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Invited review article

Erythrodermic cutaneous T-cell lymphoma: How to differentiate this rare disease from atopic dermatitis

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ABSTRACT

Sézary syndrome and erythrodermic mycosis fungoides have been recognized as part of a broader spectrum of erythrodermic cutaneous T-cell lymphoma (E-CTCL). Atopic dermatitis (AD) is the most common, chronic inflammatory skin disease and can, in its most severe form, manifest as erythroderma. It is often difficult to clinically distinguish E-CTCL from various common and benign diseases presenting as erythroderma, including AD. Differentiating E-CTCL from benign inflammatory diseases is important to ensure proper disease management, and to provide accurate prognostic information. Clinical and laboratory features, including pruritus and serum levels of soluble interleukin-2 receptor, lactate dehydrogenase (LDH), immunoglobulin E (IgE), and several chemokines, do not differentiate E-CTCL from AD. In contrast, low serum allergen-specific IgE levels, presence of Sézary cells in peripheral blood, histological findings, and high CD4/CD8 ratio and CCR10 positivity in lesional skin are helpful in reaching a correct diagnosis. Patients with E-CTCL have been treated with oral etretinate, intravenous or subcutaneous interferon, bexarotene, extracorporeal photopheresis, total body surface electron beam, chemotherapy, or any combination of these modalities. Older patients, high serum LDH levels, and high number of circulating atypical lymphocytes are associated with poor prognosis.

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1. Introduction

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common types of cutaneous T-cell lymphoma (CTCL) [1]. MF has a classically prolonged clinical course that progresses over years through patch, plaque, and tumor stages, followed by lymph node and visceral involvement. SS is characterized by the triad of generalized erythroderma (defined as affecting >80% of total body

surface area; Fig. 1A) [2], lymphadenopathy, and presence of more than 1000 mm^{-3} circulating atypical T-cells with cerebriform nuclei, so-called Sézary cells. Individuals with SS usually show rapid disease progression compared to MF. Although SS and MF are classified as distinct, separate entities, some patients with MF can evolve into SS [3,4]. In other cases with MF, skin lesions become confluent and finally develop into erythroderma without blood involvement, which is labeled as erythrodermic MF. SS and erythrodermic MF have been recognized as part of a broader spectrum of erythrodermic CTCL (E-CTCL).

A variety of other diseases such as atopic dermatitis (AD), psoriasis, drug eruption, pityriasis rubra pilaris, and chronic actinic

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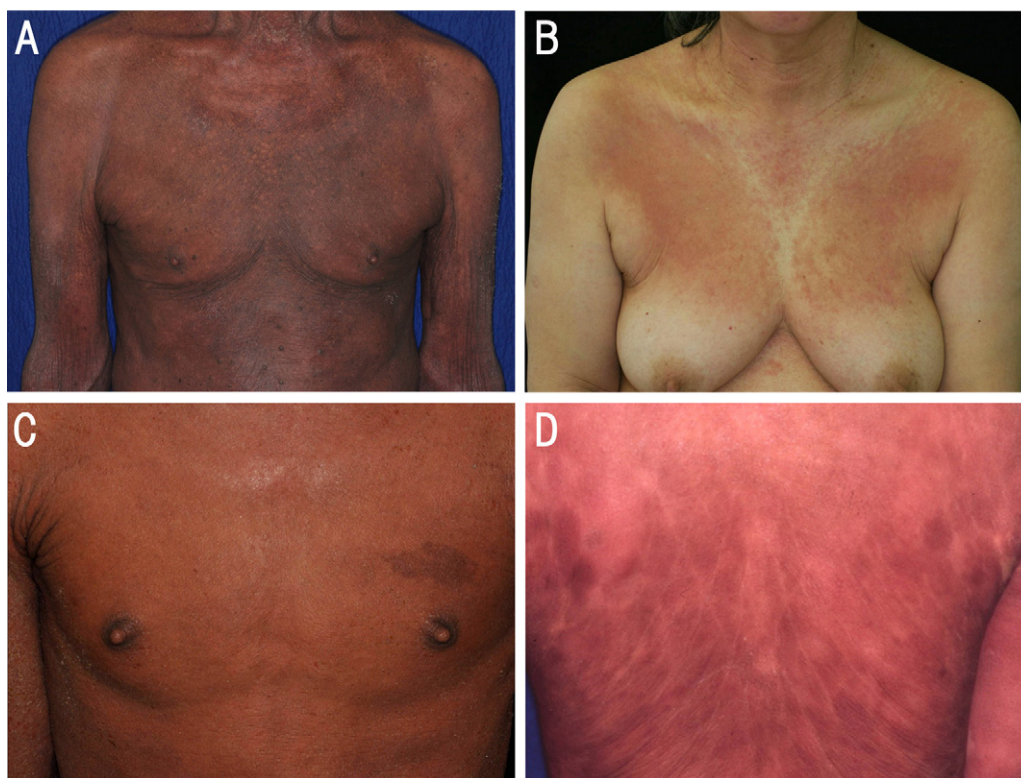


Fig. 1. (A) Erythroderma in Sézary syndrome. (B) A patient with mycosis fungoides who later developed Sézary syndrome (Case no. 7). (C) A patient with erythrodermic atopic dermatitis. (D) Excoriation in a patient with erythrodermic mycosis fungoides.

dermatitis can manifest with erythroderma [5]. AD is the most common, chronic inflammatory skin disease that is often difficult to clinically distinguish from E-CTCL because MF/SS and AD often have the same laboratory features. MF/SS is regarded as a Th2-type disease, frequently accompanied with eosinophilia and high serum levels of immunoglobulin E (IgE). Previous data also suggested that circulating tumor cells of SS have Th2-like properties, with increased capacity to secrete interleukin 4 (IL-4) and IL-5 [6,7]. In addition, in some reports, tumor cells in lesional skin of advanced MF/SS have a Th2 phenotype, characterized by increased IL-4, IL-5, IL-10, and IL-13 production [8,9]. AD is also characterized by the presence of a specific IgE response in association with Th2-mediated immune responses. Differentiation of E-CTCL from benign inflammatory diseases, including AD, although difficult, is important to ensure proper management of the patient's disease, and to provide

accurate prognostic information. In this review, we give an overview of E-CTCL, focusing on key findings to differentiate this rare disease from AD. Nine cases of E-CTCL who came to our department between 1999 and 2010 are summarized in Table 1.

2. Clinical presentation

Patients with E-CTCL have generalized erythroderma. Some cases, however, show limited skin lesions at initial visits and later develop erythroderma. Case no. 7 in Table 1 was one of those cases. This patient first had erythematous patches with slight scaling characterized by severe pruritus on the chest, lower back, lower abdomen, and both knees (Fig. 1B). The distribution of the lesions was symmetric and the plaques were poorly demarcated, covering less than 80% of the body. She also demonstrated circulating tumor

Table 1
Summary of nine cases of E-CTCL between 1999 and 2010.

Case	Age (years)	Sex	Laboratory data				Pruritus	Stage	Therapy	Outcome
			sIL-2R (U/ml)	LDH (IU/l)	Sézary cells (/μl)	IgE (IU/ml)				
1	63	M	2203	232	0	ND	–	IIIA	NbUVB Etoposide MTX Etoposide	Died of PD at 20 months
2	33	F	1519	499	0	3.3	+	IVA	CHOP Allo-PBSCT	ANED at 65 months
3	42	M	1535	408	2726	ND	+	IVA	NbUVB	Alive with disease at 13 months
4	42	F	1488	383	4048	15,000	+	IVA	NbUVB Etoposide CHOP uBMT	Died of PD at 53 months
5	77	M	1880	222	9802	44	+	IVA	Etoposide MTX	Alive with disease at 9 months
6	65	M	6060	727	13,970	37	+	IVA	NbUVB IFN-γCYP	Died of PD at 14 months
7	64	F	1824	380	14,535	5	+	IVA	NbUVB	Alive with disease at 30 months
8	63	M	2943	344	18,000	1800	+	IVA	PUVA IFN-γ	Died of PD at 48 months
9	54	F	3475	915	78,088	2600	+	IVA	NbUVB IFN-γMTX CYP Etoposide	Died of PD at 21 months

CHOP; cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy, PBSCT; peripheral blood stem cell transplantation, ANED; alive with no evidence of disease, ND; not done, NbUVB; narrow band ultraviolet B therapy, MTX; methotrexate, PD; progressive disease, PUVA; psoralen-ultraviolet A therapy, CYP; cyclophosphamide, uBMT; unrelated bone marrow transplantation.

cells. Several months later, she developed erythroderma and met clinical criteria for SS. Skin lesions of AD are also characterized by poor demarcation and symmetric distribution. They sometimes manifest as erythroderma (Fig. 1C). Thus, it is difficult to differentiate E-CTCL from AD based solely upon clinical presentation.

Patients with AD usually suffer from severe pruritus, while patients with early stage patch/plaque MF usually have no pruritus or other symptoms. Thus, pruritus is often helpful in differentiating early stage MF from AD. Patients with tumor stage MF or E-CTCL, however, often report severe pruritus [10]. Indeed, the reduction of pruritus is one of the endpoints in some clinical trials for MF/SS [11]. Among 65 total patients with MF/SS seen in our facility, only 30.8% were treated with oral antihistamine. 72.7% of patients with tumor stage MF, however, were treated with antihistamines. Moreover, eight out of nine cases of E-CTCL suffered from pruritus (Cases 2–9 in Table 1), and seven were treated with antihistamines (Fig. 1D). Thus, in most cases, we could not differentiate E-CTCL from AD using pruritus as a sole clinical criterion.

3. Laboratory features

In early stage MF/SS, Th1 immune responses are dominant, evidenced by increased IL-2 and interferon (IFN)- γ production by peripheral blood mononuclear cells [12]. On the other hand, E-CTCL and AD are characterized by Th2-dominant immune responses [13]. A Th2 pattern of cytokines may give rise to elevated serum IgE levels and eosinophilia, and may lead to increased susceptibility to infection. In our database, serum IgE levels were elevated in 86% (6/7) of tumor stage MF and 43% (3/7) of E-CTCL, while they were elevated only in 14% of patch/plaque stage MF patients (4/29). When specific IgE antibodies to food, dust mite, or microbes were examined by the radioallergosorbent (RAST) test, a high number of positive reactions are usually found in AD patients [14]. Specific IgE may play a critical role in cutaneous inflammation, activating mast cells and dendritic cells via high-affinity Fc receptors [15]. Patients with MF/SS show positive RAST reactions only in limited cases [16]. RAST reactions against house dust and house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farina*) were detected in 21 of our MF/SS cases (Table 2). RAST scores to house dust and mites were 0 in the majority of cases, which may help to distinguish MF/SS from AD. Three of seven E-CTCL cases, however, showed high serum IgE levels and positive RAST reactions to house dust or house dust mites (Cases 4, 8, and 9 in Table 1). Thus, high IgE levels and RAST scores do not necessary mean AD, while low serum IgE levels

and negative RAST reactions in erythrodermic patients favor the possibility of E-CTCL.

Serum lactate dehydrogenase (LDH) and soluble IL-2 receptor (sIL-2R) levels are reported to be disease severity markers of MF/SS [17,18]. They are, however, also elevated in AD patients [19,20], suggesting that they are not disease-specific markers. Recently, other than serum LDH and sIL-2R levels, several serum chemokine levels have been reported to correlate with disease severity of MF/SS. Chemokines are small molecules of 8–10 kDa that induce chemotaxis and activation of certain subsets of leukocytes. Serum levels of CC chemokine ligand (CCL) 17, also called thymus and activation-regulated chemokine (TARC), are elevated in patients with MF/SS and correlate with serum LDH and sIL-2R levels [21]. CCL17 recruits cells expressing its receptor, CC chemokine receptor (CCR) 4 or CCR8 [22]. Based on reports describing CCR4 expression on tumor cells of MF with large cell transformation and SS [23,24], CCL17–CCR4 interactions may play an important role in disease progression of MF/SS. Serum levels of CCL27, also called cutaneous T-cell attracting chemokines (CTACK), are also elevated in patients with MF/SS and correlate with serum sIL-2R levels [25]. Its sole receptor, CCR10, is expressed on tumor cells of MF and SS [24], suggesting that CCL27–CCR10 interactions may be involved in the pathogenesis of MF/SS. In addition, CCL11, also called eotaxin, and CCL26, also called eotaxin-3, levels are elevated in sera of MF/SS patients, and correlate with serum sIL-2R levels [26]. CCL11, CCL26, and their receptor, CCR3, may also play roles in a Th2-dominant tumor environment, which is closely correlated with the development of MF/SS [6,7,26]. Serum levels of these chemokines, however, are also elevated in patients with AD, and correlated with disease severity [27–30]. Serum CCL17, CCL27, and CCL26 levels in patients with E-CTCL, severe AD, and in healthy controls examined in our facility are shown in Table 3, which clearly shows that E-CTCL cannot be differentiated from severe AD by serum levels of these chemokines.

4. Sézary cells

SS is marked by the presence of Sézary cells in peripheral blood. They usually express CD4, but lack CD8, as a high ratio of CD4+ to CD8+ T lymphocytes (CD4/CD8 ratio; >10) in peripheral blood is one of the diagnostic criteria for blood involvement [2]. There has been an increasing awareness that Sézary cells often lack normal T-cell markers such as CD7 and CD26 [31,32]. As circulating T cells in patients with benign inflammatory skin diseases may also show CD7 deletion [31,33], loss of CD26 may be a more specific phenotype for Sézary cells [32]. Besides, Sézary cells over-express

Table 2

Summary of radioallergosorbent test (RAST) against house dust and house dust mites in MF/SS (n=21).

	Class						
	0	1	2	3	4	5	6
House dust	70%	15%	0%	0%	5%	10%	0%
<i>Dermatophagoides pteronyssinus</i>	66.7%	9.5%	4.8%	0%	4.8%	9.5%	4.8%
<i>Dermatophagoides farina</i>	66.7%	9.5%	4.8%	0%	0%	9.5%	9.5%

Table 3

Serum levels of CCL17, CCL27, and CCL26 in patients with E-CTCL, severe AD, and healthy controls.

	E-CTCL	Severe AD	Healthy control
CCL17 (pg/ml)	17856.6 $\pm$ 21352.6* (n=5)	13037.6 $\pm$ 17518.6** (n=14)	215.3 $\pm$ 119.8 (n=20)
CCL27 (pg/ml)	1198.8 $\pm$ 469.7* (n=4)	2784.8 $\pm$ 1560.0** (n=16)	577.1 $\pm$ 221.9 (n=22)
CCL26 (pg/ml)	40.4 $\pm$ 22.4** (n=5)	62.2 $\pm$ 24.2** (n=7)	11.0 $\pm$ 2.5 (n=20)

CCL, CC chemokine ligand; E-CTCL, erythrodermic cutaneous T cell lymphoma; AD, atopic dermatitis.

* P < 0.05 compared to healthy control.

** P < 0.01 compared to healthy control.

CD60 and lack CD49d [34,35]. Recently, CD158k/KIR3DL2, which is an MHC class I antigen receptor that belongs to the family of natural killer (NK) cell immunoglobulin-like receptors, has been identified as a new phenotypic marker for circulating Sézary cells [36]. In normal individuals, expression of CD158k is highly restricted to a minor NK cell subset and rare CD3+ CD8+ circulating T lymphocytes [37]. On the other hand, in patients with SS, CD158k is highly expressed on circulating Sézary cells [36,38,39]. Gene expression analysis has revealed that T-plastin (a member of a highly conserved cytoplasmic protein family), EphA4, the Eph-receptor subfamily of transmembrane protein-tyrosine kinases, and the transcription factor Twist, which functions as a regulator of mesodermal differentiation, are all aberrantly expressed on Sézary cells [40,41]. Thus, the presence of Sézary cells in peripheral blood in erythrodermic patients is highly suggestive of SS.

5. Histologic findings

Histopathologically, MF/SS exhibits dense infiltrates in the epidermis as well as the papillary dermis that includes small,

medium-sized, and occasionally large atypical mononuclear cells with hyperchromatic, indented nuclei (Fig. 2A). Because epidermotropism of atypical lymphocytes is not seen in AD skin, this histologic finding is a key in distinguishing MF/SS from AD. However, in some cases, especially in cases with E-CTCL, epidermotropism is not evident (Fig. 2B). Therefore, differential diagnosis between AD and E-CTCL by histology is sometimes very difficult.

Tumor cells of MF/SS are usually positive for CD3, CD4, and CD45RO, and negative for CD8. Due to monoclonal proliferation of tumor cells, a high CD4/CD8 ratio is detected in lesional skin of MF/SS (Fig. 2C and D), which is not commonly seen in AD. As previously described, both CCR4 and CCR10 are expressed on tumor cells of MF/SS. CCR4 is also expressed on lymphocytes from cutaneous inflammatory diseases such as delayed-hypersensitivity and chancroid, while CCR10 expression is rarely detected on normal lymphocytes [42]. When we analyzed CCR10 expression on infiltrating lymphocytes in five samples of E-CTCL and 11 samples of inflammatory skin diseases (including AD), CCR10+ lymphocytes were detected in 100% of E-CTCL, while they were seen in only 7.1% of inflammatory skin disease samples (Fig. 2E and F). Thus,

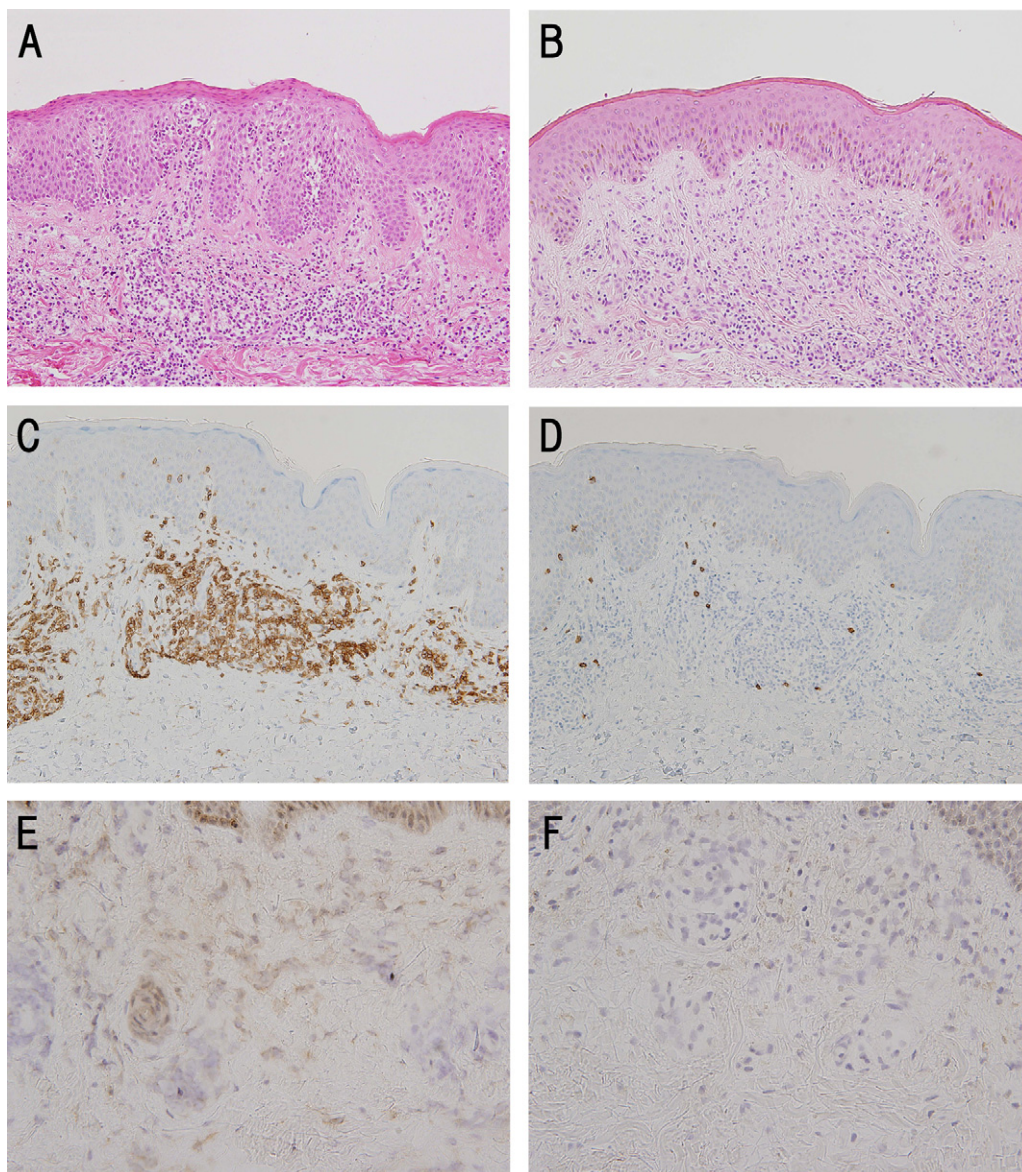


Fig. 2. Histologic findings of erythrodermic cutaneous T cell lymphoma (E-CTCL) with marked epidermotropism (A) and those with scant infiltrates in the epidermis (B). Immunohistochemical staining of E-CTCL for CD4 (C) and CD8 (D). Immunohistochemical staining of E-CTCL (E) and atopic dermatitis (F) for CCR10.

infiltration of CCR10+ lymphocytes may be helpful in the diagnosis of E-CTCL.

6. Therapy

Patients with E-CTCL are classified as stage III or IV based on the TNM classification of MF/SS proposed by the International Society for Cutaneous Lymphomas and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer [2]. In Japan, these patients are treated with oral etretinate, intravenous IFN- γ , total body surface electron beam, chemotherapy, or any combination of these modalities. There is no recommended treatment specific to E-CTCL. In some cases, ultraviolet irradiation is effective (Cases 4, 5, 7, and 8 in Table 1). Not only did we see improvement of skin lesions, but we observed decreases in Sézary cells in peripheral blood, suggesting that the skin was a source of circulating Sézary cells, or a main source for T cell growth factors [43]. Various single or combination chemotherapies have been utilized as treatment for advanced MF/SS. However, there have been no significant differences in efficacy between any single agent and combination chemotherapy. Moreover, efficacy of chemotherapy is limited [44]. Thus, considering the side effects of chemotherapeutic agents, single agent chemotherapy, but not combination chemotherapy, is usually implemented. In our country, methotrexate (MTX), cyclophosphamide, and etoposide have been frequently used. Allogeneic hematopoietic stem cell transplantation has also been tried as treatment for advanced MF/SS, and provides a potentially curative treatment option, although autologous hematopoietic stem cell transplantation have yielded disappointing results due to a high frequency of relapse [44]. A proposed graft-versus-lymphoma effect is thought to be responsible for higher effectiveness of allogeneic transplantation. Extracorporeal photopheresis (ECP), IFN- α , bexarotene, low-dose MTX, IL-2 fusion toxin (Denileukin diftitox), and their combination are recommended treatment modalities in the United States [44]. ECP is an apheresis procedure that targets the circulating malignant clone in patients with CTCL. During ECP, induction of apoptosis in tumor cells and a conversion of blood monocytes to dendritic cells are supposed to induce an immune response against the malignant clone. ECP is a well-established therapy for CTCL and has been recommended as a first-line treatment for E-CTCL. Subcutaneous or intramuscular injections of interferon- α are effective probably because of its cytotoxic, antiproliferative, and antiviral properties. Bexarotene is a synthetic retinoid that binds selectively to the retinoid X receptor isoforms, affecting tumor cells by inhibition of their proliferation, promotion to terminal differentiation, and induction of apoptosis. Denileukin diftitox is a recombinant fusion protein containing the peptide sequences for the enzymatic activity and membrane translocatory domains of diphtheria toxin followed by sequences from human IL-2. The drug is effective for the treatment of CD25 $\pm$ CTCL. Purine analogs, gemcitabine, histone deacetylase inhibitors, and humanized anti-CD52 monoclonal antibodies (Alemtuzumab) have also been utilized as treatments for MF/SS, especially in countries outside of Japan.

7. Prognosis

The overall prognosis of patients with E-CTCL, especially SS, is poor. Based on a recent study from Great Britain, the 5-year survival rate for patients with stage III disease (E-CTCL) was 40–47%; for patients with stage IVA1 disease (SS), it was 37% [45]. Median survival was 3.4–4.7 years and 3.8 years, respectively. Vidulich et al. also reported that 5-year survival rate for E-CTCL patients was 51% and that the median overall survival was 5.1 years [46]. There have been several reports describing prognostic

factors of E-CTCL or SS [46–50]. Among them, high age [46,47,49] and high serum LDH levels [46,48–50] were found to be associated with poorer prognosis of E-CTCL or SS. In addition, the number of circulating atypical lymphocytes is also considered a poor prognostic factor for patients with E-CTCL or SS [46,48]. Only one out of nine E-CTCL patients seen at our facility has survived more than 5 years (Table 1). The individual was 33-year-old woman who received an allogeneic peripheral blood stem cell transplantation. Two of three E-CTCL patients who died of progressive disease within two years after presentation showed high serum sIL-2R (>3000 U/ml) and LDH levels (>700 IU/l; Cases 6 and 9 in Table 1). Further study is needed to investigate prognostic factors of E-CTCL.

8. Conclusion

E-CTCL is characterized by erythroderma, severe pruritus, high serum IgE and chemokine levels, and less epidermotropism of tumor cells. These features make E-CTCL distinct from patch/plaque stage MF. Most of these same feature, however, are also commonly seen in AD patients, making it very difficult to reach a correct diagnosis. Low serum IgE levels and negative RAST reactions in erythrodermic patients, Sézary cells in peripheral blood, and a high CD4/CD8 ratio and CCR10+ cells in lesional skin may help distinguish E-CTCL from AD. The prognosis of E-CTCL is poor and the development of new therapeutic approaches is needed.

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