

## SHORT REPORT

# Primary cutaneous lymphoma patients seen at a referral dermatological centre in 1 year: A single-centre observational retrospective cohort study of the diagnoses and staging, comorbidities and associated symptoms, treatment performed and clinical course

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## Abstract

**Importance** Primary cutaneous lymphomas (PCL) are rare diseases, but the indolent course makes their prevalence high. Although there are many treatment options, no hierarchy is recommended.

**Objective** To identify the burden of PCL and describe clinical-pathologic features; associated comorbidities; analyse treatment approaches in real-life and the parameters associated with the achievement of complete response (CR).

**Design, setting and participants** In this study, all the PCL patients (384 patients) consecutively seen at the Dermatologic Clinic of the University of Turin from January 1, 2019 to December 31, 2019, with follow-up updated to December 2020, were included.

**Main outcomes and measures** Subtype of PCL, demographic data, time elapsed between first lesions and diagnosis, associated symptoms, comorbidities, staging at diagnosis, high-grade transformation, blood involvement, stage progression, therapies used and response were assessed.

**Results** 247 were cutaneous T-cell lymphomas (CTCL, 64.3%), 137 cutaneous B-cell lymphomas (CBCL, 35.7%) and the most frequent subtype was MF (48.4%). 62.3% of CTCL patients showed at least one comorbidity, mainly cardiovascular (28.7%), 20.2% show other not cutaneous neoplasms. The main approaches were skin-directed therapies (topical steroids 65.6%; phototherapy 50.2%). 39.3% patients achieved a CR during the disease course. Pruritus, the presence of comorbidities and high-grade transformation were factors associated with failure to achieve CR, whereas stage IA of MF was associated with greater achievement of CR.

**Conclusions and relevance** The Th2 cytokine related development of pruritus could justify increased resistance to treatment, while the presence of associated comorbidities could reduce treatment options as well as treatment compliance.

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## Conflict of interest

None.

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None.

## Introduction

Primary-cutaneous lymphomas (PCL), which include cutaneous T-cell lymphomas (CTCL, 75%–80% of PCL) and cutaneous B-cell lymphomas (CBCL, 20%–25%)<sup>1–2</sup> are rare diseases primarily

originating into the skin. In 2018 in France a PCL incidence of 0.96/100 000 was found.<sup>3</sup> A study on Dutch population reported an incidence of Mycosis fungoides (MF) in 0.19 and 0.46/100 000 persons in 2000 and 2020, respectively.<sup>4</sup> A recent analysis showed an incidence rate of CTCL of 1.02/100 000.<sup>5</sup> However, as MF as well as other PCL subtypes<sup>1,2,6,7</sup> show mainly an indolent disease course, the burden of patients in follow-up can

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be relatively high. Moreover, PCL patients are often elderly, with comorbidities and quality of life impairment reporting pruritus, the most bothersome symptoms, pain and low self-esteem.<sup>8</sup>

The objectives of our studies were: identify the burden of PCL and describe clinical-pathologic features; associated comorbidities; analyse treatment approaches in real-life and parameters associated with the achievement of complete response (CR).

### Patients and methods

#### Patient inclusion

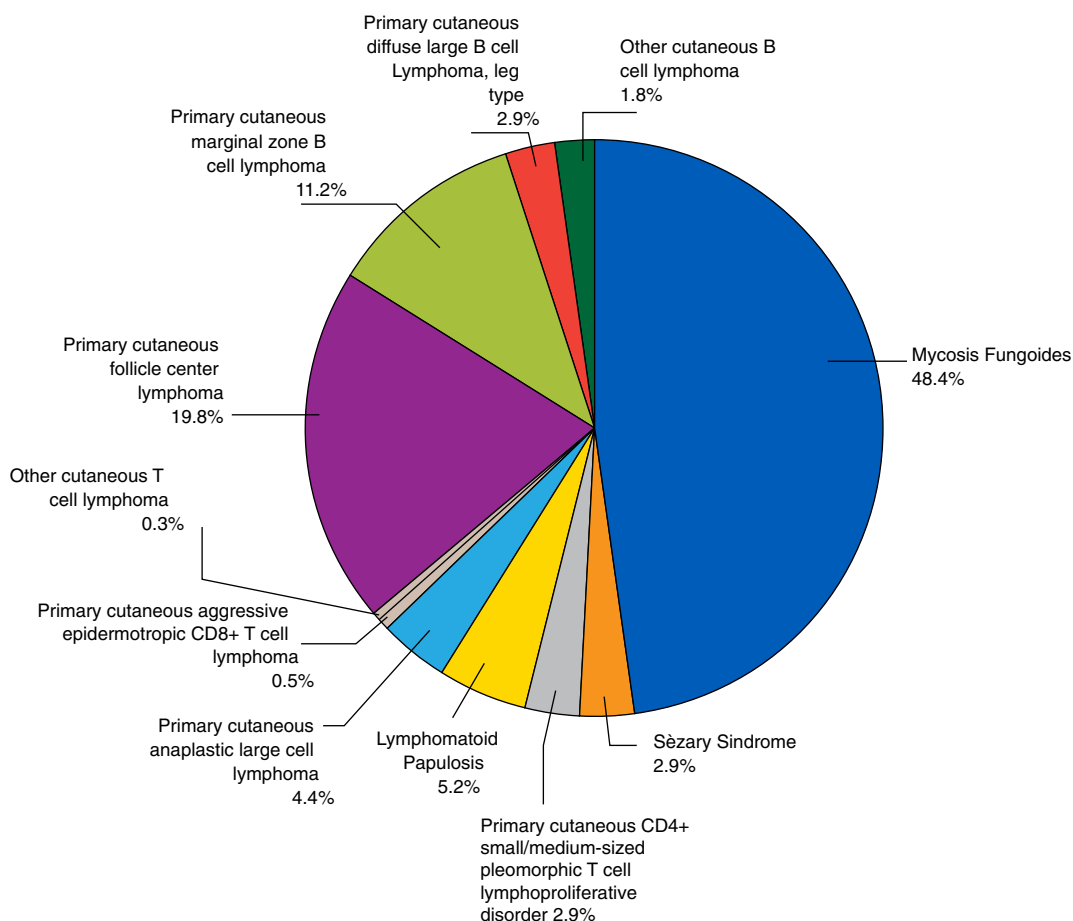
This is an observational retrospective cohort study, in which all the patients with a confirmed PCL clinical-pathologic diagnosis seen at the Dermatologic Clinic of the University of Turin, a third-level centre regional reference for this disease, in the period between 1<sup>st</sup> January 2019 and 31<sup>st</sup> December 2019, were included. A total of 384 patients were collected through the

hospital operating system. Follow-up data were updated for these patients up to December 2020. Both patients with a previous diagnosis of PCL followed-up at the Clinic and patients with the first diagnosis made in that period were included in the study. We focused on CTCL patients.

The following parameters were recorded for CTCL patients: demographic data, age at onset of lesions, time elapsed between first lesions and diagnosis, associated pruritus recorded as present/absent, comorbidities obtained by analysing the medical history present in the patients' medical records, staging at diagnosis, high-grade transformation, blood involvement, stage progression, therapies used and response. The B-score was graded according to the new EORTC indications.<sup>9</sup>

#### Statistical analysis

Continuous variables with normal distribution were expressed as mean and compared by Student T-Test, non-normal



**Figure 1** Distribution of diagnosis of CTCL and CBCL. CTCL, Cutaneous T-cell lymphoma; CTBL, Cutaneous B-cell lymphoma.

distribution was expressed as median and compared by Mann-Whitney-U test.

Categorical variables were expressed as number and percentage and compared using the Chi-square test. A *P*-value <0.05 was considered significant. 95% confidence intervals were calculated.

Statistical analyses were performed using SPSS 25.0 software (IBM, Armonk, NY, USA), GraphPad prism 4 (La Jolla, CA, USA) and Microsoft Excel (MICROSOFT CORPORATION).

## Results

### PCL subtypes

Figure 1 shows the distribution of the different PCL subtypes: 247 were CTCL (64.3%) and 137 CBCL (35.7%). The most frequent subtype was MF (48.4% of all PCL), followed by primary follicle lymphoma (19.8%), primary marginal lymphoma (11.2%), lymphomatoid papulosis (5.2%) and primary cutaneous anaplastic large lymphoma (4.4%). Sézary syndrome (SS) accounted for 2.9% of patients, small- and medium-cell lymphoproliferative disorder for 2.9% and CD8+ epidermotropic T-cell lymphoma for 0.5%.

As to CTCL, among a total of 247 patients, 95 were males (38.5%) and 152 females (61.5%), with a ratio of 1:0.6. 187 patients have MF, of these 110 patients are male (58.8%) and 77 patients are female (41.2%). The median age at diagnosis was 58 (44.5–67) years, the median time between onset and diagnosis was 13.5 months (4–38.5). Pruritus was reported by 65 of 247 patients (26.3%). Patients were followed for a median of 5.0 (3.0–9.0) years.

### MF/SS disease stages and outcome

The stage at diagnosis of the 197 MF/SS patients was most frequently IA (53.8%), followed by IB (29.4%), IIB (6.1%), IIA (3%), IVA1 (3%), IIIA-IIIIB (1.5%). Flow-cytometry data were available at diagnosis in 105 patients, B0 was found in 69 (65.7%), B1 in 26 (24.8%) and B2 in 10 (9.5%).

The progression at any stage occurred in 29 patients (14.7%), while at advanced stage occurred in 17 patients (8.6%). High-grade transformation (large cell) was recorded in 8 patients (4.1%).

### Associated comorbidities

A total of 154 out of 247 CTCL patients (62.3%) showed at least one comorbidity (Table 1). The main comorbidities were cardiovascular (28.7%), dermatologic (23.9%) and endocrinologic (15.4%). Dermatologic comorbidities were more frequently psoriasis (19 patients), atopic dermatitis (3), rosacea (3), seborrheic dermatitis (2), bullous pemphigoid (2). Primary malignant skin cancers were basal cell carcinoma in 15 (39.5%) and melanoma in 11 patients (28.9%). History of internal cancer was present in 50 patients (20.2%), the most reported was prostate cancer in 11 cases (22.0%).

### Treatment approaches (Fig. 2)

Skin-Directed therapies represent the most frequent therapeutic approaches (medium and high potency topical steroids 65.6%; phototherapy 50.2%). Oral retinoids were the most used systemic treatment (bexarotene 14.6%; other retinoids 17.8%). Chemotherapy was given to 15 patients. New drugs like brentuximab-vedotin and mogamulizumab were used, respectively, in 8 and 1 patient. A total of 149 patients (60.3%) received a second treatment line, 112 a third, 83 a fourth and 59 a fifth line.

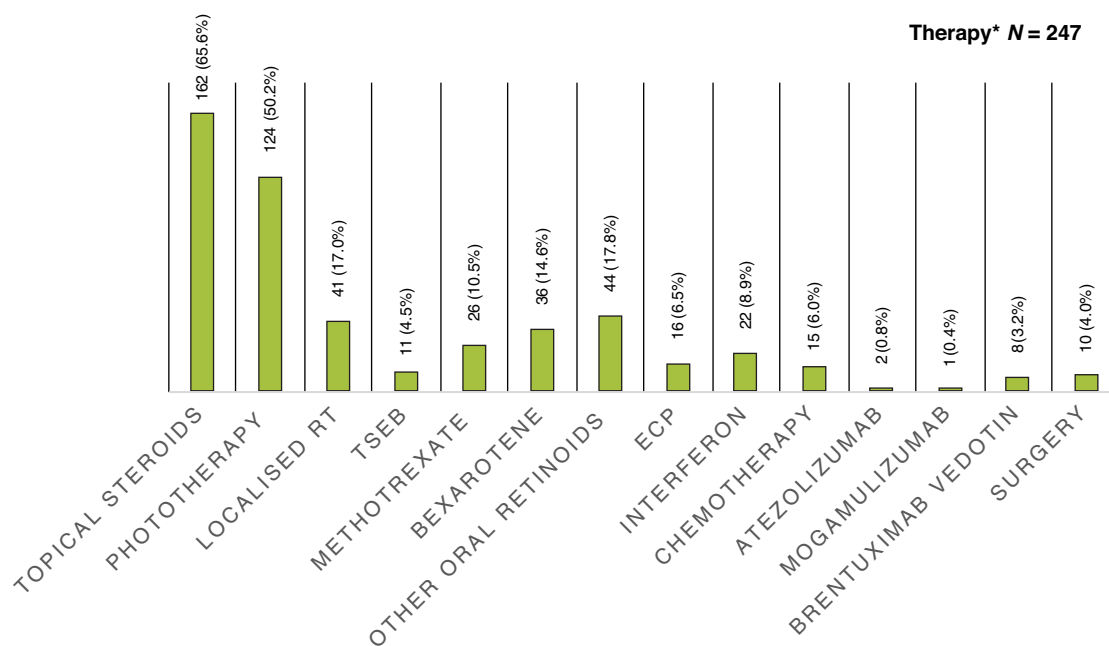
### Parameters associated with complete response

A total of 97 out of 247 (39.3%) patients achieved a CR during the disease course (Table 2). Pruritus was significantly associated with failure to achieve CR, as it was present in 38.1% of patients who did not achieve CR compared to 19.3% in complete

**Table 1** Comorbidities, other dermatologic neoplasm and other non-dermatologic neoplasm

Comorbidities	154 (62.3%)
Cardiovascular	71 (28.7)
Pneumologic	12 (4.9)
Dermatologic	59 (23.9)
Nephrologic	6 (2.4)
Immunologic	5 (2.0)
Rheumatologic	5 (2.0)
Allergologic	13 (5.3)
Gynaecologic	11 (4.5)
Hematologic	9 (3.6)
Gastroenterologic	32 (13.0)
Orthopaedic	14 (5.7)
Endocrinologic	38 (15.4)
Neurologic	20 (8.1)
Urological	26 (10.5)
<b>Another dermatologic cancer</b>	<b>38 (15.4)</b>
BCC	15 (39.5)
SCC	4 (10.5)
KA and others	6 (15.7)
Melanoma	11 (28.9)
<b>Another non-dermatologic cancer</b>	<b>50 (20.2)</b>
Lung	2 (4)
Prostate	11 (22)
Colon/rectum	4 (8)
Oesophagus	2 (4)
Bladder	4 (8)
Testis	2 (4)
Breast	4 (8)
Leukaemia/Lymphoma	9 (18)
Multiple Myeloma/MGUS	5 (10)
Uterus	2 (4)
Thyroid	1 (2)
Others	4 (8)

BCC, Basal cell carcinoma; KA, Actinic keratosis; MGUS, Monoclonal gammopathy of undetermined significance; SCC, Squamous cell carcinoma.



**Figure 2** Analysis of treatments performed. \*Data refer to all the treatment lines performed. ECP, Extracorporeal Photochemotherapy; RT, Radiotherapy; TSEB, Total Skin Electron Beam.

**Table 2** General population characteristics, symptoms, comorbidities and stage: analysis of achievement of CR

General features and comorbidity	Complete remission not achieved N = 97	Complete remission achieved N = 150	P-value
<b>T lymphomas</b>			
Sex			0.25
Male	33 (34)	62 (41.8)	
Female	64 (66)	88 (58.7)	
Age (years)	70 (60–79)	67 (55–73.25)	<b>0.05</b>
Age at diagnosis (years)	56.9 ± 16.1	55.3 ± 13.8	0.16
Age at lesion onset (years)	53.9 ± 16.9	55.7 ± 14.1	0.08
Time between onset of lesions and diagnosis (years)	16 (5–63.5)	12 (3.75–32.75)	0.25
Itching	37 (38.1)	29 (19.3)	<b>0.001</b>
<b>Any comorbidities</b>	69 (71.1)	85 (56.7)	<b>0.022</b>
<b>Another non-dermatologic cancer</b>	21 (21.6)	29 (19.3)	0.65
Mycosis Fungoides	72 (74.2)	114 (76.0)	0.55
IA	30 (37.9)	73 (61.9)	<b>0.009</b>
IB	25 (31.6)	33 (27.9)	0.96
IIA	5 (6.3)	1 (0.8)	0.04
IIB	7 (8.8)	5 (4.2)	0.26
IIIA	1 (1.3)	1 (0.8)	0.84
IIIB	1 (1.3)	0	-
IVA	5 (6.3)	1 (0.8)	0.04
High-grade transformation (large cell)	7 (8.8)	1 (0.8)	<b>&lt;0.001</b>

Bold values are statistically significant.

responders ( $P = 0.001$ ). The presence of comorbidities ( $P = 0.022$ ) and high-grade transformation ( $P < 0.001$ ) were also associated to lower CR rates. Stage IA of MF ( $P = 0.009$ ) was characterized by a significantly higher CR rate.

### Discussion

Our study allowed us to identify the burden of PCL patients and to characterize the clinical-pathologic features and treatment performed from a real world perspective of a referral centre, with

a specific focus on CTCL, although with the limitation of the retrospective nature of the study resulted in the lack of comprehensive data collection, which could partially affect our results.

The choice to collect patients' data in the year 2019 was made in order to avoid possible influence of SARS-CoV-2 infection in the accesses at our service. At the epidemic outbreak, patients with advanced pictures were seen regularly, long-stable low stages had their visits postponed for a year, new diagnoses of any stage were seen regularly. No significant diagnostic delays or impairments to our patients' health were observed.

Our data showed that even if PCL are rare diseases, the indolent course makes prevalence high, thus follow-up are needed by many patients. A significant part of these patients (62.3%) show internal comorbidities mainly cardiovascular and 20.2% other not cutaneous neoplasms. Patient receive multiple treatment lines. 39.3% reached CR, which is significantly less frequently observed in patients with pruritus and comorbidities.

A greater risk of arterial hypertension, congestive heart disease and hyperlipidaemia was previously reported for CTCL, even if the reasons for this association are not well understood.<sup>10</sup> A statistically significant association has been demonstrated with lymphomas, bladder cancer and melanoma, as reported in our study.<sup>11</sup>

Despite the numerous treatment available,<sup>9</sup> even in early-phase MF, responses are often short-lived and CR are rare.<sup>6</sup> With the limits of the heterogeneity of diseases considered as well as treatment performed, our results identified two parameters associated with lower CR rate: comorbidities and pruritus. Pruritus is a symptom often associated with CTCL, particularly in erythrodermic and folliculotropic MF, and SS. A recent study showed that about 60% of patients with MF report itching as a symptom, one third of whom describe it as severe.<sup>12</sup> In our retrospective analysis, 26.3% of patients reported pruritus and a poorer response was demonstrated ( $P = 0.001$ ). The development of pruritus is characterized by a complex interaction between lymphocytes, keratinocytes and neuronal cells, in which the upregulation of the Th2 cytokine pathway plays a major role.<sup>13</sup> Pruritus could be, therefore, associated with a less effective host immune response and thus a potentially more aggressive disease course characterized by a dominance of the Th2 phenotype<sup>14</sup> and greater resistance to treatment. As to comorbidities, possible explanations could be represented by the reduction in the possibility of treatment options as well as reduced compliance to the treatment.

Pruritus and comorbidities could represent additional clinical parameters to be considered as potential predictive factors related to response, also in view of the availability of new treatment options, even if the findings of this study need to be confirmed in multicentre larger patient cohorts.<sup>15</sup>

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## Data availability statement

Data available upon reasonable request.

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