Rare Subtypes of Extranodal T-Cell Lymphoma

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Introduction

In 2008, two major publications clarified the importance of improving the diagnosis and outcomes of peripheral T-cell lymphoma. The first was the fourth edition of the World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues [1]. This project classified the mature T-cell and natural killer (NK)-cell neoplasms into over 20 subtypes, with six new subtypes added, in an effort to standardize the diagnostic criteria for these lymphomas which are often misdiagnosed due to unfamiliarity of the clinical picture from which they arise. The second was the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes by Vose et al. [2], which showed the distribution of the different subtypes (shown in Fig. 1.1) and reported outcomes. The extranodal group includes a number of less common entities described primarily by their tissue tropism. This includes the, including hepatosplenic T-cell lymphomas (HSTLs), intestinal T-cell lymphomas, and the panniculitis-like T-cell lymphomas. A new provisional entity included in this group is the primary cutaneous gamma delta T-cell lymphomas. The frequency of these subtypes is low, and treatment algorithms for most of the rare subtypes have not been well established. Outcomes for the rare subtypes of T-cell lymphomas are shown in Table 7.1.

Hepatosplenic T-Cell Lymphoma

Normal γ/δ T-cells are a small subset of cytotoxic T-cells that preferentially exhibit homing to epithelial rich tissue and sinusoidal areas of the splenic red pulp. These γ/δ T-cells originate from CD4 to CD8- (double negative) precursors, and have the potential to mature outside the thymus. When activated, γ/δ T-cells can express NK cell-associated surface and cytoplasmic molecules, suggesting a function similar to NK cells [3]. γ/δ T-cells also bear T-cell receptors (TCRs) with less discriminate antigen specificity and can recognize antigens of multiple pathogens. One hypothesis for the origin of the γ/δ T-cell lymphomas is that polyclonal expansion of the γ/δ T-cells due to external or internal stimuli occurs and may give rise to transforming events lead to the development of a monoclonal process, such as HSTL [3].

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Table 7.1 Outcomes for PTCL by histologic type (Based on data from Vose et al. [2])

Diagnosis	5-year OS	5-year FFS
PTCL-NOS	32	20
Angioimmunoblastic	32	18
ALCL ALK+	70	60
ALCL ALK−	49	36
Nasal NKT	42	29
Extranasal NKT	9	6
Enteropathy associated	20	4
Hepatosplenic	7	0
Subcutaneous panniculitis	64	24
Adult T-cell leukemia	14	12

OS overall survival; *FFS* failure-free survival; *PTCL* peripheral T-cell lymphoma; *NOS* not otherwise specified; *NKTCL* natural killer/T-cell lymphoma; *ATLL* adult T-cell leukemia/lymphoma; *ALCL* anaplastic large-cell lymphoma

HSTL was first described in 1990 by Farcet et al. [4]. Two patients with systemic symptoms, hepatosplenomegaly, thrombocytopenia, and absence of lymphadenopathy, were described. Both were found to have a sinusoidal pattern of infiltration of the liver with CD3+TCRγ/δ T-cells. This was in contrast to the usual lymphomatous infiltration of the portal tracts of the liver and white pulp of the spleen in other types of T and B-cell lymphomas. These two patients had rapid progression of their disease despite treatment. HSTL comprises only 1.4% of peripheral and NK-cell lymphomas worldwide, but it is one of the most aggressive PTCL subtypes, with a dismal 7%, 5-year survival. Most patients succumb within one year [2]. HSTL most commonly occurs in males in the fourth decade of life and is more common in North America and Europe than in Asia.

Risk factors for HSTL include a history of immune suppression, and the disease occurs with increased frequency in the setting of organ transplant recipients and patient with autoimmune disorders, such as inflammatory bowel disease (especially those receiving thiopurines), lupus, Sjogren's syndrome, Hodgkin's lymphoma and malaria [5]. EBV does not appear to be associated with HSTL, though it has been associated with post-transplant lymphoproliferative disorder [5]. Recently, the incidence of HSTL has been reviewed in patients with inflammatory bowel disease. Schmidt et al. reported that eight cases were identified through the FDA's Adverse Event Reporting System [6]. Kotylar et al. reviewed 36 cases of HSTL in patients with inflammatory bowel disease, 20 of which received infliximab and a thiopurine and 16 received thiopurine therapy alone [7]. Most of the patients were under age 35 and only two were females. The median time from onset of thiopurine agents and diagnosis of HSTL was 5.5 years, and the median number of doses of infliximab was three. Of the 36 patients, only 8 are alive. They identified an increased risk of developing HSTL in patients receiving combination therapy with thiopurine an anti-TNF agents compared to those receiving monotherapy with thiopurines, but there was no increased risk identified in patients receiving only anti-TNF therapy.

The clinical features of HSTLs are described in Table 7.2. The morphology of HSTL demonstrates clusters of monomorphic medium-sized T-lymphoid cells with loosely condensed chromatin and a pale rim of cytoplasm. The infiltrate is seen in both the liver and the spleen. There is sinusoidal infiltration of the splenic red pulp with resultant atrophy of the white pulp, as shown in Fig. 7.1. The liver exhibits sinusoid expansion and sparing of the portal triads without hepatocyte destruction [1]. Bone marrow involvement is seen in two-thirds of patients with HSTL [8]. The immunohistochemical profile of this lymphoma is typically CD2+, CD3+, CD4−, CD5−, CD7+, CD8−, and either γ/δ or α/β, although the majority are γ/δ. Rare cases may be CD8 positive. The NK antigens, CD16 and CD56, are frequently expressed. Although the WHO 2008 does not distinguish γ/δ from α/β HSTL, the γ/δ phenotype predominates and contributes to the poor prognosis in HSTL similar to other non-hepatosplenic γ/δ T-cell lymphomas.

The HSTL cells exhibit clonality with gene rearrangements of the TCR. The TCR-Vδ expression is restricted to Vδ1, and Vδ1 associates with different Vγ regions. This is in contrast to the Vδ2 usage by non-HSTL such as primary cutaneous γ/δ T-cell lymphoma [7]. The majority of HSTL show recurrent cytogenetic abnormalities, namely

Table 7.2 Hepatosplenic T-cell lymphoma

Clinical features	Hepatosplenomegaly, no adenopathy
	Mostly occurs in young men
	Bone marrow involvement (cytopenias)
	Increased risk in IBD patients with thiopurine and anti-TNF agents
Immunophenotypic features	CD2+, CD3+, CD4−, CD5−, CD7+, CD8− Most are
	Some patients express CD8 or NK markers (CD16, CD56)
	Inactive cytotoxic phenotype (TIA-1+, perforin−)
Genetics	TCR γδ
	Isochromosome 7q in 40–70%
Outcome	Median survival 8–12 months

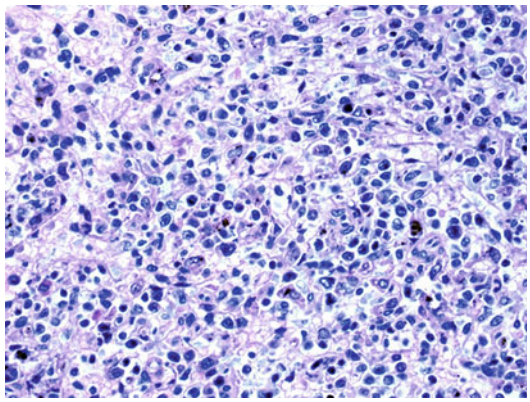

Fig. 7.1 Diffuse atypical T cell infiltrate of the splenic red pulp (hepatosplenic T cell lymphoma) (H&E stain)

isochromosome 7q which almost invariably is associated with trisomy 8 [6, 7]. These cytogenetic abnormalities while diagnostically useful do not have prognostic significance [8]. Recent data has shown that γ/δ HSTL shows a distinct gene expression profiling signature from PTCL including α/β PTCL and γ/δ PTCL. NK-associated molecules such as KIR and killer lectin-like receptors have been found to be overexpressed [9].

Published experience in treating HSTL include multiple induction regimens, most commonly CHOP-(cyclophosphamide, doxorubicin, vincristine, prednisone)-like and platinum-based lymphoma regimens [6, 7, 9]. Although responses have been seen in approximately two-thirds of HSTL, responses are brief. Platinum and cytarabine-based induction therapy has resulted in sustained responses [7]. There are also reports of patients responding to purine analog therapy, such as 2′deoxycoformycin [10]. One adolescent with HSTL treated with an aggressive pediatric T-cell leukemia regimen followed by allogeneic stem cell transplantation also has shown a sustained response [11]. Sequential combination chemotherapy such as IDSHAP/AMDBIDCOS/MINE, and monoclonal antibody combination therapy such as pentostatin/alemtuzumab have induced complete responses [12]. Falchook et al. reported 15 cases of HSTL [13]. Of these, seven had a complete response to chemotherapy and three underwent a stem cell transplant. The duration of CR was 8 months, and median OS was 13 months for the CR vs. 8 months for nonresponders. Adverse prognostic factors included male gender, failure to achieve a CR with chemotherapy, and absence of a detectable TCR rearrangement in the gamma chain. Due to demonstrable graft vs. lymphoma effect, allogeneic stem cell transplantation should be offered to all eligible patients, including those who are in first remission, as it seems to be the only chance for a durable remission [5]. With respect to newer agents, Piekerz et al. reported that one patient with relapsed HSTL had a partial response with a duration of 8 months with romidepsin.

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is characterized by infiltration of malignant T-lymphocytes in subcutaneous tissue, often rimming the fat lobules. Although SPTCL has been recognized as a distinctive entity in the category of peripheral T-cell lymphoma in the WHO classification, its diagnostic criteria has been redefined by the recent WHO-European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas. The term SPTCL is now restricted to primary tumors expressing the alpha/beta TCR

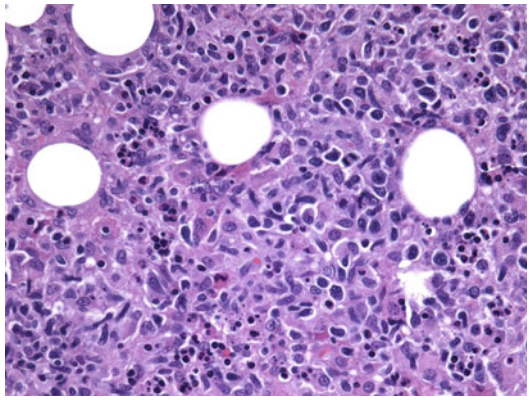

Fig. 7.2 Diffuse atypical T cell infiltrate of deep subcutaneous tissues of the thigh with growth around fat cells (subcutaneous panniculitis-like T cell lymphoma) (H&E stain)

phenotype. These lymphomas are usually CD3(+), CD4(−), CD8(+), and CD56(−), and usually have an indolent clinical course. The tumors expressing the gamma/delta phenotype have been reclassified as primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL) [14].

SPTCL usually presents with one or multiple subcutaneous nodules involving one or multiple areas of the body and often in the absence of extracutaneous disease. The nodules may resemble benign panniculitis and vary in size, but occasionally they may become necrotic and ulcerate. Systemic symptoms, including fevers, weight loss, and pancytopenia may also occur. The pancytopenia is often cytokine-mediated, as bone marrow involvement is rare [15, 16]. The histopathology is often distinctive, with atypical T-lymphocytes surrounding fat globules, as shown in Fig. 7.2.

Atypical lymphocyte lobular panniculitis is a benign entity which may be confused with SPTCL (Table 7.3). ALLP is manifest by the appearance of waxing and waning bruise-like plaques with no constitutional symptoms. The disease occurs in young women and is not ulcerative. The lesions demonstrate many of the same features as SPTCL but have less evidence of fat necrosis, and many cases are polyclonal. Another entity which overlaps SPTCL is lupus panniculitis. While clinical manifestations may be different, it is often difficult to distinguish between these entities based on histopathology. Microscopic findings that can help to distinguish LEP from SPTCL include vacuolar change at the dermal–epidermal interface, periadnexal lymphocytic infiltrates, and mucin deposition in the reticular dermis. Clusters of B-lymphocytes and plasma cells may also be seen in lupus panniculitis. Lupus panniculitis is often polyclonal and classically presents on the face or upper trunk. Studies have shown that there may be overlap between ALLP and lupus panniculitis and SPTCL, and the EORTC retrospective study reported that 19% of patients with SPTCL had autoimmune diseases, including four with lupus.

The clinical course for patients with SPTCL has been highly variable, due in part to the small number of cases reported and to the fact that until recently the distinction between the alpha/beta and gamma/delta subtypes had not been uniformly made at diagnosis. Other than alpha/beta vs. gamma/delta, Kong et al. have reviewed 22 cases of SPTCL in Asia and have identified angioinvasion as a poor prognostic marker [17]. In addition, the hemophagocytic syndrome may occur in up to one-third of patients and in some cases may be fulminant.

PCGD-TCL accounts for less than 1% of all cutaneous TCL and are believed to arise from the gamma/delta T-cell compartments within the skin and dermal appendages. PCGD-TCL most commonly presents as diffuse skin involvement with disseminated lesions that mainly affect the extremities and frequently are associated with ulceration and necrosis. The phenotype of PCGD patients is CD3+, CD8− with expression of cytotoxic markers in most cases (TIA-1, granzyme B, perforin). Unlike alpha/beta SPTCL, dissemination to other extranodal sites is frequently, and the majority of patients present with B-symptoms.

A retrospective review by Willemze et al. and the EORTC Cutaneous Lymphoma Group describes clinical features and outcomes of 63 patients with SPTCL and 20 with PCGD-TCL based on careful pathological review of the cases (Table 7.4) [14]. The median age was younger (39 years vs. 59 years) for the SPTCL patients, and there was no difference in the frequency of

Table 7.3 Differential diagnosis of panniculitis like disorders (Based on data from Magro et al. [22])

Atypical lymphocyte lobular panniculitis	SPTCLαβ	Cutaneous γδ T-cell lymphoma
Young women	All ages, 20% are children associated with SLE, RA	Median age 59
Deep plaques, legs frequently, no ulceration	Indurated, nonulcerated nodules	Ulcerative lesions
B symptoms rare	50% have constitutional symptoms, fevers, cytopenias Nodal and BM involvement rare	Most have constitutional symptoms Lymphadenopathy, hepatosplenomegaly, BM frequent
Infiltrate is less, hemorrhage, karyorrhexis, vasculitis absent	Infiltrate has fat necrosis and karyorrhexis without hemorrhage	Angiocentric, extensive hemorrhage and necrosis
No predominance of CD8 cells	CD8+ Nav3 mutation, perforin gene mutations noted	CD3+ CD56+ Few cases are CD8+
May be treated with steroids, methotrexate	Treatment with radiation, steroids, immunosuppressive agents, chemotherapy	Steroids, chemotherapy, denileukin diftitox, Allo BMT
Oligoclonal or clonal TCRR	Clonal TCRR	Clonal TCRR

Table 7.4 Characteristics of SPTCL and primary cutaneous gamma delta T-cell lymphoma (Based on data from Willemze et al. [14])

	SPTCL-AB	SPTCL-GD
PT characteristics	63	29
Age (median)	36	59
Skin ulceration (%)	6	45
Hemophagocytic syndrome (%)	17	45
Pathology		
CD8+ (%)	95	10
CD56+ (%)	0	60
Cytotoxic proteins (%)	100	100
Therapy		
CHOP (%)	49	70
Immunosuppressive (%)	38	10
Radiotherapy (%)	5	5
Response		
CR/PR (%)	67/13	30/35
5-year OS (%)	82	11
5-year EFS (%)	85	11

B-symptoms or bone marrow involvement between the groups. There was a higher frequency of hemophagocytic syndrome in the PCGD group compared to the SPTCL group (45% vs. 17%). When treatment and outcomes were reviewed, it was noted that 50–70% of patients received CHOP like regimens, 10–38% had immunosuppressive therapies, and a small number were treated with radiation or local excision of the nodules. With initial therapy, 80% of patients in the SPTCL group had a response, compared to 65% in the PCGD group. The 5-year OS for the SPTCL patients was 82% vs. 11% for the PCGD patients.

Treatment approaches for SPTCL and PCGD-TCL have not been clearly established. In the retrospective EORTC review, half of the patients were treated with aggressive chemotherapy and several had autologous stem cell transplantation as a consolidation. One-third of the patients were treated with single agent therapies such as methotrexate, prednisone, cyclosporine, chlorambucil, or cyclophosphamide. Sixteen of twenty-four had a complete response, but nine of these relapsed and five subsequently had a durable response on reinstitution of the same therapy. Eight of the patients received CHOP in relapse and three had a CR. Of five patients presenting with a solitary skin relapse, all were treated with local therapy (radiotherapy or surgery) and are in remission. In the PCGD group, 14 of 20 patients received multi-agent chemotherapy and only three had a CR; one patient went on to allogeneic transplant and had a CR

after transplant. Seven patients developed visceral disease and at 12 months, 15 of 20 succumbed from hemophagocytic syndrome or progressive disease.

Other case reports and small series have described responses in SPTCL and PCGD patients. In one single institution review of ten consecutive patients, three (two SPTCL and one PCGD) were treated initially with denileukin diftitox; one each with SPTCL- and PCGD-disease had PR on therapy and have been maintained without PD [18]. Seven patients were treated with cytotoxic chemotherapy regimens. Four of seven achieved a remission after EPOCH (2), denileukin diftitox-CHOP (1) or pentostatin/cyclophosphamide followed by alemtuzumab (1). Four patients (one with refractory -SPTCL, two with refractory PCGD and one with PCGD in first CR after denileukin diftitox-CHOP) underwent allogeneic hematopoietic stem cell (HSCT) from matched-related donors. Two patients are alive 6–13 months after HSCT with no evidence of disease; one patient died in CR from infectious complications of HSCT, and one relapsed 6 month after HSCT and died from PD. At a median follow up of 3 year from diagnosis, eight patients (80%) are alive, including the two patients with SPTCL and six of eight patients with PCGD. In patients who were refractory to CHOP in one series, response to cyclosporine was reported in four [19]. Another report has demonstrated the efficacy of a fludarabine-based regimen in one patient with aggressive disease [20].

On the basis of these findings, the treatment approach to PCGD-TCL should be similar to that of other aggressive poor prognosis T-cell lymphomas and should include multi-agent chemotherapy followed by stem cell transplantation from an allogeneic donor if one is available. Patients with SPTCL with a benign clinical behavior may be managed with single agent therapies such as prednisone, cyclosporine, or methotrexate. For those with progressive or disseminated disease or with the hemophagocytic syndrome, multi-agents chemotherapy followed by autologous stem cell transplantation should be considered.

Enteropathy-Associated T-Cell Lymphomas

Enteropathy-type T-cell lymphoma (ETCL) is a rare primary extranodal T-cell lymphoma in characterized by infiltration of malignant T-cell within the gastrointestinal epithelium, as shown in Fig. 7.3. ETCL represents 4.7% of cases of PTCL around the world, but the incidence is higher in North America and Europe compared to Asia. While the WHO classification identifies ETCL as a distinct clinicopathologic entity, there are two distinct histolopathologic subtypes, EATL type 1, which is associated with a history of celiac sprue, and EATL type 2 (Table 7.5).

EATL type 1 is more frequent (80–90% of cases) and is a pleomorphic infiltrate of anaplastic T-lymphocytes with a phenotype that is CD3+, CD7+, CD5-CD8-CD4–, CD103+. The tumor cells may express cytotoxic markers such as TIA-1, and a subset may express CD30. EATL type 2 occurs sporadically and is composed of monomorphic populations of T-cells which are characteristically CD3+, CD8+ and CD56+. Chromosomal abnormalities found in EATL include gains at chromosome 9q33-q34 in up to 70% of cases. In the International T-cell Lymphoma Project, 69% of EATL patients had Stage III/IV disease at presentation. Bone marrow involvement was rare and occurred in only

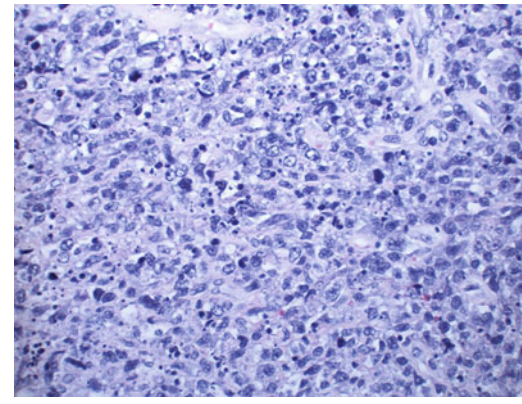

Fig. 7.3 Diffuse atypical T cell infiltrate infiltrating the wall of the small bowel (enteropathy-associated T cell lymphoma) (H&E stain)

Table 7.5 Enteropathy-associated T-cell lymphomas

EATL type1	EATL type 2
80–90% of cases	10–20%
Associated with celiac disease	Sporadic
Polymorphic lymphoid infiltrate	Monomorphic infiltrate
CD3+,CD7+, CD8− (20%+), TCRβ+/− Maybe CD30+	CD3+, CD4−, CD8+, CD56+, TCRβ+
Intraepithelial lymphocytes abnormal	Intraepithelial lymphocytes normal
9q+1q+5q+and 16q- abnormalities	9q+16q- 8q+(myc) abnormalities
Presents with weight loss	Presents with obstruction/ perforation

3% of cases, and only 25% of patients had a low IPI (0–1) [2].

The clinical approach for most patients is resection of the mass if the diagnosis is made at the time of laparotomy, followed by chemotherapy. The 5-year OS and PFS were 20% and 4% respectively. Even for the low IPI group, 5-year survival was only 29%. Recent strategies to improve outcomes have included more aggressive treatment regimens and introduction of non-anthracycline based regimens in the first line. The Nordic group reported results from 21 patients treated with CHOEP-14 followed by stem cell transplant. On that study, 33% of patients never made it to transplant due to progressive disease, and at 45 month follow up, 10 (45%) of patients were still alive [21]. Lennerd et al. have reported the use of CHOP×1 cycle followed by three cycles of ifosfamide/etoposide/epirubicin with intermediate dose methotrexate and then autologous stem cell transplantation. With this regimen, they have reported a response rate of 69% with a 5-year survival of 60%. Thus far there has been no data comparing outcomes with autologous vs. allogeneic stem cell transplantation in EATL, but patients with high IPI should be considered for clinical trials testing this approach. There is little data on efficacy of salvage therapy in EATL, so the treatment focus should be on effective first line therapy followed by a consolidation with stem cell transplantation.

Summary and Conclusions

The rare subtypes of aggressive T-cell lymphomas represent a diagnostic and a therapeutic challenge. The extranodal subtypes, including HSTL, enteropathy-associated T-cell lymphoma, and the panniculitis-like T-cell lymphomas have not been well-defined, and these patients are not well represented in multi-center trials due to their rarity. Therapeutic advances may be dependent on new insights into the biology of these diseases and identification of potential molecular targets.

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