

CASE STUDY

Treatment of primary cutaneous CD30-positive anaplastic large cell lymphoma with *Wenyang Shengji* decoction and *Huanglian ointment*: A case report

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Abstract

Primary cutaneous CD30 positive anaplastic large cell lymphoma (PC-ALCL) is a rare non-Hodgkin's lymphoma. Combined chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), or F-MACHOP (5-fluorouracil, methotrexate, cytosine-arabioside, cyclophosphamide, doxorubicin, vincristine, and prednisone) are often used for its clinical treatment. In this study, we reported a new treatment method using a traditional Chinese therapy involving oral *Wenyang Shengji decoction* (WSD) combined with *Huanglian ointment* applied externally in a 32-year-old female patient with PC-ALCL. Introduction: A 32-year-old woman who complained of an ulcer on the forehead accompanied by significant pain. PC-ALCL was diagnosed by histopathological examination and immunohistochemical analysis. Treatment plan: WSD was prepared in 300 mL water and administered orally as a 150 mL decoction twice daily, and *Huanglian ointment* was applied to the ulcer three times daily. After 8 weeks of treatment with WSD combined with *Huanglian ointment*, the lesion healed completely. Immunohistochemical analysis revealed the presence of scattered CD3+++ , CD4++ , CD8++ , CD20++ , and CD30-positive cells. After 12 weeks of treatment, the ulcer healed completely, leaving only a marked pale red-pitted scar. The patient was followed up for 3 years without recurrence and no adverse events. Conclusion: oral WSD combined with *Huanglian ointment* applied to the ulcer for PC-ALCL can promote the healing of ulcers, reduce or alleviate the formation of scar, and eliminate CD30-positive cells. This case report provides a reference for the clinical treatment of PC-ALCL using traditional Chinese medicine.

KEYWORDS

Huanglian ointment, primary cutaneous CD30 positive anaplastic large cell lymphoma, therapeutics, traditional Chinese medicine, *Wenyang Shengji decoction*

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INTRODUCTION

Primary cutaneous CD30 positive anaplastic large cell lymphoma (PC-ALCL) is an important type of primary cutaneous lymphoproliferative disease. It accounts for approximately 0.9% of primary cutaneous lymphomas and is a relatively rare form of non-Hodgkin's lymphoma [1]. This disease can occur at any age but is more common in men over 50 years. The clinical manifestations are mainly chronic recurrent skin lesions, most of which are single or multiple nodules, papules, and plaques prone to form ulcers. The characteristic feature of this disease is anaplastic CD30+ T lymphocyte infiltration, and more than 75% of tumor cells express CD30. The typical clinical manifestations are single skin tumors with ulceration in the center [2–4]. However, side effects caused by PC-ALCL treatment are not controllable and can easily lead to the recurrence of skin lesions, resistance to chemotherapy, chemotherapy-induced bone marrow transplantation, liver and kidney injury, etc. [5]. It has been reported that the recurrence rate of skin lesions is up to 39%, and the rate of metastasis outside the skin is up to 13% [6]. Therefore, exploring more effective treatment methods is of great significance.

As an independent discipline, traditional Chinese medicine (TCM) has been developed for thousands of years in China, and TCM is also widely used to prevent and treat various diseases. It is worth mentioning that TCM plays an important role in the treatment of cancer and the alleviation of side effects [7]. In recent years, a large number of pharmacological studies have shown that a variety of active ingredients in Chinese herbal medicine has a certain anticancer effect. For instance, progesterone compounds have a clear anti-pancreatic cancer effect, let-7c induced by quercetin could inhibit the growth of tumor cells, and berberine, which is the active ingredient of *Coptidis rhizoma* and the main drug of *Huanglian ointment*, can inhibit the metastasis and proliferation of cancer cells by inducing apoptosis pathways and inhibiting the cell cycle [8, 9].

This paper describes a case of PC-ALCL treated with TCM following which no recurrence was observed during 3 years of follow-up. After treatment, the patient's skin ulcer healed completely leaving only a 3.6 × 4.3 mm-colored spot. Immunohistochemical results indicated that CD30+++ cells that were abundant pretreatment became scattered posttreatment.

THE CASE

Case history

A 32-year-old female patient presented with a rash (4.2 × 5.0 mm) on her forehead, showing progressive expansion and appearing as a central ulceration with significant pain. The ulceration gradually expanded until

the edge bulged and multiple thin secretions were observed. The patient first visited the dermatology clinic of our hospital on 22 August 2015. Dermatological examination revealed a 3.5 cm in diameter roundish ulcer surface on the forehead with a central depression, a dike elevation at the margin, a large number of thin secretions, redness and swelling around the ulcer, a less smooth surface than the surrounding skin, and a yellowish base (Figure 1).

Laboratory tests: blood routine, coagulation panel, hepatic and renal function, electrolyte analysis, and C-12 results were all normal; the patient was negative for tuberculosis antibodies; the C-reactive protein concentration was <3.34 mg/L; the erythrocyte sedimentation rate was 12 mm/H; and anti-autoantibody panel ANA was negative. Histopathological examination of the skin (Figure 2a and 2b) showed epidermal hyperplasia, partial epidermal deficiency, ulcer formation, neutrophil infiltration in the epidermis around the ulcer, vascular proliferation in the dermis below the ulcer, massive plasma cells, histiocytes, lymphocytes, neutrophil infiltration, and necrosis in some areas. Immunohistochemical staining indicated the presence of CD30+++ (Figure 3a and 3b), CD3+, CD4++, CD8+, and CD20+. The peripheral blood was positive for TCR-γ gene rearrangement (Figure 4). Combined with the above clinical manifestations and relevant examinations, we diagnosed primary cutaneous-CD30 PC-ALCL, which was considered to be T-cell type PC-ALCL because it expressed T cell markers (CD3+, CD4++, and CD8+).

Treatment

We advised the patient to take a combined treatment of Chinese herbal medicine and external Chinese patent medicine ointment. After consultation with the patient, she gave consent to the treatment protocol. We prescribed a formula consisting of *Radix bupleuri* (12 g), *Ramulus cinnamomi* (10 g), dried ginger (6 g), raw oyster (30 g), raw keel (30 g), *Radix trichosanthes* (30 g), *Radix glycyrrhizae* (10 g), *Radix scutellariae* (10 g), *Radix angelicae sinensis* (15 g), *Radix paeoniae alba* (15 g), *Poria cocos* (30 g), *Rhizoma alismatis* (20 g), *Atractylodes macrocephala* Koidz (20 g), and *Rhizoma Chuanxiong* (10 g). One week after the prescribed treatment, the patient visited the doctor again, and the secretion from the frontal ulcer was significantly reduced, the ulcer was drier than before, the surrounding embankment elevation was no longer obvious, and the redness and swelling around the ulcer subsided (Figure 5a). Therefore, we prescribed a formula composed of *Rhizoma Chuanxiong* (10 g), *Radix angelicae sinensis* (20 g), *Astragalus membranaceus* (45 g), *Radix codonopsis* (20 g), *Radix rehmanniae praeparata* (10 g), *Atractylodes macrocephala* Koidz (10 g), *Poria cocos* (10 g), *Radix paeoniae alba* (10 g),



FIGURE 1 Lesions on skin before treatment.

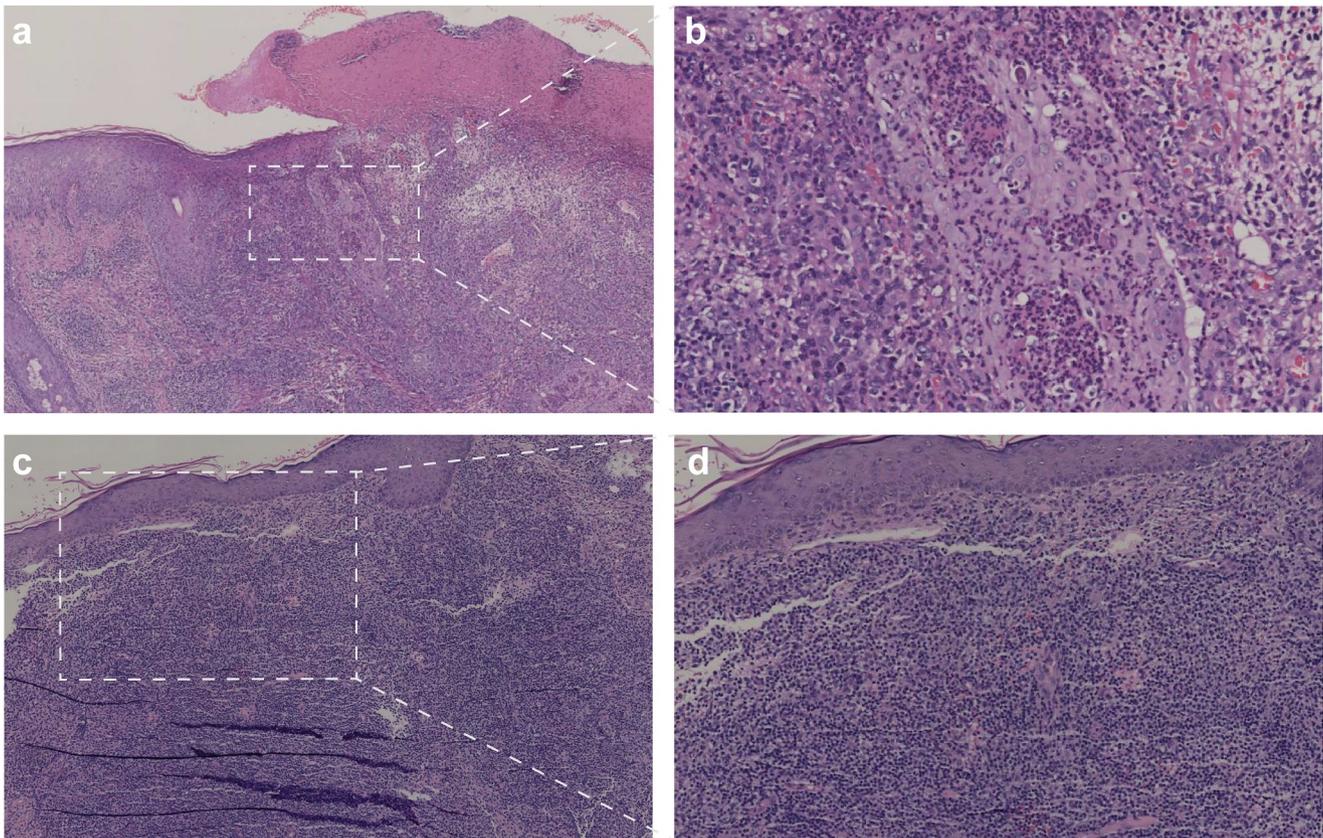


FIGURE 2 Histopathological examination of the skin tissue before and after treatment. (a) Skin pathology before treatment. (HE \times 40). (b) Skin pathology before treatment. (HE \times 100). (c) Skin pathology after treatment. (HE \times 40). (d) Skin pathology after treatment. (HE \times 100).

Radix glycyrrhizae (6 g), *Radix aconiti carmichaeli* (6 g), *Ramulus cinnamomi* (6 g), *Rhizoma dioscoreae* (10 g), *Cortex Moutan* (10 g), and *Herba leonuri* (20 g). The formula was named *Wenyang Shengji decoction* (WSD) and was combined with the external application of *Huanglian ointment* on the ulcer; the dressing was changed once a day.

Case outcome

The patient returned on 25 September 2015, after four weeks of treatment. Dermatological examination showed that the ulcer healed further; the healing surface at the edge showed an annular bulge, and the central ulcer flattened significantly (Figure 5b).

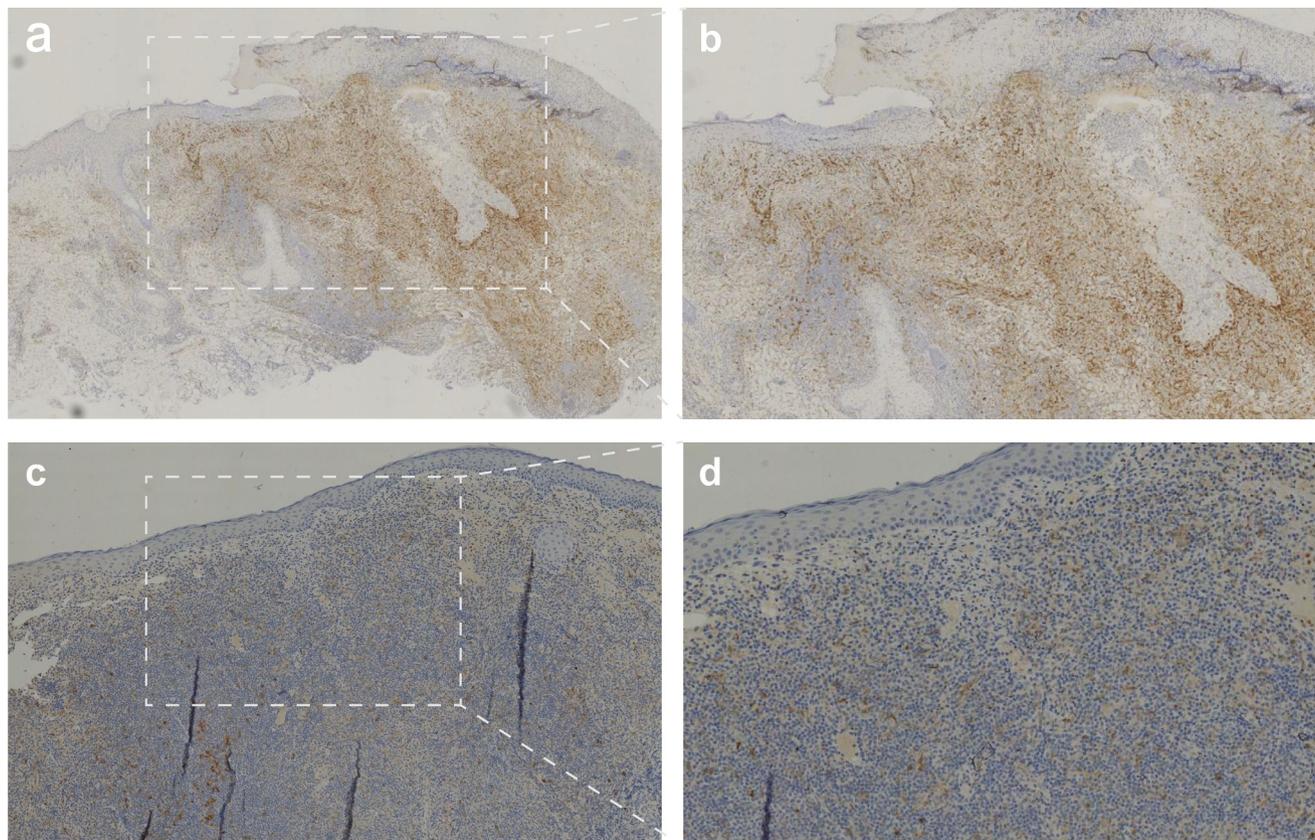


FIGURE 3 Immunohistochemical staining of the skin tissue before and after treatment. (a) Immunohistochemistry shows CD30+++ before treatment. (IHC \times 40). (b) Immunohistochemistry shows CD30+++ before treatment. (IHC \times 100). (c) Immunohistochemistry shows scattered positive CD30 after treatment. (IHC \times 40). (d) Immunohistochemistry shows scattered positive CD30 after treatment. (IHC \times 100).

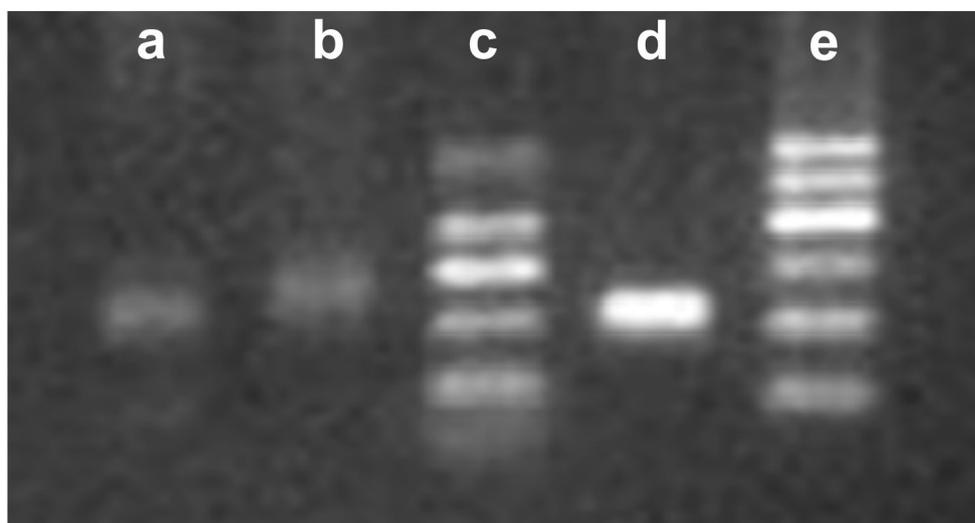


FIGURE 4 TCR- γ gene rearrangement. (a) TCR- γ (B tube) product length range 80–140 or 160–220 bp. (b) TCR- γ (A tube) product length range 145–255 bp. (c) BIOMED-2 system (internal reference primers, product lengths are 100, 200, 300, 400, and 600 bp, respectively). (d) β -globin (Internal control, product length is 196 bp). (e) Marker.

After another two weeks of treatment, the patient returned on 10 October 2015. Dermatological examination showed further healing of the ulcer and flattening

of the annular convexity on the healing surface at the margin (Figure 5c). As the patient reported that she had difficulty falling asleep at night and her mood was

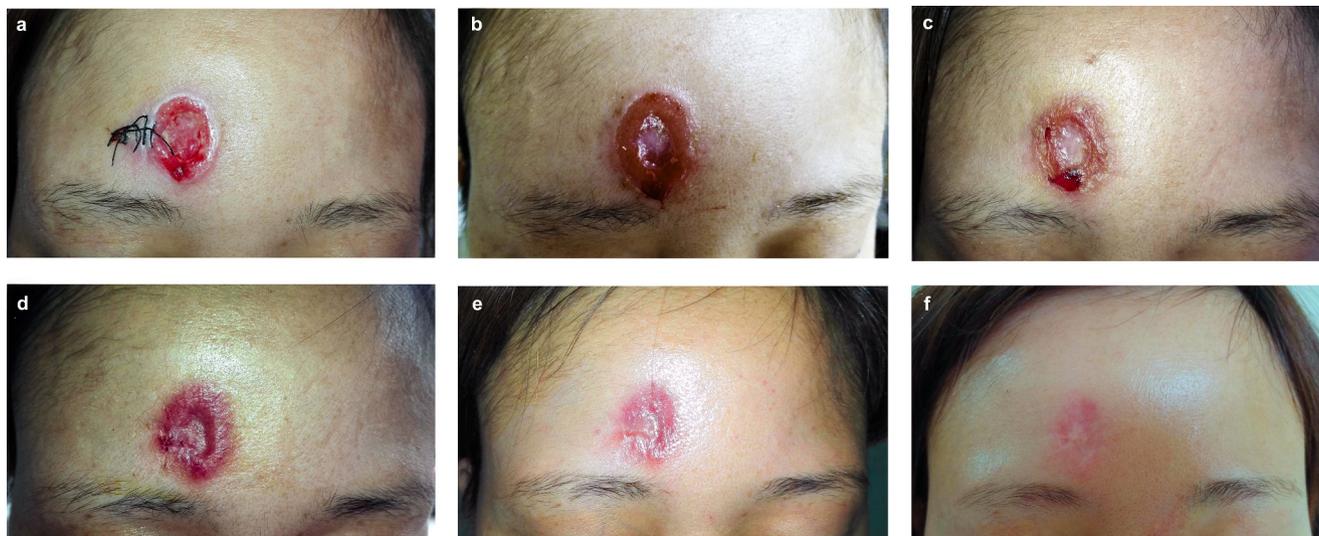


FIGURE 5 Progress in treatment. (a) One week after the prescribed treatment. (b) Four weeks after the prescribed treatment. (c) Six weeks after the prescribed treatment. (d) Eight weeks after the prescribed treatment. (e) Twelve weeks after the prescribed treatment. (f) Seven months after the prescribed treatment.

slightly irritable, we prescribed the following with the appropriate additions or subtractions based on the original prescription: *Atractylodes macrocephala* Koidz (15 g), *Radix codonopsis* (10 g), *Radix angelicae sinensis* (15 g), *Radix glycyrrhizae* (6 g), Poria cum Ligno Hospite (10 g), *Polygala tenuifolia* Willd (10 g), Parched *Ziziphi spinosae* Semen (10 g), *Aucklandiae radix* (6 g), *Fructus jujubae* (10 g), *Astragalus membranaceus* (15 g), *Radix curcumae* (15 g), *Cortex albizia* (10 g), *Radix bupleuri* (10 g), and *Rhizoma cyperi* (10 g).

From 10 October 2015 to 26 October 2015, the patient revisited the hospital twice, and additional herbal medicine was added or subtracted based on the prescription of WSD. A total of 8 weeks of treatment caused the ulcer to essentially heal, but a hard embankment-like bulge appeared on the edge; thus, the same site was taken for histopathological examination and immunohistochemistry again (Figure 5d). Pathological examination showed epidermal atrophy and numerous cellular infiltrations in the dermis, including lymphohistiocytic, plasmacytic, and neutrophilic infiltrates (Figure 2c and 2d). Immunohistochemistry has changed from pretreatment CD30+++ to post-treatment sporadic positivity (Figure 3c and 3d). The patient continued to receive the appropriate addition or subtraction of drugs based on the original prescription for 12-return visits. The ulcer completely healed, leaving a significant reddish depressed scar; hence, the drugs were withdrawn (Figure 5e). At a return visit 7 months later, the reddish depressed scar on the forehead became inconspicuous, leaving a 3.6 mm × 4.3 mm-colored spot (Figure 5f). Follow-up by telephone during the following 3 years revealed no recurrence of the ulcer. Relevant medical histories and

reports in this study have been approved for publication by the patient.

DISCUSSION AND CONCLUSION

When the patient was diagnosed with PC-ALCL, the area of the forehead ulcer was large, accompanied by significant pain and a large number of thin secretions. The patient did not receive western medicine-related treatment. After 8 weeks of treatment with TCM only, the immunohistochemistry changed from CD30+++ before treatment to scattered positive after treatment. After 12 weeks of treatment, the skin lesions healed completely. No recurrence was observed during the 3 years of telephone follow-up and no adverse reactions occurred.

Anaplastic large cell lymphoma (ALCL), a novel lymphoma type, was first observed by Stein et al. in 1985 [11]. Because tumor cells strongly express the Ki-1 antigen (i.e., CD30), it is also known as Ki-1 lymphoma. ALCL is a rare type of non-Hodgkin's lymphoma, accounting for approximately 2%–7% of non-Hodgkin's lymphomas [10, 11]. According to the physiological and pathological processes of PC-ALCL, current Western medicine treatment mainly includes chemotherapy, radiotherapy, and local surgical resection therapy as well as some targeted therapies, such as anti-CD30 monoclonal antibodies [4, 12, 13]. Surgical excision and radiotherapy are the most common therapies for solitary or localized PC-ALCL, with a good prognosis but a high recurrence rate [14]. A study of 210 patients with cutaneous lymphoma showed that only about 42% of the cases achieve partial or complete remission, and about 40% have a significant

tendency to relapse. Related studies have reported that targeted therapy can trigger peripheral neuropathy and other side effects in patients [15, 16]. In addition, chemotherapy can cause gastrointestinal reactions such as rash, fever, alopecia, nausea, and stomatitis, and even adverse reactions such as hepatotoxicity, nephrotoxicity, and bone marrow suppression [5].

According to TCM theory, diseases are caused by Yin and Yang imbalance. Chinese herbal medicine and acupuncture are both great examples of traditional Chinese therapy that treat disorders and restore the dynamic balance of Yin and Yang. The pathogenic mechanism of fluid retention syndrome, which refers to the retention of thin fluid in the viscera and tissues, usually caused by the decline or disturbance of visceral functions, is proposed in the *Treatise on Exogenous Febrile and Miscellaneous Diseases*. Through TCM dialectical analysis, we believe that the patient had a deficiency of Yang and fluid retention syndrome in the body. Therefore, according to these theories, we adopted the method of promoting fluid metabolism to solve the problem of excessive secretions from the ulcer on the patient's skin surface in the early treatment of PC-ALCL, followed by the method of warming Yang (using WSD) and the external application of *Huanglian ointment* (composition: *Coptidis rhizoma*, *Angelicae sinensis radix*, *Radix rehmanniae recen*, *Cortex Phellodendri chinensis*, and *Curcumaelongae rhizoma*), which is widely used in TCM to promote skin lesion healing and scar repair. WSD is mainly composed of *Aconiti Radix lateralis praeparata*, *Angelicae sinensis radix*, *Cinnamomi ramulus*, and *Paeoniae radix alba*. Modern pharmacological studies have shown that the active ingredients of *Aconiti Radix lateralis praeparata*, such as Higenamine and Monkshood Polysaccharide, have anticancer, anti-inflammatory, analgesic, and immune-regulating functions [17–20]. *Angelicae sinensis radix* has various biological activities, such as antitumor, antiulcer, antimutagenesis, and anti-cell proliferation [21]. *Cinnamomi ramulus* has anticancer, anti-inflammatory, and analgesic pharmacological effects [22]. *Paeoniae radix alba* extract has certain anti-inflammatory and analgesic effects, whereas albiflorin has certain antitumor effects [23–25]. *Huanglian ointment* can promote wound healing, improve anti-infective ability of ulcer surface, and improve blood circulation [26]. Therefore, the TCM formula composed of the above drugs combined with the external application of *Huanglian ointment* has anticancer, analgesia, and anti-inflammatory effects and promotes ulcer healing; thus, this TCM fulfills the purpose of treatment.

This case report provides a reference for the clinical treatment of PC-ALCL using TCM. In the future, further research can be conducted to confirm the reliability and long-term safety of TCM alone in treating PC-ALCL. In addition, the specific mechanism of TCM in the

treatment of PC-ALCL should be further clarified. Nevertheless, this study indicates that TCM is an important alternative therapy for the treatment of PC-ALCL.

AUTHOR CONTRIBUTIONS

Kai Li: Conceptualization; investigation; methodology; resources. **Tingting Bao:** Investigation; visualization; writing—original draft; writing—review & editing. **Ruonan Wei:** Investigation; writing—original draft. **Yingying Yang:** Investigation; supervision; writing—original draft. **Mengjiao Kang:** Investigation; writing—original draft. **Wei Zhang:** Investigation; methodology. **Xianyu Zeng:** Conceptualization; data curation; resources. **Yiqun Duan:** Conceptualization; investigation; resources; visualization; writing—review & editing. **Liuqing Chen:** Data curation; resources; supervision; writing—review & editing. **Linhua Zhao:** Conceptualization; investigation; methodology; supervision; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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