View Point

The conundrum of parapsoriasis versus patch stage of mycosis fungoides

K. N. Sarveswari, Patrick Yesudian

Sundaram Medical Foundation, Dr. Rangarajan Memorial Hospital, Chennai, Tamilnadu, India

Address for correspondence:
Dr. K. N. Sarveswari, Sundaram Medical Foundation, Dr. Rangarajan Memorial Hospital, Shanthi Colony - IV Avenue, Anna Nagar, Chennai - 600 040, Tamilnadu, India.
E-mail: sarveswari@smfhospital.org

DOI: 10.4103/0378-6323.51239
PMID: 19439874

ABSTRACT

Terminological confusion with benign dermatosis, such as parapsoriasis en plaques, makes it difficult to diagnose mycosis fungoides in the early patch stage. Early diagnosis of mycosis fungoides (MF) is important for deciding on type of therapy, prognosis and for further follow-up. However, until recently, there has been no consensus on criteria that would help in diagnosing the disease early. Some believe that large plaque parapsoriasis (LPP) should be classified with early patch stage of MF and should be treated aggressively. However, there is no firm clinical or laboratory criteria to predict which LPP will progress to MF and we can only discuss about statistical probability. Moreover, long-term outcome analysis of even patch stage of MF is similar to that of control population. We therefore believe that LPP should be considered as a separate entity at least to prevent the patient from being given a frightening diagnosis. We also feel that patients need not be treated with aggressive therapy for LPP and will need only a close follow-up. This article emphasizes the criteria for diagnosing early MF and has highlighted the importance of considering LPP as a distinct benign entity.

Key words: Mycosis fungoides, Parapsoriasis, Small plaque, Large plaque

Brocq, in 1902,[1] reviewed the German, French and American literature and reported 10 cases of his own for which he created the term "parapsoriasis," because of their similarity to psoriasis. The common features of these cases were chronicity of disease, absence of symptoms, resistance to available therapy and histologically round cell infiltrate in papillary dermis with spongiosis and parakeratosis. On the basis of mainly clinical manifestations, he differentiated the following subgroups as guttate, plaque and lichenoid.

Today, the first subgroup of Brocq's classification is referred to as pityriasis lichenoides, which has an acute and chronic form. The present terminology of parapsoriasis includes large plaque parapsoriasis (LPP) and small plaque parapsoriasis (SPP). The initiating cause of parapsoriasis is unknown, but the disease probably represents different stages in a continuum of lymphoproliferative disorders, ranging from chronic dermatitis at one end to frank malignancy at the other. Small plaque parapsoriasis, large plaque parapsoriasis and pityriasis lichenoides have all been shown to be monoclonal T cell disorders. These T cells belong to the skin-associated lymphoid tissue (SALT).[2] This has been demonstrated by the T cell receptor gene rearrangement and by the more sensitive polymerase chain reaction (PCR)-based test.

A "dominant" clone of lymphocytes had been demonstrated in a few cases of SPP. As this T cell clone did not undergo further mutation that are necessary for the development of mycosis fungoides (MF), SPP is now thought to be a benign disorder with little or no potential to evolve into MF.[3,4]

The lesions of SPP are generally on the upper trunk, 2 to 6 cm in diameter [Figure 1], rarely up to 20 cm, sometimes with a digitate appearance (digitate dermatosis) and without atrophy or poikiloderma. Histopathology shows non-specific changes (focal spongiosis and psoriasiform or lichenoid dermatitis with exocytosis of small lymphocytes).

LPP lesions are larger, more than 6 cm in diameter and localized to buttocks, lower trunk, upper thighs, inner upper arms and inframammary areas (non-sun-exposed areas) and frequently manifest atrophy and/or poikiloderma. Hypopigmented patches

How to cite this article: Sarveswari KN, Yesudian P. The conundrum of parapsoriasis versus patch stage of mycosis fungoides. Indian J Dermatol Venereol Leprol 2009;75:229-35.
Received: August, 2008. **Accepted:** November, 2008. **Source of Support:** Nil. **Conflict of Interest:** None declared.

are common in the Indian subcontinent [Figure 2a]. Histologically, the pattern of lymphoid infiltration in LPP is similar to SPP [Figure 3], but the infiltrates often contain lymphocytes with cerebriform nuclei called Lutzner cells similar to that seen in MF.

In LPP, the dominant clonal density has been 1% to 10% (in MF 50%). However, it is important to realize that dominant clonality does not equate to clinical malignancy. Although 7.5% to 14% of LPP cases have been reported to progress to MF, most cases run a benign course and remain indolent for many years. In some cases, there has been complete resolution of the disease. Various parameters such as nuclear contour studies, immunohistochemistry, PCR and T cell receptor gene rearrangement studies have all been used to identify the atypical lymphocytes, and thus to predict which LPP will become MF. Even then at best, the diagnosis remains conjectural. Earlier, genotypic analysis of T cell receptor rearrangement study was considered to be the gold standard of all diagnostic tests, holding the unique ability to distinguish between benign and malignant T cell infiltration.

Simon *et al.*,[5] in their study found that of six LPP patients with T cell gene rearrangement studies, only one developed LPP. In others, the disease remained virtually unchanged over follow-up. They thus concluded that even T cell receptor studies could not be relied upon to distinguish between benign and malignant T cell infiltrate. The authors also felt that whether or not LPP is truly early MF, is not the issue; what is important is which patient whether given the diagnosis LPP or early MF (stage Ia) are at risk to develop progressive disease. They concluded that both LPP and early MF do not come under this risk group.

LPP has been shown to remain indolent for many years. Close follow-up at least once in six months and repeated biopsies may be needed to rule out progression to malignancy. It can be treated with topical steroids/ topical chemotherapeutic agents or with PUVA.[6] Aggressive therapy can be considered as a last resort.

Sanchez and Ackerman in 1979[7] suggested that LPP was synonymous with patch stage of MF. Ackerman later went on to state that even SPP must be considered as patch stage of MF.[8] To consider all parapsoriasis en plaques as early MF simplified a common diagnostic dilemma, but it also raised new problems:

- in producing valid prognostic survival information for patients with "early"-stage MF (information that decides the type of therapy),
- acceptable end points of therapy, and
- ultimately, the generation of risk/benefit ratios for different therapeutic interventions.

Moreover, including patients with a "benign" course into the mix of patients who have a definite, potentially life-threatening cancer poses added risks for patients: those with "benign" disease are at risk of being treated with aggressive therapy and those with a potential for progressive disease may be deprived of more definitive therapy.

We followed up 46 patients with large plaque parapsoriasis (LPP) treated with PUVA between 2000 and 2006.

The clinical response was good. Thirty one cases had complete response (>90% clearance), 11 - partial response (50% clearance), 2 - recurrence and 2 - lost to follow-up. The clinical response was seen within 14-38 treatments (mean 29 treatments).

Total UV dose given was 99.5 J-260.5 J (mean, 180 J). Tolerance was good except for mild burning sensation in one patient Figures 2a and 2b -Hypopigmented variant of LPP - before and after PUVA therapy and Figures 4a and 4b -Poikilodermatous variant of LPP - before and after PUVA therapy.

We concluded the following:

1. As there is no firm clinical or laboratory criteria to predict which LPP will progress to CTCL and as the long-term outcome analysis[9] of even patch stage of CTCL is similar to that of control population, aggressive therapy was not needed in parapsoriasis.
2. PUVA therapy is an effective first-line therapy in treating parapsoriasis.
3. LPP should be considered as a separate entity at least to prevent the patient from being given a frightening diagnosis.

The main difficulty is to differentiate LPP from early MF, as there are no universally accepted minimal criteria for the diagnosis of MF.

Recognizing this persistent need to develop standardized diagnostic criteria for early MF, the International Society of Cutaneous Lymphoma

Figure 1: SPP - Scaly macules and patches of SPP

Figure 2a: Hypopigmented variant of LPP seen in the Indian subcontinent

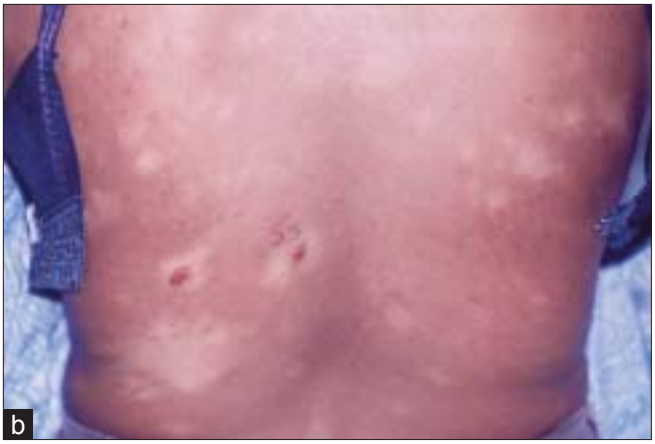

Figure 2b: Hypopigmented variant of LPP after PUVA therapy (Two scars of previous biopsies are visible)

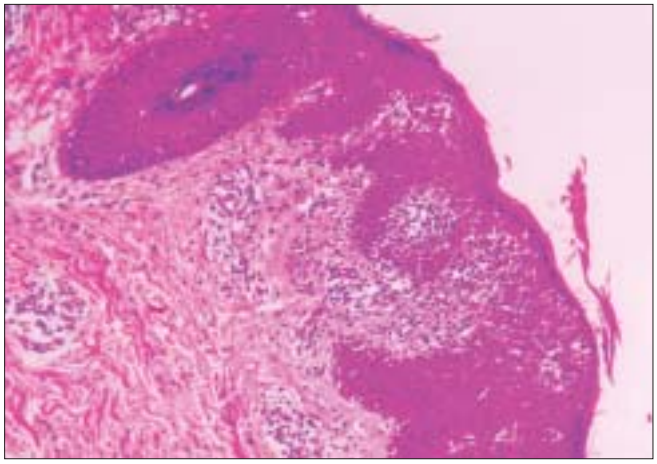

Figure 3: LPP - Exocytosis is more prominent. Interface reaction is seen. Lymphocytic infiltration is present in the papillary dermis (H and E, Low-power magnification ×40)

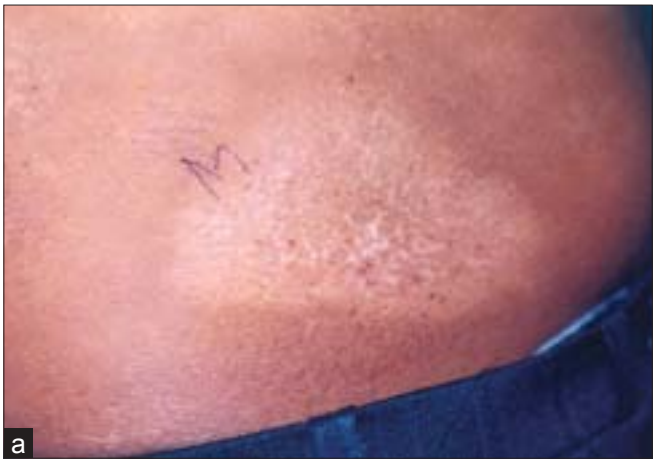

Figure 4a: Poikilodermatous variant of LPP

Figure 4b: Poikilodermatous variant of LPP after PUVA therapy

(ISCL) has analyzed early MF and have proposed an algorithm for the diagnosis of early "classic" MF that incorporates clinical, histopathologic, molecular biologic and immunopathologic features.[10,11] The diagnosis of early MF requires a total of four points. Because molecular biologic and immunopathologic criteria represent only one point each, they always require additional clinical and histopathologic criteria

to establish the diagnosis of early MF. Conversely, if sufficient clinical and histopathologic criteria are met, then molecular and immunopathologic criteria are not necessary, clinical pathologic correlation thus remaining the gold standard in the diagnosis of MF.[12]

EARLY DIAGNOSIS OF MF - CLINICAL CRITERIA

The ISCL task force for clinical definition of early MF has identified several clinical criteria that are important to recognize classic MF at the initial stage.

History

The important clue in history is a persistent nature of the disease. The lesions may increase in size and number over time. They tend to incompletely clear with topical steroids or recur when treatment is discontinued.

Differential diagnosis includes drug eruptions. Withdrawal of an offending drug will eliminate this possibility.

Morphology of lesions

Early MF lesions are usually large patches of more than 5 cm in diameter [Figure 5]. Uniformly small, less than 3 cm digitate lesions are uncommon in MF. Patches may expand slowly to form well-demarcated lesions that vary in size and may undergo spontaneous clearing in some areas.[13] This phenomenon of progression and regression of individual lesion produces irregular patches.

Another specific clinical feature is poikiloderma[14] (mottled pigmentation, telangiectasia, epidermal atrophy) interspersed with slight infiltration. Persistent poikilodermatous patches on non-sun-exposed areas should be considered as MF until proven otherwise by biopsy. Poikiloderma is not a feature of atopic dermatitis, nummular eczema, psoriasis, lichen planus, pityriasis rosea and SPP, all of which are likely to be clinically confused with MF.

Differential diagnosis includes other subtypes of CTCL such as granulomatous slack skin, connective tissue diseases such as dermatomyositis, some genodermatosis and LPP.

Number of lesions

Multiple lesions [Figure 5] and several sites of involvement are seen in most patients with classic MF. Rarely, single lesion (unilesional MF) may occur.[15,16]

Differential diagnosis includes nummular eczema, lichen simplex chronicus, erythema chronicum migrans, and tinea corporis.

Distribution of lesions

Non-sun-exposed areas (bathing suit distribution) such as trunk below the waist line flanks, breasts, inner thighs, inner arms and periaxillary areas. Lesions may appear on face or scalp especially if there is follicular involvement. Rarely, MF may present as refractory dermatosis of the palms and soles.

ISCL clinical criteria

Persistent and progressive patches/thin plaques

And

Two of the following features - 2 points

Or

One of the following features - 1 point.

- Non-sun-exposed location
- Size/shape variation Or
- Poikiloderma

EARLY DIAGNOSIS OF MF: HISTOPATHOLOGIC CRITERIA

To differentiate early MF from other benign dermatosis is an extremely difficult, much debated and yet a crucial issue. Although diagnosis of early stage MF is sometimes inconclusive, careful study may yield the correct diagnosis.[17] To enhance the chance of establishing a histologic diagnosis of MF

a. Multiple biopsies from a variety of lesions are required, including the fully evolved plaque, as well as fresh lesions.
b. It is essential to stop all topical treatment, especially steroids and also systemic immunosuppresants at least 2 to 4 weeks before biopsy, or else the salient histologic features of MF may be suppressed.

The following histopathologic criteria may help in suspecting early MF, but the simplified ISCL criteria may be followed for confirming diagnosis:[17]

1. Presence of atypical lymphoid cells that are slightly larger than normal lymphocytes and have hyper chromatic, irregularly contoured (convoluted) nuclei. Such cells have been variably termed “mycosis cells,” “Lutzner cells” or “Sezary cells.”
2. Presence of individual haloed atypical lymphocytes within the epidermis.
3. Presence of single lymphoid cells linearly arranged along the basal layer of the epidermis

Figure 5: Large and multiple patches/plaques of MF

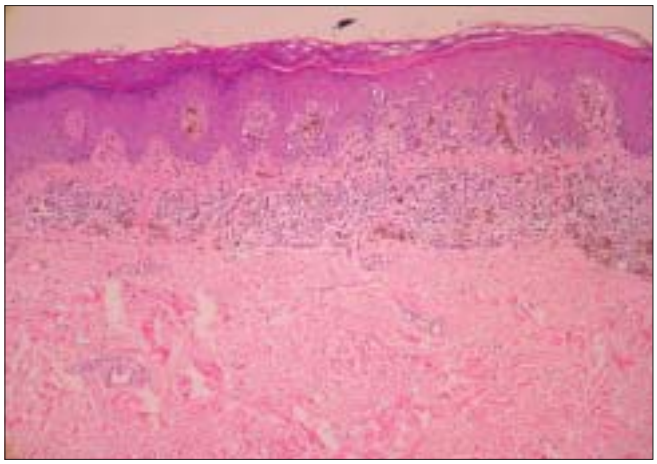

Figure 6: MF - superficial lymphoid infiltrate in papillary dermis (H and E, low power magnification, ×40)

with pagetoid spread (i.e., buckshot distribution with pericellular halos).

4. Unlike in typical dermatitic histology, there is a greater influx of lymphocytes, not necessarily atypical, distributed singly or in small collections in an epidermis devoid of microvesiculation. The term "disproportionate epidermotropism" has been used to express this concept.
5. Presence of vacuolar interface dermatitis.
6. Presence of papillary dermal fibrosis.

ISCL histopathologic criteria

Biopsy specimen must first have a superficial lymphoid infiltrate [Figure 6].

Epidermotropism without spongiosis - 1 point [Figure 7].

(Differential diagnosis - collagen vascular disease, drug-induced pseudolymphoma)

Lymphoid atypia - 1 point [Figure 7].
(Differential diagnosis-lymphamatoid contact dermatitis, drug-induced pseudolymphoma)

The utility of histopathologic criteria is preserved by the interdependence on the other criteria in order to achieve the four points needed to establish the diagnosis of early MF.

Caveat

The overall clinicopathological features cannot suggest a specific non-MF diagnosis.

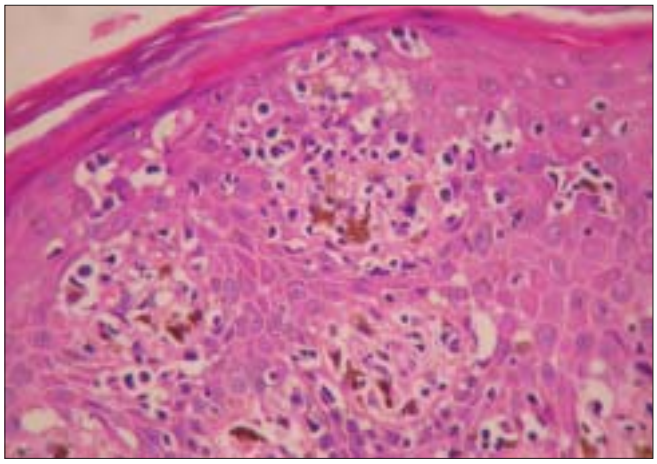

Figure 7: MF - showing epidermotropism without spongiosis (H and E, high power magnification, ×100)

EARLY DIAGNOSIS OF MF: ANCILLARY TECHNIQUES

DNA cytophotometry[18-20] nuclear morphometry, immunohistochemistry, chromosomal studies and more recently molecular genetic analysis of T cell clonality, have helped in the diagnosis of MF in the early stage. For clonality, PCR-based analysis is more sensitive than Southern blot analysis. It is recommended to use DNA extracted from fresh frozen tissue and PCR-based clonality analysis of T cell receptor gene rearrangements using denaturing gradient gel electrophoresis (PCR/DGGE).[10]

The detection of a clonal T cell population by sensitive PCR techniques on frozen specimens that otherwise do not have diagnostic histopathologic features of MF has generated the concepts of "clonal dermatitis" and

"abortive/latent lymphoma."[21] Long-term follow-up of patients categorized as having "clonal dermatitis" indicates that progression to overt MF occurs at a rate that may be as much as four times higher than that for large-plaque parapsoriasis defined by clinicopathological criteria alone.

Immunohistochemistry[22-24] can aid in diagnosis of MF. Antigen deficiency must be looked for and MF is generally a CD4 predominant T cell process. CD4/CD8 ratio >6 and loss of T cell markers (CD7 and sometimes CD5) have been used to support the diagnosis of MF.

ISCL molecular biological criteria

A dominant T cell clonal pattern must be detected by PCR-based analysis of T cell receptor gene rearrangements - 1 point. (PCR/DGGE method preferred).[25,26]

ISCL immunopathologic criteria

Any one of three features must be present to generate - 1 point.

- >50% of T cells expressing CD2, CD3 and CD5
  OR
- >10% of T cells expressing CD7
  OR
- Epidermal or dermal discordance for the expression of CD2, CD3, CD5 and CD7.

Caveats concerning the algorithm

Algorithm is designed for classic presentations of early MF. It is not intended for atypical clinical and histologic variants including hypopigmented, follicular and purpuric or palmoplantar MF.

Regardless of any individual feature, if the overall clinicopathologic correlation in a case suggests a specific diagnosis other than MF, then the algorithm ceases to apply (example connective tissue diseases, pseudolymphoma, where history is the key).

Recently, cDNA microarray profiling avoids histologic and molecular pitfalls and may be used increasingly in the diagnosis of MF. An early study indicated that a set of six genes accurately differentiated a sample of MF from that of inflammatory disorders.

CONCLUSION

When diagnosing early MF, it may be best to err on the conservative side and use strict, rigorous criteria with careful clinical follow-up of borderline cases. A major reason for this is that earlier diagnosis and treatment is not necessarily beneficial to patients. Studies have revealed that PUVA treatment of mycosis fungoides patients (stages Ia to IIa), although effective in achieving a complete response, about 50% of patients developed a relapse after a median of 33 months and one-thirds of patients developed photodamage and skin cancer.[27] Maintenance phototherapy is not warranted. Survival did not worsen in patients who had relapse.[28] Another study compared topical treatment of mycosis fungoides with electron-beam radiation and chemotherapy and found no difference in prognosis between the topical versus systemic treatments, although increased morbidity was associated with systemic treatment.[29]

We have tried to emphasize the point that in developing countries, where only clinicopathological correlation is possible in the majority of cases and hence diagnosis of MF is conjectural, we believe that the diagnosis of MF should not be offered to the patient. This can lead to unnecessary expensive aggressive therapy and may also cause great distress and even suicidal thoughts in the patient. Patients are only concerned about the cosmetic disfigurement caused by hypo- or hyperpigmented patches and are not worried about semantics, whether we call it as large plaque parapsoriasis or patch stage MF. As the treatment of both the disease is the same, for example, PUVA,[28] and as one cannot be certain which of the early mycosis fungoides will go into the tumor stage, it makes sense to use a "benign" term such as large plaque parapsoriasis rather than the "malignant" term MF. It is more compassionate for the patient whatever the demerits of the term parapsoriasis may be. That is our only argument for holding on to the "retrogressive" terminology of parapsoriasis. It is essential though to have a close follow-up of these patients. It is this aspect that has to be emphasized.

ACKNOWLEDGMENT

Dr. Jessy Thomas - Pathologist, Dr. A. Bridgette Akila - Epidemiologist, Ms. J. Shylaja - Secretarial Assistance.

REFERENCES

1. Samman PD. The natural history of parapsoriasis en plaques (chronic superficial scaly dermatitis) and prereticulotic poikiloderma. Br J Dermatol 1972;87:405.
2. Wood GS, Chung-Hong Hu, Garrett AL. Parapsoriasis and

pityriasis lichenoides. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. 'Fitzpatrick's Dermatology in General Medicine', 7th ed. New York: McGraw Hill Publishing: 2008;p: 236-240.
3. Haeffner AC, Smoller BR, Zepter K, Wood GS. Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. Arch Dermatol 1995;131:321-4.
4. Burg G, Dummer R. Small plaque (digitate) parapsoriasis is an "abortive" cutaneous T cell lymphoma. Arch Dermatol 1995;131:336-8.
5. Simon M, Flaig MJ, Kind P, Sander CA, Kaudewitz P. Large plaque parapsoriasis: Clinical and genotypic considerations. J Cutan Pathol 2000;27:57-60.
6. Whittaker SJ, Mackie RM. Cutaneous Lymphomas and lymphocytic infiltrates. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. 'Rook's Text Book of Dermatology', 7th ed. Blackwell Publishing: 2004. p. 54.2-54.13.
7. Sanchez JL, Ackerman AB. The patch stage of mycosis fungoides: Criteria for histologic diagnosis. Am J Dermatopathol 1979;1:5-26.
8. Ackerman AB, Schiff TA. If small plaque (digitate) parapsoriasis is a cutaneous T-cell lymphoma, even an abortive one, it must be mycosis fungoides. Arch Dermatol 1996;132:562-6.
9. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (limited patch and plaque) mycosis fungoides: A long-term outcome analysis. Arch Dermatol 1996;132:1309-13.
10. Christan JK. The new world health organization-European organization for research and treatment of cancer classification of cutaneous lymphomas. Adv Dermatol 2006;22:259-77.
11. Olsen D, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, *et al*. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22.
12. Naraghi ZS, Seirafi H, Valikhani M, Famaghi F, Kavusi S, Dowlati Y. Assessment of histologic criteria in the diagnosis of mycosis fungoides. Int J Dermatol. 2003;42:45-52.
13. Stevens SR, Ke MS, Birol A, Terhune MH, Parry EJ, Ross C, *et al*. A simple clinical scoring system to improve the sensitivity and standardization of the diagnosis of Mycosis Fungoides type cutaneous T-cell lymphoma: Logistic regression of clinical and laboratory data. Br J Dermatol 2003;109:513-22.
14. Bukhari IA. Poikilodermatous variant of mycosis fungoides. J Drugs Dermatol 2006. Available from: http://www.encylopaedia.com. [last accessed on 2007 Sep 15].
15. Oliver GF, Winkelmann RK. Unilesional mycosis fungoides: A distinct entity. J Am Acad Dermatol 1989;20:63-70.
16. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: Clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. J Am Acad Dermatol 2000;42:283-5.
17. Santucci M, Biggeri A, Feller AC, Burg G. Accuracy, concordance and reproducibility of histologic diagnosis in cutaneous T-cell lymphoma: An EORTC cutaneous lymphoma project group study. Arch Dermatol 2000;136:497-502.
18. van Vloten WA, van Duijn P, Schaberg A. Cytodiagnostic use of Feulgen-DNA measurements in cell imprints from the skin of patients with mycosis fungoides. Br J Dermatol 1974;91: 365-71.
19. Ralfkiaer E, Larsen JK, Christensen IJ, Thomsen K, Wantzin GL. DNA analysis by flow cytometry in cutaneous T-cell lymphomas. Br J Dermatol 1989;120:597-605.
20. Altomare G, Capella GL, Piagatto PD, Biondo B, Lavezzi AM. Densitometry of Pautrier's microabscess cells in cutaneous T-cell lymphoma. Int J Dermatol 1995;34:535-7.
21. Fung MA, Murphy MJ, Hoss DM, Grant-Kels JM. Practical evaluation and management of cutaneous lymphoma. J Am Acad Dermatol 2002;46:325-57.
22. Vonderheid EC, Tan E, Sobel EL, Schwab E, Micaily B, Jegasothy BV. Clinical implications of immunologic phenotyping in cutaneous T-cell lymphoma. J Am Acad Dermatol. 1987;17:40-52.
23. Lindae ML, Abel EA, Hoppe RT, Wood GS. Poikilodermatous mycosis fungoides and atrophic large-plaque parapsoriasis exhibit similar abnormalities of T-cell antigen expression. Arch Dermatol 1988;124:366-72.
24. Dreno B, Bureau B, Stalder JF, Litoux P. MY7 monoclonal antibody for diagnosis of cutaneous T-cell lymphoma. Arch Dermatol 1990;126:1454-6.
25. Bachelez H, Bioul L, Flageul B, Baccard M, Moulonguet-Michau I, Verola O, *et al*. Detection of clonal T-cell receptor gammagene rearrangements with the use of the polymerase chain reaction in cutaneous lesions of mycosis fungoides and Sezary syndrome. Arch Dermatol 1995;131:1027-31.
26. Curco N, Servitje O, Llucia M, Bertran J, Limon A, Carmona M, *et al*. Genotypic analysis of cutaneous T-cell lymphoma: A comparative study of Southern blot analysis with polymerase chain reaction amplification of the T-cell receptor-gamma gene. Br J Dermatol 1997;137:673-9.
27. Querfeld C, Rosen ST, Kuzel TM, Kirby KA, Roenigk HH, Prinz BM, *et al*. Long term follow up of patients with early stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. Arch Dermatol 2005;141:305-11.
28. Roupe G, Sandstrom MH, Jellstrom C (Sahlgrenska Univ. Goteborg, Sweden). PUVA in early mycosis fungoides may give long-term remission and delay extracutaneous spread. Acta Dermatol Venereol 1996;76:475-8.
29. Kaye FJ, Bunn PA, Steinberg SM, Stocker JL, Ihde DC, Fischmann AB, *et al*. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 1989;321:1784-90.