

Primary cutaneous diffuse large B cell lymphoma—other successfully treated by the combination of R-CHOP chemotherapy and surgery

A case report and review of literature

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Abstract

Rationale: The occurrence of primary cutaneous diffuse large B cell lymphoma—other (PCDLBCL-O) has been rarely reported in the literature. Its diagnosis is based on histopathological and immunohistochemical examinations. To improve the clinical diagnosis and treatment for PCDLBCL-O, we report a case of PCDLBCL-O successfully treated by the combination of R-CHOP (A chemotherapy protocol consists of cyclophosphamide, doxorubicin, vincristine, prednisone plus Rituximab) chemotherapy and surgery. The clinical manifestations, pathological characteristics, treatment and prognosis of the case were analyzed.

Patient concerns: The patient was a 56-year-old female, presenting with red plaques and nodules in her left breast for 6 months.

Diagnoses: Based on the clinical manifestation, histopathological and immunohistochemical results, the patient was diagnosed with PCDLBCL-O.

Interventions: She was treated with 6 courses of R-CHOP chemotherapy combined with surgical resection.

Outcomes: In the present case, fairly good curative effect was appeared with no recurrence within the 3 years' follow-up.

Lessons: Primary cutaneous diffuse large B cell lymphoma commonly occurs on the legs (leg type), rarely on other sites of the body. The clinical manifestations are so variant that its diagnosis depends on histopathological and immunohistochemical examinations. Like systemic diffuse large B cell lymphoma, patients should be treated with systemic chemotherapy.

Abbreviations: CR = complete remission, DLBCL = diffuse large B cell lymphoma, PCBCL = primary cutaneous B cell lymphoma, PCDLBCL = primary cutaneous diffuse large B cell lymphoma, PCFCL = primary cutaneous follicle-center lymphoma, PCMZL = primary cutaneous marginal zone B cell lymphoma.

Keywords: B cell lymphoma, diffuse large B cell lymphoma, skin perforation, R-CHOP chemotherapy

1. Introduction

Primary cutaneous diffuse large B cell lymphoma (PCDLBCL) belongs to primary cutaneous B cell lymphoma (PCBCL), which

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This study was approved by the ethic committee of the Second Affiliated Hospital of Xi'an Jiaotong University, and informed consent was obtained from the patient.

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usually occurs on the legs (leg type, PCDLBCL-LT), rarely on other sites of the body (other, PCDLBCL-O).^[1] PCDLBCL-O is characterized by clinical rarity and rapid progression, but its uncharacteristic early clinical manifestations tend to result in missed diagnoses and misdiagnosis. Correct diagnosis requires biopsy and immunohistochemical analysis. Chemotherapy of non-Hodgkin lymphoma-CHOP protocol is the first choice. Isolated lesion can also be treated by surgical resection.^[2,3] The present study reports a case of PCDLBCL-O who was successfully treated by the combination of R-CHOP (A chemotherapy protocol consists of cyclophosphamide, doxorubicin, vincristine, prednisone plus Rituximab) chemotherapy and surgery at our hospital. A review of the literature is also presented.

2. Case report

A 56-year-old female presented to the hospital with red plaques and nodules in her left breast for 6 months. Six months ago, sporadic red patches and papules appeared in the in her left breast, with itching and occasional pain. She visited local hospital and was diagnosed as “herpes zoster.” But the effect was not obvious after topically Chinese medicine and infrared radiation therapy. Thereafter the papules gradually merge into plaques. Four months ago, a finger-sized, infiltrating, red nodule formed under the left nipple (Fig. 1A and B). She used topical “Triamcinolone Acetonide” by herself and the nodule could partially subside, but continued to grow after stopping it. So she came to the department of dermatology in our hospital and was



Figure 1. Clinical manifestations before chemotherapy. (A) Image of the lesions upon initial presentation. (B) Enlarged image of the local lesions of (A). (C) Image of the lesions after relapse. (D) Enlarged image of the local lesions of (C).

suspected “Sweet Syndrome.” She received oral “Methylprednisolone tablets, 20 mg QD” and histopathological examination. A week later, the nodule and plaques significantly receded, but soon relapsed after stopping the oral drugs (Fig. 1C and D). The immunohistochemical examination showed PCDLBCL, and then she was admitted into the oncology department. Before the onset of the disease, the patient was normally healthy. No changes in diet, sleep, urination, defecation, or body weight could be found. All of her family members are healthy and had no similar diseases and other tumors history.

Physical examination showed that the patient possessed stable vital signs. The systemic superficial lymph nodes, liver, and spleen were not involved, and the systematic examination revealed no evident abnormalities. A dermatological examination revealed scattered red patches on her left breast. Under the left nipple there was an egg-sized, purple-red nodule, with smooth surface, tough texture, poor activity, clear boundary, and no tenderness. There was no palpable mass in her right breast.

2.1. Auxiliary examination

Blood routine test: neutrophils 42.30% (reference value 50–70%), lymphocytes 44.40% (20–40%), eosinophils 5.60% (reference value 0.5–5.0%), and basophils 1.61% (reference value 0–1%). Bone marrow examination: mild infection expression of myeloid, mild hematopoiesis of erythroid (Fig. 2A). Positron emission tomography/computed tomography: increased metabolism of an irregular mass in her left breast (5.5 cm × 2.6 cm × 4.6 cm), local thickening of left anterior chest skin (the thickest was about 0.4 cm), and an enlarged lymph node in her left armpit (1.2 cm × 1.0 cm) with a mild increase in metabolism (Fig. 2B–D). There was also an enlarged lymph node in her right armpit.

Histopathological examinations showed that the epidermis was not involved. The tumor cells were diffusely infiltrating in the dermis. The subcutaneous fat layer was also involved. The tumor cells were mainly centroblastic and immunoblastic cells. The former had less cytoplasm, with round or oval, bubble nuclei and a number of small nucleoli scattered near the nuclear membrane, sometimes leaf nuclei was also visible. The latter had abundant basophilic cytoplasm, the nucleus of which contained a single eosinophilic nucleolus, and mitotic figures were common (Fig. 3).

Immunohistochemical studies revealed strong positive staining for CD20, CD79 α , and Pax-5 and positive staining for CD10, bcl-2, and CD5. CD43, bcl-6, and mum-1 are positive in partial cells, with 60% to 70% Ki-67 (Fig. 3). CD1 α , CD3, CD7, CD4, CD8, CD30, CD34, CD56, CD68, CD123, HMB45, CK20, AE1/AE3, S100, TdT, TIA-1, and EBER were all negative (Fig. 4).

2.2. Diagnosis

The patient was diagnosed with primary cutaneous diffuse large B cell lymphoma-other.

2.3. Treatment

Six courses of R-CHOP chemotherapy were adopted (the first cycle: rituximab 600 mg d1, cyclophosphamide 800 mg d1, epirubicin 50 mg d1 and d2, vincristine 2 mg d1, and prednisone 100 mg d1–d5; the second, third, and fourth cycles: rituximab 600 mg d1, cyclophosphamide 1000 mg d1, epirubicin 60 mg d1 and d2, vincristine 2 mg d1, and prednisone 100 mg d1–d5; the fifth and sixth cycles: rituximab 600 mg d1, cyclophosphamide 800 mg d1, epirubicin 60 mg d1 and 50 mg d2, vincristine 2 mg d1, and prednisone 100 mg d1–d5). During the treatment, the patient also received lansoprazole (30 mg, twice a day),

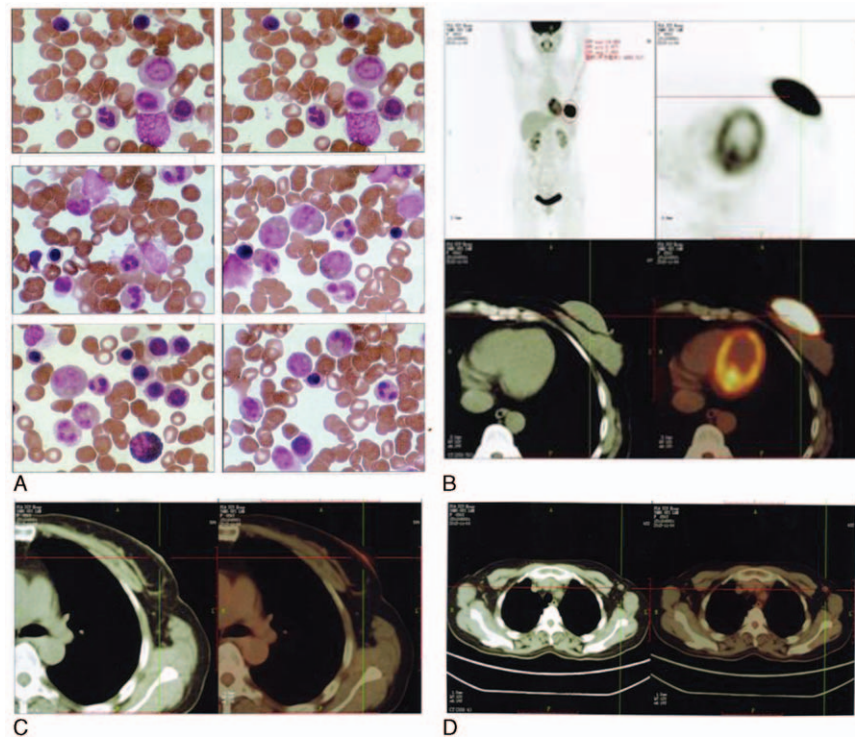


Figure 2. Auxiliary examination. (A) Result of bone marrow examination. (B) Result of PET/CTL examination of the left breast. (C) Result of PET/CTL examination of the left anterior chest skin. (D) Result of PET/CTL examination of the left armpit.

ondansetron (8 mg, twice a day), recombinant human granulocyte colony-stimulating factor (150 μ g once a day), multivitamins, and Traditional Chinese Medicine to alleviate possible side effects of chemotherapy. During the courses of chemotherapy, no obvious side effects appeared. At the end of chemotherapy, the tumor was significantly reduced and flattened, the subcutaneous infiltration disappears and the color of nodule became dark red (Fig. 5). After discussing with the patient and her families, surgical excision of left breast and dissection of left axillary lymph nodes were performed (the patient refused to be photographed after mastectomy). After the operation, another 2 courses of CHOP chemotherapy were followed (cyclophosphamide 800 mg d1, epirubicin 50 mg d1–d2, vincristine 2 mg d1, and prednisone 100 mg d1–d5). After the treatment, the patient achieved complete remission (CR) with no relapse during the 3 years of clinical follow-up.

3. Discussion

PCBCL refers to the B cell lymphoma which primarily involves the skin and do not involve other part of the body within 6 months. Compared with T cell lymphoma, it is rare, accounting 20% to 25% for cutaneous lymphoma. According to 2005 The World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas,^[1] PCBCL can be divided into 4 categories: primary cutaneous marginal zone B cell lymphoma (PCMZL), primary cutaneous follicle-center lymphoma (PCFCL), PCDLBCL-LT, and PCDLBCL-O. PCDLBCL belongs to diffuse large B cell lymphoma (DLBCL), a kind of non-Hodgkin lymphoma. Skin is the second common extranodal site besides gastrointestinal tract, and when DLBCL primarily occurs on the skin it is called PCDLBCL.^[4] PCDLBCL-O refers to the rare large B cell

lymphoma composed of large transformed B cells which primarily occurs on the skin, but does not meet diagnostic criteria for PCMZL, PCFCL, or PCDLBCL-LT.^[5] Some clinical studies suggested that such cases have an indolent clinical course and may be treated in a conservative manner; however, data regarding the actual prognosis and clinical behavior of these peculiar cases are still too limited.^[5] Some scholars have proposed that PCDLBCL-O should include cases that meet morphologic and clinical criteria for PCDLBCL-LT, but do not express Bcl-2. Nonetheless, no clear correlation prognosis and expression of Bcl-2 or other immunophenotypic markers has been identified and they are often treated similarly with PCDLBCL-LT. But there are still some ambiguous places in the classifications.^[6] In the 4th WHO classification of tumors of hematopoietic and lymphoid tissues in 2008, it was included in “diffuse large B cell lymphoma-nonspecial type (NOS),” but still classified “leg type” as an independent type. But WHO-EORTC’s classification is more commonly used.^[7]

The etiology of PCDLBCL remains unclear. It was reported to be associated with Epstein–Barr virus,^[8] human herpes virus 6, human herpes virus 8,^[9] *Borrelia burgdorferi* infection,^[10] or systematic application of methotrexate,^[11] indicating that infection and immunodeficiency play important part in its pathogenesis.

The leg type is more common in the distal leg of elderly female. The lesions can be solitary or multiple, involving the unilateral or bilateral legs. It is characterized by rapid growth of red or purple-red nodules, sometimes also ulcer. It can spread to other part of the body (such as the central nervous system, bone, liver, kidney, spleen, testis, pancreas, breast, pelvis, and brachial plexus nerve) and is a relatively malignant tumor.^[12–15] The other type may occurs in head, trunk, and limbs. It is rare but relatively slow-development, low-grade malignant than the leg type.^[5,16]

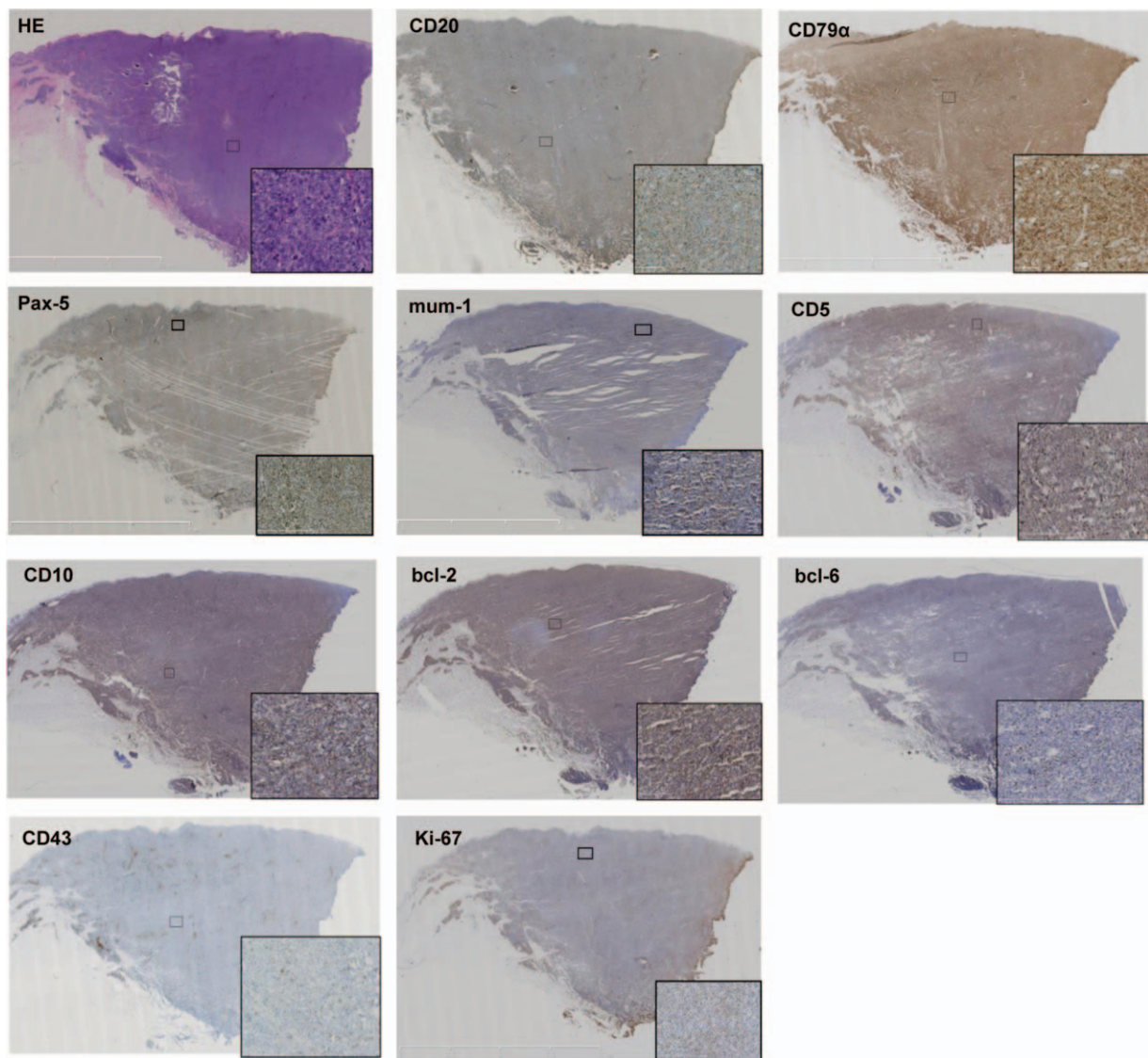


Figure 3. Histopathology and positive results of immunohistochemistry. Hematoxylin–eosin staining shows diffuse infiltration of tumor cells were in the dermis. Immunohistochemistry shows positive staining for CD20, CD79 α , Pax-5, CD10, bcl-2, CD5, CD43, bcl-6, and mum-1, with a Ki-67 proliferation index of 60% to 70%. Scale bar = 10 mm.

Patients of both types have no symptoms or only mild pruritus of the local lesions.

The histopathology of PCDLBCL is similar to systemic DLBCL. The tumor cells diffusely infiltrate the dermis, but do not affect the epidermis and thus forming the Grenz belt. The tumor cells mainly consist of centroblasts and immunoblasts.^[2,17] Tumor cells express the B cell-related antigen CD19, CD20, CD22, CD79a, and Pax-5. Most PCBCL express germinal center-related antigen bcl-6 and postgerminal center-related antigen mum-1/IRF-4, while CD5 and CD10 are usually negative, without t(14;18) (q32;q21) translocation. The apoptosis-related protein bcl-2 is strongly positively expressed in 100% of the leg type while only 50% of the other type.^[18] CD5 positive PCLBCL has also been reported.^[19] CD10 is considered to be a symbol of follicular center cells' origin, and only 28% to 40% positive in patients with DLBCL. Most scholars believe that CD10-positive patients have longer survival rate. About 25% of diffuse large B cell lymphoma patients express CD43. It been showed that CD43 expression is an independent poor prognostic factor of DLBCL.^[5]

Due to the rare morbidity and complex clinical manifestations, PCDLBCL can be easily misdiagnosed as other skin diseases. Currently there is not existed any exact clinical diagnostic criteria for it, so it is difficult to distinguish the 2 subtypes: PCDLBCL-LT or PCDLBCL-O. The diagnosis depends on pathological and immunohistochemical analyses. Some scholars suggest that the expression of Bcl-2 can be used to distinguish the 2 subtypes: positive in leg type, while negative in other type. Other scholars believe that CD10 is negative in leg type, positive in other type. But due to the complexity of PCDLBCL immune phenotype, about 10% of leg type patients do not express bcl-2, and whether bcl-2 and CD10 express or not is not closely related to prognosis. So far the distinguish characteristics of those 2 types remain unclear.^[6] In differential diagnosis, PCDLBCL is mostly needed to be distinguished from PCFCL and secondary cutaneous diffuse large B cell lymphoma.^[20]

Although there has been reports showed that PCDLBCL can be spontaneously relieved without treatment,^[21] it is a kind of malignant tumor and can spread to other part of the body. So

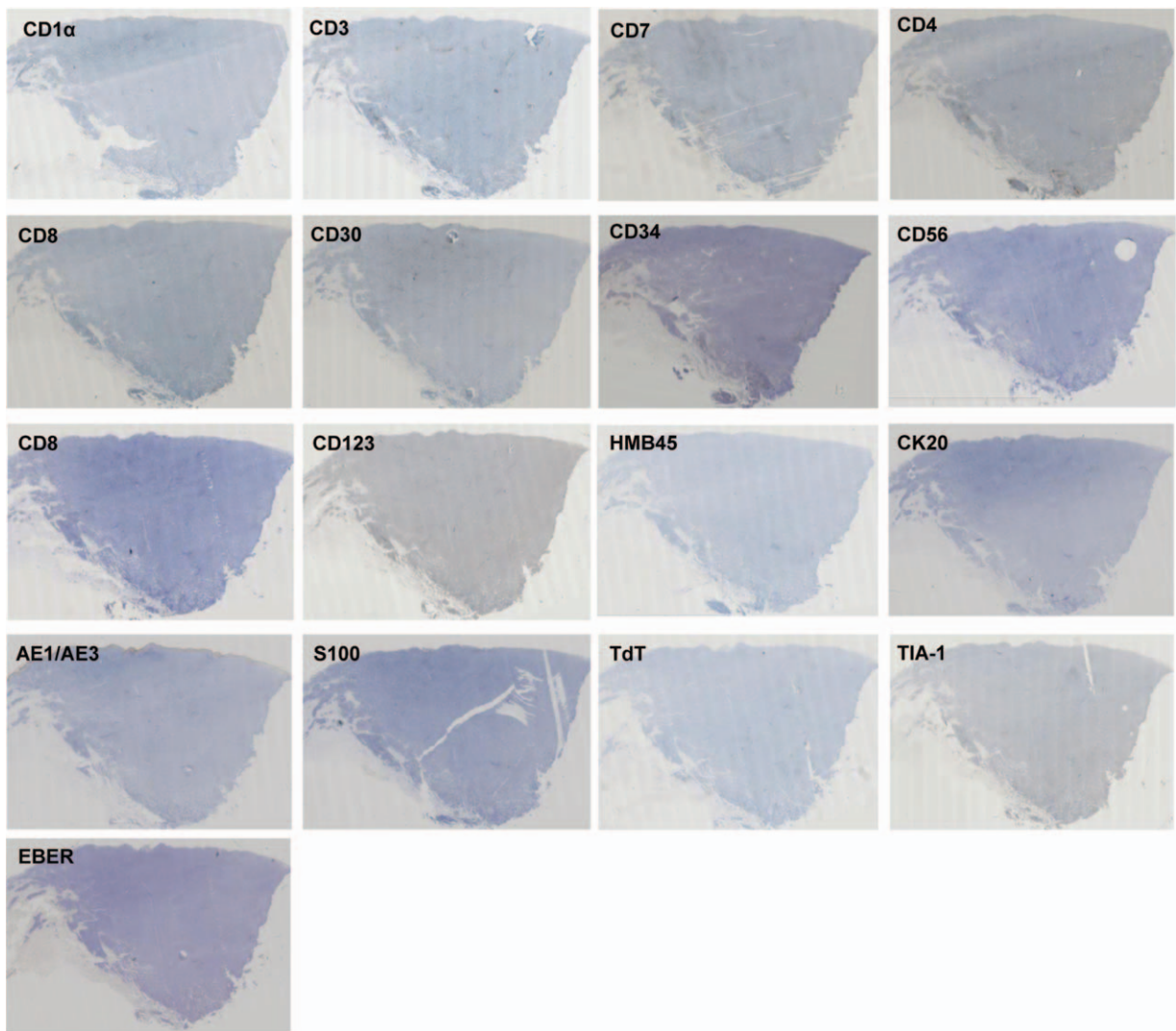


Figure 4. Negative results of immunohistochemistry. Immunohistochemistry shows negative staining for CD1 α , CD3, CD7, CD4, CD8, CD30, CD34, CD56, CD68, CD123, HMB45, CK20, AE1/AE3, S100, TdT, TIA-1, and EBER. Scale bar = 10mm.

once the diagnosis is achieved, it should be given active treatment. Patients with small single lesion can consider surgery or radiotherapy. It has also been reported to be treated by interferon, local injection of glucocorticoids, and oral acitret-

in.^[9,22] However, a more consistent view at present is that it should be treated with anthracycline-based chemotherapy. Chemotherapy of non-Hodgkin lymphoma-CHOP protocol is the first choice. Many reports have showed that the combination

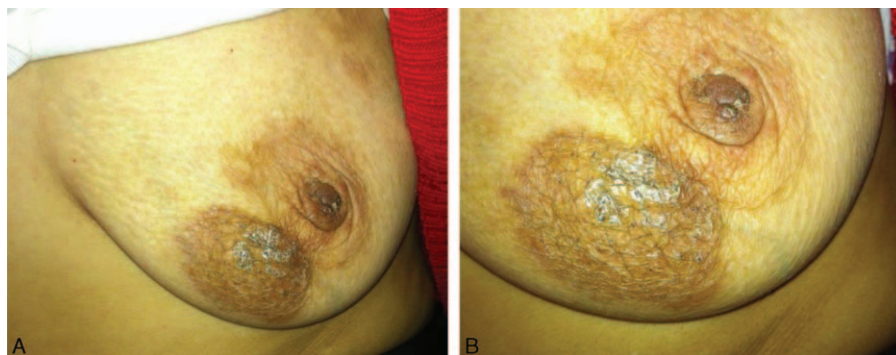


Figure 5. Clinical manifestations after chemotherapy. (A) Image of the lesions after 6 courses of R-CHOP chemotherapy. (B) Enlarged image of the local lesions of (A).

use of anti-CD20 and antibody rituximab (R-CHOP) is more effective.^[23–26] A retrospective study by Senff^[27] showed that in rituximab + anthracycline contained chemotherapy group, the CR rate was 92% and the recurrence rate was 9%. While in the single use of anthracycline contained chemotherapy group, the CR rate was 81% and the recurrence rate was 54%. The prognosis of leg type (the 5-year survival rate is 55%) is worse than other type (the 5-year survival rate is more than 90%).^[28] It is generally believed that the location and number of lesions are main prognostic factors. In the study of 14 cases of patients with PCDLBCL by Sundram et al,^[29] the overall survival rate of bcl-6(+)/mum-1(–) patients is better than bcl-6(–)/mum-1(+) patients. But so far, the judgment of prognosis by the immunohistochemical markers still remains controversial and needs more clinical data.

4. Conclusions

The patient of our case was a middle-aged woman. Her clinical symptoms are so untypical that she had been misdiagnosed many times. It was finally diagnosed as PCDLBCL-O by histopathological and immunohistochemical examinations. We took the R-CHOP chemotherapy widely recommended as the treatment method. But because the tumor did not disappear completely, operation + additional 2 cycles of CHOP chemotherapy were adopted and achieved a good response. But it still needs a close follow-up to assess the long-term effect.

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