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CASE REPORT

Primary Cutaneous CD4+ Small / Medium T-Cell Lymphoproliferative Disorder: A Case Report and Literature Review

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Abstract

Objective: To report the clinicopathological features, immunophenotype, molecular genetic alterations, and treatment strategies of primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (CD4pcSM-LPD).

Methods: A case analysis and literature review were conducted, integrating histopathology, immunohistochemistry (IHC), molecular testing, and follow-up data.

Results: ①CD4pcSM-LPD exhibited indolent biological behavior with a favorable prognosis. ②IHC revealed diffuse strong positivity for CD3 and CD4, partial loss of CD7, scattered "starry-sky" distribution of CD8, sparse expression of follicular helper T-cell markers (PD1, BCL6) in medium-to-large cells, and focal CD30 positivity. ③Molecular analysis identified a monoclonal TCR-B Vβ-Jβ rearrangement. ④ Treatment with methotrexate achieved complete resolution of skin lesions.

Conclusion: CD4pcSM-LPD is a rare polymorphic T-cell proliferative disorder characterized by indolent behavior and excellent prognosis. Due to its rarity, clinicians and pathologists often lack familiarity with this entity, leading to misdiagnosis or overtreatment. This study highlights the clinicopathological, immunophenotypic, and molecular features of CD4pcSM-LPD, emphasizing its distinct diagnostic criteria and management strategies.

Keywords: Primary cutaneous, CD4+, T-cell lymphoproliferative disorder.

Introduction

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (CD4pcSM-LPD) is a rare hematolymphoid neoplasm, accounting for 2%–3% of primary cutaneous lymphoproliferative disorders [1, 2]. In the WHO 4th edition, it was provisionally classified as "primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma." However, the WHO 5th edition reclassified it as a distinct entity under "primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder," reflecting its indolent clinical course and favorable prognosis [1]. This report presents a case of CD4pcSM-LPD and reviews its clinicopathological features, immunophenotype, molecular genetics, and therapeutic approaches to raise awareness of the disease and enhance diagnostic accuracy and optimize clinical management.

Case Presentation

1.1 Clinical History

A 61-year-old male farmer presented with multiple asymptomatic, flesh-colored papules on the back for three months (**Figure 1A**). The patient presented to our clinic on September 11, 2024, with a three-month history of multiple non-pruritic, flesh-colored papules on his back. Mild tenderness was reported, but no ulceration, fever,

chills, or systemic symptoms were noted. Physical examination revealed no superficial lymphadenopathy. Computed tomography (CT) scan identified bilateral axillary lymphadenopathy (largest node: 1 cm in diameter), with no lymphadenopathy detected in other regions. The largest cutaneous nodule (1.0 cm in diameter) on the back was excised for histopathological evaluation. Laboratory tests, including complete blood count, coagulation profile, and serology for hepatitis B, syphilis, and HIV, were unremarkable.

1.2 Methods

The excised skin nodule (1.0 cm × 0.8 cm × 0.8 cm) was fixed in 4% neutral buffered formaldehyde, paraffin-embedded, and sectioned for hematoxylin-eosin (HE) staining and IHC. Antibodies against CD3, CD4, CD5, CD7, CD8, CD20, CD30, TIA-1, GrB, CD21, CD10, BCL6, CXCL13, PD1, and Ki-67 were applied using the SP method (Maxim Biotech, China). TCR rearrangement analysis was performed using BIOMED-2 primers and polyacrylamide gel electrophoresis.

Results

2.1 Histopathology

Microscopic examination revealed nodular and cord-like infiltrates of small-to-medium lymphocytes extending from the superficial to deep dermis. Scattered Reed-Sternberg-like cells, multinucleated giant cells, high endothelial venules, eosinophils, and adnexal tropism were observed. No epidermotropism, nuclear atypia, necrosis, or mitotic figures were noted (**Figure 1B–E**).

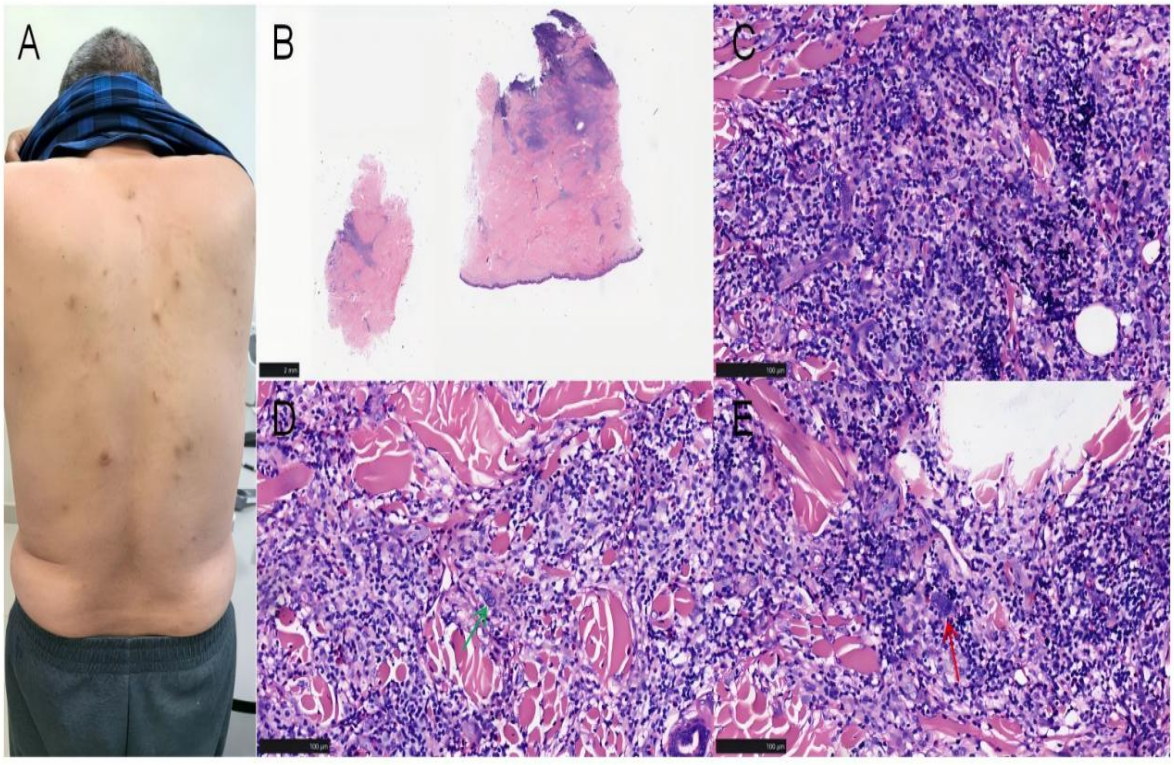

Figure 1: Clinical and histopathological features of CD4pcSM-LPD. (A: Multiple flesh-colored papules on the back. B: Low-power view: Lymphocytic infiltrates extending from the superficial to deep dermis, predominantly involving the deep dermis, with marked adnexotropism. C: Small-to-medium lymphocytes infiltrating the dermis, accompanied by prominent high endothelial venules and scattered eosinophils. D: Green arrow highlights Reed-Sternberg-like cells. E: Red arrow indicates multinucleated giant cells. (A: HE staining, scale bar: 2 mm; C, D, E: HE staining, scale bar: 100 μm).)

2.2 Immunophenotype and Molecular Findings

The lymphocytes showed diffuse positivity for CD3, CD4, and CD5, partial loss of CD7, and scattered CD8+ cells in a "starry-sky" pattern. Medium-to-large cells exhibited sparse expression

of PD1 (10%) and BCL6 (10%), focal CD30 positivity(**Figure 2A–F**), and retained TIA-1/GrB expression. CD21 highlighted atrophic follicular dendritic networks. Ki-67 labeling index was 20%. EBER in situ hybridization and CD15 was negative (Data not shown in the figures.). TCR-B Vβ-Jβ clonality was confirmed .

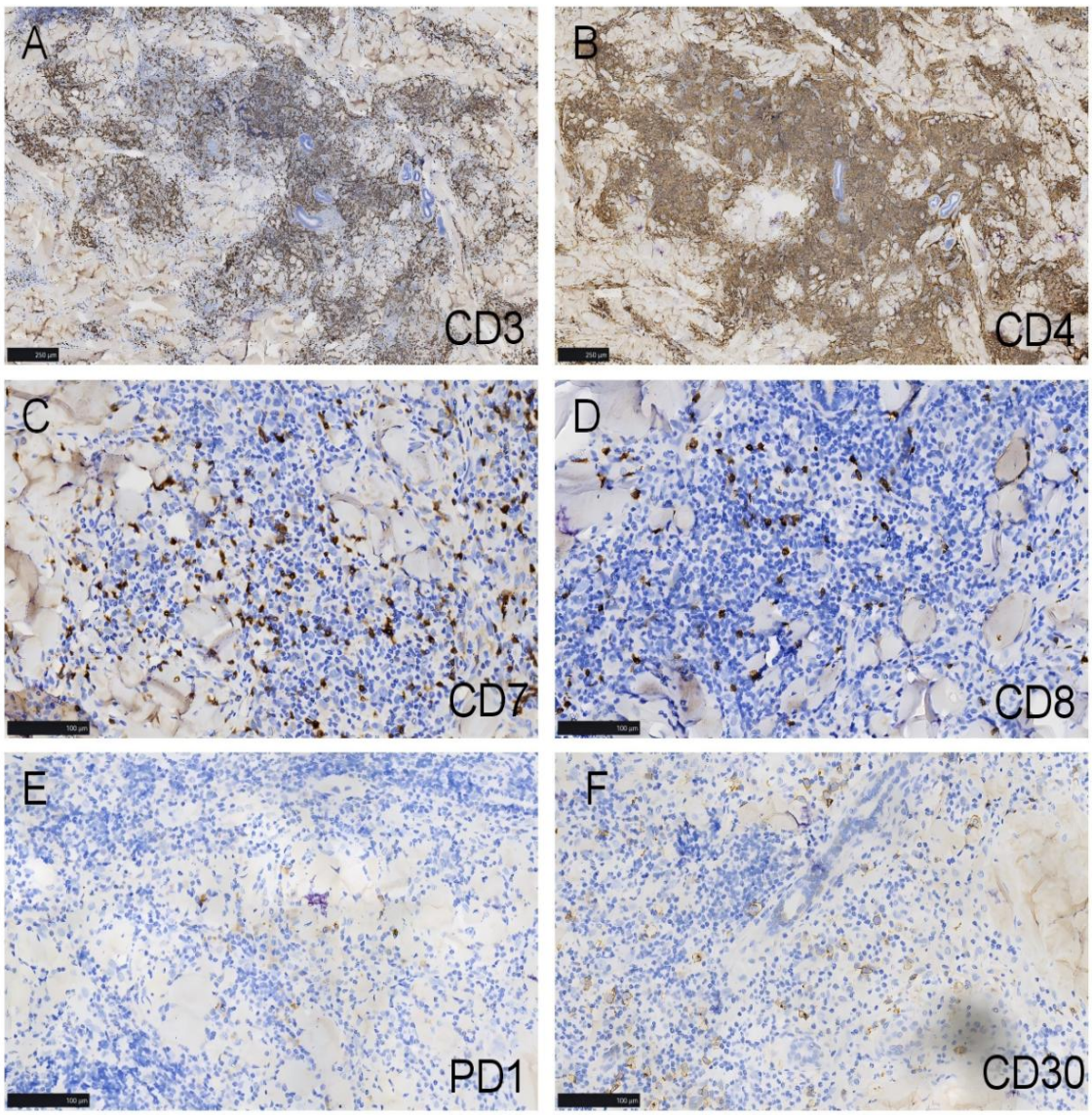

Figure 2: Immunohistochemical staining patterns. (A: Diffuse positivity for CD3. B: Diffuse strong positivity for CD4. C: Partial loss of CD7 expression. D: Scattered "starry-sky" distribution of CD8+ cells. E: Sparse positivity for PD1 in medium-to-large cells. F: Focal positivity for CD30. (A, B: IHC, SP method, scale bar: 250 µm; C, D, E, F: IHC, SP method, scale bar: 100 µm.))

2.3 Diagnosis and Differential Diagnosis

The diagnosis of CD4pcSM-LPD was established based on histomorphology, immunophenotype, and clonal TCR rearrangement. Key differentials included lymphomatoid papulosis, mycosis fungoides, pseudolymphoma, and cutaneous involvement by angioimmunoblastic T-cell lymphoma (**Table 1**).

Table 1 Differential diagnosis of CD4pcSM-LPD[2-8].

Disease	Clinical Features	Histopathology	Immunophenotype	EBER	TCR Rearrangements	Prognosis

CD4pcSM-LPD	Age: Any age (median: 55 years). Location: Head/neck > trunk > extremities. Lesions: Papules/nodules (solitary > multiple).	Pattern 1: Nodular/diffuse dermal/subdermal infiltrates of small-to-medium polymorphic lymphocytes. Pattern 2: Band-like subepidermal infiltrates with adnexotropism. RS-like cells, multinucleated giant cells, eosinophils.	CD3+, CD4+, scattered "starry-sky"CD8+. Partial loss of T-cell antigens (CD7 > CD5). Sparse follicular helper T-cell markers (PD1/BCL6). Focal CD30+.	-	+	Indolent; excellent prognosis. Lesions resolve after excision or immunosuppression.
LyP	Age: Adults (40–60years). Location: Trunk/extremities. Lesions: Papules/nodules with ulceration.	Mixed inflammatory infiltrate with large lymphocytes (clusters/sheets). RS-like cells; variable epidermotropism.	CD30+, CD3+, CD4+ (types A/B/C) or CD8+ (types D/E/F). CD15–, ALK–, EMA–.	-	90%- ; 10%+	Indolent; self-regressing. Lesions resolve spontaneously or with anti-inflammatory therapy.
Pseudolymphoma	Age: Any age. Location: Face (nose/cheeks). Lesions: Red nodules (solitary/multiple).	Superficial dermal mixed lymphocytic infiltrates. Lymphoid follicles. epidermotropism/adnexotropism.	Mixed T/B-cell markers. Intact follicular dendritic networks (CD21+).	-	-	Benign. Lesions resolve after excision or anti-inflammatory therapy.
MF	Age: middle-aged and older adults (rare in children). Location: Generalized. Lesions: Patches → plaques → tumors with ulceration.	Small-to-medium lymphocytes with cerebriform nuclei. Epidermotropism (Pautrier microabscesses) ± adnexotropism.	CD2+, CD3+, CD5+, CD4+. CD8+ (pediatric MF). Partial T-cell antigen loss (CD7 > CD5). Focal CD30+.	-	+	Aggressive; poor prognosis. Requires systemic therapy.
pcPTCL-NOS	Age: middle-aged and older adults. Location: Diffuse plaques/papules/	Pleomorphic small-to-large lymphocytes infiltrating full dermal thickness.	TCR-γ, TCR-δ CD3+, CD2+, variable CD4/CD8. Cytotoxic markers (TIA-	-	+	Highly aggressive; poor prognosis. Median OS: 2–5

	tumors with ulceration. Systemic: B symptoms.		1/GrB+). Partial T-cell antigen loss.			years.
AITL with skin involvement	Age: middle-aged and older adults. Location: Generalized. Systemic: Lymphadenopathy, B symptoms. Lesions: Maculopapular rash.	Proliferation of high endothelial venules. Perivascular clear lymphocytes ± RS-like cells.	T-cell markers + follicular helper T-cell markers (PD1/BCL6/CXCL13). Disorganized follicular dendritic networks (CD21+).	+/-	+	Aggressive; poor prognosis. Median OS: 3–5 years.

Abbreviations：CD4pcSM-LPD: Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder；LyP: Lymphomatoid papulosis；MF: Mycosis fungoides；pcPTCL-NOS: Primary cutaneous peripheral T-cell lymphoma, not otherwise specified；AITL: Angioimmunoblastic T-cell lymphoma；RS-like: Reed-Sternberg-like；OS: Overall survival.

2.4 Treatment and Follow-Up

The patient received methotrexate (10 mg weekly). Skin lesions regressed significantly within 4 days and completely resolved by 30 days. Follow-up at 6 months showed no recurrence.

Discussion

CD4pcSM-LPD is a rare polymorphic T-cell proliferative entity predominantly affecting adults, with a median age of onset at 55 years and no significant gender predilection [1]. Clinically, CD4pcSM-LPD typically presents as solitary cutaneous nodules localized to the head and neck region. Truncal involvement is less common and often manifests as multiple lesions. The disease exhibits indolent biological behavior, characterized by minimal nodal involvement and a favorable prognosis [1]. Due to its rarity, comprehensive epidemiological data remain limited. However, emerging evidence suggests an association with immunocompromised states, including post-cardiac transplantation, chronic pneumonia, and rheumatoid arthritis [7]. Therapeutic strategies are tailored to disease extent: local excision is recommended for solitary lesions, while systemic immunosuppressants such as prednisone and methotrexate achieve complete remission in multifocal cases [4, 7].

According to a comprehensive literature review, CD4pcSM-LPD is histogenetically derived from follicular helper T cells (Tfh) and exhibits two distinct histomorphological growth patterns [2]. **Pattern 1**: Dense nodular or diffuse infiltrates of small-to-medium polymorphic lymphocytes within the dermis or subdermal layer. **Pattern 2**: Band-like subepidermal infiltrates of small-to-medium polymorphic lymphocytes with adnexotropism (predilection for skin appendages). Both patterns may feature Reed-Sternberg-like cells, rare multinucleated giant cells, and admixed eosinophils and histiocytes. Immunohistochemically, neoplastic cells consistently express CD3 and CD4, with partial loss of pan-T-cell antigens (e.g., CD7, more frequently than CD5). Follicular helper T-cell-related markers (e.g., PD1, BCL6) are sparsely expressed in medium-to-large cells, typically at low percentages, as summarized in **Table 2**. Molecular studies confirm clonal TCR rearrangements, while recent evidence implicates CD27/CD70 pathway activation as a potential pathogenic driver [9]. Key differential diagnoses and discriminative features are outlined in **Table 1**.

Table 2 Expression profile of follicular helper T-cell markers in CD4pcSM-LPD[4].

Immunomarker	Expressing Cells	Expression Pattern	Expression Rate (Median)
CD10	Medium-to-large cells	Sparse	0–5% (2%)
BCL6	Medium-to-large cells	Sparse	1–10% (5%)
CXCL13	Medium-to-large cells	Sparse	1–10% (5%)
PD1	Medium-to-large cells	Clustered or "rosette-like"	10–30% (20%)
ICOS	Small-to-medium-to-large cells	Sparse	25–30% (27%)

We summarize the clinicopathological features, immunophenotypic profile, and molecular genetic alterations of CD4pcSM-LPD. Our findings aim to enhance diagnostic accuracy and mitigate unnecessary interventions by improving recognition of this entity among clinicians and pathologists. Furthermore, we emphasize the critical need for future research to elucidate the etiology and pathogenesis of CD4pcSM-LPD, which will facilitate advancements in its clinical management and therapeutic strategies.

Conclusion

CD4pcSM-LPD is a rare, indolent T-cell proliferation requiring multidisciplinary collaboration for diagnosis. This case underscores the importance of recognizing its distinct clinicopathological and molecular features to avoid misdiagnosis and guide appropriate therapy. Further research is warranted to elucidate its pathogenesis and refine treatment protocols.

Author Contributions: J.C. organized and wrote the manuscript; FG.H. Performed immunohistochemical staining and TCR rearrangement analysis, organized and annotated figures, conducted literature review and data compilation. DS.W. designed the structure and framework of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Availability of data and material

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Declarations

Conflict of interest

The authors declare no relevant competing interests to disclose.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Bishan Hospital of Chongqing

Medical University, the patient provided sample acquisition and informed consent for the study in accordance with approved guidelines.

Consent for publication

Not applicable.

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