomorphic and displayed a CD8+ cytotoxic phenotype

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**Table 3: Clinical and immunohistochemical features of secondary cutaneous lymphomas**

| Diagnosis          | Sex, age (years) | Topography               | Morphology                     | Immunophenotype (positive)                |
|--------------------|------------------|--------------------------|-------------------------------|------------------------------------------|
| EN-NK/TCL, nt      | Male, 75         | Facial skin, hard palate, orbit | Erythematous infiltrated plaques and ulcers | CD3ε+, CD2+, CD56+, perforin+, granzyme B+, TIA1+, EBER+ |
| PTCL-NOS           | Male, 78         | Trunk and upper extremities | Red to violaceous macules     | CD3+, CD4+, CD8+, CD7–, CD30–          |
| HL                 | Female, 43       | Upper and lower extremities | Small firm papules            | CD30+, CD15+                           |
| FL                 | Female, 51       | Head and trunk            | Infiltrated plaques with alopecia | CD20+, CD10+, BCL6+, BCL2+             |

EN-NK/TCL: Extranodal natural killer/T-cell lymphoma, nt: Nasal type, PTCL: Peripheral T-cell lymphoma, NOS: Not otherwise specified, HL: Hodgkin’s lymphoma, FL: Follicular lymphoma
immunopositive for CD3, CD45RA, granzyme B, perforin, TIA-1, and βF1 [Figure 5].

Hydroa vacciniforme-like lymphoproliferative disorder HVLLPD showed an infiltrate histopathologically indistinguishable from PC-NK/TCL albeit less dense, in the previously described peculiar clinical scenario. As in PC-NK/TCL, the proliferation occupied the entire dermis with prominent angiocentricity, focal angiodestruction, and scant epidermotropism. Neoplastic cells were medium-large, pleomorphic, and showed immunoreactivity to CD3, CD2, CD8, CD56, cytotoxic proteins (TIA-1, granzyme B, perforin), and EBER+ [Figure 6].

Primary cutaneous peripheral T-cell lymphomas, unspecified

Biopsies from PC-PTCL-NOS showed nonepidermotropic diffuse dermal proliferations of medium-large mononuclear T-cells. However, clinical-pathological and immunohistochemical correlations excluded them of any specific lymphoma category. Neoplastic cells displayed a double positive (CD4+/CD8+) T-cell phenotype without loss of PAN-T-cell antigen expression.

Primary cutaneous B-cell lymphomas

Infiltrates in PC-FCL cases displayed either a nodular or diffuse pattern of dermal involvement and were characterized by a mixed neoplastic population comprised chiefly of centrocytes (medium-sized lymphocytes with indented nuclei) with some admixed centroblasts (medium to large lymphocytes with peripheral nucleoli). No significant aggregates of plasma cells were observed. Independent of their morphology, neoplastic cells were positive for CD20, germinal center cell immunoreactants (BCL6 +/- CD10), and lacked expression of BCL2 and MUM-1 [Figure 7].
DLBCL leg type (DLBCL-LT) were characterized by diffuse pandermal neoplastic infiltrates with subcutaneous extension, forming sheet-like aggregates of immunoblasts (large lymphocytes with a single central nucleolus) admixed with fewer centroblasts. Neoplastic cells showed a postgerminal B-cell phenotype expressing CD20, CD79a, MUM-1, and BCL2 while lacking immunoreactivity for germinal center cell markers [Figure 8].

Our DLBCL-NOS was morphologically indistinguishable from the former (DLBCL-LT), displayed a postgerminal B-cell immunophenotype with diffuse expression of CD20 and MUM-1, without BCL2, BCL6, and CD10 expression. In addition, EBER positivity, along with the disease developing in an elderly patient suggested this case would best fit with EBV + DLBCL NOS.

**Systemic lymphomas with secondary cutaneous dissemination**

Four cases of SCL included one case each of extranodal NK/TCL nasal type (EN-NK/TCL,nt), nodal PTCL-NOS, Hodgkin’s lymphoma (HL), and follicular lymphoma (FL).

**Clinical features**

SCL occurred in two men and two women. Mean age range at diagnosis was 61.7 years. On presentation, EN-NK/TCL,nt extensively involved facial skin, nasal mucosa, and hard palate as erythematous-indurated plaques with secondary ulceration; the remaining 3 SCL were nodal lymphomas with concomitant skin involvement manifested as disseminated firm papules (HL), infiltrated plaques with alopecia (FL), and red to purple macules (PTCL-NOS). As opposed to PCL, all patients manifested B-signs including fever, weight loss, and/or palpable lymphadenopathy.

**Histopathologic and immunohistochemical features**

The histology and immunophenotype from cutaneous infiltrates of SCL were similar to their primary counterparts. Our single case of EN-NK/TCL,nt was indistinguishable from our PC-NK/TCL as was FL with the previously portrayed cases of PC-FCL except for BCL2 co-expression by neoplastic cells in FL. HL was characterized by a mixed tumoral/reactive dermal infiltrate where neoplastic cells comprised <10% of the infiltrate. These were large, atypical, with abundant amphophilic cytoplasm, bilobed nuclei, multiple nucleoli (Reed–Sternberg cells), and CD30/CD15+. PTCL-NOS was characterized by a nodular dermal infiltrate of medium-large pleomorphic lymphocytes with conspicuous expression of CD4, sporadic CD8 immunoreactivity, and negativity for CD7, CD30, CD15, CD56, and follicular helper T-cell markers (CD10, CXCL13).

**Primary oral lymphomas**

Two cases of POL were observed (65-year-old woman, 67-year-old man), and subclassified, respectively, as one extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and one PTCL-NOS. Clinically, the former appeared as a nodular, ulcerated tumor in the soft palate, whereas the latter as a multinodular erythematous plaque involving the oral mucosa and upper lip.

MALT lymphoma was characterized by a submucosal nodular lymphoid proliferation with perivascular accentuation, composed of small-sized cells with indented nuclei and prominent cytoplasm (centrocyte-like marginal feature).
As in other international

While

This apparent

This comparatively higher frequency

Primary oral PTCL-NOS showed a nodular submucosal infiltrate of small-medium pleomorphic T-cells with a double positive (CD4+/CD8+) immunophenotype, without CD30 expression, EBER positivity or loss of PAN-T-cell antigens.

Discussion

Current epidemiological data on PCL derive mainly from experience of European and Anglo-Saxon North American countries, being scant elsewhere, particularly in Latin America. Nonetheless, geographical disparities in the incidence of lymphoma subtypes have been documented which may shed light on the pathogenesis of some lymphoma variants and potentially relate to the unequal prevalence of viral carcinogens, other currently unidentified environmental factors, and ethnic and/or genetic susceptibility factors.[31-37]

Differences in the incidence, clinical, and histopathological features of MF among Latino patients living in the USA, as compared to Caucasians, have been described in large retrospective studies (lower incidence rates, higher prevalence of early-onset disease with associated worse prognosis, and higher rates of the hypopigmented variant).[28-30] however, little is known regarding non-MF/SS PCL among native Latin Americans. To date, only a handful of studies on the descriptive epidemiology of PCL have been conducted in Latin America (mainly Brazil, Peru, and Argentina),[31-40] and not, to the best of our knowledge, in Central and Northern Latin America where ethnicity and incidence of EBV and human T-cell leukemia virus I/II (HTLV-I/II) seropositivity substantially differ.

In our cohort, the mean age at diagnosis was lower than reported elsewhere, similarly to what is described for Latino patients with MF living in the USA.[40] While only one-third of the non-MF/SS PCL in our laboratory could be properly reclassified due to limited tissue availability, the frequency of lymphoma variants seems to differ in some aspects from both European/USA and South American registries.[28-42] As in other international cohorts, non-MF/SS PC-TCL outnumbered PC-BCL. The former was led by CD30+ lymphoproliferative disorders, in accordance with other international reports,[28-41] followed closely by EBV-related NK/T-cell malignancies (PC-NK/TCL and HVLLPD), commonly reported in Asia and Central America but exceptionally in Europe and the USA.[31,41-43,48] This comparatively higher frequency could potentially be explained by previously described higher prevalence of EBV subtypes associated to human pathology in developing countries and plausibly to the onset of infection at an earlier age. The same argument could hold true, to the existence of one case of EBV+ DLBCL NOS among our small cohort of 7 PC-BCL, reportedly one of the rarest entities among all PCL. By contrast, no cases of adult T-cell leukemia/lymphoma (ATCLL) were observed in keeping with a practically null incidence of HTLV-I/II in studies across Mexico, including Mexico City Greater-Metropolitan Area.[50-53] This contrasts with the higher frequency of HTLV-I/II seropositivity and the prevalence of ATCLL reported among Asians and South Americans (namely Brazil). [54-58]

PC-FCL was the most frequently identified PC-BCL in our cohort, in accordance with international registries. Surprisingly, no cases of PC-MZL were observed despite being reported as the second most common form of PC-BCL in European, USA, and South American studies, and speculated to be closely linked in its pathogenesis to microbial and/or autoimmune antigenic triggers, with potential geographical restrictions.[8,28-46] This apparent null incidence in our cohort could be artificial; however, since PC-MZL was recently described, and formerly reported in our institution as B-cell predominant cutaneous pseudolymphoma (cutaneous lymphoid hyperplasia) before ISH for immunoglobulin light chains became available. Similarly, our cohort lacks cases of PC CD4+ small/medium T-cell lymphoproliferative disorder which until recently would have likely been diagnosed in our institution as pseudolymphomatous folliculitis.
but is thought to represent one of the most common non-MF/SS PCL in some recent series.\textsuperscript{[47-59]}

All PCL in our cohort displayed classical histopathological and immunophenotypical features in accordance with the WHO/EORTC criteria and all but three showed the typical clinical features and behavior.\textsuperscript{[6,3]} One was a case\textsuperscript{[60]} of PC-NK/TCL with prolonged survival (>60 months), manifesting initially as vulvar and perianal ulcers, and recurring postradiotherapy and chemotherapy as necrotic ulcers involving one earlobe. While EBV+ mucocutaneous ulcer was considered as an alternative diagnosis, the young age of the patient, absence of immunosuppression, presence of extragenital ulcers, and finally, conspicuous evidence of angiodestruction and pleomorphism strongly favored the diagnosis of PC-NK/TCL. Similarly, a case of PC-GD-TCL presented with topographic restriction to genital skin before progressing into disseminated disease. Finally, a case of PC-AEC-D+ TCL was atypical in its clinical similarity with pemphigus vulgaris given the presence of flaccid bullae although the neoplasm behaved in the classical aggressive fashion with the patient perishing few weeks after diagnosis.

In contrast to PCL, the clinical and histopathological features of SCL remain poorly understood with very few studies from Northeast Asia and the USA.\textsuperscript{[10,61]} In the largest retrospective review from Korea, SCL consisted of mature NK/TCL (56%), mature BCL (35%), immature hematopoietic malignancies (8%), and HL (1%).\textsuperscript{[61]} In our very small cohort, half of SCL were mature NK/TCL (1 EN-NK/TCL, 1 PTCL-NOS), with one case each of mature BCL (DLBCL) and HL. While the small number of SCL in our study impede meaningful comparisons with previous series, it suggests a closer distribution trend with Asian registries as opposed to European and USA, supporting the concept of individual and/or racial susceptibility. Further, multicentric nationwide prospective epidemiological studies to foster support to our findings are warranted.

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As for SCL, extranodal lymphomas of the oral cavity have been scanty reported due to their rarity. In the few retrospective studies available, the leading histopathological subtypes are MALT lymphoma, followed by DLBCL in one cohort, and plasmablastic lymphoma, DLBCL, and PTCL-NOS in decreasing order in another.\textsuperscript{[15,16]} In our series, one case corresponded to MALT lymphoma and the other to PTCL-NOS, the rarest POL variant reported. No cases of plasmablastic lymphoma were observed though albeit our institution being a major referral center for HIV patients. This could relate to a selection bias in the HIV+ population at our hospital however since most have undetectable viral loads due to successful antiretroviral treatment.

Conclusions
In summary, albeit limitations in our study include the inherent biases of institutional series as opposed to population-based studies, and the inability to recategorize the totality of our cohort, our results support the utility of the 2005-WHO/EORTC and 2016-WHO classification systems, even when dealing with clinically atypical cases, and the notion of geographical variances in the rate of lymphomas. In particular, we report that some of the disparity may arise from viral-induced lymphomas which might show partial geographical restriction. The differential rates of oral and cutaneous lymphomas in our population may hold closer similarities to registries from Asian populations than to those from Europe and USA, supporting the concept of individual and/or racial susceptibility. Further, multicentric nationwide prospective epidemiological studies to foster support to our findings are warranted.

What is new?
• The relative frequencies of cutaneous and oral lymphomas in the first Mexican cohort hold closer similarities to Asian registries than from those of Europe and USA
• International geographical disparities in the rate of cutaneous lymphomas may arise from viral-induced lymphomas which might show partial geographical restriction.

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Conflicts of interest
There are no conflicts of interest.

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