REVIEW ARTICLE

Primary Cutaneous Lymphomas; A review of a rare but diverse cutaneous tumour.

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ABSTRACT

Introduction: Primary cutaneous lymphomas (PCLs) are rare tumours accounting for 18% of cases of extra nodal non Hodgkin's lymphomas (NHL). PCLs are potential differentials in cases of cutaneous malignant skin tumours that may pose diagnostic difficulties to the Clinicians and Pathologists. Paucity of data exists in our own environment in particular and in Nigeria in general. This article serves to review available existing literature with the goal of creating the awareness to Pathologists and Clinicians (especially Dermatologist) of its existence and a possible encounter in the line of duty.

Literature review: Primary CLs are rare tumours. Most previous studies on malignant skin tumours in Nigeria did not report a case of CLs. This is unlike the report from Lagos, Nigeria where CLs have been reported. Cutaneous T-cell lymphomas (CTCLs) makes up about 2/3rd of the PCLs. Mycosis fungoides is the most common CTCLs while Marginal zone B-cell lymphoma and Follicular centre lymphoma are the most common subtypes of Cutaneous B- cell lymphomas (BTCLs). The aetiology PCLs is largely unknown. The CTCLs are predominantly seen in males while BTCLs show no sexual predilection except in primary cutaneous follicular centre lymphoma that has a slight female predilection. Their clinical presentation is non-specific and varies from patch, to plaques to nodules. They also exhibit variable histologic, immunophenotypic, cytogenetic, and molecular features.

Conclusion: Despite being rare, we should not foreclose the possibility of finding isolated cases of CLs in our environment. Large population and molecular tools are necessary to elucidate the aetiology of the diverse spectrum of CLs. Institutional/hospital based studies are invaluable means in the gathering of data, especially for rare tumours like CLs.

Key words: Primary cutaneous lymphomas, Cutaneous T- and B- cell lymphomas, Mycosis Fungoides, Sezary Syndrome, Marginal zone B-cell

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INTRODUCTION

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of extra nodal non-Hodgkin lymphomas which, by definition, are largely confined to the skin at diagnosis.[1] Lymphomas may involve the skin as the primary and only site of involvement or may spread to the skin as a secondary site of the disease.[2] The gastrointestinal tract is the most common site of extra nodal lymphoma followed by the skin.[3] The former and the latter make up 30-40% and 18% respectively of extra nodal lymphomas. [4, 5] Cutaneous lymphomas are rare.[2, 3, 6, 7] This in conjunction with its diverse nature makes it difficult to diagnose and treat.[6] There is paucity of data on PCLs in Nigeria largely due to rarity of this tumour. This may pose a diagnostic problem to the Pathologists and Clinicians, more so that an index of suspicion for this rare tumour may be absent. To bring to fore this index of suspicion on the subject matter necessitated this review, more so that few epidemiological data are available in the literature.[3] This article is a review of PCLs based on the accessible literatures with the aim of creating the awareness to Pathologist and Clinicians (especially Dermatologist) that PCLs are a differentials in cases of cutaneous malignant skin tumours.

LITERATURE REVIEW

Primary cutaneous lymphomas (CLs) have hitherto been reported as rare tumours.[2, 3, 6, 7] This is also consistent with most studies done in Nigeria on malignant skin lesions.[8-14] These studies did not report a case of cutaneous lymphomas which is in keeping with a previous study in Ghana,[15] unlike Adeyi and Banjo[16] (Lagos) who reported that cutaneous lymphomas accounted for 4.2% of all malignant skin tumours. Adeyi and Banjo[16] (Lagos) also reported that cutaneous lymphomas occurred in adults with a male preponderance. A male preponderance is suggestive of a cutaneous T-cell lymphoma (CTCL) as observed previously in other studies,[6, 17, 18] however immunotyping was not done for the lymphoma cases found in Lagos.

Despite been rare, they comprise a diverse group of lymphoid neoplasms manifesting heterogeneous clinical, histologic, immunophenotypic, cytogenetic, and molecular features.[6] Primary cutaneous lymphomas may share similar histologic features with their nodal counterparts, but they however have different phenotype, clinical behaviour, and prognosis, giving the impression that they are unrelated to nodal lymphomas.[6]

The majority of primary CLs (approximately 75%) are T-cell lymphomas in contrast to nodal non-Hodgkin lymphoma, most of which are B-cell

derived.[1] Cutaneous T-cell lymphomas are a heterogenous group of T-cell lymphoproliferative disorders involving the skin, the majority of which are classified as Mycosis Fungoides (MF) or Sezary Syndrome (SS).[1] Two-thirds of T-cell primary CLs may be classified as Mycosis fungoides (MF) or Sézary Syndrome (SS).[1] Mycosis fungoides is a peripheral, epidermotropic, non-Hodgkin T-cell lymphoma of low grade malignancy initially presenting in the skin and showing stepwise clinical progression from patches to plaques and tumours, and distinct histological (except in early stages), phenotypic and genotypic features.[2] It is the prototype of cutaneous T-cell lymphomas (CTCL).[2] It is the most common type of CTCL and accounts for almost 50% of all primary cutaneous lymphomas.[7, 19] It is more common in men than women.[2] It is also rare in children and young adult but it usually affects adult in their 5th – 6th decade of life.[2, 7] The aetiology is unknown.[2] Histologic features depends on the stage i.e. patch, plaque and nodule or tumour.[19] Patch stage shows psoriasiform epidermal hyperplasia, collection of lymphoid cells in the epidermis and a band like infiltrate of lymphoid cells within a thickened papillary dermis.[19] The plaque stage has features similar to those seen in the patch stage, however lymphocytes may be atypical and infiltrates are denser and more band like.[19] Tumour or nodular stage show diffuse dermal infiltrate of atypical lymphocytes with convoluted nuclei and increase in the number of medium to large lymphoid cells.[19] The majority of these cells are CD3, CD4 and CD5 positive and CD8 negative.[19]

Sezary syndrome (SS) is a rare form of cutaneous T-cell lymphoma (CTCL).[2, 7] It accounts for less than 5% of all cutaneous lymphomas,[2] and in the US the incidence of 0.3/100,000 persons has been documented.[7] Cases in childhood are extremely rare and it characteristically present over the age of 60 years.[2, 7] While some authorities regard it as a manifestation of mycosis fungoides,[7] or a leukemic stage of mycosis fungoides,[7] the current World Health Organization/European Organization on Research and Treatment of Cancer (WHO/EORTC) has designated the tumour as a distinct entity from mycosis fungoides.[2] The cause of Sezary syndrome is unknown; however, HTLV-1 associated lymphoma/leukaemia produces a syndrome clinically indistinguishable from SS. Patient with the disease present with a clinical triad of pruritus, erythroderma and lymphadenopathy. Other clinical features include alopecia, ectropion, nail dystrophy, palmoplantar keratoderma and leonine facies. Bacterial cutaneous infection frequently occurs in patients with this disease.[2]

CD30+ T-cell lymphoproliferative disorders include primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis. The former accounts for 9% of all primary cutaneous lymphoma,[7] and an incidence of 0.1-0.2 patient/100,000 has been reported.[2] A male predominance has been documented.[2] It presents in older adults in their 6th decade of life. Incidence of 0.1-0.2 patient/100,000 has been reported.[2] There is clonal rearrangement of T cell receptor genes in majority of cases and absence of translocation t(2;5) (p23;q35). This translocation is a typical feature of systemic anaplastic large cell lymphoma (ALCL).[2] Histologic section shows dense dermal nodular infiltrate of cohesive sheets of large cells with irregularly shaped nuclei and one or multiple nucleoli and an abundant, clear or eosinophilic cytoplasm.[2] Mitoses are frequent and it often appears clinically as an asymptomatic, solitary firm nodule which rapidly grows and often ulcerates.[2] Less often, multiple lesions are seen in a few patients. Spontaneous regression of the tumour is seen in 10-40 % of cases that therapy was not instituted.[2] Cutaneous anaplastic large cell lymphoma (C-ALCL) is positive for CD30+ (CD30 must be expressed by at least 75% of the large pleomorphic or anaplastic lymphoid cells), CD2, CD3, CD4 and CD45RO.[2] In contrast to systemic (nodal) ALCL, C-ALCL does not express EMA, but may express the cutaneous lymphocyte antigen (CLA, HECA-452) and homeobox gene HOXC5.[2]

Lymphomatoid papulosis(LyP) is rare with an estimated prevalence of 0.1-0.2 cases/100.000 and a preference for males.[2] It commonly affects individuals in their 3rd to 5th decade of life.[2] The cause of the disease is unknown, endogenous retroviral elements have been identified in LyP lesions.[2] The complementary contact of CD30 with its ligand (CD30L) in addition to TGF-beta and its receptor play a significant role in growth regulation, including regression of the tumour. Chromosomal deletions and rearrangements of chromosomes 1, 7, 9 and 10 have been demonstrated in cytogenetic studies while clonal rearrangement of T cell receptor genes can be found in at least 40% of lesions.[2] Most times than not, new lesions grow concurrently on the same or another body region.[2] Histologic sections show a dermal lesion composed of wedge-shaped diffuse infiltrate of medium-sized to large pleomorphic or anaplastic lymphoid cells with irregular nuclei, sparse chromatin and mitotic activity. Some of the large atypical lymphoid cells resemble Reed-Sternberg cells.[2] Typically seen clinically as grouped or disseminated asymptomatic papules and/or nodules, which regress spontaneously after a few weeks sometimes leaving

behind scars resembling small pox (i.e varioliform scars). [2] This lesion is positive for CD30 (hall mark for large atypical lymphoid cells), CD3, CD4 and negative for CD8 and CD15.[2]

The Primary cutaneous B cell Lymphoma (CBCL) accounts for 25% of cutaneous lymphomas and occur in predominantly middle aged adults with no sexual predilection.[2] An incidence rate of 0.1-0.2/100,000 persons per year has been reported[2]. Among the primary cutaneous B-cell lymphoma (CBCL), Marginal zone B-cell lymphoma and Follicular centre lymphoma are by far the most common subtypes.[2, 20, 21] The former and latter accounts for 55-56.7% and 34.1% respectively of all primary cutaneous B-cell lymphomas.[20, 21] Primary cutaneous follicular centre lymphoma has a slight female predilection and occur in adults with an age range from 33-88 years with a mean of 64 years.[22] The cause has not been elucidated however there is clonal rearrangement of immunoglobulin genes, inactivation of p15 and p16 tumour suppressor genes by hypermethylation has been reported in some cases, chromosomal imbalances, Bcl-2 and t(14;18) chromosomal translocation are absent in most cases.[2] This lesion is seen under the microscope as dermal infiltrates composed of a mixture of small or large centrocytes and centroblasts in varying proportion disposed in follicular or diffused growth patterns.[2] The follicles are ill-defined comprising of monotonous population of follicular centre cells that lack starry sky histiocytes, and often has an attenuated or absent mantle zone.[2] The clinical presentation consists of firm erythematous to purple plaques, nodules or tumours of different sizes. Small papules may be seen surrounding and slightly infiltrating larger nodules.[2] They are positive for B-cell markers (CD19, CD20, and CD22), Bcl-6 (follicular lesions), CD21, CD23, and CD35 (follicles are associated with follicular dendritic cells) and are negative for slg (diffuse population of large follicular centre cells), Bcl-2, CD 5 and CD 43.[2]

Primary cutaneous marginal zone B-cell lymphoma (MZL) has no sexual predilection and most commonly affects adults aged over 40 years.[2] Borrelia burgdorferi may be an important aetiological agent since its DNA has been isolated in some cases of MZL involving Europeans but not in Asians or Americans.[2, 6] The infiltrate is characterized by residual reactive lymphoid follicles surrounded by pale staining cuffs of tumour cells.[2] The interfollicular infiltrate is composed of small to medium-sized, centrocyte-like or monocytoid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli and a rim of pale cytoplasm.[2] Present clinically as red to purple

plaques or nodules with an erythematous border.[2] They are positive for 20, CD22, CD79a, but are negative for CD5, CD10, bcl-6, and CD23.[2]

Diffuse large B-cell lymphomas (DLBCL), leg type, accounts for 5-10.9% of cutaneous B-cell lymphomas.[21, 23] DLBCL (leg type) occurs primarily in the elderly female with a median age around 70 years.[23] They exhibit clonal rearrangement of immunoglobulin genes with an increase in the expression of genes associated with cellular proliferation.[2] Histologic section show a dermal infiltrate composed of monomorphic population of medium to large sized B cells, with minimal inflammation and slight stromal reaction. The overlying epidermis is often spared, with a Grenz zone.[2] Clinically appear as rapidly developing multiple scattered or accumulated dome shaped shiny surface red tumours without scaling and a firm consistency.[2] There may be ulceration of the overlying epidermis an indication of advanced disease.[2] The tumour cells are usually strongly positive for BCL- 2 protein and MUM-1/IRF-4, positive for CD20 and CD79a, have variable BCL-6 expression and negative for CD10 and CD138.[2]

Bradford et al[6] conducted a population-based study, which avoids the biases associated with hospital and clinical series. The strengths of their study were the large sample size of rare lymphomas and unbiased ascertainment and assessment of cases.[6] Literature on the CLs has been limited because of the rarity and inability to study large numbers of patients,[6] thus the overall epidemiology including the aetiology of CL subtypes has not been well investigated using population-based data.

In conclusion, although CLs are rare we should not foreclose the possibility of finding isolated cases in our environment as reported in Lagos, Nigeria by Adeyi and Banjo.[16] We align with the submission of Bradford et al[6] that further investigations using large population and molecular tools are warranted to elucidate the aetiology of the diverse spectrum of CLs. This is however without prejudice to case reports and institutional/hospital based studies as invaluable means in the gathering of data, especially for rare tumours like CLs.

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How to cite this article: Imasogie D. E, Azeke A. T. Primary Cutaneous Lymphomas; A review of a rare but diverse cutaneous tumour. Int. J of Forensic Med Invest 2017; 3(2):1-8