MYCOSIS FUNGOIDES IN PREGNANCY : A CASE REPORT WITH ULTRASTRUCTURAL FEATURE

วิทยา นันทิยกุล
รพ. เจ้าพระยายมราช

ABSTRACT :

Nuntiyagul W. Mycosis Fungoides in Pregnancy : A Case Report with Ultrastructural Feature. (Region 7 Medical Journal 1996 ; 4 : 489-497).

Dermatologic Division, Department of Medicine, Chaoprayayomaraj Hospital, Suphan Buri, Thailand.

A 26 - year - old Thai female, 2 months of pregnancy, presented with asymptomatic large dry scaly erythematous patches with wrinkle surface on the back, abdomen and lower extremities. The lesions persisted and were not improved by many topical treatments.

Histopathology revealed epidermotrophism, single cell with halo and Electron microscope showed Pautrier microabscess with Lützner cell in epidermis and dermis. This finding is consistent with mycosis fungoides (MF) in pregnancy. The lesions did not flare up during her pregnancy until she had a normal delivery of a normal healthy new born. Her infant weighed 3,200 grams and did not show cutaneous lesion of mycosis fungoides. After delivery, she was treated with systemic photochemotherapy (PUVA) with a good result. The cutaneous lesions were clear within 6 months of treatment with no complications, and no relapse of disease after 2 years.

บทคัดย่อ :

วิทยา นันทิยกุล. Mycosis Fungoides ในหญิงตั้งครรภ์ : รายงานผู้ป่วยพร้อมลักษณะทางจุลทรรศน์ อิเล็กตรอน. (วารสารแพทย์ เขต 7 2539 ; 4 : 489-497).

หน่วยโรคผิวหนัง, กลุ่มงานอายุรกรรม, รพ. เจ้าพระยายมราช, สุพรรณบุรี.

ผู้ป่วยหญิงไทย อายุ 26 ปี ตั้งครรภ์แรกได้ 2 เดือน มาพบแพทย์ด้วยเรื่องมีผื่นแดง แห้ง และมีขุยที่บริเวณหลัง หน้าท้อง และต้นขาทั้ง 2 ข้าง ซึ่งผื่นไม่ดีขึ้นหลังได้รับการรักษาด้วยยาทาหลายชนิด

ผลการตรวจทางพยาธิวิทยา พบลักษณะ epidermotrophism, single cell with halo. ลักษณะทางจุลทรรศน์อิเล็กตรอน พบ Pautrier microabscess และ Lützner cell ในชั้นหนังกำพร้าและหนังแท้ ซึ่งลักษณะที่พบเข้าได้กับโรค mycosis fungoides ในหญิงตั้งครรภ์ ซึ่งไม่พบการลุกลามของผื่นในระหว่างการตั้งครรภ์จนกระทั่งคลอดปกติ ทารกแรกคลอดหนัก 3,200 กรัม และไม่พบความผิดปกติใด ๆ ทางผิวหนังในทารกแรกคลอด หลังคลอดให้การรักษาผู้ป่วยด้วย systemic photochemotherapy (PUVA) ซึ่งได้ผลดี พบว่ารอยโรคต่าง ๆ สามารถหายไปได้หมดภายใน 6 เดือน โดยไม่มีภาวะแทรกซ้อน และไม่พบการกลับเป็นซ้ำของโรคอีกเลยหลังการรักษา 2 ปี

Mycosis fungoides (MF) is an epidermotropic form of cutaneous T - cell lymphomas (CTCL)[1] in which a malignant clone of the immunologic markers of helper T lymphocytes invades the skin.

MF is predominantly affecting the skin, that often begins as limited patches and plaques with slow progression to systemic involvement. Classic epidermotropic and adult-onset MF has a peak occurrence in middle-aged men and least often in young white women.[2] To the best of my knowledge, MF in pregnancy in Thailand is very rare. I reported the clinical, histological, electron microscopic features and treatment of MF in pregnant woman who finally gave birth to a normal newborn.

Clinical History

A 26-year-old Thai female, 2 months of pregnancy, presented with asymptomatic large dry scaly erythematous patches with wrinkle surface on the back, abdomen and lower extremities. Peeling was also noted. The lesions persisted and were not improved by many topical treatments. She appeared healthy, no weight loss and the lesions did not flare up until she had a normal delivery.

Physical examination showed well - defined scaly erythematous patches with wrinkle surface. The diameter is more than 10 cm on the back, abdomen (Figure 1, 2), lower extremities (Figure 3), no hepatosplenomegaly and no palpable lymph nodes.

The investigation revealed hemoglobin 10 gm%, differential cell count and platelet count are within normal limit.

Urinary analysis, liver function test, BUN, creatinine, uric acid, calcium, LDH, VDRL, Antinuclear antibody titer and bone marrow biopsy are within normal limit.

The sezary cell count from peripheral blood is 228 cell/cumm.[3]

The histopathology showed hyperkeratosis, hypogranulosis, acanthosis, epidermotrophism, single cell with halo, minimal perivascular lymphoid cell and histiocyte in upper dermis.

The light microscopy and electron microscopy showed pautrier microabscess in epidermis (Figure 4, 5, 6), Lützner cell or sezary cell in dermis (Figure 7).

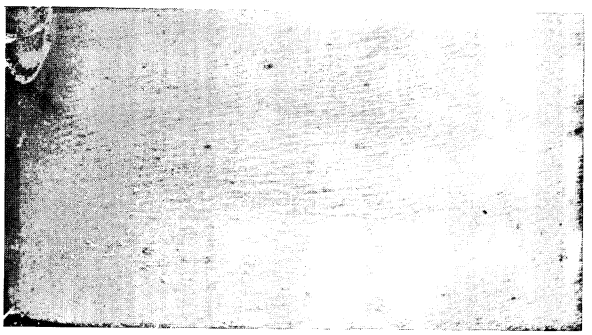

Fig. 1 Confluent dry scaly erythematous patch, wrinkle surface with mild peeling of MF lesions on abdomen.

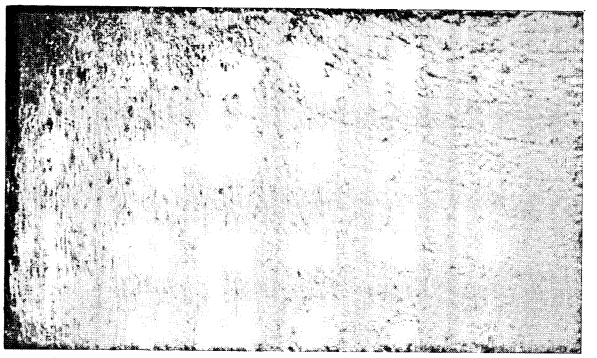

Fig. 2 Higher magnification of the lesion of abdomen.

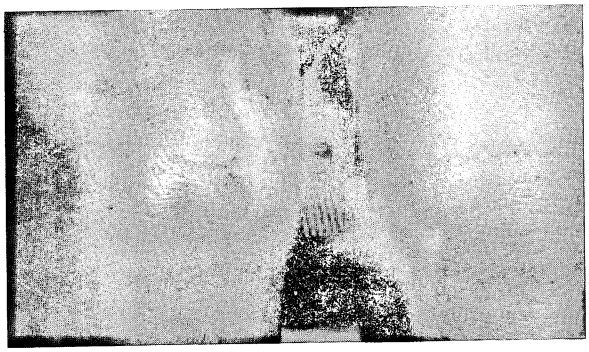

Fig. 3 Multiple patches of MF on lower extremities.

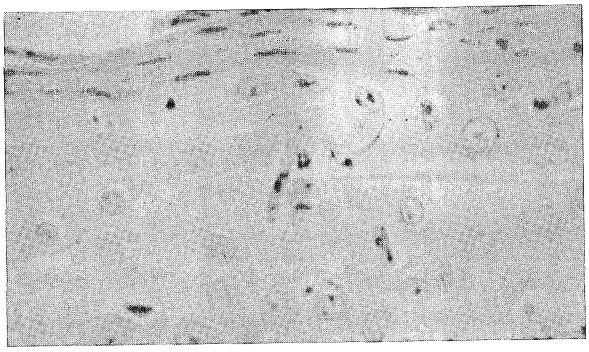

Fig. 4 Microscopic photography of a lesion from patient with MF (flat, non - atrophic patch) confined to the skin. The epidermis show epidermotrophism without spongiosis. Mononuclear cells surrounded by a halo are scattered through the epidermis with sparse superficial perivascular infiltration in papillary dermis. H & E stained section (x 40).

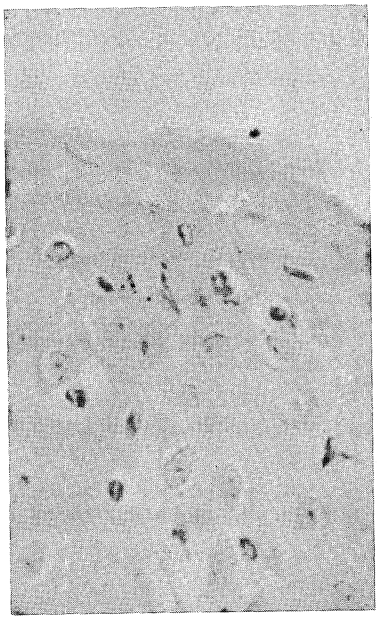

Fig. 5 Microscopic photography of a lesion from patient with MF (flat, non - atrophic patch) confined to the skin. The epidermis show epidermotrophism without spongiosis. Mononuclear cells surrounded by a halo are scattered through the epidermis with sparse superficial perivascular infiltration in papillary dermis. H & E stained section (x 40).

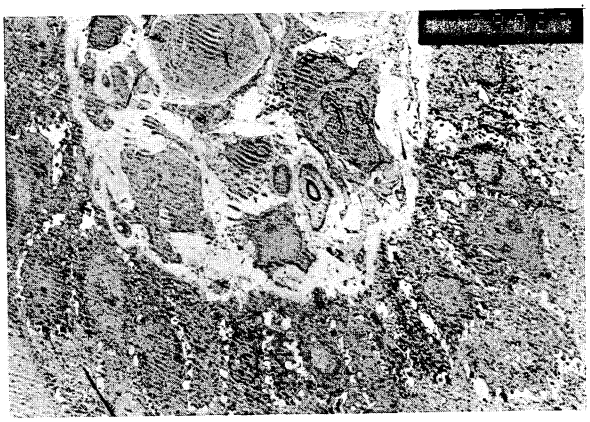

Fig. 6 Pautrier microabscess in epidermis by electron microscope (x 6,000).

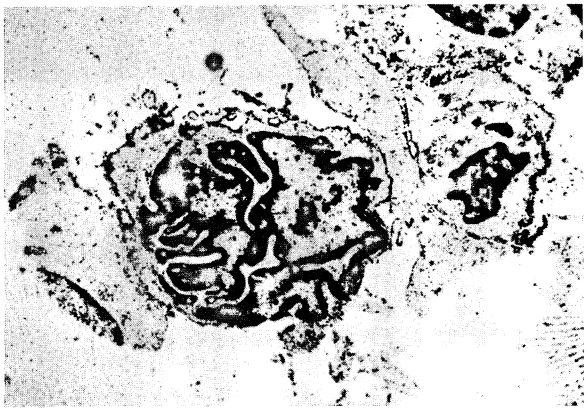

Fig. 7 Atypical lymphocyte with cerebriform or convoluted nucleus (Lützner cell) in dermis by electron microscope (x 21,000), confirmed by NCI > 7 and nuclear profile > 30 mm^3

Other special investigations were not done due to her pregnancy. These findings are consistent with Mycosis fungoides (patch stage) occured in pregnancy.

Discussion

Clinically as well as histologically, MF in typical cases can be divided into three stages : patch, plaque and tumor stage. The three stages may be overlap, so that lesions of all three stages may be present simultaneously.

In patch stage of Mycosis fungoides, The patches are usually flat and not atrophic, but in some patients, they appear atrophic. The flat, non-atrophic patches, are generally followed by infiltrative plaques within several months to several years, and later on usually followed by visceral involvement. The flat, atrophic patches undergo clinical transition into aggressive MF are only about 12 percent of the cases,[3] while persisting in the remainder without significant change. In my patient who has been reported is classified into flat, non - atrophic patches which often show scaling and then resemble psoriasis or other forms of dermatitis.[4]

The histopathologic finding in flat, non - atrophic patches, the dermis at first often shows merely a banal inflammation, infiltrate in the papillary and subpapillary portion of the dermis. The infiltration is composed mainly of lymphocytes but also contains varying numbers of histiocytes, but may be observed epidermotrophism (The presence of atypical mononuclear cells infiltrating the epidermis without evidence of spongiosis).

The mononuclear cells lying closed together and surrounded by a halo - like clear space suggestive of a small Pautrier microabscess (Intraepidermal collection of atypical lymphocytes). Cells with hyperchromatic and irregular shaped nuclei, analogues to mycosis cells are usually absent but may be present in small numbers in cellular infiltration which demonstated by electron microscope. Electron microscope facilitated the diagnosis of MF by identification the characteristic of atypical T lymphocyte with a serpentine, cerebriform or convoluted nucleus (Lützner cell or mycosis cell or sezary cell). This presence may aid diagnosis in clinically suspicious case of MF. However a more reliable way to assess[5] morphometrically the nucleus of mycosis cell is to combined two parameters : The nuclear contour index (NCI) and the nuclear surface area such as this patient. It has been demonstrated that lymphoid cells with NCI greater than or equal to 11.5 and NCI of 7 or more with nuclear profile greater than 30 mm^2 were found only in skin lesions of patient with

MF.[6] Other new techniques used to identification of Lützner cell were immunohistochemistry and Flow Cytometry with markers.

The nature of the lymphocytes infiltration in mycosis fungoides has been shown to be preponderantly T cell in nature, both by E - rosetting on extracted cell and by in situ immunohistochemical staining an anti T - cell serum raised in rabbits against Human T - lymphocyte antigen (HTLA).[7]

The skin infiltration of mycosis fungoides contains from 66 to 86 percent T lymphocyte. In dermal infiltration of MF, the great majority of T cells, usually 80 to 90 percent express the helper T -cell phenotype[8] and only 10 to 20 percent are of suppressor T - cell phenotype.

The NCI of T cells in skin infiltration increased in parallel with advancing stages of the lesions in the same patient.[9] In epidermis. epidermotropic cell reacted positive only with Leu - 3a antihelper antibody and the epidermis either demonstrated circumscribed groups of epidermal cells reacting with HLA - DR or was diffusely positive for HLA - DR.[10] Langerhan cells are OKT - 6 reactive that are increased in the dermal infiltration in all stages of MF account for up to 5 percent of the cells, where as Langerhan cells are normally seen only rarely in the dermis.

Hematologic examination has revealed the presence of circulating sezary cell in MF in from 12 to 20 percent of the patients. However this concentration is usually less than 15 percent, the minimum level for the diagnosis of sezary syndrome. In my pattient, the sezary cell count from peripheral blood is 228 cell/cumm,[3] the circulating sezary cells at low concentration are not specific finding, they are often found intermittently in various inflammatory dermatoses, generally at level below 10 percent or 1,000 per mm.[3]

Once a diagnosis of MF has been established, the extent of disease involvement should be assessed, whether the disease confined to the skin, has extended to visceral tissue, has an associated, overt leukemic component or has entered a phase of rapid cellular proliferation. Identification of the extent and nature of a lymphoma will then allow appropriate selective of therapy.

Presence of peripheral lymph node infiltration and blood involvement correlates well with the presence of extracutaneous spread. Staging procedures are important in all patients with MF with the exception of those with a limited erythematous eruption or with plaques covering less than 10 percent of the skin surface (T - 1). All patients with plaques covering more than 10 percent of the skin (T - 2, T - 3, T - 4) or with more than 4 percent of the sezary cells in their differential white blood cell count, even without palpable lymph nodes, should perform lymph node biopsy which draining an involved skin area. In this patient, she had plaques covering more than 10 percent of skin surface without palpable lymph node, and bone marrow biopsy is within normal limit, so the staging is at least stage IB.

A staging system based on histopathologic evaluation[11] of skin, lymph nodes, blood and visceral sites provides more comprehensive prognostic information than clinical evaluation of skin and adenopathy, and another investigations that should

be done for staging are bipedal lymphangiograms, chest x - ray, Long GI series, liver and spleen scan, and liver biopsy in selected patients, but staging laparotomy is the most accurate method for staging. This patient could not staging by all steps due to her pregnancy.

Differential diagnosis

The diagnosis of MF in its early stage may be very difficult because histologic diagnosis of early stage of MF lies in the fact that occasional cells with hyperchromatic, irregularity shaped nuclei corresponding to early mycosis cells and representing transformed lymphocytes can be seen in many non - specific chronic inflammatory infiltration. In this case, the presence of epidermotrophism and/or of Pautrier microabscess containing mononuclear cells can then be of great value, especially if a fairly high percentage of the mononuclear cells have the apperarance of mycosis cells or at least appear haloed. If the clinical suspects, multiple biopsy should be taken and clinicopathologic correlation is necessary, and confirmed by electron microscopy.

Treatment

In my patient whose staging is at least IB, I gave her symptomatic treatment with topical emollients, topical steroid creams and ointments during her pregenancy to relieve dry, scaling skin which is exceedingly pruritus and which leads to insomnia.

Therapy with topical nitrogen mustard (mechlorethamine hydrochloride),[12] retinoid and interferon alfa[13] are generally contraindicated during pregnancy, especially in the first trimester, because there are suspected of causing fetal malformation.

Electron beam radiotherapy is now recommended in case of MF confined to the skin with good clinical response and absence of systemic toxicity, but it is known to predispose persons to development of cutaneous malignaneies.[14]

Photochemotherapy (PUVA) is an effective and safe therapy for MF with prolonged disease-free remissions being achieved. Patients with stage I and II MF respond best to PUVA. Palliative therapy with PUVA is useful in more advanced cases of MF.[15] Combined modality of therapy has shown to give better results than single therapy alone.[16]

In my patient whose staging is at least IB, I gave her systemic photochemotherapy (PUVA) after her pregnancy had delivered already. She was treated with a standard PUVA regimen. She ingested 8 - MOP (0.6 mg/kg) 2 hours before the UVA exposure. The initial UVA dose was administered according to recommended standards for photochemotherapy for MF.[17] The dose was increased by 0.5 J/cm^2 or more at each treatment depending on the presence of erythema. Treatments were given three times a weeks for 2 months, two times a week for 1 month and followed by once weekly for 4 weeks and once every 2 weeks for 8 weeks until the lesion cleared. No complications or new lesions could be observe after clearing for 2 years, and the laboratory findings such as CBC, U/A, BUN, Creatinine, Liver function test, skin biopsy, bone marrow biopsy are within normal limit, so she had a complete response (A complete response was defined as total clinical and histologic clearing for a minimum of 4

weeks).

Course and prognosis

It is generally accepted that MF is a malignant monoclonal proliferation of helper T cell. The natural progression of MF in most patients is chronic with a symptomatic prediagnostic stage averaging 6 to 7 years. The disease usually follows an orderly progression from limited patches to more generalized patches, plaques, tumors, and finally nodal or visceral involvement.[18] As the disease advances, the number and atypicality of the lymphoma cells increase.[19] The host reaction slackens until in the tumor stage that lymphoma cells predominate. The lymph nodes affected 61 percent of the cases are the most common site of visceral involvement. However almost any organs may be affected and involvement of bone marrow represents a common terminal event.

The mortality rate among patients with MF from the disese itself is estimated to be about 80 percent, with about one half of the patients dying of infection, largely pneumonia or sepsis, and one half dying of the consequences of dissiminated lymphoma. About 20 percent of the patient died of causes that unrelated to MF.

MF is one of the skin diseases aggravated by pregnancy. In 1981 Vanderheid et al reported a patient with MF whose disease flared during the otherwise uncomplicated pregnancy. Three years after her last pregnancy, the patient achieved a prolonged remission as a result of treatment with topical mechlorethamine hydrochloride. In my patient, she appeared healthy and the lesions did not flare up during her pregnancy until she had a normal delivery of a normal healthy newborn with normal skin. After delivery, I gave her a specific treatment with systemic photochemotherapy (PUVA) for 6 months with a complete response and no relapse of the lesions after 2 years. Her infant is now 2 years of age and had a normal growth and development without any abnormal skin lesions.

Acknowledgement

I gratefully acknowledge Dr. Piti Palungwachira, The head of the department of Dermatology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand, for providing the information and techniques of Electron microscopy.

Reference

1. Evans GE, Daliziel KL. Mycosis fungoides with oral involvement. Int J Oral Maxillofac Surg 1987 ; 16(5) : 634-7.
2. Able EA, Wood GS, Hoppe RT. Mycosis fungoides : clinical and histologic features, staging evaluation, and approach to therapy. CA cancer J Clin 1993 ; 43 : 93-113.
3. Lever F. Histopatholoty of the skin. 6th ed. Philadelphia : JB Lippincott Com, 1987 : 738-46.
4. Piamphongsant T. Parapsoriasis and related condition. Ann acad Med Singapore 1988 ; 17(4) : 486-91.
5. Simon GT. The value of morphometry in the ultrastructural diagnosis of Mycosis fungoides. Ultrastruc Pathol 1987 ; 11(5-6) : 687-91.
6. Patterson JAK, Edelson RL. Cutaneous T - cell lymphoma and other leukemic and lymphomatory infiltrates of the skin. In : Fitzpatrick TB, et al. 3rd

eds. Dermatology in general medicine. New York : McGraw - Hill, 1987 : 1086-118.

7. McMillan EM, Wasik R, Matin D, Everett MA. Identification of T cells in parasporiasis infiltrates. Arch Dermatol 1982 ; 118 : 238-40.
8. Buechner SA, Winkelmann RK, Banks PM. T cells and T - cell subsetes in mycosis fungoides and parapsoriasis ; a study of 18 cases with anti - human T - cell monoclonal antibodies and histochemical techniques. Arch Dermatol 1984 ; 120 : 897-905.
9. McNutt SN, Heilbron DC, Crain WR. Mycosis fungoides : Diagnostic criteria based on quantitative electron microscopy. Lab Invest 1981 ; 44 : 466-74.
10. McMillan EM, Wasik R, Everett MA. HLA DR - positive cells in large plaque (atrophic) parapsoriasis. J Am Acad Dermotol 1981 ; 5(4) : 444-9.
11. Sausville EA, et al. Hitopathologic staging at initial diagnosis of mycosis fungoides and the sezary syndrome. Ann Intern Med 1988 ; 109(5) : 372-82.
12. Vonderheid EC, Tan ET, Kantor AF, et al. Long term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 1989 ; 20(3) : 416-28.
13. Lippman SM, et al. Non surgical treatments for skin cancer : retinoids and alpha -interferon. J Dermatol Surg Oncol 1988 ; 14(8) : 862-9.
14. Abel EA, Sendagorta E, Hoppe RT. Cutaneous malignancy and metastatic squamous cell carcinoma following topical therapies for mycosis fungoides. J AM Acad Dermatol 1986 ; 14 : 1029-38.
15. James JH, et al. Treatment of mycosis fungoides with photochemotherapy (PUVA) : Long term follow up. J Am Acad Dermatol 1995 ; 33(1) : 234-42.
16. Madeleine Duvic, et al. Combined modality therapy of cutancous T - cell lymphoma. J Am Acad Dermatol 1996 ; 34 : 1022.
17. Roenigk HH Jr. Photochemotherapy for mycosis fungoides. Arch Dermatol1977 ; 113 : 1047-51.
18. Kuzel TM, Roenigk HH Jr, Rosen ST. Mycosis fungoides and the Sezary syndrome : a review of pathogenesis, diagnosis, and therapy. J Clin Oncol 1991 ; 9 : 1298-313.
19. Haynes BF, Hensley LL, Jegasothy BV. Differentiation of human T lymphocytes : II. phenotypic difference in skin and blood malignant T - cells in cutaneous T - cell lymphoma. J Invest Dermatol 1982 ; 78 : 323-6.