Case 1

A 61 year-old Thai woman from Bangkok

Chief complaint:

Multiple nodules and ulcerative masses on both arms, forearms and legs for 2 weeks

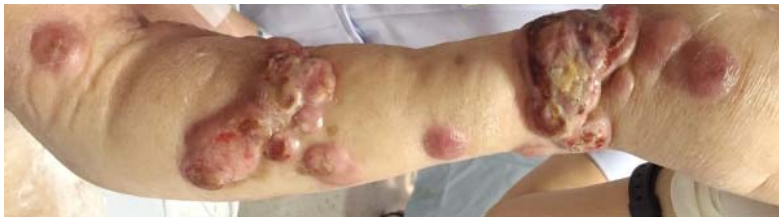

Fig. 1.1

Present illness:

Five years ago, the patient presented with multiple annular plaques on the trunk and extremities. Skin biopsy showed dense cellular infiltrate of atypical lymphocytes with large hyperchromatic and pleomorphic nuclei throughout the dermis compatible with mycosis fungoides. MF stage IB was diagnosed and she was treated with PUVA, methotrexate and acitretin and got partial response.

Four years ago, she noticed a new large plaque on her right tibia. Histopathological result revealed tumor stage MF. As a result, MF stage IIB was diagnosed and superficial radiation was started for patch and thin plaques and electron beam for the tumor on the right tibia. All skin lesions were almost cleared and maintenance treatment with low dose acitretin (10mg/day) and metrotrexate (5mg/day) were initiated.

Three years ago, her skin lesions returned and showed no improvement after a complete course of superficial radiation. Hematologic consultation was done. Bone marrow biopsy and abdominal computed tomography examination revealed no abnormal findings. Therefore, chemotherapy (CHOP regimen) was started and she responded well.

Two months after the last CHOP cycle she developed a new ulcerated mass on her left lateral malleolus. Histopathology demonstrated lymphoma cutis with positive CD30 staining. The differential diagnosis included CD30 large cell transformation of mycosis fungoides and anaplastic large cell lymphoma. The salvage regimen (romidepsin, 6 cycles) was administrated and the lesions disappeared.

One month after last romidepsin cycle she had vacation at a hot spring spa. One week later, multiple plaques, nodules and ulcerative masses erupted on both of her arms, forearms and legs. (Fig. 1.1) She had no fever but complained of fatigue. A biopsy was done and she received another cycle of chemotherapy (Ifosfamide, carboplatin, etoposide) in combination with antibiotics for the secondary infection. One day after chemotherapy, multiple bullae developed on normal appearing skin and erythematous plaques. (Fig. 1.2)

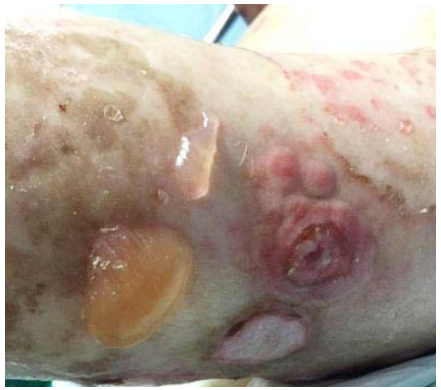

Fig. 1.2

Past history: As above

Physical examination:

VS: BT 36.8^{o}C, RR 20 /min, P 84 /min, BP 110/70 mmHg

GA: Good conscious and co-operative

HEENT: No pale conjunctivae, anicteric sclerae
CVS&RS: WNL
Lymph node: Right posterior cervical lymph node, 1*3 cm. in diameter
Abdomen: No hepatosplenomegaly
Neuro: Right eye ptosis, right eye upward gaze palsy

Skin examination: (Fig. 1.1, 1.2)

- Multiple erythematous plaques, nodules on` both arms, forearms and legs with some ulcerated masses on both arms and forearms
- Multiple tense bullae, ranging 1-7 cm in diameter on plaques and normal appearing skin

Histopathology: (S16-5881, right arm) (Fig.1.3)

- Dense diffuse infiltrate of atypical mononuclear cells in the dermis and subcutaneous tissue
- Necrosis of the overlying epidermis and upper dermis
- Atypical mononuclear cell composed 2 types of cells;
  1.Medium/large-size atypical lymphocytes with dark, hyperconvulated nuclei and scant cytoplasm
  2.Large-size atypical lymphocytes with large round or oval vesicular nuclei and abundant cytoplasm

Immunohistochemistry:

-CD3: focal positive
-CD4/20/56/ALK: negative
-CD8/CD30: positive

Histopathology: (S16-6148, left thigh) (Fig.1.4)

- Marked epidermotropism of atypical lymphocytes into the lower portion of the epidermis
- Subepidermal vesicle
- Sparse inflammatory-cell infiltrate of small lymphocytes, neutrophils and a few melanophages in the papillary dermis

Direct immunofluorescence: Negative

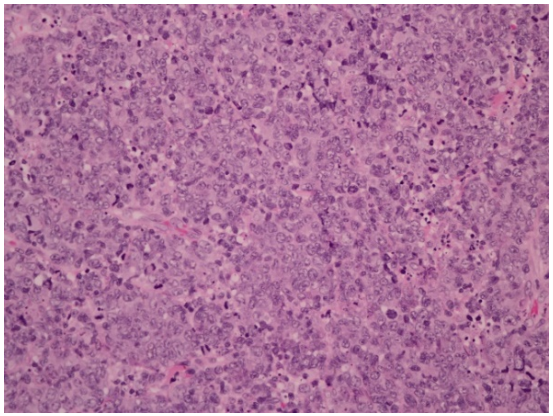

Fig. 1.3

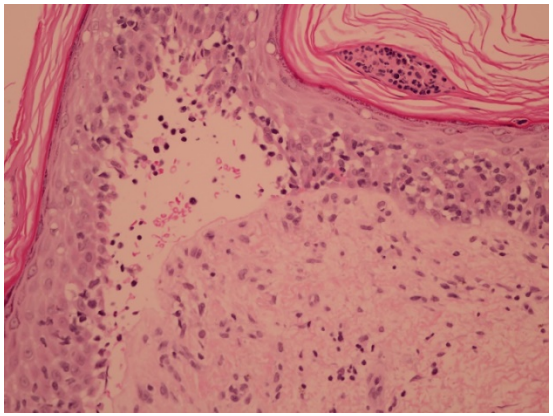

Fig. 1.4

Investigations:

CBC: WBC 5,690/cu.mm (N75%, L8%, Mo15%, Eo1%, Ba1%)
Hb 9.5 g/dL, Hct 28.6%, Plt 155,000/cu.mm

LDH 6400 U/L (125-220 U/L)
LFT: AST/ALT 163/13 U/L, ALP/GGT 60/33 U/L
BUN/Cr: 28/1.33 mg/dL
Aniti-BP180, antiBP-230: Negative
H/C: No growth
MRI brain and orbit: Suggestive of lymphomatous involvement of the right temporalis muscle, right upper eyelid, right inferior rectus, left medial rectus and left inferior rectus muscle with associated intraorbital fat reticulation

Diagnosis:

Large cell transformed mycosis fungoides stage IV B with bullous mycosis fungoides variant

Treatment:

Chemotherapy (Ifosfamide, carboplatin, etoposide)

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Discussion:

Mycosis fungoides (MF) is the most common type of cutaneous T cell lymphoma and accounts for almost 50% of all primary cutaneous lymphoma.[1] MF has an indolent course and typically present with patch, plaque and tumor stages. However, many other subtypes have been reported such as hypopigmented MF, folliculotropic MF, pagetoid reticulosis, granulomatous slack skin and also bullous MF.[1-6]

Bullous mycosis fungoides or mycosis fungoides bullosa is a rare clinical variant of MF. The first case described as pemphigus-like lesion was reported by Kaposi in 1887.[3] The term *mycosis fungoides bullosa* was first reported by Grab and Wise in 1943.[3] To date, only 23 cases have been reported in the literature.[6] Bullous MF commonly presents in the elderly and has no gender preference.[3] The bullae which can be flaccid or tense may occur before, after or concurrent with typical lesions of MF.[3] Bullae can arise in classical MF lesions or may also be found on normal-appearing skin.[3] The distribution is localized or generalized predominantly affecting the trunk and extremities.[3]

Histopathologically, blisters which may be subepidermal or intraepidermal (subcorneal or suprabasal) accompany the typical histological features of MF (epidermotropism, Pautrier's microabscesses, atypical lymphocytes).[3]

Because bullous MF is very rare, it should be diagnosed only after ruling out other coincidental vesiculobullous diseases such as infection, arthropod bite, burn, allergic contact dermatitis and autoimmune bullous disease. Cases of concomitant MF with bullous pemphigoid and pemphigus foliaceus have been reported.[6,7,8] Therefore, immunofluorescence studies have an important role to exclude coexisting autoimmune diseases. Moreover, several therapeutic modalities of MF have been shown to induce vesicles and blisters including topical mechlorethamine[9], interferon alfa therapy[5] and phototherapy.[8]

The diagnosis of bullous MF is sometimes inconclusive. Bowman et al. in 2001 proposed 4 criteria for bullous MF.[3]

1. Clinically apparent vesiculobullous lesions, with or without typical MF lesions (patches, plaques, tumors)
2. Typical histologic features of MF (atypical lymphoid cells, epidermotropism, Pautrier's microabscesses) with intraepidermal or subepidermal blisters
3. Negative immunofluorescence (both direct and indirect, if possible) to rule out concomitant autoimmune bullous diseases
4. Negative evaluation for other possible causes of vesiculobullous lesions (medications, allergy, bacterial or viral infection, porphyria, photo- or photochemotherapy)

The appearance of bullous lesions in MF patients often predicts a poor prognosis. Almost 50% of the patients with bullous MF died within 1 year of the appearance of bullae.[3]

Large cell transformation (LCT) within skin or node biopsies is defined as having large cells (≥ 4 times the size of a small lymphocyte) which are CD30+ or CD30- in 25% or more of the dermal infiltration and usually coincides with the presence of tumors.[10,13] The incidence of LCT ranges from 8% to 55%.[11,12,15] LCT has been documented to occurred in all stages of cutaneous T-cell lymphoma but more common in patients with advanced disease.[12,15] LCT has classically been divided into 3 clinical patterns:[17]

1. A new solitary nodule within a long standing classic MF patch/plaque,
2. The abrupt onset of multiple nodules that persist
3. A new or enlarging tumor

It is often advised to obtain biopsy specimens from patients with MF who develop new papules, plaques, or tumors in order to rule out LCT and prompt consideration of a more aggressive treatment regimen.[17]

The prognosis of LCT is reportedly worse than classic MF.[10,13] Previous studies reported median survival varied between 2 - 100 months with the most frequent median survival of around 2 years.[10-13,16,19] Diamandidou et al. found that early transformation (<2 years from the diagnosis) and advanced stages (≥ stage IIB) were associated with poor prognosis.[20] Benner et al. collected 100 cases of LCT-MF documented that CD30 negativity, folliculotropic MF, extent of skin lesions and extracutaneous transformation were associated with reduced disease-specific survival (DSS).[12] Another study of Talpur et al. reported poor prognosis associated with advanced age, LCT at the time of initial diagnosis of MF and high levels of lactate dehydrogenase and CD 30 expression <10%.[10,18]

Another important point is to distinguish CD30+ LCT of mycosis fungoides (LCT-MF) from cutaneous anaplastic large cell lymphoma (cALCL) which has excellent prognosis (overall survival at 5 years, 20.7% vs 77.4% respectively).[14] The most basic clue to support the diagnosis of LCT-MF is the presence of cellular pleomorphism with cerebriform T lymphocytes mixed with fewer than 75% CD30+ large Tcell.[17] However, in cases of CD30+ large cells ≥ 75% (CD30+ rich LCT), it is difficult to divide both entities. Many features were proposed to distinguish between CD30+rich LCT and cALCL.[14,15] (Table1)

Table1 Summary of useful features differentiating between CD30+ ≥ 75% LCT of MF and cALCL[14,15]

	CD30+ rich LCT of MF	cALCL
Clinical	-History of prior MF -Multiple trunk lesions -Extracutaneous disease -Elevated LDH -Abnormal CBC	-Solitary lesions -lower limb involvement
Histology	-Epidermotropism -Folliculotropism	-An abundance of neutrophils and/or eosinophils
Immuno phenotype	-Normal T-cell phenotype -GATA3+	-Abnormal T-cell phenotype -Perforin

		-Th 17 profile

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