

Primary cutaneous large B cell lymphoma, leg type: A case report and review of the literature

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Conflict of interest: none to declare

Received: 21 June 2012
Accepted: 20 December 2012

Primary cutaneous large B-cell lymphoma leg type is a rare and aggressive neoplasm as defined by the recently updated World Health Organization - European Organization for Research and Treatment of Cancer. We report a case of an 80-year-old man with multiple cutaneous lesions. Here, we review the available literature and summarize clinical features and management of this type of cutaneous B-cell lymphoma.

Keywords: B-cell lymphoma, cutaneous lymphoma, large cell lymphoma, peripheral neuropathy

Iran J Dermatol 2013; 16: 31-35

INTRODUCTION

Primary cutaneous diffuse large B-cell lymphomas are defined as malignant B-cell proliferations presenting with cutaneous involvement alone with no evidence of extracutaneous manifestation when complete staging has been performed ¹. They are rarer than T-cell lymphoma ². B-cell lymphomas comprise approximately 25% of all cutaneous lymphomas ³. The European Organization for Research and Treatment of Cancer (EORTC) – Cutaneous Lymphoma Project Group and the World Health Organization (WHO) recently proposed a new classification for primary cutaneous lymphomas. The four major types of cutaneous B-cell lymphoma (CBCL) included in this classification are the following: follicle center lymphoma,

marginal zone B-cell lymphoma, diffuse large B-cell lymphoma, leg type, and diffuse large B-cell lymphoma, other (the latter includes rare variants such as intravascular large B-cell lymphoma). Cutaneous diffuse large B-cell lymphomas are characterized by an aggressive clinical course and high mortality rate ¹. We report a case of primary cutaneous large B-cell lymphoma and present a brief review of the literature.

CASE REPORT

An 80-year-old man presented to the unit of neurology due to lower extremities pain and inability to stand up. He did not have a medical history or a family history of related diseases. He was a non-smoker and non-drinker. Incidentally,

it was found that the patient had developed cutaneous lesions; therefore, he was referred to the dermatology department. On cutaneous examination, there were erythematous and violaceous papules and nodules on the scalp, face, eyelids, lower extremities (thighs and legs), upper extremities, back and anterior part of the chest and abdomen (Figure 1-3). Retrospectively, we noticed an eruption on the trunk and extremities since 2 months ago. He presented with multiple subcutaneous erythematous nodules. He had no fever, night sweats, weight loss or other symptoms. These lesions varied in size. In some areas, the lesions were confluent and formed erythematous plaques. The largest lesion measured 2 cm in the longest diameter and was firm.

On neurological examination, mental status and cranial nerves function were normal. The motor force of the upper and lower extremities was 5/5 and 2/5, respectively. The upper extremity reflexes were (+), but they were absent in lower extremities. Sensory impairment as dyesthesia (painful paresthesia) was found in this patient. Cerebellar examination in the upper extremities was normal, but was unremarkable because of force decrease in the lower extremities. He could not walk and was paraplegic. There was no sphincteric or

autonomic impairment. No hepatosplenomegaly or lymphadenopathy was identified.

Laboratory investigations at the time of presentation, including complete blood counts, blood biochemistry, ESR, renal and hepatic parameters were within normal limits. There was no evidence of lymphadenopathy on computed tomography scans of the chest and abdomen. In addition, the results of ultrasound examination of the lymph nodes, pelvis and abdomen were all normal. In electromyogram and nerve conduction studies assessment, sensory-motor polyneuropathy was identified.

An incisional skin biopsy was performed over the abdomen. Sections showed skin tissue with neoplastic proliferation of large lymphocytes with perivascular and diffuse patterns in the upper and mid dermis with a thin grenz zone under



Figure 1. Erythematous and violaceous papules and nodules on the scalp



Figure 2. Erythematous and violaceous papules and nodules on the anterior part of the chest and abdomen



Figure 3. Erythematous and violaceous papules and nodules on the lower extremities.

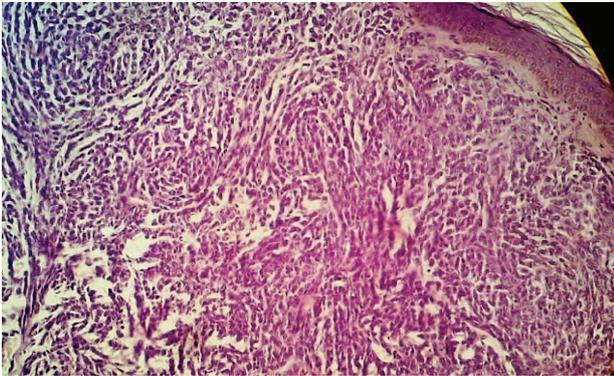


Figure 4. Neoplastic proliferation of large lymphocytes with perivascular and diffuse patterns in the upper and mid dermis with a thin grenz zone under the epidermis (H&E*40).

the epidermis. Extension of tumoral cells around adnexal structures and perineural areas and also subcutis fat were obvious, but the epidermis was intact (Figure 4). The neoplastic cells had large vesicular nuclei with prominent nucleoli, numerous mitoses and scant to moderate cytoplasm with a high nuclear:cytoplasmic (N:C) ratio. The organoid pattern of metastatic carcinoma was not seen. Melanin pigment or junctional activity was not seen. In immunohistochemistry staining LCA, CD20 and Bcl-2 were positive (Figure 5) but CD3 was negative.

DISCUSSION

In the 2001 WHO classification, both primary cutaneous large B cell lymphoma (PCLBCL) of the leg and primary cutaneous follicular center lymphoma (PCFCL) with a diffuse growth pattern were included in the general diffuse large B-cell lymphoma category. In the WHO-EORTC classification 2005, it was recognized that the PCLBCL presenting on the legs were a distinct disease entity. Since cases with similar morphology (predominance or cohesive sheets of centroblasts and immunoblasts), immunophenotype (strong expression of bcl-2 and Mum-1) and prognosis, may arise at other sites than the legs, in the WHO-EORTC classification, and subsequently in the 2008 WHO classification, the term PCLBCL, leg type was preferred for both lesions on the legs and similar lesions at other skin sites ⁴.

Primary cutaneous large B-cell lymphoma (PCLBCL), leg type comprises approximately 4 percent of all cutaneous lymphomas and 20 percent



Figure 5. Immunohistochemistry staining showed CD20 positive cells (*100)

of all primary cutaneous B-cell lymphomas ^{3,5}. It occurs almost exclusively in elderly patients, predominantly women. However, this is not a universal finding. As Hembury et al and Willemeze et al found a male predominance ⁶, we reported an elderly male patient.

There are no clearly defined risk factors for developing this disease and there is no identifiable hereditary tendency. Clinically, most patients present with solitary or clustered erythematous to red-brown nodules or tumors on one or both legs, preferentially the lower legs. 10-15% of lesions will develop outside the lower extremities ⁵. Ulceration is common. Small erythematous papules can be seen adjacent to larger nodules.

The diagnosis of PCLBCL, leg type requires a representative biopsy ⁴. Histopathologically, PCLBCL, leg type exhibits a dense monotonous dermal infiltrate of predominantly medium-sized to large cells with round (non-cleaved)

nuclei, prominent nucleoli, and frequent mitoses resembling centroblasts and/or immunoblasts obliterating the adnexa. Focal epidermotropism with Pautrier-like microabscesses may be seen⁷ and should be distinguished from cutaneous T-cell lymphoma (CTCL). Extension into the subcutis may be observed⁸.

The tumour cells are CD19⁺, CD20⁺, CD22⁺ and CD79a⁺ with monotypic expression of surface and/or cytoplasmic immunoglobulin in some cases^{3,9}. The tumour cells are usually strongly Bcl-2 positive^{9,11} and Bcl-6 is also expressed by most cases with evidence of Bcl-6 gene mutations. CD10 expression is only rarely detected in PCLBCL⁹. MUM-1 and FOXP1 are invariably expressed by tumour cells in PCLBCL in contrast to PCFCL¹⁰.

The prognosis of PCLBCL is poor, with a 5-year survival of 41-58%, but this is generally better than the prognosis of nodal diffuse large B cell lymphoma (DLBCL)^{3,11,12}. Although studies initially suggested that Bcl-2 expression was site-related (lower limbs and multifocal lesion are more frequently Bcl-2 positive) and associated with a worse prognosis¹¹, the prognostic significance of Bcl-2 expression has since been disputed¹³. Recent studies have shown that multifocal disease and location on the leg are associated with a worse prognosis in multivariate analysis^{3,10,12}.

In elderly patients with solitary tumours, radiotherapy may be appropriate but multi-agent chemotherapy is usually required, especially for multifocal disease. Patients with diffuse large B cell lymphoma, leg type (DLBCLLT) need more aggressive treatment modalities (e.g. systemic chemotherapy plus rituximab). The regimen used most frequently is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab. For patients with DLBCLLT, local radiotherapy or systemic chemotherapy plus rituximab are the standard therapy. However, in the setting of significant comorbidities, rituximab alone may be administered^{11,14}. Patients should be seen in an outpatient setting at least every 6 months for a clinical workup. They do not require any additional laboratory workup unless the regional lymph nodes are enlarged⁴.

Our case report demonstrates an unusual extra cutaneous manifestation of PCLBCL, i.e. neuropathy. In our patient, the mechanism of neuropathy was unclear. The likely cause was a paraneoplastic

phenomenon or direct lymphomatous invasion. Ho et al, reported a similar case of CLBCLLT in 2009 which presented initially as mononeuritis multiplex¹⁵. We believed that this patient was a case of PCLBCL and not a case of nodal lymphoma with metastatic skin disease, for several reasons. He had prominent skin manifestations, with progressive lesions starting initially on the leg. There were no systemic complaints and lymphadenopathy. Nodal lymphoma with metastatic skin disease would have presented as a late stage disease with extensive nodal involvement. In addition, there was no evidence of intravascular B-cell lymphoma on skin biopsy. We report a rare case of primary cutaneous large B-cell lymphoma presenting with neuropathy. This case highlights the importance of a full systemic and cutaneous examination in patients presenting with progressive painful neuropathy.

Although the pathogenesis of paraneoplastic neurologic syndrome is incompletely understood, immunologic factors are believed to be important because antibody and T-cell responses against nervous system antigens have been described in many of these disorders. The immunologic response is directed against shared antigens that are ectopically expressed by the tumor, but are otherwise exclusively expressed by the nervous system. There is evidence that some paraneoplastic neurologic syndromes without identifiable tumors may result from immune-mediated eradication of tumor cells. These syndromes may affect any part of the nervous system from the cerebral cortex to neuromuscular junctions and muscles.

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