Dermatol Ther (Heidelb) (2023) 13:835–842
https://doi.org/10.1007/s13555-023-00895-2

BRIEF REPORT

Healthcare Provider Experience in Diagnosing and Treating Cutaneous T-Cell Lymphoma

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Received: November 24, 2022 / Accepted: January 26, 2023 / Published online: February 2, 2023

ABSTRACT

Introduction: Cutaneous T-cell lymphoma (CTCL) is a rare, heterogeneous group of non-Hodgkin lymphomas characterized by various clinical, molecular, and histopathologic features of the skin. Variants of CTCL share many clinical features with common inflammatory skin diseases such as atopic dermatitis and psoriasis, making accurate and early diagnosis challenging in clinical settings. Inappropriate treatment or a delay in diagnosis can lead to increased morbidity and mortality. Here, we report findings from an online survey that investigated dermatology community practice, knowledge, and education surrounding CTCL.
Methods: An electronic survey of ten questions was developed and approved by physician experts in CTCL to assess experiences in diagnosing and treating CTCL among healthcare providers (HCPs). The survey was deployed to 10,600 US dermatology HCPs, including medical doctors (MDs), doctors of osteopathic medicine (DOs), nurse practitioners (NPs), and physician assistants (PAs) and excluding HCPs associated with CTCL centers of excellence.
Results: Among 44 HCPs who responded and were eligible for inclusion, 82% had diagnosed between one and ten CTCL cases in the last 5 years. Most respondents (91%) reported that they include CTCL in their differential diagnoses after patients do not respond to treatment of more common conditions. Patients with CTCL were frequently diagnosed with other inflammatory dermatoses—most commonly dermatitis and psoriasis—before a CTCL diagnosis, and many were treated with ineffective therapies for years. The most common length of time before a CTCL diagnosis was made was between 1 and 3 years, though 16% of HCPs reported that patients were treated for other diseases or skin conditions for ≥ 5 years. Two-thirds of HCPs agreed that further education surrounding CTCL is needed.
Conclusions: Given the infrequency of CTCL and its similar presentation to other common dermatologic conditions, increased education of CTCL is needed in the dermatology community to improve patient outcomes.

Keywords: Cutaneous; T-cell; Lymphoma; Diagnosis; Inflammatory dermatoses; Non-Hodgkin lymphoma; Survey

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Key Summary Points

Why carry out this study?

Cutaneous T-cell lymphoma (CTCL) shares several clinical features with common skin diseases such as atopic dermatitis and psoriasis, which makes accurate and early diagnosis challenging.

An electronic survey was used to assess experiences in diagnosing and treating CTCL among healthcare providers.

What was learned from the study?

91% of respondents reported that they include CTCL in their differential diagnoses only after patients do not respond to treatments of more common conditions.

Patients may be treated for other diseases and skin conditions with similar symptomatology for up to 5 years before being diagnosed with CTCL.

Increased education of CTCL is urgently needed in the dermatology community to improve patient outcomes.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of T-cell malignancies accounting for less than 4% of non-Hodgkin lymphomas [1]. The most prevalent forms are mycosis fungoides (MF) and Sézary syndrome (SS), which account for 50–60% of all CTCLs [2–5]. A hallmark throughout the progression of CTCL is the development of erythematous patches or plaques, usually located on sun-protected areas of the body, which can progress into erythroderma or tumors in advanced stages [6, 7]. However, other common skin diseases, including atopic dermatitis and psoriasis, share this symptomatology, making them difficult to distinguish from CTCL [8, 9]. Moreover, atopic dermatitis and MF/SS also share a similar immune profile characterized by a T_H2 cytokine-dominant immune response [10, 11].

Early detection of CTCL requires extensive experience, and accurate diagnosis does not rely on any one clinical, biologic, or histopathologic factor [12]. Because CTCL may mirror common inflammatory dermatoses for years, multiple tests must be utilized and performed repeatedly to form a clinicopathologic correlation, with some experts suggesting that accurate diagnosis and treatment require a collaboration between a range of physicians [13, 14]. It is critical that patients with CTCL receive an early diagnosis to ensure an optimal treatment regimen; however, difficulty with differentiating CTCL from other inflammatory diseases with similar symptomatology can lead to delays in diagnosis and poor patient outcomes. Thus, patients may live for many years with the disease without detection and confirmation of diagnosis [15, 16]. Minimizing these delays is imperative, as patients with early-stage CTCL have a 10-year overall survival rate of 50–90%, whereas patients with more advanced disease have a 10-year overall survival rate of 15–53% [2]. To shorten the time to diagnosis, improved education and greater experience are needed among dermatologists and other healthcare providers (HCPs) in the dermatology field.

Although many HCPs associated with centers of excellence (i.e., institutions designed to provide world-class care, innovation, and research for a focused area of medicine) [17] may treat a substantial number of patients with CTCL, it is unclear what the treatment knowledge and experience is among HCPs outside of these centers. Therefore, the objective of this survey-based study of HCPs who actively practice or specialize in dermatology, and who were not associated with centers of excellence, was to assess their experience with diagnosis and treatment of patients with CTCL and to determine further needs for education to decrease time to diagnosis.

METHODS

Using SurveyMonkey (Momentive Inc, San Mateo, CA, USA), we developed an electronic survey of ten questions to assess the experiences in diagnosing and treating CTCL among HCPs who actively practice or specialize in dermatology, including medical doctors (MDs), doctors of osteopathic medicine (DOs), nurse practitioners (NPs), and physician assistants (PAs). A pool of questions for the survey was developed during a virtual meeting and sent to two practicing physicians in CTCL not employed by Ortho Dermatologics, who structured the survey and determined its contents. Physicians removed any questions that represented a conflict of interest or pertained to specific medications until a consensus on ten questions was achieved and the final survey was approved.

Survey questions addressed HCP demographics, experience in diagnosing and treating CTCL, and need for future education on CTCL (Table 1). Surveys were administered through email, with a total of three separate Ortho Dermatologics-branded deployments, to approximately 10,600 US-based HCPs, excluding those associated with centers of excellence. Participants were given roughly 1 month to complete the survey. Forty-five HCPs responded to the survey; 1 respondent who had a non-US-based practice was excluded. Respondents were not compensated for their participation. This analysis was exempt from institutional review board review requirements per US Department of Health and Human Services policy (Title 45 Code of Federal Regulations, Part 46 of the United States), as the survey contains de-identified records.

RESULTS

Included respondents ($N = 44$) were MDs ($n = 18$), DOs ($n = 1$), NPs ($n = 7$), and PAs ($n = 18$) from across the USA, with experience in dermatology spanning from 4 to ≥ 20 years. The survey response rate was $< 1\%$ (44/10,600).

In the last 5 years, 82% of respondents had diagnosed between 1 and 10 cases of CTCL, 16% had diagnosed 11 or more cases, and only 1 HCP reported not having diagnosed any. Among all respondents, the number of diagnosed CTCL cases ranged from 0 to 80. Most respondents (91%) reported that they include CTCL in their differential diagnoses when treatments of more common conditions are unsuccessful (Fig. 1), with similar proportions of this response between MDs (94%) and NPs/PAs (88%). A greater proportion of MDs versus NPs/PAs include CTCL in their differential diagnoses when evaluating patients with patches or plaques (89% versus 60%) or rashes in sun-protected areas of the body (89% versus 48%).

For patients with suspected early-stage CTCL, respondents reported that their first course of action is to manage patients themselves (48%), manage patients with a CTCL-experienced HCP in their practice (32%), or refer patients to a center of excellence (34%) or oncology (32%; Fig. 2a); only 7% of respondents reported that their first course of action involved performing biopsies. A greater proportion of MDs versus NPs/PAs noted that they manage patients with early-stage CTCL themselves (83% versus 20%). Compared with MDs, NPs/PAs were more likely to manage patients in collaboration with another CTCL-experienced HCP in the same practice (17% versus 44%), refer patients to a CTCL center of excellence (28% versus 40%), and refer patients to oncology (22% versus 40%).

Atopic dermatitis, allergic/contact dermatitis, and psoriasis were the top three previously treated skin disorders in patients who were ultimately diagnosed with CTCL (Fig. 2b). The most common length of time that patients were treated for other diseases or skin conditions before receiving a CTCL diagnosis was 1–3 years (59%), though 16% of respondents reported that patients were treated for ≥ 5 years before receiving a CTCL diagnosis. When asked to rate the importance of community education surrounding diagnosis and management of CTCL on a scale of *strongly disagree* to *strongly agree*, no respondents disagreed or strongly disagreed. Two-thirds of respondents strongly agreed that more education surrounding CTCL is needed.

Table 1 Items from the electronic CTCL survey

Number	Questions
1	Which of the following best describes you? (medical doctor; doctor of osteopathic medicine; physician assistant; nurse practitioner)
2	If MD or DO, where did you complete your residency?
3	Indicate the primary 5-digit ZIP code where you currently or most recently practiced
4	How many years have you been treating dermatologic conditions (post-education/residency)?
5	When do you include cutaneous T-cell lymphoma (CTCL) in your differential diagnosis? Check all that apply. [When rash appears in sun-protected areas; When evaluating rashes presenting with patches and/or plaques; When treatment for a more common skin condition has not been successful; I rarely consider CTCL in my differential diagnosis; I always include CTCL when making a differential diagnosis; Not applicable (i.e., retired, not clinically practicing)]
6	In the last 5 years, how many times have you diagnosed CTCL in your practice?
7	When you have suspected a new case of early-stage CTCL, what has been your usual course of action? Check all that apply. [Stage patient and/or send lymph node(s) for pathology; Order imaging tests, such as CT or MRI scans; Refer to a CTCL center of excellence; Refer to oncology; Refer to another physician within my practice who has experience treating CTCL; Refer to a community dermatologist who has experience treating CTCL; Manage early-stage patients myself; Manage early-stage patients in collaboration with another provider in my practice; Not applicable; Other (please specify)]
8	I think the dermatology community would benefit from more education concerning the diagnosis and management of CTCL. (Strongly agree; Agree; Neither disagree nor agree; Disagree; Strongly disagree)
9	CTCL often goes undiagnosed for years. If you have treated a patient (or patients) for skin conditions and/or diseases that were eventually diagnosed as CTCL, for what skin disorder(s) were the patient(s) treated for previously? Check all that apply. [I have not personally diagnosed a patient with CTCL; Allergic and/or contact dermatitis; Atopic dermatitis; Drug reaction; Fungal infection (i.e., tinea corporis); Lichen planus; Parapsoriasis; Pityriasis lichenoides; Psoriasis; Other (please specify)]
10	Regarding the patient(s) in Question 9, on average about how long did the patient(s) receive treatment for the other disease or skin condition before being diagnosed with CTCL? (Check one. If you have seen more than one case like this, please provide an average)

CT computed tomography, *CTCL* cutaneous T-cell lymphoma, *DO* doctor of osteopathic medicine, *MD* medical doctor, *MRI* magnetic resonance imaging

DISCUSSION

The survey was developed to assess HCP experiences in diagnosing and treating CTCL and to determine if further education and collaboration are needed to improve early detection. Results support the premise that CTCL is uncommon, with most respondents reporting that they diagnosed ten or more cases in the last 5 years. Most HCPs reported that they included CTCL in the differential diagnosis once treatment of other conditions failed. Additionally, patients may be treated for other diseases and skin conditions with similar symptomatology for up to 5 years before being ultimately diagnosed with CTCL, suggesting that late detection of CTCL is a common issue and that increased education is needed regarding differential

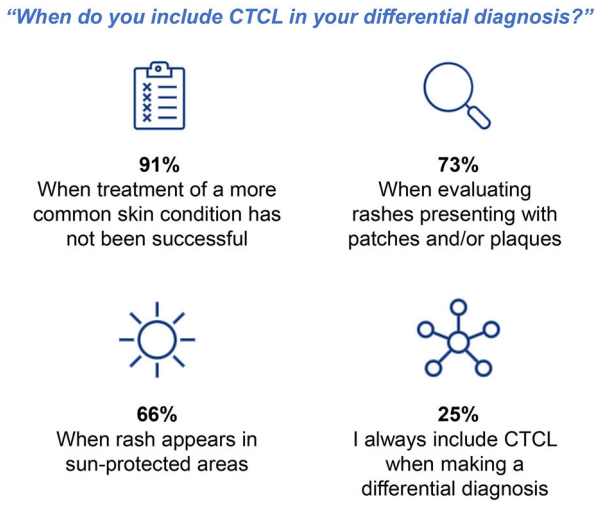

Fig. 1 HCP experience in diagnosing patients with CTCL. *CTCL* cutaneous T-cell lymphoma, *HCP* healthcare provider

diagnoses. Only one-third of respondents (34%) reported that their first course of action for patients with suspected early-stage CTCL is to refer to a center of excellence, which may indicate an access issue or a greater need for collaboration with these centers to ensure proper treatment in the early phases of disease. Two-thirds of respondents strongly agreed that more education is needed surrounding CTCL.

The most frequent differential diagnoses reported here (atopic dermatitis, allergic or contact dermatitis, and psoriasis) are chronic conditions that are often treated with topical corticosteroids—a treatment that can also provide relief in some patients with early-stage CTCL [2, 16, 18]. However, it is important to confirm a diagnosis of CTCL at early stages to avoid inappropriate treatments that may inadvertently worsen disease progression. For example, systemic biologic therapies typically prescribed for moderate-to-severe psoriasis, such as those targeting interleukin (IL)-23 and tumor necrosis factor α, have been shown to have beneficial therapeutic effects for patients with psoriasis; however, the use of immunosuppressive therapies may increase the risk of CTCL disease progression [19, 20]. Dupilumab, which is approved by the US Food and Drug Administration for the treatment of moderate-to-severe atopic dermatitis, is a fully human

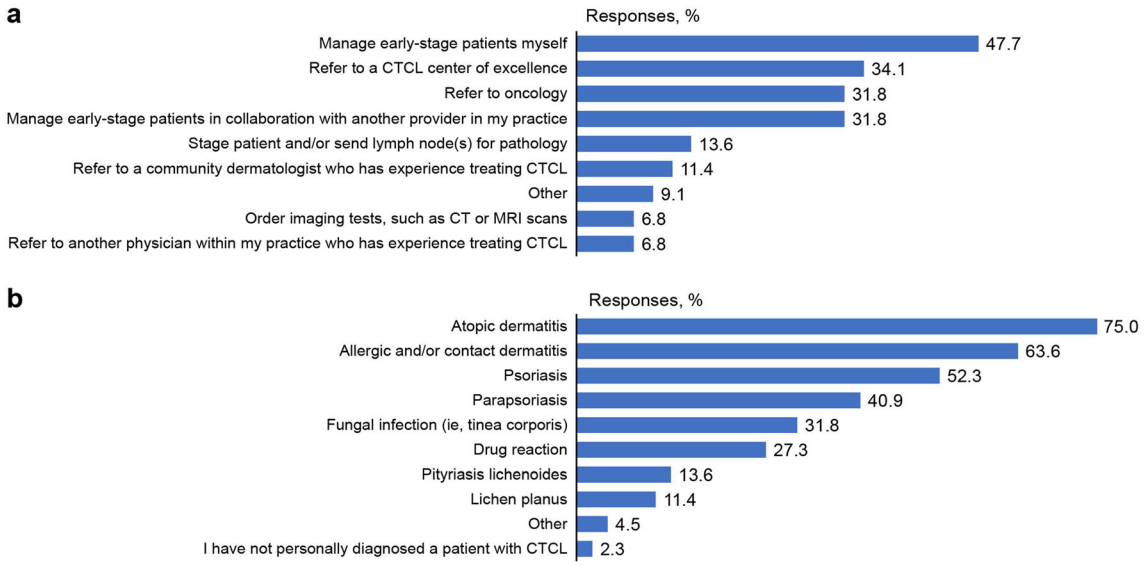

Fig. 2 Percentage of all HCPs responding to the questions, **a** "When you have suspected a new case of early-stage CTCL, what has been your usual course of action?" and **b** "If you have treated a patient (or patients) for skin conditions and/or diseases that were eventually diagnosed as CTCL, for what skin disorder(s) were the patient(s) previously treated?" *CT* computed tomography, *CTCL* cutaneous T-cell lymphoma, *HCP* healthcare provider, *MRI* magnetic resonance imaging

monoclonal antibody that binds to the shared α subunit of the IL-4 receptor, thus inhibiting the activity of both IL-4 and IL-13 [21]. The interaction of dupilumab with the immune system has the potential to accelerate progression of CTCL and can result in the clinical and histopathologic presentation of lymphoma [21, 22]. Some experts suggest that utilization of a skin biopsy and peripheral T-cell clonality panel to exclude CTCL may be needed as a prerequisite for the initiation of dupilumab treatment in certain patient populations [22, 23]. Literature is scarce on the effects of newer biologic therapies on CTCL, and additional research is needed to define the mechanisms through which these therapies aggravate CTCL. Therefore, it is essential that HCPs consider CTCL in their differential diagnosis, know the patient populations that are at greatest risk, and receive frequent education on the diagnosis of CTCL given the infrequency of the disease.

Limitations of this study include a small sample size of HCPs and brevity of the survey. The survey response rate was very low at < 1% (44/10,600), which may be attributed to the respondents not being compensated or to the rarity of CTCL. As such, statistical analysis was limited. Additionally, no HCPs with less than 4 years of experience participated in the survey; future analyses should capture this population's experience with diagnosing and treating CTCL. The survey also did not contain questions regarding the respondents' specific resident training in CTCL or extent of collaborations with centers of excellence. Lastly, this survey did not capture the distance of respondents to the nearest CTCL center of excellence; as such, access restrictions may have limited responses regarding referral of patients to a center of excellence. Despite these limitations, this study represents an initial investigation into understanding patterns of diagnosis and treatment for CTCL among dermatology practitioners.

CONCLUSION

This study emphasizes an increased need for education among dermatologists and HCPs involved in the diagnosis of CTCL to ensure proper treatment during the early phases of CTCL to prevent disease progression. Collaboration among HCPs for disease management and more education opportunities are encouraged to promote early diagnosis and appropriate treatment of CTCL.

ACKNOWLEDGEMENTS

We thank the respondents of this study for their time and participation in this study.

Funding. Funding for this study and the journal's Rapid Service Fee was provided by Ortho Dermatologics (a division of Bausch Health US, LLC).

Medical Writing and Editorial Assistance. Medical writing and editorial support were funded by Ortho Dermatologics and provided under the direction of the authors by Zade Holloway, PhD, and Jenna Lewis, MA, ELS, of MedThink SciCom. Ortho Dermatologics is a division of Bausch Health US, LLC.

Author Contributions. All named authors contributed to the study conception and design. All authors read and approved the final manuscript.

Disclosures. Erin Boh has received funding from AbbVie, Castle Biosciences, Dermira, Incyte, Janssen Biotech, Lilly, Mindera, Ortho Dermatologics, Pfizer, and Priovant. Drew Kuraitis has received funding from Ortho Dermatologics. Abby Jacobson and Martha Sikes are employees of Ortho Dermatologics (a division of Bausch Health US, LLC).

Compliance with Ethics Guidelines. This analysis was exempt from institutional review board review requirements per US Department of Health and Human Services policy (Title 45 Code of Federal Regulations, Part 46 of the United States), as the survey contains de-identified records.

Data Availability. The data sets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

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