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CHAPTER 2

Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle center cell origin and differential diagnostic significance

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Dermatopathology

Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance

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Summary

Background Primary cutaneous follicle centre cell lymphomas (PCFCCLs) are the most common type of cutaneous B-cell lymphoma. There is ongoing discussion on the origin of the neoplastic B cells in these PCFCCLs, and consequently on their relation to the groups of primary cutaneous marginal zone B-cell lymphomas (PCMZLs) and nodal follicular lymphomas.

Objectives To define better the neoplastic B cells in PCFCCLs, and to find out if differences in the expression of the antiapoptotic protein Bcl-2, and Bcl-6 and CD10, molecules which are normally expressed by the neoplastic B cells in nodal follicular lymphomas, might have diagnostic or prognostic significance in cutaneous B-cell lymphoproliferative disorders.

Methods Pretreatment biopsies of well-defined groups of PCFCCL ($n = 24$), PCMZL ($n = 14$), primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg; $n = 19$), secondary cutaneous follicular lymphoma ($n = 3$) and cutaneous pseudo-B-cell lymphoma ($n = 6$) were investigated by immunohistochemistry for expression of Bcl-2, Bcl-6 and CD10.

Results The PCFCCLs consistently expressed Bcl-6, whereas CD10 and Bcl-2 were expressed in only one and two of 24 cases, respectively. In contrast, PCMZLs were always negative for Bcl-6 and CD10, but were Bcl-2 positive, whereas skin and lymph node localizations of secondary cutaneous follicular lymphomas consistently expressed all of Bcl-2, Bcl-6 and CD10. Reactive follicle centre cells in pseudo-B-cell lymphomas expressed Bcl-6 (six of six cases) and CD10 (five of six cases), but not Bcl-2. PCLBCL-leg was Bcl-6 positive and CD10 negative in all cases, irrespective of clinical outcome, and strongly expressed Bcl-2 protein in all but two cases.

Conclusions The results of the present study provide further support for the follicle centre cell origin of both PCFCCL and PCLBCL-leg, and indicate that staining for Bcl-2, Bcl-6 and CD10 can serve as an important adjunct in the differential diagnosis of cutaneous B-cell lymphoproliferative disorders.

Key words: Bcl-2, Bcl-6, CD10, cutaneous B-cell lymphoma, differential diagnosis

Primary cutaneous B-cell lymphomas (CBCLs) represent a heterogeneous group of non-Hodgkin lymphomas presenting in the skin with no evidence of extracutaneous disease at the time of diagnosis.¹ The European Organization for Research and Treatment of Cancer

(EORTC) classification for primary cutaneous lymphomas distinguishes three clinicopathologically well-defined groups of CBCL: primary cutaneous follicle centre cell lymphoma (PCFCCL), primary cutaneous marginal zone B-cell lymphoma (PCMZL, formerly classified as immunocytoma) and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg).¹ The term PCFCCL was introduced as an encompassing term

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for CBCLs that had the morphological characteristics of small and large follicle centre cells (centrocytes and centroblasts) and that were classified as either centroblastic/centrocytic or centroblastic lymphoma, according to the criteria of the updated Kiel classification.² Clinicopathological correlation showed that these lymphomas represent a distinct disease entity generally presenting with localized skin lesions on the head or trunk, rarely disseminate to extracutaneous sites and have an excellent prognosis, with a 5-year survival of more than 95%.^{1,3–6} Most importantly, no difference in clinical behaviour was found between cases classified as either centroblastic/centrocytic or as centroblastic lymphoma.^{3,4,6} In the World Health Organization (WHO) classification these PCFCCLs are not recognized as a distinct entity, but—according to traditional morphological criteria—are classified variously as extranodal marginal zone B-cell lymphoma (predominance of small germinal centre cells; no follicular growth pattern), diffuse large B-cell lymphoma (predominance of large germinal centre cells; most cases) or cutaneous follicle centre lymphoma (rare cases with a follicular growth pattern).⁷ Cases of PCLBCL-leg are classified as diffuse large B-cell lymphoma in the WHO classification.

In recent years there has been an ongoing debate on the relation between these PCFCCLs, as defined in the EORTC classification, and the group of follicular lymphomas arising primarily in lymph nodes. By definition these follicular lymphomas have a follicular growth pattern.⁷ In contrast, most PCFCCLs display a diffuse pattern, whereas a follicular growth pattern is observed in only a minority of cases. Nodal follicular lymphomas characteristically express Bcl-2 protein and most cases exhibit the interchromosomal translocation t(14;18), whereas most studies of PCFCCL show that the neoplastic cells are Bcl-2 negative and lack the t(14;18).^{8–12} Because of these differences it has been suggested that most PCFCCLs are not derived from follicle centre cells, but more probably represent (transformed) marginal zone B-cell lymphomas.¹³ Several more recent studies described the presence of a follicular growth pattern as well as the expression of Bcl-2, the germinal centre-associated antigens Bcl-6 and CD10, and t(14;18) in variable proportions of PCFCCLs, suggesting that the neoplastic B cells in these PCFCCLs are indeed of follicle centre cell origin and that they are closely related to nodal follicular lymphoma.^{14–23}

These conflicting results and conclusions prompted us to investigate well-defined groups of PCFCCL, PCMZL, PCLBCL-leg, secondary cutaneous follicular lymphomas and pseudo-B-cell lymphomas for expres-

sion of the antiapoptotic protein Bcl-2, and Bcl-6 and CD10, molecules which are normally expressed by the neoplastic cells in nodal follicular lymphoma. The aim of our study was to define better the neoplastic cells in these PCFCCLs, and to find out if differences in the expression of Bcl-2, Bcl-6 and CD10 might be helpful in differentiating between different types of primary and secondary cutaneous B-cell lymphoproliferative disorders. As expression of both CD10 and Bcl-6 has been reported to have prognostic significance in diffuse large B-cell lymphomas, a group of 19 cases of PCLBCL-leg was studied as well.^{24,25}

Materials and methods

Patients

Pretreatment biopsies obtained at time of diagnosis from 57 patients with a CBCL, including 24 PCFCCL, 19 PCLBCL-leg and 14 PCMZL, were available for examination. Patients with CBCL were defined according to the criteria of the EORTC classification.¹ In all cases, the diagnosis had been confirmed by immunohistochemistry showing monotypic immunoglobulin light chain expression or the absence of surface immunoglobulins on large clusters of CD20+, CD79a+ neoplastic B cells. In all cases, there was no evidence of extracutaneous disease at the time of diagnosis as assessed by adequate staging procedures, which included physical examination, full blood cell counts, computed tomography of the chest and abdomen and bone marrow biopsy. Relevant clinical and follow-up data of these three groups are presented in Table 1.

Skin biopsy specimens from six patients with a pseudo-B-cell lymphoma and three patients with a follicular lymphoma presenting with both skin and lymph node localizations at the time of diagnosis were included as controls. Patients with a pseudo-B-cell lymphoma had presented with solitary or grouped skin lesions, and follow-up was unremarkable in all cases. The diagnosis was confirmed by immunohistochemistry showing polytypic immunoglobulin light chain expression in all six cases. In the three secondary cutaneous follicular lymphomas both skin and lymph node biopsies showed a predominantly follicular growth pattern.

Immunohistochemistry

Immunohistochemical staining was performed on 3-µm sections of formalin-fixed, paraffin-embedded

Table 1. Clinical and follow-up data of 57 primary cutaneous B-cell lymphomas

	PCFCCL	PCMZL	PCLBCL-leg
Number	24	14	19
Site of presentation ^a			
Head/neck	11	1	1
Trunk	13	11	0
Arm	0	5	0
Leg	0	2	19
Extent of skin lesions			
Solitary/localized	21	1	17
Multifocal	3	13	2
Initial therapy			
Radiotherapy	19	5	10
Polychemotherapy	2	2	8
Monochemotherapy	0	6	0
Other	3	1	1
Result of initial therapy			
Complete remission	24	9	16
Partial remission	0	5	3
Relapse			
Skin	7	7	10
Extracutaneous	0	0	11
Follow-up (months)			
Median	47	12	25
Range	7–179	6–95	7–76
Current status			
A°	21	6	8
A ⁺	2	8	0
D°	1	0	0
D ⁺	0	0	11

PCFCCL, primary cutaneous follicle centre cell lymphoma; PCMZL, primary cutaneous marginal zone B-cell lymphoma; PCLBCL-leg, primary cutaneous large B-cell lymphoma of the leg; A°, alive without disease; A⁺, alive with disease; D°, death unrelated to disease; D⁺, death related to disease. ^aSome patients had more than one localization of their cutaneous lymphoma.

tissues using standard procedures. After antigen retrieval by boiling for 10 min in 1.0 mmol L⁻¹ ethylenediamine tetraacetic acid (pH 8.0) for Bcl-6, CD35, CD5 and CD138, and in 10 mmol L⁻¹ citrate buffer (pH 6.0) for Bcl-2, CD10, CD79a and CD3, tissue sections were incubated overnight with antibodies

against Bcl-6 (clone PG-B6p; dilution 1 : 200), Bcl-2 (clone 124; 1 : 100), CD20 (1 : 100), CD79a (1 : 400), CD3 (1 : 100) (Dako, Glostrup, Denmark), against CD10 (clone 56C6; 1 : 10), CD35 (1 : 50), CD5 (1 : 200) (Novocastra, Clinipath, Duiven, The Netherlands), and against CD138 (1 : 800; Serotec, Oxford, U.K.). Sections were then incubated with biotin-labelled rabbit antimouse antibodies (1 : 200), except for CD3, where biotin-labelled swine antirabbit antibody was used. Immunoreactivity was detected using a streptavidin-biotin-peroxidase complex (sABC-HRP; 1 : 100; Dako). All secondary and tertiary antibodies were incubated for 30 min in 1% phosphate-buffered saline/bovine serum albumin at room temperature.

The antibodies against B-cell-associated antigens (CD20, CD79a), plasma cell-associated antigens (CD138) and T-cell-associated antigens (CD3, CD5) were used to verify the localization of the neoplastic B cells and reactive T cells. In most cases staining with monoclonal antibodies to CD35 was performed to identify follicular dendritic cells (FDCs). Expression of Bcl-6 and Bcl-2 protein was scored as positive if 25% or more of the neoplastic cells stained, and as negative if < 25% of the neoplastic cells stained.

Results

A summary of results of immunostaining is provided in Table 2.

Primary cutaneous follicle centre cell lymphoma

As illustrated in Figure 1(A–D), the biopsies of all cases demonstrated nodular to diffuse dermal infiltrates containing large clusters of medium to large-sized cleaved cells (centrocytes) and large uncleaved cells (centroblasts). In only two of 24 biopsies was a partly follicular growth pattern observed. In these two cases large clusters of tumour cells were almost completely

Table 2. Results of immunostaining

	Bcl-2+			Bcl-6+			CD10+
	0–25%	25–50%	> 50%	0–25%	25–50%	> 50%	
PCFCCL	22/24	–	2/24	–	5/23	18/23	1/24
PCMZL	–	–	14/14	14/14 ^a	–	–	0/14
PCLBCL-leg	1/19	1/19	17/19	–	2/19	17/19	0/19
Secondary FL	–	–	3/3	–	–	3/3	3/3
Pseudolymphoma	6/6	–	–	–	–	6/6	5/6

PCFCCL, primary cutaneous follicle centre cell lymphoma; PCMZL, primary cutaneous marginal zone B-cell lymphoma; PCLBCL-leg, primary cutaneous large B-cell lymphoma of the leg; secondary FL, secondary cutaneous follicular lymphoma. ^aAlways negative for Bcl-6.

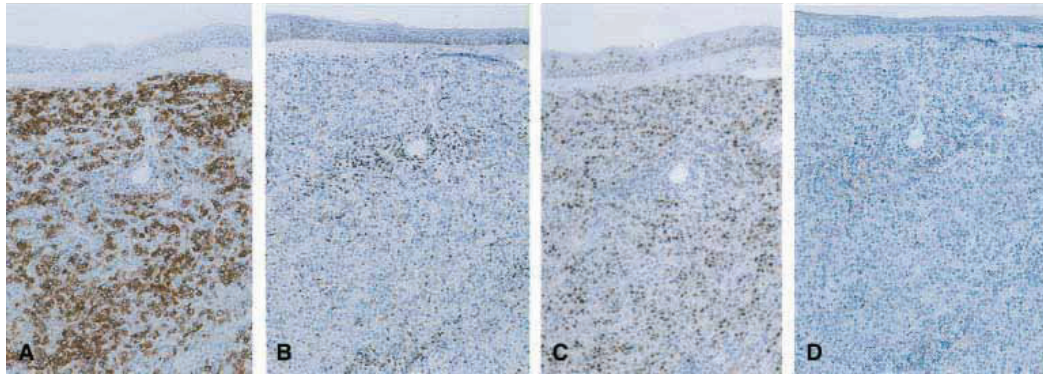


Figure 1. Primary cutaneous follicle centre cell lymphoma. The neoplastic B cells stain positive for CD79a (A) and Bcl-6 (C) and negative for Bcl-2 (B) and CD10 (D). Bcl-2+ T cells (B) and Bcl-6+ suprabasal cells of the epidermis (C) serve as internal controls. A reticular staining pattern of CD10 surrounding dermal adnexae is seen (D) (original magnification $\times 100$).

enmeshed in an FDC network of CD35+ FDCs. The other 22 biopsies showed a diffuse growth pattern, with only occasional FDCs left in diffuse areas of large neoplastic B cells. Thus, according to the criteria of the WHO classification only two cases fitted in the category cutaneous follicle centre lymphoma, whereas 22 cases would have been classified as diffuse large B-cell lymphoma.⁷

In all cases, the neoplastic cells showed a positive nuclear Bcl-6 staining with a variable intensity (Fig. 1A,C). Nuclear staining of suprabasal epidermal cells served as a positive internal control. In all biopsies CD10 showed a reticular staining pattern surrounding dermal adnexae, e.g. blood vessels and sweat and sebaceous glands (Fig. 1D). However, expression of CD10 by the neoplastic B cells was observed in only one

of 24 biopsies. In 22 of 24 biopsies the neoplastic B cells were Bcl-2 negative (Fig. 1B). Bcl-2-positive reactive T cells, which served as an internal control, were observed in all cases. The neoplastic cells of the two cases with a partly follicular growth pattern expressed Bcl-6, but neither Bcl-2 nor CD10.

Primary cutaneous marginal zone B-cell lymphoma

As illustrated in Figure 2(A–D), the PCMZL biopsies showed patchy to diffuse dermal infiltrates with variable numbers of lymphoplasmacytoid cells, plasma cells and admixed T cells. In four patients there was a predominant population of medium-sized neoplastic B cells with morphological features intermediate between small centrocyte-like cells (marginal zone B

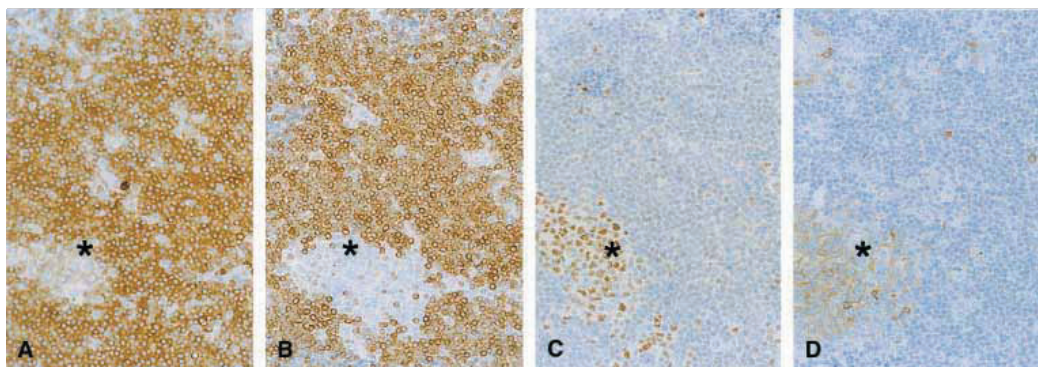


Figure 2. Primary cutaneous marginal zone B-cell lymphoma. The neoplastic cells stain positive for CD79a (A) and Bcl-2 (B) and negative for Bcl-6 (C) and CD10 (D). Reactive germinal centre cells (*) show a Bcl-2-/Bcl-6+/CD10+ immunophenotype (original magnification $\times 200$).

cells) and large cleaved follicle centre cells. In all these four cases the diagnosis of PCMZL was preferred because of the presence of monotypic immunoglobulin light chain expression by lymphoplasmacytoid cells and plasma cells on paraffin sections.

In all cases, including the four cases with a predominant population of medium-sized cleaved cells, the neoplastic B cells showed expression of Bcl-2 protein. Staining for Bcl-6 and CD10 was consistently negative (Fig. 2C,D). In all biopsies reactive germinal centres associated with FDCs and with or without distinct mantle zones were observed. Similar to the follicle centre cells in pseudo-B-cell lymphoma, these reactive germinal centre cells showed a Bcl-2-/Bcl-6+/CD10+ immunophenotype (Fig. 2B-D). A few single reactive germinal centre cells scattered among Bcl-2+/Bcl-6-/CD10- neoplastic marginal zone cells could be identified, but follicular colonization of the reactive germinal centres by neoplastic marginal zone cells was not seen.

Primary cutaneous large B-cell lymphoma of the leg

Histologically (Fig. 3A-D), these cases of PCLBCL-leg generally displayed diffuse infiltrates of large cells with the morphological appearance of centroblasts or immunoblasts. In two cases a predominance of large cleaved cells was observed. In 17 of 19 biopsies Bcl-2 was strongly expressed by more than 80% of the neoplastic B cells. Expression of Bcl-6 protein by the neoplastic B cells was observed in all biopsies, with percentages between 50% and 90% in 17 of 19 cases. Like in PCFCCL, the intensity of Bcl-6 staining varied between neoplastic cells within each individual case. In none of the cases was expression of CD10 observed at

the membranes of neoplastic cells, but most cases showed a more or less extensive reticular staining pattern as observed in PCFCCL.

Pseudo-B-cell lymphoma

Germinal centres with or without distinct mantle zones were observed in all biopsies of pseudo-B-cell lymphomas included as controls. As shown in Figure 4(A-D), the reactive follicle centre cells showed a Bcl-2-/Bcl-6+/CD10+ immunophenotype, similar to nodal reactive follicle centre cells. The staining intensity of CD10 in the germinal centres was variable. Even within one biopsy germinal centres with strong and very weak CD10 expression were found next to one another. In addition, CD10 staining showed a reticular pattern surrounding follicular and epithelial structures, as described before.

Secondary cutaneous follicular lymphoma

In all skin and lymph node biopsies the neoplastic B cells showed the characteristic Bcl-2+/Bcl-6+/CD10+ immunophenotype of follicular lymphoma⁷ (Fig. 5A-D).

Discussion

The results of the present study showed distinctive staining patterns for Bcl-2, Bcl-6 and CD10 in different types of cutaneous B-cell lymphoproliferative disorders, including PCFCCL (Bcl-2-/Bcl-6+/CD10-), PCMZL (Bcl-2+/Bcl-6-/CD10-), PCLBCL-leg (Bcl-2+/Bcl-6+/CD10-), skin localizations of nodal follicular lympho-

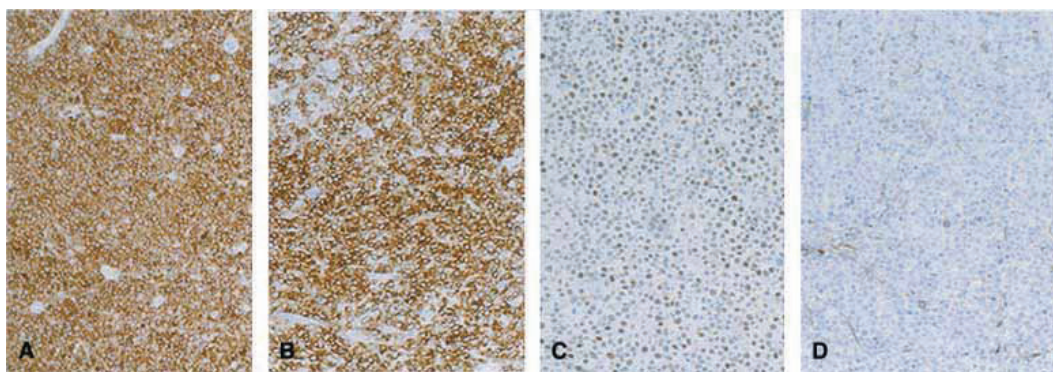


Figure 3. Primary cutaneous large B-cell lymphoma of the leg. The neoplastic cells stain positive for CD20 (A), Bcl-2 (B) and Bcl-6 (C), and negative for CD10 (D) (original magnification $\times 200$).

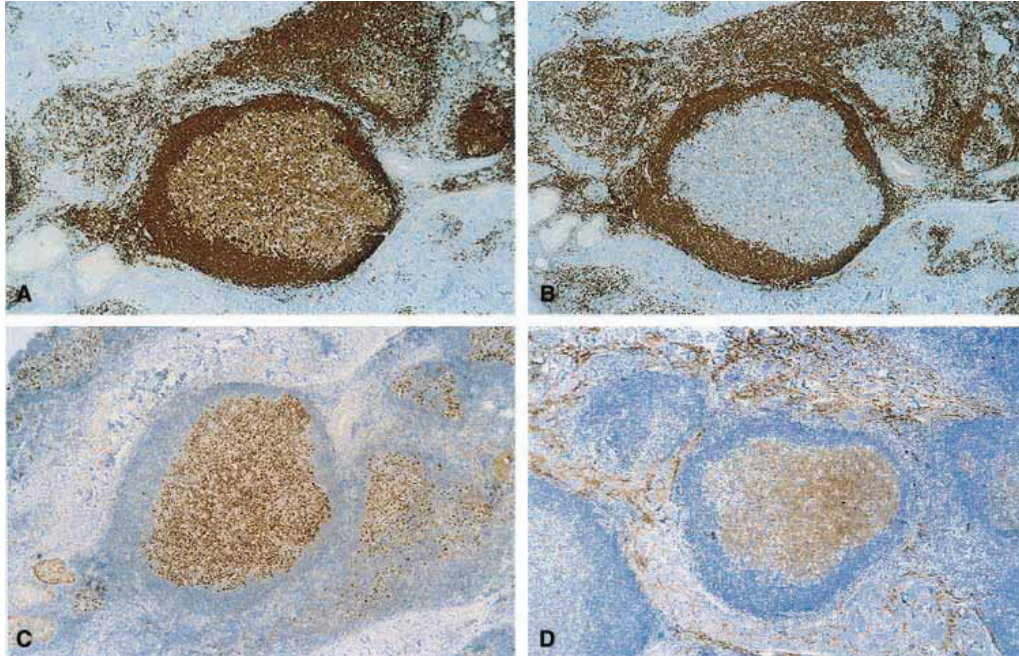


Figure 4. Pseudo-B-cell lymphoma. The CD79a+ germinal centre cells (A) of pseudo-B-cell lymphoma show a Bcl-2- (B)/Bcl-6+ (C)/CD10+ (D) immunophenotype. Note reticular staining pattern of CD10 around and between the reactive follicles (original magnification $\times 50$).

mas (Bcl-2+/Bcl-6+/CD10+) and pseudo-B-cell lymphomas (Bcl-2-/Bcl-6+/CD10+). This consistent staining pattern of the group of PCFCCLs is important for several reasons.

Firstly, as there are no reports indicating that Bcl-6 protein is expressed by malignant lymphomas other than those derived from germinal centre cells, the constant expression of Bcl-6 provides further support for the follicle centre cell origin of PCFCCLs. In the initial studies the term PCFCCL was coined because of the morphological resemblance of the neoplastic cells to centrocytes and centroblasts, whereas a follicular growth pattern is generally lacking.²⁶ However, morphological differentiation between small centrocytes (small cleaved cells) and centrocyte-like cells, now generally referred to as marginal zone cells, is arbitrary. In addition, it was found that the neoplastic B cells in these PCFCCLs, in contrast to the neoplastic cells in nodal follicular lymphomas, generally do not express Bcl-2 protein and are not associated with the interchromosomal translocation t(14;18).⁸⁻¹² For these reasons it was suggested that the neoplastic cells in these PCFCCLs are not derived from follicle centre cells, but rather represent (transformed) marginal zone B

cells.¹³ However, the results of this and other studies demonstrating that these lymphomas consistently express Bcl-6 protein and show ongoing somatic hypermutations provide further support for a follicle centre cell derivation of these PCFCCLs.^{14-23,27,28}

Secondly, the consistent staining pattern of PCFCCLs showing a Bcl-2-/Bcl-6+/CD10- immunophenotype can serve as an important adjunct in the differentiation from secondary cutaneous follicular lymphomas (Bcl-2+/Bcl-6+/CD10+), pseudo-B-cell lymphomas (Bcl-2-/Bcl-6+/CD10+) and PCMZL (Bcl-2+/Bcl-6-/CD10-). Differentiation between PCFCCL and PCMZL may sometimes be difficult, in particular in cases with a predominant population of medium-sized B cells with morphological features intermediate between small centrocyte-like cells (marginal zone B cells) and large cleaved follicle centre cells. Demonstration of monotypic light chain expression on paraffin-embedded sections is considered as a decisive criterion for the diagnosis of marginal zone B-cell lymphoma in such cases.²⁹ The results of the present study indicate that expression of a Bcl-2+/Bcl-6- phenotype by these cells may be considered as an additional criterion for the diagnosis of PCMZL. This distinction between PCFCCL

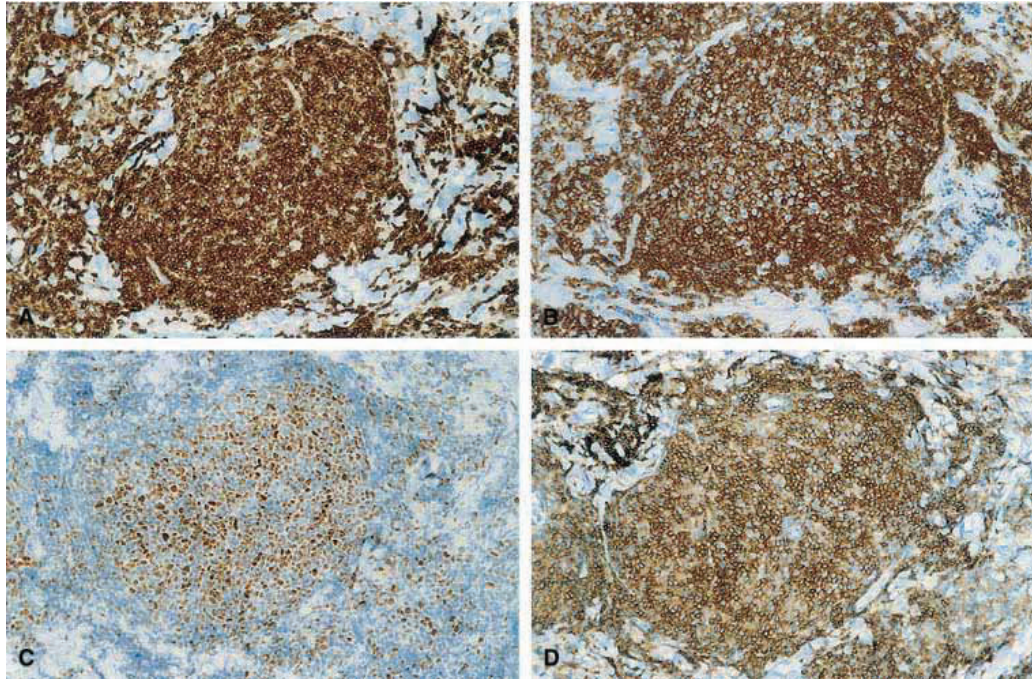


Figure 5. Secondary cutaneous follicular lymphoma. The CD20+ neoplastic cells (A) show the characteristic Bcl-2+ (B)/Bcl-6+ (C)/CD10+ (D) immunophenotype of a follicular lymphoma (original magnification $\times 100$).

and PCMZL is not only of academic interest, but may have important therapeutic consequences, in particular in patients presenting with multifocal skin lesions. In patients with a diagnosis of PCFCCL, particularly when they have the histological appearance of a diffuse large B-cell lymphoma, oncologists will often decide to give doxorubicin-based multiagent chemotherapy, whereas patients with PCMZL presenting with multifocal skin lesions will generally be treated with less aggressive therapies, such as chlorambucil or interferon alfa.

It is of interest that the group of PCLBCL-leg demonstrated the same consistent Bcl-6 expression as found in PCFCCL, suggesting that these lymphomas are derived from follicle centre cells as well. This supports early publications of our group, in which we considered PCLBCL-leg as a subgroup of PCFCCL with a more unfavourable prognosis.³⁰ In the EORTC classification PCLBCL-leg is considered as a separate disease entity, because of clinical and biological differences from large cell PCFCCL presenting on the head and trunk. In contrast to the excellent prognosis of PCFCCLs, PCLBCL-leg represents a group with an intermediate aggressive clinical behaviour and a 5-year survival of

about 50%.^{1,31} Unlike the PCFCCL with the histology of a diffuse large B-cell lymphoma located on the trunk and scalp, these cases of PCLBCL-leg are never preceded by papular or plaque-like lesions with a mixed population of small and large neoplastic B cells, and cytologically show a population of blast cells with round rather than cleaved or multilobated nuclei.³¹ The findings of different chromosomal abnormalities³² and a differential expression of polycomb genes between PCFCCL and PCLBCL-leg (Raaphorst *et al.* submitted) provide further evidence for different mechanisms in lymphomagenesis between both groups.

The reason why these cases of PCLBCL-leg have a more unfavourable prognosis than diffuse large B-cell lymphomas (PCFCCLs) on the trunk or head is at present unexplained. Recent studies in noncutaneous diffuse large B-cell lymphomas suggested that high Bcl-2 expression is associated with a more unfavourable prognosis.^{33–36} It might thus be argued that the strong Bcl-2 expression observed in PCLBCL-leg, but rarely in PCFCCLs on the head and trunk, is responsible for the more unfavourable prognosis of the first group.³⁷ However, in the group of PCLBCL-leg the

neoplastic B cells both of patients with a favourable prognosis and patients with a poor outcome consistently showed a Bcl-2+/Bcl-6+/CD10- phenotype, indicating that within this group these markers do not predict clinical behaviour.

Our results demonstrating a consistent Bcl-2+/Bcl-6- phenotype of the neoplastic B cells in PCMZLs is in accordance with the results of previous studies.^{11,16,17} In contrast, review of the recent literature on the immunophenotypic and molecular characteristics of PCFCCL shows conflicting results. Most early studies did not find or rarely found expression of CD10 and Bcl-2 or the presence of t(14;18), which is in keeping with the results of the present study.^{8–12} However, several recent studies do show expression of CD10 and Bcl-2 protein as well as t(14;18) in a significant number of cases.^{14–23}

There is at present no explanation for these discrepant results. Some of the discrepancy might result from differences in the extent of staging procedures which might result in the inclusion of secondary cutaneous lymphomas, or differences in the criteria for malignancy (monotypic light chain expression or only clonal IgH gene rearrangements). Secondly, it has been suggested that geographical differences might play a role.³⁸ However, this has to be substantiated by further studies. A third explanation for the discrepant results might be differences in the interpretation of staining results. Most authors do not describe a cut-off point in defining positive staining. In PCFCCL there is often a small proportion of centroblasts showing a weak perinuclear staining. However, as the large majority of follicle centre cells is Bcl-2 negative, in the present study we considered staining for Bcl-2 only positive if at least 25% of the neoplastic B cells expressed Bcl-2. Using this criterion only two of 24 PCFCCL biopsies were Bcl-2 positive. In contrast, in PCLBCL-leg Bcl-2 was generally strongly expressed by 75–100% of the neoplastic B cells in 17 of 19 biopsies.

In conclusion, the results of this study provide further support for the follicle centre cell origin of PCFCCL and PCLBCL-leg, and suggest that staining for Bcl-2, Bcl-6 and CD10 may serve as a valuable adjunct in the differential diagnosis of cutaneous B-cell lymphoproliferative disorders.

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