Primary cutaneous B cell lymphoma: clinical features, diagnosis and treatment

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Abstract:

Primary cutaneous B cell lymphoma (PCBCL) is defined as B cell lymphomas that present in the skin without any evidence of extracutaneous involvement at diagnosis. They are the second most common type of primary cutaneous lymphomas (PCL) accounting for 25-30 % [1-5]. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis is very important.

PCBCL is a heterogeneous group of disease consists of different B cell lymphomas with distinct treatment and prognosis. PCBCL are divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer (WHO – EORTC) classification. Primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are indolent forms and often confined to skin at presentation and during the course of the disease. But primary cutaneous diffuse large B cell lymphoma, leg type (PCLBCL-LT) and intravascular large B cell lymphoma (IVL) are more aggressive forms that may disseminate to extracutaneous tissues.

There is not a treatment consensus since they are rare entities. Local therapies like radiotherapy, surgery or intralesional steroids are options for localized disease in indolent forms. More disseminated disease may be treated with a systemic therapy like single agent rituximab. But combination chemotherapies used in systemic lymphomas are required for aggressive PCBCL. Although indolent forms have a relatively good prognosis, early relapses and disseminated diseases are mostly observed in aggressive form that creates a poor prognosis.

Key words: Primary cutaneous lymphomas, diagnosis, treatment, Bcell lymphoma

Core tip:

Primary cutaneous B cell lymphoma, is defined as lymphomas that present in the skin without evidence of extracutaneous involvement. Prognosis and treatment differ from systemic lymphomas involving the skin that makes differential diagnosis very important. It is heterogeneous group of disease that consists of indolent (primary cutaneous marginal zone lymphoma, primary cutaneous follicle center lymphoma) and aggressive forms (primary cutaneous diffuse large B cell lymphoma, leg type and intravascular large B cell lymphoma). The indolent forms are mostly confined to skin and have good prognosis. But aggressive forms are presented with disseminated disease and treated mostly with systemic combination chemotherapies.

Introduction:

Primary cutaneous lymphomas (PCL) are neoplastic proliferation of lymphocytes in the skin. They are the second most common extranodal non Hodgkin lymphomas. PCL is roughly divided into two main groups; primary cutaneous T cell lymphoma and primary cutaneous B cell lymphoma (PCBCL).

PCBCL is defined as B cell lymphomas that present in the skin without any evidence of extracutaneous involvement at diagnosis. They are the second most common type of PCL accounting for 25-30 % [1-5]. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis becomes crucial.

PCBCL is a heterogeneous group of disease consists of different B cell lymphomas with distinct treatment and prognosis. Their clinical presentation is relatively uniform mostly manifested by nodules (figure 1). The indolent forms, primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are often confined to skin during the course of the disease. Although all the body parts can be affected, specific distribution of the subtypes may provide information for differential diagnosis [6].

Classification:

PCBCL are divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer (WHO – EORTC) classification [2] (Table 1).

In WHO classification of tumors of hematopoietic and lymphoid tissues, primary cutaneous diffuse large B cell lymphoma, leg type (PCLBCL-LT) is classified under the heading of diffuse large B cell lymphoma not otherwise specified, NOS. PCFCL and intravascular large B cell lymphoma (IVL) are mentioned as specific entities. PCMZL can be classified under the heading of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [7].

Diagnosis and initial evaluation:

Throughout physical examination including the inspection of all the parts of the skin and history with attention on B symptoms (weight loss, fever, night sweats), laboratory tests including serum antibodies or polymerase chain reaction based analysis for bacterial etiologies are should be performed. An adequate biopsy of the lesion preferably excisional biopsy or a punch biopsy of at least 4 mm for routine histology and immunhistology is crucial for the diagnosis of CL (figure 2 and 3). Pathological lymph nodes should be biopsied for possible involvement. Bone marrow aspiration and biopsy (BMA/B) is optional for most of the PCBCL with indolent course but is required in more aggressive CL like PCLBCL-LT and IVL [6, 8 -10]. However, the differential diagnosis of early stage and rare variants of PCL from benign lymphoproliferative diseases is sometimes complicated. Molecular analysis using demonstration of the clonality of B cells provides an option [11]. Demonstration of monoclonal rearrangement of immunoglobulin by polymerase chain reaction (PCR) is a useful diagnostic tool when used in conjunction with data from the clinician and pathologist. Radiologic examinations (chest X - ray, ultrasonography, computed tomography (CT), and positron emission tomography combined with computed tomography (PET/CT)) are contributory tools to exclude skin involvement of a systemic lymphoma [6].

Staging:

TNM classification for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome was established by International Society for Cutaneous Lymphomas (ISCL) and Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) in 2007 (table 2). But this classification does not give much information about the prognosis and survival [8, 12].

Primary cutaneous marginal zone lymphoma:

PCMZL is an indolent B cell lymphoma characterized by infiltration of combined small B cells, marginal zone cells, lymphoplasmacytoid cells, and plasma cells [2]. According to WHO classification it is considered under the heading of extranodal marginal zone lymphoma of MALT lymphoma [7]. Cases formerly known as “immunocytoma” as well as “nonmyelomatous plasmacytomas” of skin are now included in this category. It makes up approximately 7% of all CL [12, 13]. It is mostly presented as red to violaceous nodules sometimes surrounded by an erythematous halo mainly on trunk and extremities although papules and plaques also have been reported [2,6]. Lesions may be solitary (51%), localized (26 %), or multifocal (23 %) [13]. It usually presents in the fifth or six decade and more common in men than women [13]. Extracutaneous involvement at the time of diagnosis and dissemination to extracutaneous sites are uncommon but recurrence in the skin is frequent [13]. Elevated lactate dehydrogenase, beta2 microglobulin levels, abnormal complete blood count values and B symptoms are uncommon and considered as clues for a systemic disease [13].

Although there is no clearly identified risk factor or hereditary tendency, association with infectious agents especially Borrelia burgdorferi and autoimmune diseases has been reported. Link between the PCBCL cases and Borrelia burgdorferi has been documented in some studies in Europe and healing of the lesion with antibiotic treatment is reported in some cases in the literature. However, this could not be confirmed with other studies especially in United States and Asia [14-21].

The diagnosis of the disease depends on histopathologic examination of the skin biopsy and exclusion of a systemic disease. Excisional biopsy is preferred but if an excisional biopsy is not appropriate, it can be substituted by a punch biopsy of an adequate length [9]. Morphologically, skin biopsy specimens are characterized by nodular to diffuse infiltrates with sparing of the epidermis [2, 21].

The differential diagnosis of PCMZL from reactive skin changes and other cutaneous lymphomas is important. Morphologic and immunphenotypic features and demonstration of clonality will aid for the differential diagnosis.

Treatment

Type of the treatment is dependent on the symptoms of the patient, stage of the disease and the number of the lesions. The treatment option includes antibiotics, rituximab, chemotherapy, intralesional interferon alfa, radiotherapy and excision.

Radiotherapy is a rational option especially for patients with solitary lesion or a few lesions that can be treated in one radiotherapy field [6, 22-25]. The margins of the radiation field should be clinically free of the disease [6]. Complete remission (CR) and 5 year disease specific survival (DSS) rates are more than %95 with local radiotherapy [6, 22, 24]. Even though approximately half of the patients experienced cutaneous relapses but extracutaneous relapses are very rare.

Surgery is used frequently in patients with local lesion. CR rate is nearly 100% but skin relapses are not so uncommon [6]. In an Italian study, CR and relapse rates were reported as 97.4 and 31.6% respectively. In the same study, 97.6 % of the PCMZL patients who achieved CR and 46.9 % of them relapsed after radiotherapy [24].

Topical steroids, triamcinolone, nitrogen mustard and cryotherapy are other local therapies with good responses [12, 25, 26]. Intralesional interferon treatment is another alternative strategy. In small case series of 8 patients, CR was 100% but two of them were relapsed and second CR was achieved with another cycle of IFN alpha. There is very limited data of intralesional [27] or systemic rituximab [28] treatment. 3 of 5 patients were achieved complete (1 patient) and partial (2 patients) responses [28]. Although the experience with rituximab is very limited it can be an alternative treatment option. Treatments with chemotherapy with single agent such as chlorambucil or combinations are also reported in the literature especially in multifocal diseases. The response rates are relatively good in these patients with. disseminated disease [6, 25]. In asymptomatic patients with disseminated disease a close follow up - wait and see strategy and treatment of only symptomatic lesions can also be performed.

A trial with an antibiotic treatment may be a rational option for B. *burgdoferi* positive patients before more aggressive therapies [6,25].

Primary cutaneous follicle center lymphoma (PCFCL):

It is a tumor of neoplastic follicle center cells, centrocytes and centroblasts which is the most common type of PCBCL accounts about two thirds of all cases [29]. It typically presents with solitary or multiple firm erythematous, painless, papules, plaques, or tumors in middle ages with a slight predominance in males. It has a predilection for the head, neck, and trunk. Multifocal presentation is a rare entity [2, 24, 30]. It is an indolent lymphoma with a very slow progression rate and long latent period [31]. Extracutaneous dissemination is a rare entity like PCMZL cases.

The diagnosis is based on the histological and immunhischemical examination of biopsy and ruling out the systemic disease. PCFCL shows nodular or diffuse infiltration of the dermis and subcutaneous tissue, sparing epidermis is almost a rule. Microscobically, typically large, often multilobulated centrocytes and large centroblasts with prominent nucleoli in variable numbers are shown [6]. Mainly there are 3 different growth patterns; follicular, follicular and diffuse (mixed) and diffuse.

The differential diagnosis from systemic lymphomas and reactive follicular hyperplasia is crucial since the treatment and prognosis are completely different. Strong expression of Bcl-2, Bcl-6, and CD10 and t(14,18) should raise the suspicion of systemic follicular lymphoma with skin involvement. Unlike the follicles seen in cutaneous follicular hyperplasia, the follicles in PCFCL are ill-defined, have a decreased mantle zone and lack tingible body macrophages.

According to ISCL/EORTC guidelines, bone marrow evaluation is optional for staging in PCFCL [11]. However, bone marrow involvement is demonstrated 11% of PCFCL patients presenting in the skin. Among them bone marrow involvement is the only extracutaneous site in 9 patients. Their prognosis is worse when compared with patients presenting only with skin involvement [34]. Although there is not a consensus, these results indicate that BMB/A should be considered to be integrated into staging system in PCFCL patients presenting with skin lesions [6, 34].

Treatment:

Surgery and radiotherapy are the first line treatment options for single or localized lesions. Multifocal lesions can be treated with many different modalities; radiotherapy, intralesional or local therapies. Close follow up and observation may also be an option in asymptomatic patients since it is a very slowly progressive disease.

In patients presenting with solitary or localized skin lesions, radiation therapy including clinically normal margins around the lesion is the preferred mode of treatment [9]. Although radiotherapy is mostly preferred in patients with solitary or localized disease, multifocal disease can also be treated with radiotherapy [35].PCFCL is highly sensitive to radiotherapy with a 99% CR rates and 100 % 5 year over all survival respectively [9, 36]. Solitary lesions that are small and well-demarcated can be treated with surgical excision but relapse rate is as high as 40 % after excision [9]. Other local treatment options with good results are topical or intralesional steroids, cryotherapy, intralesional interferon alpha [9, 25, 37].

In patients with very extensive skin lesions, systemic rituximab is the ﬁrst choice of treatment. Rituximab, systemic or intralesional, have been used in limited number of patients with PCFCL, in the literature. CR achieved in 10 /11 PCFCL patients treated with systemic rituximab and 3 patients relapsed after achieving CR [38]. Intralesional rituximab also have similar effectiveness that is confirmed only in small number of cases [9, 39].

Combination chemotherapy should be considered only in patients with progressive and disseminated disease or patients with large tumor burden who do not respond to other treatment modalities [9, 23, 25]. Almost one third of the patients relapsed after an initial treatment and most of the relapses occurred in the skin and can be treated with the initial treatment strategy. Dissemination to extracutaneous sites is uncommon [9]. Beside it is an indolent lymphoma lesions presenting in the leg has a worse prognosis and these lesions should be considered to be treated more aggressively [9].

Primary cutaneous large B cell lymphoma, leg type (PCLBCL –LT):

PCLBCL-LT is a PCBCL with predilection to legs that is histologically characterized by infiltration of centroblasts and immunoblasts. It is classically a disease of elderly patients in their seventies with a female predominance [7]. It is mostly presented on legs unilaterally or bilaterally but, less than one third of the patients may be presented at sites other than the leg [2, 6, 41, 42]. The prognosis is worse compared to other PCBCLs with higher relapse rates of extracutaneous dissemination. Rapidly growing red or red to bluish skin lesion especially on the lower leg are typical [2, 29, 41].

The differential diagnosis especially from PCFCL is important; PCFCL typically composed of centrocytes which don’t express bcl2 or MUM1 in contrast to PCLBCL - LT. The site of presentation is also different since PCFCL has a predilection to trunk and head.

In contrast to indolent cutaneous lymphomas, BMB/A should be examined before initiating the therapy to exclude a systemic involvement.

Treatment:

PCLBCL - LT is more aggressive disease with extracutaneous progression, lower remission and higher relapse rates [24, 42]. PCLBCL – LT that presenting on the leg with multiple lesions has worse prognosis than lesions on other sites or single lesions [43]. Local disease control methods like radiotherapy or topical treatment are not effective. 5 year overall survival and disease free survival was 67 and 33 % respectively, when treated with radiotherapy [36]. More than half of the patients relapse after RT [9]. Radiotherapy is an option as a palliative regimen especially in elderly patients who cannot be treated with systemic therapies [25, 6].

Single agent rituximab is a reasonable therapy for elderly who can’t tolerate combination chemotherapies. In a retrospective analysis of 60 PCLBCL – LT patients, all but one patient achieved CR (91.6 %) with a 2 year survival of 81 % [41] when treated with combination chemotherapies plus rituximab. 2 year survival rate was 59 % in group who were treated with other therapies and CR rate was 62%.

PCLBCL – LT should be treated antracyclin based combination chemotherapies like systemic diffuse large B cell lymphomas with or without rituximab. RT can be integrated to the systemic chemotherapies. RCHOP +/- rituximab should be considered as first line chemotherapy [2, 9, 42]. Since large randomized clinical trials are lacking, the efficacy of the treatment options are not well documented.

Primary cutaneous DLBCL others, are lymphomas rather than DLBCL-LT [2]. It is a rare entity including morphologic variants of diffuse large B-cell lymphoma, such as anaplastic or plasmoblastic subtypes or T-cell/histiocyte rich large B-cell lymphomas and [2] intravascular large B cell lymphoma cutaneous variant.

Intravascular large B cell lymphoma:

Intravascular large cell lymphoma (ILCL) is a rare subtype of large cell lymphoma that is characterized by the proliferation of lymphoma cells within the lumina of small blood vessels. They are presented mostly in elderly patients with a predilection to central nervous system and skin [2, 44-46]. It has poor prognosis.

Cutaneous variant of the disease is presented in younger female patients with nodules, plaques, or macules [46]. The clinical presentation is diverse with painful indurate erythematous eruption, poorly circumscribed plaques, large solitary plaques, painful blue-red palpable nodules, tumors, ulcerated nodules, small red palpable spots, and erythematous and desquamated plaques. Lesions may be single or multiple mostly seen in leg, thigh and trunk [46]. Pain and edema usually accompany the lesions. The differential diagnosis from inflammatory diseases and erythema nodosum is critical.

Patients are presented mostly with a disseminated disease even though there are also cases only confined to skin. The blood vessels are filled with neoplastic B cells that cause occlusion of the venules, capillaries and arterioles. Immunphenotypically, the neoplastic cells are mature B cells but rarely T cell phenotype can be seen [46]. B symptoms and bone marrow involvement are less common in cutaneous variant. Cutaneous variant has a better prognosis with a 3 year survival of 56% and better performance status [46]. Multiagent chemotherapies are the preferred therapies in these patients [9].

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Figure 1: Primary cutaneous B-cell lymphoma. Red–brown nodules scattered on the trunk

|  |
| --- |
| Primary cutaneous B cell Lymphoma |
| Primary cutaneous marginal zone B cell lymphoma |
| Primary cutaneous follicle center lymphoma |
| Primary cutaneous diffuse large B cell lymphoma, leg type |
| Primary cutaneous diffuse large B cell lymphoma, other |
| * Intravascular large B cell lymphoma
 |

Table 1: WHO – EORTC classification of primary cutaneous B cell lymphoma (2005)



Figure 2: Widespread lymphoid infiltration with clusters of mononuclear cells involving the dermis (H&E, ×10)

Figure 3: (a–c) Immunophenotype of lymphoid cells: Immunohistochemical staining shows expression of CD20 (a), CD10 (b), and Bcl-6 (c) (Original magnifications ×20)



|  |
| --- |
| T |
| T1:Solitaryskininvolvement T1a: a solitary lesion less than 5cm diameterT1b:a solitary lesion greater than 5cm diameter T2:Regional skin involvementT2a: all disease in a 15-cm-diameter circular area T2b: all disease in a 15 and 30 cm diameter circular area T2c: all disease in a 30-cm-diameter circular areaT3:Generalized skin involvement T3a: multiple lesions involving 2 noncontiguous body regions T3b: multiple lesions involving 3 or more body regions |
| N |
| N1:Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement N3:Involvement of central lymph nodes |
| M |
| M0: No evidence of extracutaneous disease (other than lymph node)M1:Extracutaneous disease is present (other than lymph node) |
|  |

Table 2: ISCL and EORTC TNM staging for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome