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MINIREVIEWS

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 presents in the skin without any evidence of extra-cutaneous involvement at diagnosis. They are the second most common type of primary cutaneous lymphomas accounting for 25%-30%. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis is very important. PCBCL is a heterogeneous group of disease comprising different B cell lymphomas with distinct treatment and prognosis. PCBCL is divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer classification. Primary cutaneous marginal zone lymphoma and primary cutaneous follicle center lymphoma 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 and intravascular large B cell lymphoma are more aggressive forms that may disseminate to extra-cutaneous 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. However combination chemotherapies which are used in systemic lymphomas are also required for aggressive PCBCL. Although indolent forms have relatively better prognosis, early relapses and disseminated diseases are mostly observed in aggressive form with a consequent poor prognosis.

Key words: Primary cutaneous lymphomas; Diagnosis; Treatment; Bcell lymphoma

Core tip: Primary cutaneous B cell lymphoma is a type of lymphoma that presents in the skin without evidence of extra-cutaneous involvement. Prognosis and treatment being different from systemic lymphomas involving the skin makes differential diagnosis very important. It is a heterogeneous group of diseases that consists of indolent (primary cutaneous marginal zone lymphoma, primary cutaneous follicle centre 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 the skin and have good prognosis whereas aggressive forms present with disseminated disease and are treated mostly with systemic combination chemotherapies.

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INTRODUCTION

Primary cutaneous lymphomas (PCL) are neoplastic proliferation of lymphocytes in the skin. They are the second most common extranodal non-Hodgkin lymphomas. PCL can be 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 extra-cutaneous 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 diseases consisting 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 the skin during the course of the disease. Although all 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 tumours 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 considered 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

Thorough physical examination including the inspection of all the parts of the skin and detailed history giving special attention to B symptoms (weight loss, fever, night sweats), laboratory tests including serum antibodies or polymerase chain reaction based analysis for bacterial aetiologies 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 immunohistology is crucial for the diagnosis of PCL (Figures 2 and 3). Pathological lymph nodes should be biopsied for possible involvement. Bone marrow aspiration and biopsy 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, differentiating early stage and rare variants of PCL from benign lymphoproliferative diseases can sometimes be complicated. Molecular analysis by demonstrating the clonality of B cells is 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. Flow cytometric immunophenotyping is also a feasible and reliable method for detecting clonality in PCBCLs and can provide additional prognostic and therapeutic information[12]. Radiologic examinations [chest X-ray, ultrasonography, computed tomography (CT), and positron emission tomography combined with CT (PET/CT)] are contributory tools to exclude skin involvement of a systemic lymphoma[6].

Table 1 World Health Organization and European Organization of Research and Treatment of Cancer classification of primary cutaneous B cell lymphoma (2005)

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

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). However this classification does not give much information about the prognosis and survival[8,13].

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

PCMZL is an indolent B cell lymphoma characterized by infiltration by a combination of small B cells, marginal zone cells, lymphoplasmacytoid cells, and plasma cells[2]. According to WHO classification it is listed under the heading of extranodal marginal zone lymphoma of MALT lymphoma[7]. Cases formerly known as "immunocytoma" as well as "non-myelomatous plasmacytomas" of skin are now included in this category. It makes up approximately 7% of all PCL[13,14]. It is mostly presented as red to violaceous nodules sometimes surrounded by an erythematous halo, mainly on the trunk and extremities although papules and plaques have also been reported[2,6]. Lesions may be solitary (51%), localized (26%), or multifocal (23%)[14]. It usually presents in the fifth or six decade and more common in men than women[14]. Extra-cutaneous involvement at the time of diagnosis and dissemination to extra-cutaneous sites

Table 2 International Society for Cutaneous Lymphomas and European organization of Research and treatment of cancer TNM classification staging for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome

T
T1: Solitary skin involvement
T1a: A solitary lesion less than 5 cm diameter
T1b: A solitary lesion greater than 5 cm diameter
T2: Regional skin involvement
T2a: 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 area
T3: 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 extra-cutaneous disease (other than lymph node)
M1: Extracutaneous disease is present (other than lymph node)

T: Tumor; N: Lymph node; M: Metastasis.

are uncommon but recurrence in the skin is frequent[14]. Elevated lactate dehydrogenase, beta-2-microglobulin levels, abnormal complete blood count values and B symptoms are uncommon and considered as clues for a systemic disease[14].

Although there is no clearly identified risk factor or hereditary tendency, associations with infectious agents, especially Borrelia burgdorferi, and autoimmune diseases have been reported. A link between the PCBCL and Borrelia burgdorferi has been documented in some studies in Europe and healing of the lesion with antibiotic treatment has been reported by some researchers. However, this could not be confirmed by other studies carried out especially in the United States and Asia[15-21].

The diagnosis of the disease can be established by 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 depict nodular to diffuse infiltrates with sparing of the epidermis[2,21].

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

Treatment

Treatment depends on the symptoms of the patient, stage of the disease and the number of the lesions. The treatment options include 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

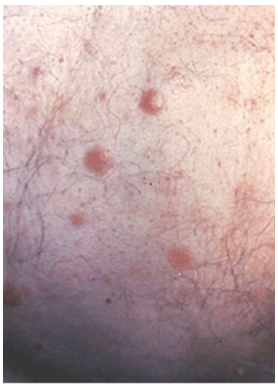

Figure 1 Primary cutaneous B-cell lymphoma. Red-brown nodules scattered on the trunk.

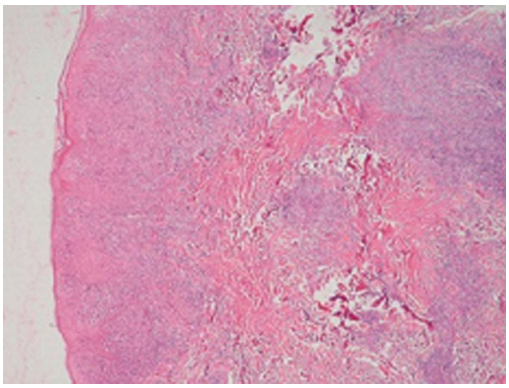

Figure 2 Widespread lymphoid infiltration with clusters of mononuclear cells involving the dermis (HE, × 10).

field should be clinically free of the disease[6]. With local radiotherapy, complete remission (CR) and 5 year disease specific survival (DSS) rates are over 95%[6,22,24]. Even though approximately half of the patients experience cutaneous relapses, extra-cutaneous 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 achieved CR and 46.9% of them had relapse after radiotherapy[24].

Topical steroids, triamcinolone, nitrogen mustard and cryotherapy are other local therapies with good responses[13,25,26]. Intralesional interferon treatment is another alternative strategy. In small case series of 8 patients, CR was 100% but two of them relapsed and second CR was achieved with another cycle of IFN-α[25,27]. There is very limited data on intralesional[28] or systemic rituximab[29] treatment. Three of 5 patients achieved complete (1 patient) and partial (2 patients) responses[29]. Although the experience with rituximab is very limited it can be an alternative treatment option.Treatments with chemotherapy with a single agent such as chlorambucil or combination of medications have also been reported in the literature, especially in multifocal diseases. The response rates are relatively good in patients with disseminated disease[6,25]. In asymptomatic patients with disseminated disease a close

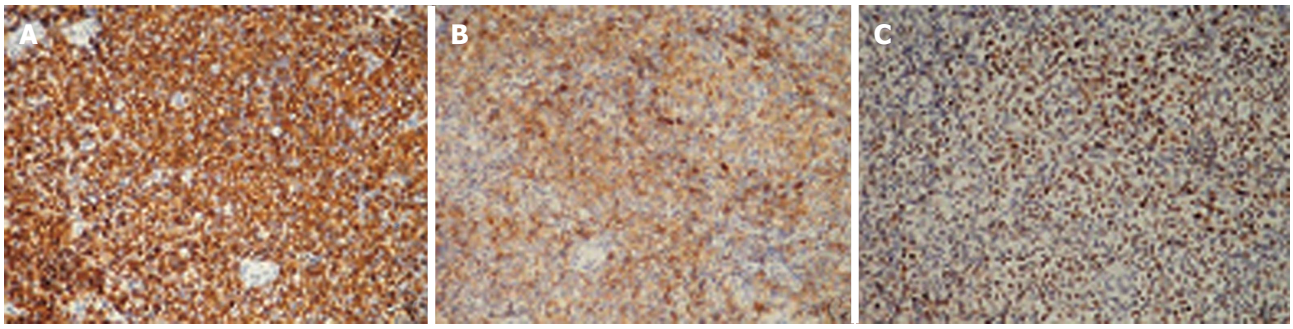

Figure 3 Immunophenotype of lymphoid cells: Immunohistochemical staining shows expression of CD20 (A), CD10 (B), and Bcl-6 (C) (Original magnifications × 20).

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 *Borrelia burgdoferi* positive patients before more aggressive therapies[6,25].

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

It is a tumour of neoplastic follicle centre cells, centrocytes and centroblasts. It is the most common type of PCBCL, accounting about two thirds of all cases[30]. It typically presents with solitary or multiple firm, erythematous, painless, papules, plaques, or tumours 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[2,24,31]. It is an indolent lymphoma with a very slow progression rate and long latent period[32]. Extra-cutaneous dissemination is a rare, just like PCMZL cases.

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

Differential diagnosis from systemic lymphomas and reactive follicular hyperplasia is critical 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[33]. 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[13]. However, bone marrow involvement is demonstrated in 11% of the patients with PCFCL presenting in the skin. Among them, bone marrow was the only extracutaneous involvement in 9 patients. Their prognosis is worse in comparison to patients presenting only with skin involvement[34]. Although there is not a consensus, these results indicate that BMB/A should be included in the 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 including 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 covering also the 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 rate and 100% 5 year over-all survival[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[9,27,37].

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 has been achieved in 10/11 PCFCL patients treated with systemic rituximab while 3 patients had relapse 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 tumour burden who do not respond to other treatment modalities[9,23,25]. Almost one third of the patients had relapse after an initial treatment and most of the relapses occurred in the skin and can be treated with the initial treatment strategy. Dissemination to extra-cutaneous sites is uncommon[9]. Even though it is an indolent lymphoma, lesions presenting in the leg

has poorer prognosis and these lesions should be treated more aggressively[9].

PRIMARY CUTANEOUS LARGE B CELL LYMPHOMA, LEG TYPE

Primary cutaneous large B cell lymphoma, leg type (PCLBCL-LT) is a PCBCL with predilection to legs that is histologically characterized by infiltration by centroblasts and immunoblasts. It is classically a disease of patients in their seventies with a female predominance[7]. It mostly occurs on legs unilaterally or bilaterally but, less than one third of the patients may present with lesions in an area other than the leg[2,6,40,41]. The prognosis is worse compared to other PCBCLs with higher relapse rates of extra-cutaneous dissemination. Rapidly growing red or red to bluish skin lesion especially on the lower leg is typical[2,30,40].

The differential diagnosis especially from PCFCL is important; PCFCL typically comprises 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.

Nearly all of the PCBCL-LT cases have at least one genetic alteration and half of them have combined several alterations. These mutations support lymphomagenesis with NF-κB activationand guide for targetted therapis[42].

Treatment

PCLBCL-LT is a more aggressive disease with extra-cutaneous progression, lower remission and higher relapse rates[24,41]. Multiple skin lesions, bcl-2 expression, are independent prognostic factors in these patients[43]. Patients who presents with multiple lesions on the leg has worse prognosis than lesions on other sites or single lesions[43]. Another factor with a high prevalence associated with poor prognosis in PCLBCL-LT patients is MYD88L265P mutation[44]. This mutation activates the nuclear factor-κB pathway and is associated with shorter survival rates. Patients harboring this mutation will be candidates for new targeted therapies in the future[44].

Local disease control methods like radiotherapy or topical treatment are not effective in PCLBCL -LT patients. Five year overall survival and disease free survival have been calculated as 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[6,25].

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%when treated with combination chemotherapies plus rituximab. Two year survival rate was 59% in the group of patients who were treated with other therapies and CR rate was 62%[41].

Similar to systemic diffuse large B cell lymphomas, PCLBCL-LT should be treated with antracyclin based combination chemotherapies with or without rituximab. RT can supplement systemic chemotherapies. RCHOP ± rituximab should be considered as first line chemo-therapy[2,9,41]. 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 more common in elderly patients, with a predilection to central nervous system and skin[2,45-47]. It has poor prognosis. The diagnosis is difficult because of divergent clinical presentation and absence of lymphadenopathy. Random skin biopsy is beneficial for early diagnosis in ILCL[48].

Cutaneous variant of the disease presents with nodules, plaques, or maculesin younger female patients[47]. The clinical presentation is diverse with painful, indurate, erythematous eruption, poorly circumscribed plaques, large solitary plaques, painful blue-red palpable nodules, tumours, ulcerated nodules, small red palpable spots, and erythematous and desquamated plaques. Lesions may be single or multiple, mostly on the leg, thigh and trunk[47]. Pain and oedema usually accompany the lesions. The differential diagnosis from inflammatory diseases and erythema nodosum is critical.

Patients mostly present with a disseminated disease even though there are also cases with lesions confined to the skin only. Blood vessels are filled with neoplastic B cells that cause occlusion of the venules, capillaries and arterioles. Immunophenotypically, the neoplastic cells are mature B cells but rarely T cell phenotype can be seen[47]. 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[47]. Multiagent chemotherapies are the preferred therapies in these patients[9].

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