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ABOUT COVER

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CASE REPORT

Chidamide combined with traditional chemotherapy for primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma: A case report

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Abstract

BACKGROUND

Traditional chemotherapy has benefited many patients with non-Hodgkin's lymphoma, but results in a very poor response in patients with rare lymphomas or refractory lymphomas. Previous studies have shown that chidamide has potential anti-lymphoma activity and reverses lymphoma cell chemoresistance to increase the chemosensitivity of lymphoma cells to traditional chemotherapy.

CASE SUMMARY

A 14-year-old boy was admitted to our hospital with a 5-d history of generalized erythema, papules, and blisters. Initially, the disease was refractory to potent anti-allergic and anti-infective treatment, and his condition progressively worsened. Skin biopsy revealed primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Considering that the disease is extremely rare in clinical practice, existing case reports have shown poor efficacy with traditional chemotherapy alone. We recommend chidamide combined with traditional chemotherapy for treatment. The regimen was as follows: Chidamide 30 mg/biw, cyclophosphamide 1100 mg/d1, pirarubicin 70 mg/d1, vincristine 2 mg/d1, dexamethasone 20 mg/d1-5, etoposide 100 mg/d1-5, in a 21 d cycle. The treatment effect was considerable, and complete remission was achieved after 4 cycles of treatment, after which the patient completed a total of 6 cycles of treatment. Subsequently, the patient regularly took chidamide 20 mg/biw as maintenance therapy for 1 year. To date, the patient has been disease-free for 3 years.

CONCLUSION

This case suggests that the combination of chidamide and traditional chemotherapy is effective in primary cutaneous aggressive epidermotropic CD8+

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cytotoxic T-cell lymphoma.

Key Words: Chidamide; Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma; Traditional chemotherapy; Case report

Core Tip: The long-term efficacy of traditional chemotherapy in the treatment of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is poor, and the main mechanism is the emergence of chemoresistance in lymphoma cells. Chidamide induces apoptosis and growth arrest of lymphoid and hematologic tumor cells and enhances the sensitivity of lymphoma cells to traditional chemotherapy. This case suggests that chidamide may enhance the efficacy of traditional chemotherapy, and that chidamide combined with traditional chemotherapy may be a promising treatment option for primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

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INTRODUCTION

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic cell T-cell lymphoma is a rare subtype of cutaneous T-cell lymphoma, accounting for less than 1% of all cutaneous T-cell lymphomas. Only dozens of cases have been reported worldwide, and there is no optimal treatment. According to existing reports, the majority of patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma currently receive doxorubicin-based traditional chemotherapy. There are case reports of treatment with CHOP, CHOPE, and Hy-CVAD regimens, but the efficacy is poor. All result in short-term benefits, with an overall survival of 12-32 mo [1]. The main reason for the poor long-term efficacy of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma to traditional chemotherapy is that lymphoma cells are prone to chemoresistance[2]. Chidamide has potential anti-hematological tumor activity and enhances the chemosensitivity of lymphoma cells. It has been recognized for the treatment of relapsed or refractory peripheral T-cell lymphoma. Based on the above theory, we boldly tried the combination of chidamide with traditional chemotherapy (CHOPE) in a patient with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma with promising results.

CASE PRESENTATION

Chief complaints

A 14-year-old boy was admitted to the Department of Dermatology with a 5-d history of generalized erythema, papules, and blisters and was transferred to the Department of Medical Oncology.

History of present illness

The patient had generalized erythema, papules, and blisters with itching since August 18, 2017. Three days after the onset of symptoms, some blisters formed blood blisters with tan crusts on the surface, accompanied by pain, and fever, fear of cold, and chills, with a maximum body temperature of 41 °C.

Physical examination

The patient's body temperature was 37.8 °C, heart rate was 110 bpm, respiratory rate

was 20 breaths/min, and blood pressure was 99/67 mmHg. Scattered blood blisters were observed throughout the body, with the most severe blood blisters on the trunk, consistent with the distribution of skin transverse striae (Figure 1). Erosive surfaces of varying sizes were seen in the oral cavity, trunk, extremities, and perineum. Physical examination of the heart, lungs, and abdomen was unremarkable.

Laboratory examinations

After admission, a blood test was performed and the patient's white blood cell count was 5.86 × 10^9/L, hemoglobin concentration was 146.70 g/L, and platelets were 129.80 × 10^9/L. His biochemical results were as follows: Total protein, 61.2 g/L; albumin, 29.5 g/L; creatinine, 54 μmol/L; lactate dehydrogenase, 351 U/L; β-2 microglobulin, 3.6 mg/L; interleukin-6, 13.34 pg/mL. The results of bone marrow biopsy showed slight microscopic bone marrow hyperplasia, cell volume accounted for 40%, tertiary hematopoietic cells were present, granulocyte/erythrocyte ratio was slightly increased, and cell morphology was normal (Figure 2A). The skin of the left thigh was biopsied, and the pathology results indicated primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (Figure 2B). The results of immunohistochemistry revealed the following: CD3 (+), CD2 (-/+), CD4 (-/+), CD5 (-/+), CD7 (+), CD8 (+ +), CD56 (-), TiA-1 (+), GB (+), AlK (-), CD30 (-), CD20 (-), and CD10 (-); EBERs (-); TCR-r gene rearrangement (-).

Imaging examinations

Positron emission tomography/computed tomography (PET/CT) showed mildly increased systemic cutaneous glucose metabolism, which was considered to be cutaneous lymphoma. Mild systemic skin swelling and a diffuse mild increase in glucose metabolism, especially in the local skin of both armpits, right upper quadrant, and posterior coccyx were observed (Figure 3). Multiple small lymph nodes of different sizes with increased glucose metabolism were observed in both armpits and groins.

FINAL DIAGNOSIS

Based on pathological biopsy, laboratory examinations, imaging examination and clinical manifestations, the patient was finally diagnosed with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

TREATMENT

The patient was diagnosed more than 20 d after the onset of symptoms, and chidamide combined with CHOPE regimen was administered as the patient's first cycle of treatment as follows: Chidamide 30 mg/biw, cyclophosphamide 1100 mg/d1, doxorubicin 70 mg/d1, vincristine 2 mg/d1, dexamethasone 20 mg/d1-5, etoposide 100 mg/d1-5, in a 21 d cycle. The patient completed a total of 6 cycles of treatment and subsequently entered maintenance therapy.

OUTCOME AND FOLLOW-UP

After 4 cycles of treatment, the patient returned to the hospital for follow-up, and his skin rash on the face, neck, trunk, and extremities had disappeared (Figure 4A). The blood tests showed that the white blood cell count was 6.14 × 10^9/L, hemoglobin concentration was 123 g/L, and platelets were 225 × 10^9/L. His biochemical results were as follows: Total protein, 68.2 g/L; albumin, 36 g/L; creatinine, 60 μmol/L; lactate dehydrogenase, 225 U/L; β-2 microglobulin 1.96 mg/L; interleukin-6, 5.3 pg/mL. PET/CT showed that after chemotherapy for cutaneous lymphoma, the original lesions were inactivated and no new lesions were observed (Deauville score: 1 point). No clear structural or glucose metabolism abnormalities were noted (Figure 3B). Complete remission was observed. The patient had grade III bone marrow suppression during the 5th cycle of chemotherapy, and continued to complete chemotherapy as planned after repeated blood tests were normal after leukocyte-elevating therapy. After completing 6 cycles of treatment, he regularly took chidamide 20 mg/biw as maintenance therapy for 1 year. No significant hematological toxicity or

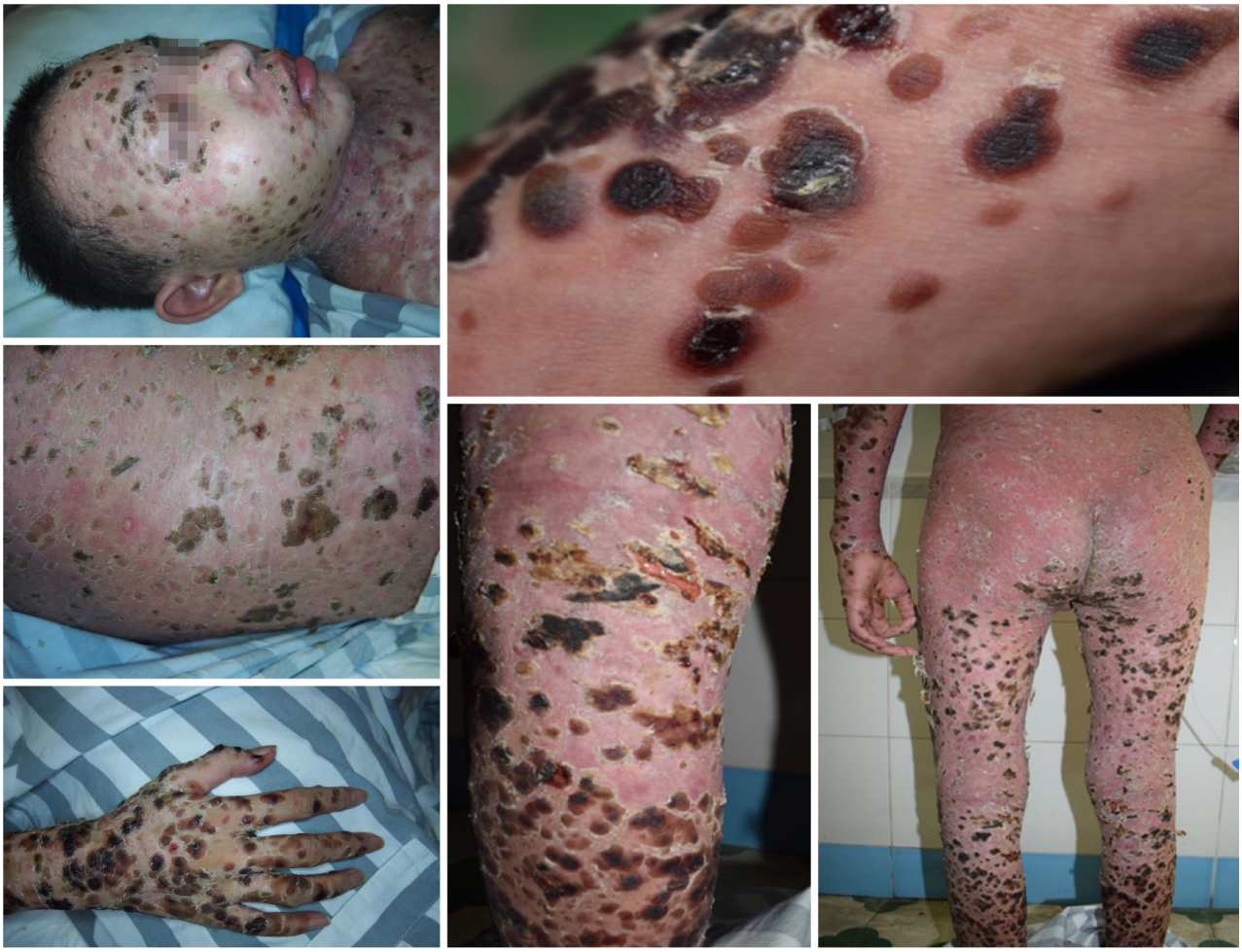

Figure 1 Photographs of skin lesions before treatment. Scattered blood blisters were observed throughout the body, with the most severe blood blisters on the trunk, consistent with the distribution of skin transverse striae.

gastrointestinal adverse events occurred during maintenance therapy with chidamide. The last follow-up was performed 2 wk ago and the patient's condition was stable without recurrence (Figure 4B).

DISCUSSION

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma was first reported as a rare histopathological subtype of cutaneous T-cell lymphoma in 1999 by Berti *et al*[3]. It was first classified as a non-specific provisional entity by the World Health Organization/European Organization for Research and Treatment of Cancer in 2005[4]. This type of lymphoma is characterized by the presence of localized or diffuse papules, nodules, or tumors, which present as central ulceration or necrosis, or plaques with surface hyperkeratosis[5]. Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is highly aggressive and can rapidly spread to various organs, such as the lungs, testes, central nervous system, or oral mucosa, with a poor response to traditional chemotherapy[6]. Some patients can benefit from doxorubicin-based multiagent chemotherapy for a short time, but most patients relapse a short time after treatment and even develop resistance to traditional chemotherapy and then it transforms into relapsed or refractory lymphoma. Treatment is still a great clinical challenge.

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is clinically heterogeneous, and its course progresses rapidly. Treatment options for advanced disease are limited, and significantly effective treatment options deserve active exploration. Numerous studies have shown that histone deacetylase inhibitors (HDAC inhibitors) are used to treat malignant tumors, such as cutaneous T-cell lymphoma and peripheral T-cell lymphoma. Moreover, HDAC inhibitors are now

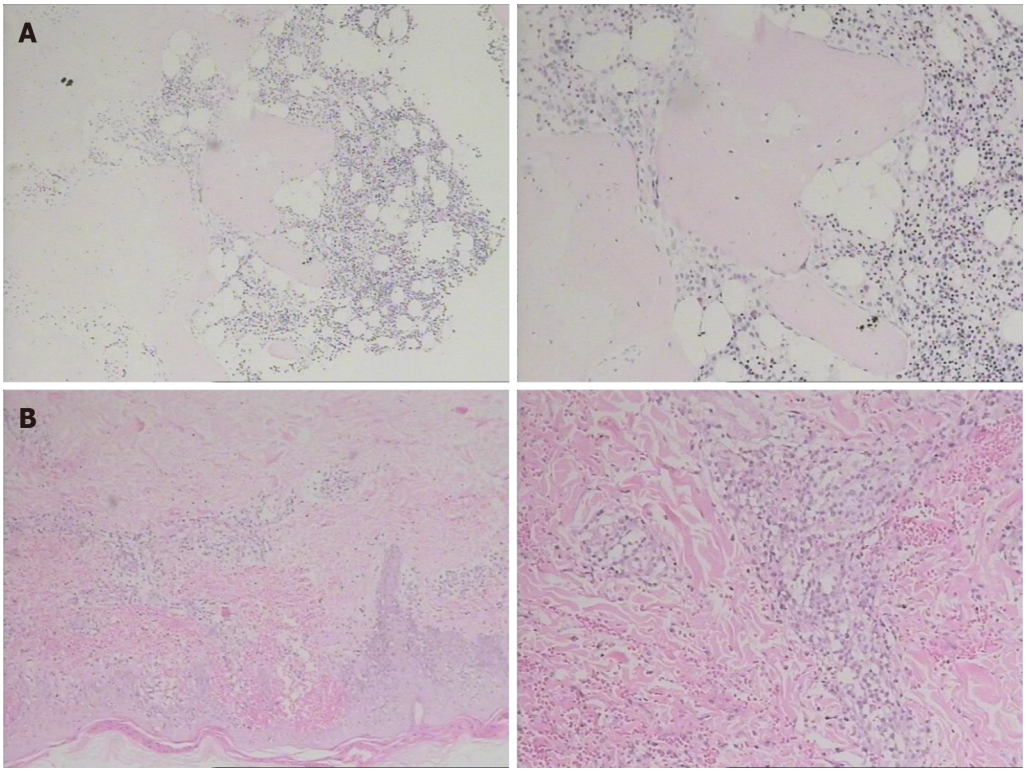

Figure 2 Bone marrow and skin biopsies. A: Bone marrow biopsy. Slight microscopic bone marrow hyperplasia, cell volume accounted for 40%, tertiary hematopoietic cells were present, granulocyte/erythrocyte ratio was slightly increased, and cell morphology was normal; B: Skin biopsy of left thigh. There was hyperkeratosis of the skin epidermis, hemorrhage in the papilla of the dermis, and local or diffuse small lymphocyte infiltration in both the epidermis and subcutaneously.

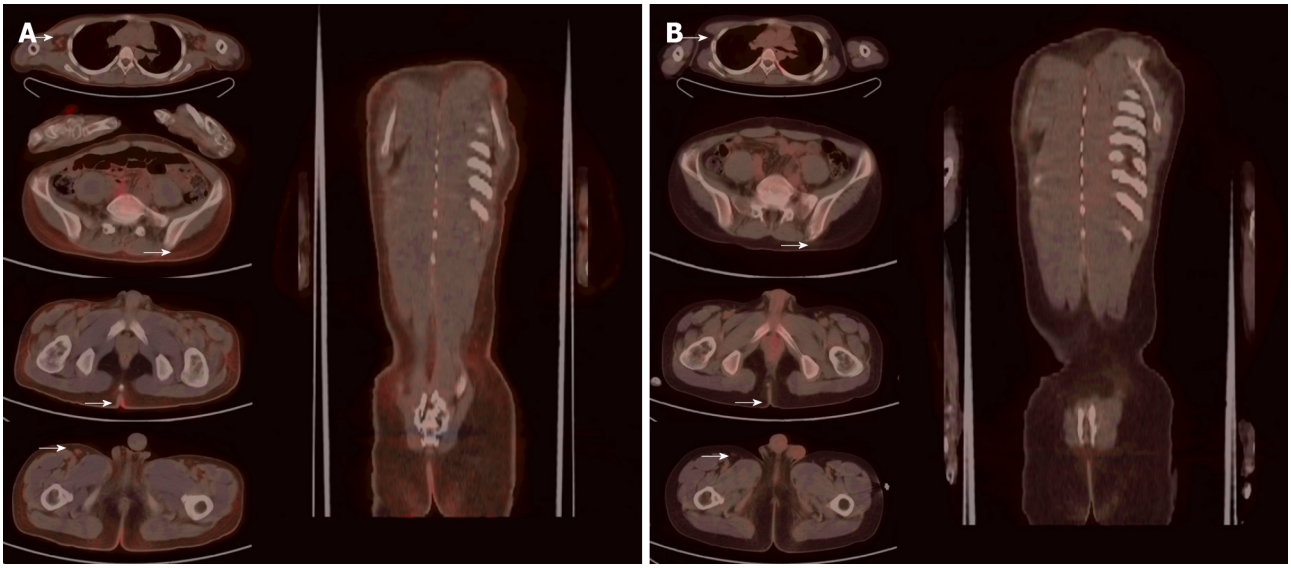

Figure 3 The patient underwent positron emission tomography/computed tomography before treatment and reexamination after 4 cycles of treatment. A: Positron emission tomography/computed tomography (PET/CT) before treatment. The figure showed mild systemic skin swelling and diffuse mild increase in glucose metabolism, especially in the local skin of both armpits, right upper quadrant, and posterior coccyx. Multiple small lymph nodes of different sizes with increased glucose metabolism were observed in both armpits and groins; B: PET/CT after treatment. The figure showed no clear structural or glucose metabolism abnormalities.

increasingly being used in combination with other types of anticancer drugs for the treatment of various malignancies. Chidamide is an innovative drug independently developed in China, which can exert anti-tumor activity by reversing tumor cell resistance, increasing tumor cell chemosensitivity, potently regulating immunity and potential direct anti-tumor effects[7,8]. In December 2014, chidamide was approved by

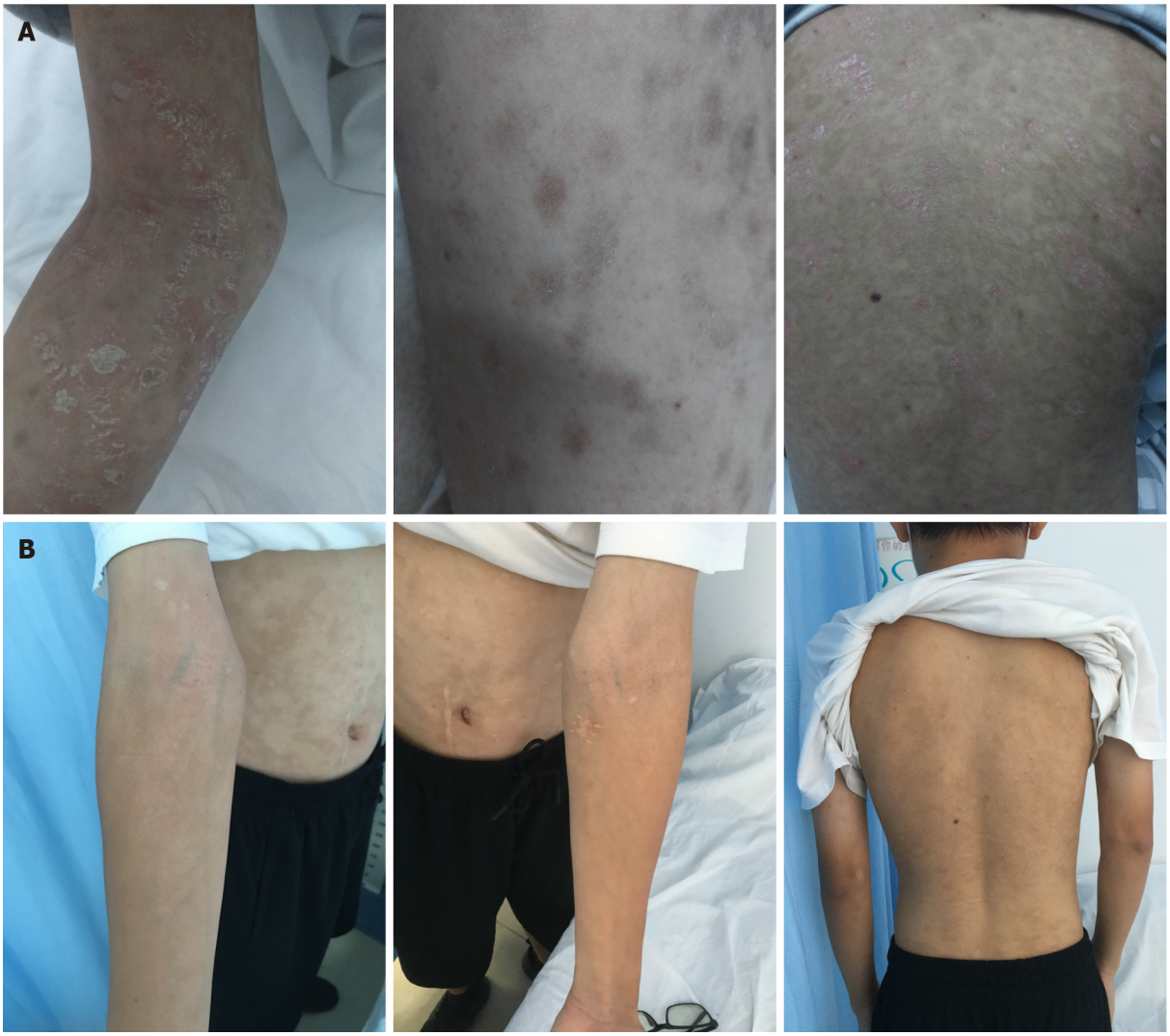

Figure 4 Follow-up photographs of the patient. A: Photographs of the patient after completion of 4 treatment cycles. Generalized scattered blood blisters disappeared, and residual scattered skin pigmentation was observed; B: Photographs of the last follow-up. No abnormal lesions were observed.

China Food and Drug Administration for the treatment of relapsed or refractory peripheral T-cell lymphoma. Previous studies have shown that chidamide can induce apoptosis and growth arrest of lymphoid or hematologic tumor cells, and can also reverse tumor cytochemical resistance to increase tumor cell chemosensitivity. Wei Guan *et al*[9] retrospectively analyzed 17 cases of refractory or relapsed T-lymphocytic lymphoma/leukemia (T-LBL/ALL) and found that chidamide has pleiotropic regulatory immune function and can enhance the sensitivity of tumor cells to chemotherapeutic drugs. Jiang *et al*[10] found that chidamide inhibited the proliferation and induced apoptosis of tumor cells and exerted potential anti-leukemia activity. Chidamide can also increase the chemosensitivity of tumor cells by disrupting the Smo/gli-1 pathway and the downstream signaling target p-AKT. Yan *et al*[8] found that the combination of chidamide and syndilimab enhanced the efficacy of syndilimab in NK/T cell lymphoma. Based on the above theory, we speculate that a treatment regimen combining chidamide may be a promising therapeutic strategy for refractory T-cell lymphoma. Common adverse events of chidamide include thrombocytopenia, leukopenia, neutropenia, QTc prolongation, fatigue, fever, and gastrointestinal symptoms. Studies have shown that the incidence of adverse events is low and easily controlled, with only a few patients discontinuing treatment due to serious adverse events[7,11].

The present patient with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma achieved complete remission following treatment with chidamide combined with CHOPE regimen. On the one hand, this may have been due to the potential antitumor activity of chidamide, and on the other hand, it may have been because chidamide reverses tumor cell chemoresistance to increases tumor cell

chemosensitivity. In this case, the patient experienced short-term hematological toxicity during chemotherapy with chidamide combined with CHOPE regimen, but recovered quickly after leukocyte-elevating therapy. The patient successfully completed 6 cycles of therapy. In addition, no significant adverse events occurred in this patient during maintenance therapy. This regimen was well tolerated and provides a promising therapeutic strategy for the treatment of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

CONCLUSION

In conclusion, we found that a combination of chidamide and a traditional chemotherapy regimen is a safe and effective treatment for primary cutaneous aggressive epidermotropic CD8+ cytotoxic cell T-cell lymphoma, but its long-term efficacy requires further evaluation. For patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma refractory to traditional therapy (*e.g.*, CHOP), we recommend early combination therapy with chidamide. This study also had limitations: Due to the rarity of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, analysis of the results obtained in this report requires caution. Whether the good efficacy in this patient was the result of synergy between traditional chemotherapy and chidamide or a separate effect of chidamide cannot be determined. In the future, we will continue to collect data to assess the efficacy and safety of chidamide in combination with CHOPE in patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

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