Cutaneous Presentation of T-Cell Prolymphocytic Leukemia

Marie O. Ventre, MD; Rocky E. Bacelieri, MD; John Lazarchick, MD; Ross B. Pollack, MD; John S. Metcalf, MD

T-cell prolymphocytic leukemia (T-PLL) is the most common mature T-cell leukemia (MTCL). Cutaneous involvement is a characteristic symptom of T-PLL and appears in up to one-third of cases; however, T-PLL is a relatively unknown disease in the field of dermatology. In this article, we seek to increase awareness and educate physicians about the clinical manifestations of T-PLL. Hopefully, an increased awareness of this disease will lead to more prompt diagnoses and better prognoses for affected patients.

Cutis. 2013;91:87-91.

A rare disorder of mature postthymic T cells, T-cell prolymphocytic leukemia (T-PLL) historically has been classified as a T-cell variant of chronic lymphocytic leukemia (CLL); however, because of its aggressive clinical course, many investigators have sought to make a distinction between T-PLL and the clinically indolent CLL. In 1974, Galton et al[1] introduced the term *T-cell prolymphocytic leukemia* to better delineate the disorder, now classified as a mature T-cell leukemia (MTCL). Although there have been debates in the literature as to whether it is a true T-cell variant of CLL,[2,3] T-PLL is a well-documented disorder supported by consistent clinical and laboratory findings. The World Health Organization recognizes several entities classified as MTCLs, including adult T-cell leukemia/lymphoma, T-PLL, Sézary syndrome (SS), and large granular lymphocytic leukemia.[4] Although T-PLL is a rare entity, it is the most common MTCL, representing up to 37.5% of cases.[2,5]

Case Report

A 74-year-old man presented to the emergency department with facial swelling of 3 weeks' duration and a sudden onset of a rash on the face and upper trunk. The patient initially attributed his facial swelling and redness to imiquimod, which he was using for the treatment of several actinic keratoses on his face, but he sought evaluation when the rash spread to his neck and upper trunk. A review of systems revealed worsening abdominal fullness and a decrease in appetite. The patient denied any substantial weight loss, fever, history of a similar rash, or a preexisting skin disorder or hematologic disease. Physical examination revealed a confluent, brightly erythematous, nonblanching, morbilliform eruption on the face and upper trunk with interspersed petechiae (Figure 1). Initial laboratory findings included marked leukocytosis of 270×10^9/L (reference range, 4.5–11.0×10^9/L) with 81% lymphocytes, mild anemia, and thrombocytopenia. A chart review showed moderately increasing leukocytosis with a white blood cell count that had slowly progressed over the last 8 months from 11×10^9/L to 75×10^9/L. The patient had been followed by his primary care physician with a presumptive diagnosis of CLL, but it was not confirmed. Five days prior to presentation, routine screening laboratory results revealed a white blood cell count of 86×10^9/L, exhibiting rapid doubling time to reach his presenting level of 270×10^9/L in only a few days. Ultrasonography and computed tomography revealed bilateral pleural effusions, mediastinal lymphadenopathy, and gross hepatosplenomegaly. An obstructive nephropathy due to an unknown bladder mass also was noted. The patient was admitted to the medical center hospital and the dermatology department was consulted for evaluation of his new-onset rash. A diagnostic punch biopsy of the left chest was performed and sent for routine hematoxylin and eosin

From the Department of Dermatology, Medical University of South Carolina, Charleston.
The authors report no conflict of interest.
Correspondence: Marie O. Ventre, MD, 281 McDowell St, Asheville, NC 28803 (marieventre@gmail.com).

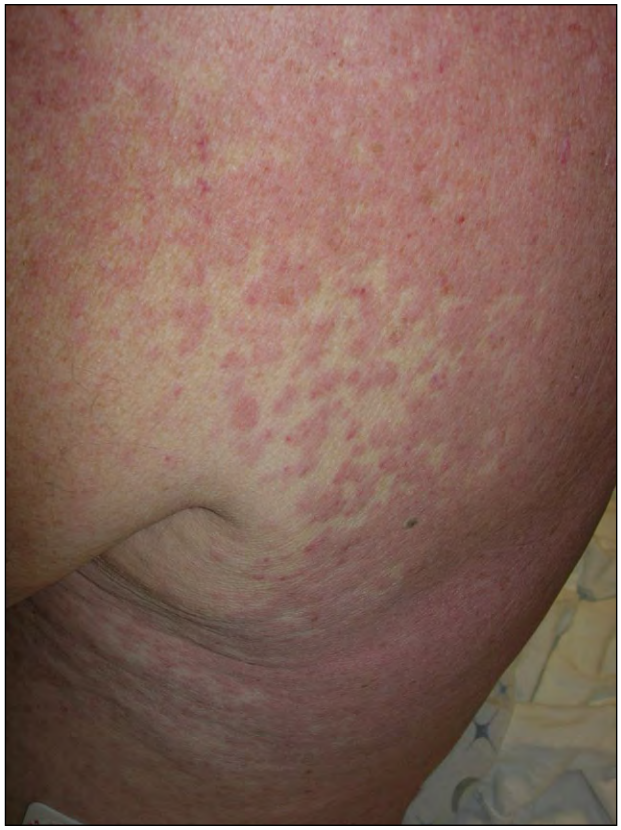
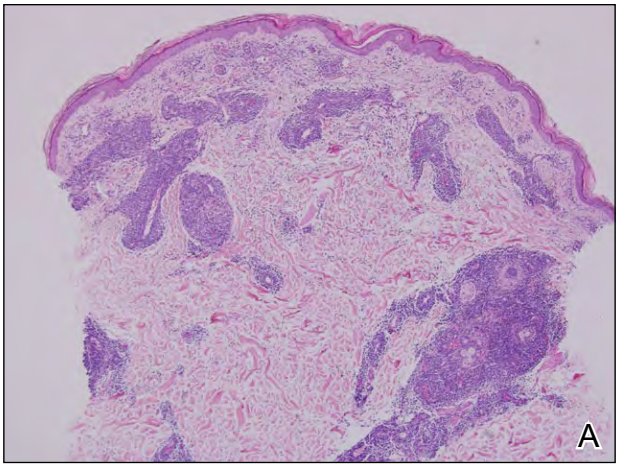


Figure 1. A nonblanching morbilliform eruption with mild petechial quality.



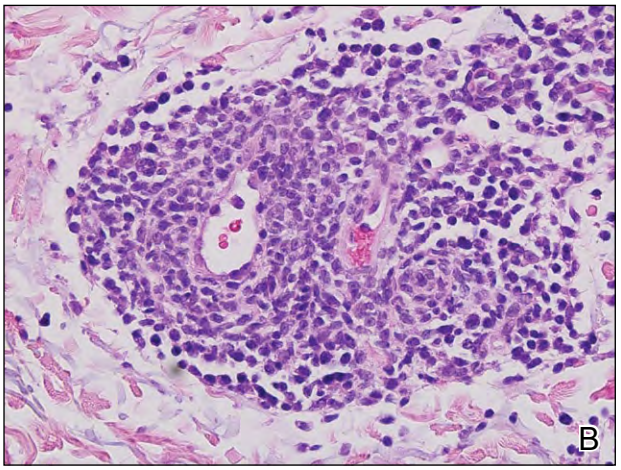


Figure 2. Histologic examination revealed dense superficial and deep perivascular and periadnexal infiltrates of small- to medium-sized lymphocytes in bandlike groups in the dermis. There was no evidence of epidermotropism (H&E, original magnification ×4)(A). A perivascular distribution of the homogenous infiltrate was shown. There was no evidence of angioinvasion (H&E, original magnification ×20)(B).

staining. A bone marrow biopsy also was performed for morphologic, immunophenotypic, and cytogenetic analysis.

Histopathologic examination of the skin specimen revealed a dense dermal infiltrate of small- to intermediate-sized lymphocytes. Eosinophilic rims of cytoplasm surrounded the nuclei, which were irregularly contoured with mild hyperchromasia and small single prominent nucleoli. The infiltrate demonstrated marked angiocentricity with lymphocytes present within vessel walls, though no changes in the vessel walls were seen (Figure 2). Lymphocytes infiltrated adnexal structures, including hair follicles and eccrine glands and ducts; focal epidermotropism could be appreciated; and immunophenotypic studies demonstrated regions of positivity for CD2, CD3, CD4, CD8, and CD7. A CD20 marker did not highlight any B cells within the infiltrate. Examination of the peripheral blood smear demonstrated a predominance of small, mature-appearing lymphocytes; many prolymphocytes; and fewer large lymphocytes with cleaved irregular nuclei (Figure 3). Flow cytometry of the bone marrow showed 45% of lymphocytes staining positively for CD2, CD3, CD5, CD7, CD38, CD52, and dual CD4/CD8. Cytogenetic studies revealed an inversion of chromosome 14 with breaks at 14q11.2 (T-cell receptor) and 14q32 (T-cell leukemia), as well as deletion of 12p within all abnormal cells.

A diagnosis of T-PLL was made, and the patient was started on alemtuzumab therapy; he received 2 treatment courses while in the hospital, but there was no initial improvement in either leukocytosis or cutaneous presentation. The patient's overall status improved during his 1-week hospitalization and he ultimately was discharged to continue outpatient alemtuzumab treatment at home. Despite this treatment, leukocytosis continued to progress, reaching a white blood cell count above 400×10^9/L, with a continued decrease in his platelet count. Foley

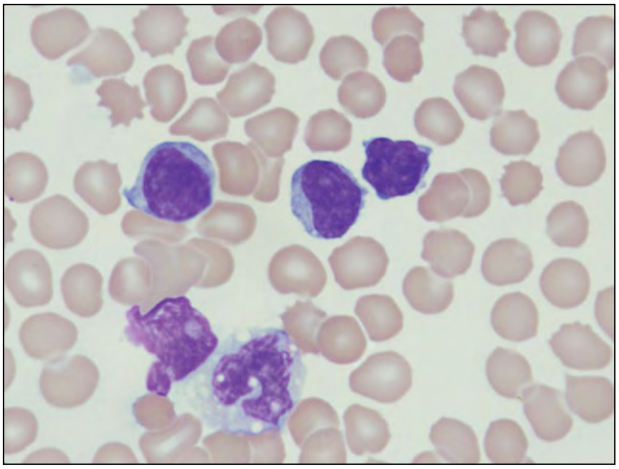


Figure 3. A peripheral blood smear showed small- to medium-sized lymphocytes with nongranular basophilic cytoplasm with blebbing and round to cerebriform nuclei. A prominent nucleolus was noted in one of these cells (Wright-Giemsa, original magnification ×50).

catheter placement failed to prevent the complication of acute-on-chronic renal failure exacerbated by the undiagnosed bladder mass. The patient's condition rapidly deteriorated, progressing to multisystem organ failure, intracranial hemorrhage, and ultimately death only 2 weeks after the initial diagnosis was made.

Comment

The abnormal T-cell population associated with T-PLL is thought to be the result of a postthymic alteration in tumor suppression. Cytogenetic studies consistently have shown an abnormality in chromosome 14, most frequently an inversion with break points at 14q11 and 14q32, occurring in approximately 60% to 80% of cases. In 10% of T-PLL patients, there is a reciprocal tandem translocation of t(14;14)(q11;q32).[3,6,7] T-cell leukemia/lymphoma 1 (TCL-1) is an oncoprotein located on the 14q32.1 locus. Both the inversion and translocation at this locus lead to increased expression of the *TCL-1* oncogene, a common laboratory finding seen in T-PLL. This same inversion and increased expression of *TCL-1* can be seen in ataxia-telangiectasia, leading to an increased incidence and earlier onset of T-PLL in patients with ataxia-telangiectasia.[8-10]

Leukocytosis above 100×10^9/L is suggestive of T-PLL; most investigators use this limit when describing the disease, though no strict criteria currently exist in the literature. The most consistent laboratory finding of T-PLL is a rapid doubling time of 2 weeks, which can lead to counts as high as 900×10^9/L. Some investigators use this rapid increase in peripheral blood lymphocytes as a diagnostic criterion for T-PLL, though similar reports have been documented in severe, end-stage cases of SS.[4] Bone marrow infiltration frequently occurs, accounting for subsequent anemia and thrombocytopenia in roughly 50% of cases.[2] Bone marrow is the most frequently biopsied site, with skin being the most frequently biopsied extramedullary site.[11] In cases of cutaneous infiltration, a diagnosis may be made on histology and immunophenotyping of the skin, though examination of the peripheral blood and cytogenetic analysis of the bone marrow typically are confirmatory.

Abnormal T cells can infiltrate the skin, spleen, liver, viscera, and lymph nodes, leading to the expected clinical findings of skin eruption, splenomegaly, hepatomegaly, lymphadenopathy, and serous effusions. In an analysis of 78 patients with T-PLL, Matutes et al[2] found splenomegaly (73% [57/78]) to be the most common clinical finding, followed by lymphadenopathy (53% [41/78]), hepatomegaly (40% [31/78]), and skin lesions (27% [21/78]). Other authors have reported similar incidence rates of skin infiltration ranging from 25% to 30%.[10,12] Although skin involvement is not the most common clinical finding, it often is a presenting symptom, characteristically involving the face and often coinciding with or following shortly after the onset of leukemia. Edema is the most commonly presenting facial eruption, though cases of facial plethora, periorbital petechia, and conjunctival involvement have all been reported.[10,13,14] Concurrent eruptions of varying morphologies (eg, macules, papules, plaques, nodules) on the chest, back, and/or knees also have been described, though cutaneous eruptions in patients with T-PLL most often are symmetric with a petechial quality, likely due to the angiocentric nature of the infiltrate. Total body erythroderma originally misdiagnosed as primary cutaneous T-cell lymphoma has been reported as a rare manifestation of T-PLL.[2,5,6,10,12]

Histologically, the infiltrate of atypical T lymphocytes in patients with T-PLL predominately involves the superficial dermis, though involvement of the adnexa is common. Occasional epidermotropism can be seen and tends to be focal, in some cases involving acrosyringium.[10] The most striking histologic feature of T-PLL is the angiocentric nature of the infiltrate, which may be present within vessel walls but seldom exhibits frank vasculitis. The infiltrate consists of small- to intermediate-sized lymphocytes with rims of eosinophilic cytoplasm. Nuclei display finely dispersed heterochromatin with irregular membranes and small single prominent nucleoli.[3,10] The phenotypic profile of the infiltrate mirrors peripheral blood and bone marrow, revealing small T lymphocytes that stain positively for CD2, CD3, and CD7; CD4 and

CD8 staining is variable, with $CD4^+/CD8^-$ being the most common pattern encountered.[15]

Some degree of clinical and laboratory overlap can be seen among patients with T-PLL, adult T-cell leukemia/lymphoma, and SS. A rapid increase in peripheral blood lymphocytes, splenomegaly, and visceral effusions are most commonly seen in T-PLL patients. Adult T-cell leukemia/lymphoma has a more chronic course, including frequent hypercalcemia and a known relationship to human T-lymphotropic virus 1 (HTLV-1). Adult T-cell leukemia/lymphoma rarely is found outside of endemic areas such as Asia, Japan, and the Caribbean.[2,4] Conversely, no relationship between HTLV-1 and T-PLL has been shown, including in Caribbean-born patients.[2,15] Sézary syndrome, which represents the leukemic phase of cutaneous T-cell lymphoma, frequently presents with erythroderma and shows the most overlap with T-PLL. Shared clinical, histologic, and laboratory features include erythroderma, lymphadenopathy, epidermotropism, and an increased leukocyte count. Distinguishing clinical features include splenomegaly, which rarely occurs in SS patients, and erythroderma, which is seldom seen in cases of T-PLL. The lymphocyte count in SS patients rarely exceeds levels of 100×10^9/L, though isolated cases have been reported.[4] Analysis of the peripheral blood and bone marrow as well as skin biopsy should be conducted to delineate the diagnosis in the event of substantial clinical overlap between SS and T-PLL.

The most distinctive laboratory finding in T-PLL patients is increased expression of the TCL-1 oncoprotein. Among the MTCLs, *TCL-1* expression is exclusive to T-PLL and is seen in approximately 71% of cases.[4] Expression of the *TCL-1* oncogene is a relatively common finding in B-cell proliferative disorders, found in nearly 90% of cases of CLL and 75% of cases of Burkitt lymphoma. Because of the well-known association of Epstein-Barr virus (EBV) with Burkitt lymphoma, it has been hypothesized that EBV may play a role in *TCL-1* overexpression.[16] A report by Lan et al[17] suggested that EBV may likewise be involved in the pathogenesis and/or maintenance of T-PLL. Studies evaluating *TCL-1* expression as a prognostic indicator for T-PLL have failed to show significant differences in overall survival, clinical presentation, or disease course among positive and negative *TCL-1* cases; however, given its relative frequency and specificity to T-PLL, *TCL-1* testing may serve as the most helpful diagnostic modality.[4,6,18]

The clinical course of T-PLL is progressive. When left untreated, the median survival period is 7 months.[2] Although most cases of T-PLL have rapid aggressive courses, cases of an initial indolent nature, similar to our case, have been reported. Garand et al[19] reported that 32% (25/78) of their institution's T-PLL cases presented with initial chronic moderate lymphocytosis with an initial indolent clinical course (median, 33 months), representing a sort of preleukemic phase. As in our patient, 64% (16/25) of their cases eventually progressed to an aggressive leukemic phase with clinical, laboratory, and prognostic findings that were characteristic of T-PLL.[19] Clinical responses to conventional treatment regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) have been poor and of limited duration. Matutes et al[2] reported that only 1 of 15 (7%) patients achieved complete remission, which lasted for only 3 months. Historically, treatment via splenectomy, leukopheresis, and alkylating and other cytotoxic agents have been utilized with little benefit. Purine nucleoside analogs such as cladribine, fludarabine, and pentostatin have shown moderate efficacy and were the most common treatment of T-PLL prior to the development of monoclonal antibodies. The greatest clinical response has consistently been shown with alemtuzumab, the monoclonal antibody to CD52. Increased expression of CD52 can be seen in both leukemic B and T cells, though especially high expression is seen in the prolymphocytic T cells of T-PLL, accounting for both the in vitro and in vivo response to alemtuzumab.[20] Response rates of 51% to 76% with a complete response rate of 39% to 60% have been reported in association with alemtuzumab treatment, both in previously treated and untreated patients.[2,21-23] The duration of the response is variable, ranging from 4 to 45 months, with a median disease-free survival period of 7 months. In patients who relapsed after initial alemtuzumab therapy, a second treatment course improved complete response duration to 16 months.[21] Alemtuzumab may work synergistically with other cytotoxic agents, especially the purine nucleoside analogs, and more durable response has been reported when these agents are used in combination.[24] Stem cell transplantation, which may ultimately prove curative, rarely is used in elderly patients who are most affected by this disease. Instead, stem cell transplantation typically is reserved for younger patients who have failed prior chemotherapy and have a greater potential for complete response.[25]

Conclusion

T-cell prolymphocytic leukemia is a rare T-cell leukemic variant with an aggressive clinical course. Although T-PLL is the most frequent MTCL, it is underrepresented and underrecognized in the field of dermatology. Because cutaneous involvement often is the presenting symptom, increased awareness of T-PLL is necessary in facilitating timely diagnosis and treatment. Any patient who presents to a

dermatologist with a suspected diagnosis of T-PLL should immediately be referred to the hematology or oncology department for diagnostic evaluation of the peripheral blood and bone marrow and rapid initiation of treatment.

REFERENCES

1. Galton DA, Goldman JM, Wiltshaw E, et al. Prolymphocytic leukaemia. *Br J Haematol*. 1974;27:7-23.
2. Matutes E, Brito-Babapulle V, Swansbury J, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. *Blood*. 1991;78:3269-3274.
3. Hoyer JD, Ross CW, Li CY, et al. True T-cell chronic lymphocytic leukemia: a morphologic and immunophenotypic study of 25 cases. *Blood*. 1995;86:1163-1169.
4. Herling M, Khoury J, Washington LT, et al. A systematic approach to diagnosis of mature T-cell leukemias reveals heterogeneity among WHO categories [published online ahead of print March 25, 2004]. *Blood*. 2004;104:328-335.
5. Foucar K. Mature T-cell leukemias including T-prolymphocytic leukemia, adult T-cell leukemia/lymphoma, and Sézary syndrome. *Am J Clin Pathol*. 2007;127:496-510.
6. Herling M, Valbuena JR, Jones D, et al. Skin involvement in T-cell prolymphocytic leukemia. *J Am Acad Dermatol*. 2007;57:533-534.
7. Herling M, Patel KA, Khalili J, et al. TCL1 shows a regulated expression pattern in chronic lymphocytic leukemia that correlates with molecular subtypes and proliferative state. *Leukemia*. 2006;20:280-285.
8. Pekarsky Y, Zanesi N, Aqeilan R, et al. Tcl1 as a model for lymphomagenesis. *Hematol Oncol Clin North Am*. 2004;18:863-879, ix.
9. Gumy-Pause F, Wacker P, Sappino AP. ATM gene and lymphoid malignancies. *Leukemia*. 2004;18:238-242.
10. Magro CM, Morrison CD, Heerema N, et al. T-cell prolymphocytic leukemia: an aggressive T cell malignancy with frequent cutaneous tropism. *J Am Acad Dermatol*. 2006;55:467-477.
11. Valbuena JR, Herling M, Admirand JH, et al. T-cell prolymphocytic leukemia involving extramedullary sites. *Am J Clin Pathol*. 2005;123:456-464.
12. Mallett RB, Matutes E, Catovsky D, et al. Cutaneous infiltration in T-cell prolymphocytic leukaemia. *Br J Dermatol*. 1995;132:263-266.
13. Nusz KJ, Pang NK, Woog JJ. Periorbital edema as the initial presentation of T-cell prolymphocytic leukemia. *Opthal Plast Reconstr Surg*. 2006;22:215-216.
14. Lee SS, Robinson MR, Morris JC, et al. Conjunctival involvement with T-cell prolymphocytic leukemia: report of a case and review of the literature. *Surv Ophthalmol*. 2004;49:525-536.
15. Pawson R, Schulz TF, Matutes E, et al. The human T-cell lymphotropic viruses types I/II are not involved in T prolymphocytic leukemia and large granular lymphocytic leukemia. *Leukemia*. 1997;11:1305-1311.
16. Teitell MA, Lones MA, Perkins SL, et al. TCL1 expression and Epstein-Barr virus status in pediatric Burkitt lymphoma. *Am J Clin Pathol*. 2005;124:569-575.
17. Lan K, Murakami M, Choudhuri T, et al. Detection of Epstein-Barr virus in T-cell prolymphocytic leukemia cells in vitro [published online ahead of print September 14, 2008]. *J Clin Virol*. 2008;43:260-265.
18. Ravandi F, O'Brien S, Jones D, et al. T-cell prolymphocytic leukemia: a single-institution experience. *Clin Lymphoma Myeloma*. 2005;6:234-239.
19. Garand R, Goasguen J, Brizard A, et al. Indolent course as a relatively frequent presentation in T-prolymphocytic leukaemia. Groupe Français d'Hématologie Cellulaire. *Br J of Haematol*. 1998;103:488-494.
20. Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. *Leuk Res*. 1998;22:185-191.
21. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. *Blood*. 2001;98:1721-1726.
22. Keating MJ, Cazin B, Coutré S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. *J Clin Oncol*. 2002;20:205-213.
23. Dearden C, Matutes E, Cazin B, et al. Very high response rates in previously untreated T-cell prolymphocytic leukaemia patients receiving alemtuzumab (Campath-1H) therapy [abstract]. *Blood*. 2003;102:2378.
24. Ravandi F, O'Brien S, Jones D, et al. T-cell prolymphocytic leukemia: a single-institution experience. *Clin Lymphoma Myeloma*. 2005;6:234-39.
25. Robak T, Robak P. Current treatment options in prolymphocytic leukemia. *Med Sci Monit*. 2007;13:RA69-RA80.