THE IMPORTANCE OF CLINICOPATHOLOGICAL CORRELATION IN THE DIAGNOSIS OF CUTANEOUS LYMPHOMAS IN ELDERLY PATIENTS

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București

Rezumat

Introducere. *Diagnosticul limfoamelor cutanate (LC) este adesea dificil, din cauza suprapunerii tabloului clinic cu caracteristicile dermatozelor benigne sau a discordanței dintre constatările clinice și patologice. Incidența limfoamelor cutanate (LC) crește considerabil cu vârsta.*

Obiectivul *studiului a fost ilustrarea importanței pe care o are monitorizarea pacienților vârstnici cu dermatoze cronice și necesitatea corelațiilor clinico-patologice în diagnosticul LC.*

Pacienți și metodă. *Datele clinice și histo-patologice a 28 pacienți din evidența Clinicii Universitare de Dermatologie și Venerologie Timișoara (2005-2010) cu diagnostic confirmat de LC, au fost examinate și reclasificate în conformitate cu Clasificare WHO-EORTC. Examinare histologică a fost efectuată pe secțiuni colorate hematoxilină-eozină și imunohistochimic.*

Rezultate*. Au fost incluși 28 de pacienți (15 bărbați; 13 femei), vârstă medie - 60 de ani. 75% (n=21) au fost inițial diagnosticați cu diferite dermatoze cronice în instituțiile de îngrijire primară. 71% (n=15) din diagnosticele eronate au fost la pacienți peste 60 ani. După evaluarea clinică și histopatologică, conform criteriilor WHO-EORTC: 82% (n=23) au fost limfoame cutanate primare (PCL) și 18% (n=5) au fost limfoame cutanate secundare (SCL). 18 pacienți (78% din PCL) au prezentat limfoame cutanate cu celule T (LCTC), din care 14 (78% din CTCL) au fost micozis fungoides si 5 pacienți (22% din PCL) au prezentat limfoame cutanate cu celule B (LCBC).*

Limite. *Acesta este un studiu descriptiv efectuat pe un număr limitat de cazuri.*

Concluzii*. Este necesară urmărirea dermatozelor cronice la pacienții vârstnici si prelevarea de biopsii repetate la cei cu leziuni suspecte. LC sunt rare și extrem de variabile iar diagnosticul definitiv este deseori întârziat.*

Cuvinte cheie: *limfom cutanat, dermatoză cronică, pacient vârstnic.*

Summary

Background. *The diagnosis of cutaneous lymphoma (CL) is often difficult, either because of overlapping features with benign dermatoses or discordance between clinical and pathologic findings. Incidence of cutaneous lymphomas (CL) increase steeply with age.*

Objective. *The aim of our study was to illustrate the importance of monitoring elderly patients with chronic dermatoses and the necessity of clinicopathological correlation in the diagnosis of CL.*

Patients and Methods. *Clinical data and histological sections of 28 patients selected from the files of the University Clinic of Dermatology and Venereology Timisoara (2005-2010) with confirmed CL, were reviewed and reclassified according WHO-EORTC classification. Histological review was performed on hematoxylin-eosin and immunohistochemical stained sections.*

Results. *28 patients (15 male; 13 female), mean age – 60 years were included. 75% (n=21) were initially diagnosed with a different chronic dermatoses in primary care institutions. 71% (n=15) of misdiagnoses were in patients over 60 years. After clinical and histopathological evaluation, according WHO-EORTC: 82% (n=23) were primary cutaneous lymphomas (PCL) and 18% (n=5) were secondary cutaneous lymphomas (SCL). 18 patients (78% of PCL) had T cell cutaneous lymphoma (CTCL), from which 14 (78% of CTCL) were mycosis fungoides and 5 patients (22% of PCL) had B cell cutaneous lymphoma (CBCL).*

Limitation. *This was a case series descriptive study.*

Conclusion. *It is important to monitor elderly patients with chronic dermatosis and to perform repeated biopsies every patient with suspicious skin lesions. CL are rare and very variable and a final diagnosis is often delayed.*

Key words: *cutaneous lymphomas, chronic dermatoses, eldery patients.*

DermatoVenerol. (Buc.), 56: 5-9

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Background

The early diagnosis of cutaneous lymphoma (CL) has important signification for therapeutic options, determination of prognosis, and outcomes in clinical trials. The inclusion of patients with a "benign" course into the mix of patients who have a definite, potentially life-threatening cancer poses added risks for patients: those with "benign" disease are at risk of being treated with inappropriately aggressive therapy and those with a potential for progressive disease are at risk of being deprived of more definitive therapy [1]. The diagnosis of CL relies heavily on clinical assessment, particularly in providing a supportive history, confirming one of several typical or suspect clinical presentations of CL and directing the choice of the critical biopsy site(s) [2].

The clinical diagnosis of CL may be difficult to make in early phase of disease because many of its clinical features may also be found in benign inflammatory diseases. Atopic dermatitis, nummular eczema, psoriasis, lichen planus, drug eruptions, tinea corporis, erythema chronicum migrans, small-plaque parapsoriasis / digitate dermatosis, pityriasis rosea, connective tissue disease such as dermatomyositis, *B burgdorferi* infection through a tick bite, tattooing or other mechanical or infectious irritants and certain genodermatoses likely to be clinically confused with CL [1].

CL, especially MF, should be suspected in patients who present with years of refractory or recurrent skin eruption with a poikilodermatous or polymorphic skin involvement in typical distribution. Clinicians must rule out also a drug reactions that can mimic the clinical or histological appearance (lymphomatoid drug eruptions) [1, 2].

It is important to know when to obtain ancillary immunohistochemical or molecular studies (because of false-positive and -negative cases) and to learn how to interpret and incorporate the information for optimal clinical pathologic diagnosis. Ancillary tests should be performed when routine histology is not diagnostic but a high clinical suspicion of CL exists[3].

Aging and age-related effects such as immune senescence may be particularly important for CLs in which incidence increase steeply with age. In addition, chronic inflammation, DNA damage, and diminished immune surveillance that occur with older age may also contribute to lymphoma development [5].

Objective

The aim of our study was to illustrate the importance of monitoring elderly patients with chronic dermatoses than can mask a CL and to show the necessity of clinicopathological correlation in the diagnosis of CL.

Materials and Methods

In the present study we evaluated clinical, pathological and immunophenotypical findings from the 40 patients suspected with cutaneous lymphoma. After clinicopathological assessment 12 patients were excluded, having another, non-malignant, diagnosis.

Clinical data and histological sections of 28 patients with confirmed CL, were reviewed and reclassified according to the WHO-EORTC classification scheme. The patients were selected from the files of the University Clinic of Dermatology and Venereology Timisoara (Romania) from 2005 to 2010. Histological review was performed on hematoxylin-eosin and immunohistochemical stained sections. The statistical analysis of data was performed by Microsoft Office Excel 2007.

Results

28 patients were included in this study (15 male; 13 female); male-female ratio=1,15.

A mean age at presentation was 60 years, age range 17- 88 years. (Fig. 1) At 22 patients, the age at diagnosis was more than 56 years (79%). (Fig. 2)

21 patients (75%) were misdiagnosed in primary care settings with a different chronic benign dermatoses (BD) such as chronic eczema (n=5), prurigo chronic (n=3), psoriasis (n=2), parapsoriasis en plaques (n=2), impetigo (n=2), lupus erythematosus (n=2), pemphigus vulgaris (n=1), erythroderma (n=2), poikilodermato-myositis – PDM (n=1), sarcoidosis (n=1) and were

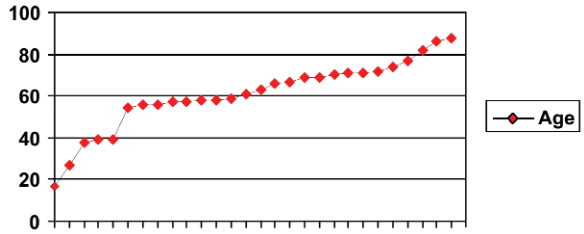

Fig. 1. Age distribution of patients with CL in our study. (a mean age at presentation was 60 years, age range 17- 88 years)

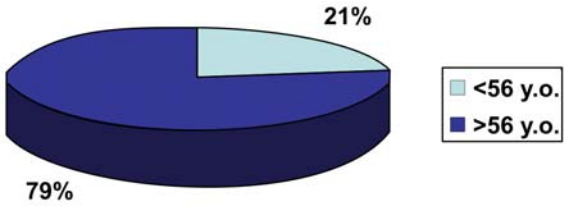

Fig. 2. The rate of CL increased exponentially with age. (At 22 patients, the age at diagnosis was more than 56 years (79%))

inadequately treated for several months before they had been referred to specialty care centers. (Fig. 3, 4) Most of misdiagnosis (n=15 ,71%) were at the patients older than 60 years.

After clinical, histopathological and immunophenotypical evaluation, according to WHO-EORTC criteria classification for cutaneous lymphomas patients were classified into the following diagnostic categories: from 28 patients, 23 (82%) had primary cutaneous lymphoma (PCL) and 5 (18%) had secondary cutaneous lymphoma (SCL); CTCL (cutaneous T-cell lymphoma) : 18 cases (78% of PCL); 55 years was a average age in this group, 67% of patients were older than 56 years. The most common type encountered was mycosis fungoides (MF) – 14 patients (78% of CTCL). Mean age in this group was 53 years, but 64% (9 patients) had more than 56 years.

10 cases (71%) were initially diagnosed as chronic dermatitis (chronic eczema (n=3), prurigo chronic (n=2), parapsoriasis en plaques (n=2), erythroderma (n=2), poikilodermatomyositis – PDM (n=1)), before dermatology consulting.

13 cases were with typical clinical picture of MF (variably large, erythematous, finely scaling lesions with a predilection for the buttocks and other sun-protected areas), one case had clinical picture of localized pagetoid reticulosis.

The nonspecific histological picture, characterized by a mild perivascular infiltrate in the upper dermis containing no atypical lymphocytes and lacking epidermotropism was described in 4 cases. A infiltrate with small, well-differentiated lymphocytes, with round or only

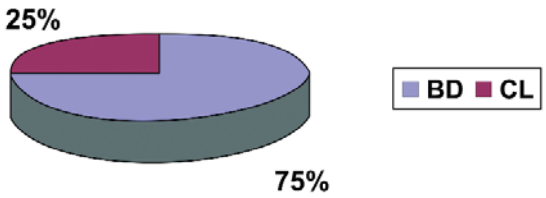

Fig. 3. Incidence of misdiagnosed CL in primary care settings in our study. (21patients (75%) were misdiagnosed in primary care settings with a different chronic benign dermatoses (BD))

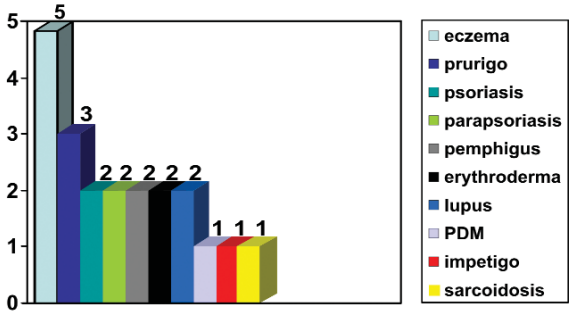

Fig. 4. Most frequent misdiagnosis (chronic eczema (n=5), prurigo chronic (n=3), psoriasis (n=2), parapsoriasis en plaques (n=2), impetigo (n=2), lupus erythematosus (n=2), pemphigus vulgaris (n=1), erythroderma (n=2), poikilodermatomyositis - PDM (n=1), sarcoidosis (n=1))

slightly cerebriform nuclei, lining up in the basal layer and showing single-cell epidermotropism in 4 cases. A dense, subepidermal, band-like infiltrate containing a high number of cerebriform cells, prominent epidermotropism, typical Pautrier microabscesses are seen only in 4 cases. Collections of atypical lymphocytes in the dermis are found in some cases.

Most of cases had typical immunophenotype (CD4+, CD8-, CD45RO+) of MF. One case was MF with rare T- cytotoxic CD3+, CD4-, CD5+, CD7-, CD8+ phenotype. One case was cutaneous anaplastic large cell lymphoma with characteristic phenotype (CD4+, CD8-, CD30+). One case was primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. (CD3+, CD5+, CD8+; CD4-, CD7-, Ki6+ 20%). A diagnosis of HTLV-1 positive adult T-cell leukemia / lymphoma was confirmed for one patient (CD3+, CD4+, CD2+, CD5+, CD25+, the serology for HTLV-1 strongly positive).

One patient had primary cutaneous peripheral T-cell lymphoma, NOS with pemphigus-like lesions. Histological picture in this case shown sever atypical lymphocytic diffuse infiltrate characterized by the predominance of medium- and large-sized pleomorphic cells within the upper dermis and periadnexal areas. Immunohistochemical analysis revealed the infiltrate to be predominantly T cells (CD3+, CD7+, CD20-). Were negative for CD4, CD8, CD56, CD30 and Granzyme B.

CBCL: 5 cases (22% of PCL), mean age was 64 years, age range 39-88 years. Cutaneous marginal zone lymphoma: one case; intravascular large B-cell lymphoma: one case; cutaneous diffuse large B-cell lymphoma: two cases; cutaneous B-cell pseudolymphoma was determinate in one case.

SCL: Five patients (18%) shown cutaneous manifestations of the extracutaneous lymphomas. Average age of these patients was 71 years with age range 57-86 years. 4 patients had diffuse large B-cell lymphoma.

Discussion

Our study was limited as a case series descriptive study. However, we compare our results with other more larger studies of incidence of CL [2, 4, 5, 7]. In our study, CTCLs constituted the majority (78%) of PCLs similar to previous studies (75%-85%) [4, 5, 6, 7].

We found that CBCLs were much less common than CTCLs, accounting for 22% of PCLs overall. This finding is consistent with previous studies in which CBCL constituted 24-29% of PCLs [4, 7]. We observed that rate of CBCL increased exponentially with age. This finding is consistent with a previous case reports where the median age at diagnosis was 68 years. In our study, the mean age was 64 years, age range 39-88 years. We also found that rate of CTCL increased with age too. 55 years was a average age in this group, 67% of patients were older than 56 years. A consistent male predominance was observed in the majority of CL subtypes in all previous studies [4, 5, 6, 7]. Male-female ratio = 1.72. The M/F ratio ranged between 1.28 to 2.55 among the various T-cell and B-cell lymphoma subtypes [4]. We not found a consistent male predominance for all CL subtypes in our study. Male-female ratio was 1.15.

MF was the most common CTCL subtype, comprising 78% (51-54% in others studies [4, 5, 6, 7]) of the CTCLs, followed by cutaneous peripheral T-cell lymphoma, cutaneous CD30+ T-cell lymphoproliferative disorders and HTLV-1 positive adult T-cell leukemia / lymphoma [4,5]. The most common CBCL subtypes were 50% (40% in others studies) primary cutaneous diffuse large-B cell lymphoma, followed by cutaneous marginal zone B-cell lymphoma and intravascular large B- cell lymphoma.

It is evident that the diagnosis of CL, especially early MF/CTCL is difficult to make. Referral centers for cutaneous lymphomas are confronted regularly with patients who have been misdiagnosed or who have been treated with unnecessarily aggressive treatment regimens. [1, 2] In our study we observed, that most of patients (75%) were misdiagnosed in primary care settings with a different chronic benign dermatoses and were inadequately treated for several months before they had been referred to specialty care centers. Most frequent misdiagnosis was chronic eczema, follow by prurigo chronic, psoriasis, parapsoriasis en plaques, impetigo, lupus erythematosus, pemphigus vulgaris, erythroderma, poikilodermatomyositis, sarcoidosis. Most of mis-

diagnosis (71%) were at the patients older than 60 years. It is reported that the mean and median durations from onset of symptoms to diagnosis of MF/CTCL were 73.2 months and 48 months respectively.

We consider that is very important to refer the entire patient with chronic dermatoses resistant to treatment to specialty care centers, because a combination of clinical and histological features remains the most reliable approach for establishing a definite diagnosis in cases of lymphoid skin infiltrates [11]. According to Kotz et al., "in every chronic disease resistant to treatment lymphoma has to be considered" [8]. In about 10% of cases, the diagnosis can only be confirmed during the course of disease [11, 12].

Intrat în redacție: 14.02.2011

Conclusion

CLs lesions are rare and very variable, and a final diagnosis of CLs is often delayed. For that reason, if lymphoma is suspected, the diagnosis must be confirmed by clinical, histological and molecular examinations and possibly repeated in the course of the disease[2].

Incidence of cutaneous lymphomas increase steeply with age. It is important to monitor elderly patients with chronic dermatosis as it could mask a CL and to perform repeated biopsies every patient, with suspicious skin lesions, particularly in cases where the patient does not respond to initial treatment.

Received: 14.02.2011

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