ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Biopsying parapsoriasis: *quo vadis*? Are morphological stains enough or are ancillary tests needed?

FLAVIA BADERCA[1,2], ELENA CHITICARIU[3], MICHAEL BAUDIS[4], CAIUS SOLOVAN[5,6]

[1] *Department of Microscopic Morphology, "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania*
[2] *Service of Pathology, Emergency City Hospital, Timisoara, Romania*
[3] *PhD Student, "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania*
[4] *Institute of Molecular Life Sciences, University of Zurich, Switzerland*
[5] *Department of Dermatology, "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania*
[6] *Department of Dermatology, Emergency City Hospital, Timisoara, Romania*

Abstract

Background: Parapsoriasis represents a group of cutaneous disorders that shows variable clinical aspects somehow resembling to psoriasis, how is reflecting by its name. It was first named by Brocq, in 1902, as an entity with three components: pityriasis lichenoides, small plaque parapsoriasis and large plaque parapsoriasis. Nowadays, under the name of parapsoriasis are included only the last two categories, that are considered disorders characterized by the presence of a mononuclear infiltrate in the dermis, composed of T-cells. Until now, there were not established pathognomonic histopathological features to diagnose parapsoriasis. *Aim*: The aim of the study was to investigate the epidemiological and morphological data of parapsoriasis cases diagnosed at Emergency City Hospital, Timisoara, Romania for a period of 12 years. *Materials and Methods*: The study had two parts; one was retrospective and another one prospective. For the retrospective part, we searched 210111 patient files recorded in our Pathology Service for a period of 11 years, from January 2002 to December 2012. The slides were searched from the archive and re-read by two individual pathologists. For prospective part of the study, we reviewed 11815 histological slides read between January and June 2013. After inspection of the recorded files, the pathologists noted, were available, the localization and number of the lesions, together with symptoms. The biopsied specimens were initially processed with routine histological technique, the archive slides being stained with Hematoxylin and Eosin. While reading the slides, the pathologists paid attention to the architecture of the epidermis, the presence of epidermotropism and interface dermatitis, type of the dermal infiltrate and its distributions. *Conclusions*: In the present study, we emphasized the histopathological aspects of parapsoriasis in order to create a basic line that could help in the establishment of a uniformly accepted definition of parapsoriasis on histopathological grounds.

Keywords: small plaque parapsoriasis, large plaque parapsoriasis, pityriasis lichenoides.

Introduction

From the histopathological point of view, parapsoriasis is a lymphoproliferative disorder that was for the first time named by Brocq, in 1902, as an entity with three components: pityriasis lichenoides, small plaque parapsoriasis and large plaque parapsoriasis [1].

Other authors previously described all these components, but they never used before the term parapsoriasis until Brocq did it [2].

Unna *et al.*, in 1890, published a paper about *parakeratosis variegata*, nowadays included in large plaque parapsoriasis group [3]. Brocq, in 1897, described small and large plaque parapsoriasis under the same name of *érythrodermies pityriasiques en plaques disséminées* [4].

Two scientists, in the same journal, independently presented *pityriasis lichenoides*, in 1894, including in this group both forms now recognized, acute and chronic [5, 6]. Five years later, *pityriasis lichenoides chronica* was designated as separate entity [7].

For the first time, in 1901, Fox and Macleod grouped all these diseases in the same entity called *resistant maculopapular scaly erythrodermias* [8]. Brocq was that who mentioned for the first time, in 1902, the term parapsoriasis for this group. He did not tried to propose a new disease, only to give a name to an entity composed by already described conditions which share some common features as unknown etiology, chronic course, and lack of the symptoms or of the response to the treatment. Even if you are tempted to believe that the name of parapsoriasis came from clinical resemblance to psoriasis, in reality Brocq called this disease parapsoriasis because of the common features mentioned before and not because of clinical aspect [1].

Another important step in the attempt to classify parapsoriasis was in 1916, when Mucha described acute *pityriasis lichenoides* as separate entity and split it by chronic form [9]. The name accepted until now of *pityriasis lichenoides et varioliformis acuta* was given by Habermann, nine years later [10]. Of course, that until now is no consensus if these two conditions are different separate entities or evolving stages of the same disease.

Even so, for almost 100 years, the debates referring to the classification, description and characterizations of the diseases from parapsoriasis group continue. Main reason is probably the subtle presentation of parapsoriasis that transform this disease in one underreported with sparse epidemiological data. The small number of patients

makes impossible the existence of large case studies and offers the attribute of orphan disease for this rare condition.

It is very important to correct diagnose different variants included in the parapsoriasis group even if their histology is similar. The possibility to progress to cutaneous lymphoma varies from none to hundred percent between different diseases of parapsoriasis group. Moreover, an interesting variant diagnosed as parapsoriasis has similar histopathological aspect as cutaneous lymphoma but it never develops a malignant counterpart [2].

Nowadays, under the name of parapsoriasis some authors include only small and large plaque parapsoriasis considered disorders characterized by the presence of a mononuclear infiltrate in the dermis, composed of T-cells.

Even so, another controversy emerged referring to the classification of large plaque parapsoriasis because other authors consider that this entity is equivalent to the patch-stage mycosis fungoides. This controversy is somehow supported by the paucity of clinical and histological features, which may allow distinguishing between these conditions [2].

Until now, there were not established pathognomonic histopathological features to diagnose parapsoriasis and to classify it in small plaque and large plaque parapsoriasis. Moreover, until now, there are not defined until now clear histopathological characteristics to distinguish between two entities with many similarities on clinical level, large plaque parapsoriasis and patch stage mycosis fungoides. Moreover, there is a large variability of the terms used in dermatology referring to parapsoriasis and mycosis fungoides.

The aim of the study was to investigate the epidemiological and morphological data of parapsoriasis cases diagnosed at Emergency City Hospital, Timişoara, Romania for a period of 12 years. In addition, we tried to propose and characterize a unique nosology of the terms used in dermatology when referring to parapsoriasis.

Materials and Methods

The study had two parts; one was retrospective and another one prospective. For the retrospective part, we searched 210111 patient files recorded in our Pathology Service for a period of 11 years, from January 2002 to December 2012. For prospective part of the study, we reviewed 11815 histological slides read between January and June 2013.

We considered in this study only those cases with clinical diagnosis of small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP). We excluded cases diagnosed with pityriasis lichenoides, even if acute or chronic form.

For retrospective group, we used paraffin blocks from the archive. For prospective part, the biopsies were fixed in 4% *v/v* buffered formalin and processed using the routine histological technique in order to obtain paraffin blocks.

For all cases, 3-μm thick sections were cut on a semi-automated Rotary Microtome Leica RM2245, displayed on microscope slides and stained with Hematoxylin and Eosin (HE).

Histopathological evaluation was performed with Leica DM750 microscope.

While reading the slides, the pathologists paid attention to the architecture of the epidermis, the presence of epidermotropism and interface dermatitis, type of the dermal infiltrate and its distributions.

Images were acquired using Leica DM Share system.

Results

After searching the files archived in the Pathology Service of the City Emergency Hospital, Timişoara, 82 patients diagnosed with parapsoriasis were selected.

We noted that in some cases multiple biopsies/ specimens were performed from various sites. If the patient presented more lesions with different clinical aspect, we tried to obtain biopsies from all these time events in order to understand the progression of the disease.

After that, we review the archived slides. From the great variability of diagnostic criteria used by different centers of Pathology in the diagnosis of parapsoriasis, our pathologists selected those more characteristic for small plaque and large plaque parapsoriasis. The archived HE slides from all the patients (n_1=82) were re-read by two individual pathologists in order to re-view the histopathological diagnosis (correlated with the clinical findings) and to decide what cases were included in the final group. In many cases, they found that the criteria used in this study for the diagnosis were not fulfilled. For a high percentage of cases, we had to change the diagnosis from psoriasis or dermatitis to small or large plaques parapsoriasis, even to lymphoma, or vice versa. In these cases, a new diagnosis was established, based on *WHO* classification of lymphomas and on diagnostic criteria announced at the beginning of the study. From the total number of 82 patients initially selected for the study from archived files, the final number of gathered cases included 55 specimens.

For all cases selected (n_2=55), 3-μm thick sections were cut on a semi-automated Rotary Microtome Leica RM2245, displayed on microscope slides and stained with HE in order to be reevaluated by the pathologists for obtaining an accurate morphological diagnosis. After re-reading the new performed HE slides, we decided that all the 55 specimens selected in the second step fulfill the criteria to be included and further analyzed in the study.

The patients were initially classified in small plaque or large plaque group according to clinical criteria. For the retrospective group we used the clinical descriptions from the archived charts of each patient. We selected from archived histopathological reports several data including: initial diagnose, biopsy site, number of biopsies, age at presentation, symptoms where available.

If the lesions were located on the trunk and extremities and their size measured less than 5 cm in diameter, the patient was enrolled in the small plaque parapsoriasis group.

Digitate variant is a form of SPP that consists of fingerlike patches following the dermatomes, most frequently displayed on the lateral thorax and abdomen, (Figure 1).

The lesions greater than 6 cm in diameter and located on the proximal extremities and the trunk were classified as large plaque parapsoriasis (Figure 2).

In the group studied, the ratio between SPP and LPP was 3:2.

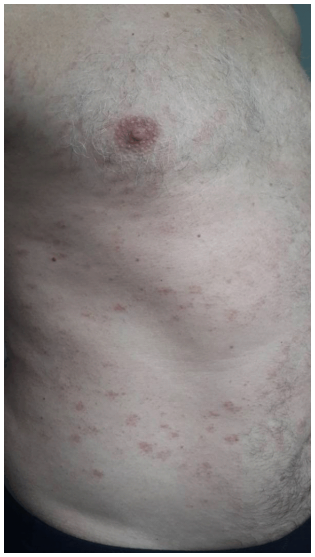

Figure 1 – ***Small plaque parapsoriasis, digitate dermatosis variant: "fingerprint" well-circumscribed patches on the flank, with slightly scaly surface and pink colour.***

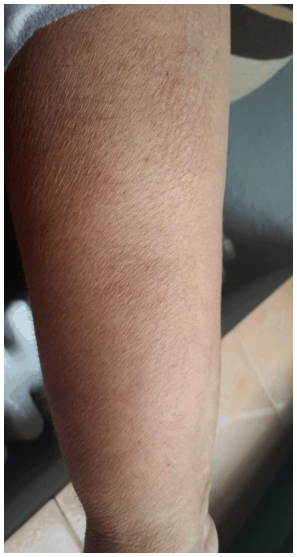

Figure 2 – ***Large plaque parapsoriasis: wrinkled forearm with tissue paper appearance and flaky thin scales.***

The number of cases, age and gender distribution for both, small plaque and large plaque parapsoriasis, are listed below in the Tables 1 and 2.

Table 1 – ***Gender distribution of parapsoriasis cases in the retrospective study***

Diagnosis	Gender		No. of cases
	Males	*Females*	
SPP	25	8	33
LPP	16	6	22
Total	41	14	55

SPP: Small plaque parapsoriasis; LPP: Large plaque parapsoriasis.

Table 2 – ***Age distribution of parapsoriasis cases in the retrospective study***

Diagnosis	Age [years]							No. of cases
	20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*	
SPP	1	3	7	10	8	3	1	33
LPP	0	1	1	7	9	3	1	22
Total	1	4	8	17	17	6	2	55

SPP: Small plaque parapsoriasis; LPP: Large plaque parapsoriasis.

In the studied group, the male female ratio was 3:1, with a clear male predominance. In the age distribution chart, it is highlighted that parapsoriasis, even if a long-standing condition, is a disease related to aging, most of our patients being diagnosed in the fifth or sixth decade of life. Only one case of small plaque parapsoriasis that we noted was in her twenties.

On the HE slides, our pathologists evaluated several characteristics proposed by Massone *et al.* for the differential diagnosis between large plaque parapsoriasis and early stage of mycosis fungoides [11].

Supplementary, our pathologists completed the analysis with three additional morphological criteria, which we considered necessary to be mentioned: presence of parakeratosis at epidermal level, the disposition of infiltrate around adnexal structures (pilosebaceous unit, sweat glands) and the presence of eosinophils in the dermal infiltrate, usually composed of lymphocytes and histiocytes.

In small plaque parapsoriasis, marked spongiosis is not a recognized feature. Thereby, and because we want to use the same characteristics for both entities, small plaque parapsoriasis and large plaque parapsoriasis, we considered necessary to note spongiosis even if their intensity was mild, and we modified this feature in the table proposed by Massone *et al.* [11].

Moreover, the evaluation of these features was not only in a qualitative manner, but also quantitative. We used a semi-quantitative score with four levels "absent" (-), "mild positive" (+), "moderate positive" (++) and "intense positive" (+++).

In the Tables 3 and 4, we included the histopathological features, which in a certain configuration give the pattern reaction of parapsoriasis. To select these features, we modified those criteria proposed by Massone *et al.* [11].

Table 3 – ***Morphological characteristics of small plaque parapsoriasis cases in the retrospective study***

Feature/Intensity	Absent (No.)	Mild (No.)	Moderate (No.)	Intense (No.)
Epidermis				
Normal epidermis	33	0	0	0
Psoriasiform hyperplasia	32	1	0	0
Irregular hyperplasia	8	21	4	0
Flat and/or atrophic epidermis	25	7	1	0
Spongiosis	22	9	2	0
Necrotic keratinocytes	33	0	0	0
Parakeratosis	31	0	2	0
Hyperpigmentation of basal layer	22	9	2	0
Changes at the dermoepidermal junction				
Focal interface dermatitis	24	9	0	0
Widespread interface dermatitis	32	0	1	0
Epidermotropism				
Single lymphocyte epidermotropism	26	7	0	0
Basilar lymphocytes	27	6	0	0
Pautrier's microabscesses (MAB)	29	4	0	0
"Haloed lymphocytes"	30	3	0	0
Disproportion exocytosis	30	2	1	0
Pagetoid epidermotropism	33	0	0	0
Absence of epidermotropism	0	0	0	0
Atypical lymphocytes				
Only in the epidermis	26	7	0	0
Both in epidermis and dermis	0	0	0	0
Only in the dermis	0	0	0	0
Dermal lymphocytic infiltrate				
Band-like	33	0	0	0
Patchy-lichenoid	31	2	0	0
Superficial perivascular	0	31	2	0
Periadnexal	25	8	0	0
Eosinophils	30	1	2	0

Feature/Intensity	Absent (No.)	Mild (No.)	Moderate (No.)	Intense (No.)
Dermal changes				
Papillary dermal fibrosis, dense collagen bundles	7	17	7	2
Melanophages	32	1	0	0
Purpura	25	8	0	0
Edema of papillary dermis	23	7	3	0

Table 4 – ***Morphological characteristics of large plaque parapsoriasis cases in the retrospective study***

Feature/Intensity	Absent (No.)	Mild (No.)	Moderate (No.)	Intense (No.)
Epidermis				
Normal epidermis	20	2	0	0
Psoriasiform hyperplasia	19	3	0	0
Irregular hyperplasia	6	13	2	1
Flat and/or atrophic epidermis	19	3	0	0
Spongiosis	6	10	6	0
Necrotic keratinocytes	14	8	0	0
Parakeratosis	11	9	2	0
Hyperpigmentation of basal layer	15	7	0	0
Changes at the dermoepidermal junction				
Focal interface dermatitis	5	15	1	1
Widespread interface dermatitis	18	4	0	0
Epidermotropism				
Single lymphocyte epidermotropism	4	16	2	0
Basilar lymphocytes	4	18	0	0
Pautrier's microabscesses (MAB)	7	15	0	0
"Haloed lymphocytes"	3	18	1	0
Disproportion exocytosis	18	4	0	0
Pagetoid epidermotropism	20	2	0	0
Absence of epidermotropism	0	0	0	0
Atypical lymphocytes				
Only in the epidermis	7	15	0	0
Both in epidermis and dermis	16	6	0	0
Only in the dermis	17	5	0	0
Dermal lymphocytic infiltrate				
Band-like	20	1	1	0
Patchy-lichenoid	15	4	3	0
Superficial perivascular	3	15	4	0
Periadnexal	13	7	2	0
Eosinophils	19	2	1	0
Dermal changes				
Papillary dermal fibrosis, dense collagen bundles	6	12	3	1
Melanophages	18	3	0	1
Purpura	12	9	1	0
Edema of papillary dermis	9	10	3	0

In the small plaque parapsoriasis group, the changes on epidermal level were represented predominantly by psoriasiform or irregular hyperplasia. Even so, in a small number of cases the epidermis was flat or atrophic with horizontalization of dermoepidermal junction (Figure 3). The epidermotropism was mild, with only single lymphocyte observed in the epidermis. In 11 cases, we observed hyperpigmentation of the basal layer and, also, spongiosis. The parakeratosis was noted in only two cases.

The changes at the dermoepidermal junction were mild, being only with focal pattern in the most cases of small plaque parapsoriasis studied.

At dermal level, the majority of the small plaque parapsoriasis cases showed a mild perivascular infiltrate. In some cases, this infiltrate extended in the periadnexal area or had patchy-lichenoid aspect. The infiltrate was composed of lymphocytes and histiocytes, but in three cases, we noted the presence of eosinophils. Other features observed were dermal fibrosis (26 cases) and papillary edema (10 cases). Purpura was noticed in eight cases and the presence of melanophages in the papillary dermis one case.

In the large plaque parapsoriasis group, the epidermis was predominantly hyperplastic, and only in three cases, we observed an atrophic epidermis. The spongiosis, necrotic keratinocytes, parakeratosis and hyperpigmentation of the basal layer of the epidermis were more frequently encountered than in small plaque parapsoriasis group (Figure 4).

The changes at dermoepidermal junction were observed in almost all cases, with focal or widespread interface dermatitis (Figure 5).

The epidermotropism was increased (Figure 6).

In the large plague parapsoriasis group, the epidermotropism was represented by the presence in the epidermis, in most cases, of single or basilar lymphocytes. In addition, at epidermal level, we observed "haloed lymphocytes" and early formation of Pautrier's microabscesses.

In most cases of large plague parapsoriasis, the infiltrate had a superficial and periadnexal distribution. In only two cases, the infiltrate had a band-like distribution and in seven cases was patchy lichenoid.

Like in small plaque parapsoriasis group, the infiltrate was composed of lymphocytes and histiocytes, but in three cases, we observed the presence of eosinophils.

At dermal level, the majority cases of large plaque parapsoriasis presented papillary fibrosis (16 cases) and edema of papillary dermis (13 cases). Purpura was observed in 10 cases and the presence of melanophages in only three cases.

Discussion

Even after 100 years since parapsoriasis was first described, there is no consensus referring to the diseases of the parapsoriasis group. In the present study, we included only those patients with lesions consistent with the description of small and large plaque parapsoriasis. Probably the changes in the terminology of parapsoriasis were caused by the interest to determine whether any of the entities included in this group progress to cutaneous lymphomas [12, 13].

Parapsoriasis is a rare disorder and its epidemiology is unknown. We did not find any epidemiological data about small and large plaque parapsoriasis took separately. As group, parapsoriasis is more common in middle aged and older patients, the peak incidence being in the fifth decade of life [13]. In our study, for entire group, most patients were diagnosed in the fifth and sixth decade of life (34/55), with 17 cases for each decade. If counted separately, the peak incidence for small plaque parapsoriasis patients was in the fifth decade and for large

plaque parapsoriasis in the sixth decade, with 10 and respectively nine cases. Even if a chronic condition, parapsoriasis is a disease related to aging, only one case in our group being diagnosed in her twenties.

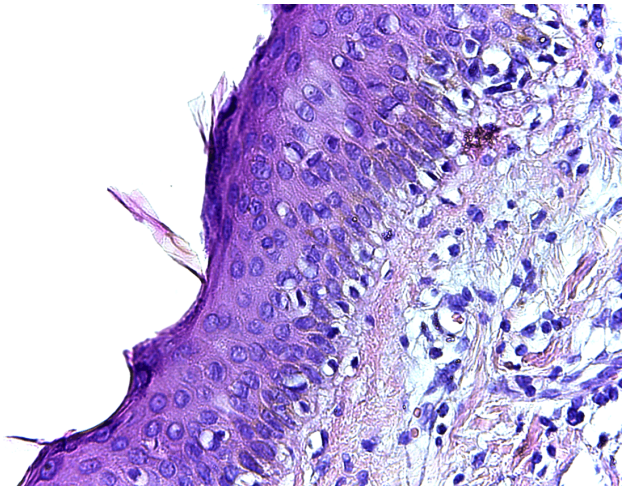

Figure 3 –*Small plaque parapsoriasis: single intraepidermal lymphocyte, hyperpigmentation of basal layer of the epidermis and horizontalization of dermo-epidermal junction (HE staining, 200×).*

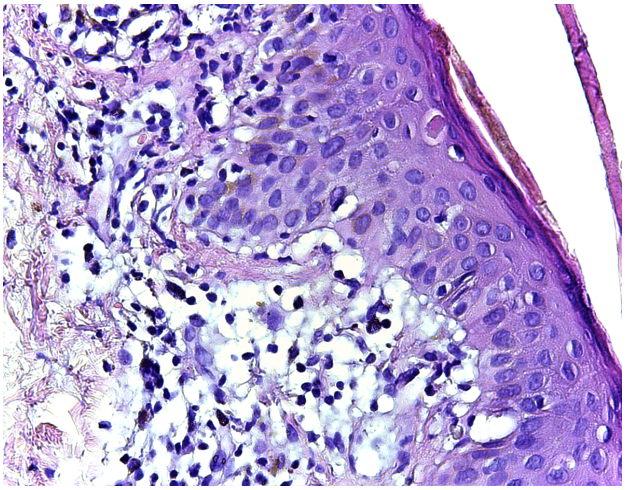

Figure 4 – *Large plaque parapsoriasis: interface dermatitis, single intraepidermal lymphocytes, hyperpigmentation of basal layer of the epidermis and necrotic keratinocytes (HE staining, 200×).*

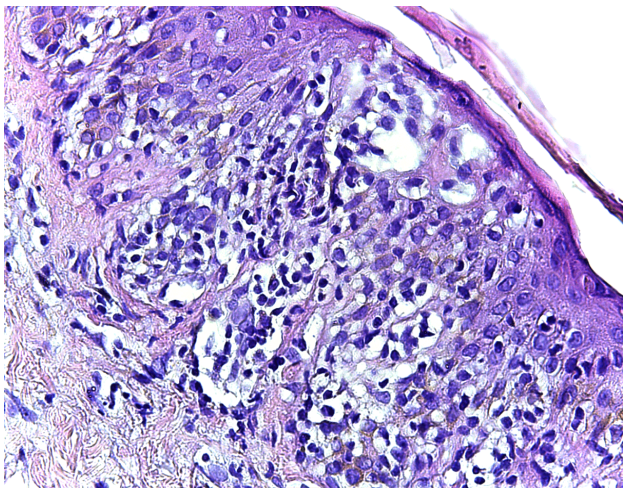

Figure 5 – *Large plaque parapsoriasis: intense interface dermatitis with early phase of microabscess formation (HE staining, 200×).*

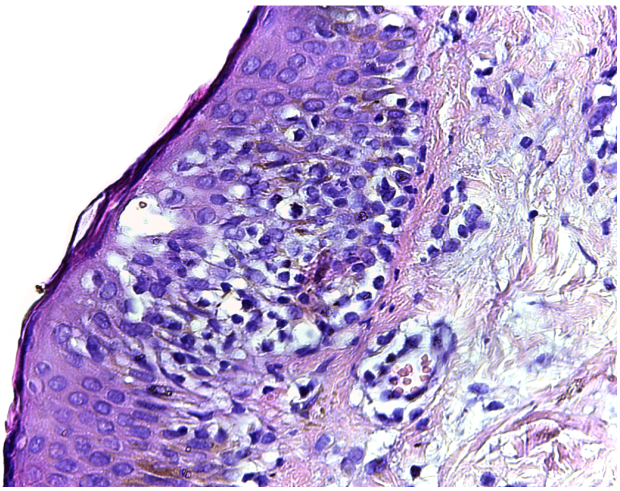

Figure 6 – *Large plaque parapsoriasis: marked epidermotropism of lesional lymphocytes and hyperpigmentation of basal layer of the epidermis (HE staining, 200×).*

As cited in literature, in the group studied, the male patients were predominant, with male female ratio 3:1, for both groups, small and large plaque parapsoriasis [13].

In the group studied, the ratio between SPP and LPP was 3:2. It is important to highlight that all the patients diagnosed on the clinical grounds with parapsoriasis in the period mentioned were enrolled in the study, without any other selection.

The etiology and pathogenesis of parapsoriasis are not known. Both are considered to be cutaneous T-cell lymphoproliferative disorders ranging from chronic dermatitis to lymphoma. Some authors demonstrated the presence of human herpes virus type 8 in 87% of cases of large plaque parapsoriasis, but the significance of this finding is still unclear [14].

Clinically, parapsoriasis represents a group of cutaneous disorders that shows variable aspects somehow resembling to psoriasis, how is reflecting by its name.

Clinical aspect for small plaque parapsoriasis comprises round, erythematous macules, with diameter less than 5 cm, slightly scaly, distributed on the trunk and extremities. The lesions are not atrophic, nor indurated. Another two presentations are included in this category: digitate dermatoses (with palisaded, elongated lesions) and xanthoerythrodermia perstans (same aspect as in digitate dermatosis, but yellow in color) [2, 15]. We diagnosed two cases of digitate dermatoses, the rest being the classical type.

In large plaque parapsoriasis, the lesions are bigger in diameter, frequent more than 10 cm and characterized usually by an atrophic appearance. Plaques, erythematous or brown in color, accompany in most cases the macules. The lesions are distributed on buttocks, thighs, and flexure part of extremities. In women, skin from the breast can be affected [2, 16]. Because of the longstanding manifestation, hyperpigmentation can occur. Some authors described a hypopigmented variant that should be included in this category [17]. Retiform parapsoriasis is a subtype that shows widespread lesions with net-like pattern composed

by small flat papules which coalescence [2]. In our study, on clinical grounds, all the cases of large plaque parapsoriasis were of classical type.

As cited in the literature, the histological aspects of small plaque parapsoriasis are not pathognomonic [2].

At epidermal level, the literature notes that all cases of small plaque parapsoriasis have a hyperplastic epithelium. In the majority of cases, we observed a hyperplastic epidermis, with moderate acanthosis resulting in a psoriasiform or irregular hyperplasia (25/33). However, even if the clinical aspect was of small plaque parapsoriasis, at nine patients we observed an atrophic epidermis, in one case the atrophy being moderate. Interesting was the histological aspect in a 57-year-old man, we noticed areas of irregular hyperplasia admixed with those of atrophy. It is well known that most of the authors consider that small plaque parapsoriasis is a condition with no malignant potential. Even if in the literature, we found only sparse data about the transformation of small plaque parapsoriasis in large plaque parapsoriasis, or even in mycosis fungoides [18, 19], we observed that rare cases of small plaque parapsoriasis have the possibility to evolve to the malignant counterpart. The presence of epidermal atrophy on biopsy specimen at patients with otherwise unequivocal clinical aspect of small plaque parapsoriasis could be a sign of disease progression.

At epidermal level, in some cases of small plaque parapsoriasis could be present spongiosis, focal hyperkeratosis with parakeratosis, and exocytosis, but these findings are non-specific and their intensity is mild. From all these, at our patients we identified only spongiosis, but in an important number of cases, 30%. In addition, even if not cited in the literature, we considered significant to note that hyperpigmentation of basal layer of epidermis appeared in 30% of cases.

At dermoepidermal junction, there are no considerable changes accepted by authors to appear in small plaque parapsoriasis. In contrary, we observed focal interface dermatitis present in 27% (9/33) of cases. Moreover, in one case the interface dermatitis was widespread and with moderate intensity.

Interesting that all cases with focal interface dermatitis showed an irregular hyperplastic epithelium except one, in which the epidermis was atrophic. The case with widespread dermoepidermal junction changes was correlated with moderate atrophy of the epidermis. Thereby, we did not find any significant correlation between epithelium aspect and interface dermatitis.

The presence of epidermotropism, atypical lymphocytes and Pautrier's microabscesses are not recognized features of small plaque parapsoriasis, but in 21% (7/33) of cases, we identified the presence of epidermotropism. From these, in four cases the epidermis was atrophic, but showed no interface dermatitis. The presence of lymphocytes in the epidermis is not a normal characteristic. Thereby, even if the lymphocytes looked bland, the only presence of "haloed lymphocytes" was considered by us as atypical and was noted in all seven cases. Moreover, in four of these cases, we observed Pautrier's microabscesses in the epidermis. Because all these cases had typically lesions for small plaque parapsoriasis, we could not reclassified them in large plaque parapsoriasis group only on histopathological grounds, but we considered these cases with high-risk of malignant transformation and suggested regularly checkup.

In the majority of cases (31/33), we observed dermal mild lymphocytic infiltrate with perivascular distribution. In the rest of two cases, the intensity of perivascular infiltrate was moderate. In the literature, it is cited that in small plaque parapsoriasis can be identified scant lymphocytic infiltrate with perivascular distribution. Instead of this, in eight cases the infiltrated extended in the deep dermis and had a periadnexal distribution also. In two cases, the lymphocytic infiltrate was patchy-lichenoid.

Classically the components of perivascular infiltrate are considered lymphocytes and few histiocytes. In three cases, we identified eosinophils in the perivascular infiltrate, with moderate intensity in one of them.

At dermal level, rarely fibrosis, melanophages, purpura and edema of papillary dermis are present in small plague parapsoriasis. Contrary, we found fibrosis in 26 (79%) cases. Moreover, even if in the majority (17) of the cases, the intensity was mild, in the rest of seven cases, the fibrosis was moderate and prominent in two. This feature was associated with edema of papillary dermis in 10 cases, purpura in eight and presence of melanophages in one.

The histopathological picture in large plaque parapsoriasis varies. It can look similarly to small plaque parapsoriasis [2] or, if the lesion is more atrophic, tend to be superposed on that of early stage mycosis fungoides [13]. At our patients, the aspect of epidermis varied a lot from case to case and from the aspect cited in the literature. We diagnosed cases of large plaque parapsoriasis with normal (2/22), hyperplastic (19/22) and atrophic epidermis (3/22). In two cases, the epidermis showed different aspects from zone to zone (hyperplastic epithelium alternated with atrophic areas). Even if in the literature it is highlighted that large plaque parapsoriasis goes with atrophy of the epidermis, in our group most of the patients showed a hyperplastic epithelium with mild psoriasiform hyperplasia in two cases and irregular hyperplasia in 16 cases. The literature describes that in atrophic lesions of large plaque parapsoriasis, the epidermis is composed of three or four layers of squamous cells and no rete ridges are observed [2]. We believe that only those cases with atrophic epithelium will further develop malignant lesion and should be carefully checkup.

The spongiosis was present in 16 cases of large plaque parapsoriasis.

A feature that we did not identify it at small plaque parapsoriasis patients was necrosis of keratinocytes. The eosinophilic necrotic keratinocytes were present at eight cases of large plaque parapsoriasis. Thereby we believe that, if diagnosed, can be a clue of large plaque parapsoriasis.

In our study, parakeratosis was present in 50% of cases of large plaque parapsoriasis.

Even if this disease is a longstanding condition, we observed hyperpigmentation of basal layer in fewer cases than in small plaque parapsoriasis.

In the dermis, the infiltrate is disposed in band or patchy lichenoid, being composed of lymphocytes and histiocytes. Usually, but not always, the infiltrate cells show atypia [2]. Like in small plaque parapsoriasis, in

our study, the infiltrate showed predominant a perivascular disposition (19/22). Also, it is true that we found more cases with band-like infiltrate (two cases of large plaque parapsoriasis compared with none case of small plaque parapsoriasis) and with patchy lichenoid infiltrate (seven cases of large plaque parapsoriasis compared with two cases of small plaque parapsoriasis). Thereby, we suggest that if noted in small plaque parapsoriasis patients, these features can be considered risk factors for further transformation in large plaque parapsoriasis.

The epidermotropism is more prominent than in small plaque parapsoriasis, the passage of lymphocytes through basal cell layer disorganizes the dermoepidermal junction [2]. In our patients, we identified the same aspect, the epidermotropism being diagnosed in all cases of large plaque parapsoriasis.

Moreover, in the epidermis, the lymphocytes can be seen single or in small groups, forming Pautrier's microabscesses. In addition, the lymphocytes are surrounded by a clear space and show cytological atypia, being called "haloed lymphocytes" and considered atypical [2]. In 68% of cases, we identified Pautrier's microabscesses and "haloed lymphocytes" in 86%. The atypical lymphocytes were found in all cases, being distributed only in epidermis (15/22), only in dermis (5/22) or both, in dermis and epidermis (6/22).

In the dermis, are present melanophages, because of the pigment incontinence, purpura, edema and fibrosis of the papillary dermis [2, 11]. We found all aspects at large plaque parapsoriasis patients included in study.

The parapsoriasis, even if small plaque or large plaque, respond badly to the treatment. If for small plaque parapsoriasis there are not documented cases that transformed in malignant counterpart, it is clearly accepted that large plaque parapsoriasis is a pre-malignant condition [2]. Dominant T-cell clonality has been demonstrated in many cases of large plaque parapsoriasis, while small plaque parapsoriasis usually shows multiple T-cell clones, which supports a reactive process [20–22].

Conclusions

The histopathological picture of small plaque and large plague parapsoriasis shares many common features. Moreover, it seems that the potential transformation of parapsoriasis in a malignant disease cannot be predicted by any important characteristics found on morphological stained slides. Thereby, the immunohistochemistry studies regarding the CD4/CD8 ratio, the aberrant expression of T-cell antigens and molecular data are helpful in establishing a conclusive diagnosis and are necessary to exclude the diagnosis of early stage lymphoma.

Acknowledgments

This work was supported by the project „From chronic inflammatory dermatoses to cutaneous lymphoma: molecular cytogenetic and gene expression profiling" with number IZERZ0_142305, from the UEFISCDI Romania in collaboration with Romanian Minister of Education, Science, Youth and Sport, "Victor Babeş" University of Medicine and Pharmacy and FNSNF – Swiss National Science Foundation under the auspice of Romanian–Swiss Research Programme (RSRP).

References

[1] Brocq L, *Les parapsoriasis*, Ann Dermatol Syphiligr, 1902, 3:433–468.
[2] Lambert WC, Everett MA, *The nosology of parapsoriasis*, J Am Acad Dermatol, 1981, 5(4):373–395.
[3] Unna PG, Santi, Pollitzer S, *Über die Parakeratosen im allgemeinen und eine neue Form derselben (Parakeratosis variegata)*, Monatschr Prakt Dermatol, 1890, 10:404–412.
[4] Brocq L, *Les érythrodermies pityriasiques en plaques disséminées*, Rev Gen Clin J Pract, 1897, 11:577–590.
[5] Neisser A, *Zur Frage der lichenoiden Eruptionen*, Verhandl Dtsch Dermatol Ges, 1894, 4():495–506.
[6] Jadassohn J, *Ueber ein eigenartiges psoriasiformes und lichenoides Exanthem*, Verhandl Dtsch Dermatol Ges, 1894, 4:524–535.
[7] Juliusberg F, *Ueber die Pityriasis lichenoides chronica (psoriasiform lichenoides Exanthem)*, Arch Dermatol Syph (Wien), 1899, 50:359–374.
[8] Fox TC, Macleod JMH, *On a case of parakeratosis variegata*, Br J Dermatol, 1901, 13:319–346.
[9] Mucha V, *Über einen der Parakeratosis variegata (Unna) bzw. Pityriasis lichenoides chronica (Neisser-Juliusberg) nahestehenden eigentümlichen Fall*, Arch Dermatol Syph (Wien), 1916, 123(4):586–592.
[10] Habermann R, *Über die akut verlaufende nekrotisierende Unterart der Parapsoriasis lichenoides („Pityriasis lichenoides et varioliformis acuta")*, Arch Dermatol Syph (Wien), 1926, 151(1):398.
[11] Massone C, Kodama K, Kerl H, Cerroni L, *Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients*, Am J Surg Pathol, 2005, 29(4):550–560.
[12] Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, Zackheim H, Duvic M, Estrach T, Lamberg S, Wood G, Dummer R, Ranki A, Burg G, Heald P, Pittelkow M, Bernengo MG, Sterry W, Laroche L, Trautinger F, Whittaker S; ISCL/EORTC, *Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)*, Blood, 2007, 110(6):1713–1722.
[13] Ackerman AB, *If small plaque (digitate) parapsoriasis is a cutaneous T-cell lymphoma, even an 'abortive' one, it must be mycosis fungoides!* Arch Dermatol, 1996, 132(5):562–566.
[14] Kreuter A, Bischoff S, Skrygan M, Wieland U, Brockmeyer NH, Stücker M, Altmeyer P, Gambichler T, *High association of human herpesvirus 8 in large-plaque parapsoriasis and mycosis fungoides*, Arch Dermatol, 2008, 144(8):1011–1016.
[15] Lewin J, Latkowski JA, *Digitate dermatosis (small-plaque parapsoriasis)*, Dermatol Online J, 2012, 18(12):3.
[16] Nag F, Ghosh A, Biswas P, Chatterjee G, Biswas S, *Ichthyosiform large plaque parapsoriasis: report of a rare entity*, Indian J Dermatol, 2013, 58(5):385–387.
[17] El-Darouti MA, Fawzy MM, Hegazy RA, Abdel Hay RM, *Hypopigmented parapsoriasis en plaque, a new, overlooked member of the parapsoriasis family: a report of 34 patients and a 7-year experience*, J Am Acad Dermatol, 2012, 67(6): 1182–1188.
[18] Belousova IE, Vanecek T, Samtsov AV, Michal M, Kazakov DV, *A patient with clinicopathologic features of small plaque parapsoriasis presenting later with plaque-stage mycosis fungoides: report of a case and comparative retrospective study of 27 cases of "nonprogressive" small plaque parapsoriasis*, J Am Acad Dermatol, 2008, 59(3):474–482.
[19] Kikuchi A, Naka W, Harada T, Sakuraoka K, Harada R, Nishikawa T, *Parapsoriasis en plaques: its potential for progression to malignant lymphoma*, J Am Acad Dermatol, 1993, 29(3):419–422.
[20] Klemke CD, Dippel E, Dembinski A, Pönitz N, Assaf C, Hummel M, Stein H, Goerdt S, *Clonal T cell receptor gamma-chain gene rearrangement by PCR-based GeneScan analysis in the skin and blood of patients with parapsoriasis and early-stage mycosis fungoides*, J Pathol, 2002, 197(3): 348–354.

[21] Bordignon M, Belloni-Fortina A, Pigozzi B, Saponeri A, Alaibac M, *The role of immunohistochemical analysis in the diagnosis of parapsoriasis*, Acta Histochem, 2011, 113(2): 92–95.

[22] Sarveswari KN, Yesudian P, *The conundrum of parapsoriasis versus patch stage of mycosis fungoides*, Indian J Dermatol Venereol Leprol, 2009, 75(3):229–235.

Corresponding author
Flavia Baderca, Lecturer, MD, PhD, Department of Microscopic Morphology, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timişoara, Romania; Phone +40733–106 101, e-mail: flaviabaderca@yahoo.com

Received: June 18, 2014

Accepted: October 29, 2014