รายงานผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิด Mycosis Fungoides ที่มีเซลล์ขนาดใหญ่ขึ้น และมีผลตรวจด้วยวิธีอิมมูโนฮีสโตเคมีพบ CD30 เป็นบวก

อารียา ศรีม่วง พ.บ.*, วรพล เวชชาภินันท์ พ.บ.**
*กลุ่มงานโรคผิวหนัง สถาบันโรคผิวหนัง แขวงทุ่งพญาไท เขตราชเทวี กรุงเทพมหานคร 10400
**กลุ่มงานโรคผิวหนัง โรงพยาบาลโรคผิวหนังเขตร้อนภาคใต้ จังหวัดตรัง ตำบลบ้านควน อำเภอเมือง จังหวัดตรัง 92000

Mycosis Fungoides with CD30-positive Large Cell Transformation: Case Report

Areeya Srimuang, M.D.*, Voraphol Vejjabhinanta, M.D.**
*Department of Dermatology, Institute of Dermatology, Thung Phayathai, Ratchathewi, Bangkok, 10400, Thailand.
**Department of Dermatology, Southern Regional Hospital of Tropical Dermatology-Trang Province, Ban Quan, Mueang, Trang, 92000, Thailand
(E-mail: areeya.srimuang@gmail.com)

(Received: 15 July, 2023; Revised: 2 October, 2023; Accepted: 3 February, 2024)

Abstract

Mycosis fungoides is the most common type of cutaneous T-cell lymphoma, accounting for 50% of all primary cutaneous lymphomas. It typically affects older adults, with a mean age of 55-60 years, and is more common in males. Although the exact cause of mycosis fungoides is unknown, various factors such as genetics, environment, and the immune system have been considered as possible contributors. Large cell transformation is a rare occurrence and is associated with a poor prognosis. This case report presented the details of a 48-year-old female patient who had multiple ulcerated tumors that emerged on scaly erythematous plaques on her neck, trunk, groin, and extremities for a duration of 4 months. Following the performance of biopsy with H&E stains and immunohistochemical studies, the patient was diagnosed with mycosis fungoides, specifically with CD30-positive large cell transformation.

Keyword: Mycosis fungoides, CD30-positive Large Cell Transformation, Lymphoma

บทคัดย่อ

Mycosis fungoides เป็นมะเร็งต่อมน้ำเหลืองชนิด T-cell ที่พบได้บ่อยที่สุด โดยคิดเป็นร้อยละ 50 ของมะเร็งต่อมน้ำเหลืองชนิดปฐมภูมิทั้งหมด มักเกิดกับผู้สูงอายุที่มีอายุเฉลี่ย 55-60 ปี และพบมากในเพศชาย แม้ว่าจะไม่ทราบสาเหตุของโรค mycosis fungoides ที่แน่ชัด แต่พบว่าปัจจัยที่มีส่วนสนับสนุนในการเกิดโรค เช่น พันธุกรรม สิ่งแวดล้อม และระบบภูมิคุ้มกัน เป็นต้น โรคมะเร็งต่อมน้ำเหลืองชนิด mycosis fungoides ที่มีเซลล์ขนาดใหญ่ขึ้นพบได้น้อยและมีการพยากรณ์โรคที่ไม่ดี รายงานผู้ป่วยรายนี้เป็นหญิงอายุ 48 ปี มีเนื้องอกที่เป็นแผลบริเวณคอ ลำตัว ขาหนีบ และแขนขา เป็นระยะเวลา 4 เดือน ผู้ป่วยได้รับการตัดชิ้นเนื้อและส่งตรวจด้วยวิธีทางอิมมูโนฮีสโตเคมี ผู้ป่วยได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลืองชนิด mycosis fungoides ที่มีเซลล์ขนาดใหญ่ขึ้น และมีผลตรวจด้วยวิธีอิมมูโนฮีโตเคมีพบ CD30 เป็นบวก

คำสำคัญ: มะเร็งต่อมน้ำเหลืองชนิด mycosis fungoides, CD30-positive Large Cell Transformation, มะเร็งต่อมน้ำเหลือง

Introduction

The most common type of cutaneous T-cell lymphoma is called mycosis fungoides. It occurs twice as often in males compared to females. Although the exact cause is unknown, it is believed that genetic, environmental, and immunologic factors may play

a role in triggering the disease. Normally, the progression of mycosis fungoides is slow and not aggressive, except when it transforms into a large cell form. Large cell transformation of mycosis fungoides is rare and generally associated with a poor prognosis. Most patient present with solitary tumors that often develop ulceration. Multiple lesions are seen in about 20% of patient. The incidence of primary cutaneous anaplastic large cell lymphoma among other types of non - Hodgkin lymphoma is 1.7%. This disease is histopathological diagnosis and immunohistochemistry studies may be required to identified subtypes. The management of mycosis fungoides depends on clinical stage. This case report describes a 48 - year - old female patient who had mycosis fungoides with CD30 - positive large cell transformation.

Case

A 48 - year - old female presented with a 4 - month history of multiple ulcerated tumors that emerged from scaly erythematous plaques on her left buttock and spread to her trunk, face, neck, and all extremities. She reported no prior occurrences of fever, night sweats, or weight loss. She had no underlying diseases, nor any history of drug or food allergies. She denied smoking, consuming alcohol, or using herbal remedies. Additionally, there were no family members who had experienced a similar condition, and no history of malignancies in her family.

During the physical examination, she exhibited multiple well - circumscribed, finely scaly erythematous plaques with ulcerated tumors at the center, affecting her neck, trunk, groins, and all extremities (Figure 1). Generalized lymph node enlargement was also observed. A biopsy was conducted on her right forearm. The tissue was collected and fixed in melted paraffin wax. The resulting block was cut into thin slices for the Hematoxylin and eosin stain. The H&E shows multiple areas of atypical lymphocytic exocytosis in the epidermis. The dermis displayed dense infiltration of atypical lymphocytes, primarily in the superficial layer. Although pleomorphism was noted, multinucleation or a “horse - shoed” nuclear appearance was not observed. Reed - Sternberg cells were not identified, but mitosis was frequent (Figure 2).

Immunohistochemical studies from tissue on the right forearm demonstrated immunopositivity to CD3, CD4, CD5, CD7, CD30 (variable), TCR - BF1, Ki - 67 (80%), and PD - 1. However, CD2, CD8, CD56, TIA - 1, Granzyme B, Perforin, CD10, BCL - 6, and CXCL13 showed negative results (Figure 3A - 3D). Laboratory tests, including a complete blood count, revealed leukocytosis with eosinophil predominance. Renal and liver function tests, CEA, and CA19 - 9 were within normal limits, while lactate dehydrogenase and CA125 levels were elevated. Tissue cultures for bacteria, mycobacteria, and fungi yielded negative results. A marrow biopsy indicated normocellularity (50%) with no evidence of lymphoma. CT scans of the chest and whole abdomen identified multiple lymph node enlargements at the left internal iliac group, left external iliac group, bilateral inguinal group, bilateral common iliac groups, para - aortic region above and below the level of left renal vein, para - caval region above and below the level of left renal vein, bilateral internal thoracic groups, both axilla, anterolateral cervical region (IV group), para - aortic (to arch) region.

Overall, the findings suggested mycosis fungoides with CD30 - positive large cell transformation. She was subsequently referred to a hematologist for appropriate management. The patient received a treatment regimen consisting of intravenous dexamethasone (10 mg), cyclophosphamide (1300 mg), vincristine (2 mg), doxorubicin (80 mg), and etoposide (150 mg) for three days, followed by oral prednisolone (100 mg) for five days, and subcutaneous filgrastim (300 mcg) daily for seven days. Initially, the lesions showed improvement. Unfortunately, she developed febrile neutropenia after chemotherapy and septicemia. The hemoculture shows *Pseudomonas aeruginosa* and she passed away 14 days after the initial course of chemotherapy.

Discussion

Mycosis fungoides is the most common form of primary cutaneous lymphoma, typically occurring in middle to late adulthood and showing a male predominance of 2:1. It affects 20 - 50% of advanced mycosis fungoides cases, resulting in a mean 5 - year survival rate of less than 20%.[1] Mycosis fungoides with large - cell transformation is an aggressive subtype. The prevalence from 3 - 34% of MF case and mortality rates vary from 8 - 69%. Histologically, large cell transformation is diagnosed when large cells constitute more than 25% of the dermal infiltrate or form microscopic nodules within the lesion. CD30+ large - cell tumors in mycosis fungoides have a better prognosis compared to CD30– large - cell tumors.[2] Distinguishing CD30+ large cell transformation in mycosis fungoides from cutaneous anaplastic large - cell lymphoma can be challenging.

Primary cutaneous anaplastic large cell lymphoma (C - ALCL) is characterized by a neoplasm composed of large cells exhibiting anaplastic, pleomorphic, or immunoblastic cytomorphology. The majority (>75%) of tumor cells in C - ALCL express the CD30 antigen. It is the second most common form of cutaneous T - cell lymphoma and primarily affects individuals in their sixth decade. Most patients present with solitary or localized nodules or tumors that often develop ulceration. Cutaneous lesions in C - ALCL may undergo partial or complete spontaneous regression. Involvement of regional lymph nodes is possible.

Histologically, anaplastic large - cell lymphoma demonstrates diffuse non - epidermotropic infiltrates with cohesive sheets of large CD30+ tumor cells. These cells display characteristic features such as round, oval, or irregularly shaped nuclei, prominent nucleoli, and abundant cytoplasm.[3,4]

The treatment of mycosis fungoides is determined by major prognostic factors and clinical stages. However, other considerations such as symptom severity, treatment efficacy, response duration, comorbidity, toxicity, accessibility, and cost - effectiveness are also taken into account. Patients with stage I - IIA disease typically receive skin - directed therapy, except when poor prognostic factors like folliculocentric MF, large - cell transformation, or low blood tumor burden involvement are present. For patients with stage IIB disease, a combination of total skin electron beam therapy and systemic therapy is recommended. Caution should be exercised when using skin - directed therapy in patients with stage III or erythrodermic skin. Stage IVA patients require intensive systemic therapy. Chemotherapy regimens are appropriate for patients with multiple lymph nodes or visceral organ involvement, or when other treatments have failed.[8] The standard chemotherapy treatment consists of 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone).[3] In Olsen's response criteria, Chemotherapy has complete response in lymph node 8%, but stable disease in blood and viscera after complete course of chemotherapy.[8] Recent studies have shown high overall response rates in advanced mycosis fungoides with the use of pentostatin, gemcitabine, and liposomal doxorubicin.[8] Asai et al. reported that gemcitabine monotherapy effectively treats large cell transformation of mycosis fungoides. They administered gemcitabine intravenously at a dose of 1000mg/m^2 on days 1 and 8, following a 21 - day schedule. After 8 cycles of chemotherapy, the patient achieved a partial response with mild side effects like nausea, neutropenia, anemia, and thrombocytopenia.[9] However, neutropenia is a side effect that cause serious complication. Laboratory investigations such as complete blood count, electrolyte, renal function test, liver function test should be monitor during and after chemotherapy. O'Donnell et al. found that brentuximab vedotin, a targeted monoclonal antibody, yielded superior treatment outcomes compared to oral bexarotene, skin - directed therapy, and chemotherapy for mycosis fungoides with large cell transformation in both early and advanced stages.[10] Radiation therapy is highly effective, although it may lead to acute side

effects such as erythema, dry desquamation (76%), blisters (52%), hyperpigmentation (50%), skin pain (48%), and skin infection (32%). Other potential side effects include alopecia, temporary loss of fingernails and toenails, hypo- or anhidrosis, chronically dry skin, blisters, radiation dermatitis, male gynecomastia, scattered telangiectasia, and skin cancer.[11] Combining romidepsin with total skin electron beam therapy suppresses CD8 T cell activity in advanced stage mycosis fungoides. The most common side effects of romidepsin are nausea, fatigue, and loss of appetite.[12] Moreover, promising results have been observed in phase 1 and phase 2 trials of novel therapeutic agents such as Lacutamab and PD-1/L-1 inhibitors for the treatment of mycosis fungoides.[13]

The prognosis of cutaneous anaplastic large-cell lymphoma is excellent, while mycosis fungoides with large-cell transformation has a poor prognosis. However, spontaneous regression of mycosis fungoides with large-cell transformation has rarely been reported in cases of patch-stage mycosis fungoides.[5] Rasso et al. reported a rare association between large cell transformed CD30+ mycosis fungoides and colonic adenocarcinoma, suggesting a potential genetic predisposition.[6] Additionally, it has been observed to develop at the site of a previous B-cell tumor, indicating a correlation with genetic alterations or T-cell regulatory alteration.[7]

In this case, the patient had further investigated such as bone marrow biopsy, CT chest and whole abdomen, blood test for tumor marker for evaluate the clinical stage. She was stage IV. She received intravenous chemotherapy due to multiple tumors with multiple lymph node involvement in CT chest and whole abdomen. However, she had got a fever. Her blood test shows leukopenia. She developed a febrile neutropenia after the chemotherapy.

Conclusions

Mycosis fungoides is the most common type of cutaneous T-cell lymphoma, typically occurring in mid to late adulthood and affecting males more often than females. The exact cause of mycosis fungoides remains unclear. However, it has been observed that genetic alterations are linked to colon cancer and prior B-cell lymphoma lesions in patients with mycosis fungoides. When mycosis fungoides undergoes large cell transformation, it tends to follow an aggressive clinical course, and diagnosis relies on both clinical and histological manifestations. Unfortunately, mycosis fungoides is currently incurable and significantly impacts the quality of life of affected individuals. Treatment options abound and are primarily determined by the clinical stage and prognostic factors. Nonetheless, it is crucial to consider the potential complications and side effects associated with these treatments.

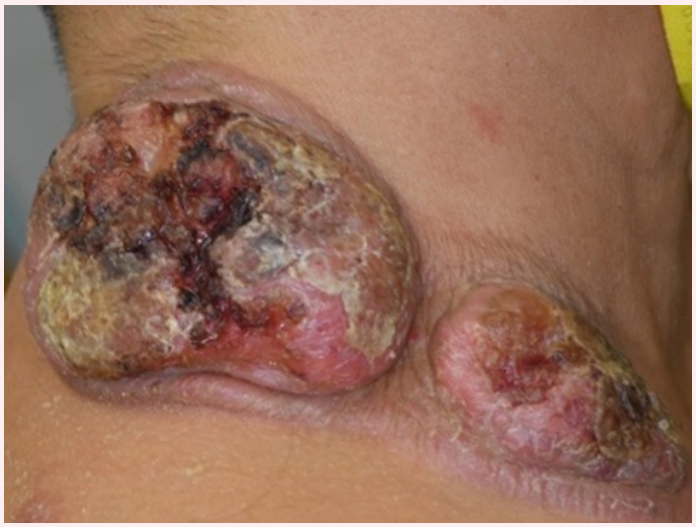

Figure 1 Two well circumscribed ulcerated tumors at the neck

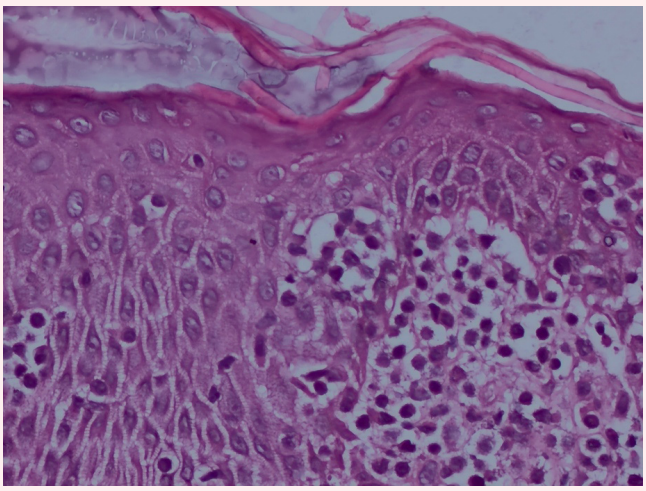

Figure 2 Multiple foci of atypical lymphocytic exocytosis in the epidermis, H&E X400

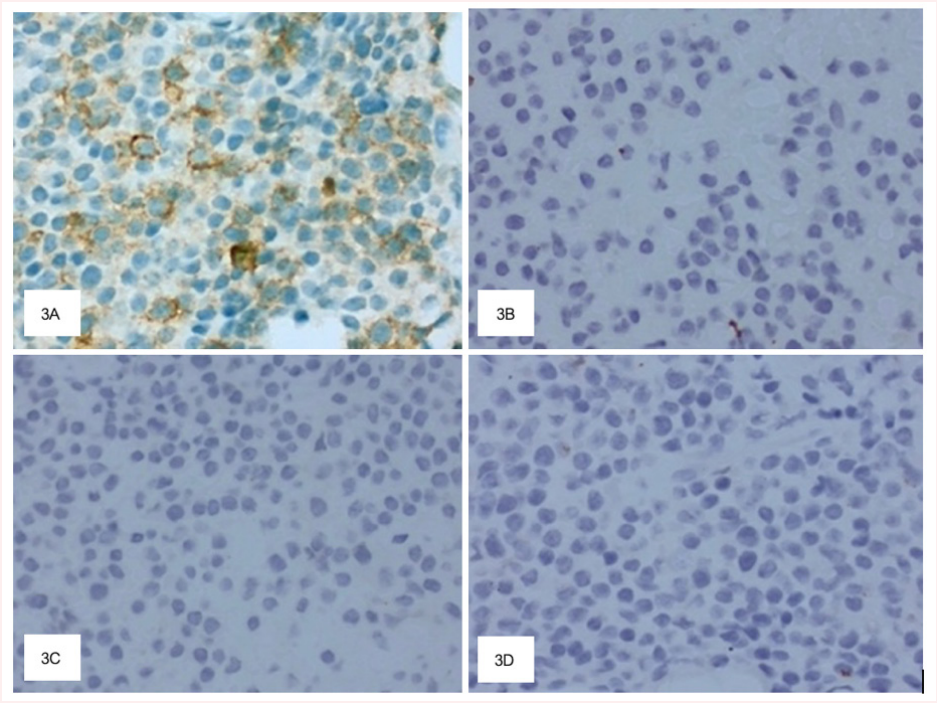

Figure 3A - 3D Immunohistochemical studies show immunopositive to CD30 (3A), and immunonegative to CD8, CD56, and Granzyme B respectively (3B - 3D)

เอกสารอ้างอิง (References)

1. Pulitzer M, Myskowski PL, Horwitz SM, Querfeld C, Connolly B, Li J, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. Pathology 2014;46(7):610 - 6.
2. Kadin ME, Hughey LC, Wood GS. Large - cell transformation of mycosis fungoides - differential diagnosis with implications for clinical management: a consensus statement of the US Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2014;70(2):374 - 6.
3. Willemze R. Cutaneous T - cell lymphoma. In: L BJ, editor. Bolognia Dermatology. 4th ed. Edinburg: Elsevier; 2018. p.2139 - 42.
4. Bagot M, Stadler R. Cutaneous lymphoma. In: Kang S, Amagai M, Bruckner AL, editors. Fitzpatrick's dermatology in general medicine. 9th ed. New York: Mcgraw - Hill; 2012. p. 2084 - 7.
5. Kubo N, Itoh M, Watanabe Y, Nobeyama Y, Asahina A. Regression of CD30 - positive large cell transformation arising on patch lesion of early mycosis fungoides. Clin Case Rep 2020;8(12):2418 - 22.
6. Rasso A, Sara E, Kaoutar A, Hanane B, Zahra MF. Mycosis fungoides with CD30 large cell transformation accompanied by hidden adenocarcinoma of the colon: a case report. PAMJ - Clin Med 2020;2:1 - 8.
7. Herrmann JL, Sami N. Large - cell transformation of mycosis fungoides occurring at the site of previously treated cutaneous B - cell lymphoma. Clin Lymphoma Myeloma Leuk 2014;14(1):e43 - 6.
8. Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sézary syndrome: a stage - based approach. J Natl Compr Canc Netw 2008;6(4):436 - 42.
9. Asai H, Takeuchi K, Ikeda Y, Ochi T, Tanimoto K, Yamanouchi J, et al. Successful treatment of large transformed mycosis fungoides with gemcitabine monotherapy. Ann Oncol 2018;29(Supplr 7):77.
10. O'Donnell M, Zaya R, Correia E, Krishnasamy S, Sahu J, Shi W, et al. Disease characteristics, prognosis, and response to therapy in patients with large - cell transformed mycosis fungoides: A single - center retrospective study. J Am Acad Dermatol 2022;86(6):1285 - 92.
11. Chowdhary M, Chhabra AM, Kharod S, Marwaha G. Total Skin Electron Beam Therapy in the Treatment of Mycosis Fungoides: A Review of Conventional and Low - Dose Regimens. Clin Lymphoma Myeloma Leuk 2016;16(12):662 - 71.
12. Jothishankar B, Almazan T, Kim Y, Liauw S, Smith S, Kline J, et al. Romidepsin and total skin electron beam therapy in advanced stage mycosis fungoides and Sézary syndrome. Br J Haematol. 2019;186(2):377 - 9.
13. Seidl - Philipp M, Nguyen VA. New systemic treatment options in mycosis fungoides and Sézary syndrome. Memo 2020;13:280 - 4.