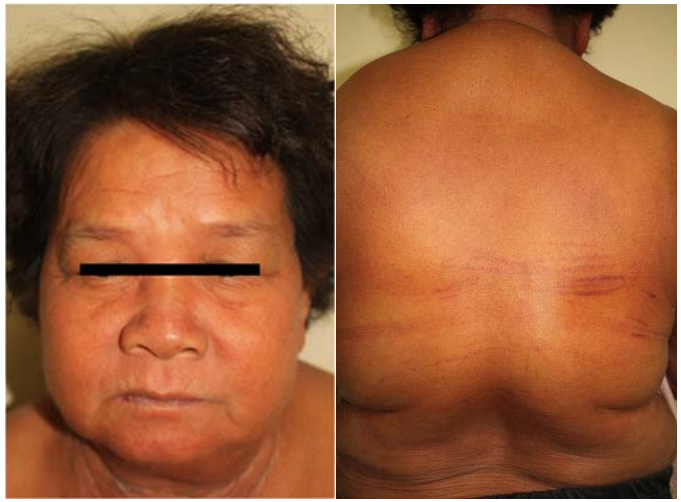
Case 3
A 51-year-old Thai woman from Ayutthaya

Chief complaint: Erythroderma for 1 month



(Fig. 3.1)

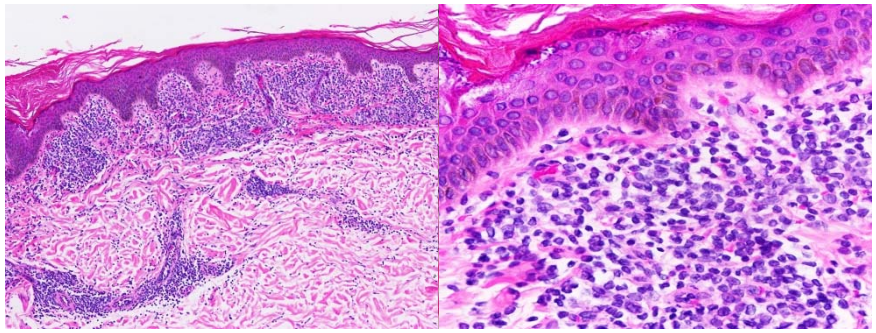
Present illness: A progressive erythroderma with pruritus for 1 month. She denied weight loss or loss of appetite.

Past history: Underlying hypereosinophilic syndrome (presented with hypereosinophilia and eosinophilic pneumonitis) treated with systemic corticosteroids combined with hydroxyurea and subsequently changed to cyclophosphamide.

Physical examination:
HEENT: Mildly pale conjunctivae, anicteric sclerae
Abdomen: No hepatosplenomegaly
Lymph nodes: Not palpable

Dermatological examination: (Fig. 3.1)
Erythroderma

Histopathology: (S17-25003, Right leg) (Fig.3.2)



(Fig. 3.2)

- Dense band-like cellular infiltrate of atypical lymphocytes in the upper to mid dermis
- Mild epidermal hyperplasia with hyperkeratosis
- Atypical lymphocytes are mainly infiltrate within the thick papillary dermis with a few epidermotrophism
- IHC: Positive CD3, CD5, and Beta-F1 staining
  Negative CD2, CD4, CD7, CD8, CD20, CD30, CD56 staining

Laboratory investigations:
- CBC: Hb 9.9 g/dL Hct 31.6%, WBC 161,700 cells/µL (N 8%, L 21%, Mono 16%, Eo 16%, Atypical L 6%, immature L 33%), Platelets 103,000 cells/µL

- LDH: 1,878 U/L
- BMBX: Presence of atypical mononuclear cells
- BM flow cytometry: Increased atypical T-cells CD3+CD7+CD4-CD8- expression of TCR αβ
- The presence of monoclonal TCRG gene rearrangement

CT chest & whole abdomen:

- Diffuse ground glass opacities both lungs are resolved
- Few mediastinal and right interlobar lymphadenopathy
- New development of lymphadenopathy along gastrohepatic ligament of both axillary regions
- Stable hepatosplenomegaly

Diagnosis: Lymphocytic variant HES transforming into erythrodermic CTCL, not other specified

Treatment: CHOEP-regimen (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)

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Discussion:

Hypereosinophilic syndrome (HES) was defined by Chusid et al (1975) who stated three diagnostic criteria; 1) Persistent blood hypereosinophilia > 1.5x 10^9/L for more than 6 months, 2) No other evident causes for eosinophilia such as allergy, parasite, drug and autoimmune diseases, and 3) signs or symptoms of organ involvement by eosinophilic infiltration.[1] There is multisystem involvement in HES including cardiovascular, cutaneous, neurologic, pulmonary and gastrointestinal.[2]

Following the diagnostic algorithm for HE incorporating 2016 WHO categories,[3] an initial investigation to exclude reactive (secondary) causes are suggested. If this investigation is negative, testing for a primary (clonal) eosinophilia should be evaluated. Evaluation includes morphologic analysis of the peripheral blood and bone marrow (BM), immunohistochemistry, flow cytometry and cytogenetic/molecular/genetic testing to identify myeloid or lymphoid neoplasm eg. chronic eosinophilic leukemia associated with the fusion gene FIP1L1-PDGFRA. Moreover, if these evaluations are negative, lymphocoid-variant HES (L-HES) and idiopathic HES should be considered. L-HES is abnormal T-cell clones in the blood, most often expressing an immature CD3+CD4−CD8- or CD3−CD4+CD8− leading to increased Th-2 production of eosinophilopoietic cytokines including IL-4 and IL-5 which cause hypereosinophilia. In this patient, she presented with hypereosinophilic syndrome with progressive erythroderma, the histopathologic study shows dense band-like cellular infiltrate of atypical lymphocytes in the upper to mid dermis. Atypical lymphocytes are mainly infiltrating within the thick papillary dermis with a few epidermotrophism. The result favors erythrodermic CTLC without preexisting MF. She also had abnormal T-cells in blood and bone marrow with CD3+CD7+CD4-CD8- which compatible with lymphoid-variant hypereosinophilic syndrome (L-HES).

L-HES usually present with cutaneous features such as pruritic papules and nodules, eczema, erythroderma, urticaria and angioedema.[4] Furthermore, 14 – 25% of patients with L-HES progress into overt T-cell Lymphoma especially CTCL.[5]

Mycosis fungoides (MF) and Sèzary syndrome (SS) can be categorized in cutaneous T-cell lymphomas (CTCL) which comprise approximately 53% of cutaneous lymphomas.[6] Classic MF is normally indolent neoplasm presenting with patches and plaques on non-sun exposed areas that may slowly evolve to tumors or erythroderma

called erythrodermic MF.

Sèzary syndrome is an aggressive, leukemic CTCL variant, diagnosed by criteria of circulating neoplastic T cells (absolute Sézary cell count of at least 1,000 cells/m3 or CD4:CD8 ratio≥10) and erythroderma, with/without lymphadenopathy. Erythrodermic MF is differentiated from Sézary syndrome by absent of Sèzary syndrome SS criteria and is regarded as a preexisting MF, whereas Sézary syndrome typically rarely preexisting MF.[7] However, sometimes patients present with erythroderma without preexisting MF and absent of Sézary syndrome criteria. Erythrodermic CTCL, not other specified (NOS) is applied for this condition.[8]

The histopathology of classic MF shows a band-like infiltrate of small to intermediate-sized atypical lymphocytes with cerebriform nuclei with epidermotropism and pautrier microabcesses with 38%. On the other hand, erythrodermic CTCL tend to have variable with less prominent features, such as epidermotrophism and pautrier microabcesses.[9]

Immunophenotyping of Sézary syndrome is the same as erythrodermic MF. Typically, atypical T-cells express CD3+, CD4+, CD 45RO+memory T-cell, CD8-phenotype. Loss of T cell surface antigens such as CD2, CD5, and CD7 is common and may associated with disease progression. Loss of CD7 is sensitive and specific findings in MF.[10,11] However, there was a study reported aberrant CD4/CD8 double-negative immunophenotype in patients with early MF. 18 of 140 patients with early MF (12%) showed CD3+, CD4-, CD8- in their intraepidermal T cell.[12]

Our patient, she was diagnosed with Lymphocytic variant HES transforming into erythrodermic CTCL, not other specified and immunohistochemistry study shows CD3+CD4-CD8-CD7- which is CD4/CD8 double-negative immunophenotype.

Patients with advanced and erythrodermic MF/SS can have profound immunosuppression, with treatments targeting tumor cells aimed for immune reconstitution. Alemtuzumab or chemotherapy generally reserves for refractory or rapidly progressive disease or extensive lymph node and metastatic involvement.[13] Our patient had bone marrow involvement so she was treated with chemotherapy: CHOEP-regimen (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone).

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