Cutaneous Anaplastic Large Cell Lymphomas: A Report of 9 Cases from Thailand

Sasima Eimpunth MD*, Panitta Sittinamsuwan MD**,
Penvadee Pattanaprichakul MD*, Narumol Silpa-archa MD*,
Piyaroj Sethabutra MD*, Leena Chularojanamontri MD*,
Suchanan Hanamornroongruang MD**, Punkae Mahaisavariya MD*

** Department of Dermatology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand*
*** Department of Pathology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand*

Background: *Anaplastic large cell lymphoma (ALCL) is one type of lymphoma, which is characterized by the proliferation of pleomorphic large atypical lymphoid cells expressing CD30 antigen. ALCL involving skin can be either primary cutaneous disease or cutaneous involvement secondary from systemic disease. Data of clinical manifestation of cutaneous ALCL in Thai patients is limited. ALCL in Thai patients may differ from other groups of patients.*
Objective: *To study the clinical manifestation of cutaneous ALCL in patients of Faculty of Medicine Siriraj Hospital, Thailand*
Material and Method: *Medical records of nine patients with histopathologic diagnosis of ALCL from skin biopsy at Faculty of Medicine Siriraj Hospital were reviewed.*
Results: *Of nine patients, four patients were diagnosed as primary cutaneous ALCL, four patients as systemic ALCL with secondary skin involvement, and one patient as combined primary cutaneous ALCL and lymphomatoid papulosis. Three primary cutaneous ALCL patients had no recurrence of disease during 6-year follow-up. However, all systemic ALCL patients died at one day to 1.5 years after diagnosis.*
Conclusion: *Clinical manifestation and clinical course of Thai patients with anaplastic large cell lymphoma corresponded with the data from other patient population.*

Keywords: *Lymphoma, Skin, CD30, Lymphoproliferative disorder*

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Anaplastic large cell lymphoma (ALCL) is a neoplasm of CD30-positive lymphoid cells of T- or null-cell lineage characterized by the proliferation of pleomorphic large neoplastic lymphoid cells, which strongly expresses the CD30 (Ki-1) antigen.

There are two types of cutaneous ALCL, which are the classical systemic type involves multiple nodal and extranodal sites (systemic ALCL) and the primary cutaneous ALCL (C-ALCL) that involves the skin without evidence of extracutaneous disease at the time of diagnosis. C-ALCL belongs to primary cutaneous CD30-positive T-cell lymphoproliferative disorders, according to World Health Organization (WHO) classification 2008[1]. C-ALCL has more favorable prognosis than systemic ALCL[2], but histopathologic features are similar.

Variation of clinical manifestation among races was demonstrated in cutaneous T-cell lymphoma, another subgroup of T-cell lineage NHL involving skin[3]. However, data of that variation in ALCL is limited. Regarding the observations in CTCL, it is possible that Thai patients with cutaneous ALCL will have different clinical manifestation when compared to other racial populations.

The present study describes the clinical manifestation in nine cases of ALCL involving skin seen at the Faculty of Medicine Siriraj Hospital, Thailand.

Correspondence to:
Eimpunth S, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Pran-nok Rd, Bangkok 10700, Thailand.
Phone: 0-2419-4333, Fax: 0-2411-9922
E-mail: doctorsasima@gmail.com

Material and Method

Medical records of nine patients with skin lesions and histopathologic diagnosis of ALCL from skin biopsy seen in Faculty of Medicine Siriraj Hospital were retrospectively reviewed.

Definite diagnoses were made based on clinical, histopathologic, and immunophenotypic findings.

C-ALCL patients defined as patients with skin lesions of ALCL (confirmed by histopathology and immunohistochemistry), without prior or concurrent lymphomatoid papulosis (LyP), mycosis fungoides (MF), or other type of (cutaneous) lymphoma, and had no extracutaneous involvement at the time of diagnosis, as assessed by adequate staging[4].

Systemic ALCL with skin involvement patients defined as patients with skin lesions of ALCL (confirmed by histopathology and immunohistochemistry) and concurrent extracutaneous disease (other than 1 regional lymph node) or patients with systemic ALCL developing specific skin lesions during follow-up[4].

The present study protocol was approved by the Siriraj Institutional Review Board.

Results

Population

Nine Thai patients with ALCL involving skin were included in the present study. Medical records of all patients were reviewed.

Clinical findings

The demographics and clinical presentation of all nine patients are summarized in Table 1. There were six men and three women. The median age of onset of skin lesions was 36 years old (range from 16 to 57 years old) and a mean duration of skin lesions before presentation was 7.94 months (1 to 36 months). Clinical presentation varied from single erythematous cutaneous nodule without systemic symptoms to multiple necrotic papules and nodules with fever, weight loss, and lymphadenopathy (Fig. 1, case number 1). There was one interesting case which presented with keratoacanthoma-like nodules (Fig. 2, case number 9). The two most common presenting skin lesions were nodules and papules.

Investigations and definite diagnosis

Definite diagnosis based on clinical presentation, laboratory investigations, imaging studies, histopathological and immunostaining findings are shown in Table 2. Staging includes, at least, physical examination, complete blood count, blood chemistry, chest radiography, ultrasonography of abdomen, and bone marrow study were done in all patients.

Four patients were diagnosed as C-ALCL, four patients as systemic ALCL with cutaneous involvement, and one patient as combined C-ALCL and LyP.

Abnormalities in laboratory investigations, imaging studies, and bone marrow study were demonstrated in systemic ALCL patients. Abnormal laboratory investigations found were pancytopenia, abnormal liver function test, and increased lactate dehydrogenase level. Mediastinal lymphadenopathy, mild splenomegaly, and increase liver parenchymatous echo were also found.

Treatment and clinical course

In four c-ALCL patients, one patient had spontaneous remission, two patients received

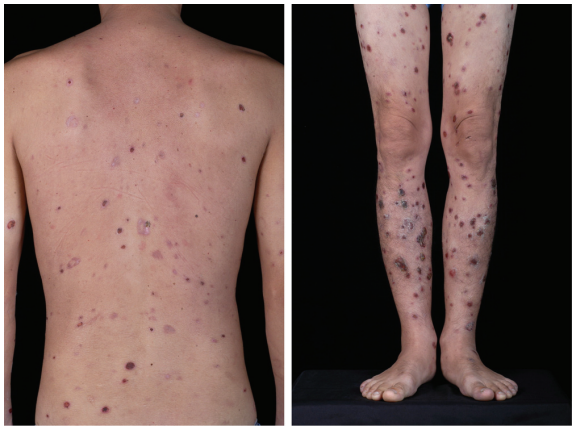

Fig. 1 Secondary cutaneous involvement from systemic anaplastic large cell lymphoma

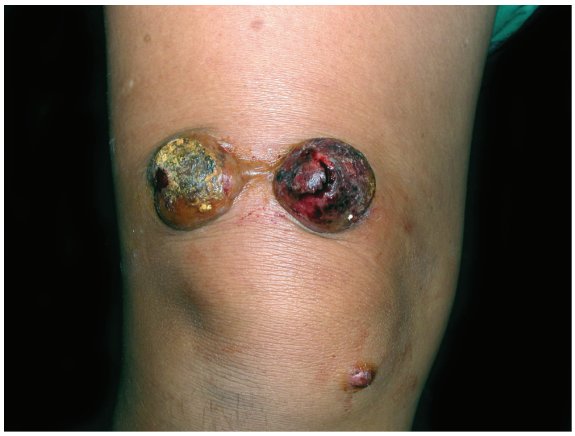

Fig. 2 Keratoacanthoma-like primary cutaneous anaplastic large cell lymphoma

Table 1. Patient demographics and clinical presentation

No.	Sex	Age	Presenting skin lesions	Duration	Other presenting signs and symptoms					Others
					Fever	Night sweat	Weight loss	Hepatosplenomegaly	Lymphadenopathy	
1	M	45	Multiple erythematous necrotic papules and nodules on legs, arms, trunk, genitalia and scalp	3 weeks	+	+	+	-	Cervical, groin	-
2	M	36	Multiple scaly erythematous nodules around left elbow	1 year	-	-	-	-	-	-
3	F	19	Erythematous scaly plaque on left axilla and brownish scaly macules	3 months	-	-	-	-	-	-
4	M	57	Erythematous annular plaque, right arm (rapid progression for 1 year)	3 years	-	-	-	-	-	-
5	M	28	Multiple erythematous nodules at both arms, forearms, thighs and legs with large verrucous mass 5 cm on sacral area	3 months	-	-	-	-	Groin	-
6	F	54	Multiple erythematous to brownish papules on both arms, abdomen, thigh	2-3 years	+2 weeks	-	-	-	Cervical, epitrochlear, inguinal	Loss of appetite 13 days
7	M	16	Few erythematous papules on trunk and legs	1 month	+1 month	-	-	-	Submandibular	-
8	M	31	Single erythmatous nodule of right arm	4 weeks	-	-	-	-	-	-
9	F	56	Multiple nodules (keratoacanthoma-liked) with contact bleeding, right knee	3 months	-	-	-	-	-	-

Table 2. Definite diagnosis, histopathologic, immunostaining, and staging findings

No.	Definite diagnosis	Histopathology	Immunostaining			Laboratory investigations*	Imaging	BM biopsy	LN biopsy
			CD30	ALK	EMA				
1	S-ALCL	CD30 + LPD	+	-	-	Abnormal	Normal	Hemophagocytosis, no tumor	NA
2	C-ALCL	ALCL	+	-	-	Normal	Normal	Normal	NA
3	C-ALCL with LyP	CD30 + LPD	+	-	+ (focal)	Normal	Normal	Normal	NA
4	C-ALCL	ALCL	+	-	-	Abnormal	Normal	Normal	NA
5	S-ALCL	ALCL	+	-	-	Abnormal	Normal	Normal	NA
6	S-ALCL	ALCL	+	-	-	Abnormal	Normal	Lymphoma	ALCL
7	S-ALCL	ALCL	+	+	+	Abnormal	Abnormal	Lymphoma	ALCL
8	C-ALCL	ALCL	+	NA	NA	Normal	Normal	Normal	NA
9	C-ALCL	ALCL	+	-	-	Normal	Normal	Lymphoma	NA

S-ALCL = secondary cutaneous involvement from systemic anaplastic large cell lymphoma; C-ALCL = primary cutaneous anaplastic large cell lymphoma; LyP = lymphomatoid papulosis; NA= data not available

* Laboratory investigations: include complete blood count, liver function test, lactate dehydrogenase, blood urea nitrogen, and creatinine

multiagent chemotherapy, and one patient received local radiotherapy and chemotherapy. Recurrence was found during the course of treatment in three patients. After the course of treatment, three patients were free of disease during the 6-year follow-up period.

In four systemic ALCL with cutaneous involvement, three patients received multiagent chemotherapy. The other patient died before the initiation of chemotherapy because of febrile neutropenia with septic shock and multiple organ failure at 2 weeks after presentation. All three patients who received chemotherapy died at 1 day to 1.5 years after diagnosis. Recurrence was found in two patients during the course of chemotherapy.

A patient with LyP combined with C-ALCL received local radiation therapy and chemotherapy. She had multiple episodes of recurrence.

Discussion

Lymphoma is a malignancy of lymphoid cells that are comprised of two main types, Hodgkin's lymphoma (HL, previously called Hodgkin's disease) and non-Hodgkin's lymphoma (NHL). Skin is the second most common site of extranodal lymphoma after the gastrointestinal tract[5]. Cutaneous involvement of lymphomas can be either primary cutaneous disease or secondary from systemic disease.

Anaplastic large cell lymphoma (ALCL), also called Ki-1 lymphoma, is a neoplasm of CD30-positive lymphoid cells of T- or null-cell lineage[6], a subgroup of non-Hodgkin's lymphoma (NHL), originally described by Stein et al[7,8]. ALCL characterized by the proliferation of pleomorphic large neoplastic lymphoid cells, which strongly expresses the CD30 Antigen (Ki-1 antigen) and has distinctive histologic features, usually growing in a cohesive pattern[7-11]. The staining pattern of CD30 in ALCL is distinctive, being intense with a membranous and perinuclear Golgi zone staining pattern.

There are two types of ALCL, the systemic type (systemic ALCL) and the primary cutaneous type (C-ALCL). Ten to 20% of systemic ALCL patients may have secondary skin involvement[6]. On the other hand, 10% of C-ALCL patients may have extracutaneous involvement[4]. Histopathologic features of both types are similar[12], but clinical and biologic features are different[13]. The systemic type is aggressive[14] with a disease-related 5-year cumulative survival of 29% to 44%[4,5,15,16]. C-ALCL has better prognosis than systemic ALCL[2]and can regress spontaneously[17] with excellent 10-year disease-related survival rates

varies from 85% to 100%[4,18]. Therefore, definite diagnosis, based on combinations of clinical, histologic, and immmunophenotypic criteria[19], is important. Immunostaining can be used to distinguish C-ALCL from cutaneous involvement by systemic ALCL, as anaplastic lymphoma kinase (ALK), a tyrosine kinase that belongs to the insulin receptor super family, expression is extremely rare (or absent) in C-ALCL. Epithelial membrane antigen (EMA) expression is also lack in C-ALCL[13].

Besides ALCL, there are some other conditions presented histologically as CD30-positive atypical lymphoid infiltration in the skin, such as lymphomatoid papulosis (LyP), MF with transformation into ALCL (transformed MF), or benign conditions that have CD30-positive blast cells, such as viral infections, arthropod reactions, and drug eruptions[20,21]. LyP belongs to CD30-positive lymphoproliferative disorders in WHO classification (2008), the same group as C-ALCL, and has overlapping clinical, histologic, and immunostaining features[4] with C-ALCL. Both diseases have favorable prognoses in most patients[4,15,16, 22-26].

Previously reported cases of C-ALCL were male predominance, had solitary lesion of nodules or tumors, and had spontaneous regression[4,15,16,22,25]. In the present study, 75% (three from four) of C-ALCL patients were male, and all four patients presented with skin nodules or plaque. Of note, one patient presented with keratoacanthoma-like nodules. Spontaneous regression was found in one of our C-ALCL patient. Three patients had been free of disease for 6 years.

Not all of systemic ALCL patients in the present study survived more than 5 years after diagnosis. Furthermore, three of them, ALK-negative systemic ALCL, died within two weeks after diagnosis (1.5-36 months after the onset of disease). One patient with ALK-positive lymphoma survived longer than those with ALK-negative disease. This data confirmed the findings from a previous study which mentioned the better prognosis in systemic ALCL patients with ALK-positive when compare to those with ALK-negative[27].

In conclusion, clinical presentation and clinical course of Thai patients with anaplastic large cell lymphoma corresponded with those of other racial populations that had previously been reported. Primary cutaneous anaplastic large cell lymphoma has better prognosis than systemic anaplastic large cell lymphoma with skin involvement. Therefore, definite diagnosis is important.

Potential conflicts of interest

None.

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มะเร็งต่อมน้ำเหลือง anaplastic large cell: รายงานผู้ป่วย 9 รายจากประเทศไทย

ศศิมา เอี่ยมพันธุ์, พนิตตา สิทธินามสุวรรณ, เพ็ญวดี พัฒนปรีชากุล, นฤมล ศิลปอาชา, ปิยะรจน์ เศรษฐบุตร, ลีนา จุฬาโรจน์มนตรี, สุชานัน หาญอมรรุ่งเรือง, พรรณแข มไหสวริยะ

ภูมิหลัง: *มะเร็งต่อมน้ำเหลือง anaplastic large cell เป็นมะเร็งที่มีการเพิ่มขึ้นของเซลล์ลิมโฟไซต์ผิดปกติขนาดใหญ่ และมีการแสดงแอนติเจนชนิด CD30 การตรวจพบเซลล์มะเร็งชนิดนี้ที่ผิวหนัง อาจเกิดจากลิมโฟไซต์ผิดปกติขนาดใหญ่เพิ่มจำนวนมากขึ้นที่ผิวหนัง (เปรียบเหมือนผิวหนังเป็นต่อมน้ำเหลือง) เกิดเป็นมะเร็งที่ผิวหนังเอง หรือ เป็นมะเร็งต่อมน้ำเหลืองที่ตำแหน่งอื่นแล้วกระจายมาที่ผิวหนัง ข้อมูลของลักษณะทางคลินิกของมะเร็งต่อมน้ำเหลืองชนิดนี้ที่ผิวหนังในผู้ป่วยไทยยังมีจำกัด และอาจมีความแตกต่างจากผู้ป่วยเชื้อชาติอื่น*

วัตถุประสงค์: *เพื่อศึกษาลักษณะทางคลินิกของผู้ป่วยมะเร็งต่อมน้ำเหลือง anaplastic large cell ที่ผิวหนังที่คณะแพทยศาสตร์ศิริราชพยาบาล*

วัสดุและวิธีการ: *ทบทวนเวชระเบียนของผู้ป่วยที่ได้รับการวินิจฉัยจากการตรวจทางจุลพยาธิวิทยาทางผิวหนังว่าเป็นมะเร็งต่อมน้ำเหลือง anaplatic large cell ที่ผิวหนังจำนวน 9 ราย ที่คณะแพทยศาสตร์ศิริราชพยาบาล*

ผลการศึกษา: *จากผู้ป่วยทั้งหมดจำนวน 9 ราย ผู้ป่วยอีก 4 รายได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลือง anaplastic large cell ที่ผิวหนังเอง ผู้ป่วย 4 รายได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลือง anaplastic large cell ที่อื่นและมีการกระจายมาที่ผิวหนัง ส่วนผู้ป่วยอีก 1 ราย ได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลือง anaplastic large cell ร่วมกับโรค lymphomatoid papulosis ผู้ป่วยมะเร็งต่อมน้ำเหลือง anaplastic large cell ที่ผิวหนังเองจำนวน 3 ราย ไม่มีการกลับเป็นใหม่ของโรคตลอดระยะเวลาที่ติดตาม 6 ปี ส่วนผู้ป่วยมะเร็งต่อมน้ำเหลือง anaplastic large cell ที่กระจายมาที่ผิวหนังทั้ง 4 รายเสียชีวิตในช่วงเวลาตั้งแต่ 1 วันถึง 1.5 ปี ภายหลังได้รับการวินิจฉัย*

สรุป: *ลักษณะทางคลินิกและการดำเนินโรคของผู้ป่วยไทยที่เป็นมะเร็งต่อมน้ำเหลือง anaplastic large cell lymphoma เป็นไปในทางเดียวกับที่พบในผู้ป่วยในประชากรอื่น*