Peculiarities of Cutaneous Lymphomas among Black Africans and Management Conundrums in Resource Limited Settings

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ABSTRACT

Background: Primary cutaneous lymphomas (PCLs) are a rare and heterogeneous group of lymphoproliferative neoplasms that very often pose a diagnostic challenge particularly in resource limited countries. People of African ancestry have a higher disease burden, a younger age at onset and poorer treatment outcome. Withal, research focusing on clinical pattern, behaviour and treatment of PCLs in blacks is scarce and as such, advances in knowledge of the pathogenesis of PCLs as well as the discovery of newer molecular markers that have revolutionized diagnosis and treatment are yet to translate to improved clinical outcomes in blacks.

Aim and Methods: This review aims to provide an overview of the unique features of PCL in blacks using data from existing scientific works describing cutaneous lymphomas in the context of the black skin. We highlight the peculiarities of the disease in blacks as well as provide an insight into the challenges of diagnosis and treatment of cutaneous lymphomas in resource-limited environments.

Conclusion: There are poorly understood racial influences on the epidemiology, clinical and histological pattern of primary cutaneous lymphomas with therapeutic and prognostic implications. The paucity of research on the subject matter among Africans precludes accurate characterization of cutaneous lymphomas in blacks. More studies are therefore required on PCLs in blacks particularly in Africa, to enhance our understanding of these peculiarities which may ultimately translate to improvement in diagnosis, preventive strategies and treatment outcomes.

Keywords: *Cutaneous lymphoma*, *Skin cancer, Africans, resource-limited*

Les Particularités des Lymphomes Cutanés chez les Noirs Africains et Énigmes de Gestion dans des Environnements à Ressources Limitées

ABSTRAIT

Les lymphomes cutanés primaires (LCP) sont un groupe rare et hétérogène de néoplasmes lymphoprolifératifs qui posent très souvent un défi diagnostique, en particulier dans les pays à ressources limitées. Les personnes d'ascendance africaine ont une charge de morbidité plus élevée, un âge d'apparition plus jeune et des résultats de traitement plus médiocres. Cependant, la recherche axée sur le schéma clinique, le comportement et le traitement des LCP chez les Noirs Africains est rare et en tant que telle, les progrès dans la connaissance de la pathogenèse des LCP ainsi que la découverte de nouveaux marqueurs moléculaires qui ont révolutionné le diagnostic et le traitement ne se traduisent pas encore par une amélioration résultats cliniques chez les Noirs Africains.

Cette revue vise à fournir un synthèse des caractéristiques uniques de la LCP chez les Noirs Africains en utilisant les données des travaux scientifiques existants décrivant les lymphomes cutanés dans le contexte de la peau noire. Nous mettons en évidence les particularités de la maladie chez les Noirs Africains et donnons un aperçu des défis du diagnostic et du traitement des lymphomes cutanés dans des environnements à ressources limitées.

Il existe des influences raciales mal comprises sur l'épidémiologie, le schéma clinique et histologique des lymphomes cutanés primaires avec des implications thérapeutiques et pronostiques. Le manque de recherche sur le sujet chez les Africains empêche une caractérisation précise des lymphomes cutanés chez les Noirs. Davantage d'études sont donc nécessaires sur les LCP chez les Noirs, en particulier en Afrique, pour améliorer notre

compréhension de ces particularités qui pourraient finalement se traduire par une amélioration du diagnostic, des stratégies préventives et des résultats du traitement.

Mots clés: Lymphome cutané, Cancer de la peau, Africains, ressources limitées

Introduction

Primary cutaneous lymphomas (PCLs) are rare malignant disorders of mature lymphoid cells occurring primarily in the skin. They have a completely different clinical behavior and prognosis from their nodal or systemic histologically similar counterparts. PCLs are defined as a heterogeneous group of lymphoproliferative neoplasms comprising of distinct clinic-pathological entities with diverse pathogenesis, clinical manifestations, clinical course and prognosis manifesting primarily in the skin without evidence of extracutaneous involvement at the time of diagnosis [1-5]. There are however some clinical and histological subtypes of PCLs that do not fit into this classic definition which may present with or develop systemic involvement early in the course of the disease.[4,5] Generally, PCLs are categorized into two main groups; Primary Cutaneous T-Cell Lymphomas (CTCLs) and Primary Cutaneous B cell lymphomas (CBCLs) based on the predominant infiltrating cell type. Each group has relatively distinct sub-classification, histopathological features and clinical behavior.

Due to their relative rarity and diverse clinicopathological features, PCLs present a substantial amount of diagnostic and therapeutic challenge even to the experienced physician. Achieving prompt and accurate diagnosis is even more difficult in resource limited settings where appropriate technical and laboratory support are lacking. Dermatologists working among predominantly dark-skinned populations are faced with the additional challenge of insufficient data on variants of PCL unique to the skin of color which may mimic a variety of less sinister skin conditions contributing to delayed diagnosis and poorer outcomes of treatment in them.

Epidemiology of Primary Cutaneous Lymphomas

Primary cutaneous lymphomas are the second most common site of extra-nodal lymphomas [5,6] constituting about 19% of all extra-nodal non-Hodgkin lymphomas (NHLs) [5]. They affect predominantly middle aged to elderly individuals with double peak incidences at 50-60 and 70-80years[5,7]. There is a consistent male predominance in all subtypes of cutaneous lymphomas [5,7,8] with a male to female ratio of 1.72:1[5].

Racial and geographical factors influence the prevalence, pattern and distribution of PCLs with variable mean ages at diagnosis and clinical behavior of the disease among different ethnic groups [5,8-10]. In the US, African-Americans are the more commonly affected ethnic group. They tend to develop the disease at an earlier age and have higher disease stage at diagnosis[5,8,11]. There however appears to be lower incidences of some types of PCLs particularly CD30+ lymphomatoid papulosis amongst them [5]. Reasons for the observed epidemiological differences in PCLs among different racial groups are not fully understood, however, it has been suggested that biological differences in the pathogenesis of the disease may be partly responsible.[8]

In Africa, PCLs are rarely reported both in hospital and community based studies [9,10]. Epidemiological surveys specifically assessing prevalence of PCLs in Africa are almost non-existent. Most data are obtained from studies on general epidemiological pattern of skin cancers in various parts of the continent most of which fail to document PCLs. This is probably ascribable to the tendency of PCLs to mimic other relatively more benign skin diseases both clinically and histologically and the scarcity of more advanced diagnostic tools in resource limited settings.

In a retrospective study of skin cancers in the Northern Cape province of South-Africa, mycosis fungoides comprised 0.07% of all skin cancers diagnosed over a 5 year period [12]. In a nine year retrospective study of cutaneous lymphomas in Botswana, only 38 cases of PCLs were documented of which mycosis fungoides was the most frequently diagnosed PCL [13]. In Nigeria, Samaila et al [14] and Ochicha et al [15] in separate retrospective studies spanning 10years each recorded no case of PCL over the study period. While a more recent study by

Oseni et al[16] documented a prevalence of 2% of all cutaneous malignancies recorded in the South-Western part of the country. Very few case reports and case series describe the occurrence, clinical pattern and behavior of PCLs in sub-Saharan Africa[13]. Given the tendency of early PCLs to mimic a variety of common dermatoses, it is possible that the low incidence rates documented among Africans is a function of the diagnostically elusive nature of PCLs rather than a true rarity of the disease.

Etiology and Pathogenesis of Primary Cutaneous Lymphomas in Black Africans

Cutaneous lymphomas are monoclonal proliferations of T and B cells in the skin[17]. The exact stimulus for clonal lymphocyte expansion is yet to be identified however, various theories about immunodeficiency and persistent antigenic stimuli by environmental or exogenous factors such as drugs (hydrochlorothiazide), bacteria (*Borrelia burgdorferi*, *Staphylococcus aureus*), and oncogenic viruses (Epstein Barr virus, Human T Cell lymphocytic virus) as well as other environmental factors have been proposed[18-26].

It is important to note that black Africans are often exposed to one or more of these proposed stimuli in the course of their life time. Hydrochlorothiazide a diuretic for instance, is one of the most commonly prescribed antihypertensive among black Africans. Similarly, mosquito bites and infectious diseases implicated in the pathogenesis of some CLs including those caused by oncogenic viruses such as Epstein Barr virus (EBV) and the Human T cell lymphocytic virus (HTLV) are endemic in Africa. It appears that dark skinned people are particularly susceptible to HTLV an important trigger for Adult T cell leukemia/ lymphoma (ATLL). In the United States, South America and Europe, the prevalence of HTLV-1 and ATLL is highest in individuals of African ancestry[27]. Studies in Africa have also found a disproportionately higher prevalence of HTLV infection amongst black Africans in comparison to other racial groups[28].

The recently revised WHO-EORTC classification recognizes a subset of cutaneous lymphoproliferative disorders associated with chronic active EBV infection termed the hydroa-vacciniforme-like lymphoproliferative disorder and hypersensitivity reactions to mosquito bite[29]. Both conditions have a potential to progress to systemic lymphomas and have been described mainly in children and adolescents from Asia, Central and South America [29,30]. There is insufficient data describing the occurrence of these disorders among black Africans despite the endemicity of EBV infection and mosquitoes.

The differences in etiologic stimulus for PCLs may thus partially account for differences in clinical subtypes and behavior of the various forms of cutaneous lymphomas in black Africans when compared with other racial groups. However, there is a dearth of studies establishing the link between these oncogenic viruses and the burden of cutaneous lymphomas in Africa.

Irrespective of skin color or the underlying etiologic stimulus, three main pathophysiologic mechanisms have been implicated in the establishment and progression of skin lymphomas[18,22,23]. These are:

- Cutaneous infiltration and expansion of specific lymphocyte clones.
- Suitable microenvironment that promotes proliferation and expansion
- Defective antitumor suppressor response.

Cutaneous T-cell Lymphomas are characterized by the persistence and proliferation of a malignant clone of CD45RO+ memory T cells in the skin[31]. Their persistence and growth is supported by the epidermal microenvironment rich in cytokines such as IL7 and IL15 produced by keratinocytes that serve as T cell growth factor[23,31]. These malignant clone of cells remain confined to the skin in the early stages, however as disease progresses, they lose their dependence on the skin environment and can spill into the blood and/or spread to the lymph nodes and other visceral organs [31]. Defective host antitumor response contributes the ability of the malignant cells to escape immune surveillance, leading to the establishment and progression of the disease[23].

Primary cutaneous B cell lymphomas on the other hand are believed to develop from skin associated lymphoid tissue following chronic antigenic stimulation. This mechanism is particularly implicated in the development of primary cutaneous marginal zone lymphoma (PCMZL) which has been

linked with infection with Borrelia burgdoferi in some geographical locations [1]. Abnormal cellular differentiation stemming from aberrant gene expression and chromosomal translocations have also been implicated in the pathogenesis of certain types of B cell lymphomas. These include t(11;18) (q21;q21) and t(14;18) (q32;q21) identified in some cases of PCMZL, deletion of chromosome 14q32.33 in cutaneous follicular center lymphoma and translocations involving MYC, BCL6 and IGH genes in diffuse large B-Cell Lymphoma, Leg Type[1,32].

Inherited genetic factors may also play a role in the pathogenesis of cutaneous lymphomas as specific Human Leukocyte Antigen (HLA) class II alleles have been found in some cases of sporadic as well as familial MF[33,34]. Genetic mutations that predispose to BCLs that are specific for black Africans have however not been described.

Classification of Primary Cutaneous Lymphomas

Cutaneous lymphomas were previously classified based on their histologic appearance in an identical manner to lymphomas arising in lymph nodes [17,35]. However because extracutaneous lymphomas behave in a clinically different manner from their nodal counterparts, this classification system had major shortcomings in predicting the outcome of CLs hence the emergence of newer classification schemes over time[17,35].

The World Health Organization classification and the World Health Organization/European Organization for Research and Treatment of Cancer consensus (WHO-EORTC) classification is the most widely accepted classification scheme. It recognizes the distinct forms of PCLs based on their clinical histological, immunophenotypic and genetic features[17]. This scheme broadly groups PCLs based on their cell type into: T-cell lymphomas or B cell lymphomas [17,35] and subsequently into various subtypes.

A relatively simpler and probably more practical classification for practice based in resource limited settings where facilities for immunophenotyping are often unavailable is one in which cutaneous lymphomas are grouped based on their clinical behavior into[36]:

a. Semi-malignant or abortive lymphomas such as lymphomatoid papulosis (worringer kollop type) and pagetoid reticulosis which are non-progressive, chronic cutaneous lymphomas that do not typically spread systemically and are not life threatening.
b. Indolent progressive malignant lymphomas such as mycosis fungoides and sezary syndrome which are slowly progressive primary cutaneous lymphomas with a tendency for systemic spread in advanced stages.
c. Aggressive progressive malignant lymphomas including disseminated large T cell, NK cell or B cell lymphomas as well as precursor haematologic neoplasms; blastic plasmacytoid dendritic cell neoplasm, which run an aggressive clinical course and have poor prognosis.
d. Pseudolymphomas: these are reactive lymphoproliferative disorders rather than lymphomas which regress either spontaneously or with treatment and generally do not recur.

Diagnosis of Primary Cutaneous Lymphomas in Resource Limited Settings

Clinical features along with histopathologic and cytomorphologic features are sufficient to make a diagnosis in about 80% of cases CLs[36]. No specific histopathological features have been found to be unique to CLs in the dark or ethnic skin. However, in sub-Saharan Africa where more advanced specialized diagnostic tests are largely unavailable or unaffordable, a consensus has been reached for the diagnosis of MFs based on a combination of characteristic clinical and histopathological findings combined with immunohistochemical tests[37].

Histopathological diagnosis is often based on growth and cellular infiltration patterns with some patterns found to be more prevalent in certain types of CLs than others [32]. The growth patterns are described based on[38]:

- The architecture of the infiltrates in relation to the layers of the skin: - superficial, deep and subcutaneous
- The relationship of the infiltrates to other skin structures: perivascular, interstitial, pilotropic, syringotropic.

- The arrangement of the infiltrating cells in relation to one another; diffuse, nodular perivascular

Commonly described histologic patterns of infiltrates thus include: epidermotropic, syringotropic, pilotropic, nodular, diffuse, subcutaneous, angiocentric/angiodestructive, and intravascular growth patterns[32,38]. These infiltrating patterns may provide a clue to the infiltrating cell type in the absence of facilities for immunohistochemistry or may guide the choice of CD markers used where resources are available[39]. Superficial diffuse dermal infiltrates of small to medium sized lymphocytes showing marked epidermotropism are more commonly found in CTCLs while dense dermal pleomorphic lymphocytic infiltrates with nodular architecture suggest CBCLs[32,38]. Infiltrates involving predominantly the lower dermis and subcutaneous layer of the skin are suggestive of panniculitis like T-cell lymphoma and extranodal NK –Tcell lymphoma nasal type[40].

It must however be emphasized that some growth patterns may cut across various forms of CLs. For instance, the histological finding of nodular and diffuse infiltrates can be found in progressive forms of CTCL such as plaque stage MF and peripheral T cell lymphoma in addition to CBCLs[32]. Other histologic features such as cellular composition (monomorphous versus mixed population, the presence of other inflammatory cells and mucin deposition can also serve as morphologic clues to the histological diagnosis in resource limited settings.

Immunophenotyping

Though not a prerequisite to the diagnosis of primary cutaneous lymphomas, immunophenotyping is useful in distinguishing, classifying and occasionally determining the prognosis of CL. The classification of CL into B or T cell lymphomas is based on the presence or absence of certain CD markers identified by use of monoclonal antibodies on infiltrating cells[39]. This diagnostic tool is however a luxury in most resource limited and as such diagnosis is largely made based on clinical and histological findings.

Peculiarities of Cutaneous Lymphomas in Black Africans

Literature specifically documenting PCLs in black Africans is sparse. Existing ones suggest significant epidemiological, clinco-morphological and behavioural differences in PCLs in individuals of African ancestry compared to other ethnic groups.

Epidemiological peculiarities: The overall prevalence of PCLs specifically CTCLs is higher in dark skinned individuals compared to whites[5,41]. There is however a dearth of studies on the relationship between race and specific types of PCLs with the exclusion of MF which has been found to be commoner in individuals with African ancestry compared with Caucasians. It also appears that overall, other non-mycosis fungoides CTCLs may be more prevalent in the dark skin8. In contrast, dark skinned individuals appear to be less predisposed to B-cell lymphomas compared with whites[8].

With regards to demographic characteristics of individuals with cutaneous lymphomas and their relationship with clinical behavior and outcome, the general consensus is that PCLs tend to occur at a younger age with more generalized or advanced disease at presentation in dark skinned individuals compared with white counterpart[8,42,43]. In an African study[13] however, the mean age at diagnosis for cutaneous lymphomas was 50 years which is similar to the reported mean age in Caucasians[5]. Aggressive forms of the disease however appear to occur at a younger age in females of African descent[44-46].

Clinico-morphological peculiarities: Some morphological variants of specific types of PCLs are observed almost exclusively in the dark skin. For instance, Hypopigmented and hyperpigmented variants of MF are rarely seen in Caucasians. In black Africans, these lesions are often characterized by cutaneous dyspigmentation presenting as hypopigmented or hyperpigmented patches or plaques. Polymorphic pigmented MF lesions has also been described almost solely in the ethnic skin[47]. Other unique presentations of MF in African descendants include: pruritus with secondary hyperpigmentation and lichenification as well as psoriasiform lesions that may mimic other common dermatosis[37,44,47-53]. The relative rarity of other forms of cutaneous lymphomas may preclude

identification of race specific morphological variants.

Exogenous influences may also play a role in the appearance of skin lesions in black Africans. The practice of skin bleaching and the highly prevalent abuse of potent topical corticosteroid amongst black Africans and other ethnic populations particularly those in resource poor countries[54-57] may induce atypical presentation of PCLs by masking characteristic clinical symptoms and signs.

Behavioural peculiarities: The clinical course of some forms of PCLs when observed in dark skinned individuals is more aggressive with higher mortality rates than in white [12,47,58]. Some morphological variants of MF in individuals of African-ancestry appear to have prognostic implications. Hypopigmented variants of MF occurring solely or with other MF variants has been found to be associated with better outcome and survival in black Africans and African Americans [59]. Whereas, erythema and hyperpigmentation without hypopigmentation are associated with increased mortality[59].

Variations also exist in choice of therapy, therapeutic response as well as prognosis of the disease in African descents compared with Caucasians [47,58]. The exact reasons for these differences are yet to be fully elucidated but may be related to genetic influences including skin pigmentation, environmental exposures such as infections as well as socio-economic factors that may result in late presentation and high rate of default from therapy. In addition persistent hyperpigmentation may complicate successful therapy [48] leading to a prolonged reminder of the disease in the skin of colour.

Challenges to Diagnosing Cutaneous Lymphomas in Resource Limited Settings

The diagnosis of cutaneous lymphomas can be challenging and elusive even in the most technologically advanced settings. It often requires a combination of astute clinical and laboratory expertise together with enduring perseverance on the part of the physician, the pathologist and most especially the patient. The heterogenous nature of CLs and their ability to mimic a wide variety of skin lesions both clinically and histologically creates a need for repeated biopsies before a conclusive diagnosis can be made. This in itself is a major hurdle to accurate diagnosis in resource poor settings were health-care is largely funded through out-of-pocket payment.

In dark skinned individuals, clinical diagnosis is made more difficult not only by the intensity of the natural skin pigmentation, but also the inherent tendency for dyschromias and hyperpigmentation which potentially obscures pertinent clinical signs such as erythema. Skin bleaching and self-medication amongst black Africans is another major hurdle to early and accurate clinical diagnosis. *Figure 1*. is an image of a young Nigerian man with a history of long term use of highly potent topical corticosteroid (Clobetasol propionate) for skin lightening and treatment of what he perceived to be acne spots on his face. The patient was subjected to multiple serial skin biopsies over a course of one year that all gave inconclusive histological findings. Facilities for immunophenotyping were not available and private facilities offering the services were not affordable for the patient. A diagnosis of CTCL was made only after he developed lymph node and blood involvement (Sezary syndrome) three years later. By then, the patient was gravely ill and could not afford the cost of treatment. He eventually succumbed to the illness and passed on a few months after the definitive diagnosis was made. This illustrates how skin bleaching and self-medication in addition to socioeconomic factors potentially impede early diagnosis of cutaneous lymphomas in black Africans. **[See Figure 1]**

The challenges to making accurate diagnosis of this rather elusive disorder, are therefore numerous in the setting of resource limitation. Although clinical expertise is not completely lacking, the spread and number of specialists with interest in cutaneous oncology is relatively minute probably because there is a tendency for gravitation of interests towards areas of perceived need. Without adequate documentation on the true prevalence of PCLs in Africans, it is unlikely that these figures will change any time soon. In addition, the shortage of resources both human and material particularly in remote areas limits access of the population to physicians

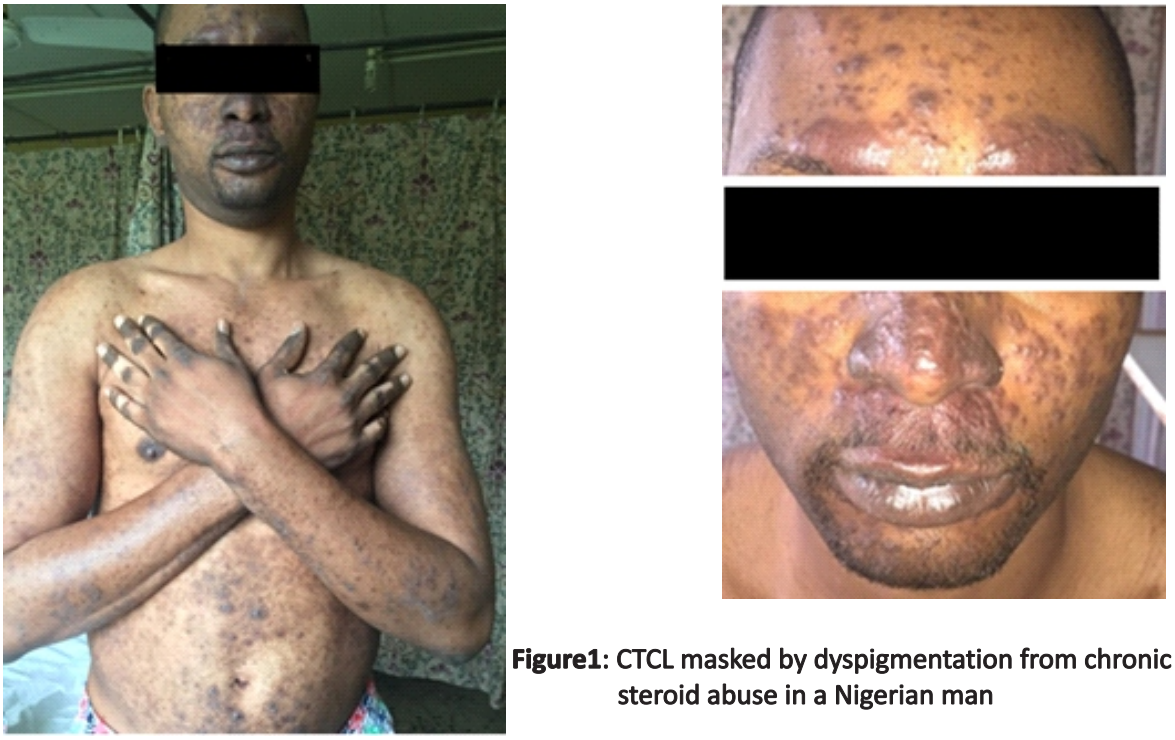

Figure1: CTCL masked by dyspigmentation from chronic topical steroid abuse in a Nigerian man

skilled at taking biopsies and processing them for histological and immunohistochemical appraisal.

Challenges to Managing Cutaneous Lymphomas in Resource Limited Settings

Late presentation for diverse reasons (low literacy levels, poverty and socio-cultural factors such as superstitious beliefs about the aetiology of diseases) is a common feature of patients presenting with cutaneous lymphomas in Africa. This also appears to be applicable to dark skinned populations in the western world where studies [8,43] have shown that African-Americans are significantly more likely to present with advanced disease than Caucasians or Hispanics. Late presentation significantly contributes to poor treatment outcomes of PCLs in black Africans particularly in the resource limited environments. There is in addition a high risk for loss to follow up attributable to poverty, ignorance, in-accessibility of health care facilities as well as sociocultural factors that contribute to poor treatment outcomes. **[See Figure 2]**

Radiotherapy is considered one of the most effective methods of treating CTCLs[58]. However, access to this form of therapy is remote in most parts of Africa and other developing nations in terms of availability and

Figure2: Advanced tumour stage of Mycosis Fungoides signifying late presentation in a Nigerian Man

cost. The choice of effective alternatives to radiotherapy such as phototherapy and chemotherapy is also limited due to non-availability and/or high cost. The lack of appropriate treatment units makes standardization of treatment difficult and increases the cost and hazards of treatment. For instance, patients who would ordinarily have received UV therapy may have to be treated with systemic chemotherapy[48]. Presently, in sub-Saharan Africa, data available is not sufficient enough to allow the recommendation of one treatment regimen over another[37].

Conclusion

There are racial influences on the epidemiology, clinical and histological pattern of primary cutaneous lymphomas and these have therapeutic and prognostic implications. Unfortunately, the dearth of studies on PCLs in black Africans precludes detailed and accurate description of clinical pattern and behaviour of the various forms of PCLs in the dark skin.

In spite of advancements in diagnostic and therapeutic options globally, early diagnosis remains a challenge and treatment outcomes are relatively poorer amongst dark skinned populations particularly in resource limited settings. There is therefore a need for more focused research and improved documentation on cutaneous lymphomas amongst black Africans. This is key, to improving our understanding of the peculiarities of cutaneous lymphomas in people of African ancestry.

Abbreviations:

ATLL:	Adult T cell leukemia/ lymphoma
CBCLs:	Cutaneous B Cell Lymphomas
Cls:	Cutaneous Lymphomas
MF:	Mycosis Fungoides
HLA:	Human leukocyte Antigen
HTLV-1:	Human T cell Leukemia Virus-1
PCLs:	Primary Cutaneous Lymphomas
PCMZL:	Primary cutaneous marginal zone lymphoma
UV:	Ultraviolet

A written informed consent was obtained from the patient whose clinical information (case summary) and photographs are included in this manuscript for publication and clinical teaching without geographical restriction.

The Authors declare that there is no conflict of interest

Funding sources: None

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