CASE 16

Patient: A 14 year old boy from Petchaburee

Chief Complaint: multiple ulcerations on trunk

Present Illness: He presented with non-painful ulcerations on lower neck and right upper trunk for 4 month duration. The lesion was first described as tiny red bumps which were asymptomatic. It initially started on the right shoulder. Later on, the lesion increased in numbers, and began to rupture and evolved into several small ulcers which were enlarging. A month after the eruption, he received local traditional herbal treatment without any improvement. Instead, the lesions worsened and became foul-smelling so he decided to come to our hospital.

Review of Systems: weight loss of 3 kg in 4 months

Past History: unremarkable

Family History: non contributory

Dermatological Examination (Figure 16.1-2)**:** Right neck, chest and trunk: multiple discrete well defined deep ulcers with thick necrotic debris in variable size from 5-12 cm

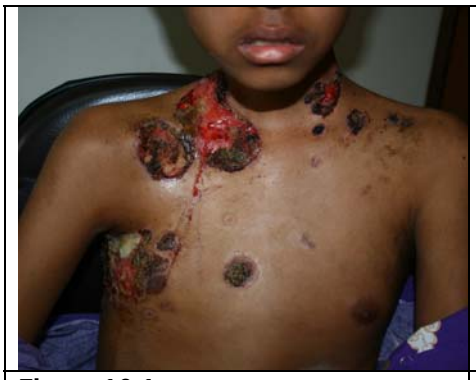

Figure 16.1

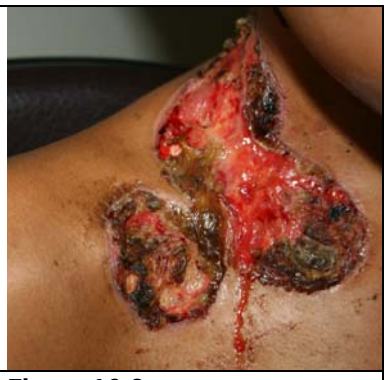

Figure 16.2

Physical Examination: Left anterior cervical 1.5 cm and Left submandibular 2 cm, firm to hard consistency, not tender**,** no hepatospleenomegaly

Investigations: normal CBC, LFT, CXR, chest and abdominal CT scan, negative bone marrow and lumbar puncture study.

Histopathology (S10-7479) (Figure 16.3-4):

- Dense diffuse mixed cell infiltrate of predominantly, neutrophilic, extravasated erythrocytes and numerous large atypical cells in dermis and subcutaneous tissue
- Atypical cells showing large rounded vesicular nuclei, with prominent nucleoli and pale abundant eosinophilic cytoplasm

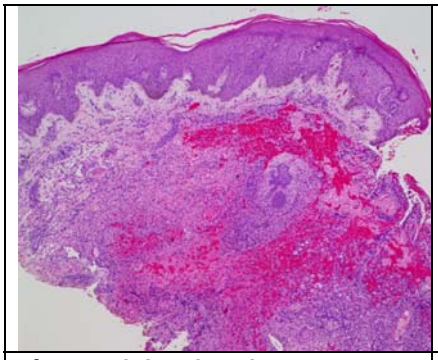

Figure 16.3, H&E 40x

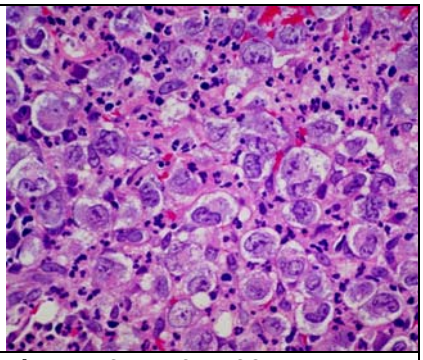

Figure 16.4, H&E 400x

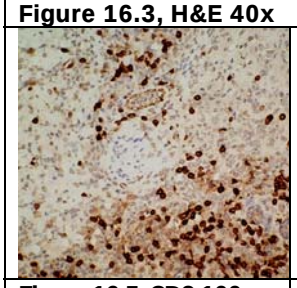

Figure 16.5, CD3 100x

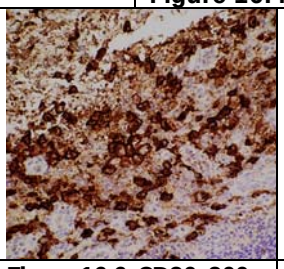

Figure 16.6, CD30, 200x

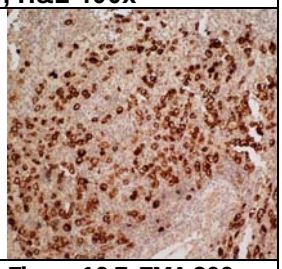

Figure 16.7, EMA 200x

Immunohistochemistry (Figure 16.5-7):

- Inflammatory-cells positive : both CD3 and CD20
- Atypical cells positive : CD30 and EMA

Diagnosis: Primary cutaneous anaplastic large cell lymphoma (C-ALCL) with secondary regional lymphadenopathy

Presenter: Marinya Pongpudpunth

Consultant: Penpun Wattanakrai

Discussion:

Primary cutaneous CD30 lymphoproliferative disorders (LPDs) are the second most common group of CTCLs, accounting for approximately 30% of CTCLs. This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis (LyP), and borderline cases. It is now generally accepted that C-ALCL and LyP form a spectrum of disease, and that histologic criteria alone are often insufficient to differentiate between these 2 ends of this spectrum. Thus, the clinical course is needed to articulate in the process of diagnosis.[1]

According to WHO-EORTC classification for cutaneous lymphomas 2005, primary cutaneous anaplastic large cell lymphoma (CALCL) is defined phenotypically by CD 30 expression of at least 75% of the large lymphoid cells with an anaplastic, pleomorphic, or immunoblastic cytomorphology.[1,2] The clinical evidence or history of LyP, MF, or another type of CTCL must be excluded.

C-ALCL affects mainly adults with a male to female ratio of 2-3:1. It is uncommon in children and adolescents under 20 years of age.[3-5] Most patients present with a solitary firm, large and often ulcerated nodule which is usually asymptomatic. The head and extremities are the site of

predilection.[3,6] Multifocal lesions are seen in about 20% of the patients. Without therapy, spontaneous regression occurs in 10-42% of tumors, as seen in LyP.[3] These lymphomas frequently relapse in the skin. Extracutaneous dissemination occurs in approximately 10% of the patients, mainly involving the regional lymph nodes.

Histologically, there is a diffuse, nonepidermotropic infiltrate with cohesive sheets of large CD30+ tumor cells. In most cases the tumor cells have the characteristic morphology of anaplastic cells, showing round, oval, or irregularly shaped nuclei, prominent eosinophilic nucleoli, and abundant pale cytoplasm. Less commonly (20%-25%), they have a nonanaplastic (pleomorphic or immunoblastic) appearance.[3,7] Clusters of small reactive lymphocytes are often found within and around the tumor. Ulcerating lesions may show a LyP-like histology with an abundant inflammatory infiltrate of reactive T cells, histiocytes, eosinophils and/or neutrophils, and relatively few CD30 cells. In such cases epidermal hyperplasia may be prominent.

Immunophenotypically, the neoplastic cells generally show an activated CD4+T-cell phenotype with variable loss of CD2, CD5, and/or CD3, and frequent expression of at least one cytotoxic proteins (granzyme B, TIA-1, perforin).[8,9] Some cases (less than 5%) have a CD8+ T-cell phenotype. CD30 must be expressed by the majority (more than 75%) of the neoplastic T cells.[10] Unlike systemic CD30+ lymphomas, most C-ALCLs express the cutaneous lymphocyte antigen (CLA), but do not express epithelial membrane antigen (EMA) and anaplastic lymphoma kinase (ALK), indicative of the 2;5 chromosomal translocation or its variants.[6,11,12] Unlike Hodgkin and Reed-Sternberg cells in Hodgkin disease, staining for CD15 is generally negative. Coexpression of CD56 is

observed in rare cases, but does not appear to be associated with an unfavorable prognosis.[13]

Genetically, clonal rearrangement of TCR genes can be found in 90% of the cases.[14] The (2;5)(p23;q35) translocation is rarely found in C-ALCL which is a characteristic feature of systemic ALCL.[12]

The prognosis is usually favorable with a 10-year disease-related survival exceeding 90%.[3,6] Patients presenting with multifocal skin lesions and patients with involvement of only regional lymph nodes have a similar prognosis to patients with only skin lesions.[3] No difference in clinical presentation, clinical behavior, or prognosis is found between cases with an anaplastic morphology and cases with a nonanaplastic (pleomorphic or immunoblastic) morphology.[3,7]

In regard to prognosis and treatment, it is crucial to differentiate primary and secondary cutaneous ALCL in order to avoid aggressive over or under treatment in both groups. In patients presenting with a solitary or few localized nodules or tumors, the first choice of treatment is radiotherapy or surgical excision. Patients presenting with multifocal but only a few lesions, can best be treated with radiotherapy or with low-dose methotrexate, as in LyP.[3,15] Patients developing extracutaneous disease or in rare instance with rapidly progressive skin disease should be treated with doxorubicin based multiagent chemotherapy.

In this case, after the negative extensive work up on systemic involvement, due to the presence of multifocal ulcerations with possibly secondary regional lymphadenopathy, he was diagnosed as stage III disease (over two single cutaneous tumors and extranodal with two or more nodal areas on both sides of the diaphragm). Thus, the systemic chemotherapy was chosen. Before the session began, due to

low grade fever and lymphocytosis, the superimposed infection of the ulcerations was suspected and subsequently treated with systemic antibiotic and local wound care until becoming clear. To date, the patient received four courses of chemotherapy in which he tolerated well. There is a dramatic improvement of the skin lesions that are healing nicely. The remaining superficial erosions are still seen but no new lesions observed. The cervical lymphadenopathy was disappeared after the first session of chemotherapy. He is still undergoing the rest of the treatment process.

References

1. Willemze R, Beljaards RC. Spectrum of primary cutaneous CD30+ lymphoproliferative disorders: a proposal for classification and guidelines for management and treatment. J AmAcad Dermatol1993;28:973-980.
2. Willemze R, Jaffe ES, Burg G, Cerroni L, et al. WHO-EORTC classification for cutaneous lymphomas. Blood2005;105:3768-85.
3. Bekkenk M, Geelen FAMJ, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30- positive lymphoproliferative disorders: long term follow-up data of 219 patients and guidelines for diagnosis and treatment: a report from the Dutch Cutaneous Lymphoma Group. Blood2000;95:3653-61.
4. Kadin M, Sako D, Berliner N, et al. Childhood Ki-1 lympoma presenting with skin lesions and peripheral lymphadenopathy. Blood1986; 68: 1042-49.
5. Hinshaw M, Trowser AB, Kodish E, et al. Three children with CD 30+ cutaneous anaplastic large cell lymphomas bearing the t(2;5)(p23;q35) translocation. Pediatric Dermatol2004;21:212-17.
6. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30_ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J AmAcad Dermatol2003; 49:1049-58.
7. Paulli M, Berti E, Rosso R, et al. CD30/Ki-1 positive lymphoproliferative disorders of the skin: clinicopathologic correlation and and statistical analysis of 86 cases. J Clin Oncol1995;13:1343-54.
8. Kaudewitz P, Stein H, Dallenbach F, et al. Primary and secondary cutaneous Ki-1_ (CD30_) anaplastic large cell lymphomas: morphologic, immunohistologic, and clinical-characteristics. Am J Pathol1989;135:359-67.

9. Kummer JA, Vermeer MH, Dukers DF, Meijer CJLM, Willemze R. Most primary cutaneous CD30-positive lymphoproliferative disorders have a CD4-positive cytotoxic T-cell phenotype. J Invest Dermatol1997;109:636-40.
10. Beljaards RC, Meijer CJLM, Scheffer E, et al. Prognostic significance of CD30 (Ki-1/Ber-H2) expression in primary cutaneous large-cell lymphomas of T-cell origin: a clinicopathologic and immunohistochemical study in 20 patients. Am J Pathol1989;135:1169-78.
11. de Bruin PC, Beljaards RC, van Heerde P, et al. Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T- or null cell phenotype. Histopathol1993;23:127-35.
12. DeCouteau JF, Butmarc JR, Kinney MC, Kadin ME. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30_ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. Blood1996;87:3437-41.
13. Natkunam Y, Warnke RA, Haghighi B, et al. Coexpression of CD56 and CD30 in lymphomas with primary presentation in the skin: clinicopathologic, immunohistochemichal and molecular analyses of seven cases. J Cut Pathol2000;27: 392-99.
14. Macgrogan G, Vergier B, Dubus P, et al. CD30-positive cutaneous large cell lymphomas. A comparative study of clinicopathologic and molecular features of 16 cases. Am J Clin Pathol1996;105:440-44.
15. Vonderheid EC, Sajjadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30- positive lymphoproliferative disorders. J AmAcad Dermatol1996;34:470-80.