Research Article

Primary cutaneous B-cell lymphomas: our experience with 22 cases

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Rubén Azcune[1], Ana M. Barbarulo[2], Silvina Gavazza[2], María Inés Fontana[2], María Gabriela Spelta[2], Mariana Barrera[3], Julieta Moya[4], María Laura Lado Jurjo[3], Silvia Vanzulli[5], Eduardo Zeitlin[5]

Abstract

Background. Primary cutaneous B cell-lymphomas (PCBCL) are a group of lymphomas with clinical, prognostic, and therapeutic characteristics differing from nodal lymphomas. These facts determined that, in the last five years, they were grouped as an independent entity.
Objective. To present the experience of our Dermatology Department as far as diagnosis, management and follow-up of primary cutaneous B-cell lymphomas are concerned, during the last eleven years
Design. Descriptive and retrospective study.
Materials and methods. 22 patients with diagnosis of primary cutaneous B-cell lymphomas were studied between 1995 and 2006, at the Dermatology Department, Policlínico Bancario.
Results. Our experience comprised 22 patients, of which 13 were follicle center B-cell lymphomas (59 percent), 4 were marginal zone B-cell lymphomas (18.18 percent), 2 were diffuse large B-cell lymphomas (leg-type), 2 were diffuse large B-cell lymphomas (other), and only 1 case was a mantle cell lymphoma.
Conclusion. The last PCBCL classification takes into account the clinical, therapeutic, histopathologic, and genetic aspects. This classification optimizes dermatologist management of this pathology and enhances their relevance within the interdisciplinary group in charge of the follow-up. However, a permanent updating must be considered that might include new changes in a not distant future (Dermatol Argent 2008;14(1):35-45).

Key words: *primary cutaneous B-cell lymphoma, PCBCL.*

Introduction

Primary cutaneous B-cell lymphomas (PCBCL) are clonal B-cell proliferations perfectly separated from nodal lymphomas and their secondary cutaneous involvement. They comprise a group with clear clinical, therapeutic, and prognosis differences. In addition, because they show different chromosome translocations, variable oncogenes expression, and specific viral sequences, primary cutaneous lymphomas comprise a clinically and biologically independent entity.
These concepts were clarified only recently, since in the last 50 years multiple classifications were proposed, not distinguishing them from nodal lymphomas.
In order to speak about a true primary cutaneous lymphoma, we must ascertain the absence of extracutaneous involvement at the time of diagnosis.
There are clinical, histopathological, and immunohistochemical guidelines and supplementary studies to establish diagnosis and staging of B-cell lymphoma.[1-5]

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1. Head of Department.
2. Staff Physician.
3. Attending Physician.
4. Resident.
5. Staff Physician, Patology Department.

Dermatology Department, Policlínico Bancario. Av. Gaona 2197, Autonomous City of Buenos Aires, Argentine Republic.

Correspondence
Rubén Azcune: Policlínico Bancario, Gaona 2197 2º P,
East Wing – Autonomous City of Buenos Aires.
Particular: José Luis Cantilo 1720,
Santos Lugares – Province of Buenos Aires – Argentine Republic.
Tel: 47572391. E-mail: razcune@intramed.net.ar

The EORTC (European Organization for Research and Treatment of Cancer) classification promotes an organ-specific classification, *i.e.* specific for cutaneous lymphomas, and incorporates the terms indolent and aggressive in its lymphoma division, thus including a prognostic feature.[6] In spite of having been diversely criticized, this classification was adopted by dermatologists worldwide and was the foundation for the unified classification known as WHO-EORTC (**Table 1**).[7-11]

Materials and method

An observational, descriptive, and retrospective study was conducted, including 22 patients with diagnosis of primary cutaneous B-cell lymphoma, during the 1995-2006 period, at the Dermatology Department of Policlínico Bancario.
Frequency was assessed according to patient age and gender, types of lymphoma, presentation, location, and treatment, as well as 5-year survival.
Diagnosis was reached according to clinical examination, histopathology, immunohistochemistry, and the study of light chains, in all cases.[12,13]
Supplementary studies were performed every 6 months, to rule out systemic involvement, with 5-year follow-up of patients.

Results

The 22 cases of primary cutaneous B-cell lymphomas compared to 38 cases of primary T-cell lymphomas seen during the same period of time, amount to 36 percent of the total of observed lymphomas, a percentage somewhat higher than the internationally stated (30 percent), possibly due to the elderly population attended at our institution.
From the total 22 cases of our experience, 13 referred to follicle center lymphomas (59 percent), 11 in male and 2 in female patients; 4 were marginal zone lymphomas (18.18 percent), with 3:1 females dominance; 2 cases were large cell lymphoma of the leg (9.09 percent), 1 male and 1 female; 2 male cases were other large cell lymphoma (9.09 percent); and only 1 male had primary cutaneous mantle cell lymphoma (4.54 p) (**Table 2** and **Graphic 1**).
Age distribution for the total sample and for each variant was as follows (in years):

- Total patients: mean 59.50 (range: 39-91).
- Follicle center lymphomas: 61.6 (48-91).
- Marginal lymphomas: 52 (39-62).
- Large leg-type lymphomas: 73.5 (71-76).
- Other large cell lymphomas: 50 (41-59).
- The mantle lymphoma patient was 55 years old.

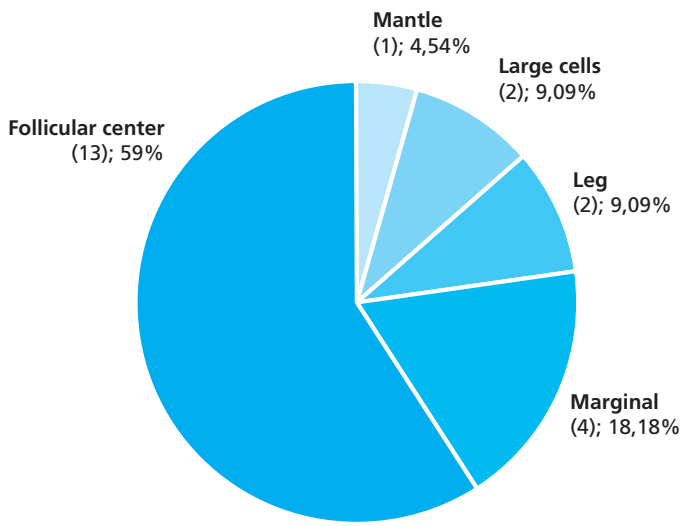
TABLE 1. CLASSIFICATION OF CUTANEOUS B-CELL LYMPHOMAS (WHO-EORTC).

• Primary cutaneous marginal zone B-cell lymphoma.
• Primary cutaneous follicular center B-cell lymphoma.
• Primary cutaneous diffuse large B-cell lymphoma, leg-type.
• Other primary cutaneous diffuse large B-cell lymphomas (includes intravascular large B-cell lymphoma).

TABLE 2. CASE HISTORY.

Case	Type	Gender	Age	Clinic	Location	Treat.	SV
1	FC	M	48	T	Scalp	RT	Yes
2	FC	M	60	T	Right temporal	RT	Yes
3	FC	M	66	T	Left temporal	RT	Yes
4	FC	M	48	T	Scalp	RT	Yes
5	FC	M	63	T	Face	RT	Yes
6	FC	F	69	T	Face	RT+CT	No
7	FC	M	65	T(4)	Face, neck, back, breast	RT	Yes
8	FC	M	61	T	Back	RT	Yes
9	FC	M	71	T(2)	Back (recurrent)	RT	Yes
10	FC	M	55	Multiple	Back (Crosti-type)	RT+CT	Yes
11	FC	M	52	Multiple	Flank (Crosti-type)	RT	Yes
12	FC	M	53	Multiple	Abdomen	RT	Yes
13	FC	F	91	T(2)	Back	S	No
14	Marg.	M	48	T, nodule	Thighs	S	Yes
15	Marg.	F	39	Plaque	Forearm	RT	Yes
16	Marg.	F	62	T	Face	S	Yes
17	Marg.	F	59	T	Scalp	RT	Yes
18	LCL	F	76	Plaque	Leg	RT+CT	No
19	LCL	M	71	T	Foot	RT	Yes
20	IVLC	M	59	Plaque	Pectoral	RT+CT	No
21	PlasLC	M	41	T(3)	Arm, thorax, neck	CT	No
22	Mantle	M	55	T(3), panniculitis	Thigh	RT	Yes

FC: follicular center. Marg: marginal. P: plasmocytoma. LCL: large cells leg type. IVLC: intravascular large cells. PlasLC: plasmoblastic large cells. T: tumor. SV: 5-year survival. RT: radiotherapy. CT: chemotherapy. S: surgery.



Graphic 1. *Lymphoma distribution [(amount of patients); percentage].*

Five-year survival percentage was assessed throughout the sample, because that follow-up period was left to include the experience cases:

- For the total sample of 22 patients, it amounted to 77 percent (5 died, but the 91-year-old patient died for causes not related to the disease).
- For each lymphoma group: follicle center, 85 percent; marginal, 100 percent; leg type, 50 percent; other large cell, 0 percent; mantle, 100 percent.

Discussion

The results were analyzed according to the WHO-EORTC classification, and our clinical, histopathological and immunohistochemical findings were compared to the reviewed literature on the subject matter. A notable coincidence was found, thus we unified concepts in the development of each variant.

Primary cutaneous follicular center B-cell lymphoma

These are follicular center cell neoplasms with variable amount of centrocytes (small and large cleaved follicular center cells) and centroblasts (non-cleaved large follicular center cells with prominent nucleus) of follicular, follicular and diffuse, or diffuse growth.[14]

Clinically, they appear as red papules, plaques, or nodules, isolated or aggregated, slow growing, usually in the head, neck, and trunk[15] (**Figure 1**). Of all patients with follicular center lymphomas (13), the most frequent clinical presentation was a tumor, with the following distribution: six in the head, six in the trunk, and one with multiple locations in face, neck, back, and breast. Two patients (cases 10 and 11) had the "Crosti's reticulo-histiocytoma of the back," with papule lesions and plaques distributed over an erythematous base, preceding the tumor in month or years[16-19] (**Figure 2**). Histologically, these lymphomas show a nodular or diffuse pattern preserving epidermis. In the early stage centrocytes, centroblasts, reactive cells and remaining reactive follicular centers are identified, without mantle cells;[20,21] and in the tumor stage, there is an increase in the number and size of neoplastic cells.[15,16,22-24] Fast growing lymphomas contain large follicular center cells, centroblasts, large centrocytes, multilobular cells, and immunoblasts. In all cases, there was marked fibroblast reaction.

Immunohistochemistry shows positive results for CD19, CD20, CD22, CD79a, CD10, Bcl-6, and negative for CD5.[18,19,25-29] Surface immunoglobulin (sIg) monoclonality was confirmed.[30]

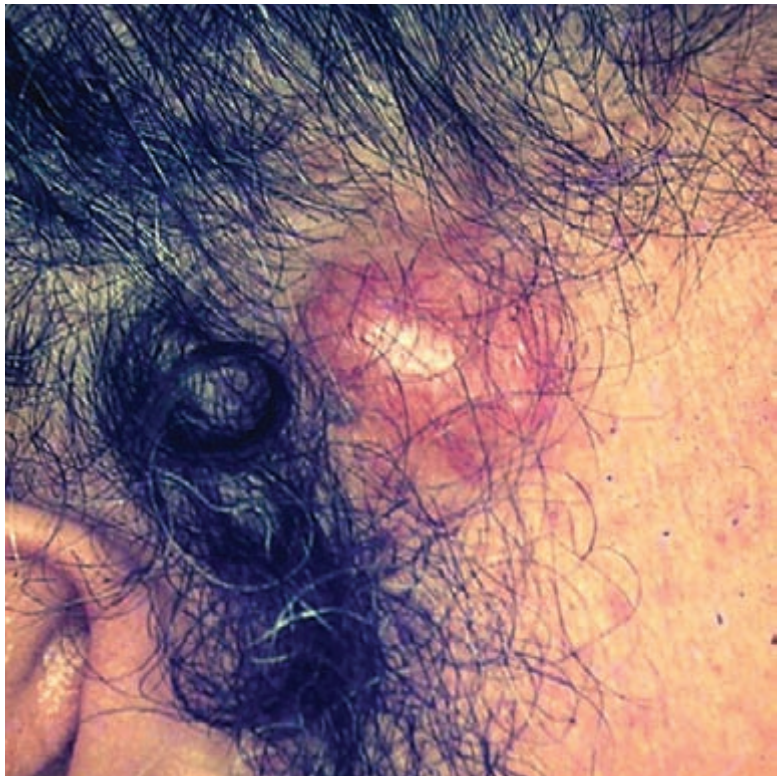


Figure 1. *Follicular center B-cell lymphoma. Classic clinic aspect (Case 2).*

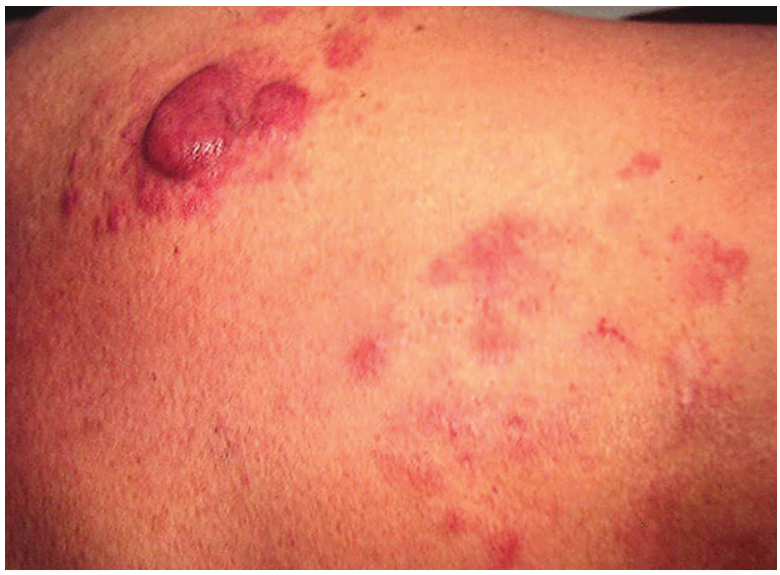


Figure 2. *Crosti's reticulo-histiocytoma of the back (Case 10).*

These lymphomas show Ig clone rearrangement, but no t(14;18) translocation. No expression of Bcl-2 protein is identified.

Additionally, somatic hypermutation of the heavy and light chain variable gene is described, thus indicating their follicular center origin.[31,32]

Independently on the nodular or diffuse growth pattern, and isolated or multiple appearance, 5-year survival is 95 percent.[21,22,33]

Our patients showed similar survival to the mentioned statistical data: one of the two deceased patients died because of the lymphoma (case 6) and the other (case 13) due to natural causes.

A recent study suggests that the patients with marked expression of

Bcl-2 with diffuse large cell infiltrate may have a poorer prognosis.[34]

We applied radiotherapy in the case of localized or few lesions, as suggested by the reviewed publications.[22,23,35-38] In the presence of tumor recurrence, the recommended treatment is also radiotherapy. Anthracycline is used as treatment of extended lesions or extracutaneous progression.[20,22]

We used radiotherapy in 12 out of 13 cases. In case 6, we supplemented treatment with chemotherapy. Case 10 showed post-radiotherapy tumor recurrence, and required surgical excision of the lesion. Only case 13 received surgical treatment exclusively, because the patient was incapable of being moved.

Rituximab was used systemically and intralesionally in small series of patients, with good results, but its long-term effect has not been assessed yet.[39,40]

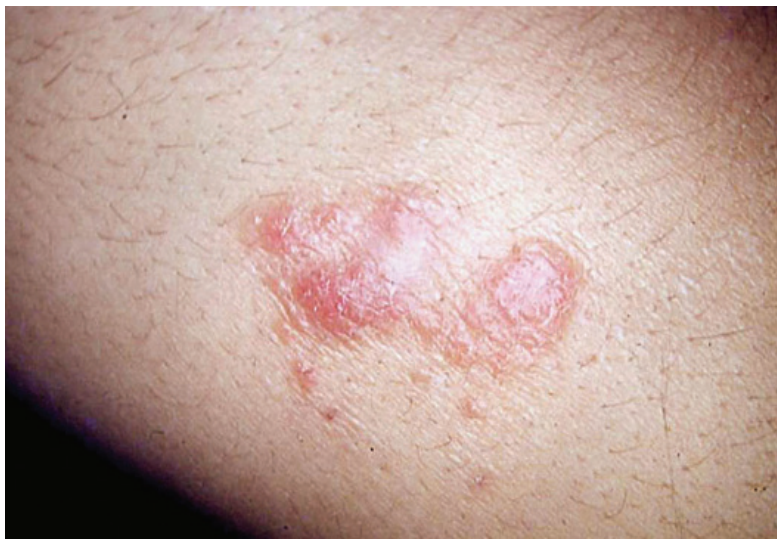


Figure 3. *Marginal zone B-cell lymphoma B, with positive Borrelia burgdorferi serology (Case 15).*

Primary cutaneous marginal zone B-cell lymphoma

This group includes different types of lymphoma receiving diverse denominations, namely: MALT-SALT, lympho-plasmocytoid, plasmocyte, lymphoid follicular hyperplasia, immunocytoma, and plasmocytoma.

The initial immunocytoma denomination was adopted by EORTC from the KIEL classification, because of its supposed plasmocytoid differenciation.[1,41] These lymphomas actually derive from the marginal zone of the germinal center. They show wide histological variety of small B cells (centrocyte-like, lympho-plasmocytoid, or plasma cells) but have always had good prognosis.[42] Therefore, and given the similarity with mucosa associated lymphoid tissues (MALT), the SALT (skin associated lymphoid tissues) denomination was suggested.

These lymphomas clearly differentiate form pseudolymphomas, and from skin involvement secondary to nodal lymphomas.[43-45]

Tick-bite transmitted *Borrelia burgdorferi* is mentioned as one etiologic factor; therefore its usual localization in exposed areas.[46,47]

These lymphomas appear as red, violaceous, solitary, or multiple, slow growing tumors located in the proximal area of limbs, gluteus, and trunk. Our experience joined four cases, whereof three had tumors, and one had plaques. As regards location, two appeared on the limbs (one on the thigh, and one on the forearm), and two on the head (one on the face [**Figure 3**] and one on the scalp). Histologically, they occur in a nodular or diffuse pattern, preserving epidermis. There was cell variability, with peripheral lympho-plasmacytoid and isolated plasma cells and central small reactive cells or reactive follicular structures, centrocytes, centroblasts, and immunoblasts. Cells with intranuclear inclusions (Dutcher bodies), characteristic of B lineage, may be found. Rarely, there is infiltration of glandular, hair, or sweat epithelia, more characteristic of node lymphomas.[41,42,46,48]

Transformation to diffuse large B-cell lymphoma is rare.

Immunophenotype of marginal zone lymphomas is: CD19, CD20, CD79a Bcl-2(+), CD5, CD10, and Bcl-6(-).[49,50] Plasma cells: CD20(-), CD138(+). Reactive germinal centers: Bcl-6, and CD10(+), Bcl-2(-).

Monoclonal cytoplasmic Ig may be found in advanced stages.

There is Ig heavy chain (IgH) clone rearrangement. Recent studies suggest the presence of t(14;18)(q32;q21) translocation involving genes codifying Ig (chromosome 14) heavy chains and MLT gene, located on chromosome 18. Also found is (3;14)(p14.1;q32) translocation involving IgH gene and FOXP1.[49,50] Gastric lymphomas have different translocations than in skin: t(11;18)(q21;q21) and t(1;14)(p22,q32).[51,52]

Cases 14 and 16 were subjected to surgical excision, and cases 15 y17, to radiotherapy; both treatments are indicated for solitary lesions.

Five-year survival is 100 percent, a similar prognosis for the 4 patients in our experience.[41,48,53]

We detected positive *B. burgdorferi* serology in case 15; thus, the patient received radiotherapy plus antibiotic treatment.[54]

In the presence of multiple lesions of primitive marginal zone B-cell lymphoma, systemic treatment with chlorambucil or interferon-alpha is suggested.[54]

Good results have been described with intralesional or systemic rituximab (anti-CD20 antibody).[55]

Case 17 is unusual in being a primary cutaneous plasmocytoma, a rare lymphoma occurring in 4 percent of extramedullary plasmocytomas.[56] This patient had a red-violet subcutaneous nodule on the scalp, of excellent prognosis, where associate multiple myeloma was ruled out[57] (**Figure 4**). Histologically noteworthy was the presence of mature plasma cells, some of them multinucleated. The immunophenotype was CD20(-), CD138(+), monoclonal for cytoplasmic Ig in plasmocytes.[58] Survival is excellent (100 percent at 5 years).The recommended treatment is radiotherapy or surgery.

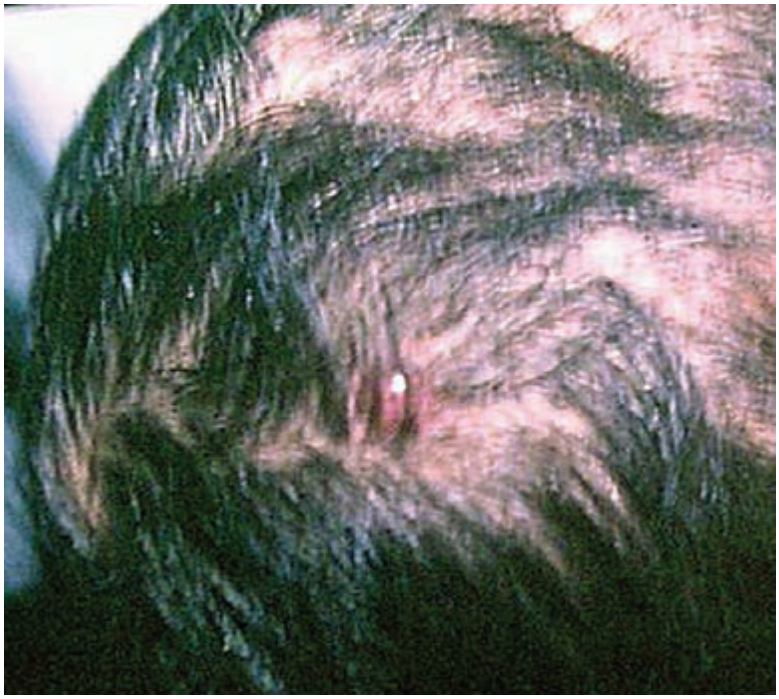


Figure 4. *Primary cutaneous plasmocytoma (Case 17).*

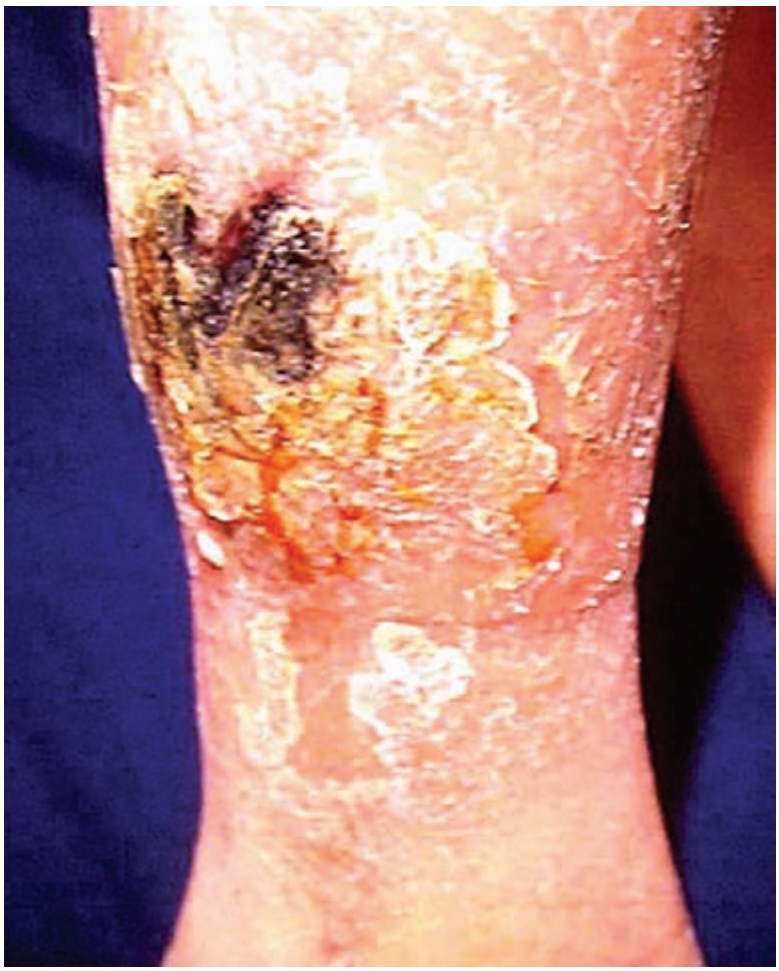


Figure 5. *Large B-cell lymphoma of the leg (Case 18).*

Primary cutaneous diffuse large B-cell lymphoma of the leg

Dominant in patients older than 70 years, female 3-4:1, and it appears as rapidly growing red nodules or tumors in one or both lower areas of the legs; they are rare in other areas.[22,59,60] (**Figure 5**)

Case 19 showed a nodule with a particular location on a toe. These last two patients were over 70 years old. We point out that locations in head and trunk are rare.[22]

Histologically, they show diffuse infiltrates of centroblasts and immunoblasts, preserving the epidermis and extending deeply to the subcutaneous cellular tissue. There are frequent mitotic figures, and scarce stromal reaction.[22,59]

The immunophenotype was CD19, CD20, CD22, CD79a, Bcl-2(+), and CD10(-).[16,29,50,61]

There is monoclonal superficial and/or citoplasmic Ig. Protein MUM-1/IRF4 is positive with immunohistochemical techniques.[30,62]

This type of lymphoma is not associated with clone rearrangement; however, Bcl-2(+) expression is common in this group.[16,29] In some cases, this overexpression is the consequence of chromosomal amplification of Bcl-2 gene.[63]

Inactivation of tumor suppressor genes *p15* and *p16* is found in 11 and 44 percent of the cases, respectively.[64] There is chromosomal imbalance in 85 percent of tumors (18q, 7p and loss of 6q).[63,65] There may be a genetic expression profile of activated B-cells,[30] and translocation of genes *myc*, *Bcl-6* and of IgH.[66]

Prognosis of these lymphomas is unfavorable, compared to follicular center lymphomas, with greater tendency to extracutaneous dissemination.[22,59] Five-year survival is 55 percent and the presence of multiple lesions is a factor of bad prognosis.[22] In case 18, the patient died 3 years after diagnosis, in spite of receiving combined treatment (radiotherapy-chemotherapy). For patients with solitary or localized tumor, radiotherapy is indicated.[22] Said treatment was administered to case 19.

Polychemotherapy is indicated for multiple lesions, with systemic anthracycline or rituximab.[22,39,59,67]

Other primary cutaneous diffuse large B-cell lymphoma

It comprises those cases of large B-cell not included in the follicular center or leg lymphoma groups.

It includes morphologic variants such as anaplastic, plasmoblastic, or large B-cell lymphoma rich in histiocytic T cells. Some cases constitute a cutaneous manifestation of a systemic lymphoma.

Plasmoblastic lymphoma appears exclusively in HIV patients or in other immunodefficiencies.[68] Case 21 is a 41-year old HIV patient with multiple tumors located in arm, thorax, and neck, which showed torpid evolution with rapid lesion dissemination that caused the patient's death.

Large B-cell lymphomas rich in histiocytic T cells are rarely seen and are characterized by the presence of large B-cells and numerous reactive T-cells.[69,70] Those having an exaggerated reactive T-cell population have better prognosis. They are clinically similar to follicular center and marginal zone lymphomas located in the head, trunk, and limbs.

Intravascular large B-cell lymphomas may be defined as an aggregation of neoplastic large B-cells within blood vessels, and they may affect the central nervous system and the lung; the latter is associated with bad prognosis.[71] Case 20 appeared as an angiomatoid plaque that evolved to a violaceous, indurated, armor-like lesion (**Figure 6**). The lesion was reduced after irradiation; two years later, the patient developed lung involvement and died. Occasionally, lesions may acquire an early telangiectasic aspect and localize on lower area of legs and on the trunk.[71,72] Interesting cases of skin hemangioma colonization by neoplastic cells, as sole presentation symptom, are described.[73,74]

Histopatologically, there are dilated vessels in dermis and hypodermis, with proliferation of neoplastic large lymphoid cells. This cell proliferation may lead to vascular occlusion of venules, capillaries and arterioles. Extravascular aggregations of atypical cells are found in 20 percent of the cases. En case 20, these findings also appeared in the lung biopsy.

Immunophenotype was CD19, CD20, CD22, CD79a(+), monoclonal for sIg. T immunophenotype appears less frequently.

This variety of lymphomas has bad prognosis, especially if affecting central nervous system or lung. Survival at 5 years is 22 percent, but if there is only cutaneous involvement, it increases to 56 percent.[72] Chemotherapy is the treatment of choice, even in cases of exclusive cutaneous involvement.[72]

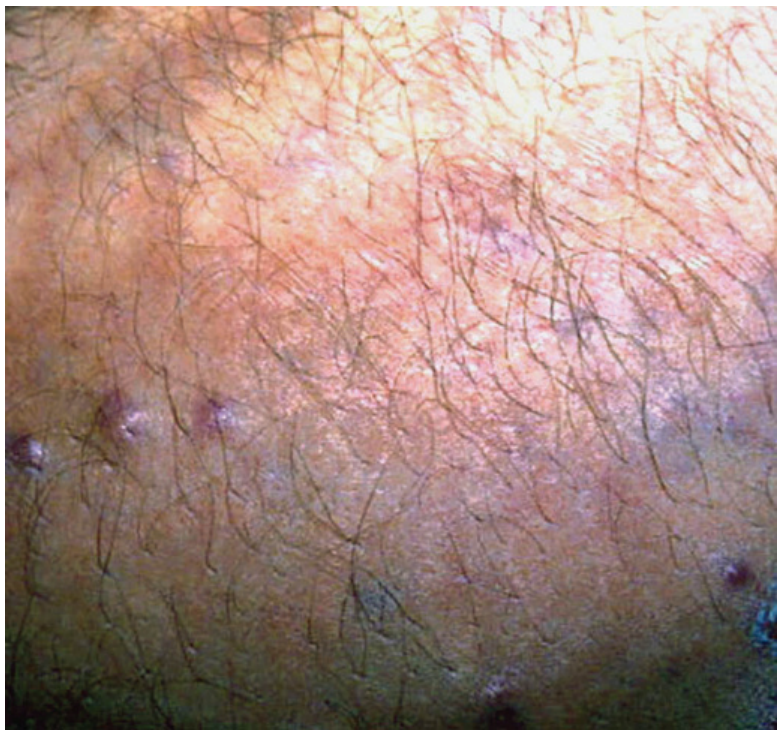


Figure 6. *Intravascular large B-cell lymphoma (Case 20).*

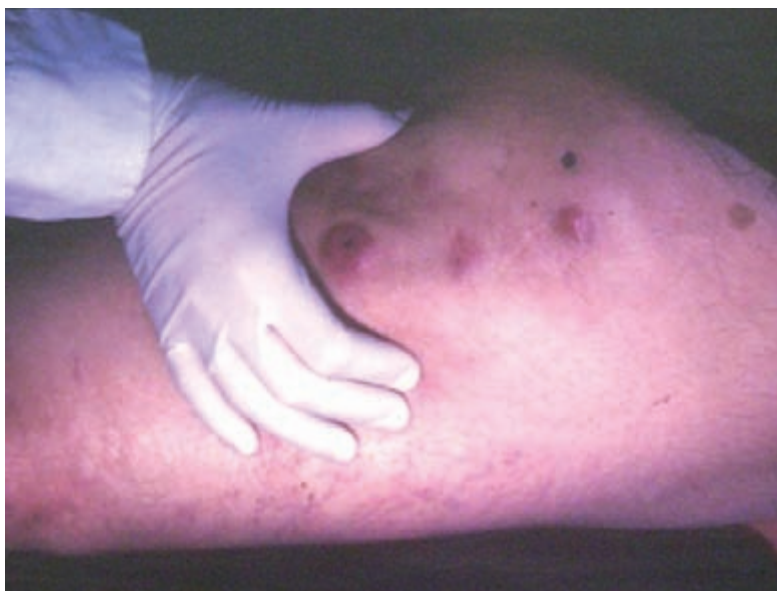


Figure 7. *Primary cutaneous mantle B-cell lymphoma. Panniculus clinical aspect (Case 22).*

Primary cutaneous mantle B-cell lymphoma

The current WHO-EORTC classification does not include primary cutaneous mantle B-cell lymphoma, which was stated in the EORTC classification.[7,75] Localized secondary skin lesions are not accounted for in this classification.[76]

In case 22 (**Figure 7**), the histology showed monomorphous and diffuse infiltrate consisting of small lymphoid cells without epidermotropism, extending towards the subcutaneous cell tissue, with scarce mitosis. The immunophenotype was CD20(+), CD3(-), and CD5(+).

If a cutaneous B-cell lymphoma is CD5 positive, two possibilities must be considered: a chronic lymphoid leukemia with secondary skin involvement (CD23 positive), or a primary cutaneous mantle B-cell lymphoma (CD23 negative).

In our patient, the immunohistochemistry was negative for CD23 and the diagnosis of leukemia was ruled out through supplementary tests; therefore, we consider that primitive mantle lymphoma should be included in the primary cutaneous B-cell lymphomas.

In contrast with nodal lymphomas, phenotype is not cyclin D1(+), or Bcl-1(+) and there is no chromosomal translocation between sector 13 of the long arm of chromosome 11 and sector 32 of the long arm of chromosome 14 t(11;14)(q13; q32).[77,78]
For all the above, we intend to highlight some facts we deem of interest.
Genetic studies of PCBCL may show monoclonality (Ig light and heavy chain tests) but without evidence of chromosomal translocation t(14,18) characteristic of nodal lymphomas.[79]
Large cell PCBCL of the leg show increased expression of genes associated with cell proliferation cellular: proto-oncogenes *Pim-1*, *Pim-2* and *Myc*; and of genes associated with transcription factors:
Mum1/IRF4 and Oct-2, which demonstrated that they derive from activated B-cells.
In contrast, follicular center lymphomas, when appearing with large cells, have increased SPINK2 expression and a secretion profile similar to germinal center B-cell lymphomas. These investigations suggest different pathogenic mechanisms, and support the WHO-EORTC subdivision.[30,80]
Epstein Barr virus is most frequently found in systemic than in cutaneous immunoblastic lymphomas.[81] Immunosuppresor states (HIV, transplants) modify the course of lymphomas. In case 12 we were able to observe that on the surgical scar of a renal transplant, the patient developed a follicular center PCBC (**Figure 8**). PCR test for Epstein-Barr virus resulted positive in the tumor mass cells. Radiotherapy was indicated, with excellent evolution. The presence of virus did not modify the lymphoma prognosis.[82-84]
Most frequent PCBCL are follicular center lymphomas (56.7 percent), followed by marginal zone (31.4 percent) and leg lymphomas (10.9 percent). These data coincide with international statistics and also with our experience.[9,16,17,38,85] In contrast, marginal zone lymphomas are predominant in Spain.[86]
A study on marginal zone lymphomas communicated four cases localized in head and neck, three with later systemic involvement (one with transformation into large cells, and two cases with Bcl-2 t(14,18) chromosomal translocation.[86] These facts evidence worse prognosis for this location, but do not match our experience (case 16).[87] Another frequently described form is multifocal (72 percent of the cases); in these cases, treatment with chlorambucil is used.[88]
Marking panel makes it possible to establish differences between follicular center and marginal zone lymphomas (**Table 3**).[89]

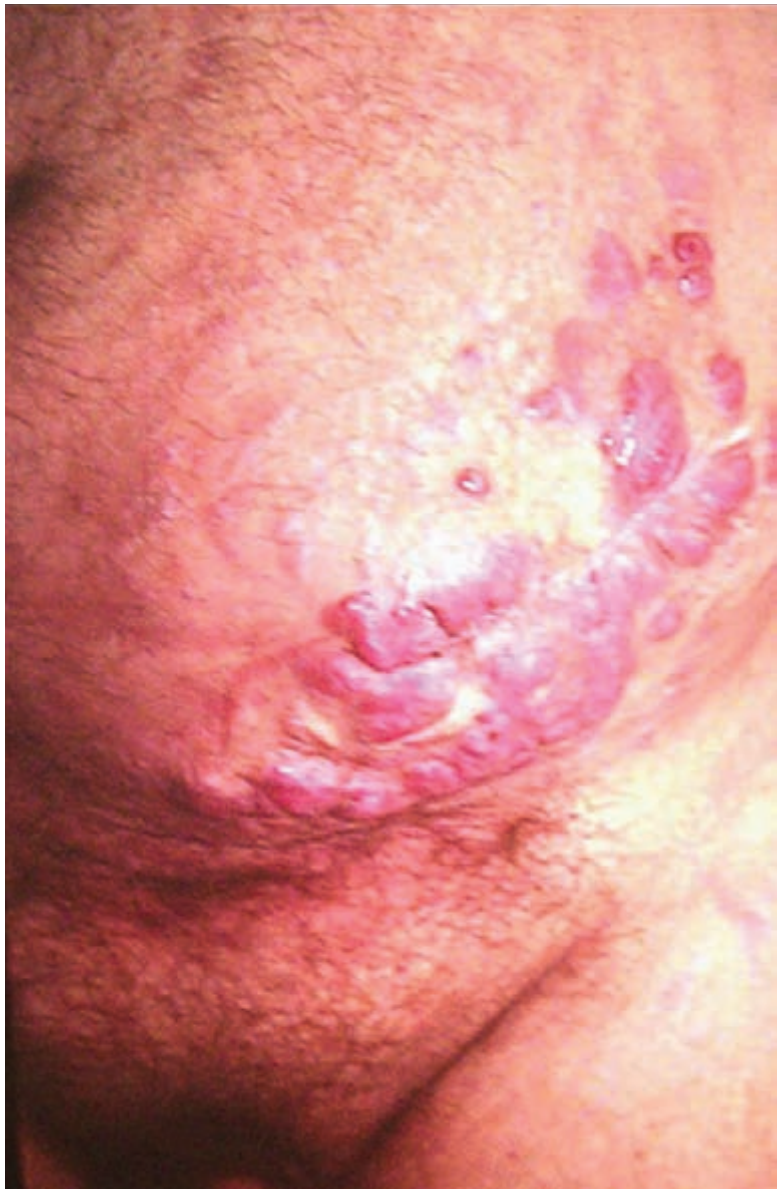


Figure 8. *Follicular center B-cell lymphoma on renal transplant surgical scar. Positive CRP in tumor tissue for Epstein-Barr virus (Case 12).*

TABLE 3. IMMUNOHISTOCHEMICAL DIFFERENCES BETWEEN PRIMARY CUTANEOUS FOLLICULAR CENTER AND MARGINAL ZONE B-CELL LYMPHOMAS.

	Bcl-6	Bcl-2	CD10	CD21
FC PCBCL *	+	+/-	+	-
MZ PCBCL **	-	+	-	+
*FC: follicular center. **MZ: marginal zone				

Ig heavy chain variable region assessment is useful to evidence monoclonality. In contrast with the light chain immunohistochemical test, this method does not require fresh material.[90,91]
The characteristic chromosomal translocation of nodal lymphomas is established between *Bcl-2* gene in chromosome 18 and the Ig heavy chain-linking region in chromosome 14. Protein Bcl-2 prevents apoptosis. Translocation of its gene leads to overexpression of the protein, thus preventing apoptosis of neoplastic cells and originating greater tumor aggressiveness in nodal lymphomas; this is the main difference with primary cutaneous lymphoma.[92]

Conclusion

The last PCBCL classification took into account clinical, therapeutic, histopatologic, and genetic aspects.[93,94] This global approach optimized dermatologist management of PCBCL and allowed their inclusion in the interdisciplinary group in charge of lymphoma patient follow-up.
Anyhow, the continuous reviewing may produce modifications in a not very distant future.

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