CASE 15

Patient: A 41-year-old Thai female

Chief Compliant: Generalized papulovesicular rash for 1 month

Present Illness: She presented with a 1-week history of the generalized asymptomatic erythematous papulovesicular rash. She was diagnosed with chickenpox and she was treated with antiviral drug for 2 weeks without improvement.

Past History: She had a systemic sclerosis with pulmonary hypertension for 5 years.

Current Medications: Prednisolone 5 mg/day, Cyclophosphamide 50 mg/day, Nifedipine 30 mg/day, Pentoxifylline 800 mg/day, Calcium carbonate 1250 mg/day.

Family History: nil

Physical Examination:
VS: T 37 ^{0}C, RR 20/min, BP 125/85 mmHg, HR 80/min
GA: good consciousness, not pale, no jaundice
CVS: normal S1 S2, no murmur
RS: normal breath sounds
Abdomen: no hepatosplenomegaly
LN: not palpable

Dermatological Examination (Figure 15.1-6)**:** Generalized discrete multistage erythematous papules and vesicles size 0.5 cm on face, trunk and extremities

Investigations:
CBC: Hb 11.7 g/dL, Hct 35%, Platelets 298,000/mm^3
WBC 6400/mm^3 (N 70%, L 19%, M 8%, E 3%, B 0%)
Chemistry: Creatinine: 0.9 mg/dl, LFT: normal

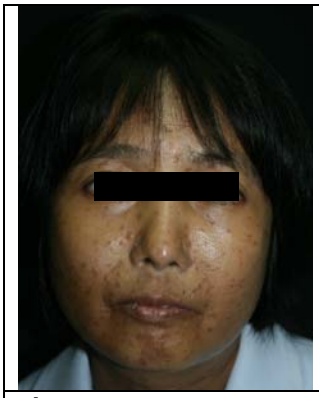

Figure 15.1

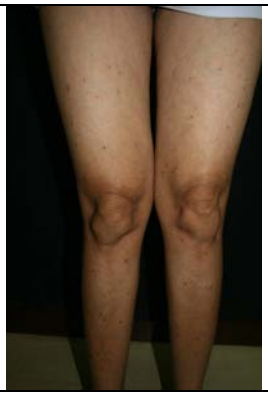

Figure 15.2

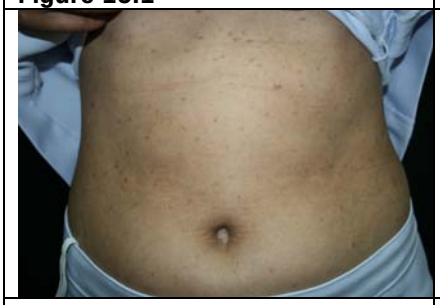

Figure 15.3

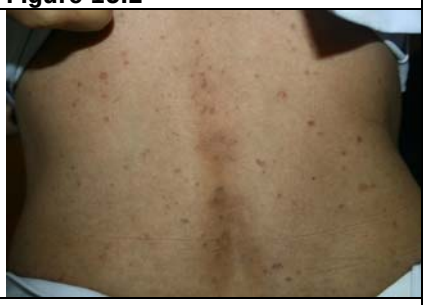

Figure 15.4

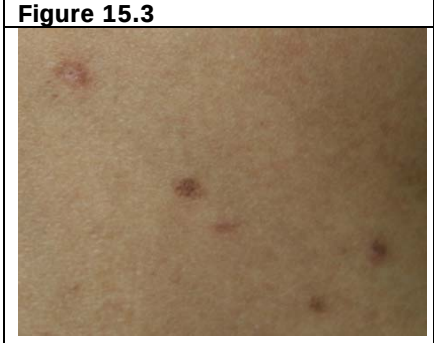

Figure 15.5

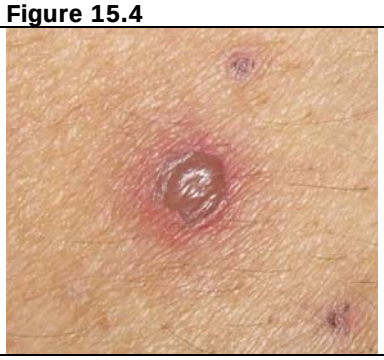

Figure 15.6

Histopathology: (S10-6648) (Figure 15.7-8):

A. mounds of parakeratosis is and occasional necrotic keratinocytes in the epidermis.Superficial and deep infiltrate of lymphocytes and a few atypical lymphoid cells in the dermis

B. scale-crust, necrotic keratinocytes in the epidermis.Dense superficial and deep perivascular and lichenoid infiltrate of lymphocytes admixed with numerous atypical lymphocytes and extravasated erythrocytes in the dermis

Immunohistochemistry (Figure 15.9-10)**:**

- CD3+ : most lymphocytes
- CD30+ : atypical lymphocytes
- CD20,CD56 : negative

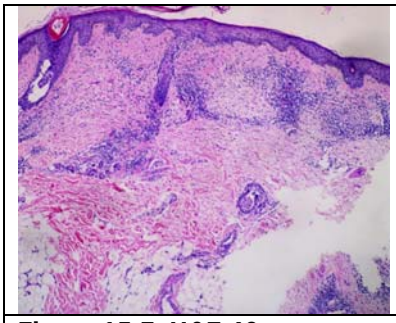

Figure 15.7, H&E 40x

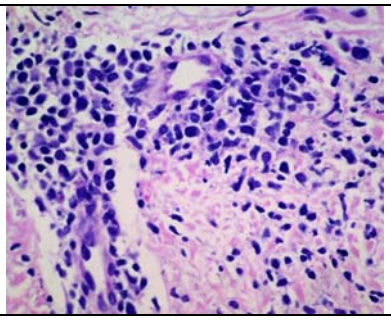

Figure 15.8, H&E 400x

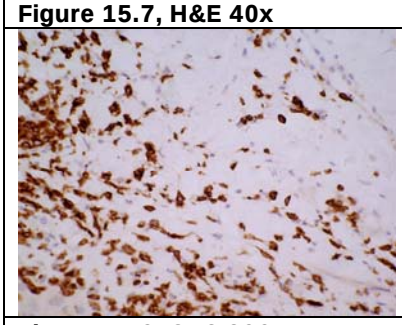

Figure 15.9, CD3 200x

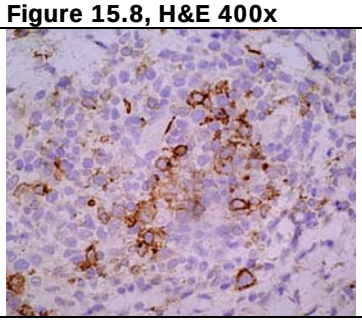

Figure 15.10, CD30 400x

Diagnosis: Lymphomatoid papulosis type A

Treatment: Methotrexate 5 mg per week

Presenter: Silada Kanokrungsee

Consultant: Natta Rajatanavin

Discussion:

Lymphomatoid papulosis (LyP) is a CD 30+ lymphoproliferative condition first described by Dupont in 1956 and later by Macaulay in 1968 [1]which is self-healing papulonodular skin eruption with histologic features of a malignant. This is a rare disease with a worldwide incidence of 1.2 to 1.9 per 1 million.[2] It occurs at all ages, but the peak incidence is in the fifth decade. The male to female ratio is 1.5:1.

LyP presents as recurrent crops of reddish papulonodular lesions (often hemorrhagic, papulovesicular or papulopustular lesion) which regress spontaneously (within few weeks) leaving only a small scar or area of altered pigmentation. The trunk and extremities, other than the palms and soles, are the most frequently affected areas. Classical LyP lesions progress through four clinical stages referring to the natural history and age of the lesions: stage I, early lesions (erythematous dermal papule); stage II, developing lesions (clinical features in between stage I and stage III); stage III, fully developed lesions (hemorrhagic/ ulcero-necrotic or crusted papular or nodular lesion); stage IV, resolving lesions (occasionally leaving a varioliform scar or a small area of altered pigmentation) .[3]

The pathogenesis of this entity is not known, although it seems that CD30+ regulatory T cells are activated by CD30L, which is produced by circulating neutrophils and eosinophils. These T cells secrete tumor growth factor (TGF) β,

which suppresses local immune response, thereby leading to the development of LyP lesions. After a while, the same TGF- β induces apoptosis of CD30+ cells. The resulting recovery of immune response leads to regression of the lesion.[4]Exploration of a possible relationship with retrovirus has yielded no conclusive results.[5]

The histologic picture of LyP is extremely variable. Three histologic subtypes of LyP (types A, B, and C) have been described as Table 1.

Histologically, LyP type C must be differentiated from CD30+ primary cutaneous anaplastic large cell lymphoma. The latter is characterized by non regressing solitary or localized ulcerated tumours or nodules, with favorable prognosis. They are closely related conditions and are classified in primary cutaneous CD 30 positive lymphoproliferatve disorders by WHO/EORTC classification of cutaneous lymphoma as Table 2.[6]

Despite its chronic course, LyP has a favorable prognosis. But patients with LyP have an increase risk for developing lymphoma (10-60%), most commonly mycosis fungoides (MF), Hodgkin's disease, and primary anaplastic large cell lymphoma.[7-9] LyP can present before, with or after the lymphoma. In the patients presenting with LyP alone, 18% later developed lymphoma with a median onset of 17.6 years. Kunishige et al. found that men with LyP were 2.5 times to have lymphoma than were women and other risk factor could not be identified.[8]

In the classical (type A) LyP the atypical CD30+ cells have a CD4+ T-helper phenotype (CD3+,CD4+,CD8−); aberrant phenotypes with loss of one or other of the Tcell antigens may occur. Atypical LyP cells are also positive for various cytotoxic granule-associated proteins (TIA-1, perforin

and granzyme B).Rare cases of LyP with a natural killer phenotype (CD56+) or CD8+ cytotoxic T-cell have been reported.[10-11]

The treatment of patients with LyP is unsatisfactory. Topical or systemic corticosteroids or antibiotics are not effective. Low-dose oral methotrexate (5-20 mg/week) is the most effective therapy for reducing the number of skin lesions however, the disease recurs within 1-2 weeks after discontinuing the medication.[12] Beneficial effects have been reported with PUVA, topical nitrogen mustard or BCNU, topical MTX[13], topical imiquimod cream,[14] intralesional interferon, low-dose cyclophosphamide, chlorambucil, medium-dose UVA-1 therapy, excimer laser therapy, and dapsone help disease suppression.

When larger skin tumors develop in the course of LyP, they can be observed for a period of 4 to 12 weeks for the possibility of spontaneous remission. If spontaneous resolution does not occur, such lesions can be excised or treated with radiotherapy. Because of the potential risk for developing a systemic lymphoma, long-term follow-up is required in all patients with LyP.

Table 1: Histologic subtypes of LyP

Characteristic	Type A (Hodgkin-like)	Type B (MF-like)	Type C (ALCL-like)
Pattern	Superficial and deep perivascular infiltration, wedge shape	Band like infiltration	Diffuse large cell type, sheets of $CD30^+$ anaplastic large cells
Atypical cell	Large (25-40 µm) $CD30^+$ cell polymorphic convoluted nuclei with prominent nucleolus and resemble Reed-Sternberg cells when binucleate	Smaller (8-15 µm) cells with hyperchromatic cerebriform nuclei resembling the atypical lymphocytes in MF	Large pleomorphic and anaplastic cells
Inflammatory cell	Numerous mixed cell	-	Few
Epidermotrophism	Rare	Common	Rare

Table 2: WHO-EORTC classification of cutaneous lymphomas

Cutaneous T-cell and NK-cell lymphomas

- Mycosis fungoides (MF)
- MF variants and subtypes
    - Folliculotropic MF
    - Pagetoid reticulosis
    - Granulomatous slack skin
- Se'zary syndrome
- Adult T-cell leukaemia / lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorders
    - Primary cutaneous anaplastic large cell lymphoma
    - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK / T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
    - Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
    - Cutaneous γ / δ+ T-cell lymphoma (provisional)
    - Primary cutaneous CD4+ small / medium-sized pleomorphic T-cell lymphoma (provisional)

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