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BRIEF REPORT

A Retrospective Clinicopathologic Study of Korean Patients with Cutaneous Peripheral T-Cell Lymphoma Not Otherwise Specified at a Single Tertiary Center

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Dear Editor:

Cutaneous peripheral T-cell lymphoma, not otherwise specified (cPTCL-NOS), is a rare disease either originating from skin or having secondary skin involvement[1,2]. In the past, cPTCL-NOS was categorized into the CD30-medium/large pleomorphic T-cell lymphoma group but now is defined as a heterogeneous category of nodal and extranodal neoplasms that cannot be classified into any other specific entities according to the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (2008)[3]. Therefore, it is a diagnosis of exclusion, and the nature of the disease is not yet clear. To better understand and define cPTCL-NOS, we assessed the clinical and histopathological features of the disease and analyzed prognostic factors.

We retrospectively reviewed the medical records, photographs, laboratory data, and histopathology of patients diagnosed with cPTCL-NOS by a hematopathologist at Samsung Medical Center from January 2008 to June 2017. We analyzed 13 patients and 15 biopsy specimens (Table 1, 2). This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2018-01-119). Skin biopsies were performed at two sites in two patients (cases #12 and #13). The prognostic index for T-cell lymphoma (PIT) was calculated from 0 to 4 by age, performance status, lactic dehydrogenase level, and bone marrow (BM) involvement. Treatment outcomes were determined as overall survival (OS) and disease-specific death and prognostic factor comparisons were performed by univariable analysis with a Cox proportional hazards regression model. The male-to-female ratio was 1.17 and the median age at diagnosis was 52 years (range, 23～81 years). Ten patients showed systemic PTCL-NOS with concurrent skin involvement and all patients, except case 7, were nodal lymphoma. Three patients showed primary cPTCL-NOS but case 2 showed BM involvement 6 months after diagnosis. Twelve patients were observed to have skin lesions and one had lymph node (LN) enlargement at first presentation. More than half the patients (61.54%) showed generalized skin involvement, 46.15% presented with nodules, and 38.46% had B symptoms. Only one patient (case #6) was in the high-risk group (PIT＝4) and died 12 months after diagnosis. The histopathological and immunohistochemical features (Table 2) of all biopsy specimens except one (case #10) showed small-to-medium-sized tumor cell infiltrations. Significant atypia was observed in six samples (40.0%). Twelve specimens were positive for CD3 (100%, 12/12) and CD4 (92.3%, 12/13). T-cell receptor (TCR) gene rearrangement showed monoclonality (100%, 6/6). Six samples were positive for CD30 (66.7%, 6/9) and one was associated with Epstein-Barr virus (16.7%, 1/6). The median OS was longer than 17 months after diagnosis. Comparisons of prognostic factors (age, sex, primary vs. secondary skin involvement, morphology, distribution, B symptoms, extranodal and extracutaneous organ involvement, diffuse infiltration, subcutis involvement, significant atypia, epidermal change, epidermotropism) showed no statistical signi-

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Table 1. Demographic and clinical data of patients

No. of case	Sex	Age at diagnosis (yr)	Outcome	Duration of Survival (mo)	Primary cPTCL-NOS†	Extranodal & extracutaneous organ involvement‡	Site of skin involvement	Morpho-logy	Distribu-tion	B Symp-toms	PIT score (0～4)	Initial treatment	Initial response
1*	Female	52	A	98	1	N	Generalized	Patches	Multifocal	N	0	CHOP	CR
2*	Male	39	A	37	1	Y	Generalized	Nodules	Multifocal	N	1	CHOP	CR
3	Male	60	D	13	2	N	Generalized	Patches	Multifocal	N	2	CHOP	CR
4	Female	52	A	30	2	N	Generalized	Tumors	Multifocal	Y	0	CHOP	CR
5	Male	23	A	17	2	N	Generalized	Nodules	Multifocal	N	0	CHOP	CR
6	Male	68	D	12	2	Y	Generalized	Nodules	Multifocal	N	4	CHOP	PD
7	Female	40	D	6	2	Y	Trunk	Nodules	Multifocal	Y	2	CHOP	N/A
8	Male	63	A	38	2	N	Upper extremities	Tumors	Localized	Y	2	CHOP	PR
9	Female	54	D	22	2	N	Lower extremities	Patches	Localized	Y	2	CHOP	PD
10	Male	81	D	6	2	Y	Generalized	Nodules	Multifocal	Y	2	Gemcitabine	PD
11	Female	49	A	106	2	N	Head & neck	Nodules	Single	N	0	ABVD	CR
12*	Female	77	A	7	1	N	Head & neck & lower extremities	Plaques	Multifocal	N	1	Gemcitabine	SD
13	Male	22	A	13	2	N	Generalized	Plaques	Multifocal	N	0	CHOP	CR

PIT: prognostic index for T-cell lymphoma, D: died, A: alive at final follow-up, Y: yes, N: no, CHOP: chemotherapeutic drug combination of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, CR: complete response, PD: progressive disease, N/A: not assessed, PR: partial response, ABVD: chemotherapeutic drug combination of adriamycin, bleomycin, vinblastine, and dacarbazine, SD: stable disease. *These cases are primary cutaneous peripheral T-cell lymphoma, not otherwise specified (cPTCL-NOS). Case 2 showed bone marrow (BM) involvement 6 months after diagnosis, †1: primary cPTCL-NOS, 2: skin involvement of systemic PTCL-NOS, case 7 showed BM, spleen, breast, liver involvements and the others showed skin and lymph node involvements at diagnosis, ‡Case 2: BM, case 6: BM, stomach, colon, case 7: BM, breast, liver, spleen, case 10: muscle, nasopharynx, tonsil.

Table 2. Histopathological features of skin biopsy specimens

No. of specimen	Biopsy site	Epidermal change	Epidermotropism	Pattern of infiltration	Location	Cell character of lymphocytes	Atypia	Other pathologic findings	IHC & molecular study
1*	Lower leg	(−)	(−)	Periappendiceal, perivascular	Whole dermis	Pleomorphic; small to medium > large	Mild	Granulomatous panniculitis, vasculitis	+: CD3, 4, 56 −: CD8, 20 TCR gene (+)
2*	Back	Vacuolization of basal layer	Mild exocytosis	Periappendiceal, perivascular	Whole dermis	Small to medium	Mild	Upper dermal edema	+: CD3, 4, PD-1 −: CD8 TCR gene (+)
3	Cheek	(−)	(−)	Nodular	Whole dermis	Pleomorphic	Significant		+: CD3, 4 −: CD8, 20, 30, 56, EBV *in situ*, TIA-1
4	Shoulder	Epidermal hyperplasia	(+); microabscess folliculotropism	Diffuse	Upper dermis	Small to medium	Mild	Mycosis fungoides-like feature	+: CD3, 4, 30, 45RO, TCRβF1 −: TCR $\gamma\delta$
5	Ankle	(−)	(−)	Nodular	Lower dermis	Small to medium	Mild	Panniculitis, vasculitis	+: CD3, 4, 8, 30 −: CD20, 56 TCR gene (+)
6	Flank	(−)	Mild	Diffuse	Upper dermis	Small to medium	Mild		+: CD3, 4 −: CD20
7	Breast	(−)	(+)	Diffuse & nodular	Whole dermis to subcutis	Pleomorphic	Significant	Panniculitis	+: CD8, EBV *in situ*†, TCRβF1 −: CD4, 56, TCR-CγM1
8	Arm	(−)	(+); microabscess	Diffuse, dense	Whole dermis	Pleomorphic; small to medium > large	Mild		+: CD3, 4, 8, PD-1 −: CD20, 30, 56, EBV *in situ*
9	Lower leg	Parakeratosis, epidermal hyperplasia	(−)	Diffuse, perivascular, periappendiceal	Upper dermis	Pleomorphic; small to medium > large	Significant		+: CD3, 4, 30 −: CD8, 20, 56
10	Buttock	(−)	(−)	Diffuse	Lower dermis to subcutis	Pleomorphic; medium to large > small	Significant	Panniculitis	+: CD3, 4, 5, 7, 20, 30, 79a, PD-1 −: CD8, EBV *in situ*, TIA-1 TCR gene (+)

Table 2. Continued

No. of specimen	Biopsy site	Epidermal change	Epidermotropism	Pattern of infiltration	Location	Cell character of lymphocytes	Atypia	Other pathologic findings	IHC & molecular study
11	Neck	(−)	(−)	Diffuse, perivascular, Periappendiceal	Whole dermis to subcutis; bottom heavy	Pleomorphic; small to medium >large	Significant	Panniculitis, vasculitis	+: CD3, 30 −: CD20, 56, EBV *in situ* TCR gene (+)
12-1*,†	Cheek	(−)	(−)	Patch, periappendiceal	Upper dermis	Pleomorphic; small to medium >large	Significant	Grenz zone, folliculotropism	+: CD3, 4, 20 −: CD8, 30, TCR-C γ M1, TIA-1 TCR gene (+)
12-2*,†	Thigh	Focal hyperkeratosis, Focal vacuolization of basal layer	(+)	Lichenoid infiltration	Upper dermis	Pleomorphic; small to medium >large	Mild	Mycosis fungoides-like feature	+: CD4, TCR β F1 −: CD8, TCR-C γ M1, TIA-1
13-1†	Neck	Ulcer, crust	N/D	Diffuse	Whole dermis to subcutis	Small to medium	Mild		
13-2†	Shoulder	Ulcer, crust	N/D	Diffuse	Whole dermis to subcutis	Small to medium	Mild		+: CD3, 4, 30, TCR β F1, TIA-1 −: CD8, 20, EBV *in situ*

IHC: immunohistochemical features, +: positive, −: negative, TCR gene (+): monoclonal T-cell receptor gene rearrangemen, EBV: Epstein-Barr virus, N/D: not determined. *These cases are primary cutaneous peripheral T-cell lymphoma, not otherwise specified (cPTCL-NOS), †EBV *in situ* was positive in only a few of tumor cells, ‡Patient number 12 and 13 were skin biopsies from two sites.

ficance.

PTCL-NOS is a heterogeneous category of cutaneous T-cell lymphoma that does not fit into other specific categories of lymphoma[4]. In this study, it was difficult to rule out other specific cutaneous lymphomas in several cases. Two specimens (cases #4 and #12) showed epidermotropism, folliculotropism, and lichenoid infiltration mimicking mycosis fungoides (MF) but PTCL-NOS was diagnosed based on the clinical course (LN involvement and B symptoms in case #4) and an additional skin biopsy (case #12). Five specimens (cases #1, #5, #7, #10, #11) had panniculitis or vasculitis features mimicking subcutaneous panniculitis-like T-cell lymphoma (SPTCL) or cutaneous extranodal NK/T cell lymphoma (ENKL) and were finally diagnosed based on immunohistochemical features (case #1) and clinical course (skin involvement of systemic PTCL-NOS in cases #5, #7, #10, #11). Immunohistochemical tests showed that all of the analyzed cases were positive for CD3 and 92.3% were positive for CD4. These immunohistochemical features were similar to those reported in previous studies[1,5]. Cases #10 and #12 were positive for CD20. Case #12 showed CD20 positivity in a minority of the infiltrating cells but not in the tumor cells. However, in case #10, the tumor cells co-expressed B-cell markers (CD20 and CD79a) and T-cell markers (CD3 and CD4) and gene rearrangement analysis also showed both B-cell monoclonality and T-cell monoclonality. This is a very rare case of gray zone tumor, so it is difficult to diagnose it as a specific lymphoma according to the WHO classification. This case could be interpreted as the coexistence of PTCL-NOS and diffuse large B-cell lymphoma.

The median age of patients with PTCL-NOS and cPTCL-NOS has been reported to range from 50 to 70 years[2]. However, case reports have been published on young adults with cPTCL-NOS[6-8]. The median age at diagnosis in this study was 52 years, which was younger than that in a study in a Western country but similar to a previous study in Korea[1,2]. Most patients (76.9%) usually present with multifocal plaques, nodules, or tumors. No differentiation was observed in skin manifestations between primary cPTCL-NOS and secondary skin involvement in this study, compared to the previous study in which primary cPTCL-NOS showed localized cutaneous involvement[1]. The most common site of extranodal and extracutaneous organ involvement was BM (three cases, 23.1%) and three cases involved multi-organ involvement, including BM, the gastrointestinal tract, liver, spleen, and nasopharynx. Five patients in this study died from the disease. The median OS was longer than 17 months and ranged from 6 to 106 months. We analyzed the association between epidermotropism suspicious of MF or subcutis involvement suspicious of SPTCL or ENKL and prognosis but there was no statistically significant prognostic factor. Extranodal organ involvement, except for skin (hazard ratio [HR]=5.849; $p=0.0599$), and significant cellular atypia (HR=7.915; $p=0.0654$) almost reached significant association with poor survival. Although the significance of the prognostic factors could not be determined in this study, the significance of extranodal organ involvement and significant cellular atypia as prognostic factors needs to be verified in more cases in the future. Since the sample size of our study was small and only three patients with primary cPTCL-NOS were analyzed, our statistical power was limited. In addition, the limitations of this study include the retrospective design and referral bias to a tertiary center for advanced stage disease. cPTCL-NOS is very rare and the disease entity has not been established, therefore, more studies on cPTCL-NOS are needed to determine its precise criteria.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Novel Anti-Inflammatory Effects of Brimonidine on *Propionibacterium acnes*-Induced Inflammatory Reaction

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Dear Editor:

Brimonidine is a highly specific $\alpha 2$ adrenergic receptor (AR-$\alpha 2$) agonist with vasoconstrictive activity and has been approved as the treatment of open-angle glaucoma for almost 20 years[1]. Brimonidine has also been approved for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older[2-4]. We clinically experienced that topical brimonidine tartrate treatment of patients with acne and rosacea resulted in alleviation of flushing as well as improvement of acne. Since it is well recognized that inflammatory reaction induced by *Propionibacterium acnes* is critically important in the pathogenesis of acne[5], we speculate that brimonidine has an anti-inflammatory effect in addition to its genuine vasoconstrictive effect.

To verify this idea, we first examined whether AR-$\alpha 2$ was expressed in both the monocytes (THP-1 cells) and keratinocytes. Reverse transcription polymerase chain reaction (RT-PCR) showed that AR-$\alpha 2$ was clearly expressed in both the monocytes and keratinocytes (Fig. 1A), suggesting that brimonidine can directly affect the cells involved in acne-related inflammatory reaction.

We investigated the effects of brimonidine on *P. acnes*-induced inflammatory cytokine secretion in monocytes that are importantly involved in acne pathogenesis. THP-1 cells were pre-treated with brimonidine (30 μM) or dexamethasone (5 μM) for 1 hour, then *P. acnes* (1×10^7 colony-forming unit/ml) were added into the cultures. After 24 hours incubation, culture medium was collected and then cytokines were measured by enzyme-linked immunosorbent assay. Although it's potential effect was not as dramatic as dexamethasone (positive control), brimonidine significantly inhibited *P. acnes*-induced secretion of interleukin (IL)-1β and IL-6 (Fig. 1B). Next, we checked the effects of brimonidine on *P. acnes*-induced messenger RNA

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