

Diffuse Large B-Cell Lymphoma Mimicking Advanced Basal Cell Carcinoma

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Primary cutaneous B-cell lymphomas (PCBCLs) are made up of a heterogeneous group of B-cell lymphoproliferative diseases confined to the skin at the time of diagnosis with no evidence of extracutaneous involvement. With early diagnosis and adequate treatment, PCBCLs as a group has excellent prognosis, with about a 95% survival rate at five years. We report a case of diffuse large B-cell lymphoma (DLBCL) in a 52-year-old woman presenting as a fungating skin ulcer mimicking advanced basal cell carcinoma. Review of available literature showed most studies of PCBCLs being done on Europeans with no universally acceptable system of classification. Clinical findings, diagnostic evaluations and treatment outcomes of PCBCLs are discussed with emphasis on comparison of European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) Classification of Neoplasms of the Hematopoietic and Lymphoid Tissue classification systems.

Key words: dermatology ■ lymphoma ■ cancer

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INTRODUCTION

Primary cutaneous B-cell lymphomas (PCBCLs) are a heterogeneous group of non-Hodgkin's lymphomas confined to the skin. The skin is the second most common site affected in primary extranodal lymphoma and has a better prognosis than systemic B-cell lymphoma. They rarely metastasize to the internal organs. There is no universally acceptable method of treatment and classification. Diagnosis can be made with use of immunohistochemical staining and histological appearance. We report a case of diffuse large B-cell lymphoma (DLBCL) mimicking advanced basal cell carcinoma.

CASE REPORT

A 52-year-old female originally from Ukraine presented to our emergency room with a seven-month history of circumscribed, reddish ulcerations and nodules over the left scapular region with extension into the left axillary region. According to the patient, the lesion started as a small dark pigmented spot seven years prior to admission into our service and began to grow rapidly nine months ago. The lesion was slow growing, nontender and nonpruritic. There was no history of fever, weight loss or night sweats. A biopsy done two years earlier by her internist was said to be inconclusive for malignancy. She applied rubbing alcohol and various Russian herbs to the lesion with no improvement. Past medical history was noncontributory except that she lived close to the Chernobyl nuclear disaster of 1986.

Physical examination revealed a 15x15-cm ulcer over the serratus anterior muscle with elevated borders and another 6x6-cm ulcer in the left axilla. The ulcer had a central area of necrosis with malodorous greenish discharge (Figure 1). No evidence of peripheral lymphadenopathy was found. Routine laboratory tests such as hemogram, serum chemistry and chest x-ray were within normal limits. Culture of the wound grew *Proteus mirabilis*, which likely resulted from urine applied to the lesion. Computed tomography (CT) scans of the chest, abdomen and pelvis showed no evidence of lymphadenopathy or systemic involvement, and a nuclear bone scan failed to reveal any evidence of metastatic bone disease, thus ruling out extracutaneous involvement.

Biopsy of the ulcer showed dermis filled with sheets of large cells with vesicular nuclei and prominent nucleoli. Mitotic admixtures were numerous with areas of necrosis. The epidermis was free. Immunohistochemical stains favored the diagnosis of diffuse large B-cell lymphoma that stained positive for CD 20, CD 79a, CD 10 and Bcl-6.

Therapy was initiated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), and radiotherapy. After three cycles of chemotherapy, the lesion was completely healed with a linear scar and disappearance of the axillary nodules (Figure 2).

DISCUSSION

PCBCL is a rare group of lymphoproliferative disorders.¹ It is a distinct subclass of non-Hodgkins lymphoma that originates in the skin and comprises the second largest group of extranodal B-cell lymphomas (after gastrointestinal).² It is estimated to be about 20–25% of all cutaneous lymphomas.³ Extracutaneous dissemination is rare, with most disease having favorable prognosis, and it has been suggested in some literature that the patient must be free of extracutaneous disease for ≥ 6 months.³

Review of literature for PCBCL is a difficult task because of the controversies and nonunification in the classification and treatment of the disease. Two commonly used methods of classification are the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) Classification of Neoplasms of the Hematopoietic and Lymphoid Tissue. Others have argued for the use of Revised European-American Classification of Lymphoma Neoplasm (REAL).⁴ The WHO classification is an updated and expanded version of the REAL classification of lymphoproliferative disorders.⁵ The WHO classification includes virtually all cutaneous lymphomas and encompasses them within the broader classification of systemic lymphoproliferative malignancies.⁶ In the EORTC system, the conditions are classified with special considerations on clinical behavior, and it restricts inclusion of PCBCL to those lesions that have no evidence of extracutaneous disease for a minimum of six months. Such restriction does not exist in the WHO system and can indeed allow for inclusion of systemic lymphomas that present in the skin.⁷

In the EORTC classification, PCBCL is divided into three distinct groups: follicle center cell lymphoma, immunocytoma/marginal-zone lymphoma and diffuse large B-cell lymphoma of the leg (DLBCL-leg). The WHO system subdivides PCBCL into follicle center, lymphoma which is a distinct entity from the follicle center cell found in the EORTC system. Other subtypes in the WHO system are: extranodal marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) type, and DLBCL. Each system has advantages and disadvantages. The major disadvantage of the WHO classification is that the disease entities are not divided according to clinical behavior. Current available literatures showed that prognoses differ depending on the type of classification system used in the study. In a case series of clinical studies of PCBCL using both EORTC and WHO classification, Yap et al.² found that disease classified originally as follicle center cell using the EORTC system can be reclassified as DLBCL. The unifying point is that both follicle center cell and DLBCL are indolent with five-year survival of almost 100%; however, it should be pointed out that outside of the skin, DLBCL is considered a very aggressive disease. It is important to know that DLBCL-leg found in the EORTC system is a rapidly growing tumor with poor prognosis. They favored use of WHO classification in future large series study because they believe it would result in better outcome for DLBCL than those of previous studies that used EORTC. It was also noted that small studies that have used the REAL classification, which is a predecessor of the WHO classification, have shown better outcomes for patients with DLBCL. To further support use of the WHO classification, Gronbaek et al.⁸ found in their study using REAL that PCBCL is distinct from follicle center cell lymphoma and more closely related to marginal zone/MALT-type lymphoma. In a study of PCBCL in 28 Japanese patients using REAL, Liu et al.¹ found that DLBCL made up 89% of cases, with an overall five-year survival rate of 61%. In a different study of Japanese patients, Tanaka et al.⁹ found that the death rate from PCBCL was much higher in Japanese (16%) than in Caucasian (2%) patients.

Studies have been done that have looked at the genetic origin of PCBCL. In a study of Dutch patients, Hoefnagel et al.¹⁰ found support for follicle center cell origin for follicle center cell and DLBCL-leg. They found that both types of lesions consistently expressed Bcl-6,

Figure 1. Skin lesions showing central necrosis and raised borders

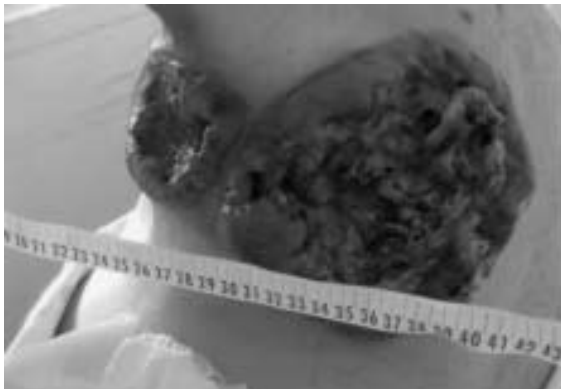


Figure 2. Healed skin lesions with linear scar after three cycles of chemotherapy and radiation



whereas Bcl-2 and CD 10 were expressed in only one and two of 24 cases, respectively, with follicle center cell; and CD 10 was negative in all cases with DLBCL-leg. Previous study by Geelen et al.¹¹ revealed negative Bcl-2 expression in PCBCL involving the head and trunk, whereas all cases of PCBCL involving the leg were Bcl-2 positive. In the Japanese study, Liu et al.² found that Bcl-2 was frequently expressed, which was not site confined, and that there was no evidence for a follicular center origin for PCBCL. Gronbaek et al.⁸ found Bcl-2 expression to be consistent in 90% of cases studied, with no differences seen in relation to site or between different histological categories. It can be inferred from above that the predictability of these tests from current available literature is very variable.^{12,13} The antibodies against B-cell associated antigens in our patient were CD 20 and CD 79a, with a morphology suggestive of DLBCL.

Various treatment options are available and depend upon the histological subtype and number of lesions. CHOP with and without radiotherapy has been used extensively. Yap et al.² achieved remissions in 92% of cases studied, with median follow-up of 28 months, and only one patient with DLBCL-leg died from progressive cutaneous disease. PCBCLs are highly radiosensitive.^{14,15} Radiation therapy can be used as adjunct with chemotherapy at presentation or relapse. It is frequently used for localized disease. Garbea et al.¹⁶ presented a case of DLBCL-leg treated with radiotherapy in which complete remission was achieved. Treatment of PCBCL with anti-CD 20 monoclonal antibody (rituximab) was recently introduced. It is usually combined with cytotoxic therapy and has shown mixed results. Hainsworth et al.¹⁷ found a response rate of 54% when treated with rituximab, while in a study of 10 cases of patients with PCBCL treated with systemic rituximab, Heinzerling et al.¹⁸ reported complete remission in only one patient out of five patients with DLBCL. Intralesional use of rituximab has also been described. Paul et al.¹⁹ reported complete remission after one year in two patients given intralesional rituximab, and Roguedas et al.²⁰ reported a case in which intralesional injection of rituximab results in both local and systemic response.

CONCLUSION

It is extremely difficult to differentiate between subtypes of PCBCL, and more studies are needed particularly in the area of immunophenotypic or genotypic markers which will aid in delineation of the subtypes of PCBCL and a universally acceptable classification system, and may help in providing more therapeutic options.

REFERENCES

1. Liu Q, Ohshima K, Kikuchi M. Primary cutaneous B-cell lymphoma in Japanese patients. *Pathol Int*. 2000;50:960-966.
2. Yap L M, Blum R, Foley P, et al. Clinical study of primary cutaneous B-cell lymphoma using European organization for Research and Treatment

of Cancer and World Health Organization classifications. *Aust J Dermatol*. 2003;44:110-115.

3. Willemze R, Kerl H, Berti E, et al. EORTC Classification for Primary Cutaneous Lymphomas: A Proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood*. 1997;90:354-371.

4. Isaac PG, Norton AJ. Cutaneous Lymphoma. In: Isaac PG, Norton AJ, eds. *Extranodal Lymphomas*. New York, NY: Churchill Livingstone; 1994:172-176.

5. Jaffe ES, Harris NL, Stein H, eds, et al. *World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Hematopoietic and Lymphoid Tissues*. Lyon, France: International Agency for Research on Cancer (IARC) Press; 2001.

6. Prince HM, O'Keefe R, McCormack C, et al. Cutaneous lymphomas: which pathological classification? *Pathology*. 2002;34:36-45.

7. Willemze R, Meijer CJLM. EORTC classification for primary cutaneous lymphomas: the best guide to good clinical management. *Am J Dermatopathol*. 1999;21:265-273.

8. Gronbaek K, Moller PH, Nedergaard T, et al. Primary cutaneous B-cell lymphoma: a clinical, histological, phenotypical and genotypical study of 21 cases. *Br J Dermatol*. 2000;142:913-923.

9. Tanaka M, Ichinohasama R, Iwasaki M, et al. Primary cutaneous B-cell lymphomas in Japan: A report of three cases and a comparison of Japanese and White patients. *J Am Acad Dermatol*. 1994;31:54-60

10. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Bcl-2, Bcl-6 and CD10 expression in cutaneous lymphoma: further support for a follicle center cell origin and differential diagnostic significance. *Br J Dermatol*. 2003;149:1183-1191.

11. Geelen FAMJ, Vermeer MH, Meijer CJLM, et al. Bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. *J Clin Oncol*. 1998;16:2080-2085.

12. Mirza I, Macpherson N, Paproski S, et al. Primary cutaneous follicular lymphoma: An assessment of clinical histopathologic, immunophenotypic, and molecular features. *J Clin Oncol*. 2002;20:647-655.

13. Hembury TA, Lee B, Gascoyne RD, et al. Primary cutaneous diffuse large B-cell lymphoma. *Am J Clin Pathol*. 2002;117:574-580.

14. Piccinno R, Caccialanza M, Berti E, et al. Radiotherapy of cutaneous B cell lymphomas: our experience in 31 cases. *Int J Radiat Oncol Biol Phys*. 1993;27:385-389.

15. Kirova YM, Piedbois Y, Bourgeois JP. Radiation in the management of cutaneous B-cell lymphoma. Our experience in 25 cases. *Radiother Oncol*. 1999;52:15-18.

16. Garbea A, Dippel E, Hildenbrand R, et al. Cutaneous large B-cell lymphoma of the leg masquerading as a chronic venous ulcer. *Br J Dermatol*. 2002;146:144-147.

17. Hainsworth JD, Burris HA III, Morrissey LH, et al. Rituximab monoclonal antibody as initial systemic therapy for patients with low-grade non-Hodgkin lymphoma. *Blood*. 2000;95:3052-3056.

18. Heinzerling L, Urbank M, Funk J, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. *Cancer*. 2000;89:1835-44.

19. Paul T, Radny P, Krober SM, et al. Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol*. 2001;144:1239-1243.

20. Roguedas AM, Watier H, Paintaud G, et al. Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. *Br J Dermatol*. 2005;152:541-544. ■

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