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ORIGINAL RESEARCH

Clinicopathological Features and Survival Prognosis of Subcutaneous Panniculitis-Like T-Cell Lymphoma: A Population-Based Study from the SEER Database with Supplementary Single-Center Case Validation

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Background: Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare entity which primarily involved skin and subcutaneous tissue, with clinicopathological features similar to subcutaneous panniculitis. The etiology, clinical features, clinical outcomes and prognostic factors remain largely unknown.

Methods: To gain insight into this distinct entity, we summarized the clinicopathologic features of 8 unpublished SPTCL cases and performed a comprehensive analysis based on SEER (Surveillance, Epidemiology, and End Results) database.

Results: Clinically, subcutaneous nodules with no tenderness appeared firstly in seven patients, and cough in one patient. Hemophagocytic syndrome developed in 3 patients. The median progression-free survival (PFS) for the whole cohort was 43 months, while the median overall survival (OS) has not reached. We identified a cohort of 210 SPTCL patients between 2000 and 2020 based on SEER database. Over half of patients had B symptoms (56.2%) and present at advanced stage (55.6%). The 5-year overall survival (OS) rate was 77.6% for the whole cohort. Multivariate analysis showed that age >60 years and diagnosis before the year 2008 were important prognostic factors of OS for SPTCL.

Conclusion: Our results identified the clinical characteristics, OS and prognostic factors of a large cohort of SPTCL.

Keywords: subcutaneous panniculitis-like T cell lymphoma, T cell lymphoma, SEER database, outcome, prognostic factors

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), a rare cutaneous lymphoma entity constituting <1% of all non-Hodgkin lymphoma, arises from skin-homing cytotoxic αβ-T cells with distinct subcutaneous tropism.[1–4] First characterized in 1991 by Gonzalez et al[5] through seminal description of eight fatal cases featuring rapid HPS progression, this malignancy continues to constitute a diagnostic challenge due to its histopathological overlap with benign panniculitides. According to the differences of TCR phenotype, immunophenotype and prognosis, SPTCL was divided into two subtypes,[1,2] α/β and γ/δ T cell phenotype. This nosological distinction carries profound prognostic weight, with γδ variants demonstrating 3.8-fold higher mortality risk.[6] In 2008, SPTCL was referred to α/β T cell phenotype by EORTC Cutaneous Lymphoma Group, while γ/δ T cell phenotype was a distinct entity.[2]

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The median survival time of SPTCL patients was 12–30 months and the 5-year OS rate was 40%–65%.[1,2,7] Previous studies demonstrated that some clinical features were adverse prognostic factors for SPTCL, including age, high International Prognostic Index (IPI) score and presentation of HPS.[1,6] Gene mutations are frequently detected in some subsets of non-Hodgkin lymphoma (NHL).[8–10] Germline mutation in *HAVCR2*, which encodes T-cell immunoglobulin mucin 3 (TIM3), was the most frequent mutation in SPTCL patients.[1,11] Recent studies have demonstrated that patients with male sex and/or germline HAVCR2 mutations showed an increased risk of developing hemophagocytic lymphohistiocytosis.[10,12–14] Compared with other PTCLs, the prognosis of SPTCL was relatively better in previous studies.[7] However, because of the limited data of SPTCL, as well as the substantial diversity of the reported SPTCLs, knowledge about this lymphoma was largely unknown. The Surveillance, Epidemiology, and End Results (SEER) database is a nationwide, population-based registry in the US that provides high-quality data on cancer incidence, survival, and demographics for epidemiological research. To further explore this rare lymphoma, we report 8 unpublished cases and perform survival analysis of SPTCL based on the SEER database.

Materials and Methods

Patient Cohort

Eight consecutive SPTCL cases diagnosed between January 2009 and December 2023 were retrospectively enrolled from the Second Xiangya Hospital of Central South University. The diagnosis of SPTCL was independently verified by two qualified pathologists based on the diagnostic criteria specified in the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues.[15] Comprehensive clinicodemographic parameters, including age, sex, clinical presentation, primary tumor localization, Ann Arbor staging, therapeutic interventions, and survival outcomes, were systematically abstracted from electronic medical records. This study was performed in accordance with the Declaration of Helsinki and approved by the ethics committees of the Second Xiangya Hospital of Central South University. Informed consent was obtained from all patients and/or their legal guardian(s).

Population-Based Data Acquisition

Epidemiological data were extracted from the Surveillance, Epidemiology, and End Results (SEER) 17-registry database (1975–2020 cohort; SEER*STAT v8.3.6, National Cancer Institute, Bethesda, MD) using ICD-O-3 code 9735/3. Exclusion criteria comprised: 1) secondary malignancies (n=27), 2) undocumented racial background (n=2), 3) missing survival duration (n=5), and 4) age indeterminacy (n=1). The final analytical cohort included 210 histologically confirmed SPTCL cases.

Statistical Methodology

Categorical variables were stratified as follows: 1) Ann Arbor staging (early-stage [I–II] vs advanced-stage [III–IV]), 2) tumor localization (cutaneous/subcutaneous vs extradermal), and 3) treatment era (pre- vs post-2008). Overall survival (OS) was defined from diagnosis to all-cause mortality or last contact. Progression-free survival (PFS) was defined from diagnosis to disease progression, death or last contact. Kaplan–Meier survival estimates with Log rank testing preceded multivariate Cox proportional hazards modeling (entry criteria: $P<0.05$ in univariate analysis). All analyses were conducted using IBM SPSS Statistics 27 (Armonk, NY) and GraphPad Prism 5.0 (La Jolla, CA), with two-tailed $P<0.05$ denoting statistical significance.

Results

Single-Institutional Cohort Analysis

Table 1 summarizes clinicopathological characteristics of the institutional cohort (median age: 23 years; range: 8–61). Advanced-stage disease predominated (stage III=4; IV=4), with extranodal involvement in bone marrow (n=2), adrenal glands (n=1), and lungs (n=1). Hemophagocytic syndrome (HPS) manifested in 37.5% (3/8) of cases. Immunohistochemical results showed that the positivity rate of CD3, CD4, CD7, CD8 were 100% (8/8), 0% (0/8), 87.5% (7/8), 87.5% (7/8). All the patients were negative for CD20 (Table 1). The median ki67 was 60%.

First-line anthracycline-containing regimens induced objective responses in all treated patients (Complete remission (CR)=3; Partial remission (PR)=3). Two patients received autologous hematopoietic Stem cell transplant (HSCT) as consolidation

Table 1 Clinicopathologic Features and Survival Outcome of the Subcutaneous Panniculitis-Like T Cell Lymphoma in Our Study and EORTC 2008 Study

Clinical Factors	This Study	EORTC 2008 Study
Total cases	8	63
Sex: female-to-male ratio	6:2	42:21
Median age at diagnosis, y (range)	23	36 (9–79)
Skin lesions, (%)		
Singular	1	8/63 (13)
Multifocal	7	(78)
Site of involvement, n (%)		
Lower extremities	6/8 (75)	(71)
Trunk	6/8 (75)	(56)
Upper extremities	3/8 (38)	(62)
Face	2/8 (25)	(25)
Ulceration, n (%)	1/8 (13)	4/63 (6)
B symptom	4/8 (50)	
Lupus panniculitis (previous diagnosis), n (%)	1(13)	4/63 (6.3)
Autoimmune disorders, n (%)	1 (13)	12/63 (19)
Elevated lactate dehydrogenase level	4/8 (50)	ND
Hemophagocytic syndrome	3/8 (38)	ND
Immunohistochemical staining		
CD3	8/8 (100)	59/62 (95)
CD4	0/8 (0)	0/61 (0)
CD8	7/8 (87.5)	60/63 (95)
Ki67 (median)	60%	ND
Treatment		
Corticosteroids w/w immunosuppressive drugs	0	24 (38)
CHOP/CHOP-like	6 (75)	31 (49)
Radiotherapy	1 (12.5)	3 (5)
GELOX	1 (12.5)	0
CAT	1 (12.5)	0
Survival status		
Dead	2 (25)	9 (14)
Alive	6 (75)	54 (86)
Follow up (months, median)	32	34 (6–233)

therapy after achieving remission. Salvage therapies (GELOX [gemcitabine/oxaliplatin/L-asparaginase] and CAT [cyclophosphamide/cytarabine/thioguanine]) achieved PR in two refractory cases. Among autologous HSCT recipients (n=2), one experienced disease recrudescence at 15 months post-transplant (survival=25 months), while the other maintained continuous remission through 25-month follow-up. The cohort demonstrated median progression-free survival (PFS) of 43 months (median follow-up=32 months), with median OS remaining undefined.

SEER Database Demographics

Table 2 delineates clinicodemographic profiles of 210 SEER-eligible cases (median age=47 years; IQR=1-85). Notable findings included: 1) female predilection (68.1%; 143/210), with a male-to-female ratio of 1:2.1, 2) early-stage predominance (55.6%; 79/142), and 3) cutaneous/subcutaneous tissue involvement in 95.2% (200/210). B symptoms were present in 56.2% (41/73) of the documented cases. The study population comprised 210 participants, of whom 129 (61.4%) were White, 37 (17.6%) were Black, and 44 (21.0%) were of other races.

Table 2 Clinical Features of Subcutaneous Panniculitis-Like T Cell Lymphoma

Clinical Factors	Number
Age (years) (n=210)	
≤60	150
>60	60
Race (n=210)	
White	129
Black	37
Other	44
Sex (n=210)	
Male	67
Female	143
Primary site (n=210)	
Skin or subcutaneous	200
Lymph nodes	8
Parotid grand	1
Orbit	1
Stage (n=210)	
I	60
II	19
III	9
IV	54
Unknown	68
B symptoms (n=73)	
Yes	41
No	32
Survival status (n=210)	
Dead	55
Alive	155

Survival Outcomes and Prognostic Determinants

The 5-year OS rate reached 77.6% (median follow-up: 63 months; deaths: 55/210) (Figure 1A). Multivariate Cox regression identified two independent mortality predictors: 1) age >60 years (HR=3.12; 95% CI=1.85–5.26; P<0.001) and 2) pre-2008 diagnosis (HR=4.17; 95% CI=2.27–7.69; P<0.001) (Table 3). Kaplan-Meier analysis showed that the overall survival of patients with age >60 was worse than those with age ≤60 (5-year OS=24.0% vs 87.0%; P=0.03) (Figure 1B). Race was an important prognostic factor affecting survival outcome, with a significant better 5-year OS in white race than other races (5-year OS=94.5% vs 75.0%; P=0.03) (Figure 1C). Post-2008 cases demonstrated superior outcomes (5-year OS=84.3% vs 68.9%; P=0.002) than pre-2008 cases (Figure 1D).

Discussion

Since its initial characterization in 1991, subcutaneous panniculitis-like T-cell lymphoma (SPTCL) has remained an enigma of cutaneous lymphomas, with fewer than 500 cases documented globally.[12,14,16,17] Currently, the etiology, clinicopathological features, survival outcomes and prognostic factors of SPTCL remain largely unknown. Our analysis aimed to evaluate the clinical features, survival outcomes and prognostic factors of SPTCL patients based on population-based study using the SEER database.

The clinical manifestations of SPTCL are complex, and the misdiagnosis rate is high.[18] Common clinical manifestation included multiple subcutaneous nodules/plaques in the limbs or trunks.[1,2,4,19] Skin and subcutaneous tissue are

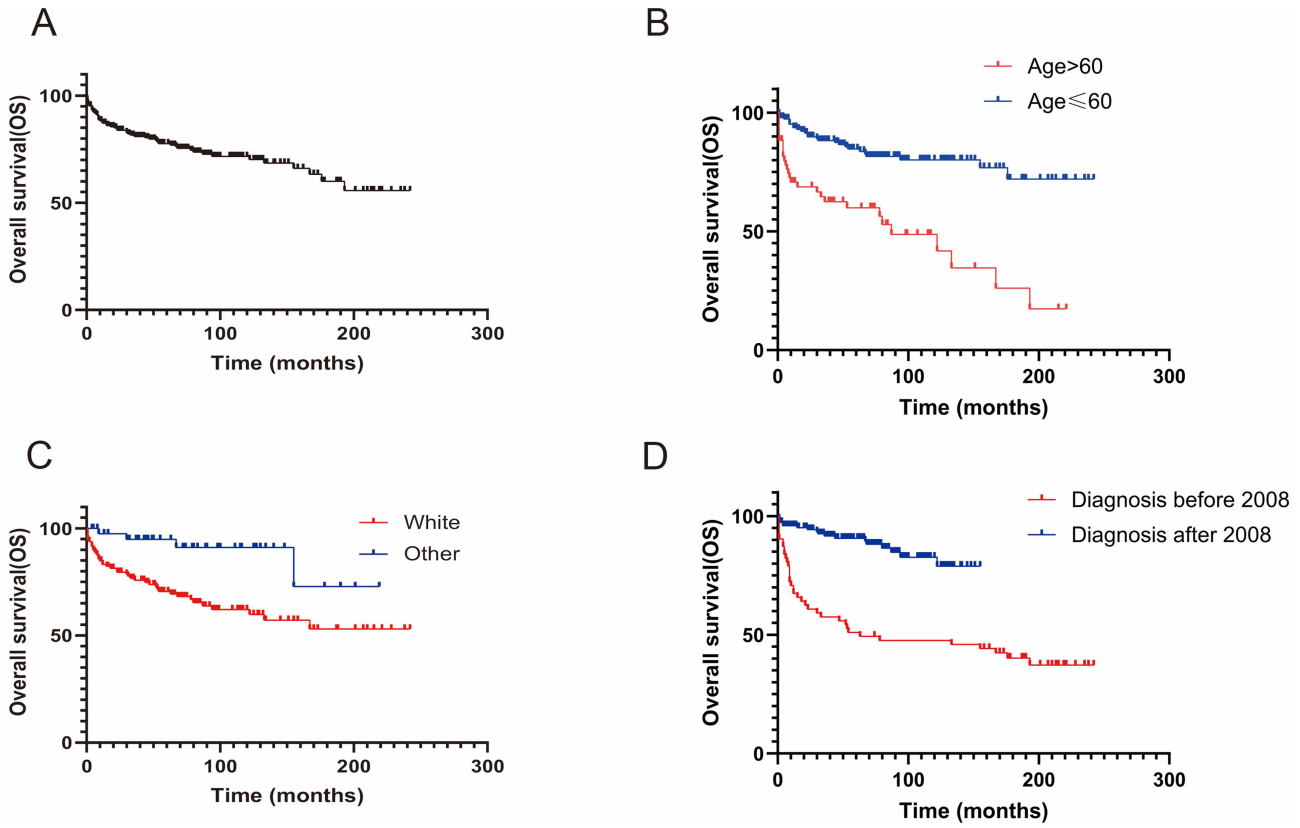

Figure 1 Survival outcomes of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) patients from the Surveillance, Epidemiology, and End Results (SEER) database. (**A**) Kaplan-Meier curve depicting the overall survival (OS) of the entire SPTCL patient cohort included in the SEER database. (**B**) Stratified overall survival analysis by age group, patients with age > 60 was worse than those with age ≤ 60 (5-year OS=24.0% vs 87.0%; P=0.03). (**C**) Stratified overall survival analysis by race, the 5-year OS in white was better than other races (5-year OS=94.5% vs 75.0%, P=0.03). (**D**) Stratified overall survival analysis by diagnosis date, the post-2008 cases demonstrating superior outcomes (5-year OS=84.3% vs 68.9%; P=0.002) than pre-2008 cases.

frequently involved, while other location was rarely invaded.[1,17,20] Other primary locations were also observed in our study, including lymph nodes, orbit and parotoid gland, and the prognosis of these cases were similar to those derived from subcutaneous tissue. In addition, HPS was observed in a small proportion of SPTCL, which was proved to be an adverse predictor for SPTCL.[12]

Table 3 Univariate and Multivariate Analysis Was Performed to Analyze the Prognostic Factors of OS in SPTCL

Clinical Factor	**Overall Survival**			
	Univariate		**Multivariate**	
	P	**HR (95% CI)**	***P***	**HR (95% CI)**
Age (≥ 60y vs < 60)	< 0.001	0.26 (0.15–0.44)	**< 0.001**	**0.32 (0.18–0.59)**
Gender (M vs F)	0.31	0.75 (0.44–1.30)		
B symptom (no vs yes)	0.10	3.90 (0.79–19.32)		
Primary tumor site (skin/subcutaneous tissue vs other)	0.96	1.03 (0.32–3.30)		
Stage (I–II vs III–IV)	0.27	1.38 (0.78–2.43)		
Diagnosis date	<0.001	0.22 (0.13–0.40)	**<0.001**	**0.24 (0.13–0.44)**
Race				
White vs Black	0.20	0.61 (0.29–1.29)		
White vs Other	0.006	0.24 (0.09–0.66)	0.16	0.47 (0.16–1.36)

Note: P values in bold are significant at P < 0.05.

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CHOP or other anthracycline-based therapy was the most common chemotherapy regimen.[2,7,17] Other treatment strategies include systemic corticosteroids with or without other agents, bexarotene, cyclosporin, autologous stem cell transplantation, localized radiotherapy with chemotherapy,[1,17] and recently chidamide,[21] mycophenolate mofetil,[22] ruxolitinib,[23] JAK inhibitors.[24] As SPTCL is a rare entity, the ideal treatment of this entity has not been identified. A systematic review summarized 63 reported cases of SPTCL and showed that the 2-year OS was 91.0%, with a median follow-up time of around 2 years.[1] The estimated 5-year OS in our study (77.6%) appears to be higher than some previously reported rates (40–65%),[1] though differences in study populations, treatment advancements, and follow-up duration should be considered.

Several literatures reported the application of hematopoietic stem cell transplantation (HSCT) in SPTCL.[1,25–28] Previous study analyzed the clinical outcomes of HSCT for 9 panniculitic T-cell lymphomas (TCLs) patients and showed that four of the seven patients are alive at 7.8, 6.9, 6.2, and 0.25 years after allogeneic HSCT. Two patients who received autologous HSCT are still alive at a median follow-up of 1.91 years.[26] A recent study summarized 16 published cases of subcutaneous panniculitis-like T-cell lymphoma associated with HPS who received HSCT, including 5 autologous HSCTs and 11 allogeneic HSCT, and found that all the above 16 patients responded well and survived.[1] More data from larger cohorts is needed to determine its efficacy as a treatment strategy for high-risk SPTCL.

Previous studies demonstrated that age >60, diagnosis before the year 2008 and HPS were important prognostic factors for SPTCL.[1,7,29] Our results showed that age >60 and diagnosis before the year 2008 were predictors for worse prognosis in SPTCL. The OS among patients diagnosed after 2008 was improved and the reason is that SPTCL was referred to TCR α/β phenotype in 2008, which excluded γ/δ phenotype.[2] As some clinical information was lost, overall assessment of the prognostic factors could not be performed. In addition, the application of novel therapeutic agents has yielded superior clinical efficacy in SPTCL.[1,30] The Thai Lymphoma Study Group reported that the cyclosporin (CSA)-based regimen achieved better clinical efficacy than chemotherapy (5-year OS 98% vs 87%, p=0.19) in SPTCL. Romidepsin, histone deacetylase inhibitor and mycophenolate mofetil have been demonstrated to be effective in SPTCL in case reports.[22,25,31] Owing to the inherent limitation of a relatively small sample size, international multicenter collaborative studies are required to comprehensively explore the prognostic risk factors.

Race emerged as an independent prognostic factor for subcutaneous panniculitis-like T-cell lymphoma (SPTCL). We synthesized prognostic data for SPTCL across distinct geographic regions and observed statistically significant disparities in survival outcomes (Table 4). Specifically, White patients exhibited superior overall survival (OS) compared with their counterparts of other racial backgrounds. Such discrepancies are likely multifactorial, encompassing biological, socio-economic, and healthcare access-related determinants. Notably, numerous studies have identified the *HAVCR2* Y82C mutation as the most prevalent genetic alteration in SPTCL,[10,12,14] a variant that correlates with younger age at diagnosis and an increased risk of hemophagocytic lymphohistiocytosis (HLH) development.[32] In addition to biological drivers, socioeconomic inequities may further modulate clinical outcomes in this patient population. Thus, large-scale, international multicenter studies are warranted to validate and further elucidate the underlying mechanisms of these racial disparities in OS.

Table 4 Survival Outcome of SPTCL Around Different Regions

	This Study (SEER Database)	**Thai Lymphoma Study[30]**	**EORTC Study[2]**	**Korean Study[32]**	**Chinese Study[27]**
Cases (n)	210	14	62	53	32
5-year PFS	N/A	N/A	N/A	N/A	29.2%
5-year OS	77.6% White: 94.5% Others: 75.0%	92%	82%	39%	74.7%
CR rate	N/A	72%	61.9%	N/A	32.1%

There are several limitations of the data from SEER database. Firstly, lack of information on specific chemotherapy regimen may lead to bias of results. Furthermore, the pathology of SPTCL is not centrally reviewed by hematopathologists, which derived from the pathological reports. Clinical data such as pretreatment LDH, IPI and treatment response, which were adverse prognostic factors for lymphoma,[8,33,34] were lost in our study. Moreover, some prognostic information was not recorded by SEER, such as lymphoma recurrence and progression. However, we could make observations and conclusions from large-volume analysis and provide evidence for clinical decision-making.

To sum up, SPTCL is an inert T-cell lymphoma originating from subcutaneous tissue. The skin lesions are mainly dark red, inelastic subcutaneous nodules or plaques, which tend to occur in limbs and trunk. At present, there is still no standard treatment scheme for SPTCL. The commonly used chemotherapy scheme is CHOP scheme, but the efficacy is uncertain; Chemotherapy regimen containing gemcitabine and asparaginase may have better efficacy; Hematopoietic stem cell transplantation can achieve satisfactory results in patients with recurrence, refractory and HPS, but its efficacy needs to be further confirmed in more prospective and multicenter studies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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