Double-positive CD4 and CD8 Sézary syndrome

Denis Miyashiro, MD,[a] Marina Passos Torrealba, MSc,[b] Kelly Cristina Manfrere, MSc,[b] Juliana Pereira, MD, PhD,[c] Maria Notomi Sato, PhD,[b] and José Antonio Sanches, MD, PhD[a]
São Paulo, Brazil

Sézary syndrome (SS) is a malignancy of $CD4^+$ central memory T-lymphocytes, characterized by the triad of erythroderma, lymphadenopathy, and involvement of peripheral blood by neoplastic cells. We describe a rare case of double-positive CD4 and CD8 SS.

CASE REPORT

An 83-year-old man presented to our clinic with pruritic skin lesions of 7 months' duration. The physical examination revealed erythroderma, nonscarring diffuse alopecia, palmoplantar keratoderma, onychodystrophy, edema of the lower limbs, and ectropion, without lymphadenopathy or weight loss (Fig 1). His medical history included hypertension and diabetes mellitus. He denied previous skin diseases, exposure to new medications, or possible allergens.

Three simultaneous skin biopsy specimens obtained for pathologic examination revealed psoriasiform dermatitis with mild spongiosis and exocytosis of small lymphocytes and, in one of the biopsy specimens obtained, there were groups of 3 or 4 atypical lymphocytes with clear halos infiltrating the epidermis (Pautrier microabscesses). Immunohistochemical staining showed positivity for CD3, CD4, and CD8, without significant loss of CD7 in dermal and epidermal lymphocytes (Figs 2 and 3).

T-cell receptor (TCR) gene rearrangement analysis detected monoclonal proliferation, with the same clone of lymphocytes present in peripheral blood and infiltrating the skin. Sézary cell count was 2192 cells/mm^3; immunophenotyping of lymphocytes showed 68.5% of lymphocytes with double positivity for CD4 and CD8 (Fig 4, *A*), 30% of these cells did not express CD7, and 100% did not express CD26. Human T cell lymphotropic virus serology was negative. The total lymphocyte count was 2610 cells/mm^3 (normal range, 900-3400 cells/mm^3) and lactate dehydrogenase was 333 U/L (normal range, 135-225 U/L). General laboratory tests showed no significant abnormalities.

Imaging studies showed axillary lymph node enlargement up to 3 cm bilaterally, without other significant findings, but a biopsy specimen was not obtained because the patient was lost to follow-up.

A diagnosis of double-positive CD4 and CD8 SS was made.

We evaluated the production of activation/inhibition molecules (CD69 and PD-1) and effector molecules (interferon gamma and CD107a), on $TCD4^+CD8^+$, $TCD4^+CD8^-$, and $TCD4^-CD8^+$ cells unstimulated and after stimulation with phorbol myristate acetate (Fig 4, *B* and Table I). Expression of CD69 and PD-1 were similar between the groups, but $CD4^+CD8^+$ T cells were less responsive to the production of interferon gamma. Also, expression of CD107a, an indicator of cytotoxicity, were 5 times lower in $CD4^+CD8^+$ cells than in $CD4^+CD8^-$ cells.

DISCUSSION

SS is a cutaneous T-cell lymphoma with peripheral blood involvement by malignant cells (Sézary cells). Clinically, it presents with erythroderma and varying degrees of skin infiltration, nonscarring diffuse alopecia, palmoplantar keratoderma, nail involvement, lymphadenopathy, intense pruritus, and weight loss.[1] One to 10% of erythroderma, or exfoliative dermatitis, is caused by SS.[2]

Diagnostic criteria include T-cell receptor (TCR) gene rearrangement analysis with a monoclonal population of T-lymphocytes in the blood and

From the Department of Dermatology[a] and the Division of Hematology,[c] Hospital das Clínicas, and the Laboratory of Medical Investigation,[b] Tropical Medicine Institute of São Paulo, University of São Paulo Medical School, São Paulo.

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: Denis Miyashiro, MD, 100 Desembargador Aragão Street, Apt 23, 04102-010 São Paulo, SP, Brazil. E-mail: denisrmiyashiro@gmail.com.

JAAD Case Reports 2017;3:485-8.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.06.036

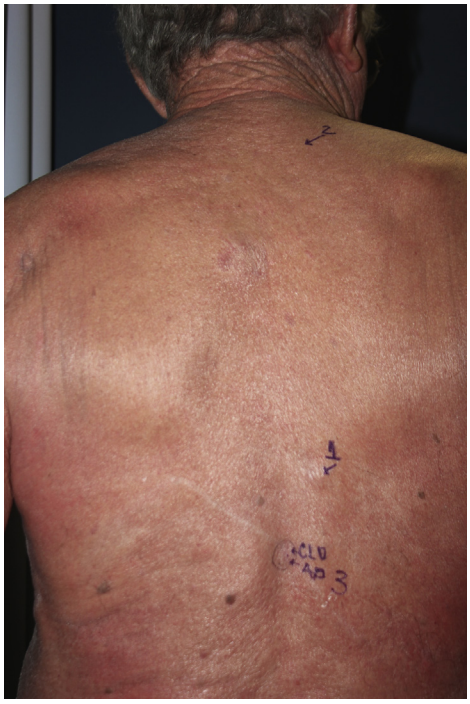

Fig 1. Diffuse erythema and scaling.

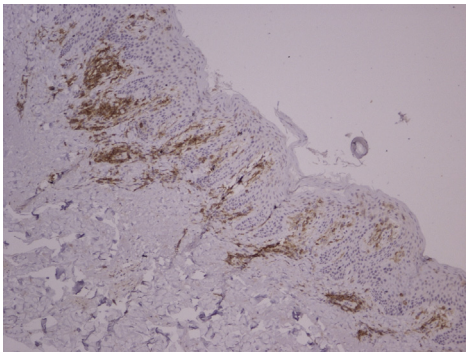

Fig 2. Immunohistochemistry showing exocytosis of small lymphocytes positive for CD4. (Original magnification: ×100.)

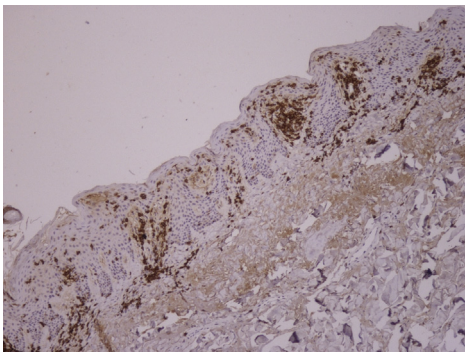

Fig 3. Immunohistochemistry showing exocytosis of small lymphocytes positive for CD8. (Original magnification: ×100.)

matching clone infiltrating the skin. Sézary cell count in peripheral blood smear should be ≥ 1000 cells/μL or should have 1 of 2 immunophenotypic criteria, which are a CD4/CD8 ratio ≥ 10 or increase in CD4 cells with abnormal phenotype ($CD4^+CD7^-$ $\geq 40\%$ or $CD4^+CD26^-$ $\geq 30\%$).[3]

Formerly thought to be a leukemic variant of mycosis fungoides, there are now different opinions if SS may be considered another disease, with different immunophenotypes of malignant cells and different genetic mutations.[4,5] Occasionally, with the improvement of erythroderma, classic lesions of mycosis fungoides become evident, contrary to the hypothesis that they may be different diseases.

Classically, SS is a $CD4^+$ T-cell neoplasm, with the lymphocytes expressing the pan-T CD3 cell marker, CD4 phenotype, CCR4 (skin homing adressin), CCR7, and L-selectin (lymph node homing adressins), the immunophenotype of central memory T-lymphocytes. By contrast, mycosis fungoides malignant cells express CCR4 and cutaneous lymphocyte antigen but lack lymph node homing adressins.[4]

There are few reports of $CD8^+$ cutaneous T-cell lymphomas, with different clinical presentations and outcomes. Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma is a provisional entity with aggressive clinical course.[6] There are few reports of other cutaneous T-cell lymphomas expressing the CD8 phenotype, such as pagetoid reticulosis, mycosis fungoides, lymphomatoid papulosis, cutaneous anaplastic large cell lymphoma, and SS.[6,7]

Double-positive CD4 and CD8 lymphoproliferative diseases are extremely rare, with anecdotal reports in the literature. Most cases had adult T-cell leukemia/lymphoma and large granular lymphocytic leukemia. There was 1 report of $CD4^+CD8^+$ mycosis fungoides[8] and 1 report of double-positive SS.[9]

A previous study from our group showed a deficient immune response in patients with SS.[10] The data suggest that double-positive $CD4^+CD8^+$ neoplastic T-cells shows a lower cytotoxic potential compared to $CD4^+CD8^-$ cells.

CONCLUSIONS

We report an unusual case of double-positive SS in an erythrodermic patient. We emphasize the need for comprehensive and detailed clinical and laboratory investigation of every patient who presents with erythroderma. Careful evaluation should be made to detect any infectious or tumoral progression in

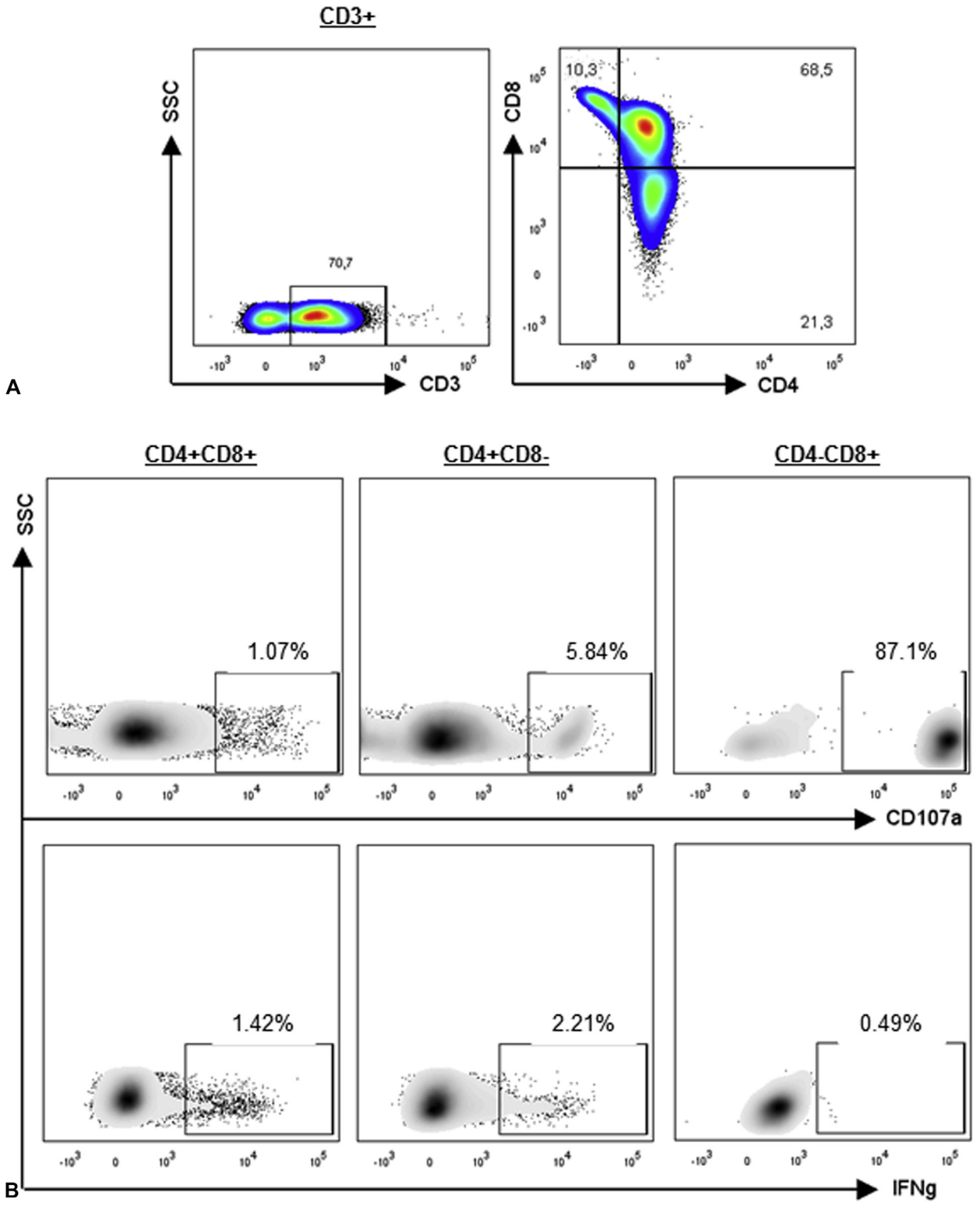

Fig 4. A, Immunophenotyping of lymphocytes. Sixty-eight percent of $CD4^+$ and $CD8^+$ malignant cells. **B,** CD107a and interferon gamma production after stimulation with phorbol miristate acetate in $TCD4^+CD8^+$ neoplastic cells, $TCD4^+CD8^-$, and $TCD4^-CD8^+$ cells. Peripheral blood mononuclear cells were cultured with phorbol miristate acetate (50 ng/mL) and ionomycin (1 μg/mL) for 20 hours. T cells were assessed for interferon production and activation markers expression by flow cytometry.

Table I. PD-1, CD107a, CD69, and interferon gamma before and after stimulation with phorbol myristate acetate

	$TCD4^+CD8^+$ (68.5%)		$TCD4^+CD8^-$ (21.3%)		$TCD4^-CD8^+$ (10.3%)	
	UNS	PMA	UNS	PMA	UNS	PMA
$PD\text{-}1^+$	0.02%	0.38%	0.01%	0.29%	0.09%	72.1%
	142 (MFI)	182 (MFI)	82 (MFI)	107 (MFI)	65 (MFI)	1246 (MFI)
$CD107a^+$	0.18%	1.07%	0.08%	5.84%	0.29%	87.1%
	882 (MFI)	447 (MFI)	416 (MFI)	297 (MFI)	437 (MFI)	11409 (MFI)
$CD69^+$	0.28%	85.1%	0.04%	53.3%	5.80%	95.9%
	608 (MFI)	5676 (MFI)	297 (MFI)	3126 (MFI)	1010 (MFI)	9491 (MFI)
Interferon gamma—positive	0.02%	1.42%	0%	2.21%	0.15%	0.49%

MFI, Mean fluorescence intensity; *PMA*, phorbol myristate acetate; *UNS*, unstimulated.

patients with double-positive CD4 and CD8 SS because of their immunosuppressive state.

REFERENCES

1. Vidulich KA, Talpur R, Bassett RL, Duvic M. Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. *Int J Dermatol*. 2009;48:243-252.
2. Vonderheid EC. On the diagnosis of erythrodermic cutaneous T-cell lymphoma. *J Cutan Pathol*. 2006;33:27-42.
3. 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;110:1713-1722.
4. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood*. 2010;116:767-771.
5. Iżykowska K, Przybylski GK. Genetic alterations in Sézary syndrome. *Leuk Lymphoma*. 2011;52:745-753.
6. Willemze R. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
7. Lu D, Patel KA, Duvic M, Jones D. Clinical and pathological spectrum of CD8-positive cutaneous T-cell lymphomas. *J Cutan Pathol*. 2002;29:465-472.
8. Tournier E, Laurent C, Thomas M, et al. Double-positive CD4/CD8 mycosis fungoides: a rarely reported immunohistochemical profile. *J Cutan Pathol*. 2014;41:58-62.
9. Wu R, Zippin JH, Magro C. Double-positive $CD4^+CD8^+$ Sézary syndrome: an unusual phenotype with an aggressive clinical course. *Cutis*. 2014;93:E18-25.
10. Manfrere KCG, Torrealba MP, Miyashiro DR, et al. Toll-like receptor agonists partially restore the production of pro-inflammatory cytokines and type I interferon in Sézary syndrome. *Oncotarget*. 2016;7:74592-74601.