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ORIGINAL ARTICLE

Lymphomatoid Papulosis in Children: Report of 9 Cases and Review of the Literature

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KEYWORDS
Cutaneous T-cell lymphoma;
Lymphomatoid papulosis;
Childhood

Abstract
Background: Lymphomatoid papulosis is a rare CD30+ T-cell lymphoproliferative disease with an excellent prognosis. It is usually seen in adults and is rare in children. The clinical and pathologic manifestations and the risk of progression to other types of lymphoma are thus not clearly defined in the pediatric age group.
Objective: To describe the characteristics of lymphomatoid papulosis in a group of children and perform a review of the literature.
Patients and methods: A retrospective study was performed of 9 patients under 18 years of age diagnosed with lymphomatoid papulosis and treated in our department between 1995 and 2009
Results: The study included 7 boys and 2 girls aged between 2 and 17 years. Lesions compatible with pityriasis lichenoides acuta appeared before the lymphomatoid papulosis in 2 cases and afterwards in 1 case. The lymphomatoid papulosis lesions resolved spontaneously, leaving postinflammatory hyperpigmentation (77%) or hypopigmentation (23%). Scarring occurred in 77% of cases. Histologically, all cases showed features compatible with lymphomatoid papulosis type A. Molecular studies showed monoclonality in all 3 cases in which this technique was performed.
Conclusions: Lymphomatoid papulosis is a rare disease in childhood and the manifestations are similar to the adult form. This lymphoproliferative disease, occasionally associated with pityriasis lichenoides acuta, has histological features compatible with a type A or histiocytoid pattern. Progression to other lymphoproliferative disorders during follow-

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up is less common in the childhood form than in adults. The frequent association of pityriasis lichenoides acuta and lymphomatoid papulosis observed in our study, and the difficulty distinguishing between these 2 conditions in some cases, suggest that these diseases could be part of a single clinical-pathological spectrum.

PALABRAS CLAVE
Linfoma cutáneo de células T;
Papulosis linfomatoide;
Infancia

Papulosis linfomatoide en la infancia: presentación de 9 casos y revisión de la literatura

Resumen

Introducción: La papulosis linfomatoide es un proceso linfoproliferativo de células T CD30+ poco frecuente y de pronóstico excelente que generalmente afecta a adultos y, en menor medida a niños, por lo que tanto el espectro clínico-patológico como el riesgo de progresión a otro tipo de linfoma en el grupo pediátrico no están bien establecidos.
Objetivo: Analizar las características de la papulosis linfomatoide infantil a partir de la descripción de nuevos casos y de la revisión de la literatura.
Material y método: Se realizó un estudio retrospectivo de 9 pacientes menores de 18 años diagnosticados de papulosis linfomatoide atendidos en nuestro servicio entre 1995 y 2009.
Resultados: Se incluyeron 7 niños y 2 niñas de edades entre 2 y 17 años. Las lesiones de papulosis linfomatoide se vieron precedidas en 2 casos y seguidas en 1 de otras compatibles con pitiriasis liquenoide aguda.
La resolución de las lesiones fue espontánea, dejando hiperpigmentación (77%) o hipopigmentación postinflamatoria (23%) y cicatrices en el 77% de los casos. Histológicamente todos los casos presentaron el patrón tipo A de papulosis linfomatoide. El estudio molecular mostró monoclonalidad en los 3 casos en los que fue realizado.
Conclusiones: La papulosis linfomatoide infantil es una entidad rara que se manifiesta clínicamente como la forma adulta. Esta enfermedad linfoproliferativa, que ocasionalmente se asocia a pitiriasis liquenoide aguda, muestra hallazgos histológicos compatibles con el patrón histiocitoide o tipo A. El desarrollo de otros procesos linfoproliferativos malignos en el seguimiento posterior es menos frecuente en la papulosis linfomatoide infantil comparado con la variante adulta. La frecuente asociación de pitiriasis liquenoide y de papulosis linfomatoide encontrada en nuestro análisis, así como la dificultad que supone en algunos casos el diferenciar entre ambos procesos, permiten sugerir que ambas patologías podrían formar parte de un espectro clínico-patológico común.

Introduction

Lymphomatoid papulosis was described by Macaulay[1,2] in 1968 as a benign clinical condition with the histological characteristics of a malignant lymphoma. Once considered an inflammatory process, it is currently defined as an indolent cutaneous lymphoma that principally affects adults. The etiology of the disease is unknown. In 20% of cases, malignant lymphoproliferative disease occurs concomitantly or during long-term follow-up.

Lymphomatoid papulosis is exceptional in childhood, and neither its clinicopathologic characteristics nor the risk of developing malignant lymphoproliferative disease has been well established. We report 9 cases of lymphomatoid papulosis in patients aged between 2 and 17 years and we analyze the main characteristics of this process in children by reviewing previously published cases and compare it with the characteristics observed in adult patients.

Material and Methods

Patients

We performed a retrospective study using the clinical history of all patients aged 1 to 18 years diagnosed with lymphomatoid papulosis at the Niño Jesús Children's Hospital in Madrid, Spain. The patients were treated between January 1, 1995 and September 30, 2009.

We analyzed the following parameters: age, sex, presenting lesion and distribution pattern, maximum number of lesions in an outbreak (1-5, 6-10, 11-20, >20),

presence of associated symptoms, residual lesions, number of outbreaks per year, and long-term follow-up (5 years of periodic checkups).

Histopathology

Conventional microscopy was performed using 4% formalin-fixed paraffin-embedded biopsy specimens stained with hematoxylin-eosin. Immunohistochemistry was performed with an automatic immunostainer (Dako Autostainer Link 48, Dako, Denmark) using the EnVision FLEX detection system (Dako). We used antibodies against epithelial membrane antigen, CD2, CD3, CD4, CD8, CD20, CD79a, CD15, CD30, and CD68. Molecular analysis of T-cell receptor rearrangement was carried out in 3 cases.

Analysis of cases was based on morphology following a recent classification differentiating 3 well-defined types of lymphomatoid papulosis: *a)* type A, or histiocytic type, which is characterized by a mixed infiltrate composed mainly of small lymphocytes and numerous large atypical lymphocytes, accompanied by varying numbers of neutrophils and macrophages, with occasional isolated eosinophils; *b)* type B, or mycosis fungoides–type, which is characterized by a monomorphous infiltrate of small to medium-sized lymphocytes with cerebriform nuclei; and *c)* type C, or large cell–type, which is defined as a dense infiltrate composed mainly of large atypical lymphocytes.[3]

Results

Patient data are shown in Table 1.

Typical Case Report (Patient 5, Table 1)

A 6-year-old child with no personal or family history of interest attended our dermatology department due to a 2-year history of repeated outbreaks (2 episodes per year) of multiple red-violaceous papules (11-20 lesions) less than 1 cm in diameter that were distributed symmetrically on his legs (Figure 1A). The lesions were asymptomatic, infiltrated, and indurated to the touch; some showed central ulceration with slough. The outbreaks tended to resolve spontaneously after 6-8 weeks of follow-up, leaving areas of residual hypopigmentation and discreet varioliform scars. No other clinical abnormalities were observed and the physical examination was normal.

Analysis of a biopsy specimen revealed a dense, predominately perivascular dermal infiltrate in the papillary and reticular dermis and along the basement membrane. Marked epidermotropism and secondary ulceration of the epidermis were also observed (Figure 1B and C). The inflammatory infiltrate was composed mainly of small lymphocytes and other, larger lymphoid cells with a vesicular nucleus and prominent nucleoli that were reminiscent of Reed-Sternberg cells (Figure 1D). Histiocytes, neutrophils, and isolated eosinophils were also present (Figure 1C and D). Immunohistochemistry revealed all the lymphoid cells to be positive for CD3 and CD8, whereas CD30 immunostaining was only observed in small groups of large cells. This infiltrate was negative for epithelial membrane antigen, CD15, CD20, and CD79a. The cells of the lesion were CD68-negative but accompanying histiocytes were CD68-positive. Polymerase chain reaction performed to analyze T-cell receptor rearrangement revealed a monoclonal population of T lymphocytes.

As type A lymphomatoid papulosis was diagnosed, no treatment was administered.

Analysis of the Results

The study sample included 7 boys (77%) and 2 girls (23%) aged between 2 and 17 years (median, 8 years). Two patients developed lymphomatoid papulosis lesions in the context of acute pityriasis lichenoides that was histologically confirmed and had started some years before.

In all 9 cases (100%), the lesions presented as mild to moderately infiltrated red-brownish and/or erythematous-violaceous papules. The maximum number of lesions per outbreak varied between 11 and 20 in 7 cases (77%); fewer than 10 were observed in the other 2 cases. The lesions were pruriginous in 33% of cases and were distributed, in descending order of frequency, on the lower limbs (9 cases, 100%), upper limbs (8 cases, 88%), trunk (4 cases, 44%), and face (1 case, 10%). Of note, the greatest concentration was on the limbs in all cases, whereas in those cases in which the face and trunk were involved, the lesions were isolated (Table 1). The lesions resolved spontaneously in all cases, leaving hyperpigmentation (7 cases, 77%) or postinflammatory hypopigmentation (2 cases, 23%). Residual varioliform scars were observed in 7 patients (77%).

The number of outbreaks per year varied between 2 and 3 in 8 patients (90%). One patient showed a single outbreak that was not subsequently accompanied by new cutaneous symptoms during follow-up. In 6 cases (66%), the disease remained active after 5 years of follow-up. Two patients (22%) were in remission after 3 years of follow-up. One case (12%) only showed activity during the first year of follow-up.

None of the 9 cases presented relevant complications during the 5 years of follow-up. Nevertheless, 1 patient developed lesions that were clinically and histologically compatible with chronic pityriasis lichenoides.

In all 9 cases, histopathology was compatible with lymphomatoid papulosis type A. The molecular study of T-cell receptor rearrangement revealed monoclonality in the 3 cases in which it was performed.

Discussion

Lymphomatoid papulosis is a disease of unknown etiology. According to the European Organization for Research and Treatment of Cancer,[2] it is classified as an indolent cutaneous CD30-positive large T-cell lymphoma.

It generally affects adults aged between 40 and 60 years, irrespective of race or sex.[3] It takes the form of multiple outbreaks of papulonodular lesions and, less commonly, vesiculopustular lesions located mainly on the trunk and limbs. The lesions tend to resolve spontaneously, occasionally leaving a residual scar.[3] The outbreaks last from weeks to months, and the disease-free interval varies

Table 1 Clinical and Pathologic Characteristics

No./Sex/Age	History of Interest	Presenting Lesion	Distribution Pattern and Severity[a]	Associated Symptoms	Maximum Number of Lesions in an Outbreak	Residual Lesions	Histopathologic Pattern	Molecular Rearrangement	No. of Outbreaks Per Year	Duration of Disease	Follow-up (5 y)
1/girl/5 y	No	Brownish nonconfluent papules with ulceration	Upper limbs (++), lower limbs (+), and trunk (+)	No	6-10	Areas of residual hyperpigmentation and varioliform scars	Type A[b]	Not done	1 single outbreak	1 y	No complications
2/boy/2 y	No	Nonconfluent infiltrated red-violaceous nodules and papules, some with central necrosis	Upper limbs (+++), lower limbs (++), and trunk (+)	No	11-20	Areas of residual hypopigmentation and varioliform scars	Type A[b]	Not done	3	Persistence after 5 y of follow-up	No complications
3/boy/8 y	No	Brownish nonconfluent papules with ulceration	Upper limbs (+++), lower limbs (+++), and trunk (+)	Pruritus	11-20	Areas of residual hyperpigmentation	Type A[b]	Not done	3	Persistence after 5 y of follow-up	No complications
4/boy/5 y	No	Brownish nonconfluent papules with ulceration	Upper limbs (++) and lower limbs (+)	No	6-10	Areas of residual hyperpigmentation and varioliform scars	Type A[b]	Not done	2	3 y	No complications
5/boy/6 y (Figure 1)	No	Brownish nonconfluent papules with ulceration	Lower limbs (+++)	No	11-20	Areas of esidual rhypopigmentation and varioliform scars	Type A[b]	Monoclonality	2	Persistence after 5 y of follow-up	No complications

6/girl/10 y	No	Erythematous-violaceous papules with a central necrotic crust	Upper limbs (+++) and lower limbs (+++)	No	11-20	Areas of residual hyperpigmentation and varioliform scars	Type A[b]	Monoclonality	2	Persistence after 5 y of follow-up	Development of lesions that are clinically and histologically compatible with pityriasis lichenoides. No complications
7/boy/8 y (Figure 2)	AVPL diagnosed at 5 y	Firm desquamative erythematous-brownish papules associated with other ulcerated violaceous papular lesions	Upper limbs (+++), lower limbs (+++), and trunk (+)	Pruritus	11-20	Areas of residual hyperpigmentation and varioliform scars	Type A[b]	Not done	3	Persistence after 5 y of follow-up	No complications
8/boy/17 y	No	Infiltrated and indurated erythematous-violaceous papules, some with central ulceration	Upper limbs (+++), lower limbs (+++), and face	No	11-20	Areas of residual hyperpigmentation	Type A[b]	Monoclonality	3	3 y	No complications
9/boy/9 y	AVPL diagnosed at 7 y	Indurated nodules and papules, some with central ulceration	Upper limbs (++) and lower limbs (+++)	Pruritus	11-20	Areas of residual hyperpigmentation and varioliform scars	Type A[b]	Not done	2	Persistence after 5 y of follow-up	No complications

Abbreviation: AVPL, acute varioliform pityriasis lichenoides.

[a]Grading of concentration of lesions: +, fewer than 5; ++, between 5 and 10; +++, more than 10.

[b]Type A lymphomatoid papulosis is a deep and superficial perivascular dermal polymorphous infiltrate composed predominately of large atypical CD3 lymphocytes and $CD30^{+}$, CD20, CD15, and epithelial membrane antigen, together with $CD3^{+}CD20^{-}$ cells and, to a lesser extent, neutrophils, histiocytes, plasma cells, and occasional eosinophils.

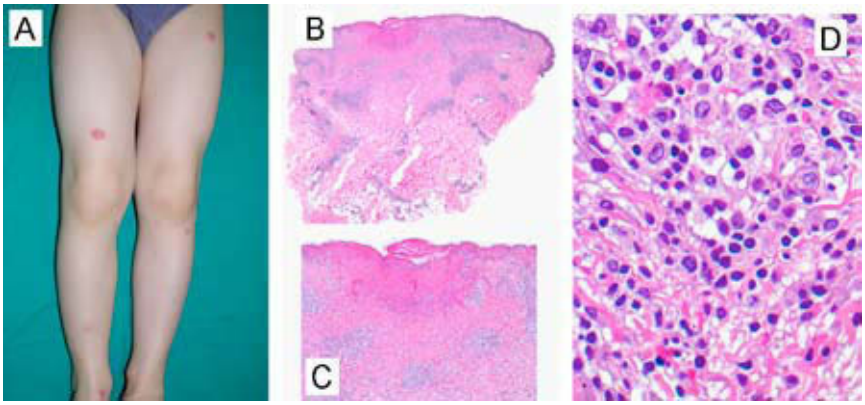

Figure 1 A, Clinical characteristics: violaceous papulonodular lesions on the lower limbs (Case 5, Table 1). B-D, Histologic characteristics. B, Ulcerated epidermis accompanied by a dense dermal inflammatory infiltrate occupying the medium and deep dermis (hematoxylin-eosin, ×40). C, The infiltrate is composed predominately of small lymphocytes, some of which are atypical, accompanied by larger lymphoid cells (hematoxylin-eosin, ×100). D, The largest lymphocytes (histiocytic) have vesicular nuclei (hematoxylin-eosin, ×400).

from weeks to years. In a large number of patients, this disease-free interval generally increases progressively until the outbreaks stop. Prognosis is excellent, with an overall survival of 100% at 5 years.[3]

The 3 histological patterns of lymphomatoid papulosis show no correlation with long-term prognosis. The most common form, affecting 75% of cases, is type A (histiocytic), which is characterized by a mixed infiltrate composed mainly of small lymphocytes and multiple large atypical lymphocytes or histiocytic cells. Up to 4% of cases are type B (mycosis fungoides-type), which is characterized by a monomorphic infiltrate of small and medium-sized lymphocytes with a cerebriform nucleus. Lastly, type C (large cell-type), which is characterized by a dense infiltrate composed mainly of large atypical lymphocytes, affects 13% of cases.[3]

The main complication of this condition during long-term follow-up is the occurrence of lymphoproliferative disease in 5%-20% of patients[3]; this mainly corresponds to mycosis fungoides, but Hodgkin lymphoma or cutaneous and systemic CD30-positive anaplastic large-cell lymphoma may also occur.[4]

Exceptionally, the process manifests for the first time in childhood (defined as all patients aged under 18 years). To date, approximately 70 cases of lymphomatoid papulosis have been described in children.[5-10] Most cases were reported in 3 large series of 35, 14, and 10 patients by Van Neer et al,[5] Nijsten et al,[6] and De Souza et al,[7] respectively.

Lymphomatoid papulosis in childhood, which accounts for 2%-9% of all cases,[3] is slightly more common in boys aged between 1 and 17 years (median, 8 years).[5-10] These epidemiologic data are consistent with the results of our series, in which 77% of patients were male, with a mean age of 7.6 years. Initial presentation tends to be earlier in boys (median, 5.5 y) than girls (median, 12 years).[5-10] It is striking that in 2 patients in our series the disease first manifested some years before as lesions that were clinically and histologically compatible with pityriasis lichenoides before progressing to CD30-positive lymphoproliferative lesions (Figure 2A and B).

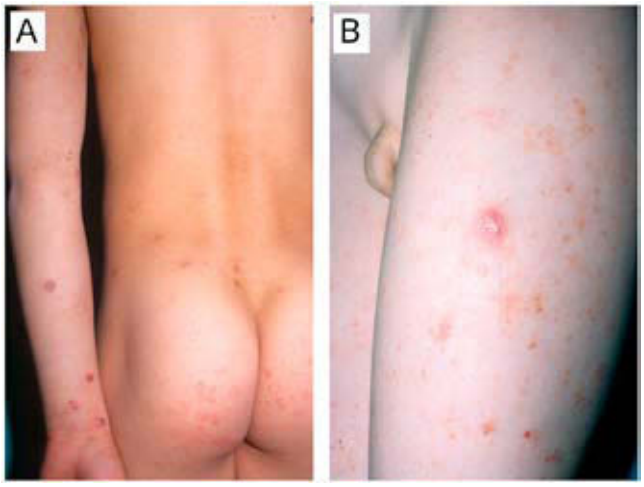

Figure 2 A and B, Boy aged 8 years with noninfiltrated erythematous-desquamative lesions on the trunk that were clinically and histologically compatible with pityriasis lichenoides. The patient subsequently developed violaceous infiltrated papulonodular lesions compatible with lymphomatoid papulosis affecting the upper and lower limbs and, to a lesser extent, the trunk (Case 7, Table 1).

The clinical characteristics of lymphomatoid papulosis in childhood do not seem to differ substantially from the adult form. The latter is characterized by recurrent outbreaks of papules and/or nodules that are symmetrically distributed on the limbs (88% of cases),

where they are more intense and common than on the trunk (44% of cases) or the face (10% of cases).[5-10] The localized and follicular variants of lymphomatoid papulosis, which are exceptional forms of this condition, have been reported more commonly in lymphomatoid papulosis in childhood.[3,8] In contrast, involvement of the oral mucosa has been reported in adults but not in children.[11] The lesions are often asymptomatic; however, in our series, 33% presented associated pruritus, which has been reported in up to 40% of cases in the literature.[5-10] Recurrent episodes of lymphomatoid papulosis typically last from 2 to 8 weeks before resolving spontaneously. Residual scarring is relatively frequent, appearing in 77% of cases in our study. This finding is consistent with those published elsewhere.[5-10] Duration was variable, although it remained active more commonly after 5 years of follow-up.

Histologically, lymphomatoid papulosis in childhood can present any of the 3 patterns described above. However, previous series show that the most common pattern is type A (histiocytic).[5-10] All of our patients presented this pattern; therefore, we conclude that, with few exceptions, type A is the histopathologic pattern that occurs in pediatric patients. Immunohistochemically atypical cells are positive for CD2, CD3, and CD30. Isolated large atypical cells and those that form small groups are positive for CD30. Nevertheless, unlike the adult form, in which the predominant lymphocytes in the infiltrate are $CD4^+CD8^-$,[3] the infiltrate in the pediatric variant more commonly contains a predominance of cytotoxic $CD8^+$ T lymphocytes.[5,6,12] The results of cell clonality testing are variable and lack prognostic value.[3,5-10] However, the monoclonal character of the 3 patients we analyzed did enable us to confirm the diagnosis of lymphomatoid papulosis.

A joint analysis of the 6 large series of lymphomatoid papulosis in childhood[5-10] revealed the existence of only 3 patients who developed a new lymphoproliferative process in their long-term follow-up. The 3 patients, who belonged to the series reported by Nijsten et al,[6] developed Hodgkin lymphoma between 1 month and 17 years after the first manifestations of lymphomatoid papulosis. In our study, no patients presented complications during the 5 years of follow-up.

Pediatric lymphomatoid papulosis should mainly be differentiated from insect stings and pityriasis lichenoides. Insect stings are self-limiting and have a shorter course. Histopathology reveals a mixed inflammatory infiltrate in the shape of an inverted pyramid with its base parallel to the epidermis and in which eosinophils predominate. In general, pityriasis lichenoides differs clinically and histopathologically from lymphomatoid papulosis. It presents as rapid outbreaks of nonindurated and noninfiltrated multiple papules and erythematous desquamative plaques. In histological terms, pityriasis lichenoides is characterized by epidermal parakeratosis with vacuolar degeneration of the basement membrane associated with multiple necrotic keratinocytes and a lichenoid inflammatory infiltrate composed mainly of mature T lymphocytes that are CD30-negative or mildly positive and disperse. However, it is sometimes difficult to distinguish clearly between acute pityriasis lichenoides and lymphomatoid papulosis, since there are cases in which both entities overlap clinically and histologically. In these cases, the symptoms and progress of the condition make it possible to establish a definitive diagnosis (Table 2). Furthermore, the difficulties in differentiating between these entities, together with the high frequency of concomitant pityriasis lichenoides and lymphomatoid papulosis in our series, suggest that they could form part of a common clinical spectrum.

In many cases, treatment of pediatric lymphomatoid papulosis is not necessary, since longer active disease is not associated with a poorer prognosis. With currently available treatments, remission is not complete, only partial and temporary. Therefore, treatment is only indicated in the presence of associated symptoms (eg, pruritus) or for cosmetic reasons in cases of outbreaks with several lesions. In lymphomatoid papulosis in childhood, the main problem lies in the parental anxiety these lesions cause. Treatment includes topical or systemic corticosteroids, oral antibiotics (mainly macrolides),[13,14] psoralen-UV-A, and UV-B.[13]

We report this series of pediatric lymphomatoid papulosis because the disease is uncommon, and, therefore, poorly characterized in children. Our clinical and pathology findings agree with those published elsewhere. It is important to remember that patients with lymphomatoid papulosis may also experience a process compatible with pityriasis lichenoides before or afterwards, as occurred in our series. The increased frequency of the association between both entities we report suggests that these diseases represent opposite poles of a common clinical and pathologic spectrum. Our results suggest that type A is the most characteristic histopathological pattern in children. Moreover, we observed that the lesions of lymphomatoid papulosis in children resolve leaving a transitory alteration of skin color in all cases, mainly in the form of hyperpigmentation accompanied by permanent scarring in more than half. Lastly, we would like to stress that, according to published series and our experience, development of other lymphoproliferative diseases is less common in childhood lymphomatoid papulosis than in the adult variant and that, according to the literature, they manifest mainly in the form of non-Hodgkin lymphoma.

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Table 2 Lymphomatoid Papulosis and Pityriasis Lichenoides: Differential Characteristics

	Lymphomatoid Papulosis	Pityriasis Lichenoides
Onset	Insidious	Rapid
Number of lesions in each outbreak	Small (1-20)	Large (>20)
Characteristics of the lesion	Papules and nodules that are sometimes associated with central necrotic slough	Erythematous-desquamative plaque[a]
	Lesions that are indurated to the touch and deeply infiltrated	Lesions that are not indurated to the touch or deeply infiltrated
Distribution pattern	Predominately on the upper and lower limbs	Predominately on the trunk
Outcome		
Duration of individual lesions	Resolution in 3-4 wk	Resolution in 1-2 wk
Residual abnormality after resolution of the lesions	Residual varioliform scars	Areas of residual hypo/hyperpigmentation
Duration of outbreaks	Years	AVPL, weeks to months CPL, months to years
Histopathologic findings	Type A, presence of atypical lymphocytic cells with bizarre nuclei accompanied by a neutrophilic infiltrate and minimum involvement of the epidermis.	AVPL, severe lymphocytic infiltrate, with rare presence of atypical isolated lymphocytes. Involvement of the epidermis with hydropic degeneration of the basement membrane, necrotic keratinocytes.
	Type B, cerebriform hyperchromatic mononuclear cells arranged in bands in the basement membrane with some hydropic degeneration.	CPL, mild lymphocytic infiltrate, absence of atypical lymphocytes, minimal vacuolar degeneration of the basement membrane.
	Type C, large cell-type, which is characterized by a dense infiltrate composed mainly of large atypical lymphocytes.	
Positivity for CD30	Present (absent in 5% of cases)	Absent[b] (present in 5%-10% of cases)
Study of molecular rearrangement	Monoclonal[c] (polyclonal in 30%-40% of cases)	Polyclonal[c] (monoclonal in 10% of cases)
Potential for malignancy	Occasional	Exceptional

Abbreviations: AVPL, acute varioliform pityriasis lichenoides; CPL, chronic pityriasis lichenoides.

[a]The uncommon febrile ulcerative-necrotic variant of Mucha-Habermann disease is characterized by localized ulcerated plaques mainly on the trunk and associated with fever.

[b]In some cases, CD30 was positive and the molecular study showed a monoclonal character. In these cases, the definitive diagnosis depends essentially on symptoms and clinical course.

[c]The existence of monoclonal rearrangement of T lymphocytes supports the neoplastic character of a process and lacks prognostic value. Nevertheless, the clinical symptoms and course of the disease are more relevant when establishing a definitive diagnosis.

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