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REVIEW ARTICLE

Leukemia cutis: clinical features of 27 Mexican patients and a review of the literature

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Abstract

Background: *Leukemia Cutis (LC) consists in neoplastic leukocytic infiltration of the skin and is strongly associated with the presence of extramedullary disease and poor prognosis. However, there are few studies in the literature regarding this entity. We perform a retrospective study of 27 mexican patients in order to analyze the clinical features and prognosis of LC in Mexico, and a brief review of the literature.* **Methods:** *Cases diagnosed as LC by skin biopsy were selected from the database of the Department of Dermatology of National Institute of Medical Science and Nutrition Salvador Zubirán. Cases were searched between the dates of January 1993 and December 2013.* **Results:** *Twenty-seven cases which were histologically confirmed with cutaneous leukemic infiltrate were included. Of these patients 60% were male and the mean age at diagnosis was 42 yr (19 to 80 yr). The predominant tipe of LC was acute myeloid leukemia (AML) with 48% of the cases. Nodular neoformations were the main clinical manifestation with 63% of the cases. The mean interval between the diagnosis of LC and death was 10 months (CI 95%).* **Conclusions:** *The presence of LC is a marker of poor prognosis and can precede the relapse of systemic leukemia. Cutaneous infiltration may be the first or the only sign of progression, so doctors should be familiar with the clinical manifestations of this disease.* (Gac Med Mex. 2016;152:629-35)
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Introduction

Leukemia is a disease where leukocytes and/or their precursors lose the capability to mature and differentiate, thus proliferating in a disordered manner and replacing normal elements of the bone marrow. The spectrum of skin manifestations on these patients varies, from those regarded as non-specific of the disease (i.e., without infiltration by neoplastic cells but, as in other conditions, they can occur as events secondary to disease evolution or to the employed treatments), to those that are disease-specific, which are secondary to infiltration by leukemia neoplastic cells, and the manifestation of which is known as leukemia cutis (LC)[1,2].

Leukemia is generally classified in two groups: lymphoid and myeloid. In turn, both subtypes are divided into acute and chronic. Acute lymphoid leukemias (ALL) are divided into: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities, non-specified

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B-cell lymphoblastic leukemia/lymphoma and T-cell lymphoblastic leukemia/lymphoma. Chronic lymphoid leukemia has no subtypes. In turn, acute myeloid leukemia (AML) is divided into AML with recurrent genetic abnormalities (M0-M7), AML with myelodysplastic changes, therapy-related myeloid neoplasms, non-specified AML, myeloid sarcoma and Down syndrome-related myeloid proliferations. As chronic lymphoid leukemia, chronic myeloid leukemia has no subtypes[3].

Chronic lymphocytic leukemia (CLL) is the most common leukemia worldwide; however, skin infiltration is more common in AML, especially in the subtypes with monocytic component; skin infiltration has been reported in 10% to 33% of patients with acute myelomonocytic leukemia (AMML, French-American-British system [FAB]-M4) and in 13% of patients with monocytic leukemia (AML, FAB-M5)[4-6], whereas in CLL skin infiltration is less common, and is reported in 6%-10% of patients[4,7,8].

Initially, AML classification was based on the FAB system, on the basis of morphology and degree of differentiation. However, in recent years, specific mutations in AML that predict treatment response and prognosis have been identified. In view of this, the WHO 2001 classification incorporated "AML with recurrent chromosomal abnormalities". Other added categories were AML with multi-lineage dysplasia and therapy-related AML. In turn, this classification was updated in 2008, where myeloid sarcoma was recognized as a subtype and deemed as a separate variety for the first time, and NK cell blastic lymphoma stopped belonging to mature T-cell neoplasms to become an AML variant and was renamed plasmacytoid dendritic cell neoplasm. On the other hand, lymphoid-precursor LC is subdivided into B-cell and T-cell LC, and B-cell lymphoblastic leukemia is subdivided according to the presence of specific genetic anomalies[7].

The pathophysiology of LC has not yet been determined, but several factors such as the expression of certain cytokines, integrins and adhesion molecules are thought to intervene. Alterations on malignant cells' surface antigens have been demonstrated in patients on treatment with transretinoic acid, and this is thought to confer malignant cells an increased capacity to produce metastasis. Other studies suggest that the presence of lymphocyte-associated antigens can increase skin tropism by leukemic cells[6,9,10].

Some studies in patients with AML have proposed LC as an indicator of poor prognosis[11,12]. In 2002, Agis et al. compared patients with AML with and without LC, and found that patients with LC tended to have less durable remissions and certain chromosomal anomalies more frequently[13].

In Latin America there are few works on clinical behavior and prognosis of this entity. In 1999, de la Barrera reported the dermatologic complaints of patients with hematological neoplasms during a 2 ½-year period and found that 12% had infiltration by leukemia or lymphoma[14]. In 2011, Sánchez-Hernández et al. carried out a 2-year follow-up of 22 patients with acute leukemia, and found that of all dermatoses developed by these patients only one case was LC[1]. However, there are few data on the prognosis of this disease in Hispanic population.

Material and methods

A retrospective cohort of patients with histologically-confirmed diagnosis of LC was reviewed over a 21-year period at the Dermatology Department of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.* By means of imaging, slides and database review of these patients, demographic, clinical, evolution, management and outcome data were obtained according to skin infiltration histological type.

The multiple multivariate analysis for the survival results was performed with Cox regression models, with probability coefficient tests adjusted for the effects of age and type of leukemia. The analyses were carried out with SPSS version 20.0.0.1 and software 3.1.1 version I.

Results

Twenty-seven patients with histological diagnosis of LC were included, out of which 60% (16 patients) were males and 40% were females; mean age was 42 years (range: 19 to 80 years) (Table 1).

Cutaneous clinical manifestations were heterogeneous; however, nodular neoformations were the most common manifestations (Fig. 1), although it should be noted that some uncommon clinical manifestations were found, such as morbilliform rash or viral rash, as well as ulcers (Fig. 2 and Table 2).

The predominant histological type was AML in 48% of cases in this cohort, with the promyelocytic (M3) and myelocytic (M4) variants being predominant. Fifteen percent of LCs was secondary to ALL, out of which those with B-cell lineage were predominant. Skin infiltration was less common with plasmacytoid dendritic cell neoplasm, chronic neutrophilic leukemia, biphenotypic leukemia (mature B myeloid/lymphoid) and T-cell prolymphocytic leukemia (T-PLL) (Fig. 3 and Table 3).

Table 1. Patient demographics, n (%)

Total number of patients	27 (100%)
Gender:	
Male	16 (60%)
Female	11 (40%)
Age (years):	
18-30	6 (22%)
31-40	7 (26%)
41-50	6 (22%)
51-60	3 (11%)
> 60	5 (19%)

In 18% of subjects, skin infiltration was the first clinical manifestation and was the basis to establish the leukemia diagnosis, with these manifestations preceding from 15 days to 4 months the systemic diagnosis. In two cases of LC secondary to chronic granulocytic leukemia (CGL), the skin infiltration was found to be related to transformation to the blastic phase at 4 and 10 years, respectively (Table 4).

With the purpose to corroborate that LC-diagnosed patients have poor survival, limited to a few months, a Kaplan-Meier survival analysis was carried out, with a median survival of 10 months with 95% CI of 2.097-17.903 being obtained (Fig. 4).

Discussion

In our series, we observed a slight predominance in men (60%, 16 cases), which is in agreement with previously reported observations. However, the age of presentation varies according to the reviewed series: Wagner et al. reported a mean age of 68-69 years, whereas Yeon Soo Kang et al. reported a mean age of 37.6 years in a series of 75 Korean patients[4,8]. In our cases, median age was 42 years (range: 19 to 80 years), which is more in agreement with reports on Asian patients (Table 1).

Leukemia cutis has a highly variable clinical presentation that includes maculae, papules, neoformations with nodular aspect, ulcers and plaques. The lesions can be localized or disseminated, and can affect any part of the body. The most common lesion varies according to the reviewed literature, and the most frequently reported in recent reviews are macula and neoformation with nodular aspect. With regard to the

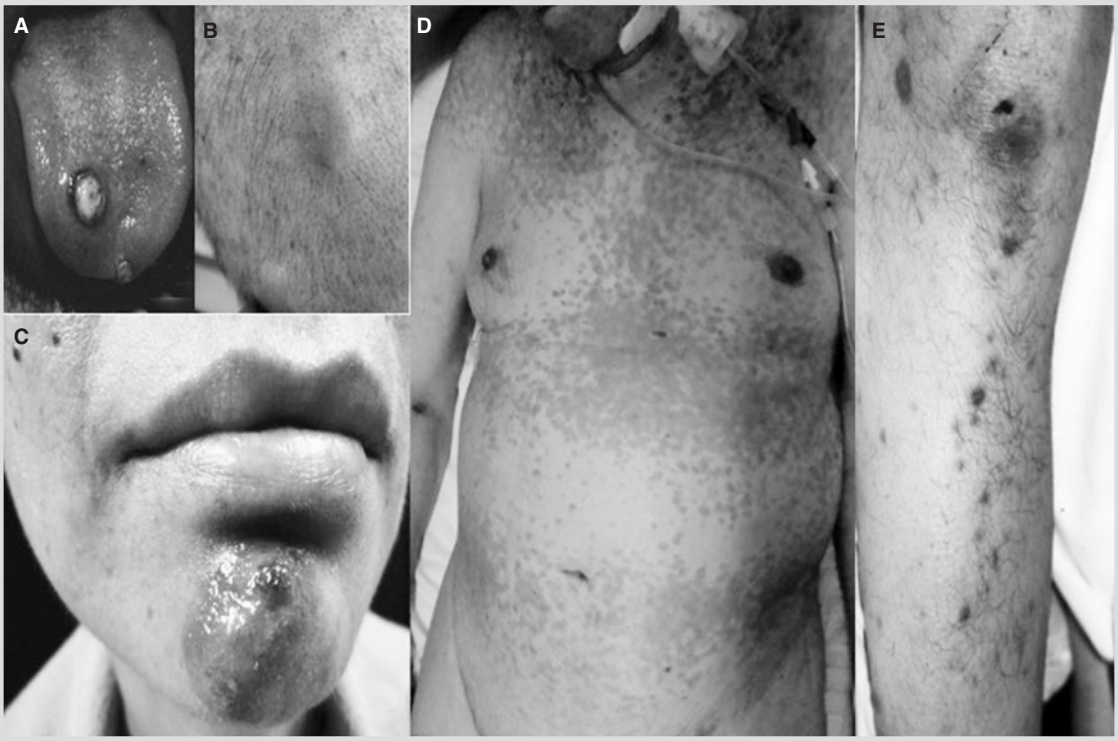

Figure 1. *Common clinical presentations.* **A** *and* **B:** *neoformations with nodular aspect.* **C:** *plaque.* **D** *and* **E:** *maculae.*

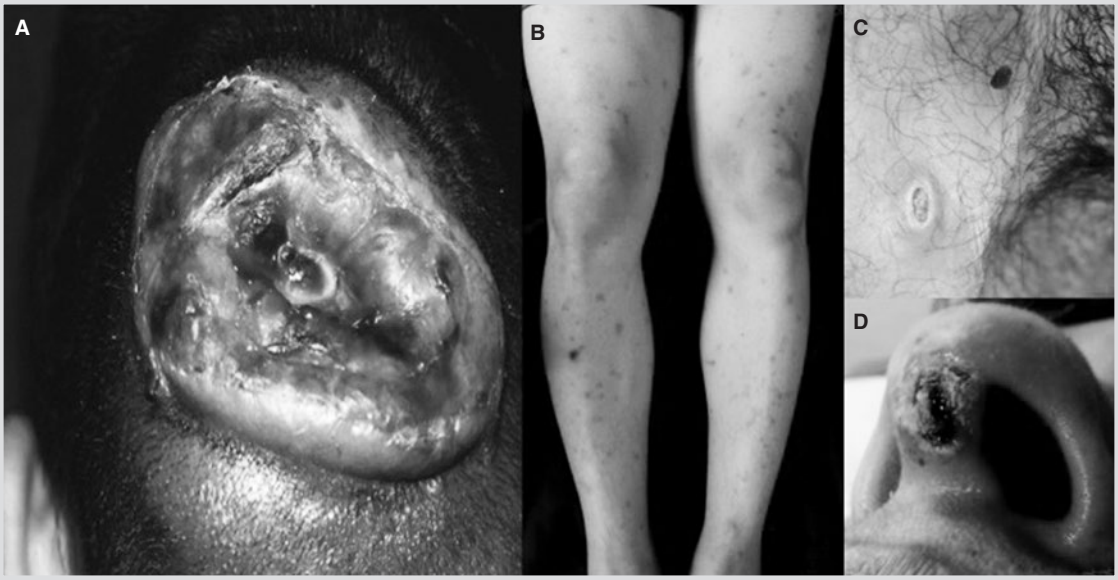

Figure 2. *Uncommon clinical presentations.* **A:** *ulcerated neoformation.* **B:** *hyperpigmented maculae.* **C** *and* **D:** *ulcerated plaques.*

most frequently affected sites, they also vary, with some authors even reporting that they vary according with the type of leukemia, but, generally, the most commonly affected sites are the trunk and limbs[6,8]. Other less frequent presentations include erythrodermia, pruriginous cutaneous eruption, circinate plaques, periorbital edema, vasculitis, ecchymosis, psoriasiform lesions, rosacea-type lesions and herpes-type dermatitis. Although infrequent, LC can be associated with herpes lesions, scarring and *Borrelia burgdorferi* infections[15-21]. This is consistent with findings in our series, where neoformation with nodular aspect and trunk involvement were the most common findings (Table 2). In our series, there was only one case of LC with hyperpigmented lesions, and it was due to CGL at blastic phase. There are few cases reported of hyperpigmentation as LC clinical manifestation. Previously, a relationship between melanocyte-stimulating hormone or adrenocorticotropic hormone hyperproduction and pigmentation has been proposed in these patients, but this has not been corroborated[15] (Fig. 2 B).

In patients with myelodysplastic syndrome (MDS), skin involvement can be the first manifestation of transformation into leukemia[6]. In two of the cases of leukemic transformation, LC was preceded by psoriasiform dermatitis up to one year prior to being able to confirm leukemic infiltration by histology. Therefore, in patients with MDS and this type of dermatosis it is important taking into account that, sometimes, multiple samples are required for the detection of leukemic cells. This could be explained by the fact that patients probably begin with a chronic inflammatory dermatosis that may act as a chemotactic factor for leukemic cells or, simply because, at early phases, the leukemic cell population is small and difficult to find on histopathological analyses (Fig. 5).

Table 2. Patient clinical characteristics, n (%)

Total number of patients	**27**
Involvement:	
Localized	12 (44%)
Disseminated	15 (56%)
Body segments involved:	
Thorax	19 (70%)
Upper limbs	10 (37%)
Lower limbs	9 (33%)
Head	8 (30%)
Clinical findings:	
Maculae	2 (7%)
Morbilliform exanthema	1 (4%)
Neoformations with nodular aspect	17 (63%)
Plaques	6 (22%)
Vesicles	1 (4%=

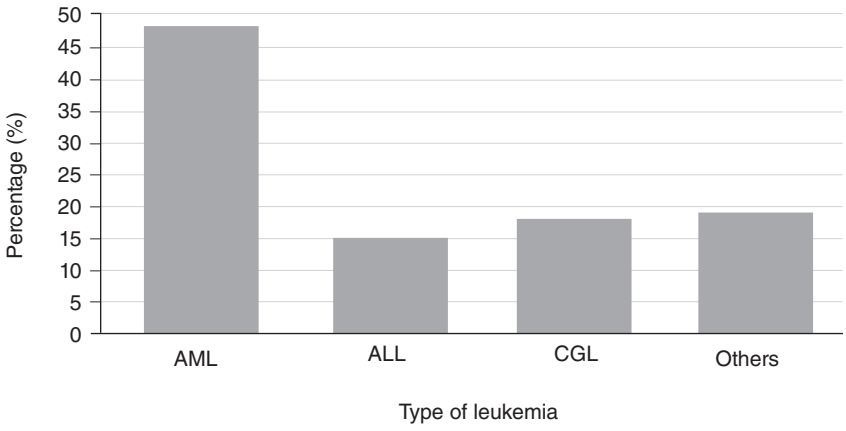

Figure 3. *Distribution by type of leukemia.*

Leukemia cutis can be detected at the moment of diagnosis in patients diagnosed with leukemia or it can even precede the leukemia diagnosis. In the majority of cases, LC occurs in patients previously diagnosed with leukemia (55%-80%), it is less common to be found at the moment of diagnosis (23%-38%), and the less common variety is the one that precedes the diagnosis of the leukemia known as aleukemic LC, which can precede from months to years the detection of leukemia in the bone marrow or peripheral blood. This variety accounts for 5%-7% of cases. Previously, approximately 18% of LCs were reported to precede the diagnosis, but recent data show an up to 5% drop, which reflects earlier diagnosis[4,6,8]. In this regard, 55.6% of our patients had already a leukemia diagnosis at the moment of LC onset, which is consistent with

Table 3. Types of leukemia, n (%)

AML:	13 (48%)
Acute erythroid (M6)	1 (4%)
Acute promyelocytic (M3)	3 (11%)
Acute myelomonocytic (M4)	3 (11%)
Undifferentiated acute myeloblastic (M0)	1 (4%)
Acute monocytic (M5)	2 (7%)
Complex karyotype	1 (4%)
With monoblastic component and trisomy	1 (4%)
AML of non-specified type	1 (4%)
ALL:	4 (15%)
Pre-B ALL	3 (11%)
T-cell ALL	1 (4%)
CGL	5 (18%)
Other:	5 (19%)
Plasmacytoid dendritic cell leukemia (PDCL)	2 (7%)
Myeloid biphenotypic leukemia	1 (4%)
Chronic neutrophilic leukemia	1 (4%)
T-cell prolymphocytic leukemia (T-PLL)	1 (4%)

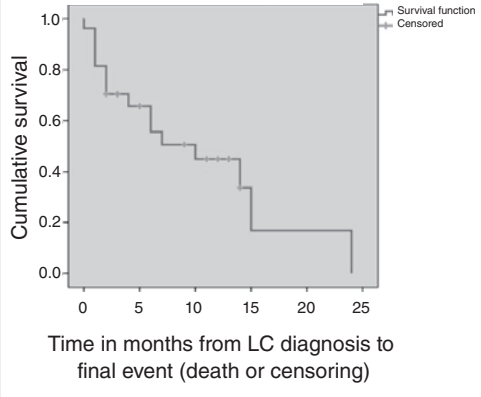

Figure 4. *Kaplan-Meier survival analysis.*

Table 4. Baseline characteristics distribution according to leukemia subtype

Type of leukemia	AML (n = 13)	ALL (n = 4)	CGL (n = 4)	Other (n = 5)
Age in years at diagnosis, median (minimum-maximum)	39 (19-67)	41 (31-70)	30 (24-39)	53 (42-80)
Time in months from leukemia diagnosis to LC diagnosis, median (minimum-maximum)	1 (0-90)	11 (0-21)	32 (0-129)	5 (0-13)
Time in months from leukemia diagnosis to final event (censoring/death), median (minimum-maximum)	12 (1-99)	15.5 (5-32)	33.5 (13-141)	7 (0-17)
Time in months from LC diagnosis to final event (censoring/death), median (minimum-maximum)	6 (1-24)	4 (3-14)	7 (1-13)	3 (0-7)

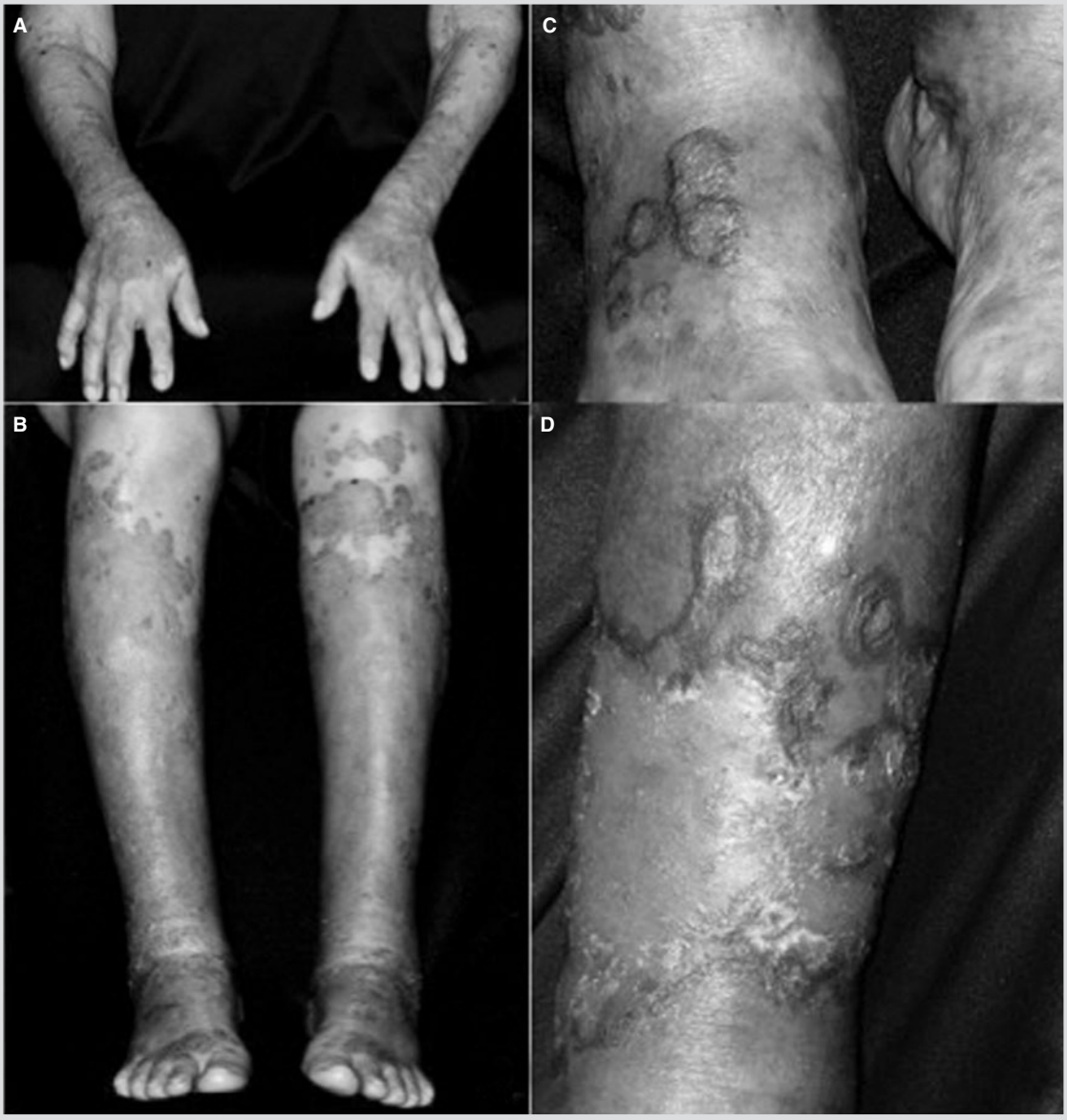

Figure 5. A *and* **B:** *eczematous dermatitis on upper and lower limbs.* **C** *and* **D:** *infiltration by leukemia 3 months later on sites where eczematous dermatitis was found.*

the literature. However, in 18.5% of cases the lesions preceded the leukemia diagnosis, which could imply that there is still delay in the leukemia diagnosis in our population, since cases are detected already at advanced phases with skin infiltration.

Owing to the multiplicity of clinical manifestations, histopathology is essential for diagnosis. Infiltrate can be diffuse, interstitial or nodular with or without perivascular and periannexial involvement. Epidermal involvement is rare, since generally there is an unaffected zone left at the level of the dermoepidermal junction (Grenz zone). However, an adequate classification of leukemia is not possible only by histopathological analysis; bone marrow cytochemical and genetic studies are required to achieve an adequate classification[4]. Differential diagnoses are highly varied, with the main including neutrophilic dermatoses, drug eruptions, erythema nodosum, vasculitis and viral exanthema[6,16,22].

A 10-month median survival was found in our patients, which is in agreement with reports in previous studies, where LC has been found to be associated with an increased risk of extramedullary involvement, with the development of a blastic phase and rapid disease progression, thus being considered a factor for progression and poor prognosis (Table 2). These studies have found that up to 88% of patients who develop it die within the year that follows the diagnosis[5,6,11,12,23,24]. Owing to this cohort's sample size, and to the scarce number of patients in the leukemia subtypes, a recoding was made in the main subtypes: AML, ALL, CGL and others, but we found no differences in the survival comparison between the different groups of leukemia.

In conclusion, although LC is a rare entity, its occurrence entails poor prognosis, as it is associated with disease progression and survival decrease in these patients. In view of the above, the dermatologist should know the different manifestations of this entity in order to establish an early diagnosis in these patients.

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