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Retrospective Study Of Clinicopathological Profile Of Primary Cutaneous Lymphomas In Western India

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Abstract

Background. Primary cutaneous lymphomas (PCLs) are rare heterogeneous family of extra nodal non-Hodgkin's lymphomas (NHL) originate in the skin with no evidence of extra cutaneous disease at the time of diagnosis.

Objectives. We retrospectively analysed epidemiology, clinical characteristics and treatment of different subtypes of PCLs in a tertiary care hospital of India.

Methods. There were 13 patients diagnosed with PCLs in 2010–2015 retrospectively reviewed in our Gujarat cancer and research institute, Gujarat, India.

Results. There were 9 (69.2%) male and 4 (30.8%) female (M: F = 2.2:1). The median age was 42 years. Most patients (12, 92.3%) had cutaneous T-cell lymphomas (CTCLs), one patient (1, 7.7%) had cutaneous B-cell lymphomas (CBCLs). The most common subtype was mycosis fungoides (MF) (6, 46.15%), followed by subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (6, 46.15%), primary cutaneous B cell lymphoma (PCBCL) (1, 7.7%).Most patients with MF presented with early-stage disease (66.7%).

Conclusions. The present study detected higher number CTCL patients with a middle age and a male predominance. MF and SPTCL were common CTCL subtype.

Keywords: CTCL: cutaneous T-cell lymphoma, SPTCL: subcutaneous panniculitis-like T-cell lymphoma, MF: Mycosis fungoides, SS: Sézary syndrome, CBCL:cutaneous B-cell lymphomas

Introduction

Cutaneous T-cell lymphoma (CTCL) is a group of lymphoproliferative disorders characterized by localization of neoplastic T lymphocytes to the skin. Collectively, CTCL is classified as a type of non-Hodgkin lymphoma (NHL). [1]. PCLs are the second most common extranodal NHLs after gastrointestinal lymphomas [2]. The estimated annual incidence of PCLs is approximately 1:100,000 [2, 3]. According to the World Health Organization-European Organization for Research and Treatment of cancer (WHO-EORTC) classification for cutaneous lymphomas published in 2005 and updated in 2018, PCLs can be divided into 2 main categories: cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) [1, 4]. PCLs may resemble their nodal counterparts in clinical and immunohistopathological findings, but differ in terms of their clinical course, management, and prognosis. Therefore, the differentiation between primary and secondary cutaneous NHLs is extremely important. CTCLs are the most common subtype of PCLs accounting for 75–80% of PCLs [1, 4]. Mycosis fungoides (MF) is the most common subtype, constituting 47–62% of CTCLs [4, 5]. Other subtypes of CTCLs vary among nationalities and geographical areas, such as subcutaneous panniculitis-like T cell lymphoma (SPTCL), which is quite rare among Caucasian populations [6, 7] but more common in Asian populations [8, 9]. CBCLs account for 20–25%

of PCLs in Western countries. There are 3 main subtypes of primary cutaneous B cell lymphomas: primary cutaneous follicle center lymphoma (pcFCL), primary cutaneous marginal zone lymphoma (pcMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (pcDLBCL-LT). The prevalence of CBCLs is relatively lower in Asian compared to Western populations [6, 8–10].

Several clinical and pathologic features are associated with adverse outcomes in patients with CTCLs such as older age , clinical stage , elevated serum lactate dehydrogenase , and large cell transformation [15]. Multiple systemic therapies have demonstrated clinical activity in CTCLs, including retinoid , recombinant interferons (IFN-α, IFN-β, IFN-γ),conventional chemotherapy , histone deacetylase inhibitors , and monoclonal antibodies such as brentuximab and mogamulizumab [11-12].
However, remissions are not durable with both conventional and novel agents. Autologous hematopoietic cell transplant (HCT) has been abandoned because of a lack of durability of responses [13]. Allogeneic (allo-) HCT has shown durable responses in patients with refractory and progressive disease in small retrospective and prospective series [14].

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Methods

We retrospectively analysed primary cutaneous lymphoma patients at the Gujarat cancer and research institute, Gujarat, India. Primary cutaneous lymphomas patients from January 2010 to December 2015 were included. Extra cutaneous lymphoma patient were excluded. Primary Cutaneous lymphomas diagnosed histopathologically according to the WHO-EORTC classification. Clinical stages and TNMB classification of patients with MF and Sézary syndrome(SS) were identified using the International Society for Cutaneous Lymphomas (ISCL) and the EORTC proposalin 2007, which was modified in 2018 [1, 4].

Data collection was performed by a review of the hospital electronic medical records. Demographic data and clinicalcharacteristics, including age at diagnosis, sex, morphology,anatomical site of the lesions, TNMB classification and stage, and nodal and extracutaneous involvement, were recorded. This study was approved by the Gujarat cancer and research institute. Slides were reassessed for histological features which were broadly divided into epidermal and dermal features. The epidermal features included degree of epidermal thickness, intensity and pattern of epidermotropism, the presence of spongiosis, parakeratosis, basal vacuolar damage, Pautrier's microabscesses, and mucinous change in hair follicles. The dermal features included the degree of dermal fibrosis, intensity of dermal infiltrate, predominant cell size of atypical lymphoid infiltrate, the percentage of large cells, periadnexal distribution, pigment incontinence, granuloma formation, and histologic stage. We performed immunohistochemical staining for various markers as needed to reach a final diagnosis, including antibodies against CD3, CD8, CD30, Bcl-6, TdT, ALK, Ki-67, k/l light chain and MUM-1; CD4, CD7 and CD56 ; CD5 ; CD10; Bcl-2; PD-1 .

Results

We identified a total of 13 patients diagnosed with PCLs from 2010 to 2015. Table 1 summarizes clinicopathologic spectrum of the PCL patients in our study. There were 9(69.2%) male and 4 (30.8%) female (M: F = 2.2:1) with male predominance. The median age was 42 years (range 25-63 years). Most patients (12, 92.3%) had cutaneous T-cell lymphomas (CTCLs), one patient (1, 7.7%) had cutaneous B-cell lymphomas (CBCLs). The most common subtype was mycosis fungoides (MF) (6, 46.15%), followed by subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (6, 46.15%), primary cutaneous B cell lymphoma (PCBCL) (1, 7.7%).

Most patients with MF presented with early-stage disease (66.7%). There were 5 (83.3%) male and 1(16.7%) female (M: F = 5: 1). The median age of disease onset was 42 years (range 15–56 years). In total, 4 (66.7%) patients were diagnosed with early-stage MF (stage IA–IIA). The most common MF variant was hypo pigmented MF (HMF), which accounted for 3(50%) of cases. A male predominance was observed in classical, HMF, folliculotropic MF (FMF) and poikilodermatous MF. The median age at the onset of symptoms and at diagnosis was younger in the hypopigmented (41 years) and poikilodermatous variants (47 years). All patients with HMF had only patch lesions. The most common sites of involvement were the trunk, abdomen and lower extremities 66.7%, followed by the upper

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extremities 50%. Lesions on the head and neck were observed in 33.3% of cases, most frequently in patients with FMF subtype. Among the 6 patients with SPTCL, the second most common subtype, 3 (50%) were male and 3(50%) were female (M: F = 1: 1). The median age at diagnosis was also 38 years (range 16–66 years). Most patients presented with nodules (83.3%), followed by plaques (33.3%) and patches (16.7%). The most common sites of involvement were the trunk and extremities. In our study, the most common extra cutaneous manifestations reported in SPTCL patients were B-symptoms(83.3%) (Figure1A,1B,1C).

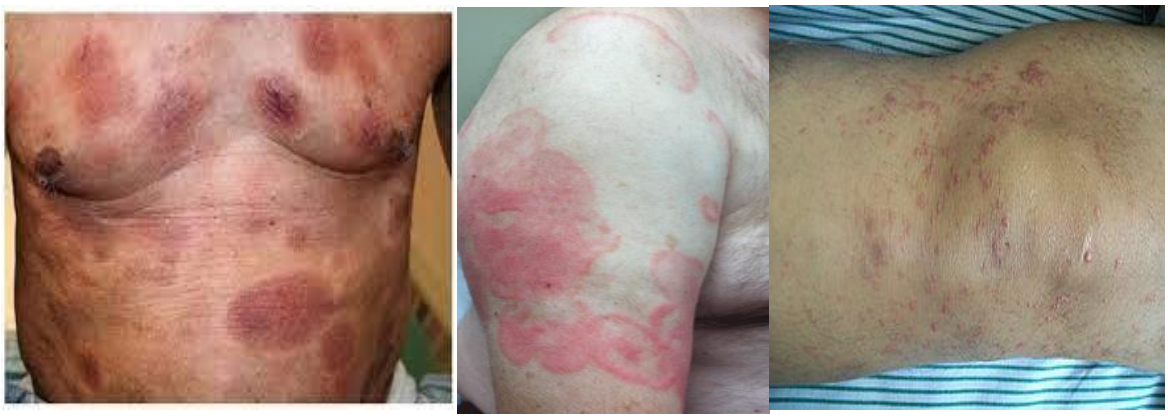

FIGURE.1 Clinical pictures of CTCLS. MF in a man manifesting a large infiltrative patches and plaques on the abdomen and Arm (A and B). Papules MF manifesting multiple lesions on knee (C).

Laboratory abnormalities included elevated LDH (76.9%), anemia (61.5%), leukopenia (53.8%), and elevated liver enzymes (46.2%). Two patients (15.4%) had hemophagocytic syndrome(HPS) or hemophagocytic lymphohistiocytosis (HLH). Histologically, MF varies with clinical stage. Patch/plaque lesions are comprised by epidermotropic infiltrates of medium-sized lymphocytes with mildly atypical to hyperconvoluted cerebriform nuclei . These cells tend to increase in size, and become less epitheliotropic as lesions progress to plaque and tumor stage . Although intraepidermal "Pautrier's" microabscesses can be seen in any stage. Spongiosis, interface dermatitis and intervening histiocytes may be seen. Dermal fibrosis is typical. SPTCL in the most diagnostic cases is comprised of diffuse sheets of atypical lymphocytes which eradicate the fat lobules as in a lobular panniculitis pattern, with some septal involvement. The dermis and epidermis are not involved by lymphoma, although reactive periadnexal lymphocytes are often seen. Mycosis fungoides is a CD4+ memory T-helper cell process. Pan-T-cell antigens CD2, CD3 and CD5 are retained in early lesions and lost later, although CD7 is lost early (fig 2A–E). Immunophenotypically SPTCL is characterized by a CD3+ CD8+ ,CD30- and CBCL is diagnosed by positive B-cell antigens, ie CD20 and CD79a.

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TABLE 1: Clinicopathologic spectrum of cutaneous lymphomas

Types	Number of patients	Percentage (%)	Age range with maximum cases	M:F ratio	Markers done in studies
Mycosis fungoides	6	46.15%	42years (range 15–56 years	5:1	CD3+,CD2+,CD8+ CD45+, LCA +

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SPTCL	6	46.15%	38 years (range 16–66 years)	1: 1	CD3+ CD8+ , CD5+,CD20(PanB) + Positive in reactive follicles LCA +,CD2 +
Cutaneous B-cell lymphomas	1	7.7%	56 years	1:0	CD3-CD20+ CD79a+

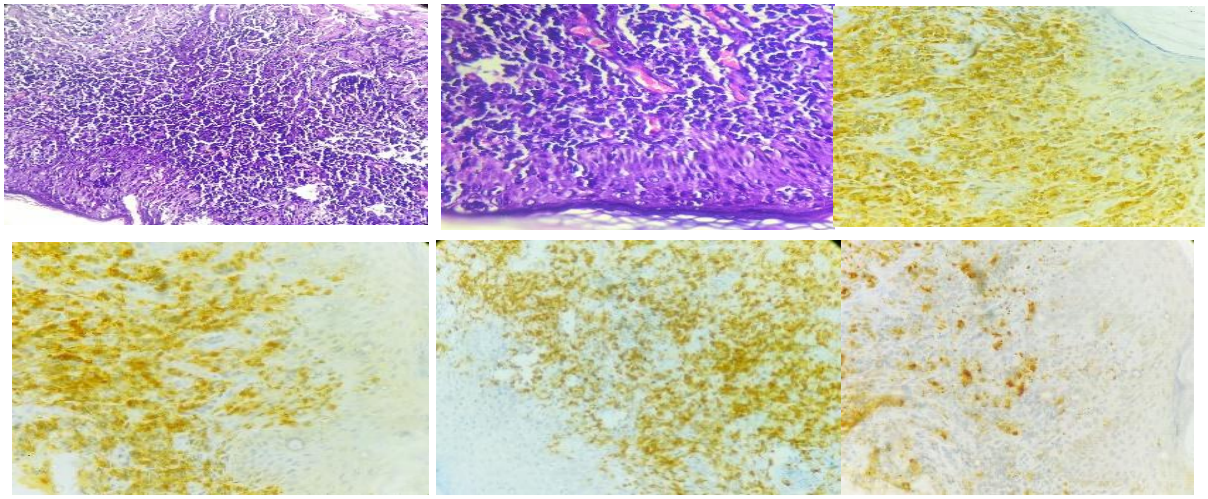

FIGURE 2A & 2B showed MF: small mature type of lymphocytic cell infiltration below the epidermis and around the vessels with other inflammatory component in form of polymorphs & plasma cells., 2C:CD 2 Positive, 2D: CD3 Positive, 2E:CD5 Positive and 2F:CD 20 Positive

Discussion

There are limited studies reported on the epidemiology and clinical characteristics of PCLs. PCLs were recognized as the second most common extra nodal NHLs after gastrointestinal lymphomas, according to most studies [2]. Our study represent the epidemiology and clinicopathological profile of PCLs in India. Of the 13 PCL patients, we found that the frequency of CTCLs (92.3%). This finding is consistent with those reported in studies from China (94.5%) [10], Iran (96%) [17], Argentina (93%) [16], and Taiwan (92.3%) [18], but relatively higher than those from Japan (85.7%) [8],Korea (88%) [9], USA, 72.4% [6]; Netherlands and Austria, 78% [4]; Germany, 85% [5]; Switzerland, 72% [19]; Italy, 78.7% [3]. In contrast, the incidence of CBCLs (7.7%) was much lower in our study than that reported in studies from Western countries. The median age at diagnosis (42 years) of patients with PCLs over all in our study was younger than those reported in many previous studies, particularly from Western countries such as Switzerland (56 years) [15], China (44.5 years)[10] and Italy (64 years) [3], but was higher to those reported in studies from Iran (36 years) [17]. This could be explained by a high rate of HMF, a variant particularly affects young adults, in this study. However, the median age of CBCL patients (56 years) was considerably higher, compared with CTCL patients (51 years). Interestingly, we noticed a male predominance (M: F = 2.2:1)) in almost all PCL. This finding was different from earlier studies that reported a female predominance from Switzerland (M: F=1: 1:4) [15] and Iran (M: F=1: 1:2) [17]. MF/ SPTCL was the most common subtype of CTCLs observed in our study. All HMF patients in this study presented with patch lesions, which correlated with their excellent prognosis.

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In terms of clinical staging, most MF/SS patients (66.7%) in the present study were diagnosed at early-stage, similar to previous studies from several countries, for instance, Taiwan (82.6%) [18], Iran (86.4%) [17], and Italy (87.2%) [3]. Early disease detection may be attributed to the development of advanced laboratory techniques, including genetics and molecular biology, and the rise in awareness among dermatologists and pathologists about PCLs in the recent years. SPTCL is a rare subtype of CTCLs that preferentially involves subcutaneous tissue. According to Park et al., the frequency of SPTCL in Korea was 10.4% of PCLs [20]. Interestingly, SPTCL was the second most common subtype (46.15%) of PCLs demonstrated in our study, which is a higher figure than we found in other studies from the literature review. B-symptoms were observed in 76.9% of SPTCL patients in the present study, which was a similar rate to those reported in Thailand (87.5%) by Rutnin et al. [21] and in Japan (81%) by Ohtsuka et al. [30]. In addition, laboratory abnormalities, including elevated LDH, elevated liver enzymes, anemia, and leukopenia, were observed, similar to in previous reports [21, 22, and 23].

Patch/plaque lesions of MF show various degrees of epidermotropism consisting of single or clusters of atypical lymphocytes (Pautrier microabscess) and/or a superficial band-like infiltrate in the basal layer and superficial dermis, composed of small and medium-sized atypical T cells with irregular, hyperchromatic and cerebriform nuclei. Tumour lesions of MF show deep dermal infiltrates, usually with absent or diminished epidermotropism. The neoplastic T-cells are CD4+ and CD8+ , with frequent loss of CD5 and/or CD7. A CD8+ phenotype is characteristic of hypopigmented MF. Large cell transformation is defined by the presence of more than 25% of large lymphoid cells of the total cell infiltrate. The large cells may express CD30 and cytotoxic markers and mimic ALCL or LyP. Histopathological features of erythrodermic MF and SS are often subtle or non-diagnostic. Peripheral blood flow cytometry can determine the absolute count of Sezary cells or circulating MF cells, which exhibit a CD4+ CD26- or CD4+ CD7-phenotypes.[25]

Treatment of CTCL depends on the stage of the disease and the general condition of the patient.Treatment strategies for MF/SS are determined by the extent of skin disease/ tumour burden, presence of unfavourable prognostic factors (folliculotropic type, large cell transformation and elevated lactate dehydrogenase and/or b2 microglobulin levels), age and other comorbidities that impact on the quality of life . Early stage MF (stages IA-IIA) has a favourable prognosis and skin-directed therapies including topical steroids, topical retinoids/rexinoids, psoralen combined with ultraviolet A (PUVA) or narrowband-UVB phototherapy, topical nitrogen mustard, spot radiation and total skin electron beam are first-line regimens[26,27,28]. Systemic treatments, such as retinoids and IFN-α have been recommended as second-line treatment of MF stages IA, IB and IIA. The 5-year survival for these patients is around 90%, significantly better compared with 30%–50% for advanced disease (IIB–IVB) [26]. Chemotherapy agents, such as monochemotherapy (gemcitabine, pegylated liposomal doxorubicine) and polychemotherapy, as well as newer systemic agents (brentuximab-vedotin and mogamulizumab) are recommended in advanced disease stage.[28]

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Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare lymphoma that represents less than 1% of all CTCL. Interestingly, SPTCL was the second most common subtype (46.15%) of PCLs demonstrated in our study. Clinically, it presents as solitary or multiple recurrent nodules, often located on the legs, with subcutaneous infiltrates of small to medium-sized atypical T-cells . Systemic B-symptoms may be present and the disease may also be complicated by a haemophagocytic syndrome [29]. The neoplastic CD8+ T-cells are confined to the subcutaneous tissue producing panniculitis-like lesions, and characteristically express an a/b phenotype. Patients usually have a protracted clinical course with skin nodules that usually respond to systemic corticosteroids, methotrexate, spot radiation and oral bexarotene [30-32]. Nodal or systemic involvement is rare and the 5-year survival is greater than 80% [33].

Primary cutaneous B-cell lymphomas (PCBCL) represent approximately 20 to 25% of all primary cutaneous lymphomas (PCL) [6]. The incidence of these rare entities is estimated to be <1 per 100,000 people/year and increases with age. In our study primary cutaneous B cell lymphoma (PCBCL) represent 7.7%.Topical imiquimod monotherapy has been recently studied in CBCL in a retrospective

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monocentric cohort in the United States. Sixteen patients with indolent CBCL (T1aN0M0 to T3aN0M0) were treated with imiquimod 5% cream. The ORR was 62% including 31% of complete and 31% of partial responses with a median duration of treatment of 4.6 months (range 1.4 to 9.8 months). [34]. Based on the recent therapeutic advances in nodal B-cell lymphomas, we focus on the development of novel treatment options applicable to primary cutaneous B-cell lymphomas, including targeted therapies, combination treatments and immunotherapeutic approaches, and cover basic, translational and clinical aspects aiming to improve the treatment of cutaneous B-cell lymphomas. The limitations of our study were a single-center retrospective study design and prospective IHC staining was not performed.

The identification of predictive biomarkers of response will help select the optimal therapeutic options. In the era of personalized medicine, large-scale translational studies and prospective clinical trials are mandatory to improve the management of these rare diseases.

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