

Primary cutaneous lymphomas: A clinical and histological study of 99 cases in Isfahan, Iran

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Background: Primary cutaneous lymphomas (PCLs) represent a heterogeneous group of T- and B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. The aim of this study was to assess and report the epidemiological characteristics of PCLs in Isfahan, Isfahan Province, Iran — as a main province of Iran. **Materials and Methods:** A total of 99 patients were recruited over a recent 10-year period (2003-2013) with diagnosis of PCLs; the patients were classified according to the The World Health Organization/European Organization for Research and Treatment of Cancer (WHO-EORTC) criteria. Mean and standard deviations (SDs) were used to describe continuous data, numbers, and percentages for categorical data. Statistical significance was defined as $P < 0.05$. **Results:** The patients comprised 45 men and 54 women aged 5-80 years (median 36) at diagnosis. The male-to-female ratio was 1:1.2. Histological examination showed features of primary cutaneous B-cell lymphomas (PCBCLs) in four cases. The mean \pm SD age in primary cutaneous T-cell lymphomas (PCTCLs) and PCBCLs was 37.9 ± 16.5 years and 39.7 ± 9.1 years, respectively ($P = 0.72$). The mean \pm SD latent period between the time of diagnosis and initiation of skin lesions in men and women was 2.3 ± 4.1 years and 5.9 ± 10.1 years, respectively ($P = 0.02$). The most frequent subtypes were mycosis fungoides (MFs) (86.9%) followed by Sézary syndrome (SS) (4%). Five patients died from PCL-related deaths. **Conclusion:** The distinguishing epidemiologic characteristics of PCL in Iran are the absence of a male predominance and a lower age of diagnosis. The study highlights the ethnic or regional variations in the clinicoepidemiological characteristics of PCLs.

Key words: B-cell lymphomas, Iran, mycosis fungoides (MFs), primary cutaneous lymphomas (PCLs), primary cutaneous T-cell lymphomas (PCTCLs), T-cell lymphomas

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INTRODUCTION

Primary cutaneous lymphomas (PCLs) are a group of extranodal non-Hodgkin lymphomas (NHLs), which represent a heterogeneous group of T- and B-cell lymphomas. PCLs present in the skin with no evidence of extracutaneous disease at the time of diagnosis.^[1,2] After the gastrointestinal lymphomas, PCLs are the second most common group of extranodal NHLs with

an estimated annual incidence of 1/100,000.^[1] PCLs must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily, which often have another clinical behavior, a different prognosis, and require a different therapeutic approach.^[2,3]

In contrast to nodal NHLs, most of which are B-cell derived, about 75% of PCLs are T-cell-derived, two-thirds of which may be classified as mycosis fungoides (MFs) and Sézary syndrome (SS),^[3-5] but different distributions have been observed in various parts of the world.^[6]

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The annual incidence of MF in the United States is 4.1 per 1,000,000 person-years.^[3] The incidence in Europe is somewhat less.^[7] The incidence rate of MF in Isfahan in 2007-2008 was 3.91 per 1,000,000 persons.^[8]

Currently, following a consensus meetings of the two organizations, a joint World Health Organization-European Organization for the Research and Treatment of Cancer (WHO-EORTC) classification was developed for the classification of cutaneous lymphomas.^[4,9]

Published data on the relative frequency and large scale epidemiologic studies of the various subtypes of PCLs are limited to European, American, and other developed countries.^[3,10,11] It should be noted that data from developing countries are particularly scarce.^[12,13] Also, the occurrence rates and epidemiologic pattern for PCLs in Asia are considered to be significantly distinct from those in Western countries.^[13-15]

The incidence of PCTCL has risen since 1973, with an annual age-adjusted incidence of 6.4-9.6 cases per 1,000,000 people in the United States.^[5] In Western countries, MF typically affects older individuals with a median age of diagnosis of 55-60 years and a male-to-female ratio of 2:1.1.^[3] However, MF can also be seen in younger populations including children.^[16,17]

Studies of the epidemiological characteristics of PCTCL in Iran are limited to one report that described a group of patients in Tehran (1998-2004).^[18] Thus, the present study aimed to investigate the clinic epidemiological characteristics of PCLs in the Cutaneous Lymphoma Center of Isfahan University of Medical Sciences, which is one of the largest academic referral centers for cutaneous lymphoma of our country.

MATERIALS AND METHODS

Patient selection

We performed a retrospective review of all patients with cutaneous lymphoma at Al-Zahra Hospital over a 10-year period from 2003 to 2013. Al-Zahra Hospital of the Isfahan University of Medical

Sciences is an academic referral center for cutaneous lymphoma in Isfahan, Iran. The patients were classified according to the clinical, histopathological, immunophenotyping, and molecular criteria of the WHO-EORTC.^[4]

Patients with "secondary cutaneous lymphomas," "clonal dermatitis," "cutaneous lymphoid hyperplasia," and cases with poor material or inadequate information were excluded from this study. After excluding, out of 118

patients with cutaneous lymphoma, the remaining 99 cases were analyzed in this study.

Clinical and histopathological classifications

The clinical data analyzed included age at the time of diagnosis, age at the time of initiation of the cutaneous lesion, sex, and status of the disease at the last follow-up examination. Hematoxylin and eosin-stained slides and immunohistochemical stains for basic B-cell and T-cell markers (CD20 and CD3 and/or CD45RO) and additional immunostainings, including CD4, CD8, CD19, CD20, CD21, CD10, CD30, Ki 67, CD5, CD1a, BCL-2 and BCL-6, were histologically evaluated by an expert dermatopathologist. Polymerase chain reaction analyses of T-cell receptor (TCR) rearrangement were reviewed.

Staging

In all the patients, the presence of extracutaneous disease at time of diagnosis were excluded by standard staging procedures. Stage workup (chest radiology, bone marrow biopsy, and computed tomography scan of the chest, abdomen, and pelvis) were obtained by reviewing clinical records. To determine the stage of PCTCL, the tumor-node-metastasis (TNM) system was used.^[19,20] The clinical staging was performed as proposed by Bunn and Lamberg.^[20]

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) version 18 for Windows (IBM Corporation, New York, USA). Mean and standard deviations (SDs) were used to describe continuous data, numbers, and percentages for categorical data. To investigate data distribution, Kolmogorov-Smirnov was used. The independent samples *t*-test was used to test the evaluation of statistical differences between the means of two groups (between age and sex/PCL subtype) and the chi-square was used to analyze categorical data (between sex and staging group). Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics of the 99 patients with PCTCL (95 patients) and PCBCL (4 patients) are summarized in Table 1.

Overall, the age of patients ranged from 5 years to 80 years, with a median of 36 years. The mean \pm SD age in PCTCL and PCBCL was 37.9 ± 16.5 years and 39.7 ± 9.1 years, respectively ($P = 0.72$).

The male-to-female ratio in PCTCL and PCBCL was 1:1.2 and 3:1, respectively [Table 1].

In PCTCL, the most prevalent skin lesions were erythematous scaly patch seen in 51.5% of the patients followed by erythematous plaques in 24.2% of the patients. Plaques were the most prevalent skin lesions in PCBCL (100%) [Table 1].

In PCTCL patients, the mean \pm SD latent period in men and women was 2.3 ± 4.1 and 5.9 ± 10.1 , respectively ($P = 0.02$) [Table 2]. Table 2 shows the patient's age at the time of diagnosis, age at the time of initiation of skin lesions, and latent period with sex distribution [Table 2].

The frequency of subtypes of PCLs according to the WHO-EORTC classification by sex and age are shown in Table 3. The most frequent subtypes of PCLs were MF (86.9%) followed by SS (4%) [Figure 1].

Primary cutaneous CD30+ T-cell lymphoproliferative disorders (PCLPDs) were clinically benign lymphomatoid papulosis (one patient) and primary cutaneous anaplastic large-cell lymphomas (two patients). Also, other rare subtypes of T-cell lymphomas included primary cutaneous natural killer (NK)/T-cell lymphoma, nasal type lymphoma (one patient), and peripheral T-cell lymphoma (one patient) [Table 3].

The early stage of PCTCL was seen in 82 cases (86.4%) and the remaining cases (13.6%) showed an advanced stage. There was no significant correlation between sex and the disease stage in PCTCL ($P = 0.53$).

About 10% of the patients had high level of lactate dehydrogenase. Among PCTCL patients, six cases had acquired ichthyosis. Lymphadenopathy (seven cases), jaundice (five cases), and hepatosplenomegaly (one case) were the extracutaneous manifestations in our patients.

TCR gene rearrangement clonality was seen in nine out of 25 cases.

All patients were treated with one or more treatment modalities, including topical corticosteroid therapy, topical nitrogen mustard, topical BCNU, radio therapy, narrowband (NB)-UVB radiation therapy, psoralen plus ultraviolet light therapy (PUVA) therapy, retinoid-PUVA therapy, interferon-PUVA therapy, and interferon alpha 2a or systemic monochemotherapy/polychemotherapy. Among these treatments topical carmustine (38.5%), NB-UVB (36.5%) and PUVA (26%) were the more common treatment modalities.

In this study, five patients died from lymphoma. PCL-related deaths were most commonly associated with SS (two patients), erythrodermic MF (two patients), and primary cutaneous lymphoblastic lymphoma (one patient).

Table 1: Clinical characteristics of PCTCL and PCBCL in Isfahan, Iran

| Characteristics of PCL | PCTCL | PCBCL |
|--------------------------------|-------------------|------------------|
| Sex | | |
| Male, n (%) | 42 (44.2%) | 3 (75%) |
| Female n (%) | 53 (55.8%) | 1 (25%) |
| Male:female ratio | 1:1.2 | 3:1 |
| Age (years) | | |
| Range | 5-80 | 28-50 |
| Median | 36 | 40.5 |
| Mean (\pm SD [†]) | 37.91 \pm 16.59 | 39.75 \pm 9.10 |
| Clinical Manifestation | | |
| Patch, n (%) | 49 (51.5%) | 0 |
| Plaque, n (%) | 23 (24.25%) | 4 (100%) |
| Other, n (%) | 23 (24.25%) | 0 |
| Total Number of cases (%) | 95 (100%) | 4 (100%) |

[†]SD = Standard deviation

Table 2: Age distribution among male and female patients with PCTCL

| Variable | Mean | Standard deviation | Standard error | P value |
|--------------------------------------------|-------|--------------------|----------------|---------|
| Age at the time of diagnosis | | | | |
| Male | 45.10 | 17.56 | 2.81 | .108 |
| Female | 39.34 | 16.25 | 2.23 | |
| Age at the time of initiation skin lesions | | | | |
| Male | 42.76 | 17.66 | 2.82 | .015 |
| Female | 34.33 | 14.93 | 2.05 | |
| Latent period | | | | |
| Male | 2.31 | 4.15 | 0.67 | .022 |
| Female | 5.94 | 10.18 | 1.39 | |

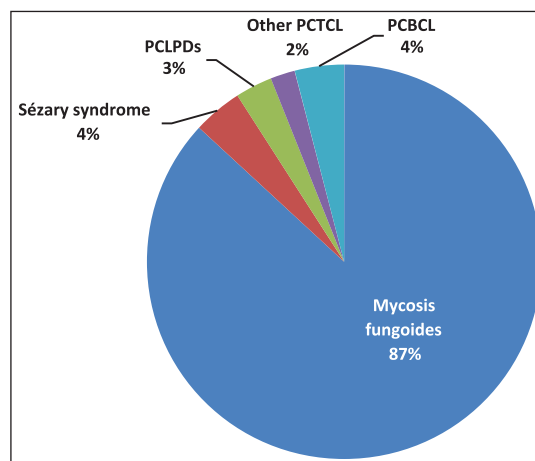


Figure 1: The distribution of patients with PCLs

DISCUSSION

The findings of our study including the sex and age preference of PCLs were different from those reported earlier.^[3-5]

Table 3: Clinical characteristics of patients based on the different clinical variants of PCLs in Isfahan, Iran

| PCL | Classification | N of cases (%) | M | F | Age, year Mean (±SD) |
|------------------|----------------------------------------------------------------------|----------------|----|----|----------------------|
| T-cell (n=95) | Mycosis fungoides | 86 (86.9) | 39 | 47 | 37.4±16.3 |
| | Sézary syndrome | 4 (4) | 2 | 2 | 59.5±15.7 |
| | Primary cutaneous CD30+T-cell lymphoproliferative disorders (PCLPDs) | 3 (3) | 0 | 3 | 27±1.41 |
| | Other rare subtypes of T-cell lymphoma | 2 (2) | 1 | 1 | 31±16.3 |
| B-cell (n=4) | Primary cutaneous follicle center lymphoma | 2 (2) | 2 | 0 | 39±15.5 |
| | Primary cutaneous lymphoblastic lymphoma | 1 (1) | 1 | 0 | 42 |
| | Primary cutaneous marginal zone lymphoma | 1 (1) | 0 | 1 | 39 |
| Total | | 99 (100) | 45 | 54 | 37.9±16.3 |

PCBCL comprises approximately 20-25% of all PCLs.^[3,21] Our study showed a higher frequency of PCTCL (96%) and a lower frequency of PCBCL (4%). The higher percentage of PCTCL in our study may provide a clue to further studies on the etiological factors of PCLs. Racial variations in factors such as human leukocyte antigen (HLA) determinants may play a role in the development of PCTCL.^[6]

There was a higher incidence of primary PCLs and MFs in the fourth to sixth decades. Earlier studies have found that the peak age at presentation of the disease was 55-60 years.^[22,23] Although MF usually affects older adults with a median age of more than 50 years, it was lower in a study in Singapore (33 years),^[24] and a study in Kuwait (35.2 years).^[25] In our series, the mean age of diagnosis in our patients was lower than that reported from the West (between the fourth decade and sixth decade)^[26,27] and Turkey (45.6 years).^[28] It seems that the age of disease presentation in Asian countries is lower, in contrast to studies in the West.

There is a male predominance in almost all of the studies on PCTCLs and MFs with a male-to-female ratio of 1.3:1 to 2:1.^[29,30] These ratios are completely in contrast to the male-to-female ratio in other studies.^[30] Compared to countries in the West, our results showed a different pattern of disease among males and females. The male-to-female ratio is 1:1.2 that is similar to a previous study on the incidence rate of MFs in Isfahan with a male-to-female ratio of 3:4 (1:1.33).^[8] This difference might be due to ethnic group diversity and support of the role of host susceptibility in the etiology of PCTCL; however, to identify the causes of this difference, studies with more patients should be conducted. Also, this finding indicates that epidemiologic studies showing regional clustering of patients may help identify the environmental triggers for PCTCL.^[10]

In the present study, the most common type of PCTCL was MF; the other type was less frequency. This shift of PCTCL to MF might be due to different environmental and genetic factors in Iran. The occurrence rates for various subtypes of cutaneous lymphoma in Asia are considered to be

significantly distinct from those in countries in the West.^[13] Compared to our study, Korea and Japan usually had higher rates of cutaneous NK/T-cell lymphomas such as extranodal NK/T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma (SPTCL).^[31,32]

Notably, other Asian countries had a considerably higher rate of SPTCL; in our study, similar to several reports in Europe the incidence rate of SPTCL reached almost zero.^[7,18]

The proportion of our patients complaining of the onset of disease 20 years ago was much higher; this result is similar to the epidemiological study in Kuwait.^[25]

CONCLUSIONS

The major differences in age and sex distribution of PCLs, especially MF in Iran, are lack of a male predominance and a lower age of diagnosis than reported from the West.

The study highlights the ethnic or regional variations in the clinicoepidemiological characteristics of PCLs.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

FFN and MP contributed to the conception of the work by conducting the study, revising the draft, approving the final version of the manuscript, and agreeing to all aspects of the work. BAN and HS contributed to the conception of the work by drafting and revising the draft, approving the final version of the manuscript, and agreeing to all the aspects of the work. JN contributed to the conception of

the work by revising the draft, approving the final version of the manuscript, and agreeing to all aspects of the work.

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