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Case Report

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Delayed Recognition of Primary Cutaneous Anaplastic Large Cell Lymphoma Mimicking Pyogenic Infection: A Lesson from Primary Care

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Abstract

Early-stage cutaneous lymphoma often mimics non-malignant skin disorders, leading to common misdiagnoses and delays in appropriate treatment. A 44-year-old Malay male presented with a progressive ulcerating nodular lesion on his left medial forearm, which had been treated for a pyogenic cutaneous infection with three different courses of oral antibiotics. The patient even attempted self-treatment with traditionally prepared chalk powder. On the fourth visit to the primary care clinic, a referral to the dermatology clinic was made. A biopsy was done, and histopathology and immunohistochemistry studies of the skin lesion were suggestive of anaplastic lymphoma kinase (ALK) negative anaplastic large cell lymphoma (ALCL). Staging of the disease showed that it was limited to an early stage without systemic involvement. The cutaneous lymphoma in this case was successfully treated with radiotherapy after the failure of oral methotrexate. Early recognition of pc-ALCL is important to avoid delayed treatment. This case highlights the need for greater awareness among primary care physicians of unusual but important dermatological disorders, particularly cutaneous malignancies. Misdiagnosis can impair the patient-doctor relationship and reduce patient compliance with treatment.

Keywords: Cutaneous malignancy, Lymphoma, Delayed diagnosis, Pyogenic infection

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INTRODUCTION

Primary cutaneous (pc) ALCL is a rare type of indolent lymphoproliferative disorder of the skin, characterised by strong expression of the cytokine receptor CD30. ALCL is a distinctive variety of non-Hodgkin's lymphoma (NHL), accounts for 2% to 3% of all NHL.[1] pc-ALCL can take many different forms in the early stages of the disease, mimicking other non-malignant or infectious skin disorders and making diagnosis challenging. Improperly managed pc-ALCL has a severe impact on patients' functioning, emotional health, and social well-being. Furthermore, misdiagnosis may lead to distrust, poor adherence to medications, and non-compliance with treatment plans.

CASE REPORT

A 44-year-old Malay male with no pertinent past medical history presented with a nodular lesion on his left medial forearm that had been present for three months. There was no history of fever and constitutional symptoms. Family history was unremarkable, without a significant family history of malignancy. The lesion began as a progressively enlarging, painless nodule, which ulcerated after one week (**Figures 1a and 1b**). He consulted two different general practitioners within two months. With impressions of a pyogenic cutaneous infection, the patient was prescribed three different courses of antibiotics: oral cloxacillin for one-week, oral amoxiclav for five days, and oral ampicillin-sulbactam for one week. He was compliant and completed the courses of cloxacillin and amoxiclav as prescribed; however, the treatment response was not as expected. He lost trust in his general practitioners and subsequently attempted to self-treat with traditionally prepared chalk powder known as "*kapur*," without completing the oral ampicillin-sulbactam prescribed.

The increase in the size of the nodular skin lesion caused anxiety in the patient (**Figure 1c**). He visited the general practitioner's clinic again and, on this occasion, he was referred to the dermatology clinic at Banting Hospital in Selangor. In light of the possible differential diagnosis of a cutaneous fungal infection, oral Itraconazole was started while awaiting the dermatology clinic appointment.

During the dermatology review, a violaceous nodule measuring 4.5 cm x 2.5 cm was noted on the medial left arm. There was no hepatosplenomegaly, and no other peripheral lymph nodes were palpated. A biopsy of the lesion was arranged, and the results revealed dense lymphoid infiltration within the dermis (**Figures 2a and 2b**). Immunohistochemistry studies of the atypical lymphoid cells showed strong and diffuse positivity for CD30. The cells were also positive for CD3, CD5, CD2, CD4, and CD56, with an aberrant loss of CD7, and negative for CD8 (**Figures 2c, 2d and 2e**). The atypical lymphoid cells were negative for pancytokeratin, CD20, and ALK (**Figure 2f**). Bacterial, fungal, and mycobacterial cultures from the skin biopsy sample returned negative results.

Whole body fluorodeoxyglucose (FDG) F18 positron emission tomography (PET) scans show multiple hypermetabolic nodules at the medial site of the left elbow, with a maximum standardised uptake value (SUVmax) of 8.2. There were no FDG-avid nodules or active disease elsewhere. No abnormal lymphoid or blast cells were seen in the peripheral blood film examination. Bone marrow aspiration showed normocellular marrow with no excess of blast cells or abnormal lymphoid cells. There was no evidence of lymphomatous infiltration from the trephine biopsy sample.

The case was co-managed with the haematology and oncology services. He was started on oral metho-

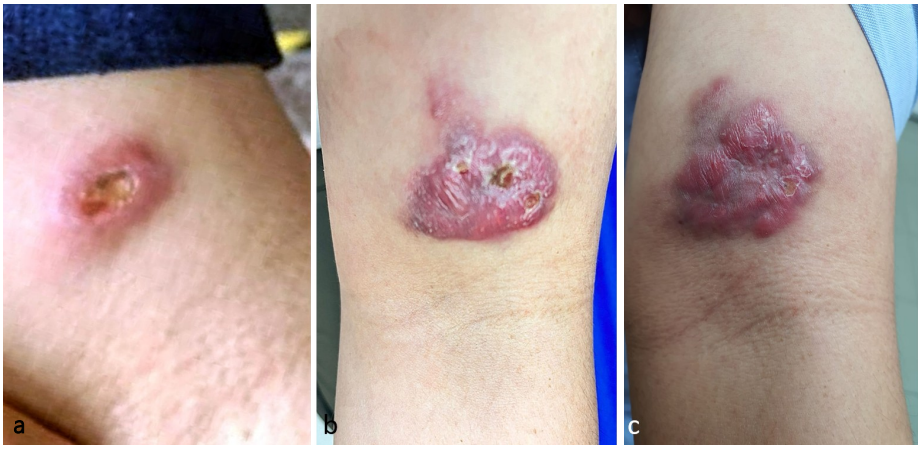

Figure 1: a) Lesion over left elbow began with ulcerated nodule, which progressively in size (b), and c) Violaceous nodule over the medial left arm during first clinic visit.

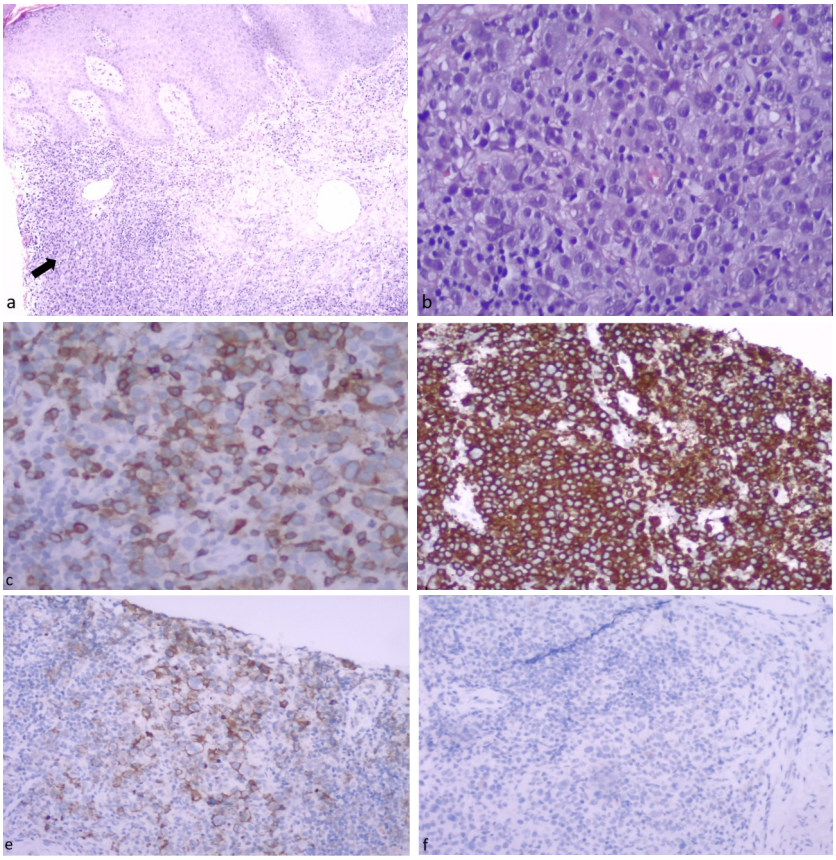

Figure 2: a) Neoplastic lymphoid cells infiltrating dermis layer (arrow) (H&E x4), b) Neoplastic lymphoid cells are large with vesicular nuclei and prominent nucleoli (H&E x20), c) Positive for CD3 immunostaining, d) Positive for CD30 immunostaining, e) Positive for CD56 immunostaining, f) Negative for ALK immunostaining.

-trexate 10 mg weekly. Despite good compliance with oral methotrexate, the response was poor after 12 weeks. The size of the nodular skin lesion continued to enlarge, measuring 5 cm x 7 cm by the 12th week of methotrexate treatment (**Figure 3a**). Targeted radiotherapy was subsequently arranged. He underwent 20 radiotherapy fractions at doses of 30 Gy doses of radiotherapy over four weeks. The outcome of radiotherapy was good. Six weeks after radiotherapy, the skin lesion resolved leaving post inflammatory hypopigmented patch with fine scales at the centre surrounded by hyperpigmented border (**Figure 3b**), no features of local disease recurrence were observed during the 8-month post radiotherapy review (**Figure 3c**).

Repeated PET CT 20 weeks after completed radiotherapy showed resolved hypermetabolic cutaneous lesions at the medial side of left elbow without new FDG-avid nodal or active disease elsewhere.

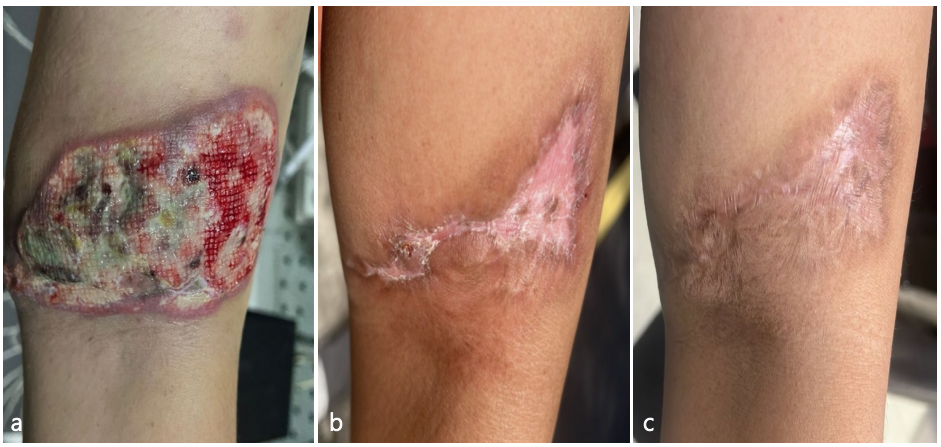

Figure 3: a) The lesion continued to enlarge, forming ulcerated plaque after 12 weeks of oral Methotrexate, b) The lesion completed flattened with remaining post inflammatory hypopigmented scar with fine scales at the centre with hyperpigmented border and, f) No features of local disease recurrence were observed during the 8-month post radiotherapy review.

DISCUSSION

pc-ALCL accounts for about 9% of cutaneous lymphomas and presents with a variety of morphologic spectra, including solitary or multifocal nodules, papules, plaques, and cellulitis-like ulcerations.[1] In this case, the lesion presented as a solitary ulcerated nodule on the left medial forearm (**Figure 1a**). The patient visited several general practitioners and was treated for a cutaneous infection with multiple courses of different antibiotics, without any improvement. Without completing the third course of antibiotics, the patient turned to traditional remedies by applying chalk powder to the skin lesion.

Misdiagnosis could lead to a negative experience for the patient, a distrust in the physician's competence, and hinder the patient-doctor relationship,[2] as shown in this case. Despite not responding to treatments prescribed, a referral to the dermatologist was delayed. Referral to dermatology clinic was only made on his fourth visit to primary care clinic. The biopsy of the skin lesion was done during the first visit to dermatology clinic. Dense CD30 positive atypical lymphocytes infiltration within the dermis (**Figure 2a, 2b**) supported the diagnosis of cutaneous ALCL (C-ALCL). Immunohistochemistry studies especially ALK-1 negativity, together with other staging modalities including whole body FDG PET scan, bone marrow aspiration and trephine biopsy excluded the possibility of systemic ALCL with cutaneous involvement.[3,4]

The disease was classified as $T_2N_0M_0$ according to the International Society for Cutaneous Lymphomas (ISCL) and the European Organisation for Research and Treatment of Cancer (EORTC) proposal on the TNM classification.[4] Low-dose oral methotrexate (5 to 20 mg/week) and psoralen and ultraviolet A (PUVA) therapy are the recommended treatments for multifocal pc-ALCL. Monotherapy with oral methotrexate at 10 mg weekly was initiated for twelve weeks; however, the results were disappointing, with an increase in the size of the skin lesion. Complete surgical excision and local radiotherapy are alternative treatment options for pc-ALCL with grouped localised lesions, up to stage $T_2N_0M_0$.[4,5] Local radiotherapy was subsequently scheduled following discussions between the multidisciplinary team and the patient in a shared decision-making process. Fortunately, he responded well to radiotherapy, with the skin lesion resolving after 20 sessions of treatment.

Follow-up recommendations for pc-ALCL are individualised: every 6 to 12 months for stable and indolent types of pc-ALCL, and every 4 to 6 weeks for active or progressive disease.[4] Whole body PET scan three months after completed radiotherapy showed complete resolution of hypermetabolic cutaneous lesions. The follow-up session was scheduled in another 4 months to monitor symptoms and disease recurrence.

Despite delayed in recognition of pc-ALCL, the disease was confined to its early stage on diagnosis. Education to increase awareness for frontline clinicians including general practitioners regarding important dermatological disorders could be implemented with dermatological conferences and continuous medical education. The use of teledermatology and teledermoscopy for referrals of patients with suspicious skin disorder should be considered to allow early assessment of dermatologists' opinions and services. The implementation of feedback loop can help to create a system for dermatologists to provide feedback on referrals, helping primary care physicians refine their referral practices.

CONCLUSION

Heterogeneity in the presentations of pc-ALCL often mimics benign inflammatory dermatoses, making the diagnosis challenging. Early diagnosis of pc-ALCL is crucial to avoid delayed treatment and distress for the patients. Misdiagnosis impairs the patient-doctor relationship and reduces patient compliance with treatment. Furthermore, it exposes patients to unnecessary and potentially harmful treatments. This case highlights the need to increase awareness for local general practitioners on important dermatological disorders, especially cutaneous malignancies. By expediting referrals and facilitating a speedy diagnosis, prompt treatment could be provided to reduce the risk of disease progression.

Take Home Message

- Early recognition is critical: pc-ALCL often mimics benign skin conditions, leading to misdiagnosis and delayed treatment.
- Biopsy persistent lesions: any atypical, non-healing, or antibiotic-resistant skin lesion warrants a biopsy.
- Misdiagnosis harms patient-doctor relationships and treatment compliance; timely referrals improve outcomes.
- Radiotherapy is effective: localised pc-ALCL responds well to radiotherapy, especially when other treatments fail.
- Education and teledermatology: primary care physicians benefit from training on important dermatological disorders, and early access to specialist consultations.

Abbreviations

ALCL	Anaplastic Large Cell Lymphoma
NHL	Non-Hodgkin's Lymphoma
FDG	Fluorodeoxyglucose
PET	Positron emission tomography
ISCL	International Society for Cutaneous Lymphomas
EORTC	European Organisation for Research and Treatment of Cancer
PUVA	Psoralen and ultraviolet A

Declarations

Conflict of interests

The authors declare no conflict of interests.

Patient Consent

Patient consent has been obtained.

Acknowledgement

None

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