Published in final edited form as:

Int J Dermatol. 2016 November ; 55(11): 1248–1254. doi:10.1111/ijd.13340.

Long-term followup and management of small/medium-sized CD4+ T cell lymphoma and CD8+ lymphoid proliferation of acral sites: a multi- center experience

Pooja Virmani, M.B.B.S.¹, Sarah Jawed, M.D.¹, Patricia L. Myskowski, M.D.¹, Steven Horwitz, M.D.², Anna Skripnik Lucas, R.N.¹, Alison Moskowitz, M.D.², Melissa Pulitzer, M.D.³, Jasmine Zain, MD⁴, Steven T. Rosen, MD, FACP⁴, and Christiane Querfeld, M.D. Ph.D.^{1,5}

¹Department of Medicine, Dermatology Service, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

²Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

³Department of Pathology, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

⁴Department of Hematology/Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA

⁵Department of Pathology, City of Hope Comprehensive Cancer Center, Duarte, CA

INTRODUCTION

Primary cutaneous CD4+ small- medium pleomorphic T- cell lymphoma (CD4+ SMPTCL) is a low grade cutaneous T cell lymphoma classified as a provisional entity among the peripheral T cell lymphoma, not otherwise specified-category (PTCL, NOS) in the WHO–EORTC classification.¹ It mostly presents as a solitary papule or nodule on face, neck or upper trunk without a history of recurrent patches or plaques typical of mycosis fungoides (MF).^{1,2} Histological hallmark of the lesions is a dense dermal diffuse or nodular infiltrate of small and to lesser extent medium-sized slightly pleomorphic lymphocytes expressing a follicular helper T cell phenotype positive for PD-1, Bcl-6 and CXCL13 without significant epidermotropism/folliculotropism and/or angiocentrism.³

Corresponding Author and Reprint Requests: Christiane Querfeld, M.D., Ph.D, Department of Pathology and Div. of Dermatology, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, Phone 626-634-4436, cquerfeld@coh.org.

Conflict of Interest: None

Author Contributions: Dr(s) Virmani and Querfeld had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Querfeld

Acquisition, analysis, and interpretation of data: All authors

Drafting of the manuscript: Virmani and Querfeld

Critical revision of the manuscript for important intellectual content: All authors

Administrative, technical, or material support: All authors

Study supervision: All authors

Financial Disclosures: None declared.

The recently described entity CD8+ lymphoid proliferation of the ear and acral sites (LP) has comparable clinical presentation and histopathologic features with preferential manifestation at acral sites, most commonly on ear and face. Often considered as a spectrum of the same disease, both entities are characterized by an indolent clinical course and favorable prognosis unlike other provisional entities in the PTCL, NOS-category.^{4,5} In contrast to CD4+ SMPTCL, CD8+ LP does not show a follicular T- helper phenotype suggesting a different cell of origin. PD-1 is often used to differentiate CD8+ LP from CD8+ cases of SMPTCL and reactive infiltrates.⁶ A large case series by Beltraminelli et al., describes 136 patients with CD4+ SMPTCL with clinical follow up of 45 patients suggesting an indolent clinical course.⁷ The authors suggested a new terminology “cutaneous nodular proliferations of pleomorphic T lymphocytes of undetermined significance” for these cases because of the difficulty in unambiguously classifying them into benign or malignant. A more recent case series by James et al., confirmed the favorable prognosis in these patients and has questioned the classification of these cases as “lymphoma”.⁸

There is still a lot of controversy regarding the correct placement of these entities in the classification, the disease outcome and appropriate management. It is imperative to differentiate CD4+ SMPTCL and CD8+ LP from other lymphomas such as PTCL, NOS, MF and aggressive epidermotropic CD8+ T cell lymphoma to avoid aggressive treatment regimens for these indolent entities. We performed a retrospective analysis of twenty- five patients diagnosed with primary cutaneous CD4+ SMPTCL or CD8+ LP at our institutions, in an attempt to better understand the clinical course, prognosis and outcome of these patients.

METHODS

Patient Selection

After approval from the Institutional Review Boards of Memorial Sloan Kettering Cancer Center (MSKCC) and City of Hope, a search by ICD-9 code was conducted to find all patients diagnosed with cutaneous T-cell lymphoma (CTCL) and/or PTCL from January 1981 to August 2015. A total of 1517 patients with T-cell lymphoma involving the skin were found with 97 patients carrying a diagnosis of peripheral T-cell lymphoma. Clinical and histopathologic data review was performed to include twenty- five patients with final diagnosis of CD4+ SMPTCL and CD8+ LP.

Clinicopathologic Evaluation

Demographic, clinical, and treatment data were recorded for each patient including age, gender, race, location, and type of skin lesions, imaging studies done to rule out extra-cutaneous disease, treatment history (type, number, response), duration of follow-up, and outcome. Histopathologic data were recorded based on architectural, cytomorphologic, and immunohistochemical features. The growth pattern of the lymphoid infiltrate including presence or absence of other features such as epidermotropism, folliculotropism/ adnexal involvement, or angiocentrism were noted. Lymphocyte size was classified as primarily small/medium or large-sized. Available immunohistochemical staining was evaluated for T

and B-cell markers (CD3, CD4, CD7, CD8, CD20, CD30, CD79), programmed cell death protein- 1 (PD-1) and proliferation index (Ki-67/MIB-1).

Staging and Response Classification

The patients were staged at initial presentation and last follow-up, according to the International Society for Cutaneous Lymphoma (ISCL)/ Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) proposal for primary cutaneous lymphomas other than MF/SS (Tumor Node Metastases [TNM] classification).⁹ Some of these patients had to be retrospectively staged based on this recent TNM classification. Based on physician's documentation and clinical photos, the patients were stratified according to the extent of skin disease represented by T-(skin) stage: T1 (solitary lesion), T2 (regionalized skin involvement) and T3 (generalized skin involvement). Treatment response and clinical end-points were determined according to the criteria of the ISCL, United States Cutaneous Lymphoma Consortium (USCLC), and the EORTC¹⁰: complete response (CR), complete resolution of cutaneous and extra cutaneous disease; partial response (PR), at least 50% resolution of cutaneous and extra cutaneous disease; stable disease (SD), less than 50% disease resolution; progressive disease (PD), greater than 25% increase in cutaneous disease; development of extra cutaneous (N, M) disease; or death from disease. Disease relapse was defined as disease recurrence after remission with no change in initial stage. Descriptive statistics were used to describe the study population.

RESULTS

Patient Characteristics

Twenty five patients consisting of twenty two patients with CD4+ SMPTCL (Figure IA, B, C; Tables 1 & 2) and three with CD8+ LP (Figure IIA, B) were identified. Most patients were Caucasians (n=21, 84%) with median age of 60 (range 16–91) years at presentation. Male to female ratio was 0.8:1. All patients presented with a single lesion, predominantly located on the head and neck or upper trunk (n=21, 84%). Two patients with CD8+ LP had lesion on the ear while one patient developed a lesion on the lower eyelid. Nine patients had a lesion on the head and/or neck, eight patients had lesion on the upper trunk, four patients presented with a lesion on the upper limb and one with a lesion on the lower limb. All patients had work-up and staging procedures at initial diagnosis and at follow-up for multiple relapses (patient #25) including flow cytometry for T and B cell subsets and imaging studies (PET/CT scans or CT scans) to rule out extracutaneous disease. None of the patients had evidence of extracutaneous disease at presentation or at re-evaluation for cutaneous relapse/s during follow up.

Histopathology

Most common histopathologic changes showed a dense nodular infiltrate of small cells with hyperchromatic nuclei without significant follicular/adnexal involvement. However, epidermotropism was seen in nine cases of CD4+ SMPTCL, with Pautrier-like collections present in one case (Figure ID). Predominant cell population was small-to-medium-sized lymphocytes with surrounding reactive infiltrate consisting of CD8+ T-cells, B-cells

(CD20+), and/or macrophages (CD68). All CD4+ SMPTCL patients expressed a CD4+ dominant phenotype with an elevated CD4:CD8 ratio (>10:1) (Figure IE).

A predominant CD8+ lymphoid infiltrate was seen in cases of CD8+ LP of ear or acral sites (Figure IIE). Partial or complete loss of CD7 expression was seen in most cases. Proliferation (Ki-67/ MIB-1) index (Figure IG, IIF) was low at 5–30% except in one case (40–50%). Staining for CD30 was mostly negative when performed (n=11/18, 61%) and was positive in <5% lymphocytes in 7 evaluated cases (39%). Two out of three patients with CD8+ LP were negative for CD30. PD-1 (Figure IF) was positive in all evaluated cases of CD4+ SMPTCL (n= 9/9), and was not evaluated in cases of CD8+ LP. Molecular analysis revealed a clonal rearrangement of the TCR beta and/or gamma in 21 (84%) patients, negative in three, not performed or inconclusive in one patient each.

Treatment Response and Outcome (Table 1 & 2)

All patients responded to local treatment regimens and did not require systemic treatment regimens. Most patients received excision (n=12, 48%), while others received local radiation (n=7, 28%) or topical/ intralesional steroids (n=6, 25%). All patients achieved complete resolution of their lesion. One patient was lost to follow up after initial consult and did not receive any treatment. Median follow-up time for all patients was 32 months (range, 0–123 months). Five patients had evidence of cutaneous relapse at sites other than the original site. Three patients developed only one relapse, while others had 2 (patient #5) and 4 (patient #25) relapses respectively. Recurrent lesions were treated as previous lesions except in patient #25 who initially received local radiation for the first two times but the subsequent 3 recurrences were excised. No relapses outside the skin were seen. All the patients were alive at the end of follow-up period without evidence of disease (Table 1). There were no differences in responses or outcomes based on treatment modalities that were used.

DISCUSSION

Primary cutaneous CD4+ small/ medium pleomorphic T-cell lymphoma (CD4+ SMPTCL), presents in most cases with a solitary nodule in the absence of recurring patches and plaques typical of MF. All twenty two patients in our cohort presented with a single erythematous nodular lesion, located mostly on the head and neck or upper trunk area. Literature review reveals that patients with CD4+ SMPTCL have an indolent clinical course and excellent response to skin-directed regimens.^{7,8} All patients in our study followed a similar favorable course and achieved complete remission with local radiation, excision or intralesional steroid injections. The reported rates of relapse in these patients are low as also confirmed in our study.⁸ Four of twenty two patients developed cutaneous recurrences which were similarly treated with skin directed regimens. None of the patients had evidence of disease at the time of last follow up visit.

CD8+ lymphoid proliferations (CD8+ LP), considered as phenotypic variant of CD4+ SMPTCL have similar clinical presentation characterized by solitary lesions on the acral sites.^{4,5} All three patients included in our study with CD8+ LP had single erythematous nodular lesion on their face. One patient however subsequently developed another lesion

located on the back. All patients responded well to local radiation and are disease free since definitive treatment.

Histologically, the lesions are characterized by dense infiltrates of small to medium-sized slightly pleomorphic lymphocytes with admixed eosinophils, plasma cells and histiocytes. Epidermotropism may focally be present. All our cases showed dense nodular or diffuse infiltrates of small- medium sized lymphocytes. There were admixed reactive B lymphocytes (CD20+) and macrophages. Epidermotropism was seen in five patients forming Pautrier like collections in one case. Lymphocytes were predominantly CD3+CD4+ except in cases of CD8+ LP which showed a CD3+ CD8+phenotype. PD-1 positivity in all evaluated cases of CD4+ SMPTCL, confirms the findings seen in other studies. Although patients with CD8+ LP in our study were not evaluated for PD-1, previous studies have shown absence of follicular T- cell markers, suggesting different cells of origin in the two entities.⁶ The proliferation index was low (median 15%) in all CD4+ SMPTCL and CD8+LP cases as expected for an indolent disease process.

Clinical and histological distinction from cutaneous T- cell pseudolymphoma (PSL) remains a challenge and the nosological status of CD4+ SMPTCL is still a matter of controversy, because of similar presentation and architecture along with overlapping immunophenotypic profile of follicular T- helper cell markers including PD-1, CXCL-13 and BCL-6.³ The indolent behavior of CD4+ SMPTCL is thought to be at least partly due to expression of programmed death-1 (PD-1), which inhibits T-cell activation and attenuates immune responses to induce tolerance. Demonstration of a T-cell clone, loss of pan-T-cell markers such as CD5 and/or CD7 and presence of causal agents/drugs are currently used as criteria to differentiate the two entities, but other differentiating criteria are lacking.¹¹ Most of our patients presented with a monoclonal rearrangement of the TCR gamma chain receptor favoring neoplastic origin.

There are few studies and case reports that report on the clinical outcome, treatment regimens and prognostic factors in patients with CD4+ SMPTCL^{7,8,12-15} and its variant CD8+ LP of acral sites.^{4,5,16} One of the largest studies by Beltaminelli et al., describes 136 patients with CD4+ SMPTCL and follow up of 45 patients suggesting an indolent clinical course.⁷ Another recent study by James et al., questions the classification of these entities as lymphoma.⁸

Consistent with previous reports, most of our patients with CD4+ SMPTCL and CD8+ LP presented with solitary lesions and received treatment with excision, topical/ intralesional steroids or local radiation achieving durable CR, suggesting that this subtype does not need aggressive therapy. The rates of remission were high irrespective of the treatment modality used. None of the patients developed extracutaneous disease during follow up suggesting that extensive work up such as bone marrow biopsy is not necessary in these patients.

To summarize, the CD4+ SMPTCL /CD8+ LP subgroup usually present with solitary lesions and have indolent clinical course. Typical presentation, classic histopathology, widespread expression of follicular T-helper cell markers, loss of a T-cell antigen and/or positive T-cell clonality are diagnostic features of CD4+ SMPTCL while monomorphous CD8+ infiltrate

with lack of follicular T-helper cell markers is consistent with CD8+ LP.¹⁷ Our data confirmed excellent prognosis in these patients and supports non- aggressive treatment approach.¹⁸ Localized skin-directed regimen is the treatment of choice in these patients.

The present study reiterates the favorable prognosis of patients with CD4+ SMPTCL and CD8+ LP. Relapses occur rarely and do not seem to alter the favorable outcomes. Multifocal disease and aggressive course suggest an alternate diagnosis. PTCL, NOS, MF and/or aggressive epidermotropic CD8+ T cell lymphoma must be ruled out to avoid unnecessary aggressive treatment regimens.

Acknowledgments

Funding Source: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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Abbreviations/Acronyms

CD4+ SMPTCL

CD4+ small/medium-sized pleomorphic T-cell lymphoma

CD8+ SMLP- acral sites

CD8+ small/medium-sized lymphoid proliferations with predilection to acral sites

CR

complete response

CTCL

Cutaneous T-cell lymphoma

EORTC

European Organization for Research and Treatment of Cancer

ISCL

International Society for Cutaneous Lymphoma

MF

Mycosis fungoides

PD

progressive disease

PR

partial response

PTCL, NOS

Peripheral T-cell lymphoma, not otherwise specified

SD

stable disease

TNM

Tumor, Node, Metastases

WHO

World Health Organization

Figure 1.

Clinical photographs of patients with CD4+ SMPTCL presenting with a solitary erythematous nodule (A, B) or papule (C). Histopathology of CD4+ SMPTCL composed of a dense diffuse dermal infiltrate of small slightly pleomorphic T cells (D) [Hematoxylin-eosin x100 magnification] Immunophenotyping results show that the T cells are positive for CD4 (E). PD-1 shows a rosette-like expression pattern (F). Ki67 is positive in 10–15% of cells within the infiltrate (G) [× 200 magnification].

Figure 2.

Clinical photographs of patients with CD8+ LP-ear presenting as solitary, violaceous plaque (A) or small erythematous papule (B) on upper helix. Histopathology of CD8+ LP- ear and acral sites revealed a non-epidermotropic T-cell proliferation infiltrating the entire dermis and subcutis [hematoxylin-eosin, $\times 20$ (C) and $\times 200$ magnification (D)]. The monotonous infiltrate is positive for CD8 (E) [$\times 200$ magnification] with a low dermal Ki67 index of 10% (F) [$\times 200$ magnification].

Table 1

Clinical characteristics of the patients with CD4+ SMPTCL and CD8+ LP- ear.

Characteristics	Category	Total Cases(n=25)	CD4+SMPTCL (n=22)	CD8+LP-ear (n=3)
Age at Diagnosis	Median (range)	60 (16–91)	60.5 (16–91)	45 (45–67)
Sex	Male	11 (44%)	8 (36%)	3 (100%)
	Female	14 (56%)	14 (64%)	0 (0%)
	M:F ratio	0.8:1	0.6:1	NA
Ethnicity	White	21 (84%)	19 (86.5%)	2 (67%)
	Black	2 (8%)	1 (4.5%)	1 (33%)
	Asian/PI	1 (4%)	1 (4.5%)	0 (0%)
	Hispanic	0	0 (0%)	0 (0%)
	Unknown	1 (4%)	1 (4.5%)	0 (0%)
T-stage (at diagnosis)	T1	25 (100%)	22 (100%)	3 (100%)
	T2	0 (0%)	0 (0%)	0 (0%)
	T3	0 (0%)	0 (0%)	0 (0%)
Initial Therapy	Excision	12 (48%)	12 (54.5%)	0 (0%)
	Intralesional steroids	5 (20%)	5 (22.7%)	0 (0%)
	Radiotherapy	7 (28%)	5 (22.7%)	2 (67%)
Result of Initial Therapy	Complete remission	25 (100%)	22 (100%)	3 (100%)
	Partial remission	0 (0%)	0 (0%)	0 (0%)
	Stable Disease/Progression	0 (0%)	0 (0%)	0 (0%)
Disease Status	AWOD	25 (100%)	22 (100%)	3 (100%)
	AWD	0 (0%)	0 (0%)	0 (0%)
	DOD	0 (0%)	0 (0%)	0 (0%)
	DOUD	0 (0%)	0 (0%)	0 (0%)

Abbreviations: AWOD, alive without disease; AWD, alive with disease; DOD, dead of disease; DOUD, dead of unrelated disease

Table 2

Summary of demographic, clinical, treatment and follow up data.

	Age/Sex	Diagnosis	Location	Stage at presentation	Treatment	Relapse/site	Stage at f/u	F/u(months)/Status
1.	45/M	CD8+LP	Ear	T1aN0M0	Radiation/topical steroids	No	T1aN0M0	26/CR
2.	45/M	CD8+LP	Eye	T1aN0M0	No treatment	Yes/ R upper back	T2bN0M0	0/CR
3.	67/M	CD8+LP	Ear	T1aN0M0	Radiation	No	T1aN0M0	45/CR
4.	59/M	CD4+SMPTCL	Nose	T1aN0M0	Intralesional steroid	Yes/ Scalp	T2aN0M0	34/CR
5.	91/M	CD4+SMPTCL	Chin	T1aN0M0	Excision	Yes/ Neck, lower back	T3aN0M0	32/CR
6.	73/M	CD4+SMPTCL	Clavicle	T1aN0M0	Excision	No	T1aN0M0	15/CR
7.	60/F	CD4+SMPTCL	Forearm	T1aN0M0	Radiation	No	T1aN0M0	28/CR
8.	65/F	CD4+SMPTCL	Shoulder	T1aN0M0	Excision	No	T1aN0M0	0/CR
9.	65/F	CD4+SMPTCL	Forearm	T1aN0M0	Radiation	No	T1aN0M0	71/CR
10.	68/F	CD4+SMPTCL	Back	T1aN0M0	Intralesional steroid	No	T1aN0M0	33/CR
11.	64/F	CD4+SMPTCL	Chest	T1aN0M0	Excision	No	T1aN0M0	45/CR
12.	72/M	CD4+SMPTCL	Arm	T1aN0M0	Excision	No	T1aN0M0	45/CR
13.	55/F	CD4+SMPTCL	Forehead	T1aN0M0	Excision	No	T1aN0M0	50/CR
14.	41/F	CD4+SMPTCL	Chest	T1aN0M0	Intralesional steroid	No	T1aN0M0	22/CR
15.	58/F	CD4+SMPTCL	Neck	T1aN0M0	Excision	No	T1aN0M0	62/CR
16.	50/M	CD4+SMPTCL	Cheek	T1aN0M0	Excision	No	T1aN0M0	13/CR
17.	75/F	CD4+SMPTCL	Forearm	T1aN0M0	Radiation	Yes/ Upper arm	T2aN0M0	123/CR
18.	33/F	CD4+SMPTCL	Chest	T1aN0M0	Excision	No	T1aN0M0	49/CR
19.	60/F	CD4+SMPTCL	Nose	T1aN0M0	Radiation	No	T1aN0M0	42/CR
20.	83/F	CD4+SMPTCL	Back	T1aN0M0	Excision	No	T1aN0M0	56/CR
21.	69/M	CD4+SMPTCL	Shoulder	T1aN0M0	Excision	No	T1aN0M0	16/CR
22.	24/F	CD4+SMPTCL	R forehead	T1aN0M0	Intralesional steroid/topical steroids	No	T1aN0M0	10/CR
23.	16/F	CD4+SMPTCL	R medial knee	T1aN0M0	Intralesional steroid	No	T1aN0M0	18/CR

	Age/Sex	Diagnosis	Location	Stage at presentation	Treatment	Relapse/site	Stage at f/u	F/u(months)/ Status
24.	55/M	CD4+SMPTCL	L cheek	T1aN0M0	Excision	No	T1aN0M0	6/CR
25.	61/M	CD4+SMPTCL	Chest	T1aN0M0	Radiation/ Excision	Yes/ Chest x4	T2bN0M0	2/CR

Abbreviations: CR- complete remission, f/u- follow up, TNM- tumor, node, metastasis stage