

LESS COMMON SKIN MANIFESTATIONS IN PRIMARY CUTANEOUS LYMPHOMA OF THE ELDERLY. CASE BASED ANALYSIS

CAIUS SOLOVAN*, **, MANFRED BELEUT*, ADELINA TIMOFTE**, IOANA GENCIA*, **

Rezumat

Limfoamele cutanate (LC) constituie un grup de afecțiuni limfoproliferative ce sunt dificil de diagnosticat la debut, mai ales pentru că pot mima dermatoze inflamatorii (eczemă cronică, dermatoze culoase, eritrodermie idiopatică, psoriazis). Pentru că incidența acestor limfoame cutanate crește cu vârsta considerăm că este necesar o monitorizare riguroasă clinică și histopatologică a pacienților în vârstă diagnosticați cu dermatoze recurente „benigne”.

În lucrarea de față am revăzut datele a 112 pacienți din Clinica Universitară de Dermatologie și Venerologie, Timișoara, cu diverse manifestări (parapsoriazis, papuloză limfomatoasă, psoriazis) diagnosticați cu limfom cutanat. Au fost selectați doar pacienții cu vârsta peste 60 de ani.

Din cele 50 de cazuri de limfoame cutanate selectate, 17 au fost limfoame cutanate clasice și 33 au fost diagnosticate ca și parapsoriazis în plăci mari. Din grupul cazurilor de limfoame cutanate 15 pacienți (88,23%) au fost limfoame cutanate primare T celulare și 2 cazuri (11,72%) au fost limfoame cutanate primare B celulare. Repartiția pe sexe a fost predominant în favoarea sexului masculin.

Scopul acestui studiu a fost să prezinte manifestări cutanate mai puțin obișnuite la pacienții în vârstă cu diagnosticul de limfom cutanat pentru a sublinia necesitatea unei monitorizări îndelungate și riguroase din perspectivă clinică și histopatologică pentru un diagnostic final.

Cuvinte cheie: limfom cutanat, placă mare de parapsoriazis, dermatoze benigne, în vârstă.

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Summary

Cutaneous lymphomas (CLs) represent a group of lymphoproliferative disorders that can be difficult to diagnose in the early stage because it could mimic many benign inflammatory dermatosis (chronic eczema, bullous dermatitis, idiopathic erythroderma, psoriasis). Considering that the incidence increases with age, a rigorous clinical and histopathological monitoring of elderly patients diagnosed with recurrent benign dermatitis must be performed.

We retrospectively reviewed dates from 112 patients with various skin manifestation (parapsoriasis, lymphomatoid papulosis, psoriasis) diagnosed as CLs in the University Clinic of Dermatology and Venereology, Timisoara between the year 2006 and January 2014. From this lot there were selected only the medical files of patients over 60 years of age.

Of the 50 cases studied 17 were classic CLs and 33 were large plaque parapsoriasis (LPP). In the CLs group there were 15 patients (88,23%) with Primary Cutaneous T cell lymphoma (PCTCL) and 2 patients (11,76%) with Primary Cutaneous B cell lymphoma (PCBCL). There was an evident male predominance.

The aim of the study was to present unusual skin manifestations of CLs in the elderly patients and to underline the necessity of rigorous monitoring/long term follow-up as well as exhaustive histopathological analysis for the diagnosis.

Key words: cutaneous lymphoma, large plaque parapsoriasis, benign dermatoses, elderly.

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* Dermatology, "Victor Babes" University of Medicine and Pharmacy, Timisoara.

** University Clinic of Dermatology and Venereology, Emergency City Hospital, Timisoara.

Introduction

Cutaneous lymphomas (CLs) represent a group of lymphoproliferative disorders that can be difficult to diagnose in the early stage, because it mimics many benign cutaneous disorders [1]. World Health Organization (WHO)- European Organization for Research and Treatment of Cancer (EORTC) classified CLs in two groups: Cutaneous T-cell lymphomas (CTCL) characterized by proliferation of T lymphocytes in the skin and Cutaneous-B cell lymphomas (CBCL) associated with a proliferation of B-cell [2].

Clinically CLs can appear like chronic eczema, psoriasis, squamous dermatosis, allergic contact dermatitis, drug eruptions, and connective tissue disease [3]. The gold standard in the diagnosis of CLs is not only the routine performed histopathological examination. Each case should have a full knowledge of the clinical aspects and course of the disease. Considering the long evolution of CLs before the diagnosis, repeated biopsies correlated with clinical aspects and immunophenotype analysis may clarify the diagnosis [4].

Because the incidence of the diagnosis increases with age, a rigorous monitoring of elderly patients diagnosed with recurrent benign dermatosis must be performed [5].

Large plaque parapsoriasis (LPP) is histopathological and clinical indistinguishable from patches stage of mycosis fungoides (MF). Some authors consider LPP as a latent prelymphoma and others believe that it should be classified as early patch stage of MF[6]. Long term follow-up of patients with LPP is necessary preventing in this way a frightening misdiagnosis [7].

The aim of the study was to draw the attention to unusual skin manifestations of CL in elderly patients and to underline the exhaustive work necessary to establish the diagnosis.

Material and methods

We retrospectively reviewed dates from 112 patients with various skin manifestation diagnosed as parapsoriasis, lymphomatoid papulosis (LyP), CLs in the University Clinic of Dermatology and Venereology Timisoara between the year 2006 and January 2014. From

this lot there were selected only the medical files of patients over 60 years of age (the age ranged from 60 to 84 years). Patients under 60 years old age were excluded. We obtained a total number of 50 cases. Clinical aspects, evolution of cutaneous lesions, the initial diagnosis were noted. Also histopathological and immunohistochemistry results were analyzed.

Results

The selected cases of CLs and LPP were diagnosed on the basis of clinical, histopathological and immunohistochemical findings.

Of the 50 cases studied 17 were classic CLs and 33 were LPP. In the CLs group there were 15 patients (88,23%) with Primary Cutaneous T cell lymphoma (PCTCL) and 2 patients (11,76%) with Primary Cutaneous B cell lymphoma (PCBCL). Diagnoses of CLs were made based on repeated biopsies, clinical evolution, response to treatment, staging and follow-up.

In LPP group the male/female ratio was 2:1 (there were 22 males and 11 females) and in the CLs group the male/female ratio was 4,6:1 (there were 14 males and 3 females) with an evident male predominance in both groups (Table 1).

Table 1. Distribution of patients over 60 years of age, with large plaque parapsoriasis (LPP) and classic Cutaneous lymphomas (CLs) by gender

Parameter	LPP (n=33)	CLs (n=17)
men	22 (67%)	14 (82%)
women	11 (33%)	3 (18%)

The median follow-up time from the first diagnosis of persistent skin lesions to a histopathological confirmed diagnosis of CLs was 5 years. During this period at least two repeated biopsies were performed.

The initial diagnosis in 11 cases (64,70%) of CLs was psoriasis (2 patients), chronic eczema (2 patients), vasculitis (1 patient), drug eruption (1 patient), idiopathic erythroderma (2 patients), prurigo nodularis (1 patient), pemphigus vulgaris (1 patient), inguinal lymphadenitis (1 patient).

6 cases (35,29%) had the initial clinical aspects of MF (erythematous, scaly patches with predilection for the buttocks on sun-protected areas).

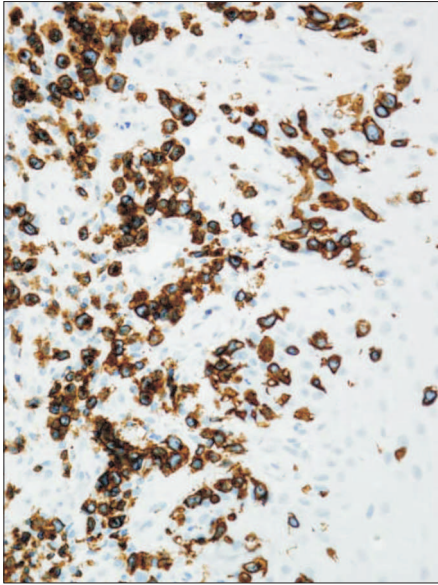


Fig. 1. IHC: the Tcell infiltrate CD3+ and with prominent epidermotropism; ob.200x

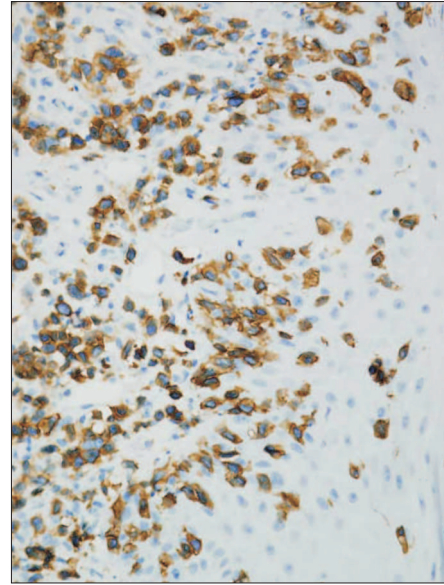


Fig. 2. IHC: the Tcell infiltrate CD7+, with marked epidermotropism and epidermal exocytosis; ob.200x

In 65 % of patients with cutaneous T cell lymphoma (CTCL) pruritus was the main symptom unrelieved by antihistamines or topical steroids.

According with World Health Organization (WHO)- European Organization for Research and Treatment of Cancer (EORTC) classification, 12 patients were diagnosed with MF (70,58%), 1 patient with LyP type B (5,88%), 1 patient with Sezary Syndrome (5,88%), 1 patient with Primary Cutaneous Peripheral T-cell lymphoma not otherwise specified (NOS) with bullous lesions (5,88%) and 2 with PCBCL (11,76%).

In the lot of patients under 60 years old age there were 7 cases of classic CLs and 55 cases of LPP and small plaque parapsoriasis (SPP).

Patients diagnosed with MF presented the classical immunophenotype CD4+, CD45RO+, CD8-(11 patients). In contrast with conventional immunochemistry one case of MF had a CD8+, CD7+ and CD4- phenotype. At histopathological examination we noted the epidermotropism, mononuclear microabscesses in the epidermis, and a monomorphic lymphocytic superficial dermal infiltrate in all cases of MF and in one case of SS. Papillary dermal fibrosis was a significant histopathological feature in MF.

The cases diagnosed as PP (SPP or LPP) showed similar histopathological aspects, but at

less intensity regarding the dermal infiltrate, interface dermatitis or epidermotropism.

One of our cases that presented with bullous lesions at onset had been diagnosed with Primary Cutaneous peripheral T-cell lymphoma NOS with pemphigus like lesions. Though Tzanck smear was negative for acantholytic cells first histopatologic examination favor the diagnosis of pemphigus vulgaris, the patient was treated accordingly with systemic corticosteroids, but with little improvement. Another cutaneous biopsy was made and histopathological aspects revealed an atypical diffuse infiltrate of lymphocytes within the upper dermis and periadnexal areas and a prominent epidermotropism. Immunocytochemistry showed an dermal infiltrate predominantly composed of T lymphocytes that expressed CD3 and CD7 markers (Fig 1, Fig 2). The infiltrate was negative for CD20, CD4, CD8, CD56 and Granzyme B. After repeated biopsy and IHC the diagnosis of CTCL NOS was done. Patient was treated with the CHOP regimen (C-Cyclophosphamide, H-Doxorubicin, O-Vincristine, P-Prednisone). Still the outcome was poor.

Case 1

We present the case of a 76 year old man, with a five year history of persistent erythematous,



Fig. 3. Erythroderma and scaly erythematous patches on the foretrunk

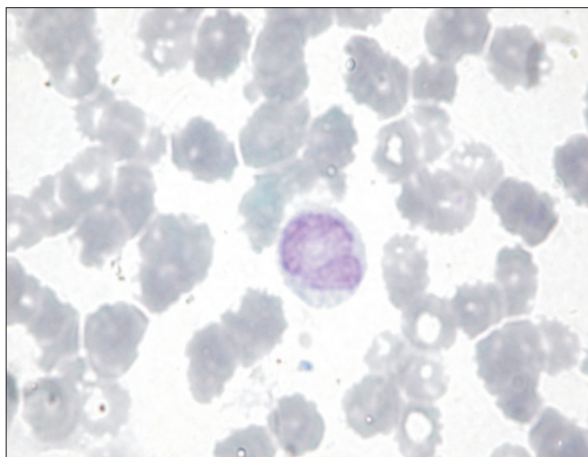


Fig. 5. Atypical lymphocyte with cerebriform nuclei in the peripheral blood

scaly patches, who subsequently developed erythroderma, bilateral axillary lymphadenopathy, palmo-plantar hyperkeratosis, ectropion (Fig 3). Previously, after many cutaneous biopsies, he has been diagnosed with psoriasis vulgaris, chronic eczema, large plaque parapsoriasis and treated with topical steroids and systemic retinoids (Fig.3).

A new skin biopsy was performed. The histopathological examination described atypical lymphoid proliferation with small and medium cells, with cerebriform nuclei; band-like infiltrate

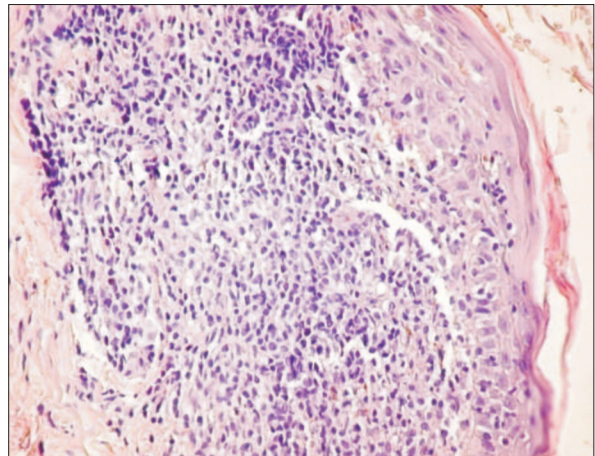


Fig. 4. H&E: band-like infiltrate of atypical T cells, involving the upper dermis and intense epidermotropism masking the basal membrane; ob.100x

of neoplastic T cells, involving the upper dermis and epidermotropism (Fig. 4).

Immunocytochemistry revealed that the tumoral cells were diffusely positive to CD5, CD4, CLA and negative to CD3, CD30, CD8, L26/CD20.

Peripheral blood smear showed 58% atypical lymphocytes with small, folded or cerebriform nuclei, resembling with Sézary cells (Fig.5).

Clinical findings, histopathological aspects and immunocytochemistry corroborated with a significant number of atypical lymphocytes in the peripheral blood smear, towards to the diagnosis of Sézary Syndrome.

Computed tomographic (CT) of the thorax, abdomen and pelvis showed only a thoracic aortic aneurysm with no involvement of other lymph nodes stations. The patient was transferred to the Haematology Department for staging and treatment.

Case 2

A 60-year-old man was referred to our hospital with six month history of progressive erythematous tumor, localized in the right inguinal area, which increased in size and ulcerated (Fig 6). Approximately a year ago the patient had been diagnosed clinically and histopathologically with inguinal lymphadenitis.

A repeated biopsy from the tumor was made. Histopathological examination showed a malig-



Fig. 6. An ulcerated erythematous tumor in the right inguinal area

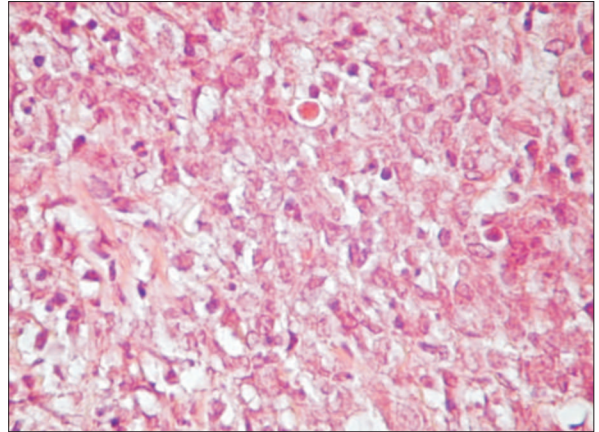


Fig. 7. H&E Medium and large atypical cells with vesicular nuclei and basophilic cytoplasm; Ob.200x

nant infiltrate in the dermis and subcutaneous tissue. The infiltrate consisted of medium and large atypical cells with vesicular nuclei and basophilic cytoplasm (Fig 7). Immunohistochemistry was positive for CD20 (90%), ki-67 (80%) and negative for Bcl-2.

No evidence of metastatic lesion had been demonstrated. Based on histopathological and immunohistochemical findings, a diagnosis of primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) was established.

The patient received R-CHOP (R-Rituximab, C-Cyclophosphamide, H-Doxorubicin, O-Vincristine, P-Prednisone) regimen with favorable outcome.

Discussions

Diagnosis of CLs remains a challenge for dermatologist and pathologist. Histopathological features of early stage MF comprise minimal lymphoid infiltrates that overlap with benign inflammatory disease, sometimes mimicking even small plaque parapsoriasis[8,9].

In early stages even immunophenotyping or clonality by T-cell receptor gene rearrangement characteristics may not differentiate MF from other inflammatory cutaneous disorders. In these cases only the evolution of the lesions, response to therapy and follow-up remain a key for the correct diagnosis and for detecting the transformation to a malignant aggressive lymphoma with a poor outcome for the patient [5].

The essential sign in history of CLs is the persistence of lesions with poor response to classic therapy or with recurrences (the appearance of untreatable, refractory pruritus, of new lesions in other areas or another clinical unexpected manifestation). Recurrent skin lesions must be evaluated clinically and histopathologically by repeated skin biopsies. Incidence of CLs is increased in elderly with a predilection for males [10,11].

LPP is a chronic scaly dermatoses classified as retiform and poikilodermatous patterns, and occurring in middle aged patients and elders. The etiology remains unknown. There are histopathologic features that overlap with MF; the superficial dermal infiltrate is composed primarily of CD4+ T cells fact that can be termed as T-cell restricted proliferation of the skin [12]. Even if most cases of LPP run a benign course for many years, a rigorous periodical follow-up and multiple cutaneous biopsies are necessary. Also, LPP cases should be treated with topical steroids, corticosteroids associated with calcipotriol or corticosteroids-sparing agents, PUVA or topical chemotherapeutic rather than with an aggressive therapy [13,14].

Guitart *et al* classified parapsoriasis, idiopathic follicular mucinosis, pityriasis lichenoides, idiopathic erythroderma as cutaneous lymphoid dyscrasias (CLD). They encompass a group of dermatoses, which are characterized by a chronic course with potential to transform/evolve into a CTCL. The hypothesis of progression of CTCL

from an initial clonal event to a selection of more proliferative subclones as the disease advances has been demonstrated [15].

Sigurgeirsson B *et al.* reported that inflammatory myositis (primarily dermatomyositis) is associated with increased risk of Non-Hodgkin lymphoma [16].

MF, though a rare entity, represents the most common type of CTCL with high incidence in elderly [17]. CTCL account for about 80% of CLs [18,19]. In our study the majority of patients had been diagnosed with CTCL (88,23%) and in this group the most frequent type was MF (70,58%).

Most MF have a phenotype of T helper lymphocyte (CD3+, CD4+, CD5+, CD8-, CD45RO+) [20]. Rare cases exhibit a CD8+ phenotype [21]. Generally the presence of this phenotype is correlated with a similar prognosis [22]. We report one case of MF with the neoplastic cells positive for CD8, CD7 and negative for CD4. The patient had an unfavorable outcome.

Peripheral T-cell lymphomas NOS is an aggressive non-Hodgkin lymphomas, characterized by poor outcome and response to therapy [23]. The diagnosis is one of exclusion. To our knowledge the case of cutaneous peripheral T-cell lymphoma NOS with bullous lesions at onset is the only that have been reported in the literature.

SS represents a leukemic variant of CTCL sharing common biological and morphological abnormalities of MF, including nuclear atypia, chromosomal aberrations, and T cell receptor (TCR) gene rearrangement [24]. Clinical and histopathological is difficult to differentiate SS from erythrodermic variant of MF. Campbell *et al.* classified MF and SS as different entities. They demonstrated that malignant T-cell in SS express central memory markers and have the capacity to migrate through the skin, blood and lymph nodes. In contrast, the malignant T-cell in MF are found only in the skin [25]. SS typically presents with the triad of erythroderma, lymphadenopathy and atypical lymphocytes with cerebriform nuclei (Sezary cells) in the peripheral blood [26]. Our patient had persistent erythroderma, bilateral axillary lymphadenopathy and peripheral blood smear showed 58% atypical lymphocytes with cerebriform nuclei. The

diagnosis was made after five years of regular clinical and histological follow-up.

Primary Cutaneous B cell lymphomas (PCBCL) represent 20-25% of primary cutaneous lymphomas [27]. There are three main type of CBCL: Primary cutaneous follicle center lymphoma (PCFCL), Primary cutaneous marginal zone B-cell lymphoma (PCMZL), Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) [28]. We found two patients with PCBCL, which account 11, 76% of all cases diagnosed with CLs. One case was diagnosed as PCDLBCL-LT after previously has been misdiagnosed with inguinal lymphadenitis. The cutaneous lesion completely healed after therapy. Absence of Bcl-2 expression is considered a hallmark of good prognosis, as in our case [29]. The second case of PCBCL was primarily diagnosed as vasculitis, and was hepatitis B virus positive; the patient died with hepatic and gastric lymphoid determination. Frequently B cell lymphomas in the elderly are related to chronic inflammation, viral infections (Epstein Barr virus, cytomegalic virus, hepatitis B virus, Herpes virus types) or even *Helicobacter pylori* or *Borrelia burgdorferi* [30, 31].

Conclusions

In conclusion, it may be said that CLs must be suspected in elderly patients who present with recurrent and refractory skin eruptions. The diagnosis may be initial a difficult one. Lesions can persist for years and histopathological findings may not be characteristic. These types of chronic dermatoses must remain under suspicion for a CL until a definitive diagnosis is made.

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Conflict de interese
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Correspondance address: Caius SOLOVAN MD, PhD
Dermatology, "Victor Babes" University of Medicine and Pharmacy, Timisoara
e-mail: caius.solovan@gmail.com