

Case report

Adult T-cell leukemia/lymphoma mimicking acute myeloid leukemia: the first case report from country with low prevalence of human t-lymphotropic virus type 1

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Abstract:

Adult T-cell leukemia/lymphoma (ATLL) is a mature T-cell neoplasm associated with the human T-cell leukemia virus type 1 (HTLV-1). HTLV-1 is not endemic in the Thai population, hence the rare occurrence of ATLL. We report here the first case report of ATLL in Thailand. A case of a 76-year-old woman presented with prolonged fever for 1 month and admitted to the hospital due to acute high-grade fever, headache and generalized erythematous rashes over her body. Her complete blood count revealed leukocytosis and atypical cells with bi-to-tri lobed nuclei were frequently found on blood smear. Initially, the patient was diagnosed with acute promyelocytic leukemia based-on morphological findings and received all-trans retinoic acid. Flow cytometric analysis with acute leukemia panel showed no significant blast population. Cytogenetic analysis revealed normal female karyotype without translocation between chromosome 15 and 17. Histopathological findings with immunohistochemical results were consistent with T-cell lymphoma. Additional flow cytometry with lymphoma panel revealed the presence of a significant lymphoid subset with CD4 and CD25 expression. Confirmative serology for HTLV-1 was positive and the diagnosis of adult T-cell lymphoma/leukemia was made. Her blood cultures were positive for *Cryptococcus neoformans*. She was initially treated with antifungal therapy. Due to her age and overall condition, palliative chemotherapy with vincristine and dexamethasone was given, which was complicated by fatal septic shock and organ failure. Our case depicted the first ATLL case in Thailand which have not been reported before.

Keywords : ● Adult T-cell leukemia/lymphoma ● Human T-lymphotropic virus type 1 ● Thailand

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รายงานผู้ป่วย

โรคมะเร็งต่อมน้ำเหลืองชนิดเอทีแอลแอลที่มาด้วยอาการคล้ายโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดมัยอีลอยด์: รายงานผู้ป่วยรายแรกจากประเทศที่มีการระบาดของเชื้อไวรัสเอชทีแอลวี1 ในระดับต่ำ

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บทคัดย่อ

Adult T-cell leukemia/lymphoma (ATLL) เป็นมะเร็งต่อมน้ำเหลืองชนิด T-cell ที่สัมพันธ์กับการติดเชื้อ human T-cell leukemia virus type 1 (HTLV-1) ในประเทศไทยพบการติดเชื้อ HTLV-1 น้อย และยังไม่เคยมีรายงานการพบผู้ป่วย ATLL ด้วยเหตุนี้ทางคณะผู้รายงานจึงได้รายงานผู้ป่วยรายแรกของประเทศไทยหญิงไทยอายุ 76 ปีมาด้วยอาการไข้มา 1 เดือน และนอนโรงพยาบาลด้วยไข้สูง 1 สัปดาห์ ร่วมกับ อาการปวดศีรษะ และผื่นแดงตามร่างกาย ผลตรวจเลือดพบเม็ดเลือดขาวสูง เม็ดเลือดขาวผิดปกติมีลักษณะ bi-to-tri lobed nuclei แร่รับผู้ป่วยได้รับการวินิจฉัยเป็นมะเร็งเม็ดเลือดขาวชนิด acute promyelocytic leukemia ได้รับการรักษาโดย all-trans retinoic acid ผล flow cytometry ไม่แสดงมะเร็งเม็ดเลือดขาว ร่วมกับ ผลโครโมโซมปกติ ผลชิ้นเนื้อไขกระดูกเข้าได้กับ T-cell lymphoma ร่วมกับผล flow cytometry ของ lymphoma panel แสดงเม็ดเลือดขาวลิมโฟยด์ผิดปกติที่มีการแสดงออกของ CD4 และ CD25 ผลตรวจเลือดพบแอนติบอดีต่อไวรัส HTLV-1 ผู้ป่วยจึงได้รับการวินิจฉัยเป็น ATLL นอกจากนั้นผู้ป่วยพบการติดเชื้อรา *Cryptococcus neoformans* ผู้ป่วยได้รับการรักษาโดยยาต้านเชื้อราพร้อมกับยาเคมีบำบัดแบบประคับประคอง หลังจากนั้นผู้ป่วยมีภาวะติดเชื้อในกระแสเลือดรุนแรง และเสียชีวิตในเวลาถัดมา

คำสำคัญ : ● Adult T-cell leukemia/lymphoma ● Human T-lymphotropic virus type 1 ● Thailand

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:301-8.

Introduction

Adult T cell leukemia/lymphoma (ATLL) is a mature T-cell neoplasm, which is pathogenetically associated with the human T-lymphotropic virus type 1 (HTLV-1 or human T-cell leukemia virus). The reported endemic areas of HTLV-1 infection are the Caribbean islands, South and Central America, Africa and southern Japan^{1,2}. In Thailand, HTLV-1 is not a major public health concerns and reports on HTLV-1 associated disease in Thai population are scarce³. Most of the patients with HTLV-1 associated ATLL in case reports presented with advanced stage disease, which could be either in the form of leukemia or lymphoma⁴. Clinical presentations and cytologic features of ATLL are extremely diverse and result in diagnostic difficulties. A cytologic feature that is highly specific for ATLL is marked nuclear pleomorphism resembling flower shape in the so-called “flower cells”⁴⁻⁶. We reported herein the first case of ATLL in Thailand, a non-endemic area for HTLV-1 infection, which imitated buttock cells and resulted in a misdiagnosis of acute promyelocytic leukemia. Correlation of clinical feature, morphologic findings, cytogenetic and histopathologic studies is important in the diagnosis of this rare entity.

Case report

A 76-year-old Thai female presented with low-graded fever, night sweat and weight loss for 1 month. She reported no organ specific symptoms, apart from intermittent non-productive cough. She denied history of traveling to other countries or history of risks for tropical infection, such as leptospirosis or rickettsial infection. Her symptoms slowly progressed over time. She presented to our hospital with history of new-onset high-graded fever and severe throbbing headache for 7 days. The headache was not aggravated by straining or coughing. She also developed erythematous pruritic rashes over her body, including thighs, trunk and both arms for 1 day.

Her comorbidities included ischemic heart disease, mild aortic stenosis, well-controlled type 2 diabetes mellitus, essential hypertension, dyslipidemia and Par-

kinson's disease. Her medications included: aspirin, metformin, glipizide, amlodipine, enalapril, metoprolol and levodopa/carbidopa.

Physical examination revealed high-graded fever of 38.6 degree Celsius and mild tachycardia, mildly pale conjunctivae, erythematous plaques at both cheeks, multiple erythematous to dusky red non-blanchable maculopapular rashes on both thighs (Figure 1). Other systemic examination revealed no lymphadenopathy, no hepatosplenomegaly and normal neurological examination without sign of meningeal irritation.

Initial complete blood count (CBC) revealed: hemoglobin (Hb) of 8.2 g/dL, hematocrit 24.8%, mean corpuscular volume 80.8 fL, red cell distribution width 20.5%, white blood cell (WBC) count $37.3 \times 10^9/L$, neutrophil 21%, lymphocyte 37%, monocyte 8%, blast 15%, promyelocyte 7%, myelocyte 4% atypical lymphocyte 8%, and platelet $318 \times 10^9/L$. Peripheral blood smear showed leukocytosis with numerous atypical cells with pleomorphic nuclei. Atypical medium-sized cell with bilobed nuclei and distinct nucleolus were also frequently found in the blood smear (Figure 2). Her electrolytes, kidney function and liver function test were normal. Serum lactate dehydrogenase (LDH) was high at the level of 650 U/L (normal value < 248 U/L). Her hepatitis

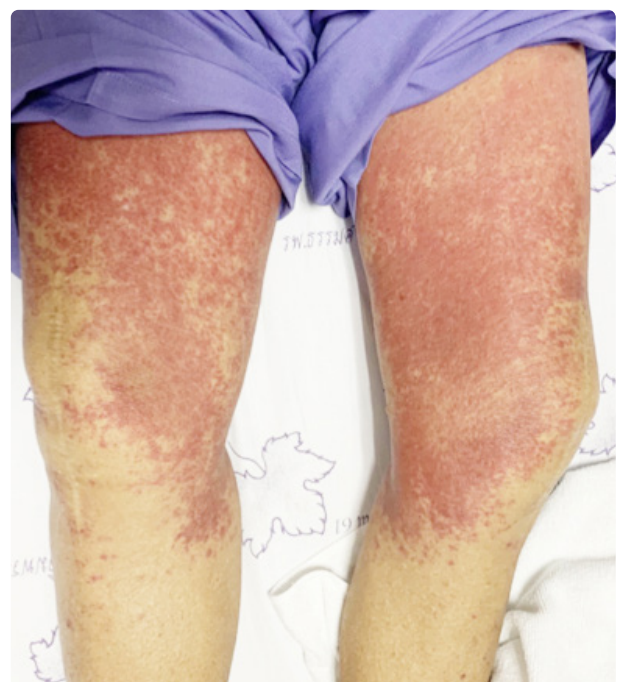


Figure 1 The patient's skin lesion on both thighs

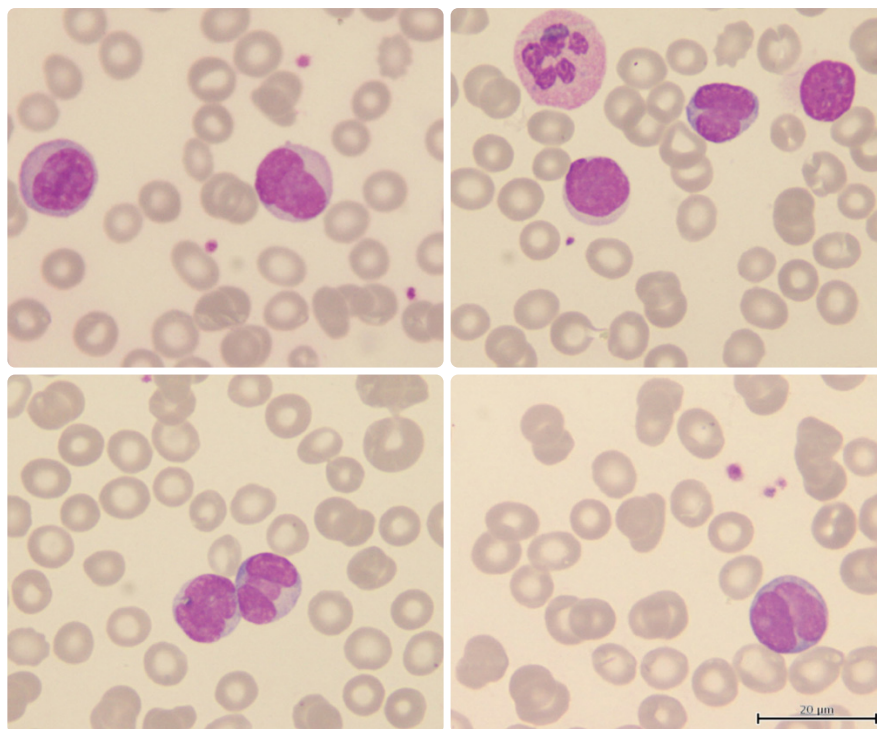


Figure 2 The patient's initial blood smear, showing frequent abnormal immature cells with bilobed nuclei, resembling acute promyelocytic leukemia

B, C and human immunodeficiency virus screening were non-reactive. The coagulation profile, including prothrombin time and activated partial thromboplastin time were normal and fibrinogen level was slightly high at 280 mg/dL.

Initially, the patient was diagnosed with acute promyelocytic leukemia (APL) based on morphologic findings. However, the flow cytometric analysis of her marrow aspirate with leukemia panel revealed no significant blast population both on CD45/side scatter (SSc) plot and on CD34 expression. The karyotype was not yet available and *PML::RARA* test was not requested at that time. She was initially treated with all-trans retinoic acid (ATRA) for a presumptive diagnosis of APL. Hemocultures were positive for *Cryptococcus neoformans* var *grubrii* and the diagnosis of cryptococcal septicemia was made. Contrast-enhanced computed tomography scan of brain showed old lacunar infarction at left external capsule, lentiform nucleus and thalamus without abnormal enhancing lesion or leptomeningeal enhancement. Due to her conditions, the patient and her family declined to have a lumbar puncture performed as part of the neurologic evaluation of cryptococcal septicemia. Bone

marrow biopsy showed trilineage hematopoiesis with maturation and few scattered medium size mononuclear cells of undetermined lineage. Few of these cells showed irregular nuclei and express CD3 (Figure 3). Skin biopsy was performed and histopathology detected small to medium size lymphoid cells infiltration at intraluminal and perivascular location of superficial dermis. The suspicious cells were positive for CD3 and had markedly irregular nuclear shape.

Over the course of 2 weeks, her overall condition was stable but the CBC was not improved after ATRA. Due to the patient's uncommon presentation for APL as normal platelet, skin rashes with the non-confirmatory histopathologic results and normal female karyotype without the expected translocation between chromosome 15 and 17, re-evaluation of the diagnosis was performed. A repeated peripheral blood smear showed numerous flower-like cells with markedly polylobate nuclei (Figure 4), which raised suspicion of T-cell lymphoma. Flow cytometric analysis of peripheral blood with non-Hodgkin lymphoma panel revealed the presence of 91.3% lymphocyte on CD45/SSc plot. The majority of the lymphocyte population expressed CD4, CD5 and CD25 with aberrant

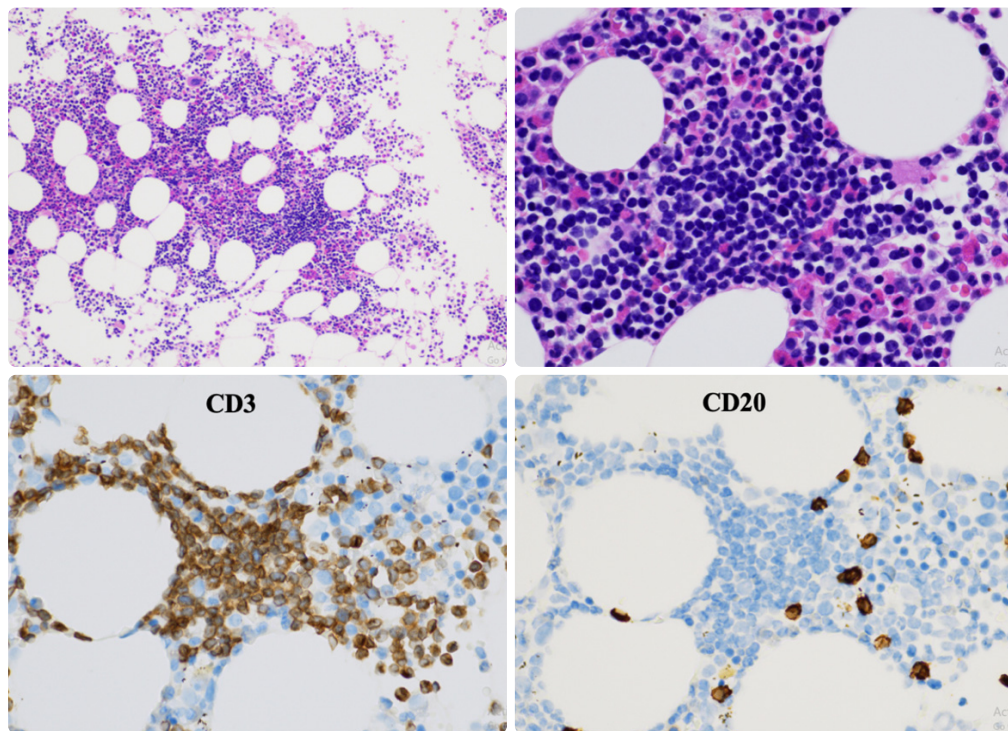


Figure 3 Bone marrow showing infiltration with CD3+ T-cells

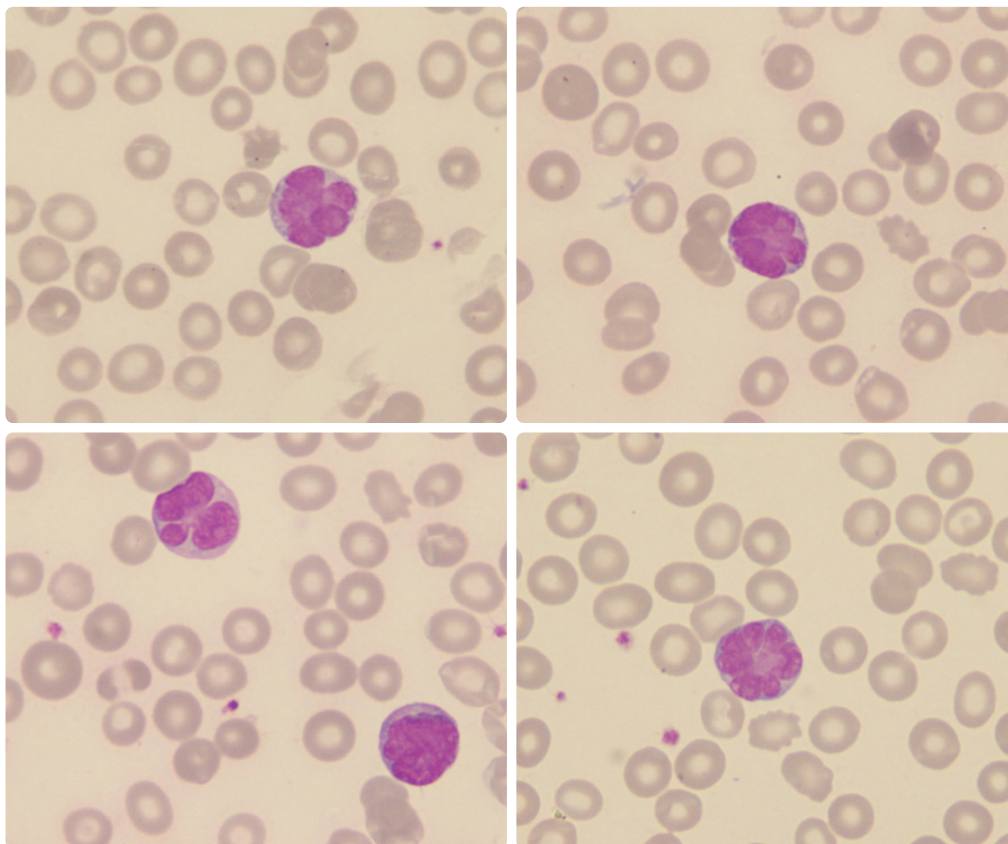


Figure 4 Re-evaluation of peripheral blood morphology revealing multiple flower cells

loss of surface CD3 and CD7 expression, compatible with abnormal regulatory T-cell origin (Figure 5). Review of the previous flow cytometric study with acute leukemia from the initial bone marrow also revealed a predominant subset of T-cell with cytoplasmic CD3 positive and aberrant loss of surface CD7. The results confirmed the presence of abnormal T-cell population with cytoplasmic CD3 positivity and aberrant loss of surface CD3 and CD7 which confirmed the findings from immunohistochemical CD3 staining, which could detect

both surface and cytoplasmic CD3. The suspicion of ATLL was raised and further serologic test for HTLV-1 was positive, confirming the diagnosis of ATLL.

Due to her overall condition, the treatment plan was discussed with the patient and her family and a palliative goal of treatment was decided, she received treatment with dexamethasone and vincristine. She developed methicillin-sensitive staphylococcal septicemia. She finally passed away with septic shock and multi-organ failure.

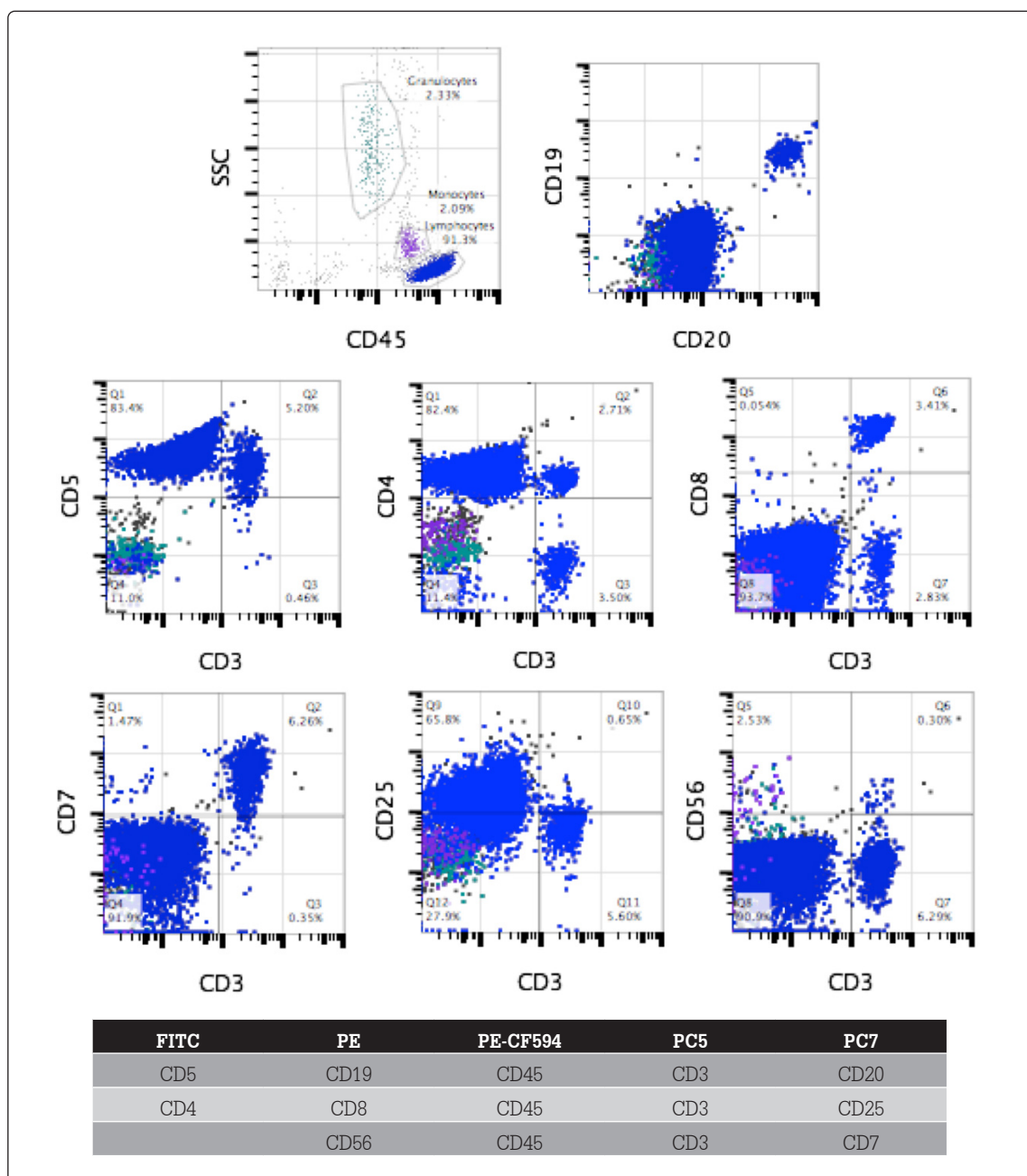


Figure 5 Flow cytometric analysis with customized lymphoma panel revealing abnormal lymphoid population with CD4+, CD5+, CD25+ and aberrant loss of CD3 and CD7, suggestive of abnormal regulatory T-cell in origin

Discussion

ATLL is an aggressive mature T-cell neoplasm of regulatory T-cell origin. The morphologic feature is most often composed of highly pleomorphic lymphoid cells (so-called “flower cells”), which caused by human T-lymphotropic virus 1 (HTLV-1 or human T-cell leukemia virus) infection. The HTLV-1 is transmitted by breast feeding, blood transfusion and sexual contact. The number of HTLV-1 carriers is estimated to be 5-20 million worldwide¹. ATLL often occurs in HTLV-1-endemic areas, such as southwestern Japan, the Caribbean islands, Central and South America, sub-Saharan Africa, and the Middle East^{2,4}. While Thailand has low seroprevalence of HTLV-1 and has been considered non-endemic area of HTLV-1³.

Most ATLL cases present in adulthood, with an average age of 58 years and a male-to-female ratio of 1.5:1. Clinical manifestations include: generalized lymphadenopathy, skin involvement (> 50% of cases), leukemic manifestations, infiltration of other organs such as the central nervous system, gastrointestinal tract, hepatomegaly and splenomegaly. Some patients may present with symptomatic hypercalcemia. Most patients also have an associated T-cell immunodeficiency, which results in opportunistic infection including *Pneumocystis jirovecii* infection, strongyloidiasis, cryptococcal infection.

ATLL is categorized into four clinical subtypes by the Shimoyama classification⁵ (acute ATLL, lymphomatous ATLL, chronic ATLL and smoldering ATLL) based on the presence of leukemic cells, additional sites of organ infiltration, hypercalcemia and LDH.

Acute and lymphomatous variants of ATLL are highly aggressive diseases. The prognosis of the two subtypes are dismal with a median survival of less than 1 year. Chronic and smoldering variants of ATLL have long clinical course and better prognosis when compared to the acute or lymphomatous forms. However, the median survival is still less than 5 years. The chronic and smoldering forms have a more protracted clinical course and better survival, but can progress to an acute

phase with an aggressive course in approximately 25% of patients at the median time of 2 years^{4,7-9}.

The cytologic characteristics of ATLL may vary depending on clinical variants. The neoplastic cells in the peripheral blood are termed flower cells with polylobate and clover-leafed appearance of nuclear lobes and condensed chromatin. However, large blast-like cells may also be seen in the peripheral blood. Lymph nodes typically show diffuse architectural effacement and preserved sinusoidal structure. The sinuses may sometime be dilated and may contain atypical cells^{4,8,10}.

Skin involvement is frequent in ATLL, which divided into 6 categories including patch, plaque, multipapular, nodulotumoral, erythrodermic, and purpuric. The histopathological of skin lesions mostly show a superficial or diffuse infiltration of pleomorphic multinucleate lymphoid cells with prominent epidermotropism and Pautrier-like abscesses. The neoplastic cells of ATLL are mostly strongly express CD4 and CD25. The cells usually express CD2, CD3 and CD5, but CD7 is nearly always absent. Additional markers including CD52, CCR4 and FOXP3 may be positive in the neoplastic cells. The large transformed cells may be positive for CD30 but negative for anaplastic lymphoma kinase (ALK)^{4,8,10}.

Current treatments of ATLL are based on clinical subtypes, symptom, prognostic factors and response to initial therapy.

For aggressive ATLL, multiagent chemotherapy regimens, such as cyclophosphamide-vincristine-doxorubicin-prednisolone (CHOP), CHOP plus etoposide (CHOEP), etoposide-prednisolone-vincristine-cyclophosphamide-doxorubicin (EPOCH) with or without dose adjustment, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone (hyper CVAD) or zidovudine/interferon gamma (AZT/IFN) are recommended. Up-front allogenic-HSCT should be considered for all suitable patients with aggressive ATLL. For indolent ATLL, watchful waiting or AZT/IFN combination therapy is recommended. All patients should be considered for entry into clinical trials where available. Ongoing trials

about targeted therapies were studied such as monoclonal antibodies (mogamulizumab), proteasome inhibitors, immunomodulatory drug, tumor vaccines etc^{6,10,11}.

Conclusion

In country with low prevalence of HTLV-1 infection, ATLL is considered a rare disease. The clinical and pathological presentation may be similar to other T-cell lymphoma or acute promyelocytic leukemia, which may make the diagnosis difficult. Careful evaluation of morphologic features and correlation with other ancillary laboratory tests will aid in making a proper diagnosis and treatment. To the best of our knowledge, this is the first case report of ATLL in Thailand. We hope that this case report would aid physicians in making proper differential diagnosis for patients who had atypical presentation like the case presented here.

Conflict of interest

The authors have no conflict of interest relevant to the article.

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