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T-cell Primary Cutaneous Lymphomas. A Clinicopathological and Immunohistochemical Study

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Within the large framework of the lymphoproliferative diseases, the primary cutaneous lymphomas are distinct pathologic conditions, defined by particular morphologic, immunologic, genetic, and clinic criteria. The study aimed to create the first clinicopathological and immunohistochemical profile of primary cutaneous lymphoma for a Romanian region. We investigated a series of 16 cases (diagnosed during a 5-year period) in accordance with the general principles of primary cutaneous lymphoma management. The methods included the clinic and morphologic exams, the latter relying on standard and immunohistochemical staining. The results revealed that all studied cases were T-type lymphomas, in terms of the WHO-EORTC classification. Most of these cases were diagnosed as mycosis fungoides; the group also included cases of Sezary syndrome, as well as rare entities such as: mycosis fungoides associated with follicular mucinosis and subcutaneous panniculitis-like T-cell lymphoma. Our discussions focused on the role of the clinicopathological assessment for the primary cutaneous lymphoma diagnosis and emphasized the importance of the immunohistochemical investigation. Compared with the previous Romanian researches on this topic, presenting only isolated cases, the current study develops a new level of analysis, based on the rigorous monitoring of a relatively large geographical area, for a long time horizon.

Introduction

Pertaining to the extranodular lymphoma class, the primary cutaneous lymphomas represent rare conditions in the context of dermatological pathology [6, 18, 23]. Their occurrence is 0.4 in 100.000 individuals per year, but because most of them are low degree malignancies, with long survival, the overall prevalence is much bigger [42]. Clinically, they appear as polymorphic lesions, sometimes not suggestive for a condition [35, 43]. Thus the histopathologic exam has an indubitable importance [5, 38], the localization of the malignant lymphoproliferations at the cutaneous level having as background the histologic and immunologic peculiarities of the skin.

For a long time, in order to diagnose the cutaneous lymphomas by their histologic cataloging the current practice required the use of the nodular non-Hodgkin's lymphoma classification [32, 33], the Working Formulation [31] and the Kiel classification [24]. These classifications did not comprise the special features of the primary cutaneous lymphomas, the precise differentiation of some lesions being extremely difficult, hence leading to incorrect and useless diagnose and treatment.

The experience of the dermatologists and pathologists yielded the idea that the classification of the nodular lymphomas cannot be applied to the cutaneous lymphomas by simple overlapping [21]. Therefore, the ulterior lymphoma classifications (REAL [34, 36], EORTC [46], WHO [20]) separately included the primary cutaneous

lymphoma category. The EORTC classification, especially used for the primary cutaneous lymphomas, includes well-defined types of T-cell (approximately two thirds of the cutaneous lymphomas) and B-cell lymphomas (approximately one third of the cutaneous lymphomas), making the distinction between the indolent, intermediate and aggressive behavior of the primary cutaneous lymphomas. The clinic validity of this new classification was established by studies including the follow-up of over 800 patients with primary cutaneous lymphomas [15, 43, 47]. In order to increase the operational level of the WHO and EORTC classifications a consensus was created - named the WHO-EORTC classification [45]. It was based on the processing of the data obtained from the investigation of 1905 patients with primary cutaneous lymphomas (registered with the Dutch and Austrian Cutaneous Lymphoma Groups between 1986 and 2002).

In the recent literature, there are reported results of extremely numerous studies on the primary cutaneous lymphomas. These studies provide clinicomorphological data [2, 3, 12, 22, 25, 28, 29, 30, 38, 47], etiologic and pathogenic information, at the cellular, molecular and genetic level [10, 11, 13, 19, 25, 27, 38, 40, 41, 44, 47, 48] and therapeutic information [1, 7, 9, 11, 16, 17, 39].

The current research represents the first step taken to develop a clinicopathological and immunohistochemical profile of the primary cutaneous lymphoma, corresponding to a relatively large geographical area of Romania (the northeastern region, including eight administrative counties with the total surface of 46173 km^2 and about 4657039 inhabitants). We investigated the clinical and morphologic features that characterized a series of primary cutaneous lymphomas diagnosed in a 5-year period (this time horizon being considered relevant in the circumstances of the disease rarity). The patients were followed up according to the general principles of primary cutaneous lymphoma management [42], allowing the sequencing of the diagnosis steps, the dynamic monitoring of the results and the placement within the staging system (I, II, III, IV) in correlation with the TNMB classification. From the point of view of the tumoral cell line origin, all lymphomas were of the T-type. Most cases were diagnosed as mycosis fungoides (MF); the group also included cases of Sezary syndrome (SzS), as well as less frequent entities: mycosis fungoides associated with follicular mucinosis (MF-FM) and subcutaneous panniculitis-like T-cell lymphoma (SP-like TCL). The contribution of our work should be evaluated in the general context of the Romanian communications and reports, which, so far, focused on isolated cases of this pathologic condition.

Material and Methods

The studied group consisted of 16 cases diagnosed as primary cutaneous lymphomas in a 5 year span (2001-2005) in the Dermatovenereology Clinic of the Railway University Hospital, the Emergency University Hospital Iasi and Recovery University Hospital Iasi, treating patients from all the northeastern region of Romania. The 16 patients were 8 females and 8 males, the age average being 56.61 years.

The clinic diagnosis of cutaneous lymphoma was established according to the type of lesions present on the teguments.

The cutaneous biopsies were routinely processed for the pathologic exam, performed in the Pathology departments pertaining to aforementioned hospitals. The microscopic specimens were stained with the hematoxylin-eosin (HE) routine stain and with special stains (trichrome Szekelly, PAS and silver-methenamine). The IHC exam, realized in the Immunology and Genetics Laboratory of the University Hospital "Sf. Spiridon" Iasi, was based on the avidine-biotin-peroxidase method. We used the following monoclonal antibodies: anti-CD3 (pan-T), anti-CD26 (activated T lymphocytes), anti-CD30 (activated T lymphocytes, B lymphocytes, monocytes), anti-CD20 (pan-B), anti-PCNA (Proliferating Cell Nuclear Antigen), anti-CD la (Langerhans cell) (DAKO, Denmark) and a LSAB working kit (DAKO, Denmark).

Moreover, the examination of the peripheral blood focused on the total number of white blood cells, lymphocytes and the presence or the absence of Sezary cells. In some cases, computed tomography was recommended for the purpose of staging.

Results

The diagnosis of the lymphoma type was established according to the WHO and EORTC classification, respectively, as follows: MF – 11 cases; MF-FM – 1 case; SzS – 2 cases; SP – like TCL – 2 cases.

Mycosis fungoides

The 11 cases of MF were 4 females and 7 males. The age group classification indicated the equal occurrence of the disorder in the patients aged between 40 and 49, 50 and 59 and 70 and 79 years old, respectively (3 cases for each group). One case was aged between 20 and 29 years old and another between 60 and 69 years old.

According to the appearance and the evolution of the lesions, the dermatological exam determined the follow-

ing repartition of the cases in correlation with the clinical stage of the disease: stage I (patch stage/premycotic stage): 2 cases; stage II (plaque stage): 6 cases; stage III (tumor stage): 3 cases. The prurigo was present in all patients. One case also presented an associated poikiloderma atrophicans vasculare, the MF plaques alternating with the poikilodermic parapsoriasis plaques.

The complete diagnosis was ascertained on the basis of the histological and IHC characteristics of the cutaneous biopsies.

In the patch stage (premycotic stage), the diagnosis was difficult, the lesions being discrete, insufficiently contoured. The inflammatory infiltrate was perivascular or diffuse in the papillary and reticular dermis, and formed predominantly by small and medium-sized lymphocytes among which we observed rare blastic large cells, with indented or cerebriform nuclei. The sparse presence of mononucleated cells among the epidermal cells, each of them surrounded by a clear halo, indicated the limited extension in the overlying epidermis; consequently, this was considered as epidermotropism in an initial stage. One of the biopsies presented a conglomeration of atypical lymphoid cells in a small intraepidermal vacuole, interpreted as Pautrier's microabscess in the process of formation. The epidermis was either atrophic or hypertrophied with obvious acanthosis and with the elongation of the interpapillary ridges. We observed also aspects of eczema with spongiosis and parakeratosis. In the plaque stage, the histologic picture was characteristic for the diagnosis. The main histological modification was represented by the ribbon-like infiltrate under the junction area, extending into the middle and deep dermis in a diffuse manner, with large cell clusters. The infiltrate consisted of lymphocytes with irregular, hyperchromatic nuclei, some of them in the process of mitosis, the morphology being typical for the mycosis cells. Pathognomonic for the diagnosis was considered also the presence of isolated lymphoid cells and of Pautrier's microabscesses (Fig. l). The epidermis, usually acanthotic with the elongation of the interpapillary ridges, was sometimes similar with the aspects of psoriasis. A fibrosis process was noticed as well, less apparent in the papillary dermis. In one case we noticed an association of the MF lesions with dispersed or nests of nevoid cells in the middle dermis. In the tumor stage, all the biopsies revealed an important expansion of the lymphoid infiltrate towards the deep dermis and the subcutaneous tissue (hypodermis). The extension was sometimes oriented also towards the epidermis, resulting in its compression and disruption and the occurrence of ulceration. In the cases where the epidermis was intact, we noted the fact that the neoplastic lymphocytes lost their tendency of invading the epidermis; consequently the epidermotropism and the Pautrier's microabscesses were very discrete. The lymphoid infiltrate consisted of mycosis cells with pleomorphic, hyperchromatic nuclei, with large variations in their sizes and presenting numerous mitoses. Rarely, some large cells were similar to Hodgkin or Sternberg-Reed cells. In one case, where large cells with vacuolated nuclei and conspicuous nucleoli predominated, without apparent epidermotropism and Pautrier's abscesses, we took into consideration the differential diagnosis with a large cell anaplastic lymphoma. Although reported mainly for the B-cell cutaneous lymphomas, the angiogenesis with vessel formation similar to the postcapillary venules was observed in some cases of MF.

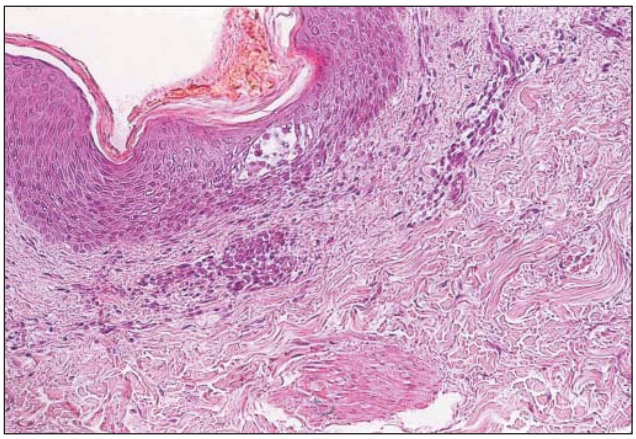

Fig. 1. MF – plaque stage, obvious Pautrier's microabscess (HE, x 100)

The IHC reaction for the monoclonal antibody anti-CD3 (pan-T) was positive in all stages. The reactions for the monoclonal antibody anti-CD30 (activated T lymphocytes, B lymphocytes, monocytes) and anti-CD20 (pan-B) were negative in all cases. For the tumoral stage we also followed the expression of the anti-CD26 marker (for the activated T-cells) which appeared intensely positive in most of the cells. Moreover, in the tumoral stage we evaluated the expression of the proliferation marker PCNA, that was positive in a percentage of 70-90%.

The complex evaluation of the cases (the cutaneous, nodular and visceral involvement and the affecting of the peripheral blood) allowed the cataloging of the 11 patients according to the TNMB classification (Table 1).

Consequently, we organized the MF cases in the staging system correlated with the TNMB classification:

- stage I A ($T_1N_0M_0B_0$) – 1 case;
- stage IB ($T_2N_0M_0B_0$) – 1 case;
- stage II B ($T_3N_0M_0B_0$) – 1 case;
- stage III ($T_4N_1M_0B_0$) – 2 cases;
- stage IV A ($T_{1-4}N_3M_0B_0$) – 3 cases;
- stage IV B ($T_{1-4}N_{0-3}M_1B_0$ – 3 cases.

TABLE 1
Cataloging of the MF cases according to the TNMB classification

Cutaneous involvement (T)		Nodular involvement (N)		Visceral involvement (M)		Peripheral blood involvement (B)	
Stage	Number of cases	Stage	Number of cases	Stage	Number of cases	Stage	Number of cases
T_0	0	N_0	3				
T_1	2	N_1	5	M_0	8	B_0	0
T_2	4	N_2	0				
T_3	3	N_3	3	M_1	3	B_1	0
T_4	2						

Mycosis fungoides associated with follicular mucinosis

MF-FM was diagnosed at a 49 years old female. At the dermatologie exam, the patient presented acneiform lesions (papules and follicular keratosis), macules and erythematous plaques, with loss of hair in the areas involved.

The complete diagnosis was established on the basis of the histologic and IHC characteristics of the cutaneous biopsy.

Concurrently with the invasion of the epidermis by atypical lymphocytes, the cutaneous biopsy revealed an infiltration with the same cells of the epithelium of the appendages, especially of the hair follicles. These also presented an accumulation of acid mucopolysaccharides in some areas of degeneration of the epithelial cells - mucinous degeneration, believed to be a consequence of the penetration of the atypical lymphocytes in the follicular structure.

The IHC reaction was strongly positive for the monoclonal antibody anti-CD3 (pan-T) and negative for the monoclonal antibody anti-CD30 (activated T lymphocytes, B lymphocytes, monocytes) and anti-CD20 (pan-B), respectively.

Sezary syndrome

SzS was diagnosed at a male and a female aged between 60 and 69 years. At the clinical exam, the two patients presented lesions characteristic for the SzS: infiltrative exfoliative erythrodermia on 80% from the cutaneous surface, hyperpigmentation, palmoplantar hyperkeratosis, nail dystrophy. Both patients presented early lymphadenopathies and later splenomegaly.

The complete diagnosis was established on the basis of the histologic and IHC characteristics of the cutaneous biopsy, as well as of the presence of Sezary cells in the peripheral blood. The cutaneous biopsies evidenced ribbon-like infiltrate mainly in the superficial and intermediate dermis but affecting the profound dermis as well. The cellular infiltrate had a much more monomorphous aspect in comparison with the one in MF, being dominated by the presence of Sezary cells: cells larger than lymphocytes but smaller than monocytes, with cleaved, cerebriform nucleus (Fig. 2) and reduced clear cytoplasm. Some Sezary cells had vacuoles containing glycogen deposits, labeled by the PAS staining. The dermal infiltrate was separated from the epidermis by a zone of unaffected dermal tissue. As opposed to MF, the epidermotropism was discrete and the Pautrier's abscesses were absent.

In the peripheral blood, characterized by moderate leukocytosis, we remarked two types of Sezary cells: some of them were large, typical, with a diameter of 12-14 μm and other smaller, with the dimension of a small lymphocyte (8-11 μm diameter). The IHC reaction revealed a marked positive expression for the monoclonal antibody anti-CD3 (pan-T) and a negative expression for the monoclonal antibody anti-CD30 (activated T lymphocytes, B lymphocytes, monocytes) and anti-CD20 (pan-B). In one case, we also used the anti-CD 1a monoclonal antibody in order to investigate the Langerhans cells, present in important numbers in the dermis.

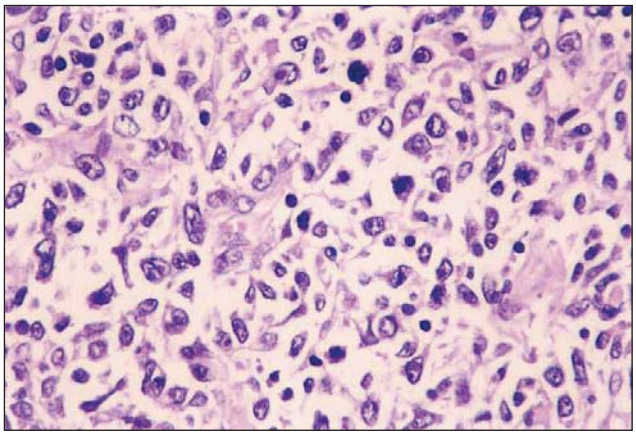

Fig. 2. SzS, Sezary cells (HE, x 400)

Subcutaneous panniculitis-like T-cell lymphoma

Two female patients, aged between 50 and 59 years old were diagnosed with SP-like TCL. Clinically, the patients presented erythematous plaques localized on the lower limbs, accompanied by systemic manifestations (fever, weakness, muscle pain, and loss of weight). The complete diagnosis was ascertained on the basis of the histologic and IHC characteristics of the cutaneous biopsy.

The lesions were situated mainly in the subcutaneous tissue and were characterized by an infiltrate with lymphoid pleomorphic cells in the adipose lobules, creating aspects similar to the lobular panniculitis. We noted liponecrosis and the presence of adipose cysts. There was also present moderate infiltration of the deeper dermis.

The differentiation between the lobular panniculitis and the SC-like TCL was possible through immunohistochemistry which revealed a positive expression for CD3 (T-cell marker) and a negative one for CD30 (activated T lymphocytes, B lymphocytes, monocytes) and CD20 (B-cell marker).

Discussion

Although in the cutaneous lymphoma it is possible to encounter nodular and internal organs involvement, we must stress the fact that the skin is the primary organ affected and usually remains the only place of manifestation for a long period of time [4, 21]. Thus, we can consider as a primary cutaneous lymphoma a cutaneous lymphoma without extracutaneous association at the moment of the diagnosis or in the 6 following months. The two large groups of primary cutaneous lymphomas, type T and B, respectively, are defined by diverse morphologic, immunologic, genetic and clinic criteria, the extranodular localization being different from their equivalents at the level of the lymph nodes [26]. We must underline the fact that all the lymphomas we diagnosed were of the T type. Although not surprising (because T-cell lymphomas are more frequent than B-cell lymphomas), this element may be regarded as a particularity of our study. Also, we have to note that in the 5 year span investigated, 34 cases were clinically suspected of being primary cutaneous lymphomas but only in 16 cases this diagnosis was confirmed.

According to the literature [42], it is recommended that all patients, possibly with the exception of those with initial stages of MF (IA) or lymphomatoid papulomatosis, should be consulted by an interdisciplinary team comprising a dermatologist, a (hemato)oncologist and a dermatopathologist. The clinical symptoms should be interpreted together with the morphologic results in order to ascertain a complete diagnosis [14]. This is an essential aspect because the treatment and prognosis can vary considerably according to the diagnosis category [8]. Moreover, a centralization of the entire pathology would be necessary, by creating a national register of the lymphomas. Ideally speaking, the management of the disease should be known both by the oncologist and by the family doctor. An ascertained laboratory, with good performances should support such an interdisciplinary team. In our study we aimed to follow-up the patients respecting the general management principles for the primary cutaneous lymphomas. We sequenced the diagnosis steps, we monitored the results in dynamics and we organized the MF cases in the staging system (I, II, III, IV) correlated with the TNMB classification.

From the pathologist's point of view, our morphologic investigation focused on three main problems: (i) morphologic and phenotypic features of the tumoral cell populations; (ii) significantly operational histoarchitectonic criteria; (iii) associated aspects with relative specificity. Thus, on the basis of our own experience, in the pathologic exam we assessed: the topography of infiltrate and its relations with the epidermis, the cytologic characteristics of the lymphocytes (cell and nucleus shape and dimensions, nucleocytoplasmic ratio), the presence of the other cell types (macrophages, Langerhans cells, plasma cells, neutrophils, eosinophils).

According to the literature, the IHC studies [37, 45], performed on paraffin-embedded specimens focus on the identification of the T-cell and B-cell markers and of the CD30 activation marker. Supplementary markers, such as p53 and PCNA, can have a prognostic signification in MF. The markers for the cytotoxic function (TIA-I), the marker for monocytes/macrophages (CD68) and the marker for the T NK lymphocyte (CD56) are useful in specific forms of T-cell cutaneous lymphoma. In our study, the performed IHC reactions allowed the identification of the phenotype for the tumoral cell population as well as for the associated/reactive population and the formulation of the primary cutaneous lymphoma diagnosis according to the WHO-EORTC classification [45].

The morphologic results should be interpreted together with the clinical symptoms in order to establish a complete diagnosis [37]. The histopathologic and IHC elements, regarded as positive diagnosis criteria, make possible the differentiation from pseudolymphomas, leukemides and other cutaneous disorders clinically similar or in correlation with the cutaneous lymphomas.

Our work achieves the first clinicopathological and immunohistochemical profile of the primary cutaneous lymphoma for a relatively large geographical area of Ro-

mania. The studied cases were catalogued according to the WHO-EORTC classification, the clinical diagnosis criteria being integrated with the classic histologic and IHC ones. The establishment of T-cell primary cutaneous lymphoma diagnosis was the result of a team activity where the dermatologist, the pathologist and the oncologist had extremely important contributions.

References

1. *Bekkenk MW, Geelen FAMJ, van Voorst Vader PC:* Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up of 219 patients and guidelines for diagnosis and treatment. Blood 2000, 95, 3653-3661.
2. *Bekkenk MW, Vermeer MH, Jansen PM, van Marion AM, Canninga-van Dijk MR, Kluin PM, Geerts ML, Meijer CJ, Willemze R:* Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. Blood 2003,102, 2213-2219.
3. *Bogle M, Riddle C, Triana E, Jones D, Duvic M:* Primary cutaneous B-cell lymphoma. J Am Acad Dermatol 2005, 53, 479-484.
4. *Bunn PA Jr, Lamberg SI:* Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. Cancer Treat Rep 1979, 63, 725-728.
5. *Burg G, KempfW, Cozzio A, Feit J, Willemze RS, Jaffe E, Dummer R, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Grange F, Harris NL, Kazakov DV, Kerl H, Kurrer M, Knobler R, Meijer CJ, Pimpinelli N, Ralfkiaer E, Russell-Jones R, Sander C, Santucci M, Sterry W, Swerdlow SH, Vermeer MH, Wechsler J, Whittaker S:* (2005). WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. J Cutan Pathol 2005, 32, 647-674.
6. *Burg G, Kempf W, Cozzio A, Dobbeling U, Feit J, Golling P, Michaelis S, Scharer L, Nestle F, Dummer R:* Cutaneous malignant lymphomas: update 2006. J Dtsch Dermatol Ges 2006, 4, 914-933.
7. *Cheng SX, Kupper T:* A new retinoid for cutaneous T-cell lymphoma. Arch Dermatol 2001,137, 649-652.
8. *Demierre MF, Kim YH, Zackheim HS:* Prognosis, clinical outcomes and quality of life issues in cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 2003, 17, 1485-1507.
9. *Dummer R:* Future perspectives in the treatment of cutaneous T-cell lymphoma (CTCL). Semin Oncol 2006, 33, S33-S36.
10. *Dummer R, Willers J, Kamarashev J, Urosevic M, Dobbeling U, Burg G:* Pathogenesis of cutaneous lymphomas. Semin Cutan Med Surg 2000, 19, 78-86.
11. *Dummer R, Cozzio A, Urosevic M:* Pathogenesis and therapy of cutaneous lymphomas – progress or impasse? Exp Dermatol 2006, 15, 392-400.
12. *Duvic M, Edelson R:* Cutaneous T-cell lymphoma. J Am Acad Dermatol 2004, 51, S43-S45.
13. *Geelen FAJM, Vermeer MH, van der Putte SCJ:* Bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. J Clin Oncol 1998, 16, 2080-2085.
14. *Glusac EJ, Shapiro PE, McNiff JM:* Cutaneous T-cell lymphoma: refinement in the application of controversial histologic criteria. Dermatol Clin 1999, 17, 601-614.
15. *Grange F, Hedelin G, Joly P, Beylot-Barry M, D'Incan M, Delaunay M, Vaillant L, Avril MF, Bosq J, Wechsler J, Dalac S, Grosieux C, Franek N, Esteve E, Michel C, Bodemer C, Vergier B, Laroche L, Bagot M:* Prognostic factors in primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome. The French Study Group on Cutaneous Lymphomas. Blood 1999, 93, 3637-3642.
16. *Heald P:* Clinical trials and efficacy assessment in the therapy of cutaneous T cell lymphoma. Ann NY Acad Sci 2001, 941, 155-165.
17. *Heald PW, Glusac EJ:* Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. J Am Acad Dermatol 2000, 42, 283-285.
18. *Isaacson PG, Norton AJ:* Cutaneous lymphomas. In: Extranodal Lymphomas. Isaacson PG, Norton AJ, eds. Churchill Livingstone, London 1994, 131-191.
19. *Jaffe ES:* Pathobiology of peripheral T-cell lymphomas. Hematol Am Soc Hematol Educ Progr 2006, 317-322.
20. *Jaffe ES, Harris NL, Stein H, Vardiman JW:* Tumours of Haematopoietic and Lymphoid Tissue. World Health Organization Classification of Tumours. IARC Press, Lyon 2001.
21. *Kempf W, Dummer R, Burg G:* Approach to lymphoproliferative infiltrates of the skin. The difficult lesions. Am J Clin Pathol 1999, 111, S84-S93.
22. *Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT:* Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003, 139, 857-866.
23. *Latkowski JA, Heald PW:* Cutaneous T cell lymphomas. In: Fitzpatrick's Dermatology in General Medicine. 6th. ed. Freedberg IM, Eisen AZ, Wolff K eds. McGraw-Hill, New York, 2003, 1537-1558.
24. *Lennert K, Feller AC:* Histopathologie des Lymphomes Malins non-Hodgkiens - selon la classification de Kiel actualisee. 2e ed. Doin Editeurs, Paris, 1991.
25. *Liu LH, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH:* CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 2003, 49, 1049-1058.
26. *Liu V, McKee PH:* Cutaneous T-cell lymphoproliferative disorders: approach for the surgical pathologist: recent advances and clarification of confused issues. Adv Anat Pathol 2002, 9, 79-100.
27. *Mao X, Lillington D, Scarisbrick JJ, Mitchell T, Czepulkowski B, Russell-Jones R, Young B, Whittaker SJ:* Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sezary syndrome and mycosis fungoides. Br J Dermatol 2002, 147, 464-475.
28. *Mendes S, Dreno B:* Diagnosis of primary cutaneous B-cell lymphoma by immunohistochemical and in situ hybridization methods. Acta Derm Venereol 2003, 83, 167-170.
29. *Michaelis S, Kazakov DV, Burg G, Dummer R, Kempf W:* Extracutaneous transformation into a high-grade lymphoma: a potential pitfall in the management of patients with Sezary syndrome. Int J Dermatol 2006, 45, 277-279.

30. *Nagasawa T, Miwa H, Nakatsuka SI, Itami S, Yoshikawa K, Aozasa K:* Characteristics of cutaneous lymphomas in Osaka, Japan (1988-1999) based on the European organization for research and treatment of cancer classification. Am J Dermatopathol 2000, 22, 510-514.
31. *National Cancer Institute:* National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas. Summary and description of a Working Formulation for clinical usage. Cancer 1982, 49, 2112-2135.
32. *Rappaport H:* Tumors of the Hematopoietic System - Atlas of Tumor Pathology (The Text of the Rappaport Classification). Armed Forces Institute of Pathology, Washington DC, 1966.
33. *Rappaport H:* The pathology of the extracutaneous lesions of mycosis fungoides. Bull Cancer 1977, 64, 275-278.
34. *Sander CA, Flaig MJ, Kaudewitz P:* The Revised European-American Classification of Lymphoid Neoplasms (REAL): a preferred approach for the classification of cutaneous lymphomas. Am J Dermatopathol 1999, 21, 274-278.
35. *Sander CA, Flaig MJ, Jaffe ES:* Cutaneous manifestations of lymphoma: a clinical guide based on the WHO classification. Clin Lymphoma 2001, 2, 86-100.
36. *Sander CA, Kind P, Kaudewitz P, Raff eld M, Jaffe ES:* The Revised European-American Classification of Lymphoid Neoplasms (REAL): a new perspective for the classification of cutaneous lymphomas. J Cutan Pathol 1997, 24, 329-341.
37. *Smoller BR:* The role of immunohistochemistry in the diagnosis of cutaneous lymphoma. Adv Dermatol 1997, 13, 207-234.
38. *Smoller BR, Santucci M, Wood GS, Whittaker SJ:* Histopathology and genetics of cutaneous T-cell lymphoma. Hematol Oncol Clin N Am 2003, 17, 1277-1311.
39. *Suchin KR, Cucchiara AJ, Gottleib SL, Wolfe JT, DeNardo BJ, Macey WH, Bromley PG, Vittorio CC, Rook AH:* Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol 2002, 138, 1054-1060.
40. *van Doom R, Dijkman R, Vermeer MH, Starink TM, Willemze R, Tensen CP:* A novel splice variant of the Fas gene in patients with cutaneous T-cell lymphoma. Cancer Res 2002, 62, 5389-5392.
41. *Whittaker S:* Molecular genetics of cutaneous lymphomas. Ann NY Acad Sci 2001, 941, 39-45.
42. *Whittaker SJ, Marsden JR, Spittle M, Russell Jones R:* Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous T-Cell Lymphomas. Br J Dermatol 2003, 149, 1095-1107.
43. *Willemze R:* Primary cutaneous lymphomas. Curr Op Oncol 2000, 12, 419-425.
44. *Willemze R:* Cutaneous T-cell lymphoma: epidemiology, etiology and classification. Leukemia & Lymphoma 2003, 44, S49-S54.
45. *Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJLM:* WHO-EORTC classification for cutaneous lymphomas. Blood 2005, 105, 3768-3785.
46. *Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Geerts ML, Goos M, Knobler R, Ralfkiaer E, Santucci M, Smith N, Wechsler J, van Vloten W A Meijer CJLM:* EORTC classification for primary cutaneous lymphomas: A proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997, 90, 354-371.
47. *Yang B, Tubhs RR, Finn W, Carlson A, Pettay J, His ED:* Clinicopathologic reassessment of primary cutaneous B-cell lymphomas with immunophenotypic and molecular genetic characterization. Am J Surg Pathol 2000, 24, 694-702.
48. *Yaw al kar N, Ferenczi K, Jones DA, Yamanaka K, Suh KY, Sadat S, Kupper TS:* Profound loss of T-cell receptor repertoire complexity in cutaneous T-cell lymphoma. Blood 2003, 102, 4059-4066.

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