Clinician's perspective on the diagnosis of primary cutaneous B-cell lymphoma

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Abstract

Of all cutaneous lymphomas, 25% are primary cutaneous B-cell lymphomas (PCBCLs). Of these, primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone B-cell lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) are the most common subtypes. For the diagnosis of PCBCLs, a biopsy combined with immunohistochemistry and histological examination is the gold standard. PCBCLs are categorized into indolent or intermediate to aggressive subtypes based on their clinical behavior in a clinically oriented approach. PCDLBCL-LT has an aggressive course that spreads to extracutaneous sites in about 45% of cases, whereas PCFCL and PCMZL are indolent diseases. As a result, instrumental staging is advised for PCDLBCL-LT but not for extracutaneous disease after a diagnosis of PCMZL or PCFCL. Lastly, dermatoscopy may offer a novel diagnostic tool to improve the clinical recognition of various PCBCL subtypes when used in conjunction with a strong clinical suspicion.

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Primary cutaneous B-cell lymphoma

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of non-Hodgkin lymphomas that primarily involve the skin, with no evidence of extracutaneous involvement at diagnosis. They are rare neoplasms that account for approximately 5% of all cases of non-Hodgkin lymphomas, with an incidence of 10 cases per million inhabitants per year.[1] According to the 2018 World Health Organization (WHO)-European Organization for Research and Treatment of Cancer classification, PCLs are classified into two major subtypes based on the cell of origin: B-cell and T-cell lymphomas.[2] Primary cutaneous B-cell lymphomas (PCBCL) are less frequent and account for approximately 25% of all cutaneous lymphomas. Within PCBCL, there are several distinct clinicopathologic entities, each with unique clinical features, immunophenotypic characteristics, and molecular traits.[3] The most common subtypes of PCBCL are primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT). A diagnosis of PCBCL, not otherwise specified, is made in the rare cases where the neoplasm cannot be attributed to any of the aforementioned subtypes.

PCBCLs have distinct clinical and biological characteristics compared to nodal non-Hodgkin lymphomas and are associated with a more indolent course.[2] However, the prognosis varies among the different subtypes of PCBCL: based on this, PCBCL subtypes are divided into neoplasms with indolent clinical behavior and those with intermediate clinical behavior. PCMZL, PCFCL, and provisional type EBV+ mucocutaneous ulcer (EBVMCU) are considered neoplasms with indolent clinical behavior, while PCDLBCL-LT and intravascular large B-cell lymphoma (IVLBCL) are neoplasms with an intermediate to aggressive clinical behavior (Table 1).[4,5]

Primary cutaneous B-cell lymphoma with indolent clinical behavior

PCFCL is a low-grade lymphoma of follicle center B-cells, with no nodal or systemic involvement at the time of diagnosis. PCFCL is the most frequent PCBCL and accounts for over 50% of cases. Patients are usually middle-aged adults of both sexes, with a slight predominance of males.[2,6] Typical lesions are represented by erythematous papules, plaques and tumors, usually distributed on the scalp, the forehead (Figure 1), and the trunk.[7] Lesions are typically asymptomatic and do not usually ulcerate. Most patients display more than one lesion, usually clustered in a delimited area; however, cases of multiple dispersed cutaneous lesions have also been reported.[6,8] Peculiar presentations of PCFCL on the head include isolated small papules or areas of diffuse erythema or alopecia[9]; also, rare cases of miliary or agminated small lesions, and granulomatous rosacea/rhinophyma-like lesions have been reported.[10,11] A peculiar presentation of PCFCL on the trunk is represented by what has been historically known as reticulohystiocytoma of the dorsum or Crosti's lymphoma.[12] It usually presents with clustered papules and/or plaques on the back; in several cases, small erythematous lesions may be observed far from the main tumor. It should be highlighted that cutaneous localization of nodal follicular lymphomas may be indistinguishable from primary cutaneous cases as they usually present with the same clinicopathologic features. Spontaneous regression of lesions may occur, and anetoderma may be observed in such cases, even if on rarer occasions if compared to PCMZL.[8]

The fourth edition of the WHO classification has categorized PCMZL within the broader category of extranodal marginal zone lymphoma.[13] PCMZL are low-grade lymphomas running an indolent course, with an excellent prognosis (the five-year survival rate is around 99%).[3] Typically, PCMZL presents during the fifth or sixth decade of life, although there have been reports of patients as young as 15 years old. Men are diagnosed with this condition roughly twice as frequently as women. The vast majority of cases of PCMZL occur in Caucasian individuals.[14,15] PCMZL typically presents with erythematous to violaceous papules, plaques, nodules, or tumors on the skin (Figure 2A). Ulceration is atypical, but peri-lesional annular or diffuse erythema may be present.[15] These lesions may be solitary or multifocal; in contrast to PCFCL, presentation with multifocal skin lesions is not uncommon. PCMZL

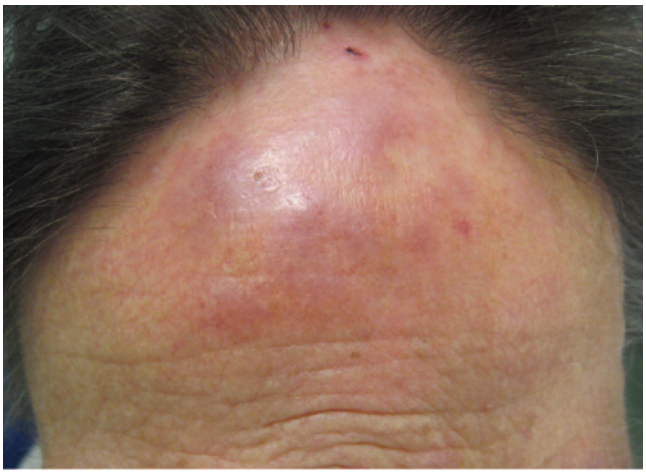

Figure 1. Primary cutaneous follicle center lymphoma. Clustered erythematous papules and plaques on the forehead.

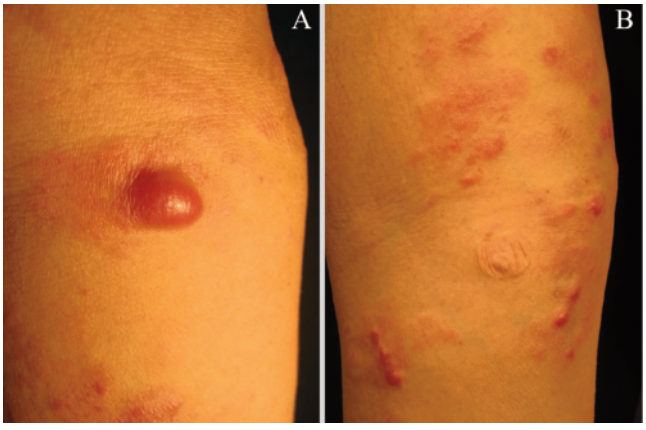

Figure 2. Primary cutaneous marginal zone lymphoma. Erythematous nodule showing perilesional erythema (**A**) and anetoderma developing after regression of the lesion (**B**).

Table 1. Classification of primary cutaneous B-cell lymphomas according to clinical behavior and skin presentation, following the World Health Organization-European Organization for Research and Treatment of Cancer classification and its 2018 revision.

PCBCL	Behavior	Cutaneous lesion	Preferential skin sites
PCFCL	Indolent	Solitary or clustered erythematous papules, plaques, or tumors Ulceration unusual	Scalp/forehead Trunk
PCMZL	Indolent	Solitary or multifocal erythematous-violaceous papules, plaques, nodules, or tumors Peri-lesional annular or diffuse erythema possible Ulceration rare	Trunk Upper extremities Head/neck
EBVMCU	Indolent	Isolated and well circumscribed ulcers	-
PCDLBCL-LT	Intermediate-aggressive	Red-bluish nodules	85-90% one or both legs 10-15% outside lower extremities
Primary cutaneous IVLBCL	Intermediate	Multiple erythematous to bluish macules a, with telangiectasi plaques, or nodules	41% thighs 35% legs 31% trunk

PCBCL, primary cutaneous B-cell lymphoma; PCFCL, primary cutaneous follicle center lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; EBVMCU, Epstein-Barr virus + mucocutaneous ulcer; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; IVLBCL, intravascular large B-cell lymphoma.

lesions are most commonly located on the trunk or upper extremities. Lesions can regress spontaneously, and anetoderma is a possible complication that may occur (Figure 2B).[14] PCMZL has a tendency to recur on the skin (relapses may occur in up to half of the cases), but it is highly unlikely for the condition to spread to extracutaneous sites.[15,16] The presence of B symptoms, abnormal blood counts, or elevated lactate dehydrogenase levels are signs that may indicate a systemic lymphoma, and further investigation is needed. There have been reports of PCMZL presenting as AL amyloidoma on the skin, in the absence of systemic amyloidosis.[17] An association between indolent types of PCBCL (both PCMZL and PCFCL) and infectious agents such as *Borrelia burgdorferi* has been postulated.[18] Studies suggest that in regions of North America and Europe where Borrelia infection is endemic (from southern Scandinavia to the northern Mediterranean countries of Italy, Spain, and Greece, as well as in areas stretching from the British Isles to central Russia and the northeastern and north-central United States), there may be a link between chronic inflammation caused by Borrelia infection and the development of the indolent type of PCBCLs.[19] On the other hand, studies evaluating the prevalence of Borrelia infection in non-endemic areas have not shown any association between the infection and PCBCL.[20] Therefore, serologic testing for Borrelia should only be performed in endemic countries.

EBVMCU constitutes a provisional type of B-cell lymphoma that is typical of elderly patients and usually associated with immunosuppression. Though the oropharyngeal location is the predominant site, EBVMCU may additionally involve the skin or the gastrointestinal system. Clinical lesions feature isolated and well-circumscribed ulcers that follow a generally favorable course undergoing spontaneous regression in many cases. This benign clinical presentation sets EBVMCU clearly apart from aggressive forms of EBV+ DLBCL and justifies a conservative approach to management.[21,22]

Primary cutaneous B-cell lymphoma with intermediate to aggressive clinical behavior

The behavior of PCDLBCL-LT differentiates this subtype from the previously discussed PCBCLs due to the tendency to an aggressive course spreading to extracutaneous sites in approximately 45% of cases. PCDLBCL-LT accounts for less than 20% of PCBCL and shows a clear predilection for elderly females, with a median age around 75 years and a 1:3 male:female ratio. Typical clinical presentation consists of rapidly growing erythematous or bluish nodular lesions on the legs (Figure 3); involvement may be unilateral or bilateral. While PCDLBCL-LT develops below the knee in 85-90% of patients, the remaining cases develop tumors in cutaneous sites other than the lower extremities: different skin locations of disease do not seem to affect prognosis. Finally, the increasing number of lesions at diagnosis is a risk factor for an adverse outcome.[2] The diagnosis of PCDLBCL-LT is established on the basis of a biopsy of lesional skin together with the exclusion of involvement beyond the cutaneous compartment. While spontaneous regression is an exceptional event that has been reported in the literature, an aggressive behavior is characteristic of this subtype with survival rates of 41% after 5 years which have improved to 66% following the routine use of rituximab in this setting.[23] Moreover, the burden of lesions has been shown to negatively affect prognosis: disease-specific survival rates were estimated at 75, 49, or 0% after 5 years with solitary, localized, or generalized cutaneous lesions, respectively.

Intravascular large-cell lymphoma features a disseminated proliferation of large lymphoid cells within the small blood vessels which are not associated with extravascular tumors or bloodstream involvement. It may involve any organ, but the skin is among the most frequently affected sites. This is a rare subtype and current knowledge is derived from small series and isolated cases: most patients are diagnosed in the sixth or seventh decade and both sexes are equally affected. The clinical presentation includes a broad spectrum of symptoms related to vascular occlusion. IVLBCL is a variant limited to the skin compartment which is mostly observed in Caucasian female subjects of younger age. Cutaneous examinations may highlight multiple erythematous to bluish macules with telangiectasia, plaques or nodules on the following body sites, in decreasing percentage: thigh, leg, trunk. These signs and their associated symptoms of pain mimic those of more common inflammatory skin disorders, such as erythema nodosum or phlebitis. Diagnosis is therefore challenging and may be achieved through deep skin biopsies which may be obtained on cutaneous lesions, senile hemangiomata, and apparently unaffected skin. Staging and management evaluations correspond to those of diffuse large B-cell lymphoma in cases of advanced disease, considering that involvement is within the blood vessels. Finally, exclusive involvement of the skin has been suggested to have a more favorable prognosis.[5]

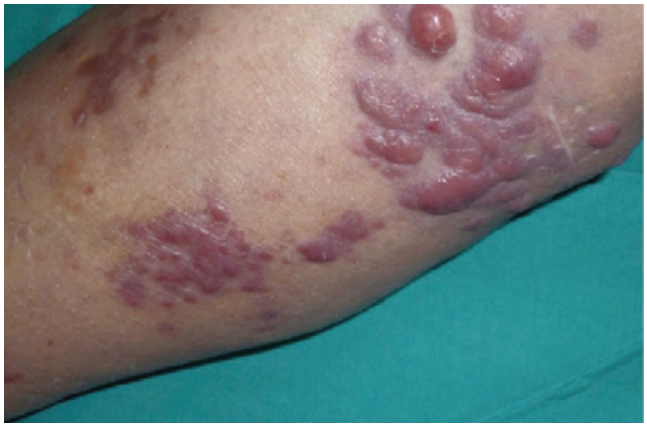

Figure 3. Primary cutaneous diffuse large B-cell lymphoma, leg type. Erythematous-violaceous nodules on the leg.

Clinician's perspectives

Currently, biopsy with histological examination and immunohistochemistry is the gold standard for the diagnosis of PCBCLs and should always be performed when there is clinical suspicion in this setting. To secure an adequate amount of tissue we recommend excisional biopsies or a punch of 6 mm diameter or more. Paraffin-embedded samples are studied for morphology and growth patterns and are also appropriate for performing immunohistochemistry. Fluorescence *in situ* hybridization and DNA sequencing techniques are not standard in the clinical setting and are reserved for investigative purposes. Instrumental staging for extracutaneous disease is negative in PCMZL and PCFCL, while additional evaluation including a PET/CT is recommended following a diagnosis of PCDLBCL-LT. Moreover, a bone marrow biopsy may be considered only in equivocal cases.

Finally, dermatoscopy may provide a novel diagnostic tool to enhance the clinical recognition of PCBCL when guided by a strong clinical suspicion. Recent studies highlighted that salmon-colored background and serpentine vessels are frequently seen in PCBCL lesions. However, dermatoscopic characteristics do not differ significantly by subtype and are characterized by limited specificity.[24] In a 2022 study, unfocused linear vessels with branches predicted PCMZL over other PCBCL subtypes.[25]

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