Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Kaur, A., Singh A., Singh A., et al. 2023. Histopathological Spectrum of Cutaneous Lymphomas. Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4712

DOI: https://doi.org/10.18103/mra.v11i11.4712

ISSN: 2375-1924

RESEARCH ARTICLE

Histopathological Spectrum of Cutaneous Lymphomas

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ABSTRACT

Background: Cutaneous lymphomas are a heterogeneous group of extra-nodal non-Hodgkin's lymphomas that are characterized by a cutaneous infiltration of malignant monoclonal lymphocytes. Less frequently, these lymphomas spread from the skin to the blood or a lymph node. The incidence of primary cutaneous lymphoma has been estimated to be 1:100,000 according to the World Health Organization. Usually, these lymphomas affect adults with a median age of 50 to 60 years. T-cell lymphomas predominate over primary B-cell lymphomas of the skin. The most important subtypes of cutaneous T cell lymphomas are Mycosis fungoides, Sezary syndrome, and primary cutaneous peripheral T cell lymphomas not otherwise specified. These subtypes present different clinical, histological, and molecular features, and can follow an indolent or a very aggressive course.

Aim: The aim of this study was to analyze cutaneous lymphomas to ascertain its clinical aspects including prevalence, histopathology and immune profile.

Material and methods: A retrospective analysis of skin biopsies over a 7-year period ranging from 2016 to 2022 was done, of which 11 cases were diagnosed as cutaneous lymphomas. These cases were analyzed in detail including immune profile.

Results & conclusions: The majority of the cases out of all cutaneous lymphomas were of T cell lymphoma and only one case was of B cell type. Definitive diagnosis of CTCL requires a multidisciplinary approach.

Keywords: cutaneous T cell lymphoma, cutaneous B cell lymphoma.

Introduction

Skin is the second most common extra-nodal site of lymphoma after the gastrointestinal tract. Primary cutaneous lymphoma refers to those cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) that are present in the skin with no evidence of extra-cutaneous disease at the time of diagnosis. The incidence of primary cutaneous lymphoma has been estimated to be 1:100,000 according to the World Health Organization.[1]

Cutaneous lymphomas are clinically present as patches, plaques, papules, and nodules along with histologically distinct features. T-cell lymphomas predominate (65%); however, there are a significant number of primary B-cell lymphomas of the skin (25%). Cutaneous T-cell lymphomas are a heterogeneous group of extra-nodal Non-Hodgkin's lymphomas that are characterized by a cutaneous infiltration of malignant monoclonal T lymphocytes. Moreover, there are a variety of unusual and rare manifestations and entities of cutaneous lymphomas that cannot be seen in the lymph node owing to the peculiarities of the skin as a distinct homing organ and vice versa.[2] It is important to note that some cutaneous lymphomas have a better prognosis when occurring primarily in the skin than their corresponding entity in the lymph node.

Cutaneous T cell lymphomas typically affect adults with a median age of 55 to 60 years, and the annual incidence is about 0.5 per 100,000. Mycosis fungoides, Sezary syndrome, and primary cutaneous peripheral T cell lymphomas not otherwise specified are the most important subtypes of CTCL. CTCL is a complicated concept in terms of etiopathogenesis, diagnosis, therapy, and prognosis.3 Primary cutaneous B-cell lymphomas are a heterogeneous group of mature B-cell neoplasms with tropism for the skin, whose biology and clinical course differ significantly from the equivalent nodal lymphomas. The most indolent forms comprise the primary cutaneous marginal zone and follicle center B-cell lymphomas that despite the excellent prognosis have cutaneous recurrences very commonly.[3,4]

To date, there is not much data available on the epidemiology of cutaneous lymphomas in India since the majority of cases of cutaneous lymphomas have been published as case reports. Hence, we decided to undertake this study to determine the clinico-pathological and epidemiological profile of cutaneous lymphomas in our tertiary care institute.

Materials and Methods

A retrospective analysis of skin biopsies over a 7-year period ranging from 2016 to 2022 was done, of which 11 cases were diagnosed as cutaneous lymphomas. During this period a total of 650 cases of lymphoma were diagnosed. The histopathology specimens were routine hematoxylin & eosin-stained biopsy sections. Clinicopathological co-relation was done. Patients of all ages with primary cutaneous lymphoma diagnosed clinically and histo-pathologically, were included in the study. Immunophenotyping was performed on formalin-fixed, paraffin-embedded tissue sections with a broad panel of monoclonal antibodies. Slides were subjected to IHC examination under both low power (100x) and high power (400x).

Inclusion criteria: All cutaneous lymphoma with immunohistochemistry for definite categorization included in the study.

Exclusion criteria: All other lymphoma not involving the skin and on which immunohisto-chemistry has not been done.

Study Design: This is a cross-sectional retro-spective study.

Methodology: The tissue obtained in the histopathology lab was processed. Paraffin embedding and subsequent staining by Hematoxylin and Eosin was done. The slides were then subjected to histopathological examination. All 11 cases with a diagnosis of cutaneous lymphoma were subjected to immunohistochemical examination.

HEMATOXYLIN AND EOSIN STAINING:
The paraffin-embedded tissue blocks are cut at 2–3-micron thickness by rotator microtome. Then the slides were kept on a hot plate in order to dewax the sections at a temperature of 60 degrees. Following this, the slides were deparaffinized in xylene and then hydrated through graded alcohol to water. Then it was stained with Harris hematoxylin for 15 minutes. The sections were washed well in running tap water until sections turned blue. The sections

were then differentiated in 1% acid alcohol (1% HCL in 70% alcohol) for 5-10 seconds, washed well in tap water for 5 minutes or less. These were then stained with 1% eosin for 10 minutes followed by washing in running tap water for 1-5 minutes. Sections were dehydrated once again through graded alcohol, cleared xylene and mounted with DPX avoiding air bubbles.

IMMUNOHISTOCHEMISTRY:
Two-three um sections were cut and mounted on Poly-L-lysine coated slides. Slides were dried overnight at 37 degree C and dewaxed in xylene and hydrated. Antigen retrieval procedure- The black box was filled 3/4th with citrate buffer and the slide carrier with slides was placed in it. The black box was placed in the microwave for 9 mins. Boiling of the solution was observed and the microwave was reset for 6 minutes and started. The box was removed and cooled under tap water. Blocking endogenous peroxidase - Sections were incubated at room temperature in 0.3% H_2O_2 in methanol for 30-45 min and rinsed in running tap water for 5-10 mins and then dipped in distilled water for 1 minute. The slides were placed in Tris buffer [only one change for 5 minutes. Blocking reagent was applied for 5-10 min and excess of it was wiped off. Primary antibodies were applied covering the whole section and incubated at room temperature for 1 hour. Slides were then washed in Tris buffer for 5 minutes. Ultra Vision One HRP polymer covering the whole tissue was applied and incubated at room temperature for 45 mins. Washing was done in a TBS buffer for 5 minutes. One drop of substrate DAB [3, 3- Diaminobenzidine] solution was applied on each slide covering the whole material and incubated for 10- 15 mins, then washed in deiodinized water. Hematoxylin was applied for a few seconds and washed under running water. Then it was dried and dehydrated in alcohol and incubated for 2 minutes. It was mounted in DPX [distyrenedibutyl phthalate xylene] IMMUNOHISTOCHEMISTRY- VENTANA BENCHMARK GX PROCEDURE (Automatic) IHC staining of slides prepared from formalin fixed paraffin embedded tissue (FFPET) on the BenchMark Classic Automated system (from Ventana). Sections from FFPET biopsies were cut using the microtome at 3–4 micron thickness and mounted onto Super Frost Plus slides. For each slide, Ventana labels were then printed which included a unique barcode containing all protocol information. The slides were then loaded onto the BenchMark carousel and read by the Ventana Barcode Reader. The automated Benchmark system put the slides through a series of user defined de-paraffinization and antigen retrieval steps before commencing with the antibody staining. The primary antibody was either applied automatically if in a pre-diluted dispenser or otherwise manually titrated onto the slide. The pre-diluted dispensers of the ultra View Universal DAB Detection Kit then provided all reagents required for staining. The counterstain and post-counterstain comprised Hematoxylin (cat #760-2021) and bluing reagent (cat #760-2037).

Results

We analyzed a total of 11 cutaneous lymphoma cases out of 650 cases over a period of 7 years. The frequency of occurrence of cutaneous lymphomas was found to be 1.7 per 100 biopsy specimens. Total number of patients analyzed in this study was 11, which constituted 7 males (63%) and 4 females (36%). The male-to-female ratio was 1.75:1. The age of distribution ranged from 34 years to 77 years with a mean age of 55.5 years. The spectrum of cases which presented to us is listed in Table-1. There were (10/11) 90.9% of patients with T-cell lymphoma, (1/10) 9.1% of patients with B-cell lymphoma.

Table -1: Clinicopathologic spectrum of cutaneous lymphomas

S.no.	Age (yrs)	Sex (M/F)	Site	Positive IHC markers in lesional cells	Negative IHC markers in lesional cells	Immuno-phenotype
1	77	M	Neck	CD45, CD20	CD3 positive in surrounding lymphocytes, CD5, CD10 and CD23	B-cell NHL
2	77	M	Chest wall	CD45, CD10, BCL2, Ki-67 (30%)	CD3, CD20, CD68, CD23, Cyclin D1, BCL6, CD30, CD5, ALK-1, C-kit, Tdt, MUM-1	T-cell NHL
3	65	M	Skin over right parotid gland	CD45, CD30, CD5, Ki-67 (80%)	CK, p16, p53 positive in overlying epidermis	T-cell NHL
4	45	F	Chest wall	CD45, CD3, Ki-67 (85%)	CD20 positive in scattered B-lymphocytes	T-cell NHL
5	36	M	Skin below knee	CD45, CD3, CD4, CD8, CD30	CD20 positive in few lymphoid cells forming follicles. CD7 loss in lymphoid cells. CD68 positive in histiocytes	T-cell NHL
6	34	M	Right forearm	CD45, CD3, CD4, CD8, CD7	CD20 positive in few scattered lymphoid cells	T-cell NHL

7	75	F	All over body	CD45, CD3, CD5	CD20 positive in few lymphocytes	T-cell NHL
8	40	M	Back of calf	CD45, CD3, CD5	CD 20 focal positive in B-cells	T-cell NHL
9	75	F	Right thigh	CD45, CD7, CD4, CD5, CD3	CD 20 focal positive in B-cells	T-cell NHL
10	40	F	Bilateral breast	CD45, CD3, CD5	CD 20 focal positive in B-cells	T-cell NHL
11	65	M	Infected wound over skin	CD7, CD4, CD5, CD30, CD8, CD3	CD 20 focal positive in B-cells	T-cell NHL (Granulomatous mycosis fungoides)

Most of these lymphomas were seen in male patients. Skin all over the body areas involved in these patients including head & neck, chest and back and extremities. There was no history of any previous dermatosis or toxin exposure or smoking or ultraviolet radiation exposure or other malignancy in any of these cases. All the patients were of Indian ethnicity. On examination there was no evidence of any lymphadenopathy or abdominal organomegaly. There was no peripheral blood involvement in all these cases. Out of CTCL, one of the cases was of rare variant of mycosis fungoides called granulomatous mycosis fungoides where CD3, CD4, CD5, CD7, CD8 and CD30 were positive on IHC. Patient was of 65 years old male presented with infected wound on skin. Microscopy showed tumour stage of mycosis fungoides which was characterized by diffuse infiltration by large lymphoid cells filling the dermis and extending into the subcutis. Granulomtous response noted in the dermis. In the other nine patients, the diagnosis was CTCL, NOS. In most of these cases, microscopy revealed presence of malignant lymphoid cells present in the dermis with cells hugging the epidermis (Figure 1). Epidermotropism noted in few of the cases. The majority of cases showed presence of large lymphoid cells with prominent nucleoli in some.

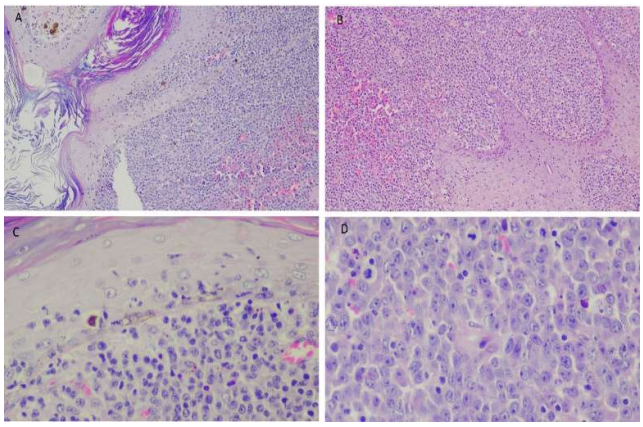

Figure 1: Large lymphoid cells are present in the dermis (A) and (B) hugging the epidermis (H&E X100). Epidermotropism was noted (C) and tumour cells (D) showed prominent nucleoli (H&E X400).

Immunohistochemistry showed positivity of T cell markers in these cases including CD 3, CD4, and CD8 (Figure 2). CD20 the B cell marker was negative in these cases. Ki-67 was high in lymphoid cells.

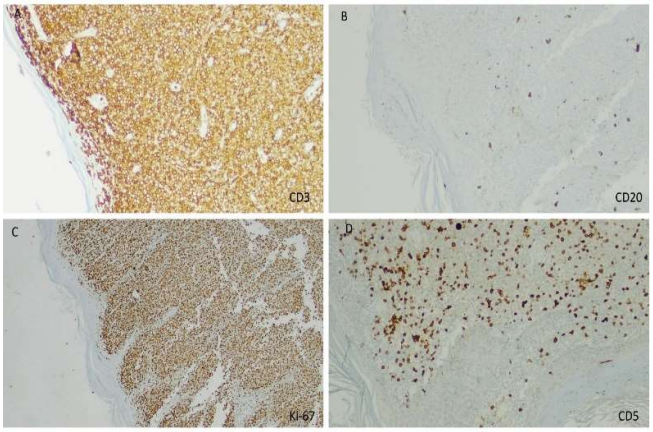

Figure 2: Immunohistochemistry showing (A) diffuse CD 3 positivity. CD20 is negative (B) in lymphoid cells. Ki-67 (C) is 85% in lymphoid cells. CD5 is positive in few lymphoid cells (D).

CD30 was diffuse positive in lymphoid cells in 2 cases (Figure 3). Loss of CD7 in lymphoid cells was observed in one case. Only one case of 77 years old male who presented with chest wall involvement showed loss of CD3.

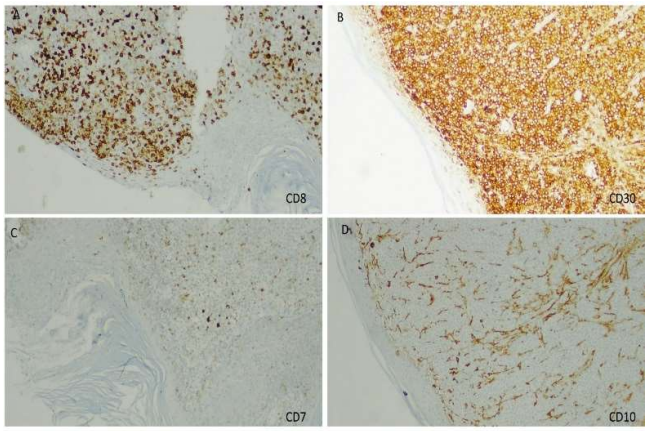

Figure 3: Immunohistochemistry showing (A) CD 8 positivity. CD30 is diffuse positive (B) in lymphoid cells. (C) showing loss of CD7 in lymphoid cells. (D) showing CD10 is negativity in lymphoid cells.

Only one case was of Primary cutaneous large B cell lymphoma, NOS. It was a 77 years old male who presented with involvement of neck skin. Intermediate to large lymphoid cells were present which showed diffuse positivity for CD20. In this study, no EBV-LMP1 or EBERISH was done.

Discussion

Primary cutaneous lymphomas are defined as Non-Hodgkin lymphomas presenting in the skin with no evidence of extracutaneous disease at the time of diagnosis. Primary cutaneous lymphomas include a heterogeneous group of cutaneous T-cell lymphomas and cutaneous B-cell lymphomas.[1,7-9,14-15] Cutaneous lymphomas are characterized by infiltration of malignant monoclonal lymphocytes in the skin. Approximately 25% to 40% of NHL cases involve extra-nodal sites. The skin is the most common site after the gastrointestinal system. The World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification has served as a gold standard for the diagnosis and classification of primary cutaneous lymphomas in the past. In 2018, an updated version of the WHOEORTC classification was published in the fourth edition of the WHO Classification of Skin Tumors Blue Book which is recently updated in The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms with no significant changes.[1,2,16,17,21] In WHO-HAEM4R, primary cutaneous gamma/delta T-cell lymphoma, CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, acral CD8-positive T-cell lymphoproliferative disorder and CD4-positive small or medium T-cell lymphoproliferative disorder were grouped together under the term 'cutaneous peripheral T-cell lymphoma, rare subtypes', but are now each listed as separate entities in WHO-HAEM5 acknowledging their specific clinicopathological characteristics.[2,14]

Not many studies have been done on the epidemiology of cutaneous lymphoma in India except for the study done by George et al.6 They had seen thirty-three cases seen over a 10-year period. In our study, we found the frequency of occurrence of cutaneous lymphomas to be 1.7%, as compared to 0.7% in study done by George et al.6 The rate of occurrence of T-cell lymphoma (90.9%) was seen in our study, as compared to the WHO and the study by George et al.6 estimated its occurrence to be around 75% and 77.5% respectively. A much lower rate of occurrence of B-cell lymphoma (9.1%) was seen in our study, whereas the WHO and the study by George et al.[6] estimated its occurrence to be around 25% and 22.5%, respectively.[5,14-15]

Mycosis fungoides (MF) and Sezary syndrome (SS) are the classic types of CTCL. MF is the most common type and accounts for 60% of CTCLs and almost 50% of all primary cutaneous lymphomas. In the WHO-EORTC classification, folliculotropic MF (FMF), pagetoid reticulosis, and granulomatous slack skin are recognized as distinct variants of MF.[1-3,12,13] Besides skin, unusual sites of involvement had been seen by some in MF like duodenum.[11] Incidence of primary cutaneous lymphoma has been estimated to be 1:100,000 according to the WHO. Men are more involved than women (1.6:1 to 2.0:1). They typically affect adults with a median age of 55 to 60 years. However, children can be affected by this disease. Black African American are more commonly affected than other populations.[6,22-23]

Although different views of CTCL etiopathogenesis have been elucidated in depth over the last few decades, the exact mechanism of initiation and progression of this disorder is not yet known. Although dysregulation of some genes and signaling pathways has been reported in the CTCLs. Bagherani el al[4] have reported an association between chronic cutaneous inflammation and subsequent development of CTCL. Chronic or professional exposure to topical chemical agents, long lasting psoriasis, UV radiation exposure and urticaria have been proposed as risk factors. Chronically activated T lymphocytes may eventually result in the creation of an atypical T cell clone. For instance, in granulomatous MF, the granulomatous inflammation may precede the lymphoma, resulting in lymphocyte proliferation through macrophage-produced IL-[6.4,12,20,25, 31] The role of retroviruses such as human T cell leukemia virus type 1 (HTLV-1) and HTLV-2 and human immunodeficiency virus and herpesvirus family members like Epstein-Barr virus, human herpesvirus 8, and cytomegalovirus have been suggested in the pathogenesis of these disorders.[6,10]

Association with other malignancies had been reported by Goyal et al[24] In their study; patients with CTCL were at increased risk of second malignancies, especially Hodgkin and Non-Hodgkin lymphoma, lung cancer, bladder cancer, and melanoma.[24,32] At the early stages, cutaneous lymphomas are often misdiagnosed as benign skin conditions. Their most important differential diagnoses include dermatitis, eczema, parapsoriasis, psoriasis, Lichen planus, Morphea, Panniculitis, folliculitis, pityriasis lichenoid chronica, pigmented purpuric dermatoses, vitiligo and lymphomatoid papulosis.[27,29] The diagnosis of cutaneous lymphomas is difficult at early stages because of the presence of multiple clinical presentations and lack of definitive diagnostic criteria. Hence, in most cases, it takes an average of 6 years from disease onset until confirmation of the diagnosis. Observation and palpation of the skin, along with palpation of lymph nodes remains the traditional approach for staging of these disorders. Frequently, many biopsies are required to make the definitive diagnosis, as morphologic and phenotypic manifestations of cutaneous lymphomas are variable, and information derived from a single biopsy can lead to misdiagnosis.

Histologically, CTCL varies with clinical stage, especially MF. Patch/plaque lesions are comprised by epidermotropic infiltrates of medium-sized lymphocytes with mildly atypical to hyperconvoluted nuclei. On IHC, Pan-T-cell antigens CD2, CD3 and CD5 are retained in early lesions and lost later, although CD7 is lost early specially in MF. CD8 is the predominant phenotype in some lesions of MF, often in younger patients. Ki-67 proliferation indices are not typically high until disease is advanced at which point Ki-67 may correlate with prognosis. The majority of CTCL's are CD30 negative by routine immunohistochemistry. Distinct from MF, the loss of pan-T-cell antigens such as CD3, CD5 and CD7 is common in anaplastic large cell lymphoma ,9ALCL) which may also be CD45 RA negative however CD2 and CD45RO can be positive.[21,30] Flow cytometry is not usually helpful.[26,28] To diagnose cutaneous lymphomas, biopsy of suspicious skin sites is must and subsequent assessment in terms of immunohistochemistry, and molecular analysis like TCR gene rearrangement. The loss of cell surface markers of CD7 is valuable sometimes.[4,8,26-28]

Primary cutaneous B-cell lymphomas are a heterogeneous group of mature B-cells neoplasms with tropism for the skin, whose biology and clinical course differ significantly from the equivalent nodal lymphomas. The most indolent forms comprise the primary cutaneous marginal zone and follicle center B-cell lymphomas that despite the excellent prognosis have cutaneous recurrences very commonly. The most aggressive forms include the primary cutaneous large B-cell lymphomas[5,15] Chronic antigenic stimulation and viral and bacterial infections appear to be predisposing factors, but studies to support these assumptions are scarce and, in most cases, the etiologic agent is not known. In general, B-cells stain positively for CD19, CD20, CD79 and they are negative for T-cell markers (i.e., CD2, CD3, CD4, CD7 and CD8). In addition, CD5 is useful to exclude secondary skin involvement by chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL), whereas CD10 may be positive in follicle center lymphoma, particularly in those from nodal origin.[5,14-15] In the present study we had seen only one case of cutaneous B cell lymphoma showed diffuse positivity for CD20. Pseudolymphoma" (reactive lymphoid hyperplasia) can sometimes be very difficult to distinguish from lymphomatous infiltration.

Granuloma formation rarely can be seen in Sézary syndrome, cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous B-cell lymphoma. However, mycosis fungoides is the most common form of primary cutaneous lymphoma which may present with associated granulomatous inflammation. Mycosis fungoides granulomatous was first described by Ackerman and Flaxman in 1970. The etiopathogenic mechanism of granuloma formation is unknown. It was suggested that the granulomatous reaction occurs due to the secretion of chemotactic factors by neoplastic cells. A polarization to produce Th1 cytokines, such as interleukin-2, interferon-gamma, and tumor necrosis factor-alpha, may also occur.[12] In present study, one of the cases included was diagnosed as Granulomatous mycosis fungoides. In this case, there was a predominant CD4+ epidermotropic atypical lymphocytic infiltrate in the overlying epidermis and focal tagging of these lymphoid cells at dermo-epidermal junction. In reticular dermis and at junction of

subcutaneous tissue was seen, collection of epithelioid cells with foreign body giant cell reaction. However, GMS and PAS stain performed for fungus were negative and 5% ZN stain for lepra bacilli was negative.

Clinicopathological co-relation plays an important role in the early detection of lymphomas.[27] This study highlights that T-cell lymphomas are the commonest lymphomas affecting the skin. Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma that confers significant mortality in advanced-stage disease, however overall survival shows variability.[17-19,21] As there is morphologic and immunophenotypic overlap among the various forms of primary CTCL, correlation with clinical history, signs, and symptoms is a key element of the diagnostic work-up. Thus, dermatological examination and clinical photographic documentation are indispensable in reaching the correct diagnosis.

Conclusion

CTCL is a rare entity with low incidence. Definitive diagnosis of CTCL requires a multidisciplinary approach. Various differential diagnosis of cutaneous lymphomas come into picture. Mimickers range from infectious diseases, autoimmune or hypersensitivity reactions, solid tumors as well as secondary involvement of the skin by another peripheral T-cell lymphoma, T-cell rich B-cell lymphoma, B cell lymphoma and even Hodgkin's Lymphoma. Since our study was a retrospective study, it has its limitations in that what is seen in the laboratory may not be the true incidence in clinical practice. Though we have not studied the prognostic features in detail, we feel that there is a need for a prospective study with a larger sample size and long-term follow-up to determine the exact epidemiological trends and disease outcome in our country and immunophenotyping should be done for further classifying lymphomas whenever possible for prognostic implications. Multivariate analysis of large groups will be needed to better assess prognostic features for these cutaneous lymphomas.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

Funding Statement

No resource to any funds.

Acknowledgments

The authors contributed equally to this work. The authors would like to acknowledge the invaluable support of the histology technicians and immunology technician's Mrs Monika & Mr Rajesh and Mr Kapil & Mr Vishal.

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