

CD30+ Lymphoproliferative Disorders Associated with Longstanding Mycosis Fungoides

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Published:

J Turk Acad Dermatol 2016; **10** (2): 16102c5

This article is available from: <http://www.jtad.org/2016/2/jtad16102c5.pdf>

Keywords: Systemic anaplastic large-cell lymphoma, lymphomatoid papulosis, primary cutaneous anaplastic large-cell lymphoma, large cell transformation

Abstract

Observation: The CD30 antigen is a type-1 transmembrane glycoprotein which is a member of the tumor necrosis factor receptor family and may be expressed on activated B and T cells. CD30+ lymphoproliferative disorders (CD30+ LPDs) mainly include primary cutaneous CD30+ anaplastic large-cell lymphoma (pcALCL) and lymphomatoid papulosis (LyP). Other CD30 +LPD showing skin lesions are large cell transformation (LCT) of mycosis fungoides (MF), Hodgkin lymphoma and adult T cell lymphoma. Herein we represent three cases of CD30+ LPDs associated with longstanding MF.

Introduction

The CD30 antigen is a type-1 transmembrane glycoprotein which is a member of the tumor necrosis factor receptor family and may be expressed on activated B and T cells [1,2]. According to World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) classification CD30+ lymphoproliferative disorders (CD30+ LPDs) mainly include primary cutaneous CD30+ anaplastic large-cell lymphoma (pcALCL) and lymphomatoid papulosis (LyP) [3]. Clinically ALCL can be subdivided into primary (systemic and cutaneous) and secondary forms [4,5]. Other CD30 +LPD showing skin lesions are large cell transformation (LCT) of mycosis fungoides (MF), Hodgkin lymphoma and adult T cell lymphoma [2,6,7,8,9]. It is important to distinguish between CD30+ LPDs because they vary in response to treatment and clinical outcome [1,2,3,4,5,6,7,8,9,10,11]. Herein we represent three cases of CD30+ LPDs associated with longstanding MF.

Case Report

Case 1: A 55-year-old woman with MF of 17 years duration presented with two nodules on her left elbow first noticed two months earlier. The patient stated that she experienced five similar lesions on the extremities six months earlier, all of which had regressed spontaneously. On her first presentation to our outpatient clinic three years previously, patch stage MF was diagnosed according to the characteristic clinicopathologic findings. For the past two years, she had received whole body systemic PUVA therapy (cumulative dose approximately 950 J/cm²). All of her lesions responded to PUVA therapy and she has been on maintenance therapy for the last two months. Dermatological examination at her last presentation revealed two 10 mm reddish nodules resembling carbuncle, in the anterior aspect of the left arm. Close to these nodules, two other erythematous, haemorrhagic and necrotic papules at different stages of development were also noticed on the left arm (Figure 1a). Except for these nodules, the whole body skin was normal. Physical examination disclosed no constitutional symptoms and laboratory investigations revealed no abnormalities (Table 1). An excisio-

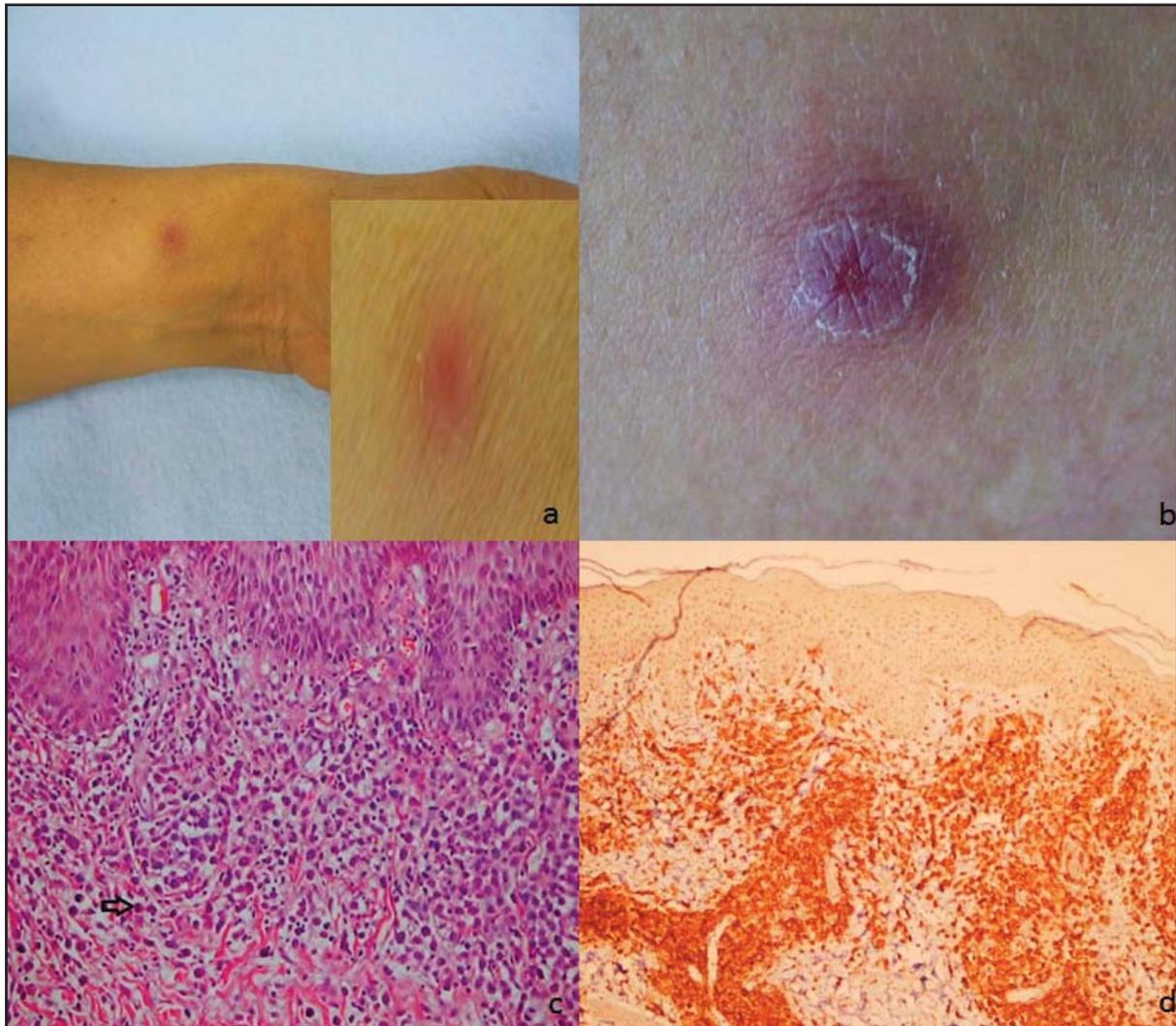


Figure 1a, b, c and d. (a,b) erythematous, haemorrhagic and necrotic papules at different stages of development on the left arm (c) Lymphomatoid Papulosis- composed of atypical lymphoid cell infiltrating dermis, mitotic figures in dermis (arrow) HE X 200 (d) CD30 expression, DAB X 100

nal biopsy of the nodules showed atypical lymphoid cell infiltration in perivascular and interstitial locations. Some of the cells in infiltrate showed hyperchromatic and prominent nucleoli with a narrow eosinophilic cytoplasm. Mitotic figures were numerous (**Figure 1b**). Eosinophils were also observed. Immunohistochemistry demonstrated that most of the large cells (>75%) were positive for CD30 (**Figure 1c**), CD3, and CD4 but negative for CD20, CD56, ALK and EMA. A diagnosis of LyP was established (**Figure 1d**). All of the lesions regressed after the biopsy. The patient is now continuing PUVA therapy (two/week) without further lesions.

Case 2: A 47-year old woman with patch stage MF of 10 years duration presented with tumors on upper extremities. A detailed anamnesis revealed

that she had been treated with PUVA therapy (two/week) for the past three years and because she continued to develop further lesions, low dose acitretin (10 mg/day) and interferon (3 x 3 MIU/week) were combined with phototherapy for the last six months. She had been out of lesions with this combination treatment until three months previously when she noticed a painful tumor occurring on her left shoulder. On further questioning, she stated that she had experienced another, solitary, nodule similar to this lesion on the elbow four months ago which had been excised and diagnosed as ALCL and TCR γ gene rearrangement study had revealed the presence of a T-cell clonal population both in the skin and lymph nodes. On dermatological examination two erythematous and haemorrhagic nodules on normal appearing skin that were painful on palpation

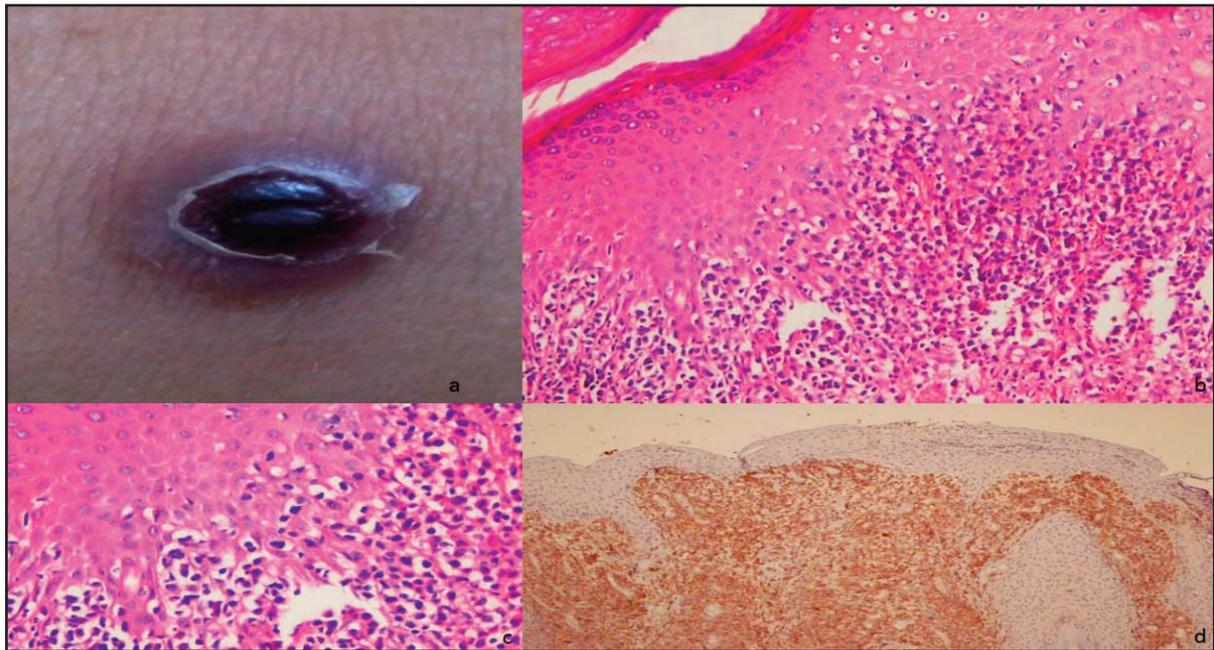


Figure 2a, b, c and d. (a) A hemorrhagic tumor of LCT of MF (b) LCT of MF; diffuse atypical dermal lymphoid infiltrate with prominent epidermotropism HE X 100 (c) Large pleomorphic cells with hyperchromatic nuclei HE X 200 (d) CD30 expression, DAB X 200

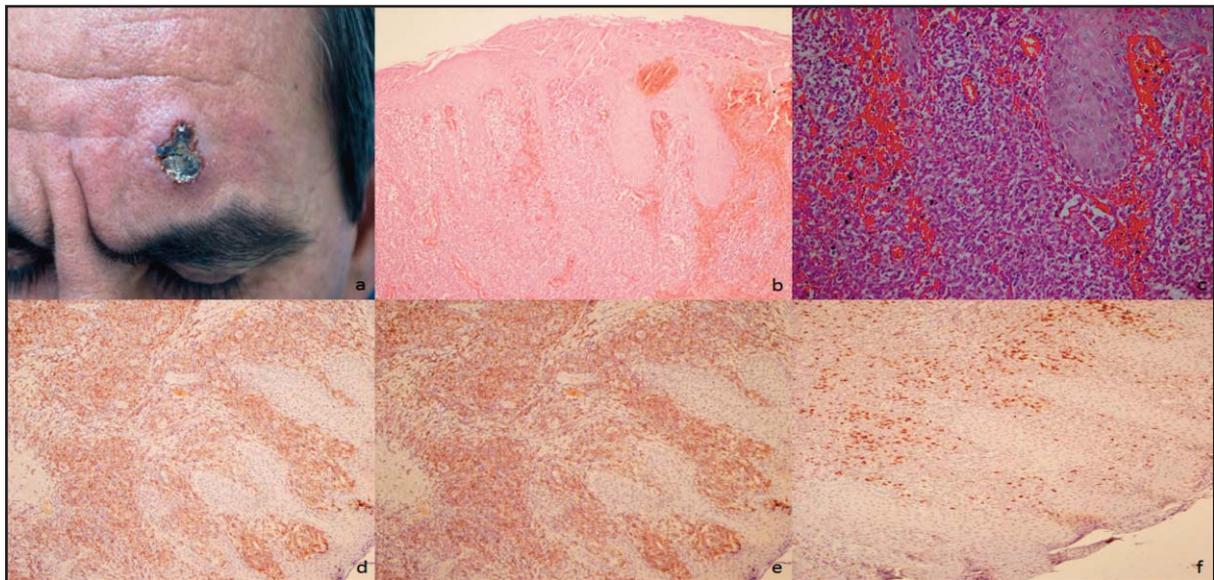


Figure 3a, b, c, d, e and f. (a) Nodules covered with thick black crust were seen on the forehead, the skin surrounding the lesion was normal except for a narrow erythematous margin (b) Primary cutaneous ALCL composed of large atypical pleomorphic cells, HE X 100 (c) the tumor cells had large and pleomorphic nuclei with eosinophilic cytoplasm, HE X 200 (d) CD30 expression, DAB X 100 (e) CD4 expression, DAB X 100 (f) CD8 positive small lymphocytes infiltrating among anaplastic large cells.

was observed on her left shoulder and inner aspects of the arm (**Figure 2a**). Physical examination revealed two palpable lymph nodes. The biopsy of the skin lesions revealed diffuse atypical dermal lymphoid infiltrate with prominent epidermotropism (**Figure 2b**). The infiltrate was predominantly composed of large pleomorphic cells often

with hyperchromatic nuclei (**Figure 2c**). Mitotic figures were also present. Immunohistochemistry demonstrated that approximately 50% of the large cells were positive for CD30 (**Figure 2d**), CD3, and CD4 but negative for ALK and EMA. The work up of the patient revealed no additional abnormal

Table 1. Clinical and Laboratory Findings of Our Patients

	Patient 1	Patient 2	Patient 3
Age	47	55	51
Duration of MF	17 years	10 years	15 years
Stage	Ib	IVa	Ib
Duration of CD30+ LPDs	6 months	4 months	10 years
Clinical findings	10-mm reddish nodules resembling carbuncle, papules	10 mm red nodule	asymptomatic, recurrent, self healing, reddish, large ulcerated nodule covered with black thick crusts
Systemic symptoms	No fever, facial swelling, night sweats, weight loss or bone pain.	No fever, facial swelling, night sweats, weight loss or bone pain	No fever, facial swelling, night sweats, weight loss or bone pain
Laboratory investigations	Normal or negative	Normal or negative	Normal or negative
	blood cell count, blood chemistry, urinalysis, chest x-ray, peripheral blood smear, chest and abdominal computed tomographic scans, bone marrow aspirate and/or biopsy	blood cell count, blood chemistry, urinalysis, chest x-ray, peripheral blood smear, chest and abdominal computed tomographic scans, bone marrow aspirate and/or biopsy	blood cell count, blood chemistry, urinalysis, chest x-ray, peripheral blood smear, chest and abdominal computed tomographic scans, bone marrow aspirate and/or biopsy
Extracutaneous disease	(-)	+ (Lymph Node)	(-)
Immunophenotype	CD30 (>%75)+ CD3+, CD4+ CD20-/CD56- ALK-/EMA-	CD30 (~%50)+ CD3+, CD4+ CD20-/CD56- ALK-/EMA-	CD30 (>%75)+ CD3+,CD4+ CD8+ CD20-/ CD56- ALK- /EMA-
T cell clonality	NA*	(+) in MF tumor (+) in Lymph node	(+) in CD30+ LPDs lesion
Diagnosis	Lymphomatoid papulosis	Large cell transformation of mycosis fungoides	Primary cutaneous anaplastic large cell lymphoma

*NA: not available

lities (Table 1). The patient was diagnosed as having transformation of MF. Unfortunately, the patient was lost to follow up before our intention to therapy.

Case 3: A 51-year-old man presented with an asymptomatic, recurrent, self healing, reddish ulcerated nodule on the forehead covered with black thick crusts of three months' duration. A detailed anamnesis revealed that ten years previously a biopsy had been performed and a histological diagnosis of MF was made for the plaques on the legs. At that time he had a course of PUVA therapy. The patient stated that he had experienced similar self healing ulcerated lesions that grew over a period of three weeks almost every four to five months for the last 10 years. He also noted

that ulcerated lesions always occurred on normal skin, and regressed spontaneously leaving slightly depressed hypopigmented scars. Past medical and family history were otherwise unremarkable. On dermatological examination, two poikilodermic patches were observed on the glutea and three nodules of two cm diameter each covered with thick black crusts were seen on the forehead, arm and shoulder area (Figure 3a). The skin surrounding the lesion was normal except for a narrow erythematous margin. Excisional biopsy specimens were obtained, one from the crusted nodule on the forehead and one from the poikilodermic lesion. They showed distinct features. Poikilodermic lesions were diagnosed as patch stage MF. The specimen from the nodule on the forehead showed

large, atypical, pleomorphic cells showing interstitial and perivascular infiltration throughout the entire dermis and upper subcutis without epidermotropism (**Figure 3b**). The tumour cells had large, bizarre and pleomorphic nuclei with eosinophilic cytoplasm (Figure 3c). Atypical mitotic figures were frequent. Small lymphocytes were also present within the infiltrate. Immunohistochemistry demonstrated that most of the large cells were positive for CD30 (>75%) (**Figure 3d**), CD3, and CD4 (**Figure 3e**) but negative for CD20, CD56, anaplastic lymphoma kinase (ALK) and epithelial membrane antigen (EMA). Small lymphocytes infiltrating among anaplastic large cells were CD8+ (**Figure 3f**). Clonal TCR γ gene rearrangement was detected by PCR analysis in the nodule on the forehead. The work up of the patient revealed no additional abnormalities (Table 1). A diagnosis of cALCL was made. The patient was treated with acitretin (25 mg/day), PUVA and interferon combination treatment.

Discussion

In CD30+ LPDs coexisting with MF, the differential diagnosis mainly include LyP, primary systemic ALCL and LCT of MF [1, 3, 4, 11]. Because there are case reports indicating that CD30+LPDs can occur concomitantly with each other [6, 13, 14, 15, 16, 17] and also because there is no single criteria that helps discriminating among CD30+ LPD, the differential diagnosis among CD30+ LPDs may be accomplished mostly by careful assessment of clinical, histological features and by performing a careful clinical staging [6, 7, 8, 9].

We diagnosed patient 1 as having LyP in the view of the clinical findings and course in combination with distinctive histopathological and immunophenotypic features. Multiple waxing and waning papules less than 2.5 cm in size seen in our patient are characteristic features of LyP. Clinical appearance and course of the disease has been accepted as key features to distinguish between pcALCL and LyP. The clinical picture in LyP resembles pcALCL whereas lesions in LyP tend to be smaller and multiple. Spontaneous regression, sometimes seen in ALCL, is frequently seen in LyP as observed in our patient. Though it is not a rule, the evolving and regressing process in LyP seems to occur in shorter periods [2, 4, 10, 11]. In 20% of patients, LyP may be preceded by, associated with or followed by cutaneous lymphomas including MF,

Hodgkin lymphoma, or ALCL. In a series of 21 patients, MF precedes LyP in 19% of patients [12]. Our patients' longstanding MF was under control with PUVA, so continuing with this therapy was decided and was found sufficient to obtain a good clinical response.

Concurrent patch lesions, positive T cell clonality, presence of large CD30+ T cells in <50% of the infiltrate and poor disease control were the diagnostic features of LCT in our patient 2. LCT of MF has been shown to represent an evolution of the original malignant clone [11] and is defined by the presence of large cells exceeding 25% of the infiltrate throughout or forming microscopic nodules [13]. LCT can occur as a new, solitary nodule within a long-standing classic MF patch or plaque, as abrupt onset of multiple pink scattered papules and/or nodules without spontaneous resolution or within new or enlarging tumors [8]. Time from diagnosis of MF to transformation is found to be 6.5 years [13], in our patient it was approximately four years. Recently, the most important prognostic factors in patients with LCT has been described as advanced age and stage at transformation, CD30 expression, folliculotropic MF, and increased extent of skin lesions [7, 13, 14]. A study showed that LCT reduced 10 year survival rate from 46.9% to 11.2% in transformed patients when compared to non-transformed patients [13]. Our patient had stage IVA disease at the time of transformation, the prognosis of her disease is not known since she was lost to follow up.

Absence of extracutaneous involvement, ALK and EMA negativity, presence of large CD30+ T cells in >75% of the infiltrate and excellent disease prognosis were features that suggest exclusion of primary systemic ALCL and LCT of MF [2, 4, 5] in our patient 3. ALK and EMA are considered among beneficial markers that differentiate pcALCL from primary systemic ALCL, generally being positive in the latter [2, 4, 5]. pcALCL are the second most common group of CTCL after MF accounting for approximately 25% of all CTCL [10]. Predominance (>75%) or large clusters of CD30+ anaplastic blast cells in skin biopsy specimens; clinically, no evidence of LyP; no prior or concurrent LyP, MF or other type of cutaneous lymphoma and no extracutaneous localization at presentation are required diagnostic issues for pcALCL [15]. In fact,

except for the presence of concurrent MF, all of our patients' features were suggestive of pcALCL. The lesions of MF and CD30+ ALCL may show the same clonal rearrangement of TCR γ gene [16,17]. Our patient had either LCT of MF according to a recent review of Kadin et al [11] or he had both MF and pcALCL similar to cases that present the coexistence of MF or LyP with pcALCL [10,11,16,17,18,19]. Patients with pcALCL present with solitary and localized tumors which can be ulcerated [3,11]. Multifocal lesions are seen in about 20% of the patients. Extracutaneous dissemination occurs in 10% of the patients and mainly involves the regional lymph nodes [3]. The disease has a good prognosis with a 95% survival rate at 5 years [11]. Considering the self healing benign nature of cALCL in our patient, he was treated with combination of PUVA, interferon and retinoid and an excellent response was achieved after six months.

As a conclusion it is generally suggested not to use histological and immunohistochemical findings as the only basis for therapeutic decision but to use them in combination with clinical findings. Evaluating CD30+ LPDs is difficult and needs to be individualized. Clinical observation of the natural course of the disease may help establishing accurate diagnosis in most of CD30+ LPDs [8]. Our patients had longstanding MF which was further complicated by the development of CD30+ LPDs with varying prognosis.

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