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Mycosis fungoides: A neglected domain?

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ABSTRACT

Introduction: Skin is second most common site for extranodal non-hodgkin lymphoma (NHL). Mycosis fungoides (MF) is a type of cutaneous NHL. There is gross dearth of literature on mycosis fungoides given the rarity and benign course of the illness. We intended to study the clinical profile and treatment outcomes of the disease at our centre.
Materials and methods: Study was by systematic review of case files of 22 patients diagnosed to have MF/SS. Clinical and treatment details, response assessment by mSWAT and 2 year survival in early and advanced MF were noted.
Results: MF constituted 3.5% of all cases of NHL. Median age was 55.5 years. Many patients received multiple lines of treatment. 2 year survival in early and advanced MF were 100% and 46.1% respectively.
Conclusion: Mycosis fungoides is a rare malignancy of skin. Since the disease has an indolent and protracted course, scoring by indices and tailoring treatment will alter course of the illness.

KEYWORDS: Mycosis fungoides, non Hodgkin lymphoma (NHL), Cutaneous T Cell Lymphoma

Introduction:
Skin is the second most common site for extranodal non Hodgkin lymphoma (NHL) after gastrointestinal tract.(1, 2) Primary cutaneous lymphomas have a different behaviour and prognosis compared to systemic lymphomas with secondary cutaneous involvement. Mycosis fungoides(MF) is the most common cutaneous NHL.(3, 4) It represents around 44% of all primary cutaneous NHLs with an excellent disease specific 5 year survival of 88%. A closely related condition, Sezary syndrome(SS) in on the other end of spectrum with an aggressive clinical behaviour.(4) SS has a poor outcome even on treatment.(5) An approach towards correct identification in early stages and management has been set by International Society of Cutaneous Lymphoma (ISCL).(6)

MF is known for its clinical heterogeneity. In early stages, it presents with patches and plaques. In advanced disease, presentation is with tumors, erythroderma and lymph node involvement. Early stage disease is treated with skin-directed therapy whereas advanced disease needs eventually some form of systemic therapy.(7)

There is a gross dearth of literature on mycosis fungoides given the rarity and benign course of the illness and a lot of clinical conditions mimicking the illness especially in its early stages. It would not be an overstatement if it is said that it is an alien child to dermatology but also a neglected child of oncology. Hence, we intended to study the clinical profile and

treatment outcomes of the disease at our centre.

Materials and methods:
Study design:
The study was conducted at the department of Medical Oncology in Kidwai Memorial Institute of Oncology at Bangalore in South India. It was by a systematic review of case files of the 22 patients diagnosed to have MF/SS and treated at the institute from January 2006 to June 2014.

Baseline assessment:
The details noted down were the demographic profile of the patient, clinical presentation, extracutaneous/lymph nodal sites of involvement, stage of the disease treatment details- both skin directed and systemic therapies, response assessment and survival details.

Staging:
Diagnosis was established by biopsy of skin lesions aided by immunohistochemistry. All the histopathology slides were reviewed and diagnosis was confirmed. A lymph node with size >/= 1.5 cm was considered to be clinically positive. Lymph node involvement if present was confirmed by excisional biopsy.(3) Involvement of blood and presence of sezary cells were determined by examination of the peripheral smear and by flow cytometry.(8) An updated staging system proposed by International Society of Cutaneous Lymphoma (ISCL) and European Organization of Research and Treatment of Cancer (EORTC) was used.(3)

Skin assessment and scoring with response:
Details of severity of the skin lesions were assessed by modified severity weighted adjustment tool (mSWAT) at various visits at 3, 6 and 12 months.(9, 10) This involved the summation of the products of assessed body surface area (BSA) multiplied by lesion specific weighting factor. The weighting factor was 1, 2 and 4 for patch, plaque and tumours respectively. It has been said that mSWAT can be used to track lesions of erythroderma.(9) Patients of erythrodermic skin lesions had T4 lesions which was BSA ≥ 80% erythematous patch/plaque disease.(11) Lymph node reassessment was by CT scans and by chesons criteria.(12) Stages I-IIA were considered as Early MF and stages IIB-IV were considered as Advanced MF.

Treatment:
Early MF was treated by skin directed therapies- topical corticosteroids, retinoids and phototherapy (Narrow band for patches and PUVA for plaques).

Advanced MF and refractory cases of early MF were given systemic treatment with/without skin directed therapies- retinoids, oral methotrexate (20-40 mg/wk), immunomodulatory agents (lenalidomide) and liposomal doxorubicin. Most of them received multiple lines of these agents. 2 of the patients of recalcitrant advanced MF also received CHOP (Cyclophosphamide-750 mg/m^2, Doxorubicin-50 mg/m^2, Vincristine 1.4 mg/m^2 and oral prednisone 100 mg/day for 5 days) based chemotherapy in fourth line treatment.

Statistics: The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows). Means and medians were calculated for all applicable parameters.

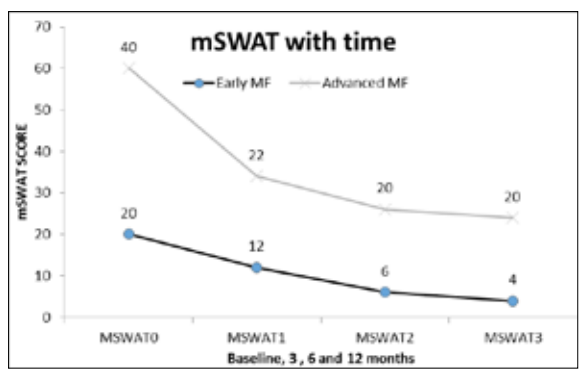
Results:
Clinical profile: A total of 22(3.5%) cases of MF were diagnosed out of 626 non Hodgkin's lymphomas. Among those patients, 9 had early MF and 13 had advanced MF at presentation.

Table I:

Characteristics	Variable
Median age	55.5 years
Gender distribution	12 males: 10 females
Median body surface area of lesions	16%
Lymph node involvement	54.5%
Visceral involvement	13.6%
Stages(I/II/III/IV)	7/10/2/3
Treatment Local therapies only Systemic therapy	 6 16

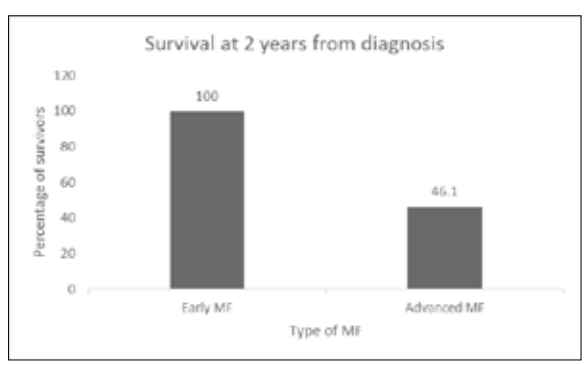
Response assessment of skin lesions to treatment:
Modified severity weighted adjustment tool at baseline, at 3 months, 6 months and at 12 months was done for all the patients of both early MF and advanced MF.

Fig 1:



Survival at the end of 2 years:
9 cases of Early MF- Stages IA, IB and IIA had a 2 year survival of 100% and 13 cases of advanced MF- stages IIB, IIIA, IIIB, IVA and IVB had the same of 46.1%.

Fig 2:



Discussion:
Primary cutaneous lymphomas(PCL) are of two broad types-cutaneous T-cell lymphomas" (CTCL) and "cutaneous B-cell lymphomas" (CBCL).(5) Of all the PCLs, 65% are of T cell type, 25% are of B cell type and the remaining 10 % are non-specific.(13) Further, CTCLs vary in their clinical behaviour, histology and markers of expression on the tumour cells.(14) The types of CTCLs which are indolent are MF and its variants, anaplastic large cell PCL, subcutaneous panniculitis-like T-cell lymphomas, lymphomatoid papulosis and cutaneous lymphomas of CD4+ T cells of small and medium-sized pleomorphic cells. Aggressive subtypes of CTCLs are Sezary syndrome, nasal-type T/NK-cell, T CD4- and CD8+ cells, unspecific T-cell and the T cell lymphoma/leukemia of adults.(5, 13)

The disease is difficult to diagnose in the early stage, with a lot of diseases mimicking it such as psoriasis, parapsoriasis, eczema, pityriasis alba, chronic lichenoid pityriasis and leprosy. (15) Diagnosis requires excellent clinical acumen with multiple sequential biopsies at times. Early MF presents with patches and plaques. Patch stage lesions are erythematous, single or multiple of varying diameters and may be accompanied by fine scaling. They are usually located in non-sun exposed areas- buttocks, thighs and abdomen. Plaques in MF are due to epidermal hyperplasia resulting from infiltration of neoplastic lymphocytes. They can arise from preexistant patch or de novo. These plaques may be either sharply demarcated or can coalesce to form various patterns. Patches and plaques are often associated with itching. When these various lesions occupy more than 80% of the body surface, it is called the phase of erythroderma. The lesions here can be in patch, plaque or tumor phases or a mixture of these in various proportions and the lesions here may or may not be accompanied by scales. Plaques rarely ulcerate before the phase of tumor. Tumor stage lesions are located generally in face and body folds. Ulceration could be from necrosis of the tumor tissue or from secondary infection. About half of all deaths in mycosis fungoides is from infections and resultant septicaemia.(16)

The most common type of CTCL is MF. The median age in our study was 55.5 years. This is similar to other studies, wherein the peak occurrence is in fifth and sixth decades. In our study, the male to female ratio was 1.2. It has two times higher incidence in men compared to women worldwide.(17-19) In our study, median age was much lesser than that in most of the studies.(20-22) This could be explained by the earlier occurrence in India of most of the haematological malignancies compared to the western population. Gender distribution showed a slight male preponderance, similar to that in most of the studies.

In an article by Novelli et al(22), there was a significantly increased relative risk of death in those patients above 60 years, with advanced disease and TBSA more than 50%. Median TBSA in that study was 47% as compared to 16% in our study. In that study, they categorized patients based on TBSA involved and studies survival. They recorded a 5 year survival of 100% in those with TBSA less than 25% as compared to 89% in those with TBSA of between 25% and 50%. We could not do the subset analysis of the age and TBSA comparing them to survival in view of smaller number of patients.

Lymph node involvement qualifying as dermatopathic lymphadenopathy was seen in 54.5% of patients. It is noticed in various studies that lymph node involvement is an adverse prognostic factor.(21, 23) In another study it has been said that prognostic impact of lymphadenopathy with a patch/plaque lesion, which is a stage IIA disease is questionable.(18) But, in our study all the lymphadenopathy we found was in advanced MF, which is stage IIB and beyond. Further, skin lesions were in tumor and erythroderma stages.

Table II:

Characteristics	Present study	Novelli et al(22)	Klemke CD(21)	Duvic et al(20)
Median age	55.5 years	61 years	70 years	67 years
Gender distribution	6:5	3:2	1.44:1	1.22:1
Median BSA of lesions	16%	47%	_	45%
Lymph node involvement	54.5%	_	34.6%	58%

Three patients in our study had visceral involvement by mycosis fungoides. The sites involved were orbit of eyes, liver and meninges. Needless to say, all three of them fared poorly and had survival of 3, 4 and 1.5 months respectively. *Literature search reveals the most common sites of extracutaneous and extranodal dissemination of the disease are spleen, liver and lungs.(24), 6 of the 22 patients in our study have been reported earlier.(25)*

The followup assessment of skin lesions was done by SWAT score and by the modified SWAT score. Various assessment tools such as physician global assessment (PGA) and total body surface area (TBSA). It has been found that SWAT correlated best with PGA score than does TBSA.(10) SWAT is sensitive in capturing disease burden of the patient under treatment with both skin directed and systemic chemotherapies. (26)

Conclusion: Mycosis fungoides is a rare malignancy of the skin though it is the most common type of CTCL. It requires a high index of suspicion to diagnose the condition and is essentially a diagnosis of exclusion. Our patients had a lower median age of incidence of MF, but a milder severity of the disease in terms of lesser TBSA and also a better survival. Since the diseases has an indolent and protracted course, scoring by indices and tailoring treatment will alter the course of the illness.

References:

1. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. Journal of the National Cancer Institute. 2000;92(15):1240-51.
2. Zucca E. Extranodal lymphoma: a reappraisal. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2008;19 Suppl 4:iv77-80.
3. Whittaker S, Hoppe R, Prince HM. How I treat mycosis fungoides and Sézary syndrome. Blood. 2016;127(25):3142-53.
4. Rook A. Rook's Textbook of Dermatology. Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors: Wiley-Blackwell; 2016.
5. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768-85.
6. Vandergriff T, Nezafati KA, Susa J, Karai L, Sanguinetti A, Hynan LS, et al. Defining early mycosis fungoides: validation of a diagnostic algorithm proposed by the International Society for Cutaneous Lymphomas. Journal of Cutaneous Pathology. 2015;42(5):318-28.
7. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. European journal of cancer (Oxford, England : 1990). 2006;42(8):1014-30.
8. Hodges E, Krishna MT, Pickard C, Smith JL. Diagnostic role of tests for T cell receptor (TCR) genes. Journal of clinical pathology. 2003;56(1):1-11.
9. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(18):2598-607.
10. Stevens SR, Ke MS, Parry EJ, Mark J, Cooper KD. Quantifying skin disease burden in mycosis fungoides–type cutaneous t-cell lymphomas: The severity-weighted assessment tool (swat). Archives of Dermatology. 2002;138(1):42-8.
11. Vonderheid EC, Bernengo MG, Burg G, Duvic M, Heald P, Laroche L, et al. Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. Journal of the American Academy of Dermatology. 2002;46(1):95-106.
12. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(5):579-86.
13. Rizvi MA, Evens AM, Tallman MS, Nelson BP, Rosen ST. T-cell non-Hodgkin lymphoma. Blood. 2006;107(4):1255-64.
14. WHO classification of tumors of haematopoietic and lymphoid tissues. SH S, E C, NL H, ES J, SA P, H S, et al., editors. Lyon: International Agency for Research on Cancer(IARC); 2008.
15. CM M, AN C, MC MJ. The cutaneous lymphoid proliferations. New Jersey: Wiley- Liss; 2007.
16. Keehn CA, Belongie IP, Shistik G, Fenske NA, Glass LF. The diagnosis, staging, and treatment options for mycosis fungoides. Cancer control : journal of the Moffitt Cancer Center. 2007;14(2):102-11.

17. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol. 2000;136(4):504-10.
18. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003;139(7):857-66.
19. Wain EM, Orchard GE, Whittaker SJ, Spittle M.Sc MF, Russell-Jones R. Outcome in 34 patients with juvenile-onset mycosis fungoides. Cancer. 2003;98(10):2282-90.
20. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood. 2007;109(1):31-9.
21. Klemke CD, Mansmann U, Poenitz N, Dippel E, Goerdt S. Prognostic factors and prediction of prognosis by the CTCL Severity Index in mycosis fungoides and Sezary syndrome. The British journal of dermatology. 2005;153(1):118-24.
22. Novelli S, Garcia-Muret P, Mozos A, Sierra J, Briones J. Total body-surface area as a new prognostic variable in mycosis fungoides and Sezary syndrome. Leukemia & lymphoma. 2016;57(5):1060-6.
23. Toro JR, Stoll HL, Jr., Stomper PC, Oseroff AR. Prognostic factors and evaluation of mycosis fungoides and Sezary syndrome. Journal of the American Academy of Dermatology. 1997;37(1):58-67.
24. Whitbeck EG, Spiers AS, Hussain M. Mycosis fungoides: subcutaneous and visceral tumors, orbital involvement, and ophthalmoplegia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1983;1(4):270-6.
25. Usha Amirtham, Nikita J Mulchandani, Chennagiri S Premalata, Rekha V Kumar. Cutaneous Lymphoma: A Descriptive Study from a Regional Cancer Centre in South India. IOSR Journal of Dental and Medical Sciences. 2016;15(5):25-31
26. Herrmann JJ, Roenigk HH, Jr., Honigsmann H. Ultraviolet radiation for treatment of cutaneous T-cell lymphoma. Hematology/oncology clinics of North America. 1995;9(5):1077-88.