Lymphomatoid papulosis - Report of two cases*
*Papulose linfomatóide - Relato de dois casos**

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Abstract: Lymphomatoid papulosis (LP) is a rare variant of cutaneous T-cell lymphomas with large CD30-positive intracutaneous T-cell infiltrate. There is a discrepancy between histology suggesting a highly malignant and aggressive disease and the chronic relapsing mostly self limiting course in most cases. We report two patients. A 64-year-old woman with a 10-year history of LP was treated with cream PUVA that was able to control the disease. The other case, a 42-year-old woman had an 18-year history of LP treated by PUVA and later by extracorporeal photochemotherapy (ECP). During ECP a rapid metastatic spread developed that could not be controlled by polychemotherapy. Eventually she died due to a central nervous system metastasis one year later.
Keywords: Photopheresis; Lymphoma, T-cell, cutaneous; Lymphomatoid papulosis; PUVA therapy.

***Resumo**: A papulose linfomatóide (PL) constitui uma variante rara dos linfomas cutâneos de células T com a presença de amplo infiltrado intracutâneo de células T positivas para CD30. O exame histológico sugestivo de doença altamente maligna e agressiva opõe-se ao curso crônico-recidivante, muitas vezes auto-limitado, presente na maioria dos casos. São apresentados os relatos de dois pacientes. Uma mulher com 64 anos de idade e história de 10 anos de PL recebeu terapia Puva em creme, sendo a doença controlada. No segundo caso, uma mulher de 42 anos apresentava história de 18 anos de PL tratada com Puva e, posteriormente, com fotoquimioterapia extracorpórea (FEC). Durante a FEC, observou-se rápida disseminação metastática que não pôde ser controlada por poliquimioterapia. A paciente foi a óbito após um ano, em razão de metástase no sistema nervoso central.*
Palavras-chave: Fotoforese; Linfoma cutâneo de células T; Papulose linfomatóide; Terapia PUVA.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) cover a wide range of diseases with different histology and clinical course. Lymphomatoid papulosis (LP) is a rare variant of CD30-positive CTCL with a relapsing chronic course. The clinical presentation is a disseminated reddish-brownish papulosis that tends to heal leaving hyperpigmented scars. Necrotic changes may occur. The incidence of LP is about 1.2 to 1.9 cases per million inhabitants. Some reports on LP in children have been published, but it seems more common among adults.[1]

LP has been differentiated based on histopathology into three types, A, B, and C.[1] Type A represents a LP variant of predominant large cells mixed with granulocytes, whereas type B is characterized by small to medium sized cerebriform mononuclear cells. Type C is composed of large pleomorphic and anaplastic cells without a significant contribution of reactive inflammatory cells.[2] The lymphocytic cells in LP are of clonal T-cell origin.[3] They usually express CD30 like Hodgkin cells but lack fascin, an active bundle protein.[4] In contrast to NK-cell lymphomas the large atypical cells of LP type A and C do not express CD56.[5]

There is no standardized treatment, controlled clinical trials have not been performed. There is some evidence from case reports and small series that photochemotherapy with psoralen may cause partial or

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complete remission,[6] but mixed outcome has also been demonstrated for photochemotherapy.[7,8]

We report two patients with a long history of LP and mixed outcome after photochemotherapy.

CASE REPORTS

Case 1

A 64-year-old woman was referred to our department with a 10-year history of chronic relapsing reddish-brownish papules. The disease was limited in its beginning to the neck and the proximal lower limbs. Two years previously a disseminated manifestation developed on the limbs and the trunk. She suffered from burning sensations. The papules were non-pruritic.

Coexistent disorders were a chronic ischemic heart disease with arterial hypertonia, diabetes mellitus type II, and nodular struma.

On clinical examination of the whole body, except the face, disseminated papules and nodules of variable size were seen, some of them covered with a crust (Figure 1). Hyperpigmented maculae and scars were also seen.

Several skin biopsies were taken from the trunk and lower limbs. Histopathologic examination disclosed a heavy broad dermal infiltrate consisting of lymphomonocytoid cells including large cells with atypical nuclei and mitoses (Figure 2). Immunostainings (PAAP) revealed positivity for CD30 (large cells). CD8, and T cell intracellular antigen TIA1 (only some cells), immunostains for fascin were negative. In addition granulocytes, especially eosinophils were intermingled.

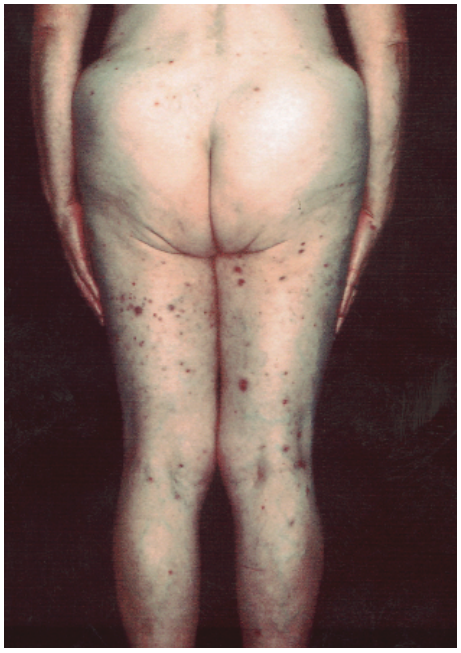

Figure 1: Disseminated papules and small nodules (Patient 1).

Laboratory investigations: There was a slight increase of eosinophil counts (5.6%) and an increased ratio of T4/T8 by flow cytometry (3.7). No atypical cells were observed in the circulating blood.

Ultrasound scan of pelvic and abdominal organs and X-ray of the thorax did not show any manifestation of the CTCL. There was evidence of hepatic steatosis.

The diagnosis of LP, type A, was made.

We performed cream PUVA for two weeks and used a urea-containing ointment in association. The short-term hospital treatment was followed by a four-week course of outpatient therapy and resulted in improvement of burning sensations and partial remission of LP.

Case 2

A 42-year-old woman was referred to our department for treatment of relapsing papulo-nodular lesions on the limbs and the trunk. She had a history of 18 years of relapsing self-healing papulosis. Previous treatments such as UVB and UVA irradiation, PUVA, dapsone, and vidarabine phosphate had only temporary and slight effects, if any.

On examination we observed multiple erythematous papules on the limbs and trunk, some eroded and covered with a crust (Figures 3 and 4).

Several skin biopsies were taken from these lesions that showed a dense dermal infiltrate composed of large, atypical lymphoid cells mixed with eosinophils and neutrophils. The immunophenotype was CD30-positive, CD3-positive, CD4- and CD8-negative (Figures 5 and 6).

Laboratory investigations: There was an increased ratio of activated T-cells as shown by fluorescent activated cell sorting analysis (FACS). Routine lab was normal, no atypical cells were found in the peripheral blood.

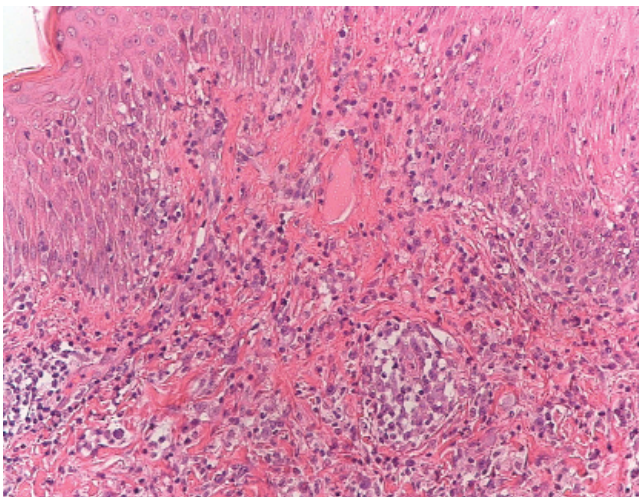

Figure 2: Overview of HE (Patient 1) (20x).

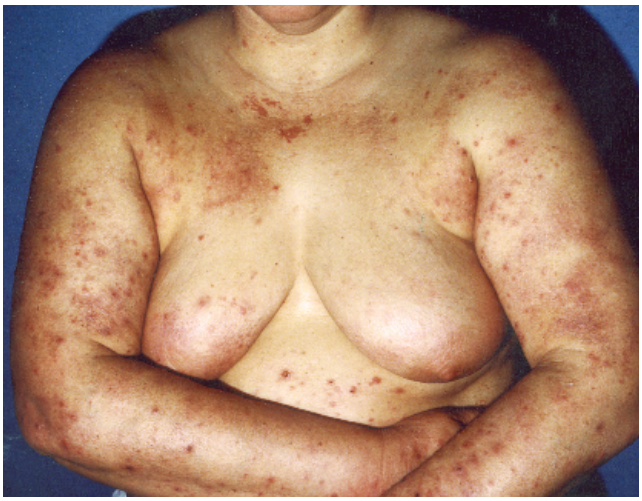

Figure 3: Disseminated papules, crusted and eroded lesions (Patient 2).

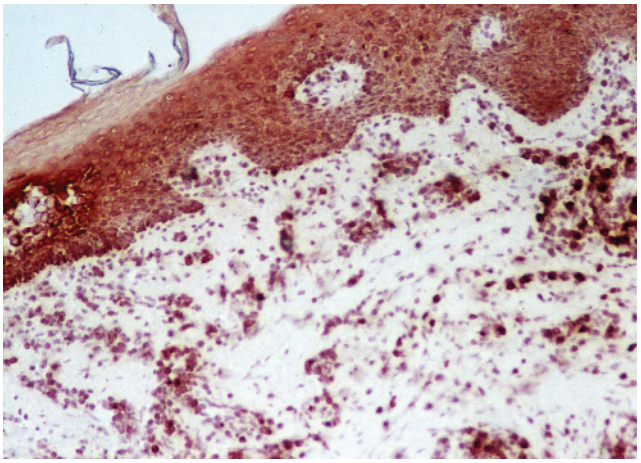

Figure 5: Histopatologic investigation of patient 2 - overview (D30 - expression) (APAAP technique).

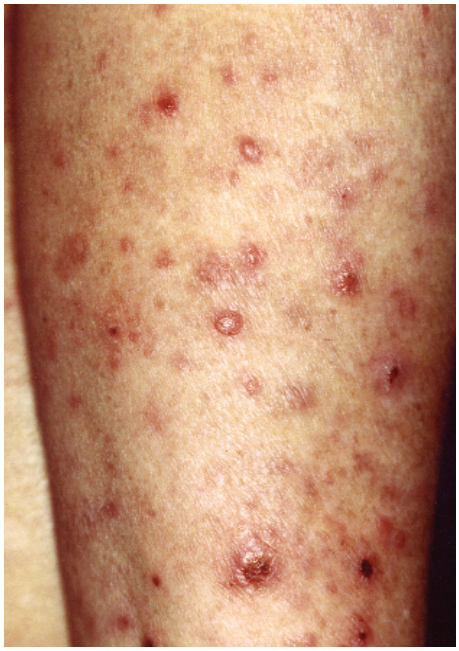

Figure 4: Detail of figure 3.

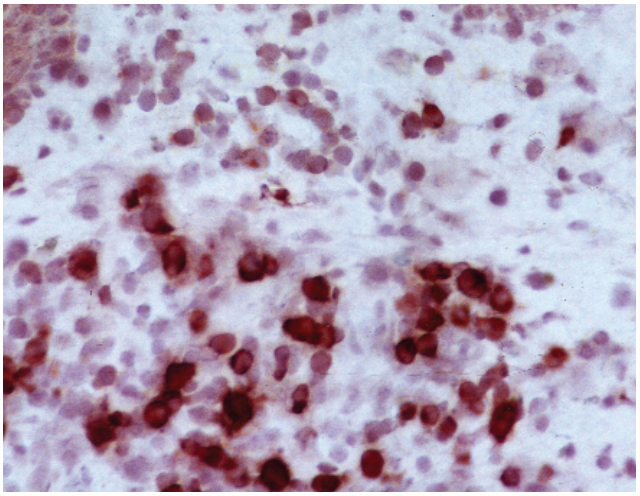

Figure 6: Detail of figure 5.

Ultrasound scans revealed a lymph node enlargement in the axilla. Computed tomography disclosed enlarged retrocaval and aortopulmonary lymph nodes.

Diagnosis of LP, type A, was made.

We used extracorporeal photopheresis with 8-methoxypsoralen at 0.6 mg/kg body weight with the Therakos® ECP unit (Johnson & Johnson) leading to an intermittent leukapheresis and *ex vivo* photochemotherapy. During each treatment 240 ml leukocyte enriched buffy coat was obtained and retransfused. Treatments were performed on two consecutive days once a month. The patient responded quickly after 3 cycles with a partial response. ECP was continued for further three months but at the end there was disease progression with secondary lymph node involvement. Systemic chemotherapy using 1 mg vincristine/day and 200 mg ribomustin (day 1 and 8) was started with an initial response of lymph node metastases. One year later, the patient died due to cerebral spread. The case seems to represent a progression of LP to CD30-positive systemic lymphoma.

DISCUSSION

LP is a chronic relapsing CTCL characterized by self-healing papules and nodules. Histologically malignant but clinically benign was the characterization Macaulay (1968) gave this disease.[1] Nowadays LP is considered a rare, distinct variant in the spectrum of CTCL.[1,2] Whereas the disease itself shows only slow progression there is a cumulative risk of malignant transformation of about 15% after 15 years.[9]

In patient #2 a progression to systemic CD30-positive lymphoma has been observed. Such a change

CHART 1: Major differential diagnoses of lymphomatoid papulosis

Differential diagnoses	Differentiation from LP by:
Pityriasis lichenoides acuta et varioliformis (PLEVA)	CD30 negativity
Pityriasis lichenoides chronica	CD30 negativity
NK-cell lymphoma	CD56 positivity
Anaplastic large cell lymphoma of skin	not self-healing
Secondary cutaneous infiltrates by Hodgkin's disease	fascin positivity

in biologic behaviour can be explained by escape of lymphoma cells from growth control by transforming growth factor (TGF)-beta and CD30 ligand.[10] Major differential diagnoses to LP are summarized in chart 1.

The treatment of LP has yet not been standardized. Based on extensive experience with CTCL multiagent chemotherapy is only indicated for patients with full-blown or developing extracutaneous disease. It is never or only rarely indicated for patients with skin-limited CD30-positive lymphomas. Low-dose methotrexate (≤25 mg given at one to four week intervals) is an effective and well-tolerated treatment in LP.[11] Hepatic steatosis and diabetes mellitus as in patient #1 are a relative contraindication since these factors increase the risk of hepatic side effects including liver cirrhosis. ECP has been used in CTCL of the mycosis fungoides and Sézary syndrome type with some success. It is thought to be a kind of vaccination therapy.[12,13] In patient #2, ECP had only a temporary positive effect but later on a progression of LP to systemic spread was observed. No other experience with ECP in LP has been published yet.

A new treatment option might be bexarotene. Ten patients with LP have been treated either orally (n = 3) or topically (n = 7) with a partial response.[14] Therefore, bexarotene might be another option in the palliative therapy of LP. Once a transition to a more aggressive lymphoma has occurred control of disease can only be achieved for a limited time.

LP is a rare disease with important differential diagnoses. It represents a low-grade CTCL with a chronic course but needs monitoring not to overlook a transition to more aggressive forms of lymphomas. The treatment is not standardized but photochemotherapy might be an option in controlling the disease. Other options with limited experience are low-dose methotrexate and probably bexarotene. ❑

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