A Rare Case of Sézary Syndrome: Leukemic Variants of Cutaneous T-cell Lymphoma

Penkhae Sirirack MD, Ploysyne Rattanakaemakorn MD, Teerapong Rattananukrom MD.

Division of Dermatology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

ABSTRACT:

Sézary syndrome (SS) is a rare form of leukemic variants of cutaneous T-cell lymphoma. Diffuse erythroderma, generalized lymphadenopathy, and evidence of cutaneous involvement and leukemic component are the classic triad of SS. We report a 66-year-old Thai woman initially presented with erythroderma without preceding clinical of patches and plaques for 2 years. After the initial skin biopsy, she was misdiagnosed as generalized eczema. Eight months later, despite treatment, the lesion worsened and still has presented erythroderma with bilateral inguinal lymphadenopathy. A second skin biopsy showed atypical lymphocytes with epidermotropism and Pautrier microabscess formation. Blood flow cytometry demonstrated Sézary cells and the presence of monoclonal T-cell receptor gene rearrangement in the blood was relevant to clone in the skin. She was diagnosed with SS and treated with acitretin, methotrexate, and PUVA. After 6 months of treatment, the lesion partially responded. Unfortunately, the patient passed away due to Covid-19 pneumonia.

Key words: Cutaneous T-cell lymphoma, Erythroderma, Sézary syndrome

Introduction

Sézary syndrome (SS) is a rare form of leukemic variants of cutaneous T-cell lymphoma (CTCL). According to WHO-EORTC classification of primary cutaneous lymphomas 2018, the relative frequency of SS is around 2%. Diffuse erythroderma, generalized lymphadenopathy, and evidence of cutaneous involvement and leukemic component are the classic triad of SS. By way of contrast, mycosis fungoides (MF) is the most common CTCL and accounts for approximately 53% of all CTCL[1]. It typically presents as slow progressive erythematous patches and plaques on predominantly non-sun-exposed sites, and it sometimes turns to erythroderma and tumor stages. The histopathologic features of SS are similar to those of MF, which is atypical lymphocytes with epidermotropism and the formation of Pautrier microabscess. However, SS presents classic triad with high blood tumor burden plus a clonal rearrangement of T-cell receptor (TCR) in the blood that clones should be relevant to clone in the skin. SS is grouped with advanced-staged MF and has a poor prognosis. SS must be distinguished from classic MF because its prognosis and treatment recommendations are different[1,2]. Herein, we report a rare case of SS presenting with generalized erythroderma with bilateral inguinal lymphadenopathy, the evidence of high blood tumor burden and presence of a similar clonal rearrangement of TCR between the blood and skin.

Corresponding author: Teerapong Rattananukrom MD., email: teerpongrattananukrom@gmail.com

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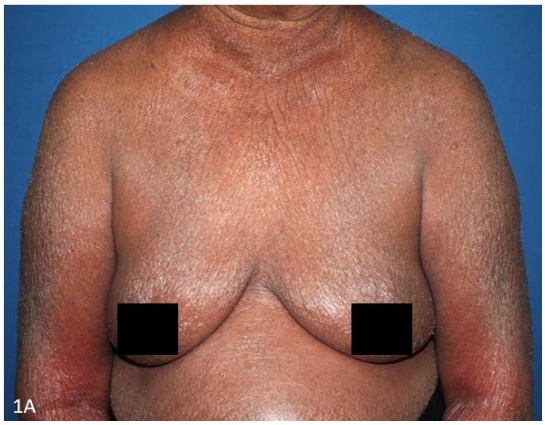

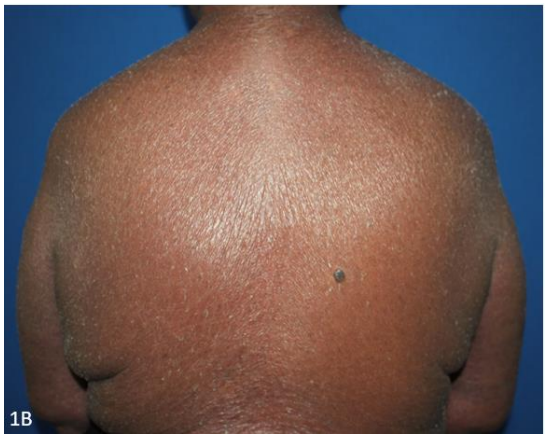

Figure 1 A, B Generalized erythematous scaly patches and thin plaques on trunk, upper and lower extremities

Case report

A 66-year-old Thai woman presented with generalized itchy erythroderma for two years. She denied neither fever nor significant weight loss. Her underlying diseases included diabetes mellitus and hypertension. The initial skin biopsy was performed at the primary hospital, and the histopathologic findings were consistent with spongiotic dermatitis. Generalized eczema was diagnosed, and the patient was treated briefly with oral prednisolone, topical corticosteroid, and antihistamine. Despite eight months of treatment, the lesion worsened with ongoing erythroderma. She was referred to Ramathibodi hospital for further management. Physical examination revealed generalized erythematous scaly patches and thin plaques on the face, trunk, upper and lower extremities, which accounted for more than 90% of BSA (Figure 1). There were bilateral inguinal lymphadenopathies which were rubbery, movable, and not tender with the size of 0.7 cm. There was no nail abnormality or palmoplantar keratoderma. Other examinations were unremarkable. The provisional diagnosis was exfoliative dermatitis. After the medication review, the patient did not receive drugs that could induce exfoliative dermatitis. A second skin biopsy was performed on her upper back. Histopathologic examination revealed dense infiltrate of lichenoid cells in the dermis. The infiltrate consisted of atypical lymphocytes with epidermotropism and the formation of Pautrier microabscesses. Immunohistochemistry of the skin were positive for CD4, CD8, CD4:CD8 ratio (3:1), CD2, CD3, CD5, and negative for CD7, CD20, CD30. Flow cytometry demonstrated 1530 Sézary cells/mm^3. Peripheral blood flow cytometry showed a CD4/CD8 ratio of 20, and 94% of CD4+ T-cells were positive for CD2, CD3, CD5, and negative for CD7.T-cell receptor gene analysis revealed monoclonal proliferation with the identical clone of atypical lymphocytes between the skin lesion and blood. Laboratory examination showed elevated lactate dehydrogenase level of 350 U/L (normal range 150-250 U/L). Computed tomography of the chest and whole abdomen showed no significant change of few mild enlarged bilateral inguinal lymph nodes. She was diagnosed with Sézary syndrome stage IVA1 (T4NXM0B2). She was treated with a combination of acitretin, methotrexate, and PUVA. After 6 months of treatment, the lesion partially response. Unfortunately, the patient passed away due to Covid-19 pneumonia.

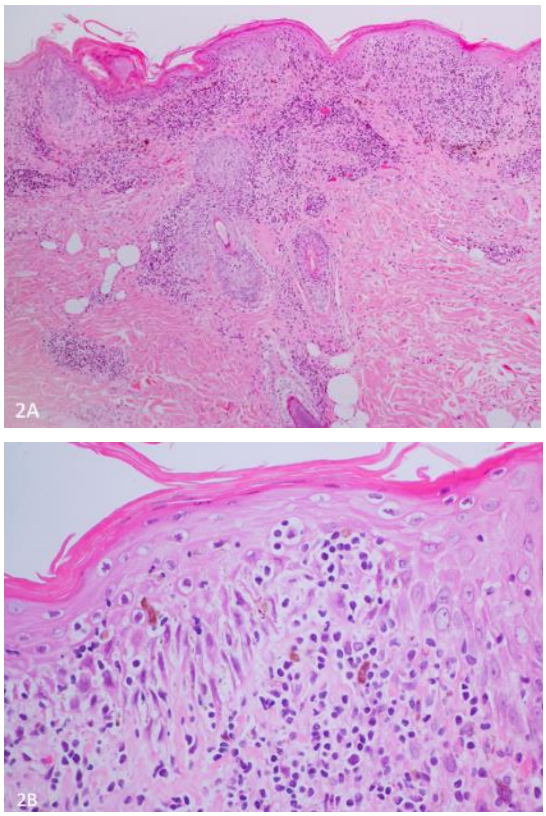

Figure 2 Histopathologic findings.
A Dense infiltrate of lichenoid cells in the dermis. HE. X100.
B The infiltrate consisted of atypical lymphocytes with epidermotropism and the formation of Pautrier microabscesses. HE. X400

Discussion

Sézary syndrome (SS) is a disease of older adults which is approximately twice as common in men as in women and higher in whites than in African Americans. The majority of patients with SS present with classic symptoms of erythroderma, lymphadenopathy, and intense pruritus and typically present de novo in a short period without clinical signs of preceding patches and plaques as in MF. However, there have been numerous reports of patients with SS who have non-classic signs. The common non-classic signs of SS were palmoplantar keratoderma, onychodystrophy, alopecia, leonine facies, and ectropion[1,8].

According to NCCN guideline 2023, the diagnosis of SS required clinical erythroderma (≥ 80% of body surface area affected) with or without lymphadenopathy and criteria for high blood tumor burden or B2 blood involvement by flow cytometry. B2 blood involvement is defined as Sézary cells (atypical T cells with cerebriform nuclei) ≥ 1000 cells/mm3 determined by cytopathology or ≥1000 CD4+/CD26- cells/mm^3 or ≥1000 CD4+/CD7- cells/mm^3 or other abnormal subsets of T lymphocytes by flow cytometry with clone in blood same as that in the skin. Other criteria include CD4+/CD7- cells ≥40% and CD4+/CD26- cells ≥30% plus a clonal rearrangement of TCR in the blood that should match the same clone in the skin[1,3,4].

The histopathologic pattern of SS is similar to those of MF which shows a band-like infiltrate of lymphocytes in the superficial dermis and epidermotropism of atypical lymphocytes in the intraepidermal vesicles (Pautrier microabscesses)[5,6]. The evidence of leukemic involvement in the bloodstream helps differentiating the two diseases. However, epidemortropic infiltrate may not be observed. Only 23 of 41 SS patients (60%) had epidermotropism in a previous case series. Other microscopic findings included spongiosis, parakeratosis, and acanthosis[7]. Moreover, SS usually presents with erythroderma or exfoliative dermatitis which can mimic other inflammatory disorders such as severe atopic dermatitis, erythrodermic psoriasis, pityriasis rubra pilaris, drug-induced exfoliative dermatitis or drug reaction with eosinophilia and systemic symptoms (DRESS). Therefore, repeat skin biopsies and long-term follow-up should be considered in nondiagnostic cases.

In our case, the patient presented with erythroderma without preceding clinical of patches and plaques. The differential diagnosis

of erythroderma in the elderly case included SS, erythrodermic psoriasis, pityriasis rubra pilaris, and drug-induced exfoliative dermatitis. Erythrodermic psoriasis is characterized by pre-existing psoriatic plaques, nail involvement, inflammatory arthritis, and personal or family history of psoriasis. Pityriasis rubra pilaris is characterized by erythroderma with islands of normal skin rather than diffuse erythroderma. From the patient's medication history, she did not receive drugs that could induce exfoliative dermatitis or DRESS. Because of the same clinical variation of erythroderma, repeated skin biopsy is useful for definite diagnosis.

The International Society for Cutaneous Lymphoma and the EORTC has recently proposed a recommendation for staging mycosis fungoides/Sézary syndrome that includes primary tumor (T), lymph node involvement (N), visceral organ involvement (M), and atypical lymphocytes/Sézary cells in peripheral blood (B). The classification distinguishes four clinical stages of the disease. Each of these stages is associated with an estimated 5-year survival rate. Sézary syndrome with proven high tumor burden in peripheral blood or B2 blood involvement is at least at stage IVA. The prognosis of Sézary syndrome is poor, with 24% 5-year survival. Apart from the clinical stage, risk factors for disease progression and poor survival include advanced age, male, high LDH levels, and large cell transformation. Most patients die from an opportunistic infection, and spontaneous resolution of Sézary syndrome has rarely been described[6,8].

The goal of SS treatment is to control disease symptoms, improve the patient's quality of life and limit disease progression. The NCCN guidelines 2023 are structures with SS therapy regimens categorized into two group: low to intermediate burden and high burden group. Preferred regimens for low to intermediate burden group (absolute Sézary cells count $\leq$5000 cells/mm^3), the combination of systemic treatments and skin-directed therapy are mandatory. Systemic treatments consist of bexarotene, extracorporeal photopheresis, retinoids, interferon-alpha, and methotrexate. Skin directed therapy is phototherapy mainly PUVA, topical corticosteroids, and total skin electron beam therapy[9,10].

We report an elderly patient who has suffered from generalized erythroderma with bilateral inguinal lymphadenopathy for 2 years. She was misdiagnosed and the lesion progressed to erythroderma within eight months. A second skin biopsy showed atypical lymphocytes with epidermotropism and Pautrier microabscess formation. Blood flow cytometry demonstrated Sézary cells and the presence of monoclonal TCR gene rearrangement in the blood was relevant to clone in the skin. Significant peripheral lymphadenopathy in SS was larger than 1.5 cm with firm, irregular, clustered, or fixed characters. For TNMB staging, excisional lymph node biopsy is indicated for histopathologic features of atypical lymphocytes or Sézary cells. In our case, inguinal lymphadenopathy was relatively not significant by size and morphology. Lymph node biopsy was not performed which categorized NX for nodal staging. Laboratory examination showed elevated lactate dehydrogenase. The patient has been diagnosed with stage IVA Sézary syndrome. She was treated with acitretin, methotrexate, and PUVA. After 6 months of treatment, the lesion partially responded. Unfortunately, the patient passed away due to Covid-19 pneumonia.

In conclusion, SS should be one of the differential diagnoses of erythroderma in elderly patients with intense pruritus and lymphadenopathy. Repeat biopsies in suspected case of SS should be considered and the evidence of cutaneous involvement and leukemic component characterized by cytopathology and flow cytometry should be confirmed. Moreover, a clonal rearrangement

of TCR in the blood that clones should be relevant to clone in the skin. Because of the poor prognosis of SS, early diagnosis and appropriate treatment can improve a patient's quality of life and limit disease progression.

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