International Journal of Science and Healthcare Research
[Indexed, Peer-Reviewed Journal]
Vol. 10; Issue: 4; Oct.-Dec. 2025
Website: ijshr.com
Case Series *ISSN: 2455-7587*

The Clinicopathologic Spectrum of Primary Cutaneous Lymphomas - A Single Centre Experience

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DOI: https://doi.org/10.52403/ijshr.20250423

ABSTRACT

Background: Primary cutaneous lymphomas (PCL) are non-Hodgkin lymphomas that present primarily in the skin with, primary cutaneous T-cell lymphoma (CTCL) being the most common sub-type. CTCL is associated with malignant CD4+ T-cells and often involves genetic dysregulation. Diagnosis of PCL can be challenging due to its varied clinical presentations.

Objective: This study evaluated the clinical, histopathological, and immunohistochemical (IHC) features of PCL and highlighted the importance of biopsy in early diagnosis.

Materials and Methods: We retrospectively reviewed 10 cases of diagnosed PCL over a four-year period at a tertiary care center. Clinical data including age, sex, presenting complaints, HIV status were collected and histopathological examination and IHC staining for T-cell (CD3, CD4, CD8, CD30) and B-cell markers (CD19, CD20) were performed on skin biopsies. All patients were thoroughly evaluated clinically for the type of skin lesions, organomegaly, lymph node status and their hematological profile was also looked into.

Results: The mean age of patients was 65 years. Clinical presentations included hyper pigmented patches (20%), hypopigmented patches (30%), erythematous lesions (30%) and infiltrative lesions (10%). Among 10cases, 9were primary cutaneous T-cell lymphoma and 1was primary cutaneous B-cell lymphoma

Conclusion: PCL presents with diverse clinical manifestations, making early diagnosis challenging. Histo pathological examination and IHC are essential for accurate diagnosis and treatment planning.

Keywords: Primary cutaneous lymphoma, Sezary syndrome, Histopathology, Immunohistochemistry, Clinical presentation, Skin biopsy, Lymphoma diagnosis, T-cell markers, B-cell markers

INTRODUCTION

Primary cutaneous lymphomas comprise a wide variety of B and T cell non-Hodgkin lymphomas that clinically manifest in the skin without extracutaneous involvement. Mycosis fungoides (MF) and Sezary syndrome are the most common type of primary cutaneous T-Cell lymphoma (pCTCL), comprising 75-80% of pCTCL (1,2). MF is known for its diverse clinical manifestations ranging from patches, plaques, papules and nodules to ulcerated lesions progressing to involve the lymph nodes and blood (3–5). The second most common CTCLs are primary cutaneous

CD30+ LPDs which include both primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. The rare variants represent only 1–2% of all cutaneous lymphoma cases and mostly include entities with uncertain malignant potential and run an indolent clinical course (1). Symptoms include a wide variety of cutaneous lesions which affect the quality of life of these patients and primarily depend on the stage of the disease (6). Pruritus, scaling and erythroderma are the most common symptoms observed (6). The physical and mental health of these individuals are affected, with many patients showing signs of depression and severe anxiety (7). MF mimics several inflammatory dermatoses making it difficult to diagnose it at an early stage. The histopathological parameters of MF are found to overlap with many benign dermatoses, hence a careful assessment of histology along with immunophenotyping is necessary to arrive at a conclusive diagnosis (8). This study conducted at a tertiary care centre gives an insight to its varied clinical presentations, pathological and immunohistochemical (IHC) features of PCL. It also highlights the significance of biopsy in providing an early diagnosis and treatment.

METHODOLOGY

This study was conducted in dermatology department of tertiary care centre, located at Thrissur, Kerala. The study was conducted from January 2019 to December 2023 after obtaining the approval of the Institute Ethics Committee. This study includes ten diagnosed and confirmed cases of MF highlighting their clinical presentations, histopathological and IHC features, treatment and outcomes. We excluded patients with hypertension and neuroendocrine disease.

Patient information such as age, sex, presenting complaints, HIV status, treatment received, response to treatment, and outcome were recorded. All ten patients underwent relevant investigations, including a hemogram with peripheral smear and biochemistry tests. Skin biopsy was taken from all patients. The diagnosis of T cell lymphoma was made by presence of band like infiltration composed of atypical lymphocytes in 9out of 10 cases. For confirmation, we used immunohisto-chemical markers like CD45, CD3, CD5, CD7, CD4, CD8, CD30 which showed positivity in the atypical T cells with an altered CD4:CD8 ratio with aberrant loss of CD7. One among these 9 cases showed positivity for ALK and turned out to be ALCL. Skin biopsy from a single patient showed a nodular neoplasm composed of atypical lymphoid cells with bottom heavy appearance. On immunohistochemical examination, the cells showed positivity for B cell markers like CD19 and CD20. Hence diagnosed as B cell lymphoma.

RESULT

Ten patients diagnosed in the past 4 years (2021 & 2024) were evaluated (6 males and 4 females) with a mean age of 65 years. Among them, two patients presented with hyperpigmented scaly patches (20%), three with hypopigmented patches (30%), three presented with erythematous lesions (30%) (Figure1). One patient presented with pruritus and scaling resembling psoriasis (10%) (Figure 2), and another patient had infiltrating lesions around eye, nose and throat (10%) (Figure 3). None of the patients had lymphadenopathy. Hematological profile of all 9 were normal, only one case with hypopigmented lesions presented with atypical lymphoid cells in the peripheral blood; she was then referred to a higher centre for flowcytometric immunophenotyping and was diagnosed as Sezary Syndrome. Biopsy from hyper and hypopigmented lesions showed epidermotropism with dermal atypical lymohoid infiltrates (60%), Some of which showed convoluted morphology with irregular hyperchromatic nuclei. Band like atypical lymphocytic infiltrate in the papillary dermis without epidermotropism was seen in patients with erythematous

papular lesions (30%). Papillary dermis also showed coarse fibrosis with interstitial pattern of dermal infiltration. Patient with infiltrating lesions in eyes, nose and throat showed nodular neoplasm of B cell origin with bottom heavy appearance composed of centrocyte like cells with cleaved nuclei (10%). No systemic symptoms like lymphadenopathy / weight loss were observed in any of our cases. All cases were confirmed by immunohistochemistry with the following IHC markers CD45, CD3, CD5, CD7, CD4, CD8, CD30, ALK. Nine out of ten cases were of T cell origin with one being ALCL. All T cell lymphomas showed altered CD4:CD8 ratio with aberrant loss of CD7. The one with nodular infiltrate was confirmed by positive B cell IHC markers like CD19 and CD20.

Table 1: Clinical Presentation of The Mycosis Fungoides Patients (*n*=10)

Clinical presentation	Frequency	Percentage
Pruritus	6	60
Scaliness	5	50
Erythema	3	30
Hyperpigmented lesions	2	20
Hypopigmented lesions	3	30
Keratoderma	1	10
Weight loss	0	0
Lymphadenopathy	0	0
Sezary syndrome	1	10
Infiltrating lesions	1	10

Figure 1: TCell lymphoma presenting as scaly patches & plaques

Figure 2: Tcell lymphoma presenting like psoriasis, with erythematous scales

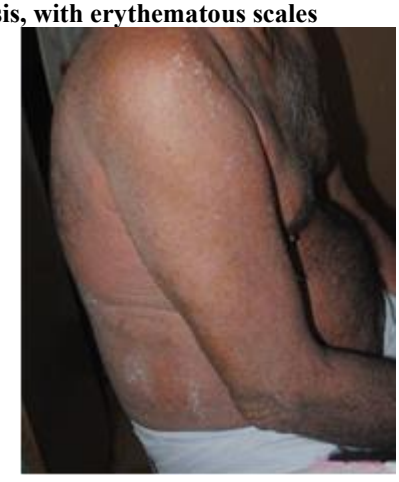

Figure 3: B cell lymphoma presenting as erythematous plaques & nodules

DISCUSSION

According to the current World Health Organization and European Organization for Research and Treatment (WHO & EORTC) Primary Cutaneous Lymphomas have been classified into B and T cell non-Hodgkin lymphomas with cutaneous involvement and those without cutaneous involvement at the time of presentation. (1) MF is the most commonly encountered Primary Cutaneous T Cell Lymphomas (pCTCL) and accounts for approximately half of the cases of pCTCL. (9) Mycosis Fungoides is

considered a "great mimicker" as it resembles several benign dermatoses both clinically and histologically. (10) It is often misdiagnosed especially in the early stages which results in profound delay and hence is considered a reason for its poor prognosis. (11,12) Primary cutaneous T cell lymphomas differ from other lymphomas because of their unique clinical presentation, morphological features, genetic and immunological characteristics. Classic cases of MF present as cutaneous patches, plaques or tumors. Several unusual clinical and histopathological variants have been described including Granulomatous slack skin disease (GSS), Folliculotropic and Pagetoid reticulosis (PR). (13) Granuloma annulare like MF and cutis laxa like MF have also been described recently. (14)

The diagnosis of MF is often delayed for several months or even years consequently resulting in a higher stage at presentation thereby affecting the prognosis. (15) Proper diagnostic protocols should be followed to enable a timely diagnosis particularly in cases refractory to treatment and a high index of suspicion necessary to avoid misdiagnosis. Among the factors that determine the prognosis include age, extent of involvement, cytomorphology and exact subtype. (16) The differential diagnosis of pCTCL should be considered in any skin biopsy with dense lymphoid infiltrate because of the overlapping histological features and it is mandatory to perform immunohistochemistry in all doubtful cases to exclude cutaneous reactive lymphoid hyperplasia /pseudolymphoma. (15,17)

The diagnostic hallmark of MF is the small / medium sized atypical lymphoid cells with irregular convoluted nuclei and perinuclear halo. (8,18) The histological features to be considered for all suspicious cases are the type of lymphoid infiltrate, extent of epidermal and dermal involvement, immunophenotypic findings and gene rearrangement studies to prove clonality. (15,17) Morphologically, the atypical lymphoid cells are enlarged with irregular convoluted nuclei, perinuclear halo and they tend to localize as aggregates in the epidermis termed Pautrier's microabscess. (8) Fibrosis in the papillary dermis is also commonly observed. (19) Since MF morphologically mimics several inflammatory dermatosis ancillary tests are required to confirm the diagnosis. The lymphoid cells in MF are positive for CD3, CD5 with down-regulation of CD 7 and majority showing increased CD4:CD8 ratio. (5) Hence the diagnosis of MF is confirmed by immunohistochemically demonstrating atypical CD4+ T cells in the dermis with most cases showing associated epidermotropism as well. Of the various histological parameters employed for diagnostic purpose of MF, the most robust discriminator found was the presence of haloed atypical lymphoid cells. (8,20) The atypical cells may also disseminate into blood and lymph nodes in advanced stages of MF; more often seen in patients presenting with advanced clinical stage, erythroderma, patch and plaque stage. (11) From the prognostic point of view, patients with extra cutaneous disease, systemic involvement and hematogenous dissemination are found to have a worse outcome. (11,12,21)

This study was conducted to give an insight into the various atypical clinical presentations of MF and to sensitize clinicians regarding the need for a biopsy in long standing chronic dermatosis refractory to conventional treatment modalities. Aggressive variants of pCTCL like anaplastic large cell lymphoma may mimic atopic dermatitis prolonging treatment for several months and even years as in our case. (10) Skin biopsy is mandatory in all such cases to arrive at a prompt and timely early diagnosis as survival rates are found to drastically decrease with systemic involvement. Prognosis is grim as the stage advances. (15) Hence it is of utmost importance to have an awareness of the different clinical presentations of MF so as to avoid delay in diagnosis. A high index of suspicion and a prompt clinicopathological assessment are required in all skin patches

and plaques masquerading as inflammatory skin lesions, especially those with a chronic course not responding to treatment. Prognosis is vague in advanced stages of primary cutaneous T cell lymphoma and it in turn affects the physical and mental status of the patients. (7)

Diagnosis of MF particularly in the early stages is quite challenging. Serial repeat biopsies may be required in some cases to arrive at a conclusive diagnosis. (18) Amongst the several histological features, presence of enlarged atypical lymphoid cells with convolutions and perinuclear halo, demonstrating epidermotropism, exocytosis and Pautriers micro-abscesses were found to be most helpful in distinguishing MF from their inflammatory mimics. (8) Basal layer tagged with lymphoid cells were also a consistent feature in most cases. Morphological features and immunohistochemical findings should be interpreted with caution taking into consideration a detailed clinical history including treatment modalities used. An interdisciplinary team comprising a dermatologist, dermatopathologist and a hematooncologist is necessary to ascertain the diagnosis of pCTCL. (22) Recent diagnostic modalities with advances in imaging and novel molecular technologies including DNA micro array have greatly helped in early diagnosis and improving the patient outcome. (2) The overall survival seems to be better in those patients with limited disease without constitutional symptoms and bone marrow involvement. (18).

CONCLUSION

Mycosis fungoides simulates many non-neoplastic dermatological conditions and poses a diagnostic challenge to most clinicians and pathologists alike. Diagnosing MF at an early stage is particularly important because of the impact it has on treatment and patient survival. Many patients with skin lesions are erroneously diagnosed and treated for several months and years together as chronic eczema or psoariasis due to lack of clinical suspicion and dearth of sufficient tissue for histopathological diagnosis. Hence it is of utmost importance to recognize the different atypical presentations of MF and follow up all chronic dermatological conditions not responding to treatment to prevent further progression and reduce morbidity and mortality due to the disease.

Declaration by Authors

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Deepthy Vijayaraghavan, Varghese James, David Pudukadan. The clinicopathologic spectrum of primary cutaneous lymphomas - a single centre experience. *Int. J. Sci. Healthc. Res.* 2025; 10(4): 158-164. DOI: *10.52403/ijshr.20250423*

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