# Primary cutaneous B-cell lymphomas

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## SUMMARY

Primary cutaneous B-cell lymphomas are a heterogeneous group of B-cell lymphomas that present in the skin without evidence of extracutaneous disease at the time of diagnosis. In recent classifications three main types of cutaneous B-cell lymphomas are recognised: primary cutaneous marginal zone lymphoma, primary cutaneous follicle center lymphoma and primary cutaneous large B-cell lymphoma, leg type. In this review, the main characteristics and practice guidelines for the management and treatment of these three types of cutaneous B-cell lymphomas are presented. Other types of B-cell lymphomas that can present with skin-limited disease, such as intravascular large B-cell lymphoma, B-lymphoblastic lymphoma and immunodeficiency-associated B-cell proliferations will shortly be discussed.


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## INTRODUCTION

Primary cutaneous B-cell lymphomas (CBCL) are a heterogeneous group of B-cell lymphomas that present in the skin, without evidence of extracutaneous disease at the time of diagnosis.[1] In Western countries CBCL constitute about 20–25% of all primary cutaneous lymphomas, and their overall annual incidence rate is estimated at 3.1 cases per million individuals. Compared with their nodal counterparts that may involve the skin secondarily, CBCL often have a completely different clinical behaviour and prognosis, require a different therapeutic approach, and are therefore classified separately. To exclude secondary cutaneous disease, in every patient with a diagnosis of B-cell lymphoma in the skin careful physical examination, routine blood examination and appropriate imaging studies (CT or PET-CT) are required. Bone marrow examination is mandatory in high-grade malignant CBCL, but optional in low-grade malignant CBCL.[2]

In the WHO-EORTC classification for cutaneous lymphomas three main types of CBCL are recognized: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma, leg type (PCDLBCL, LT).[1] In the 2008 WHO classification for Tumours of Haematopoietic and Lymphoid Tissues and in the revised WHO 2016 classification PCFCL and PCDLBCL, LT have been included as separate entities, as defined in the WHO-EORTC classification.[3,4] PCMZL was however not categorized separately, but included in the broad group of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma). However, most cases of PCMZL differ from extranodal marginal zone lymphomas arising at other extranodal sites in the expression of class-switched immunoglobulins (Ig), chemokine receptors, translocations, associated infectious agents and frequency of blastic transformation and systemic dissemination.

In this review, the main characteristics and practice guidelines for the management and treatment of these three types of CBCL are presented. Other types of B-cell lymphomas that can present with skin-limited disease, such as intravascular large B-cell lymphoma, B-lymphoblastic lymphoma (B-LBL) and immunodeficiency-associated B-cell proliferations will shortly be discussed.

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**Keywords:** cutaneous lymphoma, diagnosis, leg type, primary cutaneous follicle center lymphoma, primary cutaneous large B-cell lymphoma, primary cutaneous marginal zone lymphoma, prognosis, treatment.

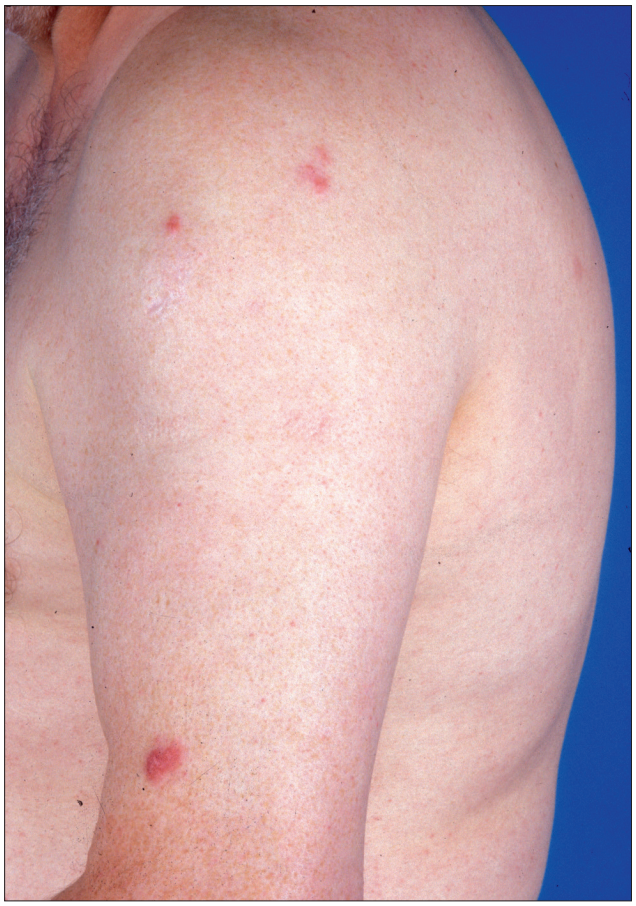


**FIGURE 1.** Primary cutaneous marginal zone B-cell lymphoma. Typical clinical presentation with multiple papules and plaques on left shoulder and arm.

## PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

Primary cutaneous marginal zone lymphoma (PCMZL) is an indolent lymphoma composed of small B-cells including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells and plasma cells. Because of overlap in clinicopathological features, differentiation between PCMZL and cutaneous pseudo-B-cell lymphoma (cutaneous lymphoid hyperplasia) can be difficult. Demonstration of monotypic plasma cells expressing either kappa or lambda light chains by immunohistochemistry or *in situ* hybridization on paraffin sections is generally used as a decisive criterion for PCMZL.[1] However, the observation that both PCMZL and cutaneous pseudo-B-cell lymphoma may develop from chronic antigenic stimulation by intradermally applied antigens (e.g. tattoo pigments, tick bites and antigen injections), suggests that they represent a continuous spectrum of cutaneous B-cell proliferations.[5] These observations have also resulted in discussions whether PCMZL, or at least a major subset of PCMZL, should be considered as an overt malignant lymphoma.[6]

### CLINICAL FEATURES

PCMZL particularly affects young adults and presents with solitary or more commonly multifocal red to violaceous papules, plaques or nodules localized preferentially on the trunk and arms (*Figure 1*). Cutaneous relapses are common, in particular in patients presenting with multifocal skin lesions, but dissemination to extracutaneous sites is rarely observed (*Table 1*).[7,8] Bone marrow involvement is exceedingly rare and a bone marrow biopsy is therefore not required unless indicated by other staging procedures.[2,9] An association with *B. burgdorferi infection* has been reported in a minority of European cases of PCMZL, but not in Asian cases or cases from the United States.[10] In endemic regions Borrelia serology and if positive Borrelia PCR on skin lesions is therefore advised.

### HISTOPATHOLOGY

These lymphomas show patchy, nodular or diffuse infiltrates composed of small lymphocytes, marginal zone cells, lymphoplasmacytoid cells and plasma cells and many reactive T-cells. Reactive germinal centres are frequently observed. Monotypic plasma cells are often located at the periphery of the infiltrates and in the superficial dermis beneath the epidermis.[1] Recent studies suggest the existence of two types of PCMZL.[11] Unlike most other MALT lymphomas, the clear majority of PCMZL express class-switched immunoglobulins including IgG, IgA and IgE, and do not express the chemokine receptor CXCR3, which has been suggested to play a role in the homing of the malignant B-cells to mucosa-associated malignant tissue. These cases show a predominance of T-cells and only a small proportion of neoplastic B-cells. A small subset of (P)CMZL shows a diffuse proliferation or large nodules of neoplastic B-cells, which express IgM and often CXCR3. These cases contain a much lower number of admixed T-cells and more likely have extracutaneous disease.[11]

### GENETIC FEATURES

Clonal rearrangements of the immunoglobulin heavy chain (IgH) are found in most cases. The presence of the t(14;18)(q32;q21) involving the *IGH* gene on chromosome 14 and the *MLT* gene on chromosome 18, and the t(3;14)(p14.1;q32) involving *IGH* and *FOXP1* genes, has been reported in a proportion of PCMZLs.[12] However, other translocations observed in MALT lymphomas at other sites, such as t(11;18)(q21;q21) and t(1;14)(p22;q32) are not or rare in PCMZL.

### THERAPY

Following EORTC/ISCL consensus recommendations patients with a solitary tumour can be treated with radiotherapy or

**TABLE 1.** Clinical characteristics of the main three types of primary cutaneous B-cell lymphomas.

| | PCMZL | PCFCL | PCDLBCL, LT |
|---|---|---|---|
| Age group | (young) adults | Middle-aged adults | Elderly |
| Male/female ratio | 3:2 | 3:2 | 1:2 |
| Clinical presentation | Solitary or multifocal papules, plaques or nodules mainly on the trunk and arms | Solitary or localized plaques or tumours on the head (scalp) or trunk. Multifocal lesions in rare cases. | Skin tumours on the (lower) leg(s). Uncommonly, lesions at other sites than the leg (15%) |
| First choice treatment | Solitary: radiotherapy; excision<br>Multifocal: wait and see; intralesional steroids, interferon alpha or rituximab; low-dose RT | Localized: radiotherapy<br>Multifocal: wait and see; rituximab i.v. | R-CHOP |
| Cutaneous relapse | 50% | 30% | 65% |
| Nodal/visceral dissemination | 5% (1) | 10% | 35% |
| 5-year DSS | 99% | 95% | 50% (→ 70%) (2) |
| 5-year OS | 94% | 87% | 36% |

(1) in particular non-class-switched (IgM positive) cases.
(2) better survival in patients treated with R-CHOP.

surgical excision.[13] In patients with associated *B. burgdorferi* infection systemic antibiotics should be tried first, before more aggressive therapies are employed. For patients presenting with multifocal skin lesions or patients with relapsing disease, a wait and see strategy can be followed. Symptomatic lesions can be treated with topical or intralesional steroids, intralesional interferon alpha or rituximab or low-dose radiotherapy (4 Gy). Systemic multi-agent chemotherapy is rarely needed and should be reserved for rare patients developing extracutaneous disease.

### CLINICAL COURSE AND PROGNOSIS

PCMZL have an indolent clinical course. The prognosis is excellent with a 5-year-disease-specific survival rate close to 100%.[7,8]

## PRIMARY CUTANEOUS FOLLICLE CENTRE LYMPHOMA

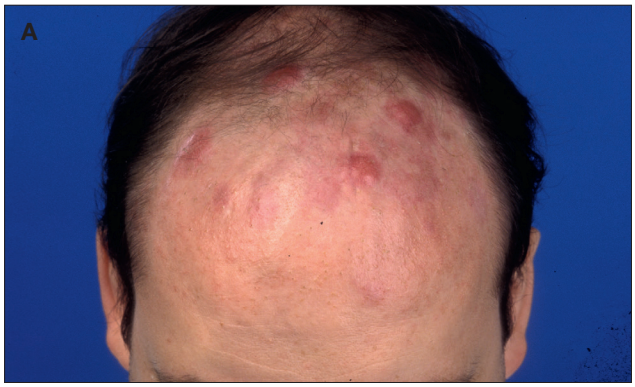
Primary cutaneous follicle centre lymphoma (PCFCL) is a tumour of neoplastic follicle centre cells, with a predominance of large centrocytes (large cleaved cells), which generally present on the head or trunk.[1,3,4] Lymphomas with a diffuse growth pattern and a monotonous proliferation of centroblasts and immunoblasts are, irrespective of site, excluded and are classified as PCDLBCL, LT.

### CLINICAL FEATURES

PCFCL most commonly affects middle-aged adults with a slight male predominance. They show a characteristic clinical presentation with solitary or grouped plaques and tumours, preferentially located on the scalp or forehead or on the trunk, and uncommonly on the legs (*Figure 2, Table 1*).[7,14] Presentation with multifocal skin lesions is observed in approximately 15% of patients, but is not associated with a more unfavourable prognosis. Dissemination to extracutaneous sites is uncommon.

### HISTOPATHOLOGY

PCFCL show nodular or diffuse infiltrates, which may show a follicular, a follicular and diffuse or diffuse growth pattern.



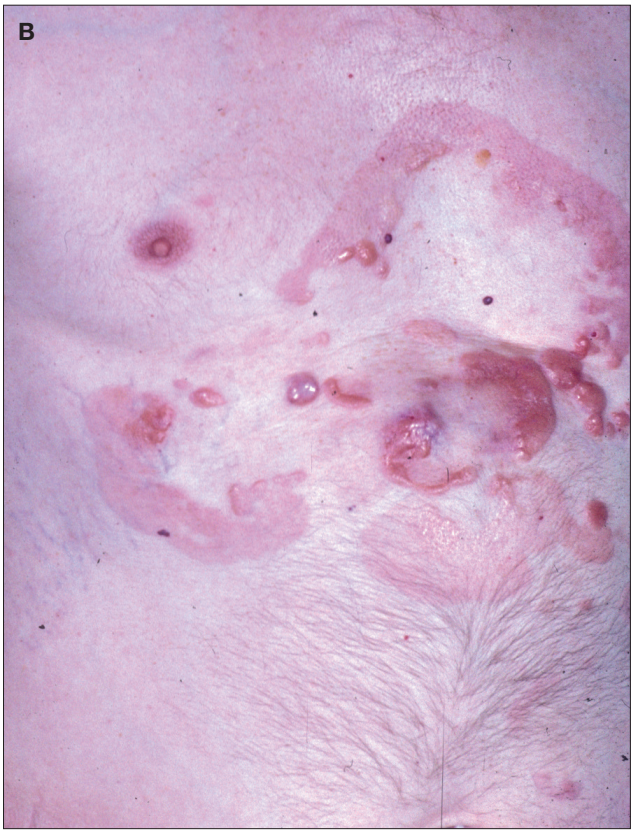




**FIGURE 2 A+B.** Primary cutaneous follicle centre lymphoma. Characteristic clinical presentation with localised skin lesions **(A)** on the scalp and **(B)** on the chest.

Cases with a diffuse growth pattern are characterized by a proliferation of medium-sized to large centrocytes and variable numbers of admixed centroblasts. These cases, previously often classified as diffuse large B-cell lymphoma, should be differentiated from PCDLBCL, LT. Clinical, histological, immunophenotypical and genetic differences between both conditions are summarized in *Table 2* and mostly suffice to make a correct diagnosis. The neoplastic cells express the B-cell-associated antigens CD20 and CD79a, but are usually Ig negative. PCFCL consistently express BCL6, while CD10 is particularly positive in cases with a follicular growth pattern.[7] Unlike nodal and secondary cutaneous follicular lymphomas, most PCFCL do not express BCL2 protein or show faint BCL2 staining in a minority of neoplastic B-cells.[7,15] Strong and diffuse expression of both BCL6, BCL2 and CD10 may be observed in a minority of PCFCL, but should always raise suspicion of a systemic lymphoma involving the skin secondarily.

## GENETIC FEATURES

Clonally rearranged immunoglobulin genes are present in most cases. PCFCL do not or rarely show the interchromosomal (14;18) translocation, which is characteristically found in most nodal follicular lymphomas.[16] Gene expression studies demonstrated that PCFCL have a gene expression profile of germinal centre B-cell (GCB)-type DLBCL.[17] Genotypic studies found *c-REL* amplifications (63% of cases), deletion of 14q32.[33] containing the *IgH* gene locus (68% of cases), which may account for the lack of surface Ig in cases of PCFCL, and aberrant somatic hypermutation of certain protooncogenes.[18,19] In contrast to PCDLBCL, LT, *MYD88* L265P mutation is absent and inactivation of *CDKN2a* and *CDKN2B* gene loci on chromosome 9p21.3 by deletion or promotor hypermethylation is not or rarely found in PCFCL.[18,20]

## THERAPY

In patients with localised skin lesions, radiotherapy is the preferred mode of treatment.[13] Recent studies suggest that a dose of 24 Gy is sufficient.[21] Small solitary lesions can be treated with surgical excision. Cutaneous relapses do not indicate progressive disease and can be treated with radiotherapy as well. For relapses, a palliative dose of 4 Gy can be used, which will result in effective local control in 90% of cases.[22] In patients with few scattered lesions both low-dose radiotherapy as well as a wait and see policy with treatment of only symptomatic lesions, similar as recommended in PCMZL, can be considered. Systemic, or intralesional administration of rituximab is a safe and effective treatment for patients with generalized skin lesions, but cutaneous relapses are frequently observed.[23,24] Multi-agent chemotherapy (R-CHOP) should be reserved for patients developing extracutaneous disease and only for exceptional patients with generalized skin lesions not responding to other treatment modalities. Patients with a PCFCL presenting on the leg(s) have a similar prognosis as patients with PCDLBCL, LT and should be treated likewise.[7,15]

## CLINICAL COURSE AND PROGNOSIS

PCFCL have an indolent clinical course. Cutaneous relapses after initial treatment occur in approximately 30% of patients, while extracutaneous dissemination is reported in ca. 10%.

**TABLE 2.** Clinical, histological, phenotypical and genetic differences between PCFCL (diffuse type) and PCDLBCL, leg type.

| | PCFCL, diffuse type | PCDLBCL, LEG TYPE |
|---|---|---|
| Clinical presentation | Localized skin lesions on head or trunk | Skin tumours on (lower) leg(s) |
| **Histopathology** | | |
| Morphology tumour cells | Predominance of large centrocytes (large cleaved cells) | Predominance of centroblasts and/or immunoblasts (large non-cleaved cells) |
| Admixed T-cells | Often abundant | Sparse, mainly perivascular. |
| **Immunohistochemistry** | | |
| B-cell lineage markers | CD20+, CD79a+, PAX5+, IgM- | CD20+, CD79a+, PAX5+, IgM+ |
| Germinal center markers | BCL6+, BCL2-, CD10- | BCL6+/-, BCL2+, CD10- |
| Post-germinal center markers | MUM1-, FOXP1- | MUM1+, FOXP1+ |
| MYC expression | negative | positive |
| **Molecular genetics** | | |
| Gene expression profile | GCB-type DLBCL | ABC-type DLBCL |
| Translocations *BCL6, MYC, IgH* | Absent | *BCL6* (30%), *MYC* (30%), *IgH* (50%) |
| Copy number variations (Array-based CGH; FISH) | amplification 2p16.1 region, del(14q11.2-q12) | Del(6q) (*BLIMP1*;60%) del(9p21.3) (*CDKN2A*; 67%) |
| NF-kB pathway mutations | not available | *MYD88* (60%), *CD79B* (20%), *CARD11* (10%), *TNFAIP3/A20* (40%) |

Irrespective of the growth pattern (follicular, follicular and diffuse or diffuse), the number of blast cells, the presence or absence of BCL2 expression or t(14;18), or the presence of either localised or generalised skin lesions these PCFCL have an excellent prognosis with a 5-year-disease-specific survival of 95%. Rare cases of PCFCL presenting on the leg are reported to have a more unfavourable prognosis, similar to that of patients with PCLBCL, LT.

## PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

PCDLBCL with a predominance or confluent sheets of centroblasts and immunoblasts, characteristically presenting with skin lesions on the (lower) legs. Uncommonly, skin lesions with a similar morphology and phenotype can arise at sites other than the legs.

### CLINICAL FEATURES

PCDLBCL, LT predominantly affect elderly patients, particularly females.[7,15] Patients present with generally rapidly growing red or bluish-red tumours on one or both (lower) legs, or in approximately 15-20% at sites other than the legs (*Figure 3*). In contrast to PCFCL, these lymphomas more often disseminate to extracutaneous sites and have a more unfavourable prognosis (*Table 1*).[1,7,14,15]

### HISTOPATHOLOGY

These lymphomas show diffuse non-epidermotropic infiltrates, which contain a monotonous population or confluent sheets of large cells with round nuclei and prominent nucleoli, generally a mixed population of centroblasts and immunoblasts. Mitotic figures are frequently observed. Reactive T cells are relatively few and often confined to perivascular areas.

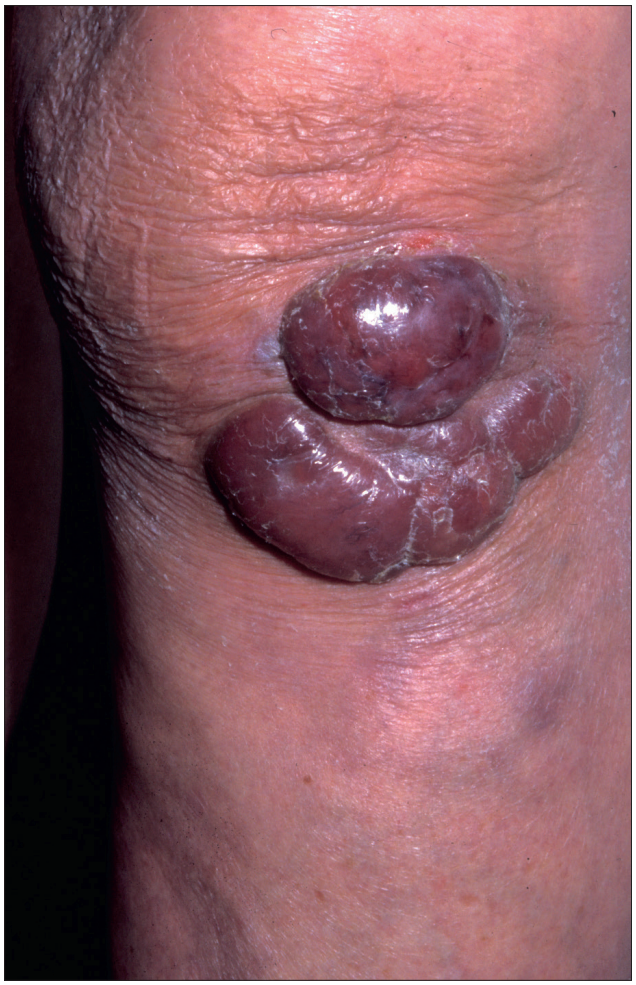


**FIGURE 3.** Primary cutaneous diffuse large B-cell lymphoma, leg type. Clinical presentation with large tumours on the right lower leg.

The neoplastic cells express B-cell-associated antigens CD20 and CD79a, and unlike PCFCL are strongly positive for BCL2, MUM1, FOXP1, MYC and cytoplasmic IgM.[7,15,25] BCL6 is expressed by most cases, whereas CD10 staining is generally absent. Ki-67 stains generally more than 75% of the neoplastic cells.

### GENETIC FEATURES

Genetic studies showed marked differences between PCLBCL, LT and PCFCL, diffuse type (*Table 2*). In line with their immunophenotypic profiles, PCLBCL, LT have a gene expression profile of ABC-type and PCFCL that of GCB-type DLBCL.[17] Translocations involving *BCL6, MYC* and *IGH* have been found in PCLBCL, LT, but not in PCFCL.[26] Studies on copy number alterations described high level amplifications of the *BCL2* gene in 67% of cases, which may well explain the strong BCL2 expression in PCLBCL, LT, particularly because the t(14;18) is not found in these lymphomas.[18] Loss of *CDKN2A* either by gene deletion or promoter methylation has been reported in up to 67% of PCLBCL, LT and correlates with an adverse prognosis.[27] Recent studies reported $MYD88^{L265P}$ mutations (60%), and mutations in different components of the B-cell receptor signalling pathway, including *CARD11* (10%), *CD79B* (20%) and *TNFAIP3/A20* (40%), that all strongly suggest constitutive NF-kB activation in PCLBCL, LT.(26;28) The similarities in gene expression profile, and cytogenetic alterations, including translocations and NF-kB activating mutations, underscore that PCLBCL, LT may be considered as a cutaneous counterpart of ABC-type DLBCL.[26,28]

### THERAPY

PCDLBCL, LT should preferentially be treated with R-CHOP, with or without in-field radiotherapy in patients with solitary or localized disease.[13] Recent studies report complete responses in more than 80% of patients, but relapses are common.[29] In patients ineligible for multi-agent chemotherapy because of advanced age and/or multiple comorbidities, local radiotherapy can be considered as an alternative first treatment. Cutaneous relapses are often also treated with local radiotherapy. Novel drugs targeting different components of the NF-kB pathway are currently under investigation.

### CLINICAL COURSE AND PROGNOSIS

PCDLBCL, LT have a much more aggressive clinical behaviour and a worse prognosis than PCFCL and PCMZL. Previous studies reported a disease-specific 5-year survival of approximately 50%. More recent studies reported a significantly better clinical outcome for patients treated with a combination of multi-agent chemotherapy (CHOP or CHOP-like) and rituximab than patients treated with multi-agent chemotherapy regimens alone.[29,30] The presence of multiple skin lesions at diagnosis, inactivation of *CDKN2A* either by deletion or hypermethylation and the presence of MYD88 L265P mutation have been reported to be associated with an inferior prognosis.[7,27,31]

## INTRAVASCULAR LARGE B-CELL LYMPHOMA

Intravascular large B-cell lymphoma is a well-defined subtype of large B-cell lymphoma, defined by an accumulation of large neoplastic B-cells within blood vessels. These lymphomas preferentially affect the central nervous system, lungs and skin and are generally associated with a poor prognosis.[32] Patients often have widely disseminated disease, but cases with only skin involvement may occur. Clinically, intravascular large B-cell lymphoma may present with violaceous patches and plaques or teleangiectatic skin lesions usually

on the (lower) legs or the trunk (*Figure 4*). Patients presenting with only skin lesions appear to have a significantly better survival than patients with other clinical presentations (3-year overall survival 56% versus 22%).[32] Multi-agent chemotherapy in combination with rituximab is the preferred mode of treatment, also in patients presenting with skin-limited disease.

## B-LYMPHOBLASTIC LYMPHOMA

B-LBL particularly affects children and young adults and often involves extracutaneous sites, most frequently the skin. Characteristically, patients present with a solitary tumour in the head and neck region, which can be the only manifestation of the disease.[33] Histologically, they show a diffuse monotonous infiltrate of medium-sized blast cells with often round nuclei, which usually express CD79a, PAX5, CD10 and TdT, while CD20 expression may be weak or absent. Patients should be treated with aggressive multi-agent chemotherapy analogous to that designed for B-acute lymphoblastic leukaemia, even when presenting with a solitary skin tumour. Following this approach, the prognosis is often good.[34]

## CUTANEOUS IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

Apart from post-transplant and HIV-associated lymphoproliferative disorders, the WHO 2008 classification and the revised WHO 2016 classification contain a group of iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD), which develop in patients using methotrexate (MTX) or other immunosuppressive drugs.[3,4] MTX-associated LPD can present in the skin, sometimes as the only manifestation of the disease. Most cases show the histologic features of a DLBCL and an association with EBV has been reported in 30-40% of cases. In contrast to PCFCL and PCDLBCL, LT they often present with generalized and/or ulcerating skin lesions.[35] Differentiating these MTX-associated DLBCL from PCLBCL, LT is important, as they may regress after discontinuation of MTX therapy and have a much better prognosis.[36] Therefore, in such cases the effect of cessation of MTX should first be awaited before more aggressive therapies are considered. In a recent study a 5-year disease-specific survival of 90% was reported in cases first presenting in the skin.[35] There is considerable overlap between EBV+ MTX-associated B-cell LPD and EBV+ mucocutaneous ulcer, which is a recently described EBV-positive B-cell LPD, which presents with sharply demarcated oropharyngeal or cutaneous ulcers.[37] They may develop in the setting of drug-related (MTX, cyclosporine, azathioprine) or age-related immunosuppression, may regress either spontaneously or after withdrawal of the immunosuppressive drug and have an excellent prognosis. The exact classification of these different EBV-positive LPD is a matter of debate.[6]

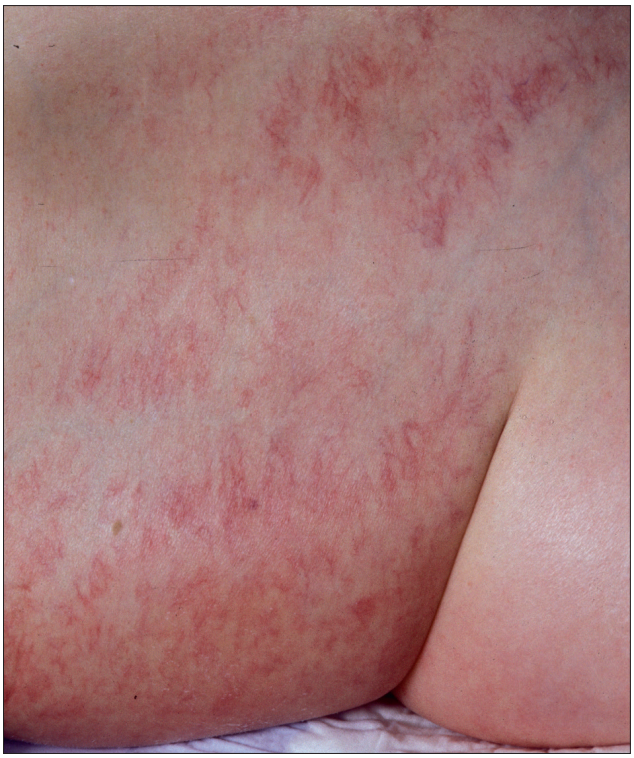


**FIGURE 4.** Intravascular large B-cell lymphoma. Clinical presentation with teleangiectatic lesions on the trunk and legs.

## CONCLUSION

PCMZL, PCFCL and PCLBCL, leg type are the most common types of CBCL. It should be recognized that PCMZL and PCFCL are indolent diseases, which should be treated with radiotherapy or other non-aggressive therapies. Multi-agent chemotherapy should be reserved for patients developing extracutaneous disease and only for exceptional patients with generalized skin lesions not responding to other treatment modalities. PCDLBCL, LT should preferentially be treated as other diffuse large B-cell lymphomas with R-CHOP.

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## KEY MESSAGES FOR CLINICAL PRACTICE

1 **A definite diagnosis of primary CBCL can only be made if extracutaneous disease has been ruled out by adequate staging procedures.**

2 **The localization of the presenting skin lesions in CBCL provides important diagnostic information. PCFCL preferentially present with localized skin lesions on the head (mainly the scalp) or trunk, PCMZL on the trunk and/or arms, and PCDLBCL, leg type on the (lower) legs.**

3 **Radiotherapy is the first choice of treatment in primary cutaneous follicle center lymphoma, also in cases with a diffuse proliferation of large centrocytes previously classified as diffuse large B-cell lymphoma.**

4 **The similarities in immunophenotype, gene expression profile, and cytogenetic alterations, including translocations and NF-kB activating mutations, suggest that PCDLBCL, LT should be considered as a cutaneous counterpart of ABC-type DLBCL.**

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