CME/SAM

Analysis of Cutaneous Lymphomas in a Medical Center in Bahia, Brazil

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ABSTRACT

Objectives: *To evaluate the frequency of the different types of cutaneous lymphoma (CL) in 1 university hospital in Brazil and compare this frequency with those observed in other countries.*

Methods: *After review, 72 (84.7%) cases of primary cutaneous T-cell lymphoma (CTCL) and 13 (15.3%) cases of primary cutaneous B-cell lymphoma (CBCL) were included.*

Results: *Of the CTCLs, 40.3% were mycosis fungoides (MF); 26.4% were adult T-cell leukemias/lymphomas (ATLs); 23.6% were peripheral T-cell lymphomas, unspecified; and 8.3% were anaplastic large cell lymphomas. Of the MF cases, 17.2% progressed to transformed MF. Five-year survival for primary human T-cell lymphotropic virus type 1–negative CTCL, ATL, and CBCL was 64.0%, 42.1%, and 62.5%, respectively. MF and ATL were the most frequent primary CTCLs.*

Conclusions: *The frequencies observed here are close to those observed in Peru but different from those of European countries. Unfortunately, the World Health Organization/European Organization of Research and Treatment of Cancer classification does not include primary cutaneous ATL.*

Upon completion of this activity you will be able to:
- compare the frequency of different cutaneous lymphomas types in diverse areas of the world.
- define the necessity of having serology for human T-cell lymphotropic virus type 1 for all patients with cutaneous T-cell lymphoma.
- discuss the fact that adult T-cell leukemia/lymphoma can present as a primary cutaneous form.
- analyze the features of transformed mycosis fungoides.

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Questions appear on p 440. Exam is located at www.ascp.org/ajcpcme.

Different types of lymphoproliferative diseases vary in frequency in different geographical areas, and this variation may be ascribed to genetic and environmental etiologic factors.[1] For example, while hydroa vacciniforme–like cutaneous lymphoma, a rare type of Epstein-Barr virus–associated lymphoma, is more common in children from Asia, Mexico, and Peru, it has not been reported in Brazil.[2] Likewise, in Brazil, adult T-cell leukemia/lymphoma (ATL), a disease caused by the human T-cell lymphotropic virus type 1 (HTLV-1), occurs predominantly in Bahia and Rio de Janeiro, while in other states, the disease has been reported rarely or not at all.[3,4]

After the gastrointestinal tract, the skin is the site most commonly affected by extranodal non-Hodgkin lymphomas (NHLs).[5] Accordingly, primary cutaneous NHL accounts for 18% of cases of extranodal NHL, with an estimated annual

incidence of 1 in 100,000.[6] Differentiation between primary and secondary cutaneous NHL is extremely important, since prognosis and treatment differ between the two.

Nevertheless, very few studies have reported on the frequency of cutaneous lymphoma (CL) in South America and on its clinical and pathologic characteristics,[7-9] with no studies having been conducted in Brazil. Therefore, it is of the utmost importance to evaluate the frequency of the different types of CL to identify the possible factors involved in the genesis of these tumors in South America.

This study was conducted in the pathology laboratory of the Professor Edgard Santos Teaching Hospital of the Federal University of Bahia in Salvador, Bahia, Brazil. The objective was to review and classify the diagnosis of CL made between January 1998 and December 2009 in unselected consecutive cases of CL, differentiating primary from secondary CL and evaluating prognosis. A further aim was to compare the frequency of primary CL observed here with rates reported in other countries, as well as evaluate the applicability of the World Health Organization/European Organization of Research and Treatment of Cancer (WHO/EORTC) classification for a diagnosis of CL in the present study.

Materials and Methods

A total of 153 consecutive and unselected cases were retrieved from the records at the pathology laboratory of the Federal University of Bahia's Teaching Hospital in Salvador, Bahia, Brazil. The period evaluated was from January 1998 through December 2009. Of these 153 cases, 131 consisted of NHL with cutaneous involvement and 22 of cutaneous lymphoid hyperplasia. All these cases referred to adult patients. The inclusion criteria for histologic review were (1) cases involving patients older than 18 years and (2) cases in which the initial diagnosis was made between 1998 and 2009. The exclusion criteria consisted of (1) cases in which the material remaining in paraffin blocks was insufficient for further immunohistochemical analysis and (2) cases in which serology for HTLV-1 and human immunodeficiency virus (HIV) had not been performed. Following application of these criteria, 137 (115 of CL and 22 of lymphoid hyperplasia) cases were then included in the study and subsequently reviewed.

The original diagnosis in the 115 cases of CL included 64 cases of cutaneous T-cell lymphoma (CTCL), 38 cases of ATL, 2 cases of precursor T-cell lymphoma infiltrating the skin, and 11 cases of cutaneous B-cell lymphoma (CBCL). Primary skin involvement was defined as the presence of CL without leukemia, nodal, or visceral involvement after staging procedures. Clinical data analyzed included age and sex of patients, data of diagnosis, and duration of follow-up. The status of the patients was considered as follows: (1) alive without disease, (2) alive with disease, or (3) dead. The follow-up of the patients was evaluated until December 2012.

The ATL cases were diagnosed and clinically classified according to preexisting criteria.[3,10,11] In all cases of smoldering ATL, only the skin was affected, there were no atypical cells or less than 5% of atypical cells in peripheral blood, there was no lymphocytosis or hypercalcemia, and lactate dehydrogenase levels were low. The smoldering and primary cutaneous tumoral (PCT) types of ATL were considered to represent cases of primary CL.[3] In 11 ATL cases, analysis of clonality using Southern blot[12] or long-inverse polymerase chain reaction[13] was performed.

Histopathologic and Immunohistochemical Studies

In each case, the original diagnosis was reviewed by at least 2 pathologists (A.L.B. and I.A.) with experience in lymphomas, based on clinicopathologic criteria, according to the WHO/EORTC classification of primary CL.[5] Immunohistochemical studies of the paraffin sections were carried out using immunoperoxidase procedures (avidin-biotin-peroxidase complex method). The antibodies employed in these cases were CD3, CD4, CD7, CD8, UCHL-1, and/or OPD4, CD20, CD30, CD68, and Ki-67. For ATL cases, the antibodies CD2, CD5, and CD25 also were used. All the CTCLs with large cells were stained for CD30 and the anaplastic large cell lymphomas (ALCLs) for anaplastic lymphoma kinase-1 (ALK-1). For B-cell lymphomas, the following markers were used: CD5, CD10, CD20, CD79a, CD23, CD38, CD43, Bcl-2, and Bcl-6 and, in some cases, cyclin D1. Monotypic expression of immunoglobulin light chains was also assessed. For precursor lymphomas, the markers TdT, LCA, CD10, CD34, CD56, and myeloperoxidase were also employed. Histologically, mycosis fungoides (MF)/Sézary syndrome (MF/SS) was classified as transformed MF (T-MF) if the biopsy specimen showed large cells exceeding 25% of the infiltration or if they formed microscopic nodules in at least 1 skin biopsy specimen.[14] When necessary, analysis of the genic rearrangement of the T-cell receptor[15] was performed for differential diagnosis between lymphoma and lymphoid hyperplasia. The protocol of the present study was approved by the Institutional Review Board of the Federal University of Bahia's Teaching Hospital.

Statistical Analysis

Clinical data were collected from the medical records and included in tables created using Excel (Microsoft, Redmond, WA), then exported to the SPSS version 20.0 (SPSS, Chicago, IL) for statistical analysis. Data were registered sequentially using a coding system to preserve patients' anonymity. Analysis was conducted of their demographic characteristics, the frequency of histologic patterns, and survival, the latter being calculated using the Kaplan-Meier method. The log rank test was used to compare the median survival time (MST)

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between cases of primary and secondary lymphomas and to compare the MST in cases of CTCL, ATL, and CBCL.

Results

Following review and further ancillary studies, few cases of CL were determined to be a different category of disease, and 3 cases of lymphoid hyperplasia were reconsidered as CL. In total, 112 cases of CL were evaluated in this study. Of these, 60 consisted of HTLV-1–negative CTCL, 37 of ATL, 2 of precursor T-cell lymphoma, and 13 of CBCL. There was a predominance of primary CL (n = 85; 75.9%) over secondary CL (n = 27; 24.1%). Of the 85 cases of primary CL, 72 (84.7%) consisted of CTCL and only 13 (15.3%) of CBCL **Table 1**. The histologic diagnoses of the cases of primary and secondary CL are shown in **Table 2**, as well as their frequencies.

The mean (SD) age of the overall population with CL was 56.1 (16.4) years, while the mean (SD) age of the patients in the HTLV-1–negative CTCL group was 54.7 (16.0) years vs 54.6 (15.9) years in the ATL group and 66.7 (18.2) years in the CBCL group. With respect to sex, 53.6% of the overall population was female, while 46.4% was male.

Cases of MF included 3 cases of follicular MF, 2 cases of SS, 1 case of T-MF, and 1 case of granulomatous slack skin. Most cases of peripheral T-cell lymphoma, unspecified (PTCL-U), had primary involvement of the skin. All cases of ALCL were ALK-1 negative, with 6 having primary and 2 secondary skin involvement. One of these cases consisted of primary cutaneous folliculotropic and lymphohistiocytic ALCL, and the other was of primary cutaneous eosinophil-rich ALCL. Both cases have already been published.[16,17]

With respect to the clinical type, 16 of the 37 cases of ATL were of the smoldering type, 11 were chronic, 4 were acute, 3 were of the lymphoma type, and 3 were of the PCT type. In 19 cases, a microscopic pattern of MF was present **Image 1**, while there were 16 cases of PTCL-U **Image 2** and 2 of ALCL, both of which were ALK-1 negative. Some cases of ATL presented uncommon aspects, such as an MF dyshidrosis-like pattern **Image 3A** and **Image 3B**,[18] purpuric cutaneous lesions,[19] or an association of hyalohyphomycosis and ATL in the same lesions.[20] In general, 33% of the

Table 1
Primary and Secondary Cutaneous Lymphomas

Lymphoma	Precursor T-Cell Lymphomas, No.	HTLV-1–Negative T-Cell Lymphomas, No.	ATLs, No.	B-Cell Lymphomas, No.	Total No. (%)
Primary	—	53	19	13	85 (75.9)
Secondary	2	7	18	0	27 (24.1)
Total	2	60	37	13	112 (100.0)

ATL, adult T-cell leukemia/lymphoma; HTLV-1, human T-cell lymphotropic virus type 1.

Table 2
Patients' Histologic Diagnoses and Current Status

Lymphoma	Alive and Well, No.	Alive With Disease, No.	Dead, No.	Without Follow-up, No.	Total No. (%)
Primary cutaneous T-cell lymphomas	72 (100.0)				
MF/SS	2	13	10	4	29 (40.3)
PTCL-unspecified	—	9	6	2	17 (23.6)
ALCL	3	2	1	—	6 (8.3)
Lymphomatoid papulosis	1	—	—	—	1 (1.4)
ATL	—	8	11	—	19 (26.4)
Secondary cutaneous T-cell lymphomas	27 (100.0)				
PTCL-unspecified	1	1	1	—	3 (11.1)
ALCL	—	1	1	—	2 (7.4)
Aggressive epidermotropic CD8+ T-cell lymphoma	—	—	1	—	1 (3.7)
Extranodal NK/T-cell lymphoma nonnasal type	—	—	1	—	1 (3.7)
Lymphoblastic T-cell lymphoma	—	—	1	1	2 (7.4)
ATL	—	2	16	—	18 (66.7)
Primary cutaneous B-cell lymphomas	13 (100.0)				
MZBL	1	3	—		4 (30.8)
FCL	1	1	1	2	5 (38.5)
DLBCL, leg type	—	3	—	—	3 (23.0)
DLBCL, others	1	—	—	—	1 (7.7)

ALCL, anaplastic large cell lymphoma; ATL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; FCL, follicle center lymphoma; MF, mycosis fungoides; MZBL, marginal zone B-cell lymphoma; NK, natural killer; PTCL, peripheral T-cell lymphoma; SS, Sézary syndrome.

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CTCLs consisted of cases of ATL. Of the cases of primary CTCL, 26.4% consisted of primary cutaneous ATL (smoldering and PCT types) and 73.6% of primary cutaneous HTLV-1–negative CTCL. All CBCL cases were HIV negative and had primary involvement of the skin (Table 2).

Follow-up

Of the entire group, we lost 9 patients to follow-up (Table 2). Progression to T-MF was observed in 4 MF cases, with 3 progressing to CD30-negative large cell lymphoma and 1 to CD30-positive large cell lymphoma. In 1 case, transformation also occurred in a superficial lymph node. In the case diagnosed as T-MF during review, in which transformation to a CD30-negative large cell lymphoma occurred, the lesions progressed despite treatment, but this patient is still alive. Three of the 5 patients with T-MF have died, and 2 remain alive with the disease. Two other patients were considered to have MF in transformation, since lesions were present with

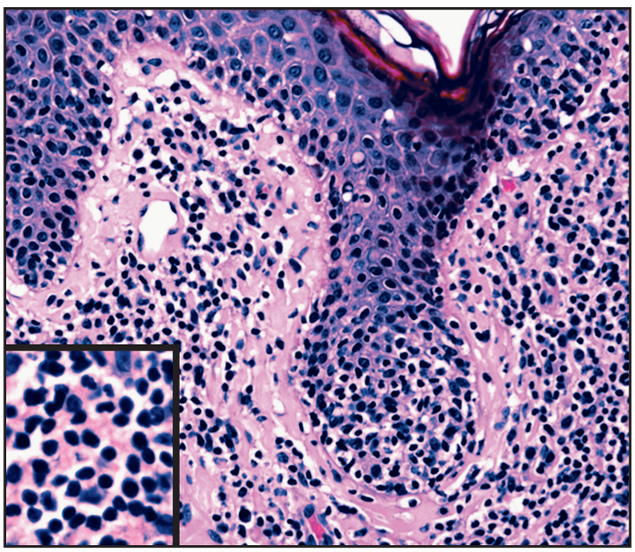

Image 1 Mycosis fungoides–like adult T-cell leukemia/lymphoma. Infiltration of small and atypical lymphocytes in the upper dermis with epidermotropism (H&E; ×250). Inset: Higher magnification of the infiltrate (H&E; ×500).

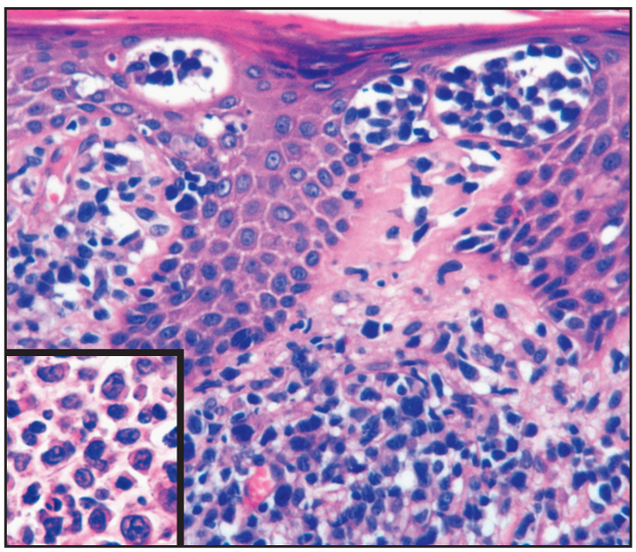

Image 2 Adult T-cell leukemia/lymphoma. Unspecified peripheral T-cell lymphoma pattern. Pleomorphic medium and large cells infiltrating the dermis with Pautrier abscesses (H&E; ×320). Inset: Higher magnification of the pleomorphic cells (H&E; ×500).

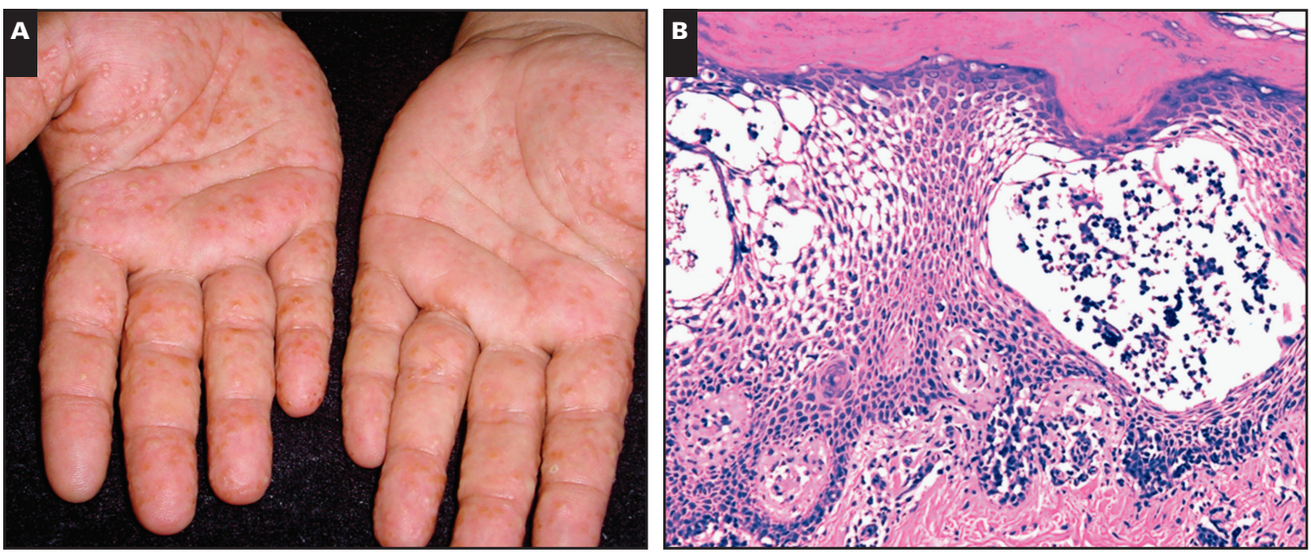

Image 3 Dyshidrosis-like variant of adult T-cell leukemia/lymphoma. **A**, Many vesicles on the palms of both hands. **B**, The epidermis shows spongiosis and large intraepidermal vesicles with atypical lymphocytes (H&E; ×100).

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many large cells during the course of the disease; however, these cells did not exceed 25%. Both of these patients died, at 68 and 38 months, respectively, from having developed the disease and despite treatment.

Of the cases of primary HTLV-1-negative CTCL for which follow-up was available, 30 patients are alive, while 17 have died. Of the 10 deaths in patients with MF/SS, 3 were due to T-MF, 2 to MF in transformation as mentioned above, 2 to follicular MF, 1 to erythrodermic MF (stage IIIa), and 2 to an unknown cause. Of the 11 deaths in primary ATL cases, 3 corresponded to PCT, 1 to progression of the smoldering type to PCT, and the others to infection or unrelated diseases. The lesions in the patient with lymphomatoid papulosis disappeared completely. The 2 deaths that occurred in patients with primary ALCL were due to other causes.

Evaluation of Survival

The MST for the entire population was 48 months. There was a statistically significant difference of MST between primary and secondary CL ($P = .0001$). The primary HTLV-1–negative CTCL group presented the longer MST in comparison to primary ATL and CBCL cases, but this difference was not statistically significant **Table 3**.

Discussion

Evaluations on the frequency of CL in South America are rare, and sample sizes are generally small. In 2 evaluations carried out in Argentina, one with 57 cases of CL over a 10-year period and the other with 39 cases of CTCL over a 16-year period, no pathologic or immunohistochemical review of the material was performed.[7,8] An evaluation of primary CL that included a review of the pathology findings in 65 cases in Lima, Peru, showed that 83.4% of cases consisted of CTCL and only 16.6% of CBCL.[9] These findings are similar to the results of the present study, in which 84.7% of the cases consisted of primary CTCL and 15.3% of primary CBCL. Studies conducted in Japan and Korea also showed a marked predominance of primary CTCL in relation to CBCL.[1,21-23] Notwithstanding, in the European studies, although CTCL is more common than CBCL, this difference is much less marked compared with that found in the present study.[24-26] In the WHO/EORTC classification, in which 1,905 cases of primary CL were reclassified, 77.5% of cases corresponded to CTCL and 22.5% to CBCL.[27] However, no case of primary ATL was included in that register, probably because ATL is not endemic in Europe. Furthermore, in the WHO/EORTC classification, ATL is considered exclusively as secondary CL.[28]

In the present evaluation, the most common type of CTCL was MF (40.3%), followed by primary cutaneous ATL (26.4%). Included in MF were 2 cases of SS, 3 cases of follicular MF, and 1 case of granulomatous slack skin. MF/SS was less common compared with the European data[24-26] but similar to the findings of Fujita et al[23] in Japan. The results of the present study are closer to those found in Lima, Peru, where 46% of cases corresponded to MF/SS and 19.4% to primary cutaneous ATL.[9] In another evaluation conducted in Osaka, Japan, the percentage of cases of MF/SS in primary CTCL was even smaller at 33%.[21] The ATL cases, in general, represented 33% of T-cell lymphomas and 26.4% of primary cutaneous T-cell lymphomas. In Rio de Janeiro, Brazil, an evaluation of 188 cases of T-cell malignances in general revealed a frequency of 26.5% of ATL cases.[4] The frequency of ATL in the present CTCL cases is high because Salvador, Bahia, Brazil is an endemic area for HTLV-1 infection.[29] Notwithstanding, this high frequency may in part reflect a biased recruitment of ATL cases in the pathology laboratory of the university teaching hospital, since this is a reference center for ATL studies. The frequency of PTCL-U was higher compared with that found in other studies,[27] possibly because some cases of T-MF may have been included in this diagnosis. In a few cases diagnosed as PTCL-U, it proved impossible to obtain the patients' previous clinical history and previous biopsy specimens for review. In relation to ALCL,

Table 3
Median Survival Time in Primary and Secondary Cutaneous Lymphomas

Lymphoma	No. of Cases	MST, mo	2-y Survival, %	5-y Survival, %
Primary	76	109	75.3	57.5
HTLV-1–negative CTCL	47	109	80.6	64.0
ATL	19	47	68.4	42.1
CBCL	10	65	62.5	62.5
Secondary	26	11	38.5	19.2
Precursor CTCL	1	6	0	0
HTLV-1–negative CTCL	7	19	42.9	42.9
ATL	18	11	38.9	11.1
Global	112	48	65.5	46.3

ATL, adult T-cell leukemia/lymphoma; CBCL, cutaneous B-cell lymphoma; CTCL, cutaneous T-cell lymphoma; HTLV-1, human T-cell lymphotropic virus type 1; MST, median survival time.

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the frequency found in the present study was similar to that reported in other studies.[23,25]

In view of the common difficulty found in performing a differential diagnosis between CL and lymphoid hyperplasias,[30] these conditions were reviewed and 2 cases of lymphoid hyperplasia were rediagnosed as marginal B-cell lymphoma and another as ALCL. Of the cases of CBCL, the most common type of lymphoma was the centrofollicular type, and this finding is in agreement with reports from other studies.[5,28]

Five cases of T-MF were found in the group of CTCL: 1 that had been previously diagnosed as MF and 4 observed during disease progression. Only 1 progressed to CD30-positive large cell lymphoma and, curiously, this was the case with the poorest prognosis. In all 5 of these cases, clinical and histologic transformation was seen concomitantly, and 3 of these patients have already died.

The MST was longer in HTLV-1–negative CTCL than in ATL and CBCL, but the difference was not statistically significant. Among the cases of smoldering ATL, most of the deaths were due to infection or other causes, but among the PCT type, all deaths were due to a severe cutaneous dissemination of tumors. There is a great difference in the MST between those with primary and secondary T-cell lymphomas, which indicates the importance of differentiating these 2 types of CTCL.

The Brazilian and Japanese experiences had shown that ATL may also appear primarily in the skin.[31-33] Although the Japanese authors do not refer to primary cutaneous ATL, their published reports about cutaneous ATL really correspond to primary cutaneous ATL.[32,33] Thus, it is important that the Latin American countries with a high prevalence of HTLV-1 infection share their experiences and, together with Japan, should include this entity in the next primary CL international classification. It is important to emphasize that primary cutaneous ATL has a much better prognosis than secondary cutaneous ATL, as observed in the present study, confirming previous observations.[31]

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