

Clinicopathological Characteristics of Subcutaneous Panniculitis-like T-cell Lymphoma An article review

Hermin Aminah Usman¹, Fadhilat Sabila Rahmi², Rio Bayu Nugroho², Eva Krishna Suteja³

Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia¹

Department of Medical Undergraduate, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia²

Department of Dermatology and Venerology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia³

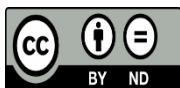


Keywords:

Clinicopathology
Characteristic, Subcutaneous
Panniculitis-Like T-Cell
Lymphoma.

ABSTRACT

Subcutaneous Panniculitis-like T-cell lymphoma (SPTCL) is a rare malignancy and difficult to diagnose. The clinical and histopathological characteristics of SPTCL overlap with infectious, autoimmune, and aggressive malignancies so that they often miss provisional diagnosis and misdiagnosis. A structured scientific study of the clinicopathological characteristics is needed to increase the clinician's knowledge as consideration for diagnosis. This review aimed to describe the clinicopathological characteristic of patients with SPTCL. This study used a literature review approach which was searched using Pubmed, EBSCO, and Science Direct with the keyword 'Subcutaneous Panniculitis-like T-cell Lymphoma. The articles were selected based on the inclusion and exclusion criteria set by the researcher. 50 cases obtained from this study indicate that cases of SPTCL occur at a median age of 28.5 years and are dominated by women. Clinicopathological characteristics studies are very helpful in the diagnosis of SPTCL. The clinical characteristics of SPTCL lesions vary, namely in the form of plaque, erythema edema, and mostly nodules on the trunk, extremities, or head. The most common lesion is a predilection nodule on the trunk. Systemic symptoms most commonly include fever and extracutaneous involvement in the form of lymphadenopathy, hepatosplenomegaly, bone marrow involvement, and hemophagocytic syndrome. The histopathological characteristics of adipocyte rimming, karyorrhexis, and fat necrosis with small-medium sized atypical T-cell infiltration and also a lobular pattern. The immunohistochemistry characteristics of SPTCL are CD3+, CD8+, CD56-, TIA-1+, Beta-F1+, Granzyme B+, and Ki-67 >30%. as well as the CD3+, CD8+, CD56-, Beta F1+, Granzyme B+ and Ki-67 levels >30%.



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1. INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare primary skin extranodal lymphoma that originates from T cells and natural killer (NK) cells. This was first described by when 8 cases of T-cell

lymphoma were reported, mainly located in adipose tissue without lymph node involvement [1], [2]. The incidence of SPTCL is less than 1% of all cutaneous lymphomas, and is the most common among young adults, with an M:F ratio of 1:2. The median age at diagnosis of SPTCL is 36 years (9-79 years), and 19% of patients are 20 years old. The incidence of SPTCL in Asian countries is 2.3% to 3%. The incidence of SPTCL in Japan from the national study of cutaneous lymphoma from 2007 to 2011 was 2.3% of all cutaneous lymphoma cases. In Malaysia, only 5 cases were reported from 2001 to 2004 [1- 3]. SPTCL is classified based on T cell receptor phenotype and immunohistochemistry characteristics. The first is the α/β T cell receptor, which is characterised by a protracted indolent pathway, usually, CD4-, CD8+ and CD56-. The second type is γ/δ T cell receptors, usually CD4-, CD8- and CD56+. According to the 2005 WHO-EORTC classification of primary cutaneous lymphoma, the α/β T cell receptor subtype is described as SPTCL, and the γ/δ T cell receptor is described as primary cutaneous peripheral T cell lymphoma, which is A rare subtype [4], [5]. The pathogenesis of SPTCL is not fully understood. Recent studies have shown that lymphoma cells express certain chemokine receptors and are related to the pathology and clinical behaviour of cutaneous lymphoma. In 2017, A case of SPTCL was reported, and immunohistochemical analysis of the expression of CCR4, CCR5, and CXCR3 was presented. The mechanism of tumour cell migration and proliferation in the subcutaneous tissue of SPTCL is not fully understood. [6] demonstrated that the regulation of IDO-1 and the upregulation of IFNG, CXCR3, and CCL5 are characteristic of SPTCL lesions. IDO-1 expression induced by IFNG contributes to the establishment of the microenvironment and provides favourable immune suppression for malignant T cells [7].

The main challenge is to distinguish this lesion from benign panniculitis. The clinical and histological characteristics of SPTCL may overlap with Lupus Erythematosus Panniculitis (LEP), leading to misdiagnosis. LEP and SPTCL are clinically indistinguishable. This case highlights the importance of a high level of suspicion and experience in the diagnosis of rare malignant neoplasms. Early diagnosis may help determine an appropriate treatment, which ultimately reduces morbidity and mortality in patients with SPTCL [8- 15]. The diagnosis of SPTCL may require clinicopathological correlation and immunohistochemistry confirmation especially to exclude α/β T-cell lymphomas of more aggressive nature and poorer prognosis, such as progressive mycosis fungoides and entities belonging to the Primary Cutaneous Peripheral T-cell lymphoma [15]. The diagnosis of SPTCL is at the first doctor's visit, especially if the symptoms are similar to other more common conditions such as panniculitis, eczema, dermatitis, psoriasis, cellulitis, and other soft tissue infections. It is difficult. The clinical and systemic symptoms of SPTCL are non-specific and include fever, chills, and weight loss. The course of the disease is slow with an indolent nature, similar to the process of inflammation and infection, and may delay diagnosis. More serious conditions associated with SPTCL may include hepatosplenomegaly, mucosal ulcers, serous exudates, HPS, and pancytopenia. SPTCL was a rare malignant tumour, but delayed diagnosis may exacerbate symptoms and increase mortality and morbidity from the disease [12- 14].

The clinical manifestations of SPTCL are usually skin colour or erythema subcutaneous nodules, most commonly on the limbs and trunk, but may also affect the face and neck. According to reports, the duration of skin lesions before a diagnosis is approximately 7 months, and most patients report multiple lesions or generalised skin involvement. More than 50% of patients may have systemic symptoms. Histologically, SPTCL is characterised by primary subcutaneous infiltration of the small, medium, or large-shaped α/β T cells and macrophages, similar to panniculitis, and occasionally complicated by hemophagocytic syndrome (HPS) [8], [9]. Immunohistochemistry in SPTCL is the first step in determining whether the dominant cell population is T cells or B cells. CD3 is the most consistent positive marker for T cells, while CD20 is the true marker for B cells. The T cell type, CD4 and/or CD8, characterise the disease as an inflammatory process, malignancy, or a combination thereof [5], [32].

Based on the consideration that SPTCL was a rare malignancy, the pathogenesis was unknown, the diagnosis was difficult, the course of the disease was slow may cause a delay in the diagnosis due to the clinical symptoms were not specific and the characteristics overlap with other diseases so that it often escapes provisional diagnosis and was misdiagnosed with benign disease or malignant type. It is important to raise awareness and identify clinicopathological characteristics so that clinicians can consider the diagnosis based on clinicopathological characteristics and start treatment immediately for a better prognosis. The prognosis of SPTCL is usually good and the disease course is slow, but the aggressive course of HPS patients is associated with high mortality. The five-year survival rate is described as over 80%. According to reports, HPS occurs in approximately 20% of patients and is associated with a poor prognosis, with a 5-year survival rate of 46% [34- 36]. Until now, there has been no thorough research on SPTCL so that this article may help to give information about the clinicopathological characteristics of SPTCL. In a previously published study conducted by, they reviewed the clinical characteristics, differential diagnosis, and treatment outcomes of 16 cases of Japanese patients with SPTCL published in Pubmed. Reviewed the clinicopathology, immunophenotypic and molecular analysis of 16 cases of SPTCL diagnosed from 2007 to 2016 at Ramathibodi Hospital, Thailand. The aim of this review provides information about the clinical, histopathological, and immunohistochemistry characteristics of patients with SPTCL from case reports published from 2016 to 2021.

2. Research Methods

2.1 Search Strategy

This research design is a qualitative study with a literature study approach. Researchers carried out an electronic search in Medline (PubMed interface), EBSCO, and ScienceDirect, using the keyword “Subcutaneous Panniculitis-like T-cell Lymphoma”, between 2015 to 2021, without date restrictions. The reference list of all identified documents was scrutinised with the aim of identifying additional potentially eligible studies.

2.2 Selection Criteria

All literature was assessed for eligibility by authors. All authors assessed the title, abstract, and full text of each article identified in the search. Studies were deemed eligible for inclusion criteria and exclusion criteria. The inclusion criteria of this study are articles containing the same keywords as the research topic such as clinical characteristics and histopathological features, the article is a full paper, the articles are published in 2016 to 2021, the article must be a case report, and the article must be the English language. An exclusions criterion of this study is article duplicated, mismatch with title and abstract in article. All articles are published in all countries worldwide. When data on clinicopathological characteristics were identified, the article was translated into English to enable data collection. Any disagreements arising during the selection assessment were resolved by discussion.

2.3 Data Extraction

Data were extracted from the included case report of SPTCL studies by authors. The data extracted included: authors, research design, year of publications, the origin of country, clinical characteristics including; age, gender, type of skin lesion (nodule/papule, erythema, plaque, or edema), extracutaneous involvement (such as lymph node, hepatosplenomegaly, bone marrow, and hemophagocytic syndrome), systemic symptoms, histopathological features such as infiltration patterns (lobular or septal), type of T-cell (small/moderate/large), a layer of infiltration (epidermal or dermal), rimming adipocytes, karyorrhexis, fat necrosis, and immunohistochemical CD3+, CD4-, CD8+, CD20-, CD30-, CD56-, TIA-1, β -F1, granzyme- β , level Ki-67. When unavailable data such in literature, we will write not available on data collection.

3. Result and Discussion

3.1 Study selection and characteristics of included studies

A flow of studies through the analysis is shown in Figure 1. After the repeated screening, 120 articles were initially identified, 71 of which were excluded because they were duplicate articles (n = 20), non-English articles, or articles that did not match the abstract (n = 10), and the article was not the full text (n = 21), not relevant with our topic (n = 20). Therefore, the pooled analysis finally included the 49 studies in Figure 1 of the qualitative study. Based on clinical, histopathological, and immunohistochemical findings, there were a total of 50 confirmed subcutaneous panniculitis-like T-cell lymphoma patients.

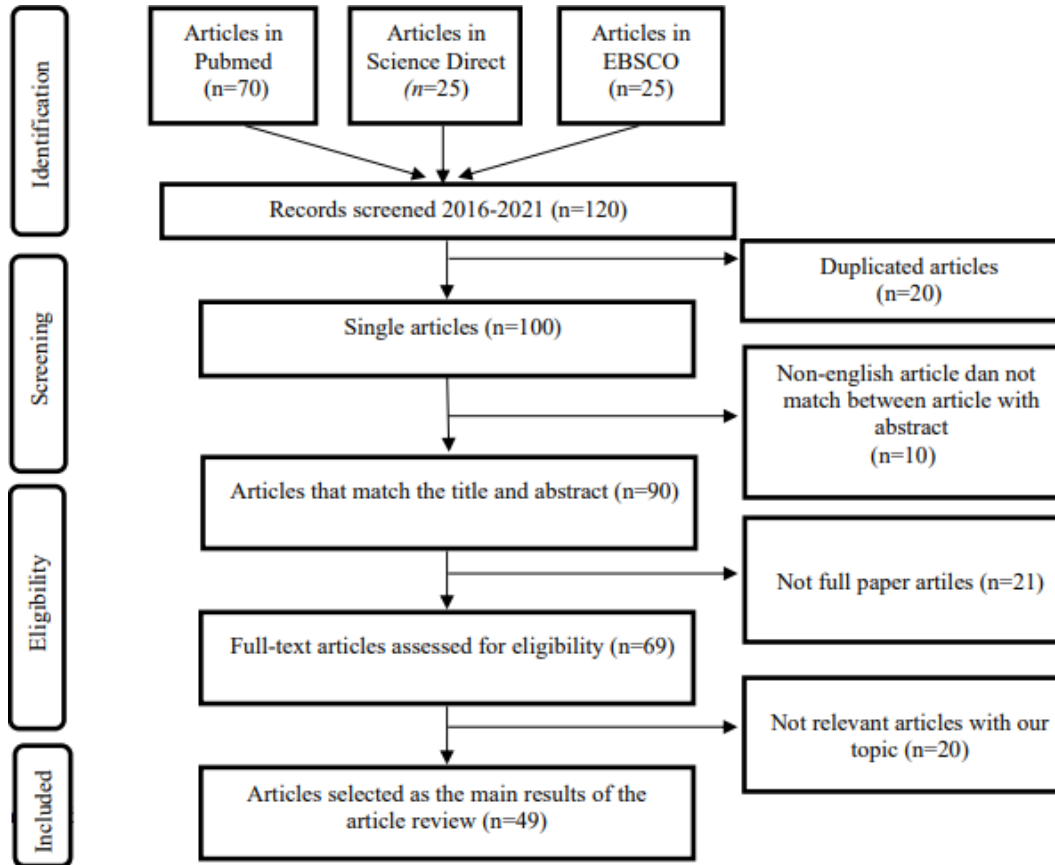


Figure 1. Study Flow Chart

3.2 Clinical Characteristics of SPTCL

Table 1. Clinical Characteristics of SPTCL

Clinical Characteristics of SPTCL	
Gender, rasio	
Female: Male	27:23
Onset of Age Diagnose, n (%)	
0-10	4 (8)
11-20	11 (22)
21-30	11 (22)
31-40	8 (16)
41-50	5 (10)
51-60	6 (12)

Clinical Characteristics of SPTCL	
61-70	3 (6)
>70	2 (4)
Type of Skin Lesion, n (%)	
Nodule/Papule	23/44 (53,3)
Erythematous	17/44 (38,6)
Plaque	9/44 (20,5)
Edema	14//44 (31,8)
Location of Skin Lesion, n (%)	
Head and Neck	17/44 (38,6)
Trunk	26/44 (59,1)
Upper Extremity	20/44 (45,5)
Lower Extremity	18/44 (40,9)
Extracutaneous Involvement, n (%)	
Lymph node	10/39 (25,6)
Hepatosplenomegaly	7/11(63,6)
Bone Marrow	7/11 (63,6)
Hemophagocytic Syndrome	7/8 (87,5)
Systemic Symptoms, n (%)	
Present	30/44 (68,2)
Fever	29/30 (96,7)
Fatigue	7/30 (23,3)
Weight loss	5/30 (16,7)

Based on the literature that has been collected during the data collection, 50 cases were obtained from 49 literature in the form of case reports of patients diagnosed with SPTCL. Table 1. and 2. describe the clinical characteristics of SPTCL cases from several countries, namely, India (n=12), United States (n=10), Japan (n=9), China (n=9), Germany (n=3), North Africa (n=1), Australia (n=1), Canada (n=1) Philippines (n=1), Malaysia (n=1), Singapore (n=1) and Taiwan (n=1).

Among the 50 reported cases of SPTCL, the patients were relatively young adults. The median age at diagnosis was 28.5 years, and the age range was 3 months to 82 years, mainly female, and the male to female ratio was 23:27. The diagnosis age is mostly from 10 to 20 years old and up to 14 cases, 21 to 30 to 10 cases, 31 to 40 to 7 cases, and >40 years old is 16 cases. It takes about two weeks to four years to be diagnosed before the duration of the skin lesions, with an average of 16 months. Twenty-eight out of 50 patients developed nodular lesions (56%), erythema (42%), edema (28%), or plaques of different diameters (18%), most likely to occur on the trunk. (58%) followed by upper limbs (42%), lower limbs (42%), and very little head and neck (36%). One patient reported ulcers [37], and another patient had secondary lipoatrophy on the face [38]. Two patients from Germany and Japan reported presenting with fever, fatigue, and night sweats without skin lesions and were diagnosed by random skin biopsy [39], [40].

Among 39 cases of reported lymph node involvement 10 cases (25.6%) confirmed as many as 6 cases in the axilla, 4 cases in the groin, and multiple peripheral lymphadenopathies in the neck, submental, submandibular, and deep parts of the neck. 1 case each, 1 case of anterior mediastinal central lymph nodes. Hepatosplenomegaly and bone marrow involvement were found in 7 of 11 reported cases (63.6%). Seven of the eight reported cases developed hemophagocytic syndrome, which is characterised by fever. Of the 7

SPTCL cases with HPS, 6 occurred in patients under 35 years of age. Of the 50 reported cases, 30 (68.2%) developed systemic symptoms (B symptoms), among which 29 cases (96.7%) had a fever as the most common symptom, followed by fatigue (23.3%) and weight loss (16.7%). Two patients from China and India reported nervous system involvement in the form of numbness, paresis, and visual impairment [41], [42]. Before SPTCL was diagnosed, 5 patients were diagnosed with an infection, 4 patients were diagnosed with cellulitis, 7 patients were diagnosed with lupus panniculitis, angioedema, and 1 patient was bitten by accident. The mucous membrane is left with scars.

3.3 Histopathological Characteristics of SPTCL

Table 2. Histopathological Characteristics of SPTCL

Histopathological Characteristics of SPTCL	
Layer of Infiltration, n (%)	
Epidermal	0
Dermal	8/11 (72.7)
Mixed	3/11 (27.3)
Infiltration Pattern, n (%)	
Lobular	23/24 (95.8)
Septal	0
Mixed	1/24 (4.2)
Type of T-cell, n (%)	
Small	0
Medium	6/27 (22.2)
Large	0
Small-Medium	13/27 (48.1)
Medium-Large	2/27 (7.4)
Small-Medium-Large	5/27 (18.5)
Rimming of Adipocyte, n (%)	40/40 (100)
Karyorrhexis, n (%)	10/10 (100)
Fat Necrosis, (%)	9/9 (100)

The histopathological characteristics of SPTCL are summarised in Tables 2 and 4. Based on the literature obtained, the histopathological characteristics of SPTCL are dominated by atypical subcutaneous lymphocytic infiltration with variable T cell cytology. In the 27 cases reported, most were small-medium (48.1%), only moderate (22.2%), and varied in size small-large (18.5%) almost all of the 24 cases reported had a lobular infiltration pattern (95.8%). Only one patient had a mixed lobular-septal panniculitis pattern (4.2%). Atypical minimal cell infiltration extension was reported in eleven cases, eight cases in the dermal layer (72.7%) some peri-adnexal or perivascular with mucin deposition, and three cases with extension mixed (epidermal-dermal). The appearance rimming of adipocytes by atypical lymphocytes was a common feature found in the 40 cases reported. Karyorrhexis and fat necrosis of varying degrees were found in all reported cases. Multinucleated giant cells are rare and histiocytes are observed in some cases. One case showed panniculitis granuloma appearance and one European case had two different histopathological patterns on three biopsies, twice LEP on scalp biopsy with periadnexal lymphocytic infiltration, and one SPTCL on upper extremity biopsy. indicates the presence of LEP and SPTCL simultaneously [43], [44].

3.4 Immunohistochemistry Characteristics of SPTCL

Table 3. Immunohistochemistry Characteristics of SPTCL

Immunohistochemistry Characteristics, n (%)	
CD3+	38/38 (100)
CD4-	27/32 (84,4)
CD8+	39/39 (100)
CD20-	19/21 (90,5)
CD30-	9/10 (90)
CD56-	23/23 (100)
TIA-1	15/16 (93,8)
Beta F-1	14/14 (100)
Granzyme B	15/15 (100)
Level Ki-67	
<30%	0
30-100%	9/9 (100)

The characteristic immunohistochemistry findings in SPTCL are summarised in tables 3 and 6. Based on 50 cases that reported immunohistochemistry examination of SPTCL patients, 38 cases were T-cell positive on CD3 examination (100%). CD3 is the most specific marker for the identification of T-cells filling the lymphocytic area of the infiltrate and conspicuous on the rimming appearance of adipocytes. 27 of the 32 reported cases were CD4 negative (84.4%). There are 5 cases with positive CD4. CD4 staining for identification of T-helper cells and macrophages was generally negative in SPTCL but according to the findings of CD4 was found to be positive in 42% of SPTCL cases [16]. 39 cases of T-cells were positive on the CD8 examination (100%). CD8 markers stain cytotoxic and T-cell populations rimming adipocytes. CD20 is a marker commonly used for B-cell identification, in this study 19 out of 21 cases were reported as negative (90.5%). One CD20 positive case had a granulomatous-panniculitis biopsy. CD30 positive was found in only one in ten cases reported. Cases with CD30 expression had ulcerated lesions with a diagnosis onset duration of 4 months. Most cases had a negative CD30 result (90%). All cases with a CD56 examination were reported as negative (100%). Negative CD56 indicates that there is no atypical proliferation of NK cells, positive NK cell markers will be detected in the γ/δ phenotype. TIA-1 is a marker associated with activated cytotoxic T cells. In this study, 15 of the 16 reported cases had positive TIA-1 results (93.8%). 14 cases were found to be positively expressed on the Beta-F1 examination which is a marker for confirming the α/β T-cell phenotype or SPTCL (100%). 15 cases of T-cells were positive on Granzyme B examination (100%), which is an enzyme that plays a role in the work of cytotoxic T-cells by inducing apoptosis of target cells. Ki-67 levels were highly expressed (>30%) in nine reported cases (100%). Ki-67 protein expression associated with cell proliferation was detected in all active phases of the cell cycle (G(1), S, G(2), and mitosis) [32], [43], [45-47].

Table 4. Result of Findings Clinical Characteristics of SPTCL

Year	Research Design	Country	Age/ Gender	Nodule / Papule	Skin Lesion			Location of Lesion				Extracutaneous Involvement			
					Erythema	Plaquer	Edema	HN	T	UE	LE	LN	HSM	B M	HP S
2019	Case Report	China	64/F	+	-	-	-	-	+	+	-	Axillary	N/A	N/A	N/A

Year	Research Design	Country	Age/ Gender	Nodule / Papule	Skin Lesion			Location of Lesion				Extracutaneous Involvement			
					Erythema	Plaques	Edema	HN	T	UE	LE	LN	HSM	B M	HP S
2019	Case Report	US	53/F	-	-	-	+	-	-	+	-	N/A	N/A	N/A	N/A
2019	Case Report	German	65/M	-	-	-	-	-	-	-	-	N/A	N/A	N/A	+
2019	Case Report	Malaysia	23/M	-	-	-	+	-	-	+	+	Cervical , axillary	N/A	N/A	+
2020	Case Report	China	27/M	+	-	-	-	+	+	+	-	-	N/A	+	N/A
2020	Case Report	China	32/M	+	-	-	-	-	+	-	-	Axillary	N/A	N/A	N/A
2017	Case Report	India	25/F	+	+	-	-	-	+	+	+	-	N/A	N/A	N/A
2019	Case Report	India	11/M	-	+	+	-	+	+	+	+	-	+	+	+
2018	Case Report	US	60/F	+	+	+	-	-	+	+	+	-	N/A	N/A	N/A
2016	Case Report	China	24/M	+	-	-	-	+	+	+	-	-	+	N/A	+
2019	Case Report	India	59/F	-	-	+	-	-	+	+	+	-	N/A	N/A	N/A
2016	Case Report	India	19/F	-	-	-	+	+	-	-	-	-	N/A	N/A	N/A
2016	Case Report	India	5/F	+	+	-	-	+	+	+	+	-	+	-	+
2019	Case Report	China	25/M	-	-	+	+	+	-	-	-	-	-	N/A	N/A
2018	Case Report	China	15/F	-	-	-	+	-	+	+	-	Inguinal	-	-	N/A
2017	Case Report	US	8 months /F	+	-	-	-	-	-	-	+	Inguinal	-	-	+
2016	Case Report	India	17/M	-	+	+	+	+	+		+	-	+	+	N/A
2017	Case Report	US	20/F	+	+	-	-	-	+	-	+	-	N/A	N/A	N/A
2019	Case Report	Japan	3 months /M	-	-	-	+	-	+	-	+	Cervical , axillary	N/A	+	N/A
2016	Case Report	Japan	19/M	-	-	-	+	+	-	-	-	-	N/A	N/A	N/A

Year	Research Design	Country	Age/ Gender	Nodule / Papule	Skin Lesion			Location of Lesion				Extracutaneous Involvement			
					Erythema	Plaques	Edema	HN	T	UE	LE	LN	HSM	BM	HP/S
2019	Case Report	India	38/F	+	+	-	-	-	+	+	+	-	+	+	N/A
2017	Case Report	German	42/F	-	-	-	-	+	-	+	-	-	+	N/A	N/A
2019	Case Report	Singapura	39/M	+	-	-	-	-	+	-	-	-	N/A	N/A	N/A
2018	Case Report	US	15/F	+	-	-	-	+	-	+	-	Axillary	N/A	N/A	N/A
2017	Case Report	Japan	44/M	+	+	-	-	-	+	+	+	-	N/A	N/A	N/A
2018	Case Report	Japan	82/M	+	-	+	-	+	+	+	-	-	N/A	+	N/A
2019	Case Report	Filipina	26/F	+	-	-	-	-	+	-	-	-	N/A	N/A	N/A
2020	Case Report	German	17/M	-	-	-	-	-	-	-	-	-	+	+	+
2020	Case Report	Japan	30/F	-	-	-	-	-	-	-	-	-	N/A	N/A	N/A
2016	Case Report	Japan	71/M	+	-	-	-	-	-	+	-	-	N/A	N/A	N/A
2020	Case Report	US	40/F	+	-	-	-	+	+	+	+	-	N/A	N/A	N/A
2020	Case Report	US	49/F	+	+	-	-	+	+	+	+	-	N/A	N/A	N/A
2017	Case Report	China	70/M	-	+	-	+	+	-	-	-	Submental, submandibular, deep neck	N/A	N/A	N/A
2019	Case Report	India	43/F	-	+	+	-	-	-	-	+	-	N/A	N/A	N/A
2019	Case Report	India	33/M	-	-	-	+	-	+	-	-	-	N/A	N/A	N/A
2016	Case Report	China	27/M	+	+	-	-	-	+	-	-	Inguinal	N/A	N/A	N/A
2018	Case Report	Japan	54/M	+	+	-	-	-	-	-	-	-	N/A	N/A	N/A
2018	Case Report	US	53/F	+	+	+	-	-	+	-	+	N/A	N/A	N/A	N/A
2016	Case Report	India	20/F	-	+	-	+	-	-	-	+	N/A	N/A	N/A	N/A
2017	Case Report	Japan	19/M	-	-	-	+	+	-	-	-	N/A	N/A	N/A	N/A
2020	Case Report	India	25/M	-	-	-	+	+	-	-	-	-	N/A	N/A	N/A
2020	Case Report	Australia	18 months	-	+	-	+	-	+	-	-	-	-	-	-

Year	Research Design	Country	Age/ Gender	Nodule / Papule	Skin Lesion			Location of Lesion				Extracutaneous Involvement			
					Erythema	Plaques	Edema	HN	T	UE	LE	LN	HSM	BM	HPS
			/F												
2016	Case Report	Taiwan	23/M	+	+	+	-	-	+	+	+	Axillary , ant.medi- astinum	N/A	N/A	N/A
2016	Case Report	India	11/F	+	-	-	-	+	+	-	-	N/A	N/A	N/A	N/A
2021	Case Report	US	40/F	+	+	-	-	-	+	-	+	N/A	N/A	N/A	N/A
2021	Case Report	Moroco	57/F	-	+	-	+	+	-	-	-	sub- epiderm al	-	-	-
2021	Case Report	US	48/M	+	+	-	+	-	-	-	+	+	-	+	+
2021	Case Report	China	40/F	+	+	-	-	-	-	+	+	-	-	-	-
2021	Case Report	Japan	27/M	+	-	-	+	-	+	-	-	-	-	+	-
2021	Case Report	Canada	32/F	+	-	-	-	-	+	-	-	-	-	-	-

Note: BM, bone marrow; T, trunk; UE, upper extremity; LE, lower extremity; HSM, hepatosplenomegaly; HPS, hemophagotic syndrome; HN, Head and Neck; LN, lymph nodes; M, male; N/A, data not available; F, female; US, united states.

Table 5. Result of Findings Histopathological Characteristics of SPTCL

Research Design	Country	Age/Gender	Infiltration pattern	Type of T-cells	Layer of Infiltration	Rimming of Adipocytes	Karyorrhexis
Case Report	China	64/F	Lobular	S-M-L	N/A	+	+
Case Report	US	53/F	Mixed	M	N/A	+	+
Case Report	Jerman	65/M	Lobular	S-M	N/A	+	N/A
Case Report	Malaysia	23/M	Lobular	S-M	N/A	+	N/A
Case Report	China	27/M	N/A	S-M-L	N/A	+	N/A
Case Report	China	32/M	N/A	S-M-L	N/A	+	N/A
Case Report	India	25/F	N/A	M	N/A	+	N/A
Case Report	India	11/M	N/A	S-M	N/A	+	N/A

Research Design	Country	Age/Gender	Infiltration pattern	Type of T-cells	Layer of Infiltration	Rimming of Adipocytes	Karyorrhexis
Case Report	US	60/F	N/A	S-M	N/A	+	+
Case Report	China	24/M	N/A	S-M	N/A	+	+
Case Report	India	59/F	Lobular	S-M	N/A	+	+
Case Report	India	19/F	N/A	S-M	N/A	+	+
Case Report	India	5/F	Lobular	S-M	N/A	+	+
Case Report	China	25/M	Lobular	M	N/A	+	+
Case Report	China	15/F	N/A	N/A	N/A	N/A	N/A
Case Report	US	8 Months /F	N/A	S-M-L	N/A	+	N/A
Case Report	India	17/M	Lobular	N/A	Mixed	+	N/A
Case Report	US	20/F	N/A	N/A	Mixed	+	N/A
Case Report	Japan	3 Months /M	N/A	N/A	N/A	+	N/A
Case Report	Japan	19/M	N/A	N/A	Dermal	+	N/A
Case Report	India	38/F	N/A	N/A	Dermal	+	+
Case Report	Jerman	42/F	Lobular	S-M-L	Dermal	+	N/A
Case Report	Singapura	39/M	N/A	N/A	N/A	+	N/A
Case Report	US	15/F	Lobular	N/A	Dermal	+	N/A
Case Report	Japan	44/M	Lobular	N/A	N/A	+	N/A
Case Report	Japan	82/M	Lobular	N/A	N/A	+	+
Case Report	Filipina	26/F	Lobular	N/A	Mixed	+	N/A
Case Report	Jerman	17/M	Lobular	S-M	N/A	+	N/A
Case Report	Japan	30/F	Lobular	M	N/A	+	N/A
Case Report	Japan	71/F	Lobular	M-L	N/A	+	N/A
Case Report	US	40/F	N/A	N/A	N/A	N/A	N/A
Case Report	US	49/F	N/A	S-M	N/A	+	N/A
Case Report	China	70/M	Lobular	N/A	N/A	+	N/A
Case Report	India	43/F	Lobular	S-M	N/A	+	N/A
Case Report	India	33/M	Lobular	S-M	Dermal	+	N/A
Case Report	China	27/M	Lobular	M	N/A	+	N/A

Research Design	Country	Age/Gender	Infiltration pattern	Type of T-cells	Layer of Infiltration	Rimming of Adipocytes	Karyorrhexis
Case Report	Japan	54/M	Lobular	M-L	N/A	+	N/A
Case Report	US	53/F	Lobular	N/A	Dermal	+	N/A
Case Report	India	20/F	N/A	N/A	Dermal	+	N/A
Case Report	Japan	19/M	N/A	M	N/A	+	N/A
Case Report	India	25/M	Lobular	S-M	N/A	+	N/A
Case Report	Australia	18 Months /F	N/A	N/A	N/A	+	N/A
Case Report	Taiwan	23/M	N/A	N/A	N/A	N/A	N/A
Case Report	India	11/F	N/A	N/A	Dermal	N/A	N/A
Case Report	US	40/F	N/A	L	Dermal	+	+
Case Report	Morocco	57/F	N/A	N/A	subepidermal	N/A	N/A
Case Report	US	48/M	Lobular	N/A	Subcutaneous	+	+
Case Report	China	40/F	N/A	N/A	Subcutaneous	+	-
Case Report	Japan	27/M	Lobular	N/A	N/A	+	-
Case Report	Canada	32/F	Lobular	N/A	Dermal	+	+

Note: L, large; S, small; M, male; N/A, data not available; F, female; M, medium; US, united states.

Table 6. Result of Findings Immunohistochemistry of SPTCL

Year	Research Design	Country	Age/Gender	Immunohistochemistry								
				CD3	CD4	CD8	CD20	CD30	CD56	TIA-1	Beta-F1	Granzym
2019	Case Report	China	64/F	+	-	N/A	-	N/A	N/A	+	N/A	+
2019	Case Report	US	53/F	+	N/A	+	+	N/A	N/A	+	N/A	N/A
2019	Case Report	Jerman	65/M	+	-	+	-	-	N/A	N/A	N/A	N/A
2019	Case Report	Malaysia	23/M	+	-	+	N/A	N/A	N/A	+	N/A	N/A
2020	Case Report	China	27/M	+	N/A	+	-	-	-	N/A	N/A	+
2020	Case Report	China	32/M	+	-	+	-	N/A	-	+	N/A	+
2017	Case Report	India	25/F	+	-	+	-	N/A	-	N/A	N/A	+
2019	Case Report	India	11/M	+	N/A	+	N/A	N/A	-	N/A	N/A	+

Year	Research Design	Country	Age/ Gender	Immunohistochemistry								
				CD3	CD4	CD8	CD20	CD3 0	CD5 6	TIA-1	Beta-F1	Granzym
2018	Case Report	US	60/F	+	N/A	+	N/A	N/A	N/A	N/A	+	N/A
2016	Case Report	China	24/M	+	-	+	-	N/A	-	+	N/A	+
2019	Case Report	India	59/F	+	+	+	-	N/A	-	N/A	N/A	N/A
2016	Case Report	India	19/F	+	N/A	+	-	N/A	-	N/A	+	N/A
2016	Case Report	India	5/F	+	-	+	-	-	-	N/A	N/A	N/A
2019	Case Report	China	25/M	+	N/A	+	+	N/A	N/A	+	+	+
2018	Case Report	China	15/F	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2017	Case Report	US	8 Months /F	+	+	+	N/A	N/A	-	N/A	N/A	N/A
2016	Case Report	India	17/M	+	-	+	-	N/A	-	N/A	N/A	N/A
2017	Case Report	US	20/F	+	-	+	N/A	N/A	N/A	+	+	N/A
2019	Case Report	Japan	3 Months /M	+	-	+	N/A	N/A	-	N/A	+	N/A
2016	Case Report	Japan	19/M	+	N/A	+	N/A	-	-	+	+	+
2019	Case Report	India	38/F	N/A	-	+	-	N/A	-	N/A	N/A	+
2017	Case Report	Jerman	42/F	N/A	+	+	N/A	N/A	-	+	+	+
2019	Case Report	Singapur a	39/M	N/A	-	+	N/A	N/A	N/A	N/A	N/A	+
2018	Case Report	US	15/F	+	-	+	N/A	N/A	N/A	+	+	N/A
2017	Case Report	Japan	44/M	+	-	+	N/A	N/A	-	N/A	N/A	+
2018	Case Report	Japan	82/M	+	-	+	-	-	-	+	+	N/A
2019	Case Report	Filipina	26/F	+	-	+	N/A	N/A	N/A	-	N/A	+
2020	Case Report	Jerman	17/M	+	-	+	N/A	N/A	N/A	N/A	N/A	N/A

Year	Research Design	Country	Age/ Gender	Immunohistochemistry								
				CD3	CD4	CD8	CD20	CD3 0	CD5 6	TIA-1	Beta-F1	Granzym
2020	Case Report	Japan	30/F	+	-	+	N/A	-	-	N/A	N/A	N/A
2016	Case Report	Japan	71/F	+	-	+	-	-	N/A	N/A	N/A	+
2020	Case Report	US	40/F	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2020	Case Report	US	49/F	+	-	+	N/A	N/A	N/A	+	+	N/A
2017	Case Report	China	70/M	+	-	+	N/A	+	-	+	N/A	N/A
2019	Case Report	India	43/F	+	-	+	-	N/A	-	N/A	N/A	N/A
2019	Case Report	India	33/M	+	+	+	-	N/A	-	N/A	N/A	N/A
2016	Case Report	China	27/M	+	-	-	-	N/A	N/A	N/A	+	N/A
2018	Case Report	Japan	54/M	+	N/A	+	N/A	N/A	N/A	+	+	N/A
2018	Case Report	US	53/F	+	+	+	N/A	N/A	N/A	N/A	+	N/A
2016	Case Report	India	20/F	+	-	+	-	N/A	N/A	N/A	N/A	N/A
2017	Case Report	Japan	19/M	+	-	+	-	N/A	-	+	N/A	+
2020	Case Report	India	25/M	+	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A
2020	Case Report	Australia	18 months /F	+	-	+	-	-	-	+	+	N/A
2016	Case Report	Taiwan	23/M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2016	Case Report	India	11/F	+	-	+	N/A	-	-	N/A	N/A	N/A
2021	Case Report	US	40/F	+	+	+	-	-	+	N/A	N/A	N/A
2021	Case Report	Morocco	57/F	+	-	+	+	-	-	-	-	-
2021	Case Report	US	48/M	+	+	+	-	-	-	+	-	+
2021	Case Report	China	40/F	+	+	+	-	-	-	+	-	-
2021	Case Report	Japan	27/M	+	-	+	-	-	-	-	-	-
2021	Case Report	Canada	32/F	+	-	+	-	-	-	+	-	+

Note: CD, cluster of differentiation; M, male; N/A, data not available; F, female; TIA, T-cell intracellular antigen; US, united states.

4. Discussion

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was defined by the WHO classification of hematopoietic and lymphoid tissue tumours in 2008 as primary cutaneous T-cell lymphoma involving the subcutaneous tissue and expressing the immunophenotype of α/β cytotoxic T-cells. SPTCL tumour cells express α/β TCR, while tumour cells in the form of γ/δ T-cell lymphoma express γ/δ TCR. [8] These lymphomas account for 1% of all skin lymphomas and 75% of all forms of subcutaneous T-cell lymphomas. SPTCL can occur in children and adults, with an average age of 35 years. It is more common among women, but there are no reports of racial or ethnic orientation [16]. No specific etiological factors have been identified in SPTCL. In about 20% of cases, SPTCL may be associated with autoimmune diseases, and some cases show overlap with histological features of cutaneous lupus. About half of patients with T panniculitis-like lymphoma have autoimmune diseases, mainly related to lupus. In both series, autoimmune diseases are associated with SPTCL: Gougerot-Sjögren syndrome, type I diabetes, and lupus and Raynaud's syndrome [84]. Further research is needed to be carried out to make a definitive conclusion regarding the aetiology of SPTCL [17]. The pathogenesis of SPTCL remains unclear. The mechanism of tumour cell migration and proliferation in the subcutaneous tissue in SPTCL is not fully understood. [67] found that the expression of chemokine receptors such as CCR5 and CXCR3 on tumour T cells promoted the migration of tumour T cells to the fat cell membrane. CCR5 and CXCR3 are chemokine receptors, which are usually expressed on cytotoxic T cells and T helper 1 cells, and can activate mitogen-activated protein kinase (MAPK) in response to their ligands, leading to T cell proliferation and activation. Ligands for CCR5 (CCL3, CCL4, CCL5) and CXCR3 (CXCL10) can be secreted by adipocyte membranes, especially when activated immunologically. [6], [18-26]. Overexpression of aberrant MYC proto-oncogenes or MYC transcription factor activity plays a role in neoplastic processes, including lymphoma. Suggest that MYC protein expression appears in SPTCL cases [22], [23].

The diagnosis of SPTCL should be considered from clinical, pathological, immunohistochemical, and molecular characteristics. The clinical features of SPTCL are always subcutaneous nodular lesions or plaques. In most cases, it spreads all over the body, mainly affecting the limbs, trunk, and sometimes the face [31]. The clinical manifestations are usually characterised by subcutaneous nodules and plaques with erythematous surfaces, which are usually painless and vary in size from 0.5 to 2.0 cm. There may be obvious lesions in the healing stage, indicating that the clinical process is gradually slowing down. Compared with primary γ/δ T-cell lymphoma, SPTCL ulcers are less common. The predominant parts are on the limbs, trunk, and face. About 50% of patients may experience systemic symptoms, including fever, weight loss, fatigue, chills, and myalgias. These symptoms are more common in HPS patients. Lymph nodes and bone marrow involvement are usually absent [24- 26].

In our review, the authors reviewed data from 50 patients published in the last five years regarding the clinicopathological characteristics of SPTCL. This is related to the characteristics of SPTCL which is a rare case of cutaneous T-cell lymphoma with indolent nature and resembling an inflammatory or infectious process so that diagnosis is difficult and often late in establishing. Its rarity and atypical clinical manifestations make SPTCL often missed as one of the important provisional diagnoses to consider. Misdiagnosis is common both with benign lesions such as cellulitis and LEP and with aggressive cutaneous lymphomas such as PCGDTL [1], [3], [10], [77]. Clinically, SPTCL is similar to lupus erythematosus panniculitis (LEP). However, LEP is more commonly located on the face and proximal extremities whereas SPTCL appears on the lower and upper extremities and also the trunk accompanied by systemic symptoms such as fever and hepatosplenomegaly [8], [33]. SPTCL follows a slow clinical course with subtle painless lesions at the beginning of the disease process, which often looks similar to the benign skin disease. SPTCL lesions are usually non-ulcerated, multiple, and commonly found in the trunk and lower extremities, but upper and facial

lesions have also been reported. In contrast, lupus erythematosus panniculitis (LEP) lesions are usually ulcerated and present on the head and face. Erythema nodosum is classically localised to shin [83]. Other differential diagnosis may include Primary Cutaneous γ/δ T-cell Lymphoma (PCGDTL). The incidence of PCGDTL is mostly in middle-aged adults and the lesions are more superficial with ulcerated surfaces. Systemic symptoms and lymphadenopathy are common and develop HPS in 50% of cases [15]. The clinical characteristics of patients with SPTCL include the majority of patients were young adults with a median age of 26.5 years and predominantly female. The most common skin manifestation is a nodule with a predilection area of predilection on the trunk. In line with research conducted by showed the most findings were in the form of nodular lesions on the trunk [36]. The median duration of lesion appearance to the diagnosis of all cases was approximately 16 months, this is due to the non-specific clinical characteristics, protracted course of the lesion, and misdiagnosis with cellulitis, lymphadenopathy, and lobular panniculitis. Two patients with monozygotic twins were reported to have concurrent SPTCL at different periods with an interval of 11 years [48] which confirms the statement of that genetic, infectious, and environmental factors had implications for the etiopathogenesis of T-cell cutaneous lymphoma in general [78]. Systemic symptoms were present in 68.2% of reported cases, a higher percentage reported in the study of in Japan in 2017 by 81% and lower in the study of in Europe in 2008 by 59% [36], [79]. Extracutaneous in contrast to previous studies, involvement in the form of lymphadenopathy was found in 25.6% of patients whereas 40% in the study of [80]. Hepatosplenomegaly and involvement were bone marrow found in seven patients according to a study in Thailand [80] of eight patients while studies reported in China [79], Korea [81], and Europe [8] only one to five patients. This difference may be due to the different stages of the disease reported. Four of the seven patients with hemophagocytic syndrome appeared in children and two patients were aged 23 and 24 years [3], [10], [50], [50], [51], [54], [64]. This should be a clinician's attention to prevent complications of more fatal conditions.

Histologically, SPTCL showed subcutaneous lobular infiltration of atypical T cells. Histological examination showed that the subcutaneous infiltration was similar to lobular panniculitis. The infiltrate contains a mixture of tumorous pleomorphic cells of various cell sizes (small, medium, and large), involving fatty lobules, some with septa, and the order of the epidermis and dermis may be small. Adipocytes may appear as tumorous lymphocytes. Macrophages, histiocytes, fat necrosis, fragmented nuclear rupture, and red blood cell phagocytosis are common manifestations of SPTCL [11], [14], [15], [23]. In our review, the histopathological characteristics of SPTCL reported, in general, are characterised by atypical subcutaneous cell infiltration with a lobular pattern of varying size, mainly small-medium, rimming adipocyte, karyorrhexis, and fat necrosis. Histologically, T-cell infiltration is a sign of a benign process, but histopathological criteria for rimming of adipocytes by neoplastic T cells, karyorrhexis, and fat necrosis can be important diagnostic signs in SPTCL. Rimming typical adipocyte cells in SPTCL and rarely found in other types of lymphoma cutis and also at LEP [15]. Our study found some features overlapping between SPTCL and LEP in six cases in the form of lobular infiltration pattern, epidermal extension, dermal or periadnexal [26]. Cases with concurrent SPTCL and LEP were previously identified by who reported five patients exhibiting features of overlapping SPTCL and LEP. In one case from Europe, the histology of SPTCL was found to be dominated by granulomas [43]. This can obscure the view of atypical lymphocytic infiltration and widen the differential diagnosis in infectious diseases such as tuberculoid leprosy or malignancies of the adult T-cell lymphoma and PCGDTL subtypes. This case demonstrates that accurate diagnosis of this disease is important in clinical management. To exclude the possibility of a diagnosis of other diseases required immunohistochemical examination (IHC) [26], [43], [44]. Histologically, LEP and SPTCL can show similar characteristics, especially the involvement of the epidermis. There is a mixture of CD4 and CD8, the low proliferation index of Ki-67 in T-cell rimming adipocytes is a feature that can be used to differentiate SPTCL from LEP. Inflammatory cells such as eosinophils, neutrophils, and plasma cells are common in LEP [8], [33]. Histological pattern to different

SPTCL with PCGDTL were three patterns that can be observed are epidermal-tropic, dermal, and subcutaneous. A subcutaneous pattern may appear similar to lobular panniculitis in SPTCL. Rimming adiposity is less prominent [15].

An immunohistochemistry examination is one of the diagnostic modalities for SPTCL although it has different varieties. In immunohistochemical confirmation, the first step is to determine whether the main cell population is T cells or B cells. CD3 is the most consistent positive marker for T cells, and CD20 is the marker for B cells. The T cell type, CD4 and/or CD8, characterise the disease as an inflammatory process, malignancy, or a combination thereof. If T cell proliferation is confined to the epidermis and/or superficial dermis, using CD30 staining. T cells are located in the lower dermis and subcutaneous tissues and stained with CD56. Molecularly, T cell receptor (TCR) expression is detected to detect glycoprotein molecules on the surface of T cells. The task of these molecules is to recognize antigens as peptides that bind to major histocompatibility complex (MHC) molecules [5], [32]. Immunophenotype shows SPTCL neoplastic cells express a mature α/β cytotoxic T-cell phenotype, several clusters of differentiation (CD) including CD3+, CD4-, CD8+, CD56-, CD30-, T-cell intracellular antigen 1+, granzyme- β +, and F1+. Expression of F1 (TCR α/β) by immunohistochemistry is an important diagnostic marker in this entity [9], [29]. Identification of cytotoxic T cell phenotype by IHC examination is important especially because α/β or SPTCL phenotype with γ/δ are two entities with very different disease courses and prognoses. In our review, all cases were positive for CD3, CD8, Beta F1, and Granzyme B expression and negative for CD56 expression of all reported cases; these findings may help in excluding the possible phenotype γ/δ . Initially, other CD4/CD8 expression patterns were described to occur in TCR $\gamma\delta$ SPTCL/PCGD-TCL, particularly of the CD4-/CD8- double-negative phenotype. At times, CD4/CD8 were indeterminate in TCR $\alpha\beta$ SPTCL. Rare cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) with SPTCL features and SPTCL with CD4+ /CD8- phenotypes, are described; in the latter case series, the inclusion of cases with TCR $\gamma\delta$ gene rearrangement raises the question of whether those cases truly demonstrate a rare CD4+variant of TCR $\alpha\beta$ SPTCL or would now be more correctly categorised in the provisional PCGD-TCL by strict WHO (2008)-EORTC criteria [88]. Although positive for CD8, Beta F1, Granzyme B is a typical finding for the diagnosis of SPTCL, these markers can still be found in lupus panniculitis [15]. This can be overcome by checking the Ki-67 with a level of more than 30%. In LEP, the Ki-67 index was detected to be low (less than 10%) so the finding of Ki-67 levels >30% could rule out the possibility of a diagnosis of LEP [37- 40]. Immunohistochemistry examination to different SPTCL with PCGDTL neoplastic cells were positive for CD56, TCR-, TIA 1, granzyme B, and perforin and typically negative for CD4, CD8, and beta F1 [15].

The prognosis for SPTCL is generally good with an indolent course except for patients with HPS who are associated with an aggressive course with high mortality. Five-year survival is described as more than 80%. The development of HPS is reported to occur in about 20% of patients and is associated with poorer outcomes with a five-year survival of 46% [34- 36]. The prognosis for SPTCL is favorable with an indolent disease course and 5-year overall survival (OS) of more than 80%. In our review, of the 50 cases, 1 patient died of organ failure characterised by tumours in the mesenteries with hemophagocytic syndrome (HPS) without clinical involvement or morphology of the lesions. The presence of HPS is a poor prognostic indicator in SPTCL with a reduced 5-year OS. In a recent EORTC study, the 5-year survival rates for patients with and without relevant HPS were 46% and 91%, respectively [53], [82], [89].

5. Conclusion

In our conclusions, the clinicopathological characteristics are helpful in diagnosing SPTCL. The clinical characteristics of SPTCL lesions vary in the form of plaques and erythematous edema, most often nodules on the trunk, limbs, or head. The most common systemic symptoms are fever and also the involvement of

extracutaneous symptoms such as lymphadenopathy, hepatosplenomegaly, bone marrow involvement, and hemophagocytic syndrome. The histopathological characteristics are rimming of adipocyte cells, karyorrhexis, and fat necrosis. The immunohistochemistry characteristics are CD3+, CD8+, CD56-, Beta F1+, Granzyme B+, and Ki-67 levels specific to the diagnosis of patients with SPTCL.

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