Hematology/Oncology and Stem Cell Therapy

Volume 16 | Issue 2 Article 3

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RESEARCH ARTICLE

Diagnosis and Treatment of Subcutaneous Panniculitis-like T-cell Lymphoma: A Systematic Literature Review

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Abstract

Objectives: **The aim of this systematic review is to investigate different diagnostic methods and the available treatment options for subcutaneous panniculitis-like T-cell lymphoma (SPTCL).**

Methods: **We searched PubMed, Web of Science, SCOPUS, EBSCO, and CINAHL Plus for published case reports of SPTCL. From each record, we extracted data of the diagnostic methods, immunohistochemical profile, clinical characteristics, and the treatment approaches provided. Data were summarized and narratively synthesized to highlight the various diagnostic methods and treatment options of SPTCL.**

Results: **Our literature search yielded 1293 unique citations. Following screening, nine articles reporting a total of 15 cases were included in this systematic review. All patients presented with subcutaneous nodules. Three of the 15 cases were initially misdiagnosed. The atypical lymphoid cells were positive for CD2, CD3, granzyme B, and TIA-1 and negative for CD1a, EBER, and CD20 in all the reported cases. The atypical lymphoid cells were positive for CD45RO in four out of seven cases, positive for CD56 in three out of 12 cases tested, while positive for CD5 and CD8 in the majority of cases. Therapy ranged from topical agents to immunosuppressive agents all the way to multiagent chemotherapy.**

Conclusion: **SPTCL is a rare lymphoma. Diagnosis is highly dependent on the immunohistochemical stains added to histopathologic and radiologic findings. Therapy is dependent on the pace of the disease, with encouraging results obtained with single-agent cyclosporine.**

Keywords: Panniculitis-like, SPTCL, Subcutaneous, T-cell lymphoma

1. Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cytotoxic T-cell lymphoma that accounts for less than 1% of all peripheral T-cell lymphomas. Incidence is nearly equal in men and women, and both children and adults may be affected. The median age at diagnosis is 46.5 years, but approximately 20% of patients are younger than 20 years. The World Health Organization (WHO) classification of lymphoid neoplasms (2016) and WHO-European Organization for Research and Treatment classification (2018) define SPTCL as a tumor that expresses α/β T-cell receptor (TCR) gene rearrangement. Tumors expressing γ/δ TCR are separately classified as primary cutaneous γ/δ T-cell lymphomas [1–4].

The histology of the disease is characterized by pleomorphic malignant T-cell infiltration of the subcutaneous adipose tissue accompanied by a large number of macrophages, with absence of dermal or epidermal involvement. The infiltrate is characterized by rimming of atypical T cells around

Received 3 February 2021; revised 24 March 2021; accepted 25 April 2021.
Available online 17 January 2023

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https://doi.org/10.1016/j.hemonc.2021.04.001

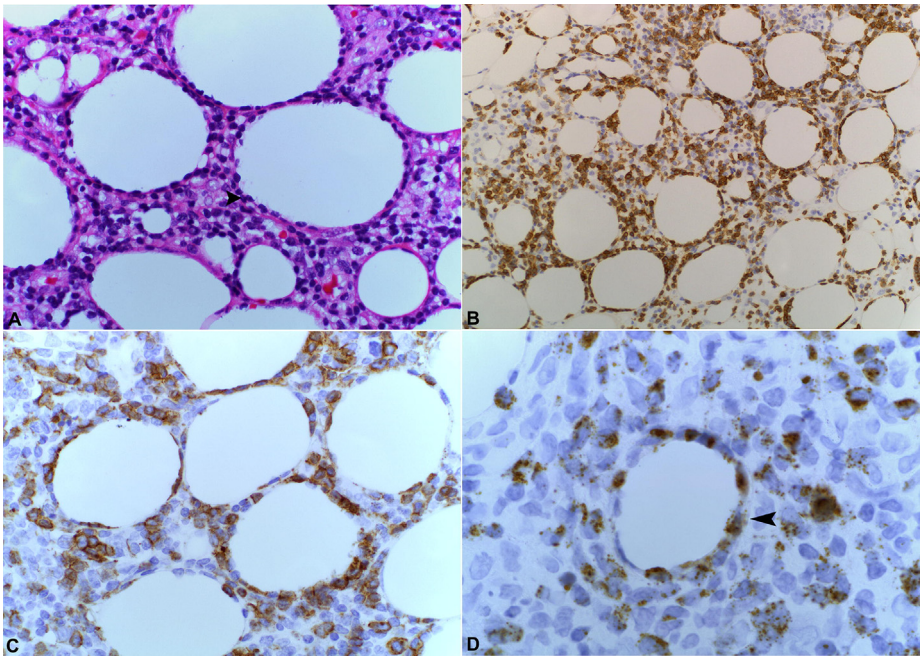

Fig. 1. (A) Hematoxylin and eosin–stained section (400× magnification) of a punch biopsy of a skin lesion from the right upper arm of a patient with deep subcutaneous nodules. It shows infiltration of the deep subcutis involving mainly the lobular fat and highlighting the characteristic "rimming" of atypical lymphoid cells around the fat spaces (arrowhead). (B) Immunohistochemical staining for CD3 depicting positive staining of neoplastic lymphoid cells (200× magnification). (C) Immunohistochemical staining for CD8 showing positive expression (400× magnification). (D) Immunohistochemical staining for cytotoxic granules, granzyme A showing strong positive expression in a vast majority of atypical lymphoid cells (arrowhead, 1000× magnification).

fat cells with frequent necrosis and karyorrhexis. The infiltrate is primarily lobular in distribution with no or occasional septal involvement (Fig. 1A). Immunohistochemically, in most cases, the atypical lymphoid cells are positive for CD2, CD3, CD7, CD8, beta F1, and activated cytotoxic proteins (T-cell intracellular antigen [TIA-1], granzyme B [GzB], and/or perforin), negative for CD4 (Fig. 1B), and negative for CD56 and CD30. There is no definitive association with Epstein–Barr virus (EBV) and EBV virus-encoded small nuclear RNA (EBER-1); therefore, it is negative in almost all reported cases. Because of overlapping clinicopathologic features with non-neoplastic panniculitides as well as other T-cell lymphomas involving the skin, the diagnosis of SPTCL is relatively difficult and is based on a combination of the patient's histopathologic features, immunophenotype, and clinical manifestations. Accordingly, SPTCL must be differentiated from the following diseases:

1. Primary cutaneous γ/δ T-cell lymphoma: This disease often involves the dermis and epidermis and leads to epidermal ulcers. The immunophenotype is similar to that of SPTCL, but this lymphoma simultaneously expresses CD56 and TCR-γ. In contrast to SPTCL, primary cutaneous γ/δ T-cell lymphoma has a poor prognosis.

2. Extranodal natural killer (NK)/T-cell lymphoma: This is a peripheral T-cell lymphoma of NK/T-cell lineage that can sometimes affect the skin but is never restricted to the subcutaneous tissue. Its immunophenotype is similar to that of SPTCL, but is negative for CD8 and positive for CD56, is often associated with EBV infection, and is negative for TCR gene rearrangement.

3. Lupus panniculitis (lupus profundus): This is a group of diseases characterized by inflammation involving the subcutaneous fat. The clinical manifestations are similar to those of SPTCL, but histopathologic examination reveals mixture of T cells, B cells, and plasma cells (numerous) with fibrinoid changes in the connective tissue surrounding the blood vessels and lacks cytologic atypia. Both CD4 + and CD8 + T cells are present along with a good number of plasmacytoid dendritic cells (CD123 +). Additionally, clonal TCR gene rearrangement is absent.

Most patients with SPTCL have a slow disease course and recurrent episodes of skin lesions. The overall prognosis is excellent with a 5-year survival rate > 80% and a low risk of nodal involvement or dissemination. Occasionally, the lesions resolve spontaneously. Multidrug combination chemotherapy is no longer the first-line treatment for this disease; however,

immunosuppressive agents can result in curing of some patients with SPTCL, especially those with presentation similar to lupus erythematosus [5–7].

Few reviews have been published on this topic. Most of these, however, have focused mainly on histopathologic characteristics and clinical features, with limited discussion of available diagnostic options and therapeutic regimens. In this systematic review, we aimed to discuss the available diagnostic methods and treatment regimens used for patients with SPTCL.

2. Methods

2.1. Study design and literature search

A systematic literature review of all published literature was conducted. We searched PubMed, Web of Science, SCOPUS, EBSCO, and CINAHL Plus through October 2019 using the following strategy ("panniculitis" AND "lymphoma"). Then, an offline search was performed in the references of the relevant previous reviews to ensure the comprehensive inclusion of all relevant reports.

2.2. Eligibility criteria

Included studies were selected according to the following criteria:

1. Observational studies, mainly case reports
2. Studies on patients with SPTCL

Case reports with the following conditions were excluded:

1. Patients with other diseases that mimic SPTCL
2. Case reports with no diagnostic or therapeutic options
3. Case series and prospective cohorts

2.3. Screening of records

Results of the literature search were obtained and screened for eligibility. Eligibility screening was conducted in two steps. The first step was to screen titles/abstracts of the retrieved records. The second step was to screen full-text articles of the abstracts selected in the first step.

2.4. Data extraction

For each case, we extracted the following data: (a) expressed diagnostic markers, (b) diagnostic method/s, and (c) disease management plan. We also extracted data of the case characteristics such as patient's age, sex, duration of disease, current treatment, positive and negative immunohistochemical tests, and Ki67 proliferation rate.

3. Results

Our literature search yielded 1293 unique citations. Following titles and abstract screening, 35 articles were assessed for full-text screening. Finally, nine articles reporting a total of 15 cases were included in this systematic review. The PRISMA flow diagram of the study selection process is shown in Fig. 2.

Seven patients were males and eight were females. The mean age of the patients was 29.7 years. Collected immunohistochemical markers included: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, TIA-1, EBER, GzB, TCR-β (beta F1), TCR-γ, CD20, CD45RO, and CD56. Ki67 was reported in four articles (7 cases) [7–10]. Summary of the characteristics of the included cases is listed in Table 1.

Regarding immunostaining of the atypical cells, CD1a was negative in five cases and CD2 was positive in eight cases. Of 14 cases tested for CD3, all were positive and three of them were positive for CD4. Of eight cases tested for CD5, six were positive. Of 14 cases tested for CD7, only three were positive. Of 11 cases tested for TIA-1, all were positive. Of five cases tested for EBER and CD20, all were negative. Of three cases tested for GzB, all were positive. TCR-β and TCR-γ were positive in five of eight and four of 10 cases, respectively. Of seven cases tested for CD45RO, four were positive, and finally, of 12 cases tested for CD56, only three were positive.

Dong et al. [6] reported regarding a 15-year-old female diagnosed with SPTCL who received multiagent chemotherapy 7 years prior to returning with suspicious nodules. Upon suspicion of relapse (subcutaneous nodules), a positron emission tomography (PET) scan showed multiple scattered subcutaneous nodules. She was treated without histologic confirmation of relapse with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy and achieved remission by PET.

Heyman et al. [11] reported regarding a 53-year-old female misdiagnosed with cellulitis at first and treated with sulfamethoxazole and trimethoprim. Skin biopsy showed atypical lymphocytic infiltrate for which the patient received prednisone 40 mg. PET/computed tomography (CT) scan showed hypermetabolic lesions in the subcutaneous tissues felt to be suggestive of SPTCL. The patient received bexarotene at first followed by mycophenolate mofetil resulting in partial remission per PET/CT.

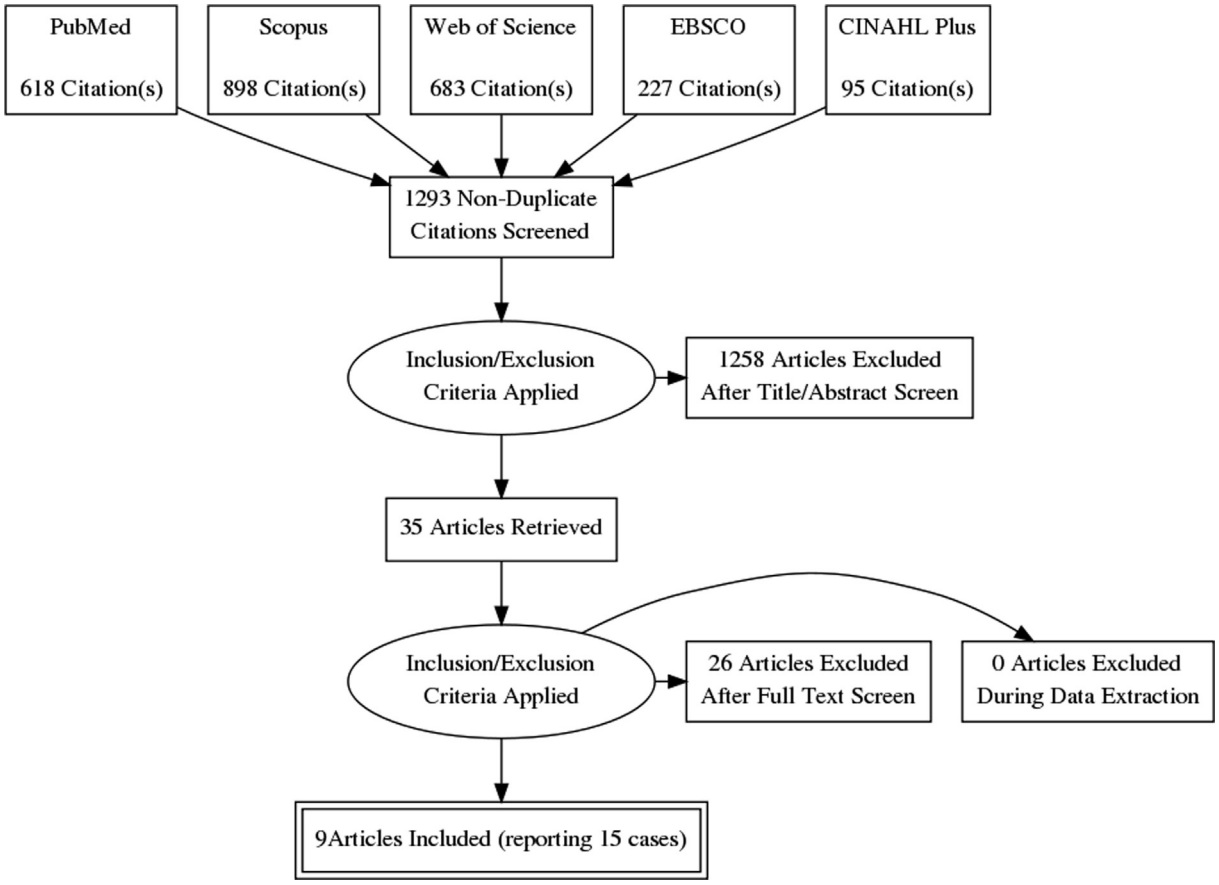

Fig. 2. The PRISMA flow diagram of the study selection process. Exclusion criteria: case series, prospective cohorts, and case reports that did not report treatment or diagnostic details.

Hoffman et al. [12] reported regarding a 47-year-old female who presented with a nodule that showed abnormal lymphocytic infiltration on biopsy. Ki67 reactivity was diffusely positive.

Hrudka et al. [7] reported regarding a 65-year-old male with a big retroperitoneal mass found on CT scan after presenting with abdominal pain and rigors; biopsy was performed which showed dense small- to medium-sized lymphocytes with hyperchromatic irregular nuclei and little rim of pale cytoplasm infiltrating the adipocytes. There was a pattern of isolated adipocytes surrounded by a dense rim of hyperchromatic lymphocytes. Necrotic adipocytes and reactive macrophages phagocytizing lymphocytes and erythrocytes were also seen. Immunohistochemically, the atypical cells rimming the adipocytes stained for CD45 (LCA), CD2, CD3, CD5, CD7, CD8, GzB, perforin, TIA-1, and TCR-beta F1 and did not stain for CD4, CD20, CD79a, CD56, CD30, EBER, CD1a, S100, myeloperoxidase, cytokeratin CAM5.2, and TCR-γ. The proliferation index Ki67 varied between 10% and 50%. These morphologic and immunologic features were consistent with SPTCL. The patient died from sepsis with multiorgan failure before receiving any lymphoma therapy. Postmortem autopsy was consistent with the initial biopsy results.

Johnston et al. [8] reported regarding four pediatric cases. The first case was a 3-year-old female with erythematous skin lesions during a viral infection; biopsy confirmed SPTCL. The findings resolved spontaneously without any therapy. The second case was a 14-year-old female treated with chemotherapy with no evidence of disease recurrence. The third case was a two-year-old male who was similar to the first case and experienced spontaneous resolution. The fourth case was a 2-year-old female who developed a small red bump on her cheek. A skin biopsy was consistent with SPTCL, the patient was followed-up for 2 years, and no progression or worsening of symptoms was evident, suggesting a possible misdiagnosis of SPTCL.

Ma et al. [13] reported regarding a 25-year-old man with sickle cell disease who developed a buccal nodule. A skin biopsy of the nodule revealed an immunohistochemical profile consistent with

Table 1. Summary of Included Case Reports in the Review.

Study ID	Age	Sex	Previous therapy	Ki67 positive	CD1	CD2	CD3	CD4	CD5	CD7	CD8	TIA-1	EBER	GzB	TCR-β	TCR-γ	CD20	CD45RO	CD56
Dong et al. [6]	15	F	CHOP																
Heyman et al. [11]	53	F	Mycophenolate mofetil				+	+			+				+	−			
Hoffman et al. [12]	47	F				+	+	−	+		+						−	−	−
Hrudka et al. [7]	65	M	Platelet transfusions, fibrinogen, prothrombin complex concentrates, and broad-spectrum antibiotics	10−50%	−	+	+	−	+	+	+	+	−	+		−	−	−	−
Johnston et al. [8]	3	F	No therapy	20%			+	−			+	+	−		+	−	−		−
	14	F	MTX, Ara-C, Cy, Doxo	50%			+	−			+	+	−		+	−	−		−
	2	M	No therapy	70%			+	−			−	+	−			+	−		+
	3	F	No therapy	15%			+	−			+	+	−		−	+			−
Ma et al. [13]	25	M	Prednisone			+	+	−	+	+	−	+		+					−
Marzano et al. [14]	53	M	Mitoxantrone, Cy, etoposide, vincristine		−	+	+	+	−	−	−	+			−	+		+	+
	56	F	Methylprednisolone, CEOP		−	+	+	+	−	−	−	+			−	+		+	+
	10	M	Steroids, cyclosporine, and CHOP		−	+	+	−	+	−	+	+			+	−		+	−
	10	F	Steroids, cyclosporine, and CHOP		−	+	+	−	+	−	+	+			+	−		+	−
Qiu et al. [15]	27	M	Cy, epirubicin, vincristine, and prednisolone				+	−			−							−	
Shen et al. [10]	24	M	10 mg dexamethasone, 40 mg prednisone	50%		+	+	−		+	+	+		+					−

Note. Ara-C = cytarabine; CEOP = cyclophosphamide, etoposide, vincristine, and prednisolone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; Cy = cyclophosphamide; Doxo = doxorubicin; EBER = Epstein−Barr virus-encoded small nuclear RNA; F = female; GzB = granzyme B; M = male; MTX = methotrexate; TCR = T-cell receptor; TIA-1 = T-cell intracellular antigen.

SPTCL. The patient received prednisone only and improved with no recurrence.

Marzano et al. [14] described four cases in which immunohistochemical stains were consistent with SPTCL. The first case was treated with methylprednisolone, two other cases were treated with other immunosuppressive therapy. In the fourth case, chemotherapy treatment failed, and death occurred secondary to disease progression.

Qiu et al. [15] reported regarding a 27-year-old man with a diagnosis of SPTCL based on a skin biopsy. The patient was treated with CHOP and only achieved partial remission; he was then treated with etoposide, methylprednisolone, cytarabine, and cisplatin followed by skin radiation and achieved remission for 8 months. He then presented with progressive headache, nausea, and vomiting, and the workup showed evidence of atypical lymphocytes in the cerebrospinal fluid. He was treated for central nervous system relapse with fotemustine, teniposide, and dexamethasone and achieved long-term remission.

Shen et al. [10] reported regarding a 24-year-old man with a chest nodule. The patient was initially misdiagnosed for nodular panniculitis and was treated with dexamethasone followed by prednisone with poor response. A skin biopsy was performed, and histopathology was suggestive of SPTCL. PET/CT scan revealed numerous subcutaneous nodules. After confirmation of SPTCL diagnosis, the patient received a higher dose of dexamethasone (40 mg/day) combined with cyclosporine A (250 mg/day) and achieved complete remission.

4. Discussion

Panniculitis T-cell lymphoma is a rare entity and poses a diagnostic challenge. In this systematic review, we found that three of the 15 cases were misdiagnosed initially [8,10,11]. Diagnosis is highly dependent on the immunohistochemical stains added to histopathologic findings as well as imaging studies, mainly PET/CT scan. Regarding immunohistochemical tests on the atypical cells, all cases were positive for CD2, CD3, GzB, and TIA-1, most cases reported in literature were positive for CD5, CD8, and TCR-β, and all cases were negative for CD1a, EBER, and CD20. PET/CT scan was performed in a minority of patients, and in the majority of these, it was useful in terms of showing the number of lesions with abnormal uptake. Two cases developed hepatopulmonary syndrome (HPS), of which one patient died [7].

Because it is a rare entity, there are no published guidelines addressing the diagnosis and management of SPTCL. This fact is reflected in the current review, as the treatment approaches were different, ranging from topical to immunosuppressive agents all the way to cytotoxic agents, in combination or alone, mimicking the approach taken in the management of other cutaneous T-cell lymphomas. Current treatment options for SPTCL include single-agent corticosteroids. Go and Wester [16] reported regarding 20 cases, initially treated with steroids, resulting in complete and partial remissions in six (30%) and four (20%) cases, respectively. However, when steroids were gradually discontinued, patients developed recurrence after 6 months of treatment. Those patients either required chemotherapy or died from disease complications.

In addition to steroids, many studies reported steroid-sparing medications in combination with immunosuppressive and nonimmunosuppressive agents. Cyclosporine is a well-established immunosuppressive drug that acts by irreversible binding to and inhibiting calcineurin. This leads to decreased formation of interleukin-2 and other cytokines expressed in T-cell lymphomas, causing a significant decrease in the growth of T cells [17]. Shani-Adir et al. [18] were the first to administer cyclosporine in two children with SPTCL as an adjuvant therapy. Both the children initially responded well to treatment and achieved complete remission. Later on, one patient had disease relapse and required salvage chemotherapy [18]. Cyclosporine was first attempted in adults with refractory SPTCL by Rojnuckarin et al. [19]. In their case series, they included four patients with refractory SPTCL (failed CHOP and at least one salvage therapy). All four patients showed rapid improvement within weeks of starting cyclosporine 4 mg/kg/day, with three of them achieving complete remission [19].

The pace of the disease is important to direct the treatment decisions. For patients with a relatively indolent condition, the suggested first-line treatments include immunosuppressive agents such as prednisone, cyclophosphamide, or methotrexate; severe conditions with aggressive infiltrative lymphocytes may require combination chemotherapy regimens [16]. In patients resistant to chemotherapy, cyclosporine A alone or combined with steroids lead to good results including in patients with HPS [19,20].

Recent studies have identified germline *HAVCR2* mutations in 60% of SPTCL that abrogates TIM-3 (T-cell immunoglobulin domain and mucin domain 3) membrane expression leading to persistent immune activation and cytokine production. Reported to be more common in Asian and Eastern than European

patients, these mutations affecting TIM-3 expression are associated with hemophagocytic lymphohistiocytosis—refractory and severe disease course. TIM-3 mutant SPTCL, however, are controlled with immunosuppression [21,22].

Our study has several strengths: (a) we included recently published case reports and reviewed each case adequately for any missing data, and (b) we assured proper reporting of immunohistochemical stains in all studies, except one [23]. Our main limitation is the low number of included cases ($n = 15$). Another limitation is that not all cases were tested for the same immunohistochemical stains; therefore, a complete comparison could not be made. We recommend future studies to combine immunohistochemistry possibly with next-generation sequencing or gene expression profiling along with imaging (PET/CT) to better delineate this entity.

In conclusion, SPTCL is challenging to diagnose. In this systematic review of published case reports, we summarized the reported cases in terms of diagnostic and therapeutic information provided in these reports. We strongly recommend lymphoma societies to publish guidelines regarding the diagnostic and therapeutic approaches needed for the practicing physicians. We also recommend to conduct collaborative studies so that a good number of patients can be recruited to further elucidate this disease entity from different aspects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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