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Case Report

Aggressive mycosis fungoides/sézary syndrome in Nigeria: case report and literature review

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ABSTRACT

Mycosis fungoides and its variant, sézary syndrome are rare neoplastic conditions which are part of a larger group of lymphomas that primarily affect the skin known as cutaneous T-cell lymphomas. We report a case of fatal aggressive mycosis fungoides/sézary syndrome in a 55-year old Nigerian man who initially developed pruritic hyperpigmented spots on his skin which progressed over the course of 5 years to widespread scaly mixed hyperpigmented and hypopigmented plaques and nodules with features of organ involvement despite being managed with Psoralen and ultraviolet A radiation (PUVA), total skin electron-beam (TSEB), local electron-beam radiation, bexarotene, and oral prednisolone and chlorambucil (Winklemann regimen). In the process, we highlight the rarity of the condition, its ease of misdiagnosis and its predilection for people of Sub-Saharan decent.

Keywords: Mycosis fungoides, Sézary syndrome, Cutaneous T-cell lymphomas, Nigeria, Africa

INTRODUCTION

Mycosis fungoides (MF) was first described in 1806 by Jean-Louis Alibert, a French physician, as a mushroom-like skin neoplastic condition.[1] Over a century later, Lutzner et al categorized the spectrum of skin-based lymphomas of T-cell origin, including MF and Sézary syndrome (SS), which have a characteristic tissue distribution (skin infiltration, marrow sparing, localization in T-cell regions of lymphoid tissue), and distinctive morphology collectively as cutaneous T-cell lymphomas.[2] Median age of occurrence for MF/SS is 55 years.[3] Incidence is higher in the black population compared to Caucasians, at a proportion of 1.7:1, and higher in men than women by a ratio of approximately 2:1.[4,5]

MF typically begins as slowly progressive dermatitis-like patches and plaques, which when untreated evolves to nodules and eventual systemic dissemination. The patch/plaque stage of the disease is the result of skin infiltration with small to medium sized malignant T cells while the more advanced stage develops as a consequence of exclusively dermal involvement of non-epidermotropic malignant T cells.[6,7] SS is particularly associated with generalized erythroderma, lymph-adenopathy, atypical T-cells (Sézary cells) in the peripheral blood, hepatosplenomegaly, skin edema, immunosuppression and palmoplantar keratoderma.[8,9] The primary etiological factor in MF/SS is not known, but genetic (e.g. alterations in TNFR2), environmental e.g. sunlight exposure, and infectious agents like human T-cell leukemia virus 1 (HTLV-1), Epstein-Barr Virus (EBV), cytomegalovirus (CMV) and human papilloma virus (HPV) have been implicated.[10-16]

MF/SS has a formal staging system proposed by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) based on the degree of skin, lymph node, visceral and peripheral blood involvement.[17] The modified severity-weighted assessment test (mSWAT) (Table 2) shows severity of skin involvement. Treatment options for patients with MF/SS include photodynamic therapy (Psoralen and ultraviolet A radiation (PUVA) and extracorporeal photochemotherapy), radiation therapy (total skin electron-beam (TSEB), ultraviolet B radiation and local electron-beam radiation), biologic therapy (interferon alpha and interferon gamma), chemotherapy, and bone marrow transplantation.[18]

Table 1: ISCL/EORTC classification of mycosis fungoides/Sézary syndrome.

TNMB	Description
Skin	
T1	Limited patches, papules, and/or plaques covering <10% of the skin surface
T2	patches, papules, or plaques covering ≥10% of the skin surface
T3	One or more tumors (≥1 cm diameter)
T4	Confluence of erythema covering ≥80% body surface area
Node	
N0	No clinically abnormal lymph nodes
N1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_0–LN_2
N2	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N3	Clinically abnormal lymph nodes; histopathology Dutch grade 3 or NCI LN_4
NX	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: <5% of peripheral blood Sézary cells
B1	Low blood tumor burden: >5% of peripheral blood Sézary cells
B2	High blood tumor burden: ≥1000/μL Sézary cells with positive clone
	One of the following can be substituted for Sézary cells:
	− CD4/CD8 cells ≥10%
	− CD4+/CD7− cells ≥40%
	− CD4+/CD26− cells ≥30%
STAGE	**TNMB**
IA	T1, N0, M0, B0–B1
IB	T2, N0, M0, B0–B1
IIA	T1–T2, N1/N2/NX, M0, B0–B1
IIB	T3, N0/N1/N2/NX, M0, B0–B2
IIIA	T4, N0/N1/N2/NX, M0, B0
IIIB	T4, N0/N1/N2/NX, M0, B1
IVA1	T1–T4, N0/N1/N2/NX, M0, B2
IVA2	T1–T4, N3, M0, B0–B2
IVB	T1–T4, N0/N1/N2/N3/NX, M1, B0–B2

Table 2: ISCL/EORTC modified severity-weighted assessment test (mSWAT).

Body Region (% BSA)	Patch	Plaque	Tumor
Head (7%)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior Trunk (13%)			

Continued.

Body Region (% BSA)	Patch	Plaque	Tumor
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	1	2	4
Subtotal of Lesion BSA × weighting factor			
mSWAT score = Summation of each column line in final row above			

CASE REPORT

A 55-year old Nigerian man developed a pruritic hyperpigmented skin rash 5 years ago. There was no history of exposure to chemicals or radiation. The skin lesions were biopsied (results are unavailable) and he was initially managed as a case of chronic dermatitis with no significant improvement. Three years later, he had a repeat biopsy done, as a result of progressive spread of the lesions to his face, results of which suggested a diagnosis of mycosis fungoides, stage IIB (ISCL/EORTC). The skin lesions did not improve with PUVA. A year later, at an mSWAT score of 98, he was commenced on low dose TSEB at 12GY/8F which yielded complete remission of the skin lesions. However, 5 months later, he developed cervical lymphadenopathy. A PET-CT revealed lymph node progression but a histology report of an excision biopsy carried out revealed dermatopathic lymphadenitis with no evidence of malignancy. Four months later, there was a relapse of the skin lesions (mSWAT 40) after which he was commenced on bexarotene. There was no improvement and he experienced severe treatment-related side effects including leg swellings and worsening skin lesions, and after another three months, the disease had progressed to mSWAT 80. A month later, he received low dose TSEB retreatment and further local electron-beam radiation to the perineum, eyelids, hands and arms with no improvement. Peripheral blood film revealed abnormal lymphocytes. A repeat PET-CT scan carried out a month later showed lymph node progression. He developed malignancy-associated hypercalcemia (Ca - 4.36 mmol/L (2.1-2.6)) and was promptly admitted and managed with Zoledronic acid for about a week and discharged on 30 mg oral Prednisone.

At the time of presentation at our oncology clinic, he was at stage IVB with extensive pruritic scaly mixed hyperpigmented and hypopigmented plaques and nodules, worse on his torso, neck and face. He also complained of a cough, chest pain, arthralgia, fever, fatigue, loss of appetite and weight loss. He had pallor, generalized peripheral lymphadenopathy and hepatosplenomegaly with ascites. Full blood count showed hemoglobin levels of 8.4 g/dL (13.5-17.5) and relative lymphocytopenia. Viral screens for HIV I & 2 were negative. He was commenced on palliative chemotherapy with daily low dose oral chlorambucil and prednisone (Winklemann regimen) while being worked up for possible stem cell transplantation. He had severe adverse reactions including eye swelling, palm swelling and aggravated skin peeling. More lesions appeared on his hands, back and abdomen but there was improvement in the areas of the chest, head and axilla. CT scan findings revealed patchy consolidations in the lungs. Patient did not survive.

DISCUSSION

Mycosis fungoides and its more aggressive variant, Sézary syndrome belong to a group of rare skin neoplastic disorders known as cutaneous T-cell lymphomas.[2] MF has an incidence of approximately 0.36 per 100,000 persons, with a male to female ratio of approximately 2:1.[5,19] The incidence of SS has been reported to be about 0.8 to 0.9 cases per million persons per year.[18] MF/SS is more common in people of Sub-Saharan decent than in people of Asian or European decent.[11] It is primarily a disease of adults even though cases have been reported in adolescents and children.[20] Our patient is a black male whose age is similar to the median age of 55 years reported by Weinstock and Reynes.[3]

In Nigeria, cases of MF and SS are largely unreported due to paucity of medical specialists and equipment to carry out accurate diagnosis. Other problems facing the management of MF/SS include shortage of radiotherapy facilities, high cost of chemotherapy drugs which an average patient cannot afford to buy.[21]

MF usually begins as slowly progressive dark patches and plaques which evolve to nodules and eventual systemic dissemination. It is suspected that SS can evolve gradually from MF or occur spontaneously. In the early phases, distinguishing MF/SS from other conditions, such as chronic dermatitis, psoriasis, parapsoriasis, sclero-atrophic lichen, chronic lichenoid pityriasis, pityriasis alba, atopic dermatitis and leprosy is very difficult.[18,20] In this case, the patient was initially misdiagnosed as a case of chronic dermatitis. SS is particularly associated with generalized erythroderma, lymphadenopathy, atypical T-cells (Sézary cells) in the peripheral blood, hepatosplenomegaly, skin edema, immunosuppression and palmoplantar keratoderma, all which this patient

presented with. In addition, in the terminal stage, this patient developed patchy consolidations in the lungs which could have been as a result of visceral spread of the disease or infection due to immunosuppression.[8,9]

The exact cause of MF/SS remains largely unknown, although genetic and environmental factors, as well as infectious agents have been implicated.[11-16] Viral screens for HTLV-1, EBV, CMV and HPV were not carried out but his HIV I & II screens were negative.

A diagnosis of MF/SS is made through a combination of the clinical picture and examination, and is confirmed by a skin biopsy and staged appropriately based on the degree of skin, lymph node, visceral and peripheral blood involvement. Immunophenotyping confirming T-cell origin (CD3+ and CD4+) and lack of expression of CD2, CD3, CD5 and CD7 (mature T-cell antigens) are supportive of SS.[17] Tests carried out in the case of our patient include a skin biopsy for histology and a peripheral blood film which revealed atypical lymphocytes. Immunophenotyping was not done in this case.

MF/SS can be staged according to the ISCL/EORTC revised classification. The mSWAT could also be used to estimate the degree of skin involvement. This patient progressed from a stage IA to a stage IIB within the course of 3 years, and from a stage IIB to a stage IVB within 2 and a half years in spite of the multiple treatment modalities carried out. He had a general feeling of ill health (malaise) and weakness, elevated temperatures, weight loss, and anemia which are common in patients in the late stage of the disease.

Treatment options for MF/SS can be skin directed therapy (SDT), systemic therapy or combined. Choice and combination of treatment modalities largely depends on the stage of the disease. The EORTC recommendations highlight stage specific guidelines for MF/SS. In summary, the recommendations are as follows: expectant management for Stage IA disease, SDT (such as topical corticosteroids, UV phototherapy, localized radiotherapy) for stages IA, IB and IIA, and systemic therapies for more advanced disease.[22] This patient was treated with psoralen plus ultraviolet A (PUVA), total skin electron beam therapy (TSEB), local electron-beam radiation, oral bexarotene, oral prednisolone and chlorambucil (Winklemann regimen) with no success.

Prognosis of SS is poor, with a median survival of 2.9 years.[17] Factors associated with worse prognosis include advanced age, black race, male sex, tumorous skin involvement and stage IV disease.[2,23,24] Five-year disease-specific survival (DSS) is 98% for stage IA disease and as low as 18% for stage IVB disease.[25] The prognosis in the case of our patient was very poor, resulting in mortality.

CONCLUSION

Mycosis fungoides and Sézary syndrome are rare conditions which have a race predilection towards people of Sub-Saharan decent and are not easily distinguishable from other benign skin conditions in the early stages. More awareness of these conditions among dermatologists and oncologists in Nigeria and other sub-Saharan countries, and appropriate diagnostic skill and equipment are required for prompt diagnosis and management.

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