CD25+CD8+, CLA+CD4+, CD11a+ CD4+, and CD11a+ CD8+ T Cell Counts Are Elevated in the Blood of Brazilian Patients With Chronic Plaque Psoriasis

Los linfocitos T CD25+CD8+, CD4+CLA+, CD11a+CD4+ y CD11a+ CD8+ están elevados en la sangre de los pacientes brasileños con psoriasis en placas crónica

To the Editor:

Psoriasis is a recurrent, chronic inflammatory disorder that mainly affects the skin and joints[1]. In view of the scarcity of studies on peripheral lymphocyte subpopulations in Brazilian psoriasis patients, we performed cytofluorometric analysis of peripheral blood mononuclear cells (PBMC) in psoriatic patients and healthy controls in order to characterize the lymphocyte subpopulations and certain molecules involved in cell activation and migration.

The study was approved by the Ethics Committee of Escola de Medicina e Cirurgia (UNIRIO, MEC, Brazil) and all patients signed an informed consent.

Twenty-five individuals were recruited from the Dermatology Department of HUGG/UNIRIO/MEC-Brazil. Seventeen had chronic plaque psoriasis and there were 8 healthy controls. None of the psoriasis patients was receiving systemic treatment. The physician's global assessment score[2–4] was 4 in 6 cases, 5 in 6 cases, and 6 in 5 cases.

A 20-ml blood sample was drawn from each patient and PBMCs were separated using the Ficoll-Hypaque gradient (Sigma Chemical Co, St.Louis, USA). Five microliters of each monoclonal antibody—anti-CD3, anti-CD4, anti-CD8, anti-CD11a (Immunotech, Beckman Coulter, France), anti-CD25, anti-CD69, and anti-CLA (BD Biosciences, California, USA)—were added according to the combinations listed in the table 1. Laboratory procedures were performed according to the manufacturer's instructions[5]. The nonparametric Mann-Whitney and Kruskal-Wallis tests were used for the statistical analysis, which was performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA).

Analysis of the lymphocyte subpopulations ($CD3^+$ or total T cells, $CD4^+$ or helper T cells, and $CD8^+$ or cytotoxic T cells) revealed no significant differences between patients with psoriasis and healthy controls. The relative percentages of each lymphocyte subpopulation in patients and controls are shown in Figure 1. Lymphocyte activation was determined through analysis of CD25 and CD69 expression (figs. 2 A and B). Higher percentages of activated ($CD25^+$ and $CD69^+$) cells were detected in the 2 lymphocyte subpopulations ($CD4^+$ and $CD8^+$) in psoriatic patients; the difference compared to controls was significant for the percentage of $CD25^+$ cells in the $CD8^+$ T-cell subpopulation (mean [SD], 39.2% (26.9); median, 35.1%; P <.05), and there was a trend to elevation of the $CD25^+$ $CD4^+$ subpopulation. There was also a trend to elevation in the percentage of $CD69^+$ cells in both T-cell subpopulations ($CD4^+$: mean, 16.0% [19.6]; median, 7.8%; $CD8^+$: mean, 2.0% [1.47]; median, 2.23%) in psoriatic patients when compared to controls (fig. 2B). Migration of circulating T lymphocytes to the skin was studied through an analysis of CLA and CD11a expression. Compared to control subjects, patients with psoriasis presented an increase in the percentage of $CD4^+$ T cells expressing CLA (control group: mean, 19.30% [13.13]; median, 14.67%; psoriasis group: mean, 38.86% [20.67]; median, 39.76%; P<.05). However, this was not observed in the $CD8^+$ T cells, although increased CLA expression was detected in 4 of the 10 patients with high levels of $CD8^+$ lymphocytes (fig. 3A). A significant increase in the percentage of cells with CD11a expression was observed in psoriasis patients compared to controls in both $CD4^+$ (mean, 82.17%

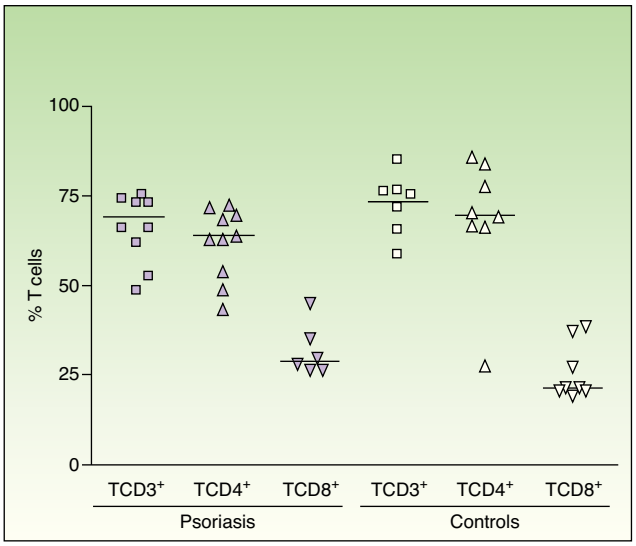

Figure 1 Quantification of T lymphocyte subpopulations ($CD4^+$ and $CD8^+$ T cells) in the peripheral blood of patients with chronic plaque psoriasis. The results are expressed as percentage of positive cells. The horizontal bars represent the median values of the results. Each point represents an individual.

Table 1 Set of monoclonal markers

Monoclonal markers	Analysis			Source
CD3-PC5/CD4-PE/CD8-FITC	CD3 in total lymphocytes	CD4 into CD3	CD8 into CD3	Immunotech, Beckman Coulter, France
CD4-PC5/CD8-FITC/CD25-PE	CD25 in total lymphocytes	CD25 into CD4	CD25 into CD8	BD Biosciences, CA, USA
CD4-PC5/CD8-PE/CD69-FITC	CD69 in total lymphocytes	CD69 into CD4	CD69 into CD8	BD Biosciences, CA, USA
CD4-PC5/CD8-PE/CLA-FITC	CLA in total lymphocytes	CLA into CD4	CLA into CD8	BD Biosciences, CA, USA
CD4-PC5/CD8-PE/CD11a-FITC	CD11a in total lymphocytes	CD11a into CD4	CD11a into CD8	Immunotech, Beckman Coulter, France

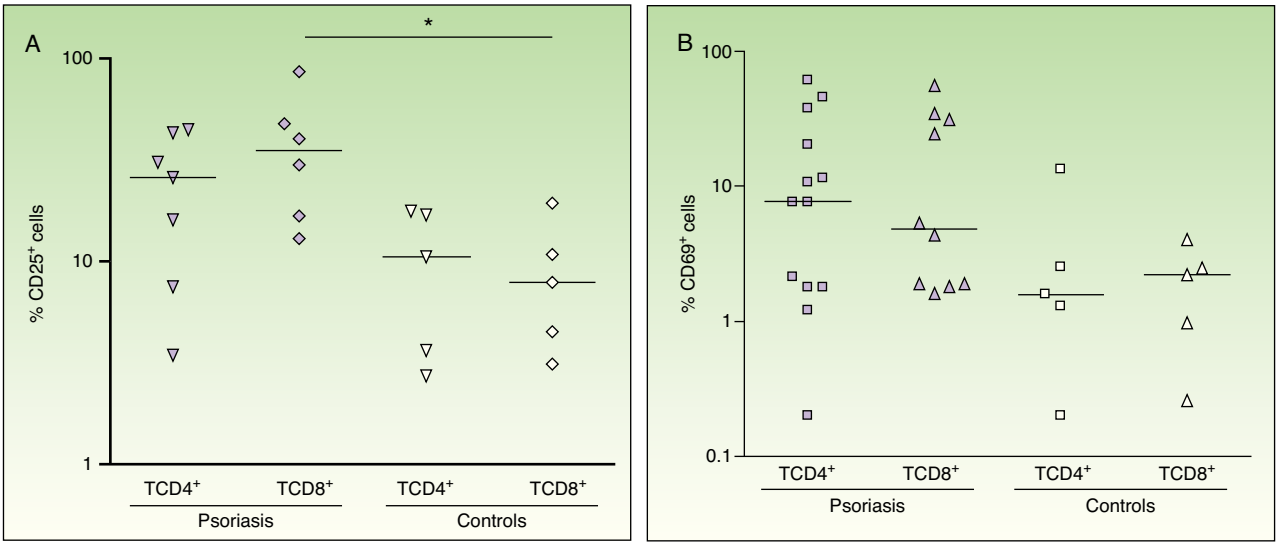

Figure 2 A and B: Assessment of the degree of activation of $CD4^+$ and $CD8^+$ T cells in psoriasis patients and controls. Each point represents an individual. The horizontal bar represent the median.

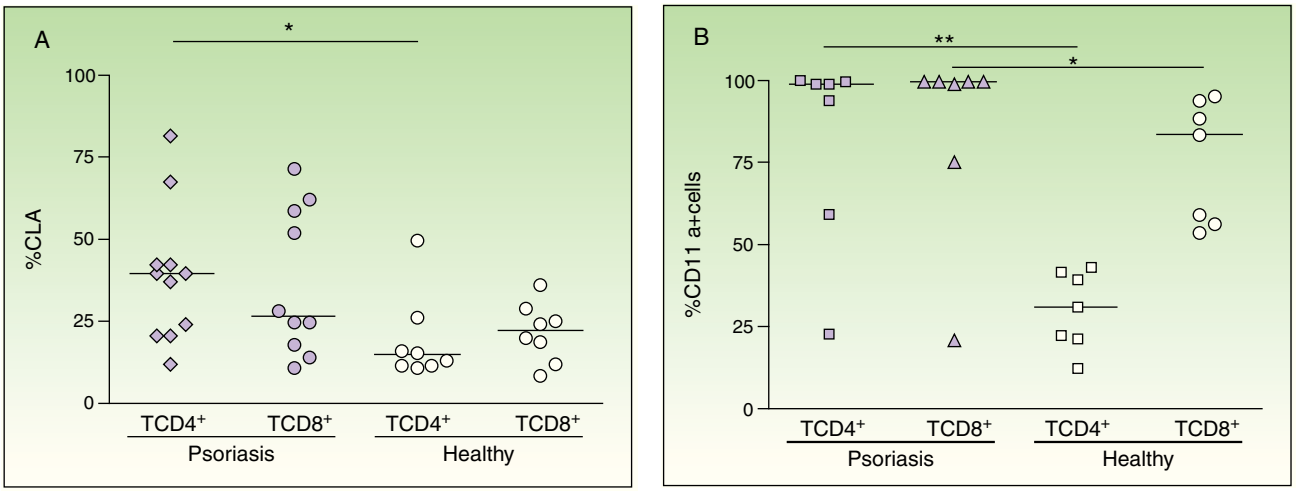

Figure 3 A. Elevated expression of molecules related to cutaneous cell migration (cutaneous lymphocyte associated antigen [CLA]) B. Endothelial tissue inflammation (CD11a) in $CD4^+$ and $CD8^+$ T cells in psoriasis patients and controls. Each point represents an individual. The horizontal bars represent the median values.

[29.91]; median, 99.45%; $P < .01$) and $CD8^+$ T cells (mean, 84.96 [29.77]; median, 99.75; $P < .05$) (fig. 3B).

Although our study is somewhat limited by the small sample size, the results showed that there was no change in the proportion of $CD4^+$ and $CD8^+$ T cells in the PBMC population in psoriatic patients when compared with general population, as has been reported in previous studies[6]. However, we observed qualitative differences between the 2 groups in the expression of activation molecules CD25 and CD69. Although the results were significant only for CD25 expression in $CD8^+$ T cells, there was a trend to increased expression of CD25 and CD69 in both $CD4^+$ and $CD8^+$ T cells, findings not reported by other authors[7]. The presence of activation molecules has been detected in the initial stages of psoriasis, even prior to the onset of clinically apparent lesions; these molecules are therefore presumably involved in lymphocyte recruitment and migration[8,9].

Our data indicate that, although there is no significant increase or variation in the relative percentages of circulating mononuclear cells in psoriatic patients, these cells are qualitatively different because they express activation molecules that are involved in the initiation and progression of psoriasis lesions.

Acknowledgments

We are grateful to Ana Cristina de Almeida for her valuable suggestions, to Gustavo Estef Lino da Silveira for the linguistic revision, and to the medical staff of Serviço de Dermatologia-HUGG/UNIRIO, Rio de Janeiro, Brazil. C Porto-Ferreira is a graduate student at Programa de Pós-Graduação em Ciências Médicas, FCM-UERJ, Rio de Janeiro, Brazil. AM Da-Cruz is a research fellow from FAPERJ, Rio de Janeiro, Brazil.

Bibliografía

1. Christophers E. Psoriasis—epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26:314—20.
2. Puig L, Bordas X, Carrascosa JM, Daudén E, Ferrándiz C, Hernanz JM, et al. Documento de consenso sobre la evaluación y el tratamiento de la psoriasis moderada/grave del Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. Actas Dermosifiliogr. 2009;100: 277—86.
3. Gottlieb AB, Chaudhari U, Baker DG, Perate M, Dooley LT. The National Psoriasis Foundation Psoriasis Score (NPF-PS) System versus the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA): a comparison. J Drugs Dermatol. 2003;2:260—6.
4. Porto Ferreira C, Martins CJ, Issa PR, de Vasconcellos Carvalhaes de Oliveira R, Da-Cruz AM. Psoriasis affects individuals of African descent and white Brazilians similarly. Actas Dermosifiliogr. 2010;101:230—4.
5. Bogh LD, Duling TA. Flow cytometry instrumentation in research and clinical laboratories. Clin Lab Sci. 1993;6:167—73.
6. Koreck A, Surányi A, Szöny BJ, Farkas Á, Bata-Csörgö Z, Kemény L, et al. CD3+CD56+NK T cells are significantly decreased in the peripheral blood of patientswith psoriasis. Clin Exp Immunol. 2002;127:176—82.
7. Sigmundsdottir H, Gudjonsson JE, Jonsdottir I, Ludviksson BR, Valdimarsson H. The frequency of CLA+ CD8+ T cells in the blood of psoriasis patients correlates closely with the severity of their disease. Clin Exp Immunol. 2001;126:365—9.
8. Santamaría-Babi LF. CLA+ T cells in cutaneous disease. Eur J Dermatol. 2004;15:13—8.
9. Teraki Y, Miyake A, Takebayashi R, Shiohara T. Homing receptor and chemokine receptor on intraepidermal T cells in psoriasis vulgaris. Clin Exp Dermatol. 2004;29:658—63.

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doi:10.1016/j.ad.2010.11.008

Rabdomiólisis durante el tratamiento con isotretinoína

Rhabdomyolysis During Isotretinoin Therapy

Sr. Director:

La isotretinoína es un tratamiento utilizado en el acné nódulo-quístico y en el acné vulgar que no responde a otros tratamientos. La toxicidad muscular es una complicación poco conocida, y su incidencia real y manejo están por determinar.

Un varón de 16 años inició tratamiento con 30 mg/ 24 h de isotretinoína (0,4 mg/ kg/ 24 h) para un acné pápulo-pustuloso resistente a otros tratamientos. En la analítica rutinaria previa al inicio de la terapia con retinoides todos los parámetros fueron normales. En la revisión a los dos meses presentaba una queilitis severa, por lo que se redujo la dosis a 20 mg/ 24 h (0,3 mg/ kg/ 24 h). El seguimiento posterior, con exploración física y analíticas bimensuales (hemograma, bioquímica básica y perfil lipídico), cursó sin incidencias y el acné mejoró notablemente. Debido a la reducción de dosis el tratamiento se prolongó más de lo habitual. En una revisión ordinaria, realizada a los 11 meses y próxima a la finalización del tratamiento, el paciente refirió astenia moderada. Por ello se solicitó una nueva analítica con enzimas musculares que demostró una elevación de la creatinfosfoquinasa (CPK) y de la mioglobina plasmática con valores de 801 UI/l (normal: 5-110) y de 504 ng/ ml (normal: 0-75), respectivamente. Días antes de la recogida de la muestra el paciente había realizado ejercicios de levantamiento de pesas, que no hacía habitualmente. Suspendimos la isotretinoína y recomendamos hidratación abundante y evitar ejercicio físico intenso. En la analítica de control a las tres semanas todos los parámetros se habían normalizado.

La rabdomiólisis es un síndrome producido por la necrosis de las células musculares estriadas y la consiguiente liberación de material intracelular tóxico a la circulación[1]. Se ha definido como una elevación de la CPK mayor de 5 veces el límite superior del rango de normalidad[2]. Puede estar provocada por tóxicos (drogas, alcohol y medicamentos), traumatismos, sobreesfuerzo y enfermedades del metabolismo muscular[2]. Los fármacos son una de las causas más frecuentes de rabdomiólisis, aunque en la mayoría de los pacientes se encuentran varios factores etiológicos simultáneamente. Los medicamentos habitualmente implicados son los antipsicóticos y las estatinas[2]. El cuadro clínico clásico de debilidad y dolor muscular y orina rojiza ocurre en menos de la mitad de los pacientes[1], pudiendo encontrarse cifras elevadas de CPK en ausencia de síntomas[3].

La isotretinoína es un derivado de la vitamina A ampliamente utilizado en dermatología y, en general, bien tolerado. Poco después de su introducción se publicaron varios casos de elevación de la CPK en pacientes que recibían este tratamiento. En los últimos años casi no ha habido publicaciones al respecto, probablemente debido a la tendencia a disminuir la frecuencia y exhaustividad de los controles[4]. En algunos de los casos descritos los pacientes presentaron dolor muscular intenso y debilidad de inicio agudo[5—7]. En otros la rabdomiólisis fue detectada en pacientes asintomáticos en los que se objetivó la elevación de la CPK en los controles analíticos rutinarios[8]. La elevación de la CPK en pacientes que realizan tratamiento con isotretinoína suele