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### Authors

Wilmas, Kelly  
Duvic, Madeleine  
Oki, Yasuhiro

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## Case Report

### Atypical lymphoproliferative disorder-clinical and pathological features

Kelly Wilmas<sup>1,2</sup>, Madeleine Duvic<sup>2</sup> and Yasuhiro Oki<sup>3</sup>

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<sup>1</sup> University of Texas Medical School at Houston, Houston, TX

<sup>2</sup> Department of Dermatology, University of Texas M.D. Anderson Cancer Center, Houston, TX

<sup>3</sup> Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

#### Correspondence:

Kelly Wilmas, BS

Email: Kelly.m.wilmas@uth.tmc.edu

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## Abstract

Definitive diagnosis of cutaneous lymphoproliferative disorders is one of the most challenging issues in dermatopathology owing to the broad spectrum of clinical and histopathological presentations. We report a case of a 73-year-old woman who presented with a single, asymptomatic plaque limited to her left collarbone. This was followed by the appearance of several plaques and patches in addition to a tumor. Her initial biopsy suggested a CD4/CD8 double negative mycosis fungoides (MF). However, the rapidly progressive course of her disease is worrisome for peripheral T-cell lymphomas-not otherwise specified (PTCL-NOS). Subsequent biopsies revealed epidermal spongiosis with subepidermal edema and possible nodal involvement by cutaneous T-cell lymphoma. The rare combination of these pathologic features demonstrates the difficulty of diagnosing atypical lymphoproliferative disorders.

## Introduction

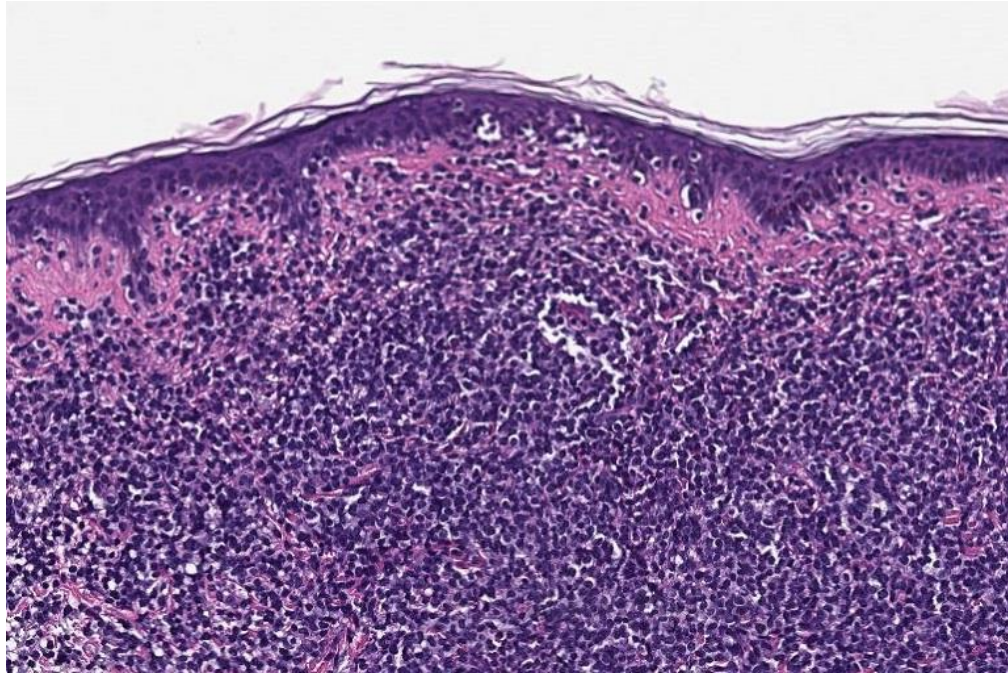
Cutaneous T-cell lymphomas (CTCLs) and peripheral T-cell lymphomas (PTCLs) are rare forms of non-Hodgkin's lymphoma. CTCLs are characterized by malignant, atypical, clonal T-lymphocyte infiltrate of the skin, with mycosis fungoides (MF) being the most common subtype [1]. MF typically begins with multiple patches on the skin that may progress to plaques and tumors [2]. Late in the disease, lymph nodes and visceral organs can become involved [2]. The stages of disease are based on skin, lymph node, visceral, and blood involvement, and the extent of involvement is assessed by medical history, physical exam, skin biopsy, flow cytometry, and molecular studies [2]. Patients with limited patches or plaques involving less than 10% of the body, stage IA or T1, often do not progress in their disease [2]. There is no cure for CTCL, but correct identification and management of the disease can reduce symptoms and induce remission [2].

PTCL-NOS is one of the most common subtypes of PTCL and consists of a heterogeneous group of cases that do not fall into more specific PTCL categories [3]. PTCL-NOS is characterized by aggressive disease and unfortunate outcome, with 20-30% of patients having a 5-year survival [4]. Although the disease is usually nodal, it can have skin involvement [3].

We present a case of an undiagnosed lymphoproliferative disorder with unusual clinical and pathological features.

## Case synopsis

A woman in her 70s with no significant past medical history was referred to the clinic with a one-month history of a single, non-painful, non-pruritic, red plaque overlying her left collarbone that remained stable in size. A biopsy showed atypical lymphoid infiltrate of the dermis associated with multiple foci of epidermotropism including Pautrier microabscesses (Figure 1). The biopsy was negative for CD4, CD8, CD30, and CD56, but positive for CD3, CD5, and CD7. This finding is suggestive of CD4/CD8 double negative MF, which is a rare variant of CTCL. Furthermore, the patient noticed a similar eruption on her left posterior flank area a few weeks after the initial plaque. Staging of her disease was IA with limited plaque involvement.



**Figure 1.** Hematoxylin and eosin (H&E) staining of left upper chest shave biopsy showing atypical lymphoid infiltrate of the dermis associated with multiple foci of epidermotropism including Pautrier microabscesses, 200x.

Considering the patient's rapid clinical progression, a more aggressive therapy was needed. The patient was given local electron beam radiotherapy that resolved the left posterior flank lesion and softened and thinned the left clavicular lesion to a red, ill-defined patch within 2 months. However, 3 months after radiotherapy, the patient began developing new, symmetrically distributed plaques above her waist and right hip (Figure 2).



**Figure 2.** Breakout of patches and plaques 3 months after radiation.

The patient had annular plaques on her left breast in an unusual chrysanthemum pattern with gyrate erythema, a maze-patterned plaque on her left antecubital fossa (Figure 3), oval light patches in the groin, and annular plaques on her trunk, right lower abdomen (Figure 4), right lateral thigh, medial left thigh, right shin, and bilaterally on the dorsum of her hands. In addition, she

had a relapse of the original tumor overlying her left clavicle, composed of erythematous patches and plaques seven months after radiotherapy. She was restaged to IIB or T3, with patches and plaques covering more than 10% of her skin surface in addition to a tumor. The combination of diverse pathologies found in biopsies further complicated the case.

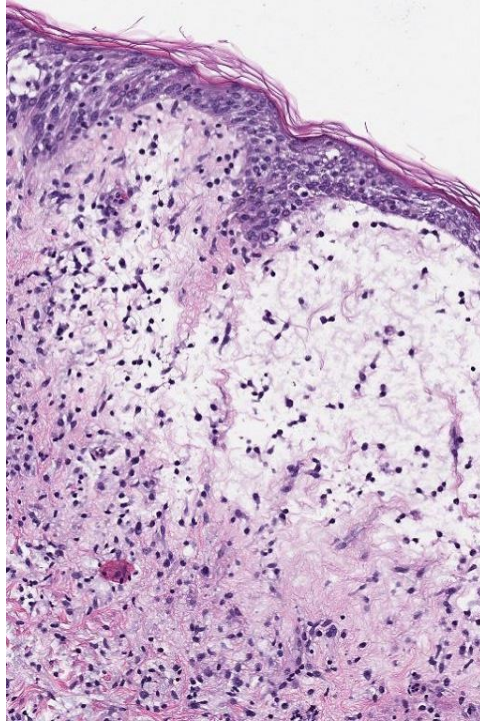


**Figure 3.** Chrysanthemum patterned plaque on left breast and maze-patterned plaque on left antecubital fossa.



**Figure 4.** Annular plaques on right lower abdomen with edematous microvesiculations.

The patient was administered romidepsin 9 months after her initial plaque eruption. Approximately 12 days later, a left arm skin punch biopsy showed extensive subepidermal edema and lymphocytic infiltrate with eosinophils and rare neutrophils (Figure 5). Her plaque lesions had superficial spongiotic vesicles. The patient's right axillary node enlarged two months later, and a biopsy showed diffuse infiltrate of small lymphocytes with oval, irregular nuclei. The node was nearly 100% CD3 positive in most areas. A flow cytometry showed aberrant T-cells in 51% of lymphocytes and was positive for CD2, CD3, CD5, CD7, CD25, CD26, and CD52, partially positive for CD8 cells, and negative for CD4, CD56, and TCR gamma delta. Three months after starting romidepsin, the patient developed a tumor on her right dorsal wrist and left lateral neck. Her disease was restaged to IVa due to her skin, blood, and lymph node involvement, but lack of visceral organ involvement.



**Figure 5.** H&E staining from left upper arm skin punch biopsy showing epidermal spongiosis and subepidermal edema with interstitial and perivascular lymphocytic infiltrate after treatment with romidepsin, 200x.

Approximately two years after her initial eruption, the patient started single agent gemcitabine. After two doses, the patient attained a near partial response. The maze-patterned lesion on her left antecubital fossa decreased in height and erythema. The plaque on her left hip resolved and the chrysanthemum patterned plaque on her left breast flattened.

## Discussion

The broad clinicopathological spectrum of lymphoproliferative disorders make diagnosis challenging. MF can range from a presentation of classic lymphoma to lesions mimicking other inflammatory dermatoses, and is typically diagnosed based on the presence of atypical epidermotropic T-lymphocytes predominating over spongiosis, lichenoid lymphoid infiltrate with lining up of atypical lymphocytes at the dermoepidermal junction, Pautrier microabscesses, or wiry collagen in the papillary dermis [4, 5]. Some variants consist of lesions in unique anatomical sites, a single lesion, clinical variation of the lesion, or masked disease due to other medical conditions [6]. The patient's initial biopsy showed prominent atypical lymphoid infiltrate of the dermis with epidermotropism and Pautrier microabscesses that are rarely found in MF, but are pathognomonic of the disease. A critical feature for histopathological diagnosis of MF has typically been the absence of spongiotic microvesiculation, so the finding of epidermal spongiosis with subepidermal edema and interstitial and perivascular lymphocytic infiltrate with eosinophils and rare neutrophils in a biopsy was not consistent with typical MF [6]. Yet, the findings could also be due to her treatment with romidepsin that can remove epidermal cells and cause fluid edema. The romidepsin decreased her epidermal tumors after 3 weeks and prevented transformation into large cell lymphoma. Her lesions are not classically MF and have an edematous, microvesicular appearance seen in inflammatory dermatoses such as contact dermatitis. The chrysanthemum patterned lesion with edematous gyrate, oval light patches, and maze-patterned lesions are also unusual. The diffuse infiltrate of lymphocytes with irregular nuclei in her axillary lymph node suggests nodal involvement by cutaneous T-cell lymphoma.

Our case is noteworthy because the patient initially presented with a single, solitary plaque instead of multiple patches or plaques that would be seen in MF. She responded to radiotherapy with near-complete resolution of her plaques, but new lesions erupted aggressively 3 months after radiotherapy in a symmetrical distribution. Her biopsies showed a combination of pathologies suggesting possible double negative mycosis fungoides, inflammatory dermatoses, and potential cutaneous reaction to romidepsin, while her rapid clinical progression of new lesions was more suggestive of PTCL-NOS. The unusual clinical and pathological features are demonstrative of an atypical lymphoproliferative disorder that is yet to be definitely diagnosed.

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Abbreviations:

MF: Mycosis fungoides

CTCL: cutaneous T-cell lymphoma

PTCL-NOS: Peripheral T-cell lymphoma, not otherwise specified

TCR: T-cell receptor