Cutaneous T-cell Lymphoma

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The diagnosis and treatment of cutaneous T-cell lymphoma are challenging due to the many clinical and histopathologic presentations of the disease.

Background: Cutaneous T-cell lymphoma (CTCL) represents a spectrum of diseases composed of malignant helper T lymphocytes. An accurate diagnosis of early CTCL is difficult because of the varied clinical and histologic expressions of the disease.

Methods: The authors review the epidemiology, possible risk factors, clinical manifestations, diagnostic techniques, staging, prognosis, and treatment options for CTCL.

Results: The varied and often nonspecific clinical and histologic presentations of CTCL may delay diagnosis and staging, thus necessitating further studies such as immunophenotyping, flow cytometry, and T-cell receptor gene rearrangement analysis.

Conclusions: A multidisciplinary approach to the diagnosis, staging, and treatment of CTCL assists in optimizing outcomes from management of patients with this disease.

Introduction

Cutaneous T-cell lymphoma (CTCL) is generally classified as a type of non-Hodgkin’s lymphoma, and it represents a spectrum of diseases composed of malignant clonal helper T lymphocytes of the CD4 phenotype. CTCL is the most common type of primary cutaneous lymphoma, representing 65% of cases of skin lymphoma. Widely known variants include Sézary syndrome, Wöringer-Kolopp disease (pagetoid reticulosis), CD8+ (suppressor) T-cell lymphoma, granulomatous slack skin, peripheral T-cell lymphoma, angiocentric lymphoma, adult T-cell leukemia/lymphoma, CD30+ (Ki-1+) large-cell or anaplastic lymphoma, and lymphomatoid granulomatosis. Poikiloderma atrophicans vasculare, small and large plaque parapsoriasis, alopecia mucinosa, and lymphomatoid papulosis likely represent early forms of CTCL, but considerable debate still exists as to whether these represent CTCL or separate “premalignant” entities. Accurate diagnosis of early CTCL is difficult because of the varied clinical and histologic expressions of the disease and because of a lack of uniformity regarding diagnosis and treatment.

Issues in CTCL such as epidemiology, possible risk factors, clinical manifestations, diagnosis, staging, and treatment are summarized, with a special emphasis on a multidisciplinary approach in management based on staging information.

Epidemiology

The incidence of CTCL has increased from 0.19 cases per 100,000 in 1973 to 0.42 cases per 100,000 in 1984.1 CTCL is approximately twice as common in men as in women, while blacks have twice the incidence of whites. Most cases are diagnosed in the fifth and sixth decades (median age: 50 to 55 years). The course of CTCL is often unpredictable. Mycosis fungoides usually demonstrates epidermotropism by involving the skin first but, with time, it may spread to lymph nodes, blood, and viscera. Survival ranges from only a few months to several decades, depending on the stage of the disease. Most patients experience a prolonged survival with little morbidity, while some patients develop a fulminant course with rapid dissemination and death. The diagnosis and treatment of CTCL may be delayed for years and occasionally decades, thereby increasing the risk of severe morbidity and mortality.

Etiology

The term “mycosis fungoides” was initially used by Alibert2 in 1806 to describe a skin eruption that developed into tumors shaped like mushrooms. Mycosis fungoides is a misnomer because there is no association with a fungus. Several theories of the etiology of CTCL have been postulated, including exposure to environmental, genetic, and infectious agents. Early epidemiologic studies suggesting a causative role of environmental exposure to chronic antigenic stimulation (eg, industrial chemicals, metals, and herbicides/pesticides) have not been substantiated by recent case-control studies.3,4

At the forefront of etiologic research has been the hypothesis of a retroviral cause of CTCL. The human T-cell lymphotropic virus type-1 (HTLV-1) was found to have a causal relation to adult T-cell leukemia/lymphoma. However, most CTCL patients are negative for the virus, and the known HTLV-1 epidemiologic patterns have not been observed in CTCL. Nevertheless, HTLV-1-like retroviral particles have been found in Langerhans cells, B lymphocytes, and the blood of some CTCL patients, and thus the role of retroviruses in CTCL remains uncertain.5-9 Some groups have found serologic evidence of the Epstein-Barr virus in CTCL patients, suggesting a possible role in the pathogenesis.7,8 Other implicated risk factors include genetic predisposition, radiation exposure, and pre-existing malignancies, although there are little supporting data.9 There is some evidence to suggest immunosuppression as a risk factor for CTCL, including cases of documented CTCL arising in patients infected with the human immunodeficiency virus,10 in organ transplant patients,11 and in treated lymphoma patients.12

Clinical Manifestations

Three classical cutaneous phases of CTCL -- patches, infiltrated plaques, and tumors -- were described by Bazin13 in 1876. The disease may progress through each of these phases, which frequently overlap or occur simultaneously. In 5% to 10% of cases, the tumor phase may be the initial disease presentation without evolution,
originally termed the "d’emblee" variant by Videl and Brocq in 1885.

Early skin lesions may mimic eczema or papulosquamous eruptions such as tinea corporis, secondary syphilis, or psoriasis. Most investigators believe that large-plaque parapsoriasis represents an early form of CTCL, although this theory remains controversial. Sequential biopsies of such lesions may be necessary to establish or confirm a diagnosis of CTCL.

Patch-stage lesions are erythematous patches or slightly raised plaques with a fine scale. The lesions may be single or multiple and are often located on the buttocks, thighs, and abdomen (Fig 1). Patch lesions may be intensely pruritic or entirely asymptomatic. "Poikiloderma atrophicans vascularis" is a term used to describe patch lesions with cigarette paper-like atrophy, telangiectasia, and mottled hyperpigmentation.

Plaques of mycosis fungoides are elevated due to epidermal hyperplasia or significant neoplastic lymphocytic infiltrate (Fig 2). These lesions may develop from pre-existing patches or de novo. They are usually red-brown and sharply demarcated, but they may coalesce to form annular, arciform, or serpiginous patterns, sometimes with central clearing. Infiltrative plaques occurring on the face may result in leonine facies, and those appearing in hairy areas may produce alopecia or cysts. Erythroderma (exfoliative dermatitis) may occur as a result of diffuse infiltration of the skin by neoplastic cells with or without scale.

Tumor-stage CTCL may arise from patches, from plaques, or de novo. Lesions are typically violaceous, exophytic, mushroom-shaped tumors that preferentially affect the face and body folds (Fig 3). Lesions often undergo ulceration or necrosis and secondary infection. Pruritus may decrease in intensity during this stage. Over 50% of deaths from CTCL are caused by Staphylococcus aureus or Pseudomonas aeruginosa sepsis. Tumors may undergo transformation into a CD30+ (Ki-1+) large-cell anaplastic variant of CTCL with aggressive biological behavior. Transformation has been reported to range between 8% and 55% of tumor CTCL. In contrast to the primary Ki-1+ large-cell lymphomas that generally have a good prognosis, the prognosis for secondary Ki-1+ lymphomas developing in association with CTCL is extremely poor.

Sezary syndrome accounts for approximately 5% of new cases of CTCL and represents the leukemic variant of CTCL. Sezary syndrome is recognized by the classic triad of generalized erythroderma, leukemia, and lymphadenopathy. Malignant T cells with hyperconvoluted cerebriform nuclei circulate in the blood, whereas epidermotropic properties have been lost. Sezary cells can be detected in the peripheral blood in 90% of erythrodermic CTCL patients. Nevertheless, as the disease progresses, the ratio of CD4 (T helper) to CD8 (T suppressor) becomes elevated by an expansion of the malignant CD4 clonal population in Sezary syndrome, as well as a decrease in the normal CD4 and CD8 populations. Circulating Sezary cells have also been found in up to 20% of plaque or tumor-stage CTCL, as well as in several benign dermatologic conditions. A CD4:CD8 ratio above 5 and nuclear contour indexing using electron microscopy are more sensitive indicators of the quantity of circulating Sezary cell than light microscopy. Despite the continued uncertainty over the extent of peripheral blood involvement, widespread pruritic erythroderma is the major clinical manifestation of Sezary syndrome. Patients may have fever, chills, weight loss, and malaise. Other features may include hepatomegaly, onychodystrophy, leonine facies, ectropion, alopecia, and palmar-plantar keratoderma.
Diagnosis

The diagnosis of CTCL is usually made by recognizing the characteristic clinical manifestations of the disease plus routine histology. In difficult cases, a preliminary diagnosis may be supported by additional laboratory tests such as immunophenotyping, flow cytometry, and T-cell receptor (TCR) gene rearrangement analysis. Light microscopy of hematoxylin and eosin-stained sections from involved skin is still the diagnostic gold standard, but the diagnosis in early stages may be difficult. It takes two to 10 years to diagnose mycosis fungoides since some cases initially resemble other chronic inflammatory dermatoses.\textsuperscript{31} Frequently, sequential biopsies are necessary before the diagnosis is made. In the prototypical plaque stage, the histologic picture is often diagnostic. Histology reveals a band-like or lichenoid infiltrate of mononuclear cells within the papillary dermis with overlying epidermotropism. These lymphocytes may be found singly or in collections within the epidermis, often surrounded by a clear halo (Pautrier microabscesses) (Fig 4). High-power examination of mononuclear cells reveals hyperchromatic and irregular nuclear contours (Fig 5). The epidermis frequently shows a pattern of psoriasiform epidermal hyperplasia with hyperkeratosis and focal parakeratosis.

TCR gene rearrangement (TCRGR) analysis, using Southern blot or polymerase chain reaction (PCR) methods, helps to confirm early or atypical CTCL when the histology is suggestive but not diagnostic.\textsuperscript{32} TCRGR analysis is well established as a determinant of clonality within lymphoid populations. The TCR is a glycoprotein with four subunits (alpha, beta, gamma, and delta). In normal peripheral blood T lymphocytes, the TCR genes are composed of 90% to 98% alpha/beta subunits. During the process of antigen recognition, the beta subunit undergoes TCRGR and, as a result, each T cell produces a singly unique TCR gene. A polyclonal population of T cells produces a variety of TCR gene products. In contrast, the T-cell expansion population in CTCL is monoclonal as multiple copies of the same TCRGR are produced by identical daughter cells. The cells may be detected by Southern blot analysis (DNA hybridization) or PCR if found in large enough quantities.

Most reported cases of CTCL have a clonal rearrangement detected by TCRGR analysis. The diagnostic value of TCRGR analysis by Southern blot is limited by a low sensitivity, since a level of abnormal T-cell clone infiltration below 5% may be too low for detection. PCR has a sensitivity that is 10\textsuperscript{3} times greater than Southern blotting, and the increase in the limit of detection may allow a diagnosis of CTCL in very early disease stages.\textsuperscript{33,34}

The PCR method for detection of TCRGR is a promising diagnostic technique. Further advances in our knowledge of clonality in CTCL are necessary before PCR can be used as a sole diagnostic test for CTCL. For example, some nonneoplastic T-cell disorders such as pityriasis lichenoides et varioliformis acuta may display some level of clonality.\textsuperscript{21}

Further clinical evaluation of CTCL patients includes a complete history and physical examination, emphasizing the types of skin lesions, body surface area, lymph node, liver, and spleen involvement. Baseline tests should include a complete blood cell count, peripheral blood flow cytometry for T-cell subsets, serum chemistries (liver and renal function tests, calcium, phosphorus, uric acid, lactate dehydrogenase), chest radiograph, and biopsy or fine-needle aspiration of palpable lymph nodes. Additional staging procedures for patients with advanced disease include computed tomography scan of the abdomen and pelvis, gallium scan, and bone marrow biopsy.

Staging and Prognosis

A number of staging systems for CTCL have been proposed. The simplest and most widely used system, adopted by Lamberg et al.,\textsuperscript{35} incorporates the tumor-node-metastasis (TNM) system. This staging system combines both clinical and histopathologic perspectives (Table). Patients can be divided into three prognostic groups at initial presentation:\textsuperscript{36} (1) good-risk patients with patch or plaque skin lesions without lymph node, blood, or visceral involvement (median survival = 12 years), (2) intermediate-risk patients with plaques, tumors, or erythroderma with lymph node and or blood involvement but no visceral disease (median survival = 5 years), and (3) poor-risk patients with visceral involvement or complete lymph node effacement (median survival = 2.5 years).

Another classification based on lymph node involvement is the LN system, used to define prognosis once the diagnosis of CTCL has been established in the skin. In this system, LN1 nodes have single infrequent atypical lymphocytes in paracortical T-cell regions, LN2 nodes have small clusters of paracortical atypical cells, LN3 nodes have large clusters of atypical cells, and LN4 nodes are partially or totally effaced by atypical cells. The LN classification directly correlates with disease progression as well as with survival and prognosis. Detection of the TCR rearrangement in lymph nodes is associated with an inferior survival rate regardless of the LN class. Therefore, the LN classification is helpful in detecting patients with lymph node involvement who may benefit from more aggressive therapy.\textsuperscript{37}
Treatment

Treatment regimens in CTCL include skin-directed therapies such as psoralen with UVA irradiation (PUVA), topical chemotherapy with mechlorethamine (nitrogen mustard) and Carmustine (BCNU), and electron beam radiation, as well as systemic therapies such as chemotherapy, photopheresis, and interferons. A stage-adapted approach to CTCL therapy is used most often.

Currently, a conservative approach using topical therapy is the preferred first-line treatment for early-stage CTCL. A recent randomized study failed to show a survival benefit in patients with CTCL using aggressive combination chemotherapy and radiotherapy. For minimally perceptible lesions that are clinically and/or histopathologically suggestive of CTCL (stage 0), a trial of glucocorticoids is indicated and has been shown to induce clinical remission in early CTCL. If there is no response to glucocorticoids, oral PUVA is most commonly used, although some patients may respond to UVB therapy.

Topical nitrogen mustard (mechlorethamine) is an alternative topical therapy for minimal disease burdens and sites that are unresponsive or difficult to reach with PUVA. Topical nitrogen mustard induces a complete remission rate of approximately 30% to 60%, with better results in early than advanced disease. Mechlorethamine can be applied as an aqueous solution that is prepared by dissolving the contents of a 10-mg vial in 50 mL of water, or it can be compounded as an ointment. Side effects of mechlorethamine include allergic and irritant contact dermatitis, pruritus, and hyperpigmentation. Hypersensitivity reactions to the topical solution may develop in 35% to 58% of patients. An immediate-type hypersensitivity reaction with urticarial lesions may also occur in up to 8% of patients. Unlike delayed hypersensitivity reactions where desensitization may be used to continue with therapy, patients who develop immediate hypersensitivity reactions must terminate therapy to avoid a potentially life-threatening anaphylactic reaction. Ointment-based mechlorethamine has been used since 1982, and the response, survival, and relapse rates are similar for both the aqueous solution and the ointment. However, the incidence of hypersensitivity reactions is significantly less with the ointment than with the solution. The frequency of delayed hypersensitivity reactions to the solution was only 8% in patients with a history of allergy to mechlorethamine and 0% in patients being initially exposed to the ointment. In addition, the ointment remains stable for at least 40 days at 37 degrees Celsius and 80 days when refrigerated at 4 degrees Celsius. In contrast, the same concentration of aqueous solution is fully degraded after only four days.

Treatment of CTCL by PUVA was described by Gilchrest et al in 1976 and is considered the initial treatment for stage I through IIa disease. PUVA is effective in clearing early-stage CTCL and in prolonging remission with maintenance therapy. In a study of 82 patients with a mean follow-up of 45 months, complete clearing of lesions was shown in 88% with limited plaque disease and in 51.9% with extensive plaque disease. The mean duration of remission was 13 months for patients with limited plaque disease and 11 months for patients with extensive plaque disease. PUVA is generally well tolerated; few side effects such as erythema, nausea, and pruritus occur in 10% to 20% of patients. Because of the high rate of relapse with TSEB, adjuvant maintenance therapy with retinoids–PUVA or interferon (IFN)–PUVA should be considered. If there is no clinical response to these measures, total-skin electron-beam (TSEB) therapy may be instituted. An 84% complete response rate and a 10-year survival rate of 46% have been reported. Because of the high rate of relapse with TSEB, adjuvant maintenance therapy with PUVA alone or combined with low-dose oral methotrexate or IFN-alfa is recommended. Side effects associated with radiation therapy include xerosis, erythema, telangiectasia, extremity edema, and alopecia.

Radiation therapy is the treatment of choice for patients with tumor-stage (stage IIb) CTCL. With local-field electron beam radiation, 71% of tumor-stage patients achieved a complete remission over a five-year period. After completion of local-field electron beam therapy, PUVA maintenance is recommended. If there is no response, patients require treatment according to stage IV guidelines. Patients with patches, plaques, and nodules who have responded to PUVA in the past may be treated with PUVA in conjunction with local radiation. If there has not been a prior response, patients should receive TSEB radiation.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T: Skin</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>Lesions clinically and/or histopathologically suggestive of CTCL</td>
</tr>
<tr>
<td>T1</td>
<td>Limited plaques, papules, or eczematous patches covering &lt;10% of skin surface</td>
</tr>
<tr>
<td>T2</td>
<td>Generalized plaques, papules, or erythematous patches covering ≥10% of skin surface</td>
</tr>
<tr>
<td>T3</td>
<td>Cutaneous tumors</td>
</tr>
<tr>
<td>T4</td>
<td>Generalized erythroderma</td>
</tr>
<tr>
<td>N: Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No palpable lymphadenopathy, lymph node pathology negative for CTCL</td>
</tr>
<tr>
<td>N1</td>
<td>Palpable lymphadenopathy; lymph node pathology negative for CTCL</td>
</tr>
<tr>
<td>N2</td>
<td>No palpable lymphadenopathy; lymph node pathology positive for CTCL</td>
</tr>
<tr>
<td>N3</td>
<td>Palpable lymphadenopathy, lymph node pathology positive for CTCL</td>
</tr>
<tr>
<td>B: Blood</td>
<td></td>
</tr>
<tr>
<td>B0</td>
<td>Atypical circulating cells not present (&lt;5%)</td>
</tr>
<tr>
<td>B1</td>
<td>Atypical circulating cells present (≥5%)</td>
</tr>
<tr>
<td>M: Viscera</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No visceral organ involvement</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral organ involvement, pathology present</td>
</tr>
</tbody>
</table>

The treatment of choice for patients with erythrodermic disease (stage III) is photopheresis, which was first described as a treatment for CTCL by Edelson in 1987. Photopheresis involves the removal of leukocytes by leukophoresis after ingestion of 8-methoxypsoralen (8-MOP). The ex vivo cells are exposed to UV light and then reinjected into the patient. Although the exact mechanism is not fully elucidated, the resultant alteration of cell-surface antigens is thought to stimulate a host response. The majority of patients show complete clearance or >50% improvement with therapy and a prolonged survival compared with historical control groups. Photopheresis can achieve a significant improvement in quality of life with minimal side effects. The most frequently reported side effect is transient nausea from the psoralen.

If there is no response to photopheresis alone for stage III disease, low-dose IFN or low-dose oral methotrexate may be added. The three classes of IFNs (alpha, beta, and gamma) exhibit antiviral, antiproliferative, and immunomodulatory effects. The most commonly used IFN for the treatment of CTCL is IFN-alpha subtype 2a. The first use of systemic IFN-alpha-2a for CTCL was first reported by Foon and Bunn in 1986. The optimal dose of IFN has yet to be determined. Kohn et al. studied the use of intermittent high-dose IFN-alpha-2a therapy in 24 patients with advanced CTCL who had failed at least one previous treatment. Complete response was seen in 4% of patients, while a partial response was achieved in 25% of patients. Side effects of IFN-alpha-2a include fever, chills, lethargy, hepatotoxicity, leukopenia, and a reversible nephrotic syndrome.

The first-line treatment for patients with refractory disease or extracutaneous involvement (stage IVa or b) is single or multi-agent chemotherapy. Methotrexate may be administered in high intravenous dosages. The purine analogues such as 2-chloro-deoxyadenosine, fludarabine, and pentostatin have demonstrated promising clinical results in refractory CTCL. EPOCH, a combination of etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide, is reserved for patients with resistant, extensive, or advanced CTCL. With combination chemotherapy, responses may be seen in approximately 80% of patients and complete remission in 38% of patients. DAB IL-2 is the product of the fusion of the IL-2 gene with a portion of the diphtheria toxin gene. The resulting chimeric protein selectively targets cells with a high number of IL-2 receptors. Other toxins such as ricin have been used instead of the diphtheria toxin. This method of treatment remains experimental and is being administered only within clinical trials. There is no widely accepted standard combination therapy for CTCL, but chemotherapy may be used with TSEB radiation with or without IFN. PUVA may supplement chemotherapy to reduce tumor cell burden. Photopheresis is recommended as an adjuvant to chemotherapy if large numbers of circulating Sezary cells are present. If intensive chemotherapy is used, however, the resultant immunosuppression may negate the activity of PUVA or photopheresis.

Conclusions

The diagnosis and treatment of CTCL remain challenging. A multitude of clinical and histopathologic presentations of the disease exist, as well as a variety of therapeutic options with a lack of randomized trials to establish efficacy. Management is further complicated by the involvement of several specialists with differing protocols, such as hematology/oncology, dermatology, pathology, and radiation oncology. A multidisciplinary center based on a stage-adapted therapeutic approach to CTCL has been established at our institute for the treatment of CTCL patients. A personal computer software package has recently been developed for use at the center that documents patient history, physical examination, diagnostic examination, staging, treatment, and follow-up. This system is designed to interface with other regional databases and will serve as a tool to conduct research protocols.

References

5. Zucker
15. King


