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INVESTIGATIVE REPORT

A Retrospective Study of the Probability of the Evolution of Parapsoriasis en Plaques into Mycosis Fungoides

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Parapsoriasis en plaque has been suggested to be an early manifestation of mycosis fungoides (cutaneous T-cell lymphoma). We explored the disease course of patients with small plaque or large plaque parapsoriasis in a 26-year retrospective cohort analysis of 105 parapsoriasis patients, who were clinically and histopathologically followed up in Helsinki and Tampere University Hospitals. Eventual later cancers of these patients were verified from the Finnish Cancer Registry. In the small plaque parapsoriasis group, 7 patients (10%) and in the large plaque parapsoriasis group 12 patients (35%), developed histologically confirmed mycosis fungoides during a median of 10 and 6 years, respectively. No significant differences were found regarding the risk of developing mycosis fungoides or the tendency to remission in patients treated with or without phototherapy. Our results show that not only large plaque parapsoriasis, but also small plaque parapsoriasis, as currently defined in textbooks, can progress to mycosis fungoides. The benefits of phototherapy are equivocal in parapsoriasis treatment as far as progression to cancer is concerned.
Key words: parapsoriasis; mycosis fungoides; cutaneous T-cell lymphoma; phototherapy; PUVA.

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Mycosis fungoides (MF) is the most common manifestation of primary cutaneous T-cell lymphomas (CTCL) (1). The aetiology and exact steps in the pathogenesis of MF are not well understood. Most patients with MF first present with long-standing reactive inflammatory conditions such as parapsoriasis en plaques (2, 3). The development of CTCL is assumed to require multifactorial stepwise processes with promotional exogenous and endogenous factors (3). Interleukin (IL)-15 and IL-7, produced by keratinocytes, appear to be growth factors for CTCL (4). Currently, we do not have unanimous diagnostic criteria for early MF, and it is possible that at least some patients with parapsoriasis en plaque in fact represent early MF (5, 6).

According to current dermatology textbooks, parapsoriasis en plaques is divided into two clinically different entities: small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP). LPP in particular is often clinically indistinguishable from MF (7, 8). The differential diagnosis of SPP and LPP is usually based both on clinical and histopathological findings, because both diseases have superficial lymphocyte inflammation with various degree of epidermotropism. The diagnosis of MF is based on the atypical features of infiltrating lymphoid cells and the finding of Pautrier microabscesses in the epidermis. However, we do not yet have criteria that would predict which patients with LPP will progress to MF. Also, long-term epidemiological data on parapsoriasis en plaques and MF are quite sparse (9, 10), and to conduct a prospective trial over several decades would be very demanding. Phototherapy (UVB, selective UV and PUVA) is widely used for treating parapsoriasis en plaques and early stage MF (11). PUVA induces complete remission in 78–90% of patients with early MF (stages I–IIa) and the better response rates are seen in patients with thin skin lesions (12). However, it is not known what effect phototherapy treatment has on the prognosis of parapsoriasis.

As yet there have been no studies regarding the frequency of either SPP or LPP developing into histologically confirmed MF and the possible benefit of phototherapy in these patients, therefore we conducted a retrospective study on all patients with a confirmed diagnosis of parapsoriasis en plaques treated in Helsinki and Tampere University Central Hospital areas, representing together a population of 2.5 million inhabitants. Since the development of MF is mostly very slow, a retrospective study was considered informative despite obvious drawbacks.

MATERIALS AND METHODS

Patients

We collected data from all patients diagnosed with parapsoriasis in Helsinki and Tampere University Hospitals during

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the period 1975–2001. The study was approved by the ethics review boards of both hospitals. We have individually examined all medical charts of 105 persons with parapsoriasis. The original clinical descriptions of skin lesions were made by dermatologists working in the aforementioned hospitals. The total follow-up time started from the moment when a skin abnormality (rash) was first mentioned and described in medical charts and ended at the last check-up, or when the MF diagnosis was made (see also histological characteristics). The categorization criteria between SPP (digitate dermatitis or chronic superficial dermatitis) and LPP were based on clinical descriptions from the charts of each patient. If the size of the lesion was $\leqslant 6$ cm and the lesions were located on the trunk and sides as in digitate dermatosis, we categorized the lesions as SPP (8, 13). If the lesions were >6 cm in diameter and located on the hips and thighs, the lesions were classified as LPP. No solitary lesions were detected in either group.

Histological characteristics

One or more biopsy specimens from each patient were histologically analysed by one of two experienced dermatopathologists in both university hospitals, acting as dermatopathology reference laboratories for the country. Histologically, parapsoriasis lesions were divided into two categories as indicated in the current histopathological textbook division between these categories (13). In the 'superficial eczema-like type of inflammation', the characteristic histological features were mild spongiosis and parakeratosis in the epidermis and a sparse infiltration of mature lymphocytes around the superficial capillaries. Some lymphocytes could invade into the epidermis, but no atypical cells were found. In the other type of inflammation, the epidermis was psoriasiform, lichenoid or atrophic. The infiltrates of lymphocytes were usually band-like and more dense than in the eczema-like type. Also, some of the lymphocytes infiltrated diffusely into the epidermis, but typical Pautrier microabscesses were not seen. Some scattered large lymphocytes were seen in the infiltrate. Histologically, this type of inflammation was called 'atypic lymphocyte infiltration', although the nuclear atypia was so sparse that the diagnosis of MF could not be made. After a follow-up period with repeated skin biopsies, the diagnosis of MF was based on the finding of moderate infiltrate of atypical lymphocytes in the upper dermis and Pautrier microabscesses in the epidermis (14). To ensure the authenticity of this study, no re-evaluations of the original histological evaluations were made.

Statistical analysis

To evaluate the disease evolution, the patients were divided into three categories according to their clinical stage at the end of the follow-up time: parapsoriasis, healed (or complete response) parapsoriasis, and MF. The diagnosis of MF was always based on histological examination of a skin biopsy (see above). Phototherapy treatments and parapsoriasis subtypes were compared to this end point. In Finland, we have national guidelines for phototherapy treatment and phototherapy equipment is standardized between Helsinki and Tampere University Hospitals. As an example, the cumulative UVB dose was 17 in erythemal units and 325 mJ/cm^2. In addition to phototherapy, the patients had received only local emollients and corticosteroids for their skin symptoms.

The Kaplan-Meier method and log-rank tests were used to compare the rates and times to develop MF between different phototherapy groups. For comparison of proportions the Fisher-Freeman-Hamilton test was used. Statistical analyses were performed using SPSS for Windows version 11.0 (Chicago, IL, USA) and StatXact 5 (Cytel Software Corp., MA, USA) software packages. p values <0.05 were considered statistically significant. The χ^2 test, t-test and Mann-Whitney's test were used to compare background factors between SPP and LPP.

The Finnish Cancer Registry

As the follow-up time for some patients was short, we wanted to rule out the possibility of late development of MF. We double-checked the information on possible later cancer with the Finnish Cancer Registry, to which all cancer diagnoses are reported by pathologists according to law.

RESULTS

Clinical and histopathological features of parapsoriasis en plaques patients

Our cohort consisted of 105 patients of whom 76 (72%) were men and 29 were women; 69 (66%) of the patients had SPP and 36 (34%) had LPP. The mean age of all patients at diagnosis was 54.6 years. In the SPP group 66% of patients were between ages 41 and 70 years, whereas in the LPP group the ages were more evenly distributed. Regarding the possible predisposing factors, no accumulation of any specific group of profession was found (data available from 72 patients). Only two men had been exposed to chemical solvents and five others were outdoor workers (four men, one woman).

The histopathological examination revealed eczema-like histology in 37 (35%) of all cases while atypical lymphocytic infiltration was present in 68 (65%) of the cases: in SPP, 37 cases had eczema-like histology and 32 cases had atypical lymphocyte infiltration (Table I). An example of lichenoid infiltration in SPP is shown in Fig. 1. In LPP, the numbers were 31 and 5, respectively. In 16% of patients who later developed MF, the initial histological picture was atypical lymphocytic infiltration not yet fulfilling the criteria of MF. However, the initial histological picture was not a statistically predictable factor for the later development of MF.

Table I. *Clinical and histological features of patients with small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP) by gender and histology*

Parameter	SPP (n=69)	LPP (n=36)
Gender		
men	48 (70%)	28 (78%)
women	21 (30%)	8 (22%)
Histology*		
atypical lymphocyte infiltration	37 (54%)	31 (85%)
eczema-like	32 (46%)	5 (15%)

*For definition, see M&M and methods section.

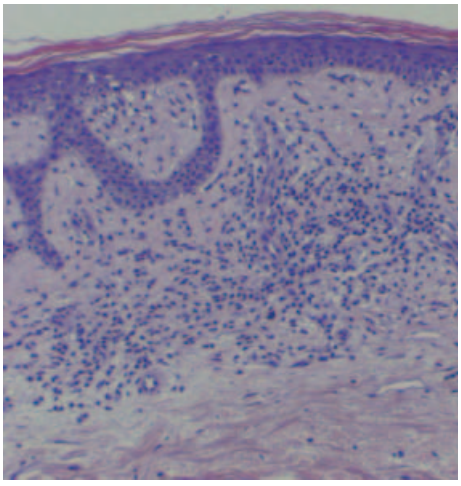

Fig. 1. Lichenoid infiltration in a patient with small plaque parapsoriasis (SPP).

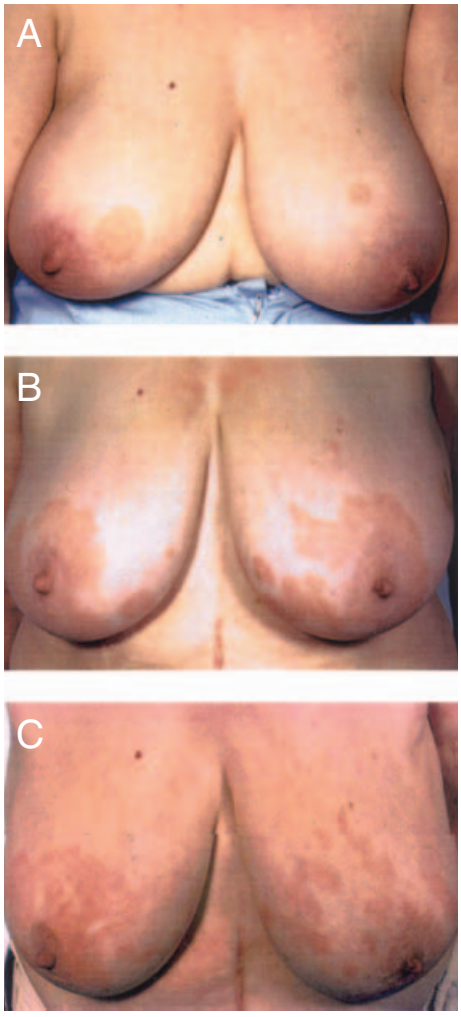

Fig. 2. A 72-year-old woman with large plaque parapsoriasis, (A) year 1989, (B) year 1995, (C) year 1999. Her lesions were followed for 11 years and during that time six biopsies were taken showing no progression [25].

Disease evolution and the development of MF

The mean follow-up time was 123 months (range 1–480), and the mean time from the beginning of the first persisting skin symptoms until the dermatologist-confirmed diagnosis of parapsoriasis was 25 months. For those patients whose follow-up time was short, we double-checked their information with the Finnish Cancer Registry for possible later development of MF; we did not detect any new later cases of MF.

At the end of the follow-up, the skin lesions of 43% of the parapsoriasis patients had healed (complete response), while they were still active in 33%. Most of the healed patients had received some type of phototherapy. Six per cent of the patients had died of unrelated causes. The majority of the patients with SPP had healed, while in the LPP group, equal amounts of patients were healed and 28% had active disease (Table II, Fig. 2). Altogether, in 19 patients, a histologically confirmed MF developed: 7 (10%) in the SPP group and 12 (33%) in the LPP group (Fig. 3 and Table II). The median follow-up time from the first persistent skin symptoms to histologically confirmed MF was 10 years in the SPP group and 6 years in the LPP group. At least one or two repeated biopsies were obtained during this period. There was no significant difference in sex ($p=0.3746$, χ^2 test), age ($p=0.2433$, t-test) or follow-up time ($p=0.0581$, Mann-Whitney test) between SPP and LPP groups and no difference in the development of MF in men versus women ($p=0.7776$, χ^2 test). Two of the five outdoor workers (a sailor and a carpenter) developed MF.

Table II. *Evolution of the skin lesions in 105 patients with parapsoriasis en plaques (irrespective of phototherapy) during a mean follow-up time of 123 months (p=0.0009, Fisher-Freeman-Hamilton)*

Clinical diagnosis	Healed, *n* (%)	Active, *n* (%)	Developed MF, *n** (%)	Median time from first skin symptoms to MF
SPP (*n*=69)	35 (51)	25 (36)	7 (10)	10 years
LPP (*n*=36)	10 (28)	10 (28)	12 (33)	6 years
Total (*n*=105)	45 (43)	35 (33)	19 (18)	…

*In the small plaque parapsoriasis (SPP) group two patients and in the large plaque parapsoriasis (LPP) group four patients died from causes unrelated to mycosis fungoides (MF).

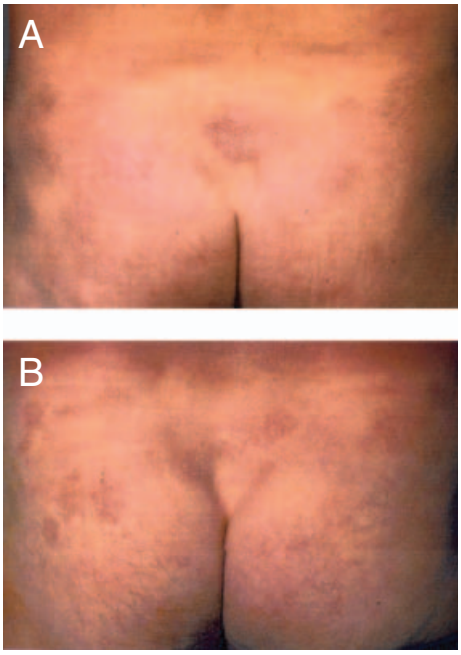

Fig. 3. (A) A 44-year-old man with large plaque parapsoriasis at initial examination (B) 7 years later the lesions had progressed to mycosis fungoides. Note how difficult it is clinically to determine a difference between these two conditions. This patient had chromosomal clone and TCR-clone in both blood and skin [22].

Phototherapy and disease evolution

Altogether, 30% of the patients had received either SUP or UVB or both and 45% had received PUVA therapy (bath or systemic) for their parapsoriasis. Of the patients who had received either SUP or UVB, 16% had also received PUVA treatment; 43 patients (41%) had never received any phototherapy. None of our patients received local electron beam irradiation or systemic therapy (e.g. retinoids, steroids) before a diagnosis of MF.

In patients who had undergone phototherapy (SUP or UVB, but not PUVA), the risk of developing MF was not significantly different compared with parapsoriasis patients not treated with phototherapy (OR 0.36 ; 95% CI 0.10–1.35, $p=0.13$). Only three of those who developed MF had PUVA prior to MF (Table III). One of these patients had reached complete remission after PUVA, but later the disease progressed. Several biopsies from these patients were obtained during the follow-up. Thus, PUVA did not predispose to the development of later malignancy.

In a further analysis taking into account the clinical subtype of parapsoriasis, usage of phototherapy and disease outcome (Table IV), two of 39 (5%) SPP patients who were treated with phototherapy developed MF, while 5 of 30 (16%) cases not treated with phototherapy progressed to MF. In the LPP groups, an equal proportion of MF cases (26%) developed in patients treated with and without phototherapy.

Table III. *The association of different types of phototherapy with disease evolution in small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP) (n=105 in total)*

Phototherapy*	Healed (*n*)	Active SPP or LPP (*n*)	Developed MF (*n*)
None (*n*=43)	16	11	16
SUP (*n*=27)	12	12	3†
SUP+UVB (*n*=3)	1	2	0
UVB (*n*=2)	2	0	0
PUVA (*n*=48)	27	18	3†

*The same patient may have received several modes of phototherapy.
†Same patients. SUP: selective ultra-violet phototherapy.

DISCUSSION

The diagnosis of CTCL is easy to make when the clinical features and the histological characteristics are typical and present at the same time. However, patients may often go for months to years with skin abnormalities before the correct diagnosis is made (15). The most common skin manifestation preceding histologically typical MF is parapsoriasis en plaques (16). One aim of this study was to find out clinical features that could be valuable for predicting a future development of parapsoriasis into MF. No clear hints for occupational or other predisposing factors were found. The majority of patients were men, which is in accordance with our previous study of 319 patients with MF where 57% of patients were men (17). Thus, it is possible that some as yet unidentified genetic or environmental factors that are predominantly active in men may play a role in the evolution of parapsoriasis en plaques into MF.

One possible bias in our study is the difficulty in differentiating LPP from early stage MF. We categorized SPP, LPP and MF according to current dermatology and histopathology textbook criteria. Although the histological picture between SPP and LPP can be sliding, we made the division between these two groups as accurately as possible from the original dermatopathologists' statements. There is no 'gold standard' for precise clinical, histological or ancillary criteria for parapsoriasis en plaques, although the International Society for Cutaneous Lymphoma is working on guidelines on the diagnostic criteria for early CTCL.

Table IV. *The outcome of parapsoriasis en plaque in relation to phototherapy*

Outcome	SPP (*n*=39)	LPP (*n*=23)
Healed	22	7
Active or progressed	16*	12†

This table represents all small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP) patients who received phototherapy. MF, mycosis fungoides.
*Two MF+one exitus. †Six MF+four exitus.

As this was a retrospective study we did not have any other sources for data except medical charts and the histological examinations performed by experienced dermatopathologists at the university hospital reference laboratories. It is always possible that lesions with a few clonal T lymphocytes, not yet morphologically altered, are not recognized by histological or immunohistological examination. Likewise, the association of follicular mucinosis with MF, whether idiopathic or lymphoma-associated, has recently been reappraised (18). The best laboratory method, in addition to detailed cytogenetics, is the demonstration of dominant T-cell clones on the basis of T-cell receptor (TCR) gene re-arrangement. Re-arrangement of the TCR gene shows clonality, and monoclonal expansions are a sign of malignancy (19–21). The TCR re-arrangement studies on parapsoriasis patients have yielded somewhat conflicting results, however. Muche et al. (22) found high percentages of dominant T-cell clones in the blood of patients with SPP. Simon et al. (23) found TCR re-arrangement in half of LPP patients but the TCR status showed no prognostic significance and did not help in differentiating early MF and LPP, as TCR clonality was found in both with a similar frequency. Klemke et al. (24) found monoclonal T-cell infiltrates in almost half of SPP patients, both in blood and skin, while only 2 of 8 LPP patients had such clones in the blood and 3 of 14 in the skin lesions. These findings are in line with the present findings except that in our cohort the proportion of patients evolving to MF was three times higher in the LPP group than in the SPP group.

In our study, patients with LPP were more likely to be treated with phototherapy than patients diagnosed with SPP. This may be a reflection of the fact that LPP resembles early stage MF, both clinically and histologically. However, our final analysis showed no significant difference between UV-treated or non-treated groups regarding the development of MF in either SPP or LPP groups. Our results thus imply that phototherapy is at least not harmful to parapsoriasis patients.

Stachowitz et al. (10) investigated 30 patients with parapsoriasis diagnosis. During the follow-up time ranging from 1 to 23 years, none of the patients developed terminal MF, but in $>30\%$ the diagnosis of MF was made at least once during the course of parapsoriasis. Some studies have speculated that patients with parapsoriasis may have a reactive immune response that finally overcomes their early clonal disease (21).

Taken together, our findings show that not only LPP but also SPP may evolve to MF, although most patients will heal. Therefore, we suggest that the histological guidelines for SPP and LPP and early stages of MF most likely need to be revised in the future with the aid of upcoming molecular cytogenetic data. Regarding therapy the benefits of photo(chemo)therapy in SPP and LPP are not unequivocally shown. Large, prospective studies should be set up to carefully evaluate the benefits and risks of phototherapy in these patient groups.

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