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CASE REPORT

Primary cutaneous anaplastic large-cell lymphoma with *DUSP22-IRF4* rearrangement following insect bites

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Abstract

Primary cutaneous anaplastic large-cell lymphoma (pC-ALCL) is distinguished from systemic anaplastic large-cell lymphoma (S-ALCL) with cutaneous involvement. Although pC-ALCL is a unique entity with different genetics, clinical characteristics, and prognosis, its causes are unknown. Herein, we report the case of a Chinese woman with a 4-month history of a gradually enlarged ulcerative mass in her right forearm following an unidentified insect bite. Biopsy revealed an extensive infiltrate with patches of large anaplastic lymphoid cells. These cells were immunohistochemically positive for CD45, CD30, and TIA-1 and negative for CD2, CD3, CD4, CD5, CD20, CD7, CD8, and ALK-1. *DUSP22-IRF4* rearrangement was detected; on the other hand, *TP63* rearrangement was not observed by fluorescence in situ hybridization (FISH). No Epstein-Barr virus-encoded small RNAs (EBERs) were detected by ISH. Rearrangement of monoclonal *TCR* gene was found using BIOMED-2 polymerase chain reaction. No abnormality was found on the subsequent positron emission tomography-computed tomography (PET-CT) scan. After five cycles of cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP) chemotherapy, the patient achieved complete remission. This is the first report of a unique pC-ALCL with *DUSP22-IRF4* rearrangement following an insect bite other than S-ALCL involving the skin.

KEYWORDS
anaplastic large-cell lymphoma, cutaneous, *DUSP22-IRF4*, insect bite, primary

1 | INTRODUCTION

Primary cutaneous lymphomas are a heterogeneous group of T- and B-cell lymphomas manifesting in the skin, with no other organ involvement at presentation. Based on the 2018 update of the World Health Organization-European Organization for Research and Treatment of Cancer consensus classification, the different subtypes of primary cutaneous T-cell lymphomas (pC-TCLs) can be classified by histopathological criteria and immunohistochemical staining combined with clinical manifestations.[1,2] Primary cutaneous CD30+ lymphoproliferative disorders (LPDs) account for a quarter of all pC-TCLs.[2] Owing to the similarity between histopathology and immunophenotype, primary cutaneous CD30+ LPD includes primary cutaneous anaplastic cell lymphoma (pC-ALCL) and lymphomatoid papulosis. The causes of pC-ALCL and S-ALCL are still unknown. However, mosquito bites with subsequent reactive infiltration of CD4+ T lymphocytes

have been reported to be associated with ALK+ S-ALCL other than pC-ALCL.[3] Herein, we report the case of a Chinese woman with pC-ALCL without CD4+ T lymphocytes infiltration following an unidentified insect bite. To the best of our knowledge, this is the first report of ALK− pC-ALCL following an insect bite. We consider that this report may provide specific clinical clues to the definite diagnosis of cutaneous lymphoma.

2 | CASE REPORT

A 68-year-old Chinese woman who had no previous history of insect bite hypersensitivity presented with a 4-month history of a progressively enlarged nodule in her right forearm. The lesion initially presented as a blister following a bite by an unidentified insect. Incision and drainage were performed at a local hospital. The lesion became a nodule with a superficial ulcer after 3 weeks. Gross examination revealed a red solitary mass measuring 3.0 cm × 2.5 cm, with an ulcer of 1.8 cm × 0.5 cm in the surface of central. The ulcerated mass was surrounded by patches and plaques. The whole lesion was 0.8 cm above the surface of the skin (Figure 1A). No more skin lesions or any lymphadenopathy was found. The patient did not complain of any systemic symptoms such as B symptoms and malaise. Laboratory analyses revealed normal lactate dehydrogenase (LDH) levels and hepatorenal function tests.

A biopsy of the cutaneous nodules was performed. Histopathology revealed nearly normal epidermis and diffuse infiltrate with large anaplastic lymphoid cells in the dermis without evident small lymphocytes background (Figure 1B). The large lymphoid cells had the common morphological characteristics of anaplastic cells, having round, oval, or horseshoe-shaped nuclei, abundant cytoplasm, and prominent eosinophilic nucleoli. Mitotic figures could be easily found (Figure 1C). Immunohistochemically, the large lymphoid cells were positive for CD45 (Figure 1D), CD30 (Figure 1E), TIA-1, and ki-67 (+, 80%), and negative for CD2, CD3, CD5, CD7, CD20, ALK-1, CD4, and CD8. *DUSP22-IRF4* rather than *TP63* rearrangement was detected by fluorescence in situ hybridization (FISH) (Figure 1F). No Epstein-Barr (EBV) virus infection was detected. Rearrangement of monoclonal *TCR* gene was found using BIOMED-2 polymerase chain reaction. The clinicopathological diagnosis was pC-ALCL with common histopathology. No abnormalities were detected in the subsequent PET-CT. The Ann Arbor classification revealed stage IE. The patient underwent an extensive excision of the mass. After the patient's intensive application, five cycles of CHOP chemotherapy at 4-week intervals were taken. The hyperplastic scar and pigmentation gradually decreased and eventually disappeared. The patient achieved complete remission (CR) 6 months after diagnosis. Two years of follow-up showed no recurrence or systemic disease.

3 | DISCUSSION

ALCLs are an uncommon subtype of peripheral/mature T-cell lymphomas, heterogenous in clinical, pathological, and genetic aspects.[4] The tumor cells are usually large, have abundant cytoplasm and

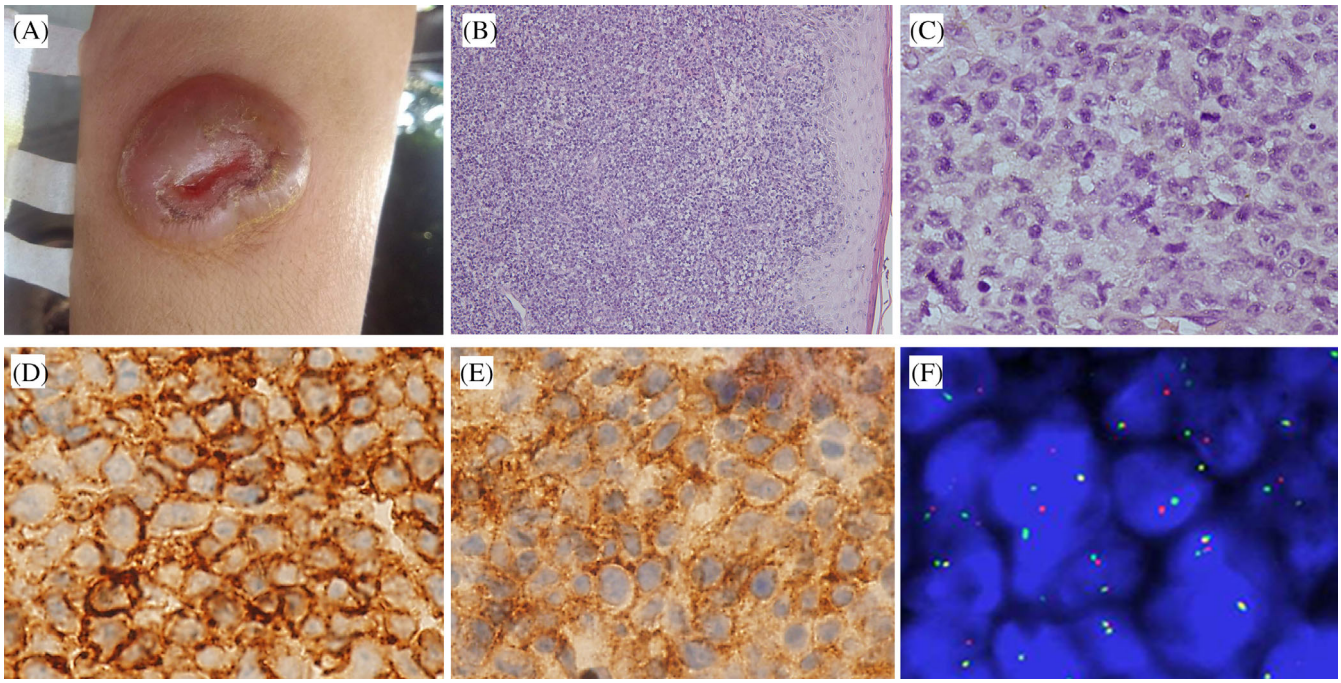

FIGURE 1 Primary cutaneous anaplastic large-cell lymphoma with *DUSP22-IRF4* rearrangement. Gross appearance of skin lesion (A). Medium-to-large distribution of the dysplastic lymphocytes in the dermis (B, H&E ×200). Abundant nucleoli and pathological mitotic image (C, H&E ×400). The cells were positive for CD45 (D, immunohistochemistry (IHC) ×400) and CD30 (E, IHC ×400). Fluorescent in situ hybridization shows *DUSP22-IRF4* gene rearrangement (F, fluorescence in situ hybridization)

horseshoe-shaped nuclei, and are positive for CD30. ALCLs are classified into two distinct entities, namely, ALK+ and ALK−, according to ALK rearrangement and expression of the ALK protein; the two ALCLs share comparable morphological and phenotypic features.[5] The main difference of clinical features between ALK+ and ALK− ALCL is the prognosis. Overall, the long-term prognosis of ALK+ ALCL is better than that of ALK− ALCL.[6] ALK+ or ALK− ALCL frequently involves lymph nodes and extranodal sites including the skin.

Nevertheless, pC-ALCL is a distinct entity localized in the skin without any extracutaneous disease at diagnosis. Unlike systemic ALCL, pC-ALCL does not express ALK and usually has a favorable prognosis. It must be distinguished from systemic ALCL with cutaneous involvement. pC-ALCL has unique cytogenetics, clinical features, and outcomes. Rearrangements of *DUSP22-IRF4* located on chromosome 6p25.3 are found in approximately 25% of pC-ALCLs that might be related to the specific biphasic pattern: Extensive epidermotrophism with small-to-medium-sized T-cells with cerebriform nuclei and dysplastic medium-to-large cells infiltrate in the dermis, simulating transformed mycosis fungoides.[7,8] *DUSP22* rearrangements are also detected in about 30% of systemic ALK− ALCL and promote better prognosis.[9]

As to the pathogenesis of cutaneous TCLs, a common assumption is that cutaneous TCLs are the result of chronic T-cell activation by antigen presentation mediated by Langerhans cells.[10] Rare cases of skin involvement by ALK+ ALCL rather than pC-ALCL following insect/arthropod bites have been reported.[3,11] The role of insect/arthropod bites in the etiology of ALK+ ALCL is unknown. It is assumed that antigens associated with mosquito bites may cause an inflow of CD4+ T lymphocytes. The subsequent release of cytokines from the insect bite could serve as a "second hit," triggering the activation and proliferation of the cells.[11] However, in our case, CD4 was expressed neither in tumor cells nor in small lymphocytes. Therefore, we do not speculate that CD4+ T lymphocytes play a similar role in such circumstances.

Some children and adolescents who suffered from CD30+ lymphoma with cutaneous involvement have been reported. The condition of a 14-year-old girl with isolated cutaneous ALK+ ALCL after mosquito bites rapidly progressed to central nervous and cardiac involvement. Our patient, however, was elderly and had presented with a good prognosis.[12,13] Why these differences occurred warrants further studies, we consider that ALK rearrangement, the expression of ALK-1 protein, aging, and immune degeneration may be some of the underlying reasons.

The common clinical features of hypersensitivity to mosquito bites (HMB) are local skin lesions including erythema, bulla, ulceration, or scar formation. Sometimes systemic manifestations such as hyperpyrexia, hepatosplenomegaly, and lymphadenopathy are also observed.[14] Patients with HMB usually suffer from chronic EBV infection and natural killer cell leukemia/lymphoma.[15-18] It has also been reported that such patients can develop other types of lymphoma mostly with EBV infection.[19-21] However, our case is not ALK+ systemic ALCL involving the skin, or EBV-associated LPD, rather pC-ALCL following an insect bite.

To the best of our knowledge, this is the first report of a case of pC-ALCL with *DUSP22-IRF4* rearrangement following an insect bite that presents typical morphology, immunotype, and outcome. No infiltration of CD4+ lymphocytes in the background was found. More similar cases should be studied for clinicopathological characteristics of pC-ALCL.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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