Title
Erythroderma with circulating atypical T-cells, likely Sézary syndrome

Journal
Dermatology Online Journal, 25(12)

Authors
Ugonabo, N
Kim, R
Chen, L
et al.

Publication Date
2019

DOI
10.5070/D32512046726

Erythroderma with circulating atypical T-cells, likely Sézary syndrome

N Ugonabo, R Kim, L Chen, S Meehan, J Weed

Affiliations: Ronald O. Perelman Department of Dermatology, NYU School of Medicine, NYU Langone Medical Center, New York, New York, USA

Corresponding Author: Nkemjika Ugonabo, 240 East 38th Street, 12th floor, New York, NY 10016, Tel: 917-549-9470, Email: nkemjika.ugonabo@nyumc.org

Abstract

The erythrodermic patient is often challenging and requires careful evaluation. Work-up should include an extensive and careful medication history, histological and laboratory testing, and if necessary, molecular studies for the evaluation of underlying malignancy. Herein, we present an erythrodermic patient with repeated biopsies demonstrating a spongiotic process who was found to have circulating atypical T-cells concerning for an underlying erythrodermic T-cell leukemia, most closely related to Sézary syndrome.

Keywords: erythroderma, Sézary syndrome, cutaneous T-cell lymphoma, CTCL

Introduction

Erythroderma is defined as erythema and desquamation of greater than 90% of the body surface area and is often the clinical sign of a wide range of cutaneous and systemic diseases [1]. Although psoriasis is the most common underlying cause, other conditions in the differential diagnosis include drug-related reactions, atopic dermatitis, contact dermatitis, pityriasis rubra pilaris, and lymphoproliferative disorders. Erythroderma is associated with an increased risk of fluid and electrolyte abnormalities, high output cardiac failure, secondary bacterial infections, and potential malignancy, making a thorough evaluation for the underlying diagnosis critical [2]. Herein, we present an erythrodermic patient with cutaneous findings consistent with a spongiotic process on histopathology. However, the patient was found to have circulating atypical T-lymphocytes, raising the possibility of primary Sézary syndrome.

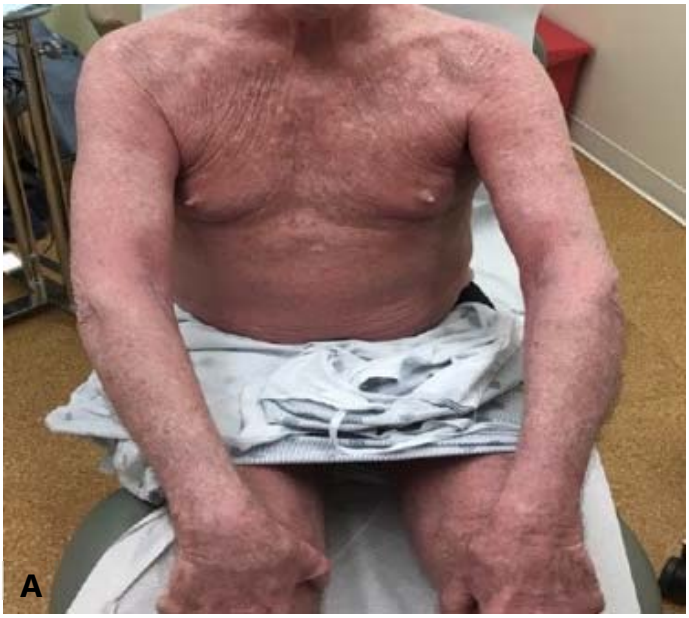
Case Synopsis

An 81-year-old man presented to the Skin and Cancer Unit at the Ronald O. Perelman Department of Dermatology for the evaluation of a generalized, pruritic, and scaly eruption. He also reported diffuse hair loss for several months. He denied any new or recent environmental exposures, personal or family history of atopy, or oral medications. Physical examination was confluent blanching, erythematous patches associated with superficial desquamation on the head, neck, trunk, and upper and lower extremities, covering >95% of his total body surface (**Figure 1**). There were no islands of sparing, palpable lymphadenopathy, vesicles, or bullae.

A complete blood count was normal except for an elevated eosinophil level of 14% (reference range: 0.8-7.0%) and an elevated absolute eosinophil count of $1.3\times10^3/\mu L$ (reference range: 0.0-$0.5\times10^3/\mu L$). A comprehensive metabolic panel was normal except for an elevated creatinine level of 1.44mg/dL (reference range: 0.7-1.3mg/dL). A lactate dehydrogenase level was within normal limits. A serum flow cytometry showed that 43% of the circulating lymphocytes were immunophenotypically aberrant T-cells. A T-cell receptor (TCR) gamma chain gene rearrangement study on peripheral blood was positive for a monoclonal T-cell population. No HTLV-1 DNA was detected.

Two broad shaves were performed of the left flank and right medial upper arm. There was a superficial

perivascular and patchy band-like lymphohistiocytic infiltrate with numerous eosinophils. Lymphocytes and eosinophils extended into the epidermis, which was hyperplastic with prominent spongiosis (**Figure 2**). A specimen submitted for direct immunofluorescence failed to reveal reactivity for C3, IgA, IgG, IgM, or fibrinogen. TCR gene rearrangement studies on the left flank skin biopsy specimen was negative.



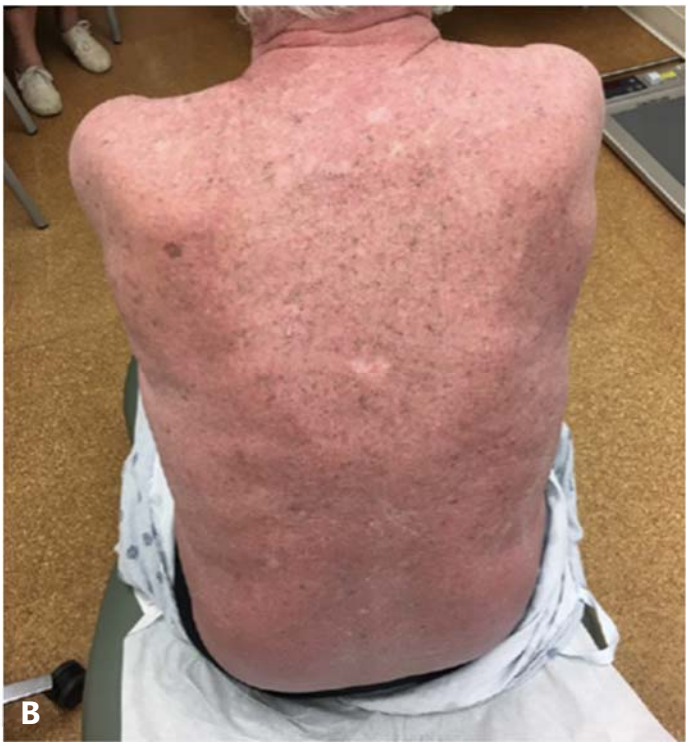


Figure 1. ***A)*** *Face, chest, upper and lower extremities with confluent blanching, erythematous patches associated with superficial desquamation.* ***B)*** *Back with confluent blanching, erythematous patches associated with superficial desquamation.*

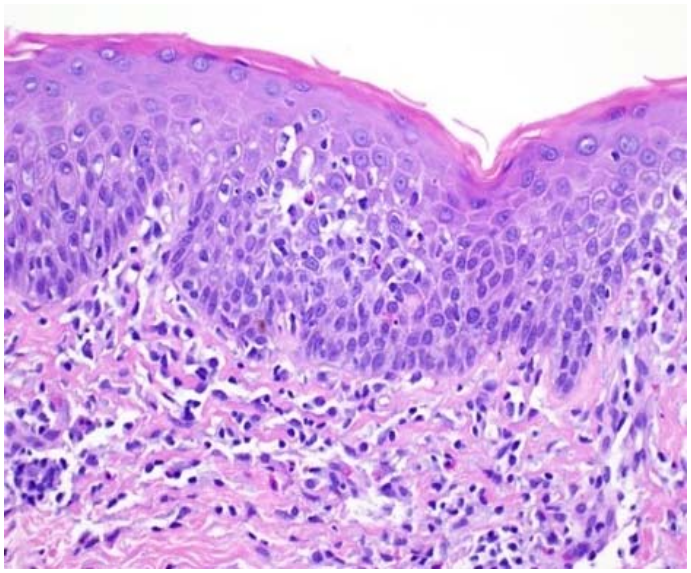


Figure 2 *Shave biopsy with hematoxylin and eosin stains (40×) showing a superficial perivascular and patchy band-like lymphohistiocytic infiltrate with numerous eosinophils. Lymphocytes and eosinophils extended into the epidermis, which was hyperplastic with prominent spongiosis.*

A computed tomography (CT) of the abdomen/pelvis without intravenous (IV) contrast showed no hepatosplenomegaly or lymphadenopathy. A CT of the chest without IV contrast showed no evidence of intrathoracic lymphoma, cutaneous nodules, or plaques.

Case Discussion

Sezary syndrome (SS) is a rare and more aggressive variant of cutaneous T-cell lymphoma (CTCL) that occurs at an incidence rate of 0.1-0.3 per 1,000,000 person-years in the United States and represents 2.5% of all CTCL [3, 4]. The disease occurs most commonly in older adults, males, and, in contrast to other types of CTCL, Caucasians [4]. The World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) define SS in broad terms, which includes desquamative erythroderma, lymphadenopathy, and leukemic involvement [5]. Generalized lymphadenopathy,

palmoplantar keratoderma, nail abnormalities, and alopecia are other commonly associated findings [6].

Although cutaneous infiltration of atypical T lymphocytes is helpful in the diagnosis of SS, a significant number of skin biopsies show non-specific findings [7, 8]. In our patient, no atypical lymphocytes were seen on histological examination and TCR gene rearrangement studies performed on the biopsy specimen were negative. Therefore, if malignancy remains in the differential diagnosis for the work-up of erythroderma, evaluation of the peripheral blood is recommended. Abnormalities in SS include >1000 Sézary cells, which is defined as circulating malignant T lymphocytes with cerebriform nuclei, an increased CD4/CD8 ratio of >10 by flow cytometry, a loss of CD7 expression in more than 40% or loss of CD26 expression in more than 30% of circulating T cells, and evidence of a circulating T-cell clone by T-cell receptor gene rearrangement [5].

Recent studies demonstrate a median survival of 4.0 years and overall survival of 42.3% at 5 years after diagnosis of SS [6]. Because SS is so rare, its prognosis is often grouped with CTCL staging and is equivalent to stage IV disease. The disease is further stratified by presence or lack of visceral involvement. Older age (>60 years) and increased lactate dehydrogenase at diagnosis and may predict a worse prognosis [5].

The low incidence of SS has limited the study of effective therapies and treatment options and there is little consensus on initial treatment choice. First-line therapies for SS may include extracorporeal photophoresis, subcutaneous interferon-α, oral bexarotene, and low-dose oral, subcutaneous, or intramuscular methotrexate (≤100mg per week), [7]. Systemic therapy may also be combined with various skin-directed therapies such as psoralen plus ultraviolet A (PUVA), topical nitrogen mustard, and total skin electron beam therapy (TSEBT), [7]. Localized radiation therapy may be added for local control of skin tumors or lymph node involvement; patients with visceral involvement are often treated with histone deacetylase inhibitors (e.g., vorinostat or romidepsin), [9].

Cutaneous colonization with *Staphylococcus aureus* may influence the disease activity of SS, and the eradication of *S. aureus* with antibiotics in patients with erythrodermic mycosis fungoides (MF) and SS has been shown to lead to a significant improvement of erythroderma and skin disease burden [10]. For symptomatic management of pruritus, which is often the most debilitating symptom and should be addressed to improve overall quality of life, topical corticosteroids and emollients along with systemic medications such as antihistamines, doxepin, and gabapentin should be considered.

Recently, mogamulizumab, a humanized monoclonal antibody directed against the chemokine receptor CCR4, was approved for treatment of adults with SS after failure of at least one prior systemic therapy [11]. A randomized, controlled phase III trial comparing mogamulizumab to vorinostat showed that treatment with mogamulizumab resulted in a significant improvement in progression-free survival (7.7 versus 3.1 months), overall response (37 versus 2 percent), and quality of life for patients with SS who failed a previous systemic therapy [12].

Conclusion

Our patient was initially started on mycophenolate mofetil with short-term cyclosporine as a bridge prior to the diagnosis of SS. However, cyclosporine was discontinued owing to elevating creatinine. He was also treated with class I topical corticosteroids and antihistamines, which resulted in partial symptomatic improvement. He was eventually started on methotrexate by the hematology/oncology department and phototherapy with improvement in his erythroderma and his pruritus.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Whittaker S. Erythroderma. In: Dermatology. Bolognia JL, Schaffer JV, Cerroni, L, editors. 3rd ed. Philadelphia: Elsevier Saunders; 2012. p. 175-187.
2. Cuellar-Barboza, A, Ocampo-Candiani K, Herz-Ruelas, ME. A Practical Approach to the Diagnosis and Treatment of Adult Erythroderma. *Actas Dermosifiliogr*. 2018;109:777–90. [PMID: 30316452].
3. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. *Arch Dermatol*. 2007;143:854-59.[PMID: 17638728].
4. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood*. 2009;113:5064-73. [PMID: 19279331].
5. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC) *Blood*. 2007;110:1713–22. [PMID: 17540844].
6. Kubica AW, Davis MD, Weaver AL, Killian JM, Pittelkow MR. Sézary syndrome: a study of 176 patients at Mayo Clinic. *J Am Acad Dermatol*. 2012;67:1189-99. [PMID: 22640839].
7. Spicknall KE. Sézary Syndrome-clinical and histopathologic features, differential diagnosis, and treatment. *Semin in Cutan Med and Surg*. 2018;37:18–23. [PMID: 29719016].
8. Möbs M, et al. Diagnostic tools in Sezary Syndrome. *G Ital Dermatol Venereol*. 2010;145:385-91. [PMID: 20461046].
9. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome): part II. Prognosis, management, and future directions. *J Am Acad Dermatol*. 2014;70: 223.e1-17; quiz 240-2. [PMID: 24438970].
10. Talpur R, Bassett R, Duvic M. Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sezary syndrome. *Br J Dermatol*. 159:105–112 [PMID: 18489588].
11. U.S. Food and Drug Administration. Drug Approval Package: Poteligeo (mogamulizumab-kpkc). 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761051s000lbl.pdf. Accessed on August 9, 2018.
12. Kim YH, et al. Mogamulizumab versus Vorinostat in Previously Treated Cutaneous T-Cell Lymphoma (MAVORIC): an International, Open-Label, Randomised, Controlled Phase 3 Trial. *Lancet Oncol*. 2018;19:1192-1204. [PMID: 30100375].