Clinical and Pathological Features of Primary Cutaneous Lymphomas in Nepal: A retrospective cohort study from a dermatology referral centre

Paudel U, Parajuli S

Department of Dermatology and Venereology

Maharajgunj Medical Campus,

Institute of Medicine, Tribhuvan University,

Maharajgunj, Kathmandu, Nepal.

Corresponding Author

Sudip Parajuli

Department of Dermatology and Venereology

Maharajgunj Medical Campus,

Institute of Medicine, Tribhuvan University,

Maharajgunj, Kathmandu, Nepal.

E-mail: sudipparajuli@gmail.com

Citation

Paudel U, Parajuli S. Clinical and Pathological Features of Primary Cutaneous Lymphomas in Nepal: A retrospective cohort study from a dermatology referral centre. *Kathmandu Univ Med J.* 2024;86(2):154-9.

ABSTRACT

Background

Primary cutaneous lymphomas (PCLs) are rare diagnoses in Nepal and are not well characterized till date.

Objective

To evaluate clinical and pathological features of Primary cutaneous lymphomas in Nepal.

Method

We retrospectively reviewed outpatient and inpatient records of a dermatology referral centre of Kathmandu, Nepal for clinical and pathological findings of cases diagnosed as cutaneous lymphomas from July 2010 through July 2020. The final diagnosis was made based on 2008 World Health Organization classification and its update 2018.

Result

There were 12 cases of Primary cutaneous lymphomas diagnosed during this period. The age of presentation ranged from 19 years to 81 years (Mean: 53.4 years ± 21.5 years, SD). There were ten cases of cutaneous T-cell lymphoma (CTCLs) and two cases of cutaneous B- cell lymphomas (CBCLs). Among cutaneous T-cell lymphoma, there were four cases of primary cutaneous anaplastic large- cell Lymphoma (PCALCL), two cases of classic (patch/plaque) mycosis fungoides (MF), two cases of folliculotropic mycosis fungoides (FMF), and one case each of primary cutaneous aggressive epidermotropicCD8+ T-cell lymphoma and lymphomatoid papulosis. Among cutaneous B- cell lymphomas, there was one case of primary cutaneous marginal zone B- cell lymphoma, and one case of primary cutaneous follicle centre lymphoma. Most cases of MF presented at stage IB (75%), and three patients of primary cutaneous lymphomas died during this period.

Conclusion

Primary cutaneous lymphomas appear to be very rare in this study and presentations ranged from classic Mycoses Fungoides to aggressive T-cell lymphomas. Cutaneous T-cell lymphomas appeared to be more common than cutaneous B- cell lymphomas in this study.

KEY WORDS

Anaplastic, B-cell, Cutaneous, Lymphoma, T-Cell

INTRODUCTION

Primary cutaneous lymphomas (PCLs) are non-Hodgkin's lymphomas and constitute cutaneous T- cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs).[1] They present in the skin with no extra cutaneous involvement at the time of diagnosis. These different types of CTCLs and CBCLs have completely different clinical behaviour, prognosis and treatment compared to their nodal counterpart.[2] World Health Organization- European Organization for Research and Treatment of cancer (WHO-EORTC) classification, updated in August 2018, summarized in table 1 serves as a gold standard for classification of PCLs.[3]

The frequencies of PCLs often show wide regional variation and can be due to geographic and environmental factors.[3] Information on prevalence of PCLs remains sparse with a need of additional studies. Existing literature shows that the annual incidence of PCLs is around 1:100000.[4] Among PCLs, CTCLs constitute 75-80% of all PCLs and CBCLs 20-25% in western part of the world.[3,5] Reports on PCLs in Nepal and in this South Asian region is limited. With improved diagnostic facilities in recent years, the reports of PCLs in literatures are increasing from India and surrounding regions.[6-8]

This retrospective study is first of its kind to study primary cutaneous lymphoma in Nepal from the records of the patients who were diagnosed with cutaneous lymphoma from July 2010 to July 2020. This study will help to improve our knowledge about the disease and to better plan and allocate resources for timely management of this disease.

METHODS

We retrospectively reviewed available medical records from department of dermatology and venereology, Tribhuvan University Teaching Hospital, a tertiary referral centre in Kathmandu, Nepal for clinical and pathological findings of cases diagnosed as cutaneous lymphomas from July 2010 through July 2020. The records were searched for a diagnosis of cutaneous lymphoma, Mycosis Fungoides, Sezary syndrome, and lymphomatoid papulosis. The resulting patients list was checked by retrieving outpatient, inpatient department, and procedural records from the operation theatre of department of dermatology and cross checked with electronic record from department of pathology. In our routine practice, the diagnostically challenging cases of skin disorders are evaluated by a dermatopathologist in University of Zürich, Switzerland to reach a final diagnosis. In all cases immunohistochemical staining were done as needed to reach to a final diagnosis and included CD2, CD3, CD4, CD7, CD8, CD25, CD30, CD45RA, Ki67, Betaf1, CD56, TIA1, ALK, EMA, Epstein Barr virus encoded RNA, CD20, CD21, CD38, Bcl6, Bcl2, k/l light chain, TCR, CD45RO, PD-1, granzyme B and bF-1. For this study PCLs were defined as lymphoma presenting in the skin without evidence of extra cutaneous involvement except regional lymph node at the time of diagnosis. The final diagnosis was made based on 2008 World Health Organization classification and its update 2018 (table 1).[3] The types of PCLs were specified as per WHO-EORTC and its update 2018.[3] The staging on PCLs was based on the new Tumour-node-metastasis-blood (TNMB) proposed by International Society of Cutaneous Lymphomas (ISCL) and cutaneous lymphoma task force of European Organization for Research and Treatment of Cancer (EORTC).[3] In all cases gender, age at diagnosis, duration of illness at the time of diagnosis, examination findings (type and site of skin lesions, lymph node enlargement, and hepatosplenomegaly), staging, therapy and survival were recorded. The data were recorded in SPSS-20 and descriptive analysis of data was done.

The study was approved by Institutional review committee of Institute of Medicine, Tribhuvan University, Kathmandu, Nepal {Ref no: 81(6-11) E2 077/078}.

RESULTS

There were twelve cases of PCLs diagnosed during this period out of which six were males and six were females. The mean age of presentation in this study was 53.4 years ± 21.5 years, SD with age range 19 years to 81 years. The duration of illness at diagnosis ranged from 10 days to 16 years.

There were ten cases of CTCLs, out of which four were PCALCL, two were Classic MF (Patch/Plaque), two were Folliculotropic Mycosis (FMF) Fungoides, one each case of Primary cutaneous aggressive epidermotropicCD8+ T-cell Lymphoma and Lymphomatoid papulosis.

There were 2 cases of CBCLs, out of which there was one case each of Primary cutaneous marginal zone B -cell lymphoma and Primary cutaneous follicle centre lymphoma.

Mycosis Fungoides

Two patients had Classic MF. The first one was a 70-year-old female who presented with multiple plaques of variable sizes on trunk, arm, forearm, thighs, and legs in the last four years. This patient developed right inguinal lymphadenopathy later and was subsequently diagnosed as Classic Hodgkins lymphoma associated with EBV infection . Second patient was a 39-year- old male who presented with hyperpigmented plaques on thorax, both arms and thighs in the last six years. Both were in stage IB at presentation. The first patient died after six months of diagnosis while the second patient had achieved partial remission at follow-up after chemotherapy.

There were two cases of FMF. The first patient (Fig. 1a) was an 18-year-old lady who was a patient of Hepatitis B, and developed multiple inflammatory plaques and nodules present over forehead, nose cheek, glabellas along with

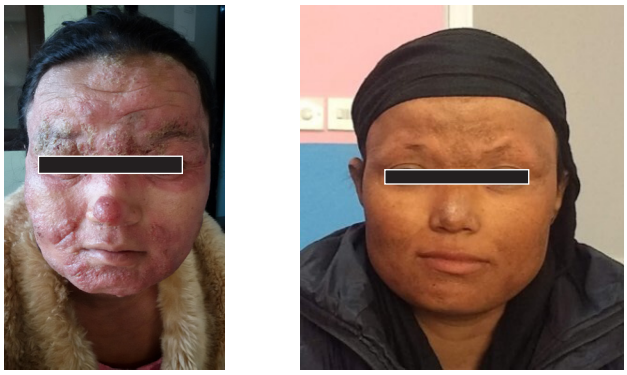

Figure 1 a. Folliculotropic MF b. Folliculotropic MF post treatment with TSEB

generalized follicular prominences in the last two years. This patient was in stage IB at presentation and received total skin electron beam (TSEB) and was in remission at last follow-up at 12 months (Fig. 1b). The second patient was a 59-year-old man who presented with erythematous plaque/nodules on left side of cheek since one and half years and one was in stage IB at times of presentation. This patient was initially misdiagnosed as Jessners lymphocytic infiltrate and had received intralesional steroid injection with remission at last follow-up.

CD 30 positive lymphoproliferative disorders

There were four cases of CD30+ PCALCL and one case of lymphomatoid papulosis. The first patient was a 24-year-old lady who presented with a single papule on root of left nose for 10 days. This initial lesion was excised; however, a second lesion appeared after 6 weeks on same site, excised again, and was subsequently diagnosed as CD30 positive PCALCL and was in stage T1N0M0. The patient was in remission at last follow-up. The second case was an 81 -year-old male who presented with multiple erythematous to skin-coloured nodules on arms, legs, back, and abdomen since one and half years. This patient was in T3bN0M0 at presentation and was treated with methotrexate and was in remission at follow up period of one and half months. The third patient was an 80-year-old male who presented initially with noduloulcerative growth on flexor aspect of left forearm and subsequently developed multiple lesions on upper extremities. This patient was in T2aN0M0 at the time of diagnosis. He was taking methotrexate intermittently and was in remission at last follow-up of 8 years. The fourth patient was an 81-year-old male presented with multiple nodules on face, back of neck, chest, both arms and thighs in the last six months and was T3bN0M0at the time of diagnosis. This patient died within one month of diagnosis.

There was one 48-year-old lady with lymphomatoid papulosis who presented with recurrent itchy crusted papules on extremities and abdomen in the last one year. She was in stage T3bN0M0 at the time of diagnosis; was started on methotrexate and was in remission at last follow-up at 4 months after diagnosis.

Primary cutaneous Peripheral T-cell lymphoma

There was one 40-year-old male with primary cutaneous CD8 positive aggressive epidermotropic T-cell lymphoma (Fig. 2a). He presented with multiple ulcerated necrotic, and crusted plaque on scalp, face, trunk, and extremities in the last 6 months. The final diagnosis was based on histopathology and immunohistochemistry (Fig. 2b). He was in stage T3bN0M0 and died within 2 months of diagnosis.

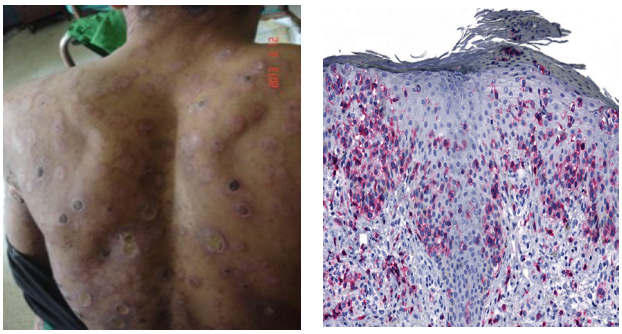

Figure 2 a. CD8+ve Aggressive Epidermotropic Primary cutaneous T- cell lymphoma b. Histopathology showing CD8+ staining in CD8+ Aggressive Epidermotropic Primary Cutaneous T-cell Lymphoma

Primary cutaneous B-cell lymphoma

There was one case of primary cutaneous follicle centre lymphoma (PCFCL) in a 55-year-old female who presented with two erythematous and shiny plaque behind left ear in the last three months and was in stage T1N0M0 at the time of diagnosis. She was treated with intralesional triamcinolone and was in remission at follow-up of at seven months. The second patient was a 45-year- old lady with primary cutaneous marginal zone lymphoma (PCMZL) with multiple erythematous juicy nodules on forehead, both malar areas, both ear, and nasal septum in the last 16 years. She was in stage T2aN0M0 at the time of diagnosis and was not on any chemotherapy and had recurrence of lesions at last follow-up.

Survival

There were three deaths in this study; one case of MF (IB) died after six months of diagnosis, one cases of Primary cutaneousCD8+ aggressive epidermotropic T-cell lymphoma (T3bN0M0) died within two months of diagnosis, and one case of PCALCL (T3bN0M0) died after one month of diagnosis.

DISCUSSION

These cases collected over ten years though small has increased our knowledge on clinical and pathological features of primary cutaneous lymphomas diagnosed so far in Nepal and in this region. The first case of primary cutaneous lymphoma in Nepal using WHO classification

Table 1. Spectrum of Primary cutaneous lymphomas

Cutaneous T-cell Lymphomas	Cutaneous B-cell lymphomas
Mycosis Fungoides (MF)	-Primary cutaneous marginal zone B-cell lymphoma -Primary cutaneous follicle center lymphoma -Primary cutaneous diffuse large B-cell lymphoma, leg type -EBV-positive mucocutaneous ulcer (provisional)
MF variants Folliculotropic MF Granulomatous slack skin Pagetoid reticulosis	
Sezary syndrome	
Adult T cell- leukemia/ lymphoma	
Primary cutaneous CD30+ lymphoproliferative disorders -Lymphomatoid papulosis -Primary cutaneous anaplastic large cell lymphoma	
Subcutaneous panniculitis-like T- cell lymphoma	
Primary cutaneous peripheral T -cell lymphoma, rare sub types -Primary cutaneous gamma/delta T-cell lymphoma -Primary cutaneous aggressive epidermo-tropicCD8+positive T-cell lymphoma (provisional) -Primary cutaneous CD4+ small /medium- sized Pleo-morphic T cell-lymphoproliferative disorder (provisional) -Primary cutaneous acral CD8+ T cell lympho-ma (provisional)	
Primary cutaneous Peripheral T- cell lymphoma, not otherwise specified	
ExtranodalNK/T- cell lymphoma, nasal type	
Chronic active EBV infection	

Table 2. Summary of patients with PCLs

Age	Diagnosis	Staging at presentation	Duration of illness at the time of diagnosis	Treatment received	Status of patient
70 years/F	MF plaque stage with co existent Hodgkins's lymphoma diagnosed few months later	IB	48 months	Methotrexate only as patient could not afford chemotherapy	Death after 6 months of diagnosis
24 years/F	Primary cutaneous CD30 positive anaplastic large cell lymphoma	T1N0MO	10 days	Excision	No lesions till date
19 years/F	Folliculotropic Mycosis Fungoides with Follicular mucinosis	IB	3 years	TSEB	Remission at follow up of 6 months
55 years/F	Follicle centre lymphoma	T1N0M0	3 months	Intralesional triamcinolone injection	Remission till date at follow up of 7 months
48 years/F	Lymphomatoid papulosis, Type E	T3bN0M0	12 months	Methotrexate	Remission till date at 4 months follow- up after diagnosis
45 years/F	Cutaneous marginal zone lymphoma	T2aN0M0	16 years	Not an any chemotherapy	Recurrence
59 years/M	Folliculotropic mycosis fungoides with follicular mucinosis	IIB	18 months	Not on any treatment /pt received intralesional injection before the diagnosis (previously diagnosed as jessners lymphocytic infiltrate)	Self remission at follow-up
81 years/M	CD30 Positive Anaplastic large cell lymphoma	T3bN0M0	5 months	Methotrexate	Remission at follow up of one and half months
80 years/M	CD 30 positive Anaplastic large cell lymphoma	T2aN0M0	3 months	Methotrexate	Remission at follow-up of 8 years
40 years/M	Primary cutaneous CD8+ aggressive epidermotropic T cell lymphoma	T3bN0M0	6 months	Did not receive treatment because of affordability	Death after 2 months of diagnosis
81 years/M	Primary cutaneous CD30+ anaplastic large cell lymphoma	T3bN0M0	6 months	No treatment	Died within one month of diagnosis
39 years/M	Mycosis Fungoides	IB	2 years	Chemotherapy	Partial remission at follow-up

was reported in 2012.[9] The article had highlighted that in absence of expertise, immunohistochemistry, and follow-up, most of the cases were probably treated initially as eczema and other granulomatous conditions. Since then, a substantial number of cases have been diagnosed which could be due to both improved diagnosis and awareness about the disease.

The age of distribution in our study ranged from 19 years to 81 years, predilection towards young age, results similar to one of the study from south India.[10] It is different from other study in United States, where older age seems to be more affected.[11] Contrary to other studies, we found equal distribution of males and females which again is too early to comment because of low number of cases in our study and requires further study in future with large number of cases.[12-14]

The time to diagnosis in this study ranged from 10 days to 16 years much worse than reported median 3 years (1-7.5 years) by Hodak et al.[15] This could be due to decreased awareness amongst physician about cutaneous lymphomas, contributed largely by absence of laboratory essentials for its diagnosis. In our cohort, we saw predominant CTCL (83.3%) than CBCL (16.7%) as seen in other studies from US, and other European country.[11,13] No cases of Adult T-cell leukemia/lymphoma, subcutaneous panniculitis like T- cell lymphoma , Peripheral T –cell lymphoma, not otherwise specified were diagnosed in our study in contrast to the study from neighbouring country India , where these cases were reported which could be due to low number of cases in our study.[10]

Primary cutaneous CD30 positive lymphoproliferative disorders were predominant (5 out of 10 cases of CTCL, 50%) in our study in contrast to MF, 4 out of 10, 40%) which is predominant all over the world.[5,14] This could again be due to low number of cases or because most MF are treated as eczemas before they transform into nodular stage which brings attention of the patient and warrants for physician visit.

In our cohort, CBCL constituted 16.7% of PCLs like the studies from Austria where CBCL accounted for 17% of all PCLs.[13] In our study, the frequency of PCFCL and PCMZL were equal as seen in the studies from Austria.

Staging of the disease is very crucial in management of the patients of PCLs.[16] In our cohort the staging was based on the new Tumour-node-metastasis-blood (TNMB) proposed by International Society of Cutaneous lymphomas (ISCL) and cutaneous lymphoma task force of European Organization for Research and Treatment of Cancer (EORTC).[3] The staging of our cases has been summarized in table 2. It was seen that, most of the cases were diagnosed in stage IB contrary to findings in studies from west, where the disease was diagnosed at stage IA-IIA.[13]

We had one rare variant Primary cutaneous aggressive pidermotropicCD8+ T-cell lymphoma, unusual to be diagnosed even in this small number of cohort (different from other series).[4,11-13] There were three deaths in our series, because of unaffordability and delay in diagnosis.

Although this study adds new data on clinical and pathological features of PCLs in Nepal, there are limitations of this study i) this study was conducted in only one centre located in one geographic location ii) this is retrospective study and the data were retrieved from the department of dermatology and pathology; there are high chances that we missed data of the patients who were not suspected as having cutaneous lymphomas and were not subjected to biopsies. Moreover, there may be observer variation from the department for initial diagnosis. However, this is the first cohort of primary cutaneous lymphomas described from Nepal. The study highlights importance of considering cutaneous lymphomas as one of the important diseases in our context.

CONCLUSION

In conclusion, this is the first study to clinically characterize PCLs in Nepal. CTCLs and CBCLs were both seen in this cohort with predominance of CTCLs. Mycosis Fungoides and PCALCs were predominant diagnoses in this study. This was a single hospital-based cohort study which could be the reason for small number of cases. Dermatologists should have high index of suspicion to diagnose patients with PCLs early for timely intervention. Furthermore, this study calls for nationwide studies to further characterize cutaneous lymphomas for strengthening/allocating resources for both diagnosis and treatment of this condition.

ACKNOWLEDGEMENTS

We would like to acknowledge and thank Prof. Werner Kempf, from University of Zurich, Switzerland for his unwavering support by reviewing the biopsy samples and help us reach the final diagnosis in difficult to diagnose cases. At the same time, we would like to thank Prof. Ramchandra Adhikari, Department of Pathology for his dedication in reviewing skin biopsy samples send from our department.

REFERENCES

1. Lima CDS, Lima CDS, Goes HFD, Duraes SMB. Clinical and epidemiological characteristics of primary cutaneous lymphomas in a university hospital in Rio de Janeiro – Brazil. *J Am Acad Dermatol*. 2017 Jun;76(6):AB72.
2. Stoll JR, Willner J, Oh Y, Pulitzer M, Moskowitz A, Horwitz S, et al. Primary cutaneous T-cell lymphomas other than mycosis fungoides and Sézary syndrome. Part I: Clinical and histologic features and diagnosis. *J Am Acad Dermatol.* 2021 Nov;85(5):1073–90.
3. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood.* 2019 Apr 18;133(16):1703–14.
4. Pruksaeakanan C, Teyateeti P, Patthamalai P, Thumrongtharadol J, Chairatchaneeboon M. Primary Cutaneous Lymphomas in Thailand: A 10-Year Retrospective Study. Nikkels AF, editor. *Bio Med Res Int*. 2021 Jun 11;2021:1–8.
5. Kempf W, Zimmermann A, Mitteldorf C. Cutaneous lymphomas—An update 2019. *Hematol Oncol.* 2019 Jun;37(S1):43-7.
6. Raychaudhury T. Cutaneous lymphomas in India: Prospects and limitations. *Indian J Dermatol.* 2017;62(2):135.
7. Aziz Z, Ali N. Primary Cutaneous B-Cell Lymphoma in a Young Female. Cureus [Internet]. 2023 Jul 19 [cited 2024 May 31]; Available from: https://www.cureus.com/articles/154084-primary-cutaneous-b-cell-lymphoma-in-a-young-female
8. Barman TK, Shahidullah M, Rahman MH, Huda MN. Sixty years old man with primary cutaneous lymphoma. *Mymensingh Med J*. 2015 Jan;24(1):182–5.
9. Parajuli S, Gurung D, Paudel U, Pokhrel DB, Kempf W. Primary cutaneous CD30-positive anaplastic large cell lymphoma in an 80-year-old man: a case report from Nepal. *Int J Dermatol.* 2014 Dec;53(12):1498–500.
10. Khader A, Manakkad S, Shaan M, Pillai S, Riyaz N, Manikoth PB, et al. A clinicopathological analysis of primary cutaneous lymphomas: A 6-year observational study at a tertiary care center of south India. *Indian J Dermatol.* 2016;61(6):608.
11. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood.* 2009 May 21;113(21):5064–73.
12. Maurelli M, Tessari G, Colato C, Schena D, Girolomoni G. Incidence and ten-year follow-up of primary cutaneous lymphomas: a single-centre cohort study. *Eur J Dermatol.* 2018 Jan 1;28(1):44–9.
13. Eder J, Kern A, Moser J, Kitzwögerer M, Sedivy R, Trautinger F. Frequency of primary cutaneous lymphoma variants in Austria: retrospective data from a dermatology referral centre between 2006 and 2013. *J Eur Acad Dermatol Venereol.* 2015 Aug;29(8):1517–23.
14. Lee CN, Hsu CK, Chang KC, Wu CL, Chen TY, Lee JYY. Cutaneous lymphomas in Taiwan: A review of 118 cases from a medical center in southern Taiwan. *Dermatol Sin.* 2018 Mar;36(1):16–24.
15. Hodak E, Geskin L, Guenova E, Ortiz-Romero PL, Willemze R, Zheng J, et al. Real-Life Barriers to Diagnosis of Early Mycosis Fungoides: An International Expert Panel Discussion. *Am J Clin Dermatol.* 2023 Jan;24(1):5-14.
16. Cerroni L. Past, present and future of cutaneous lymphomas. *Semin Diagn Pathol.* 2017 Jan;34(1):3-14.