Relapsed Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

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Indian J Dermatol 2017:62(6):676

Sir,
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is recognized as a rare heterogeneous malignancy with characteristic clinicopathological and immunohistochemical features. It accounts for 10%–20% of all the primary cutaneous B-cell lymphoma and always manifests as red or violaceous infiltrated plaques on the legs of the elderly persons. Approximately 10%–20% of patients present with skin lesions at body sites other than legs.[2] PCDLBC-LT has a high tendency involving extracutaneous sites, most frequently the regional lymph nodes, bone marrow (BM), and central nervous system. Given the aggressive behavior and high recurrence rate, it has an unfavorable prognosis with 5-year disease-specific survival rate approximately 50%.[2,3] With the aim of providing useful information for clinicians to treat similar cases and highlighting the importance of seeking new therapy regimens, we describe a rare case of relapsed PCDLBC-LT.

A 51-year-old man was admitted to the First Affiliated Hospital of General Hospital of the Chinese People’s Liberation Army in November 2013 with an 8-month history of a progressively enlarging red plaque on his right lower leg. It presented as a red plaque of 1.5 cm × 1.5 cm in March 2013. A skin biopsy revealed a dense atypical lymphocytic infiltrate composed of centroblasts and immunoblasts with round nucleolus and noticeable mitotic figures. Immunohistochemical (IHC) staining showed that these tumor cells were widely expressed for CD20, CD79a, PAX-5, BCL-2 and MUM-1, Ki-67 50%+, but negative for CD3, CD5, CD10, CD21, CD30, Cyclin D1, and EBV-EBER. Positron emission tomography-computed tomography (CT) scan was significant for multiple hypermetabolic nodes focused on cutaneous and subcutaneous tissues of the right lower leg and right testicle. Neither BM smear nor BM biopsy (BMB) showed evidence of BM involvement. Thus, the patient was diagnosed as non-GCB PCDLBC-LT with a stage of T3bN0M1. He was treated with two cycles of GDP (gemcitabine, CP, and DXM) regimen and obtained PR. One month later, he suffered an aggravation of stuffy nose and an increase of plaques on his right lower leg. Then, we changed to radiotherapy for the lesion of his right lower leg and bilateral testicles which bring about CR2.

However, 5 months after the end of radiotherapy, the patient sought care at our hospital with a complaining of the stuffy nose on the right side in March 2015. The medical history included chronic hepatitis C and Type 2 diabetes mellitus treated with insulin regularly. Physical examination revealed many red plaques of varying sizes (range from 1 cm × 1 cm to 4 cm × 4 cm) distributing on the whole body skin [Figure 1 and 2], a swollen right testicle of 6 cm × 6 cm, and several contiguous irregular red plaques accompanying with ulceration and edema on the inside of his right lower leg [Figure 3]. There were no evidences of superficial lymphadenopathy and hepatosplenomegaly. B symptoms (fever, night sweats, and weight loss) were absent. Laboratory tests detected an abnormally increased alanine aminotransferase of 183U/l, aspartate aminotransferase of 170 U/l, and lactate dehydrogenase of 288U/l. The blood routine tests, coagulation tests, total protein levels, and renal function were normal. Serological tests for hepatitis B virus, cytomegalovirus, and Epstein-Barr virus were negative. BM smear and BMB were normal. A contrast-enhanced CT scan pointed out some tumor-like lesions in his right maxillary sinus, ethmoid sinus, nasal cavity, testicle, and both lower legs. The features of the skin biopsy performed on the plaque of his left lower leg, and IHC staining [Figures 4 and 5] coincided with the conclusion of the First Affiliated Hospital of General Hospital of the Chinese People’s Liberation Army. A diagnosis of non-GCB PCDLBC-LT with a stage of T3bNOM1 was made. The patient was treated with two cycles of GDP (gemcitabine, CP, and DXM) regimen and obtained PR. One month later, he suffered an aggravation of stuffy nose and an increase of plaques on his right lower leg. Then, we changed to radiotherapy for the lesion of his right lower leg and bilateral testicles which bring about CR2.

Figure 1: Many red plaques of varying sizes distributing on his face
MINE (mitoxantrone [MTZ], VP-16, and IFO) combining with thalidomide. There was no significant changes after two cycles. As a replacement, methotrexate and cytarabine were implemented for a further one cycle and resulted in PR. Unfortunately, the skin plaques enlarged once again after 2 months. We chose lenalidomide (25 mg/d, d1-21, repeated every 28 days) as a new treatment. However, he was forced to stop taking this drug because of Grade 4 thrombocytopenia and infectious complication during the first treatment cycle. Subsequently, he was treated with two cycles of carmustine and achieved PR. Regrettfully, the patient died of disease progression after 1 month on February 2016. The overall survival of this patient was 35 months.

At present, the pathogeny of PCDLBCL-LT is poorly understood which may hinder the treatment to a certain extent. So far, there is only one documented clinical case resolved spontaneously. The recommended first-line therapeutic protocol is rituximab in combination with CHOP-based chemotherapy. In a retrospective study, the 3- and 5-year specific survival rates were improved dramatically for patients that received rituximab combining with chemotherapy compared with those who treated with other therapies (80% and 74% vs. 48% and 38%, $P < 0.001$). In our report, the first-line treatment reflected remarkable effect in an early stage.

It is controversial on the management of refractory and relapsed PCDLBCL-LT due to the insufficiency of convictive clinical studies. Rituximab-based combination chemotherapy or radiotherapy is suggested to be the secondary therapy if patients had not been given previously. Lenalidomide is proved beneficial to refractory and relapsed PCDLBCL-LT with reliable security and tolerable toxicity according to the latest researches. However, our patient was unable to tolerate this remedial drug. It may be attributed to individual difference. It is expected that new clinical trials about radioimmunotherapy, and novel monoclonal antibody such as dacetuzumab (SGN-40, anti-CD40), lumiliximab (anti-CD23), and ofatumumab (anti-CD20) are under way.

Although therapeutic effects were observed partly in this report, frequent recurrence in a short period increased the difficulty of treatment. Therefore, further
researches about exploring novel approaches for patients with PCDLBC‑LT will be practically significant.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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**How to cite this article:** Wu S, Gui W, Su L, Xi Y. Relapsed primary cutaneous diffuse large B‑cell lymphoma, leg type. Indian J Dermatol 2017;62:676.

**Received:** December, 2016. **Accepted:** August, 2017.