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Case Series

The Importance of Excluding Cutaneous T-Cell Lymphomas in Patients with a Working Diagnosis of Papuloerythroderma of Ofuji: A Case Series

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Abstract
Papuloerythroderma of Ofuji (PEO) is an erythroderma-like eruption with flat-topped papules that spare the skin folds (a "deck-chair sign" finding). Many infections, medications, and systemic diseases have been associated with PEO, including cutaneous T-cell lymphomas (CTCL). The relationship between the clinical presentation of PEO and CTCL remains poorly elucidated. Clinical, laboratory, and histopathological data were obtained from the Lymphoma Clinic at the Ottawa Hospital, Canada. We report 5 patients with deck-chair-sign-positive CTCL, mycosis fungoides, and Sézary syndrome variants. We contend that PEO should be viewed as a diagnosis of exclusion and that these patients should be monitored carefully for possible

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emergence of CTCL. Skin biopsy alone is not sufficient to exclude CTCL in these patients. A skin eruption demonstrating a positive deck-chair sign may signify systemic/leukemic CTCL and, therefore, warrants a thorough investigation, including skin biopsy, flow cytometry, and T-cell receptor clonality studies.

Introduction

A distinct clinical entity, now known as papuloerythroderma, was first identified by Ofuji et al. in 1984 [1]. Described in 4 male patients in Japan (a human T-cell lymphotropic virus-1 (HTLV-1)-endemic region), this report found an erythroderma-like eruption and flat-topped papules that spared the skin folds, a finding later termed the "deck-chair sign" [2]. Peripheral eosinophilia and lymphopenia were also observed in some patients. Unfortunately, the HTLV-1 status in these patients was not reported at that time. With an estimated incidence of 1.5 cases per million individuals per year [3], papuloerythroderma of Ofuji (PEO) remains a rare condition. However, multiple factors indicate that PEO is often underdiagnosed and underreported. Many infections, medications, and, more importantly, systemic diseases have been associated with PEO, including cutaneous T-cell lymphomas (CTCL). The relationship between the clinical presentation of PEO and CTCL remains poorly elucidated.

Materials and Methods

The 5 patients reported in this case series provided written informed consent in accordance with the Declaration of Helsinki. Clinical, laboratory, and histopathological data were obtained from the Lymphoma Clinic at the Ottawa Hospital, Canada, and are presented in Table 1 and Figure 1.

Case Presentations

Case 1

A 75-year-old Caucasian male was diagnosed with rapidly progressing Sézary syndrome. The initial skin biopsy was diagnostic of $CD30^+$ mycosis fungoides (MF). Notably, during later visits, a re-biopsy of his erythrodermic skin showed nonspecific excoriations, spongiotic changes, and dermal edema with superficial, mixed, acute, and chronic inflammation. Over a period of months, this patient rapidly progressed from 10% body surface area (BSA) patch-plaque disease to 80% BSA involvement, in addition to developing palpable lymph nodes and blood disease with frequent soft-tissue infections. On the physical exam in our clinic, he had classic polygonal, erythematous-brown papules, covering his skin surface and clearly sparing the skin folds (a positive deck-chair sign) (Fig. 1a).

Based on recently reviewed diagnostic criteria [4], his laboratory findings confirmed extensive stage IVA_1 Sézary syndrome disease and showed lactate dehydrogenase (LDH) 718 U/L (reference range, 100–205 U/L); HTLV-1-negative serology; high Sézary cell count, 85%

T cells on flow leukemia/lymphoma profile, 80% with $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, and loss of CD26 and CD7 expression, and a CD4:CD8 ratio of >10 (blood stage B_2 disease); T-cell receptor (TCR) β clonality was confirmed on gene rearrangement analysis by polymerase chain reaction; and bilateral inguinal lymphadenopathy on CT thorax, abdomen, and pelvis. His treatment regimen included topical steroids, topical and systemic antibiotics, isotretinoin, interferon-α, and extracorporeal photophoresis. Later, he developed tumors and acquired large-cell transformation on histology. At that point, extracorporeal photophoresis was discontinued, and the patient was started on brentuximab vedotin.

Case 2

A 72-year-old Caucasian female was followed for long-standing stage T1b MF and cutaneous mastocytosis (telangiectasia macularis eruptiva perstans) for over 40 years. Over time, she developed progressive, biopsy-proven, plaque MF, covering 80% of her BSA, but notably sparing her skin folds (Fig. 1b). Further investigations revealed leukemic CTCL. Interestingly, while her leukemic CTCL was diagnosed with flow cytometry and TCR clonality studies, repeat skin biopsy of her erythrodermic skin was not diagnostic and only showed a psoriasiform and spongiotic dermatitis with a lymphocytic inflammatory infiltrate. She was then treated with systemic alitretinoin (as bexarotene is not available in Canada) and interferon-α in addition to skin-directed topical therapies.

Laboratory results confirmed stage IVA_1 CTCL: LDH 196 U/L; HTLV-1/2 antibodies nonreactive; tryptase 5.3 ng/mL (reference range, 3.8–11.4 ng/mL); 38% circulating Sézary cells, 33% abnormal $CD4^+$ T cells with loss of CD26 and CD7 expression, and T cells comprising 70% of lymphocytes with a CD4:CD8 ratio of 21:1 on flow cytometry leukemia/lymphoma profile (blood stage B_2 disease); β, δ, and γ clonality on TCR gene rearrangement; and bilateral, enlarged, inguinal, and axillary lymph nodes on CT thorax, abdomen, and pelvis.

Case 3

An 89-year-old male presented with patch lesions affecting ~30% of his BSA, consistent with MF (Fig. 1c). He had a 2-year history of a nonresolving eruption on the trunk that spared the skin folds. Notably, a skin biopsy was not diagnostic of CTCL, and imaging did not reveal any lymphadenopathy or visceral disease. However, flow cytometry analysis documented the presence of Sézary cells, consistent with blood stage B_2 disease. Based on these findings, the patient was diagnosed with leukemic CTCL (stage IVA_1) and was started on multimodality treatment, including topical steroids, narrow-band ultraviolet B phototherapy, isotretinoin, and interferon-α.

Laboratory testing revealed LDH within normal limits and negative HTLV-1 serology. Further investigations demonstrated 44% circulating Sézary cells. Flow cytometry revealed 82% T cells, with 59% of CD4 T cells (44% of lymphocytes) negative for both CD7 and CD26, and a CD4:CD8 ratio of 8.5. β and γ clonality were found on TCR gene rearrangement studies.

Case 4

An 82-year-old male with a 5-year history of a pruritic rash that did not respond to topical steroids presented with plaque lesions affecting ~20% of his skin surface with a positive deck-chair sign (Fig. 1d). His MF disease was diagnosed on skin biopsy, and he was found to have a mild blood involvement, based in the TCR β clonality findings in the blood. He did not

fulfill any other blood involvement criteria, as recently reviewed elsewhere [4]. He was diagnosed with stage IB ($T_2N_0B_{0b}$) MF. He received treatment with topical steroids, narrow-band ultraviolet B phototherapy, and alitretinoin. LDH was found to be normal, and HTLV-1 status was negative. Imaging studies did not reveal lymph-node or visceral involvement.

Case 5

An 86-year-old African-Canadian female native of Guyana had a long-standing indolent T1b plaque MF. Her initial biopsy was diagnostic of CTCL and showed mild acanthosis, keratosis, patchy parakeratosis, spongiosis, moderate epidermotropism, atypical lymphocytes forming Pautrier's microabscesses, a CD4:CD8 ratio of 6:1, and loss of CD7 expression in the epidermotropic population. Her plaque MF disease had been treated for 6 years with topical steroids. She then developed a positive deck-chair-sign skin eruption (Fig. 1e) and was found to have a leukemic (blood stage B_{1a}) disease with high numbers of $CD30^+$ cells on flow cytometry. Because the patient was mostly asymptomatic, she was treated with alitretinoin and narrow-band ultraviolet B phototherapy.

This patient had LDH 207 U/L; HTLV-1/2 antibodies nonreactive; 8% circulating Sézary cells, 49% T cells, 84% $CD4^+$ T cells with loss of CD26 and CD7 expression, $CD8^+$ cells also exhibited a loss of CD7, and co-expression of CD30 in both $CD4^+$ and $CD8^+$ T cells on flow leukemia/lymphoma cytometry profile; no clonality was detected on gene rearrangement studies.

Discussion

In a systematic review published in 2010, Torchia et al. [5] proposed diagnostic criteria and etiological classification of papuloerythroderma (summarized in online suppl. Table 1, www.karger.com/doi/10.1159/000487473). Ofuji and others have commented that, while clinically distinct, multiple causative factors including CTCL underlie the development of papuloerythroderma [6]. Two historic case reports are noteworthy for suggesting cutaneous lymphoma as a differential diagnosis of PEO [7, 8]. Since that time, numerous case reports of PEO have supported the diagnosis of CTCL based on histological findings alone [3, 9–14]. The specific diagnosis of folliculotropic MF was made in several cases [10, 12–14]. Notably, a case report of 3 patients from South Korea observed that PEO might be a variant of early MF, leading these authors to recommend a close follow-up for possible emergence of MF/CTCL once PEO is diagnosed [10]. A systematic review further concluded that "papuloerythroderma-like CTCL" [5] is appropriate nomenclature in cases where the histology under consideration is compatible with CTCL. However, it is very important to note that skin biopsy in erythrodermic MF or Sézary syndrome is often not diagnostic [15], and, hence, flow cytometry and TCR rearrangement studies are necessary before a diagnosis of CTCL can be excluded.

These combined results and previous studies argue that PEO should be viewed as a diagnosis of exclusion and these patients should be monitored carefully for possible emergence of CTCL. Skin biopsy alone is not sufficient to exclude CTCL in these individuals. A positive deck-chair-sign skin eruption may signify systemic/leukemic CTCL. Therefore, these patients warrant a thorough investigation including flow cytometry and TCR clonality stud-

ies. Where appropriate, HTLV-1 serology should be ordered in patients originating from HTLV-1-endemic areas, in intravenous drug users, or in individuals at risk of exposures to this virus. We summarize our recommended work-up for these patients in Table 2.

Statement of Ethics

All patients provided written informed consent in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors declare that they have no competing interests.

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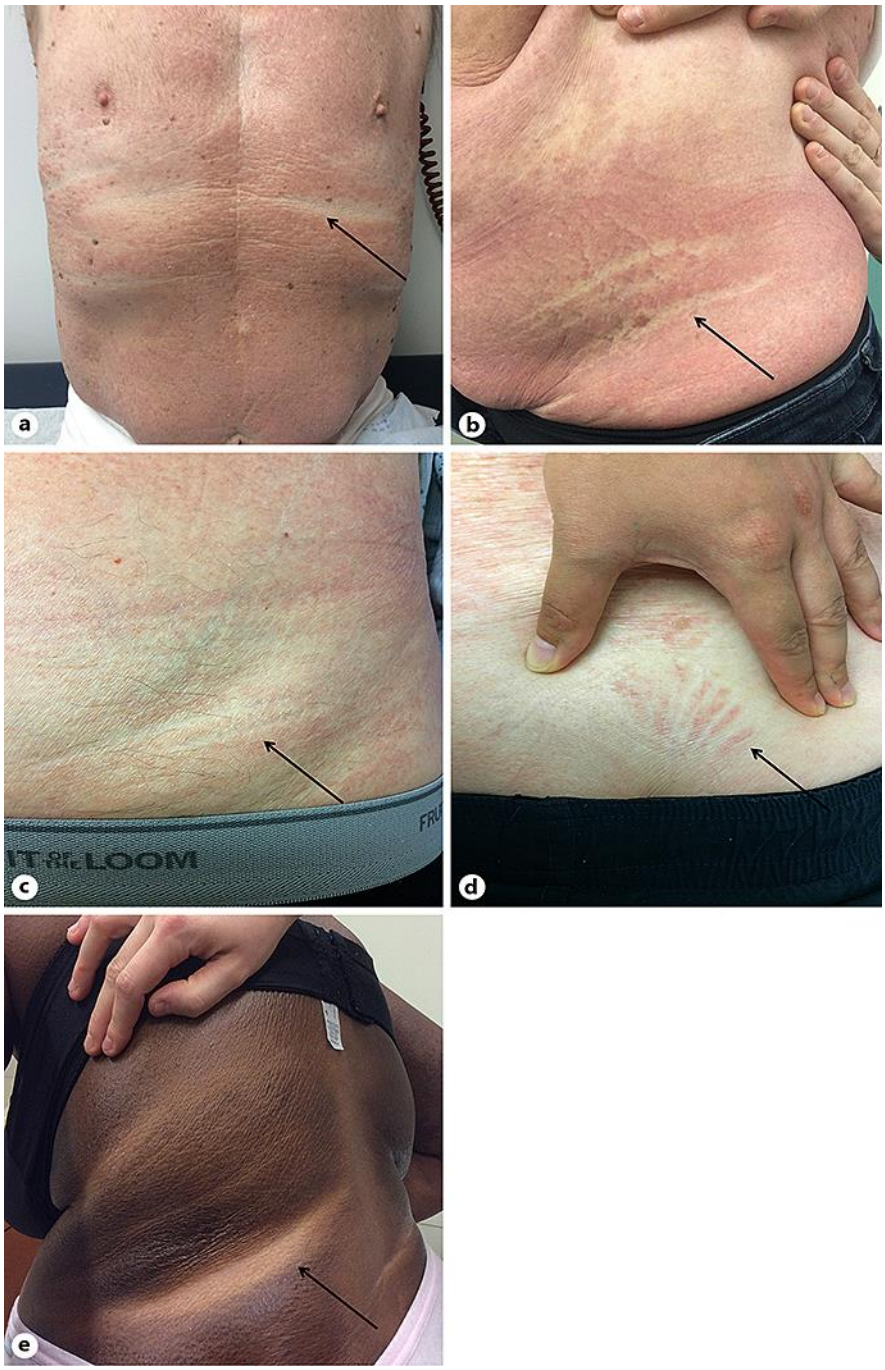

Fig. 1. Positive deck-chair-sign (arrows) skin eruption on the trunk of patient 1 (**a**), who was found to have Sézary syndrome, and on the trunks of patients 2–5 (**b–e**), who were diagnosed with mycosis fungoides / cutaneous T-cell lymphoma with evidence of blood involvement.

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Table 1. Patient characteristics in the present case series

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years	75	72	89	82	86
Sex	Male	Female	Male	Male	Female
Skin phototype	II	II	II	II	V
Country of origin	Canada	Canada	Canada	Canada	Guyana
Skin involvement	80% BSA, plaque lesions with deck-chair-sign skin findings	80% BSA, patch lesions with deck-chair-sign skin findings	~30% BSA, patch lesions with deck-chair-sign skin findings	~20% BSA, plaque lesions with deck-chair-sign skin findings	75% BSA, plaque lesions with deck-chair-sign skin findings
Laboratory findings					
LDH	High	Normal	Normal	Normal	Normal
HTVL-1	Negative	Negative	Negative	Negative	Negative
Blood involvement					
Sézary count	80%	38%	44%	–	8%
Flow cytometry	85% T cells 80% CD7/CD26$^-$ CD4:CD8 ratio: >10	Abnormal T cells with discrete loss of CD26$^-$ in 50% of cells CD4:CD8 ratio: 21	82% are T cells 59% of CD4 T cells (44% of lymphocytes) are negative for both CD7 and CD26 CD4:CD8 ratio: 8.5	Reversed CD4/CD8 ratio of 0.24 observed	49% T cells 84% of CD4$^+$ T cells are CD26$^-$, CD7$^-$, CD30$^+$ CD4:CD8 ratio: 1.3
TCR clonality analysis					
Blood	TCR β clonality	TCR β, δ, and γ clonality	TCR β and γ clonality	TCR β clonality	Clonality not detected
Skin biopsy	Diagnostic of MF / Sézary syndrome with CD30$^+$ cells	Skin biopsy initially not diagnostic of MF	Skin biopsy not diagnostic of MF	Skin biopsy diagnostic of CTCL	Skin biopsy diagnostic of CTCL
Imaging studies	Extensive disease	Bilateral, enlarged, inguinal, and axillary lymph nodes on CT thorax, abdomen, and pelvis	No lymphadenopathy or visceral disease	No lymphadenopathy or visceral disease	–
Treatments	Topical steroids; antibiotics; isotretinoin; IFN-α; ECP; brentuximab vedotin	Topical steroids; NBUVB; PUVA; alitretinoin; IFN-α	Topical steroids; NBUVB; isotretinoin; IFN-α	Topical steroids; NBUVB; alitretinoin	Topical steroids; NBUVB; alitretinoin
Diagnosis	Sézary syndrome	Leukemic CTCL	Leukemic CTCL	MF with evidence of blood clonality	Leukemic CTCL
Clinical disease outcome	Rapidly progressing, T1a to stage IVA disease in months with lymph-node and high blood tumor burden He was started on IFN-α, ECP, and isotretinoin Patient then developed skin tumors (large-cell transformation) at which point ECP was stopped and brentuximab vedotin was started	Indolent stage IB patch MF for 4 years, progressed to stage IVA leukemic CTCL with lymph-node involvement as confirmed by a CT scan Patient is stable on a multimodality treatment	Patient with a 2-year history of nonresolving eruption on the trunk that spared skin folds Patient was found to have a leukemic CTCL and was started on multimodality treatment	Patient with a 5-year history of itchy rash on the trunk that did not respond to topical steroids and was sparing skin folds Patient was found to have T-cell clonality in the blood and was started on alitretinoin in addition to skin-directed therapy	Indolent stage IB patch/plaque MF for 6 years, progressed to leukemic CTCL with a high proportion of CD30$^+$ T cells in the blood

BSA, body surface area; CTCL, cutaneous T-cell lymphoma; LDH, lactate dehydrogenase; HTVL-1, human T-lymphotropic virus-1; CD, cluster designation; TCR, T-cell rearrangement gene study; NBUVB, narrow-band ultraviolet B phototherapy; PUVA, psoralen with ultraviolet A phototherapy; MF, mycosis fungoides; ECP, extracorporeal photophoresis.

Table 2. Proposed work-up to confirm or exclude a "deck-chair sign" or papuloerythroderma of Ofuji-like cutaneous T-cell lymphoma (CTCL) based on present study findings and recent review [15]

History and physical examination
Age
Sex
Ethnicity and geographic place of origin
History of presenting illness
Onset and progression
Previous and current treatments
Past medical history
Family history
Cutaneous involvement
Patch, plaque, tumor
Alopecia (folliculotropic presentation)
Presence of ectropion
Deck-chair-sign skin eruption
Body surface area involvement based on the modified severity-weighted assessment tool (mSWAT)
Systemic involvement
Palpable lymph node(s)
Hepatosplenomegaly
Skin biopsy
Histopathological examination of skin biopsy consistent with CTCL
Blood involvement
Flow cytometry
B_1 Sézary cell count (>5%)
B_2 Sézary cell count (≥1,000 cells/μL) with a positive clone or
Increased $CD4^+$ or $CD3^+$ cells with a CD4:CD8 ratio of ≥10 or
Increased $CD4^+$ cells and $CD4^+CD7^-$ cells ≥40% or
Increased $CD4^+$ cells and $CD4^+CD26^-$ ≥30%
T-Cell Clonality
T-cell rearrangement in blood and skin (PCR analysis)
Other
LDH (blood)
HTLV-1 status (serology)
Immunophenotype analysis (skin biopsy)
Presence of large-cell transformation (skin biopsy)
$CD30^+$ positivity (skin biopsy and flow cytometry analysis)

PCR, polymerase chain reaction; LDH, lactate dehydrogenase; HTLV-1, human T-lymphotropic virus-1.