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Kempf, Werner ; Kazakov, Dmitry V ; Hübscher, Eugen ; Tinguely, Marianne

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# Cutaneous Borreliosis With a T-Cell–Rich Infiltrate and Simultaneous Involvement by B-Cell Chronic Lymphocytic Leukemia With t(14;18)(q32;q21)

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and Marianne Tinguely, MD\*

**Abstract:** Pseudolymphomatous infiltrates in *Borrelia* infection of the skin most commonly manifest with dense B-cell infiltrates and plasma cells. Cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) may accumulate at sites of infection, including *Borrelia* infection. We report an unusual constellation in a patient with synchronously diagnosed B-CLL and *Borrelia* infection of skin presenting with a dense dermal T-cell–rich infiltrate masking specific leukemic infiltrates of neoplastic B cells in the context of B-CLL harboring t(14;18)(q32;q21). Specific cutaneous involvement by B-CLL was confirmed by the detection of t(14;18)(q32;q21) (BCL2–IGH) using FISH in neoplastic B cells within the skin infiltrates. *Borrelia burgdorferi* (sensu lato) DNA detected by nested polymerase chain reaction in the skin biopsy and serological findings proved *Borrelia* infection. Complete resolution of the cutaneous infiltrates was observed after antibiotic treatment. This case demonstrates that *Borrelia* infection of the skin may present with dense T-cell–rich infiltrates mimicking cutaneous T-cell lymphoma and masking the synchronous presence of neoplastic B cells in the context of B-CLL.

**Key Words:** cutaneous lymphoma, leukemia, borreliosis, t(14;18), BCL-2, pseudolymphoma

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## INTRODUCTION

B-cell chronic lymphocytic leukemia (B-CLL) is one of the most common form of leukemias. Specific cutaneous infiltrates of B-CLL are found in about 25% of patients.<sup>1</sup> The onset of skin lesions has been suggested in some cases to be triggered by antigenic stimulation. In line with this proposition is the occurrence of specific skin infiltrates at the sites of herpes simplex, herpes zoster, chicken pox, and *Borrelia burgdorferi* infection.<sup>2–5</sup> In 2 previously published articles focused on the association of cutaneous involvement by B-CLL and *B. burgdorferi* infection, the infiltrate of B-cells dominated the histopathological picture and was readily recognizable by the

predominance of B cells having typical immunophenotype.<sup>6,7</sup> We present an extraordinary case of B-CLL involving the skin, in which the neoplastic population comprised only a minority of the infiltrate and was masked by a predominantly T-cell infiltrate as a result of underlying *Borrelia* infection.

## CASE REPORT

A 72-year-old man presented with a solitary skin lesion on his left side of his chest wall that had been present for 3 months according to the patient. His complaint also included fatigue. Apart from the fatigue and skin lesion, the medical history was unremarkable. Clinical examination revealed a 7-cm annular plaque with accentuated and more infiltrated margins and a clear central portion showing fine scaling (Fig. 1A). The initial laboratory investigation revealed an elevated peripheral blood lymphocyte count ( $53.21 \times 10^6/\text{mL}$ ; the norm: 1.5–4.0); the differential diagnosis included specific cutaneous involvement by CLL or cutaneous T-cell lymphoma, such as unilesional mycosis fungoides (MF). However, because of the solitary presentation, which would be unusual for B-CLL, and the patient living in an endemic area for borreliosis and resemblance of the skin lesion with erythema migrans, borreliosis was considered as a further differential diagnosis. Subsequent serological studies revealed elevated titers of both immunoglobulin (Ig) M and IgG for *B. burgdorferi*. The patient was investigated simultaneously to clarify the nature of the skin lesion and underwent a workup for his peripheral blood leukocytosis at a hemato-oncology department. Fluorescence-activated cell sorting analysis of the peripheral blood yielded a predominant B-cell population, with 95% B cells expressing the following phenotype: CD19<sup>+</sup>, CD20 weakly<sup>+</sup>, sIgM weakly<sup>+</sup>, CD5<sup>+</sup>, CD23<sup>+</sup>, CD22<sup>-</sup>, CD79a<sup>-</sup>, and CD38<sup>-</sup>. A bone marrow aspirate revealed an increased number of lymphocytes (48%, the norm 3%–17%). A diffuse involvement by small B cells (up to 50%) of the bone marrow was evident in a bone marrow biopsy. A t(14;18)(q32;q21) (BCL2–IGH) was detected by FISH in the bone marrow specimen. Computer tomography investigation revealed mild splenomegaly (14 cm) and slightly enlarged retroperitoneal, axillary, and inguinal lymph nodes (up to 2.2 cm).

After diagnosis of cutaneous borreliosis was rendered, doxycycline (100 mg bid for 2 weeks) was administered, which resulted in complete remission of the skin lesion (Fig. 1B). No treatment for B-CLL was initiated because the patient was asymptomatic. No relapse of the skin lesion was observed during a follow-up period of 12 months.

## CUTANEOUS HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS

A skin biopsy demonstrated a dense band-like lymphoid infiltrate in the upper dermis and perivascular infiltrates

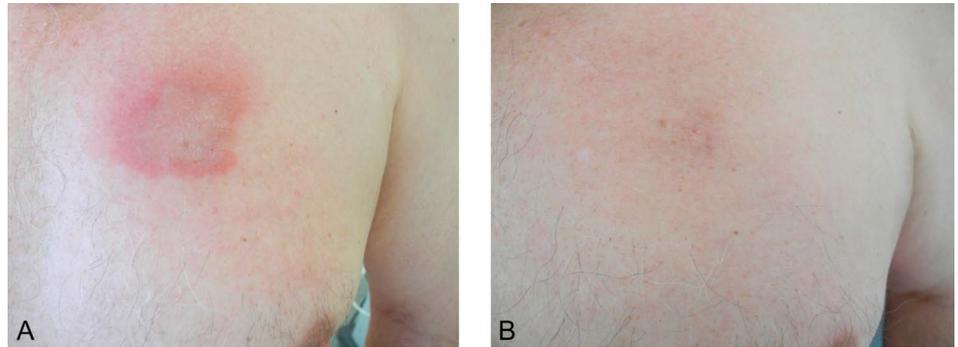
From the \*Kempf und Pfaltz, Histologische Diagnostik, Zürich, Switzerland; †Department of Pathology, Faculty of Medicine in Pilsen, Charles University in Prague, Pilsen, Czech Republic; and ‡Dermatology Practice, Biel, Switzerland.

The authors declare no conflicts of interest.

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**FIGURE 1.** An annular plaque on the left side of the chest with accentuated and more infiltrated margins and a clear central portion showing fine scaling before treatment (A). Complete remission of the skin lesion followed by administration of rudocycline (B).



in the mid dermis composed predominantly of small lymphocytes with chromatin dense nuclei but in addition admixture of a few medium-sized lymphocytes with slightly atypical nuclei (Figs. 2A, B). Only a few plasma cells were present. There were foci with minimal exocytosis of lymphocytes and subtle vacuolization at the junctional zone, but largely, the epidermis was uninvolved. A few interstitial histiocytes and mild fibrosis in the papillary dermis were found.

Immunohistochemically, the T-cell population comprised about 90% of the infiltrate and mostly consisted of small and medium-sized lymphocytes co-expressing CD3 and CD4, whereas about 10% of the infiltrate represented CD20- and CD79a-positive B cells (Figs. 3A, B). Most T cells also expressed CD5 and CD7. Staining for CD138 showed the presence of only a few plasma cells. A small number of lymphocytes which accounted for less than 5% of the entire infiltrate, expressed CD5 and CD23 (Fig. 3C). There was no expression of CD30 or cytotoxic proteins, such as T-cell intracellular antigen-1.

### MOLECULAR BIOLOGICAL AND CYTOGENETIC FINDINGS

Multiplex polymerase chain reaction using BIOMED 2 primers for T-cell receptor gene rearrangement revealed a polyclonal pattern. Nested polymerase chain reaction for *B. burgdorferi* (sensu lato)-specific DNA sequences proved positive in the skin biopsy.

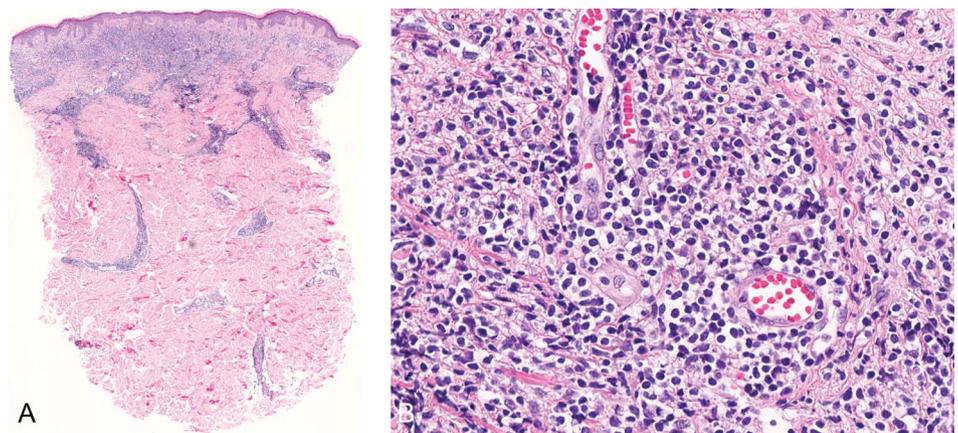
Interphase FISH analysis for BCL2 break-apart probe (Abbott Molecular) was performed according to the

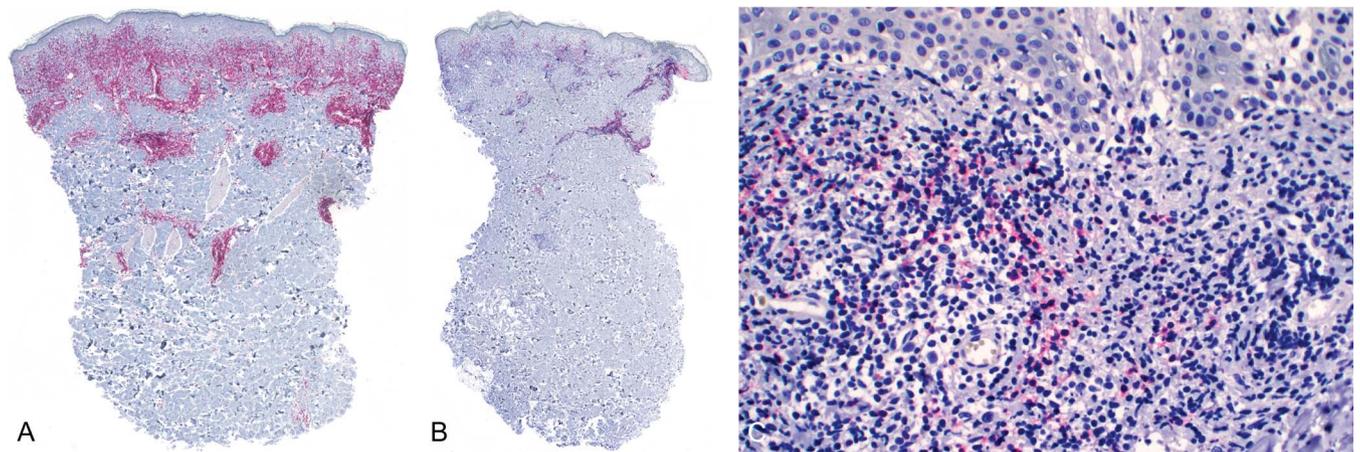
manufacturer's instruction, accustomed to the need of our tissue. Briefly, deparaffinization and pretreatment of a 3- $\mu$ m section were followed by 9 minutes incubation in Pronase E (0.05%) (VWR, Dietikon, Switzerland). Denaturation at 73°C and overnight hybridization at 37°C were performed (HyBrite, Abbott Molecular). One hundred nuclei were evaluated at a Zeiss Axio Imager.Z2. Images were acquired with a Z stack using ZEN 2012 software (Carl Zeiss AG, Feldbach, Switzerland). Twenty-six out of 100 nuclei (26%) showed a split signal, indicating a break in the BCL2 gene and hence a translocation at 18q21 (cutoff: 3% assessed as mean and 3-fold SD) (Fig. 4).

### DISCUSSION

We report on an unusual case of borreliosis mimicking T-cell lymphoma because of the presence of atypically appearing T cells and the presence of neoplastic B cells of concurrently diagnosed B-CLL. Specific cutaneous involvement by B-CLL has a plethora of clinicopathological manifestations.<sup>1,8</sup> The commonest presentation is with multiple patches.<sup>9-12</sup> An unusual but well-documented presentation is the occurrence of specific B-CLL infiltrates in the vicinity of epithelial and nonepithelial lesions, including squamous cell carcinoma, keratoacanthoma, melanoma, Merkel cell carcinoma, dermatofibroma to name but a few.<sup>13-18</sup> Additionally, an association of B-CLL and various cutaneous T-cell lymphomas has been documented, including MF, Sézary syndrome, peripheral T-cell lymphoma involving the skin, and natural

**FIGURE 2.** A dense band-like lymphoid infiltrate in the upper dermis and perivascular infiltrates in the mid dermis (A) [hematoxylin and eosin (H&E), original magnification,  $\times 10$ ]. Close-up: small lymphocytes with chromatin dense nuclei admixed with few medium-sized lymphocytes with slightly atypical nuclei (B) (H&E, original magnification,  $\times 400$ ).





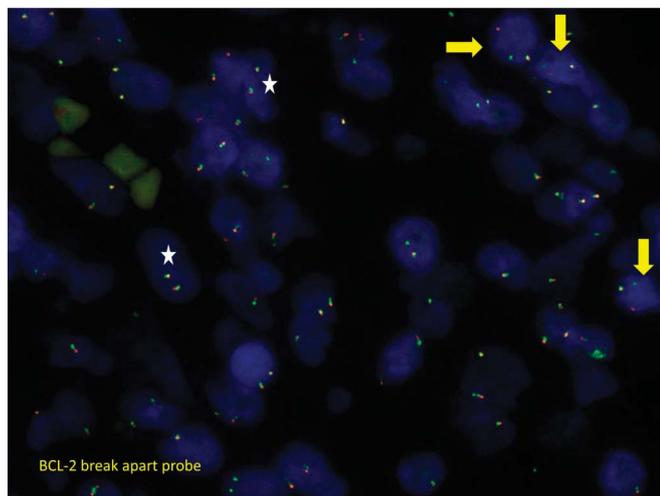
**FIGURE 3.** Staining for CD3 (A), CD20 (B), and CD23 (C) demonstrates that the majority of the infiltrate consists of CD3-positive T cells with only very few CD20-positive B cells and admixture of a few scattered B cells (immunohistochemistry, alkaline phosphatase-anti-alkaline phosphatase). Note also focal exocytosis with lining up of lymphocytes within the basal cell layer.

killer-cell lymphoma.<sup>19–21</sup> Occurrence of leukemic infiltrates on the site of a previous herpes simplex or herpes zoster infection leads to the speculation that specific skin infiltrates of B-CLL can be triggered by antigenic stimulation.<sup>2–5,22</sup> We are aware of 2 previously published articles documenting the association of specific B-CLL infiltrates and *B. burgdorferi* infection. In 2002, Cerroni et al<sup>6</sup> reported 6 patients with specific cutaneous involvement of B-CLL at the sites typical for *B. burgdorferi*-induced pseudolymphoma, namely, the nipple and scrotum. Remarkably, the lesions were solitary, thus making separation from *Borrelia*-induced benign lymphoid hyperplasia difficult. Parenthetically, pseudolymphoma at the above

sites has been shown to manifest some atypical histopathological features, including an Indian file pattern simulating specific cutaneous involvement by B-CLL.<sup>23,24</sup> In 2011, Kash et al<sup>7</sup> reported a 69-year-old woman with specific cutaneous infiltrate of B-CLL occurring at the site of erythema chronicum migrans due to of *B. burgdorferi* infection. In all the above cases, infiltrates of B-CLL were readily identifiable based on their monotonous infiltrates and their immunophenotype. In contrast, in our patient, the neoplastic B cells of B-CLL were few and masked by a predominantly T-cell infiltrate, which is another unusual finding.

Pseudolymphomatous infiltrates in *Borrelia* infection of the skin most commonly manifest with dense B-cell infiltrates with admixture of plasma cells. Furthermore, cases of low-grade malignant cutaneous B-cell lymphomas, such as plasma cell-rich variant of cutaneous marginal zone lymphoma (formerly referred to as cutaneous immunocytoma), have been found in *Borrelia* infection. Exception to these B-cell-predominant dense lymphocytic infiltrates in *Borrelia* infection, erythema migrans, is a T-cell-dominated process.<sup>25</sup> Apart from the latter work, Tee et al<sup>26</sup> described 11 patients with acrodermatitis chronica atrophicans, of which 8 cases showed a band-like T-cell-predominant lymphocytic infiltrate, exocytosis of lymphocytes, and a fibrotic papillary dermis resembling features in MF. In addition, we recently described a case of *B. burgdorferi*-associated lobular panniculitis resembling subcutaneous panniculitis-like T-cell lymphoma typified by a T-cell infiltrate with cytotoxic phenotype.<sup>27</sup> These observations and the presented case demonstrate that cutaneous *Borrelia* infection is occasionally associated with T-cell-rich infiltrates mimicking various forms of cutaneous T-cell lymphomas or secondary cutaneous infiltrates of T-cell neoplasms, such as prolymphocytic T-cell leukemia/lymphoma.

In addition to the T-cell-predominant component of the infiltrates in our patient, B cells were found, including a few CD5 and CD23<sup>+</sup> B cells. FISH analysis demonstrated that these cells in the skin carried the very same t(14;18)(q32;q21) translocation as identified in the neoplastic cells of B-CLL in the bone marrow and peripheral blood. This



**FIGURE 4.** FISH break-apart probe of the BCL-2 gene showing many reactive infiltrating cells with a normal genotype for BCL-2 as indicated by 2 fused yellow (green and red) fusion signals on each chromosome (asterisk). A few cells show a clear split of 1 green and 1 red signal (arrow) on 1 chromosome, indicating a translocation at this gene locus. We interpret this as scarce infiltrate of circulating B-CLL cells demonstrating a translocation t(14;18) of the IGH and BCL-2 genes in this patient.

translocation is a cytogenetic hallmark of extracutaneous follicular lymphoma and can also be found in a subset of nodal diffuse large B-cell lymphomas. In addition, occasional cases of CLL/small lymphocytic lymphoma with t(14;18) have been reported.<sup>28,29</sup> In our case, the break in the BCL2 gene detected in a portion of the cellular infiltrate is compatible with the presence of the same clone of B-CLL cells with a translocation t(14;18)(q32;q21) as previously detected in the bone marrow of this patient. This is interesting because morphologically and by immunohistochemistry, the B-CLL infiltrate was below the detection limit. Taken together, we face here the unusual constellation of a T-cell–driven immune reaction to *B. burgdorferi* admixed with malignant B-CLL cells carrying a translocation involving the BCL2 gene. This also stresses the usefulness of FISH in biopsies with B-CLL, in which leukemic infiltrates are not readily apparent on hematoxylin and eosin–stained sections. In analogy, Mitteldorf et al<sup>30</sup> documented a patient with B-CLL manifesting histologically an insect bite–like reaction, in which interphase FISH performed on the skin biopsy revealed a deletion of TP53 previously found in the peripheral blood of the patient. Recently, Tang et al<sup>31</sup> indicated that the t(14;18) in CLL was associated with relatively young age at diagnosis, mutated Ig heavy chain variable region genes, and a more aggressive clinical course usually requiring chemotherapy. In contrast, B-CLL in our patient exhibited an indolent course.

In conclusion, we have described an extraordinary case with specific cutaneous involvement by B-CLL with t(14;18)(q32;q21) translocation that presented in the skin with a minor neoplastic cell population masqueraded by a predominant T-cell infiltrate associated with *B. burgdorferi* infection.

## REFERENCES

- Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2007;48:855–865.
- Cerroni L, Zenahlik P, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia arising at the site of herpes zoster and herpes simplex scars. *Cancer*. 1995;76:26–31.
- Aberer W, Zonzits E, Soyer HP, et al. Post-zoster-specific skin infiltrates in chronic lymphatic leukemia. *Hautarzt*. 1990;41:455–457.
- Pujol RM, Matias-Guiu X, Planaguma M, et al. Chronic lymphocytic leukemia and cutaneous granulomas at sites of herpes zoster scars. *Int J Dermatol*. 1990;29:652–654.
- Doutre MS, Beylot-Barry M, Beylot C, et al. Cutaneous localization of chronic lymphocytic leukemia at the site of chickenpox. *J Am Acad Dermatol*. 1997;36:98–99.
- Cerroni L, Hoffer G, Back B, et al. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for *Borrelia burgdorferi* infection. *J Cutan Pathol*. 2002;29:142–147.
- Kash N, Fink-Puches R, Cerroni L. Cutaneous manifestations of B-cell chronic lymphocytic leukemia associated with *Borrelia burgdorferi* infection showing a marginal zone B-cell lymphoma-like infiltrate. *Am J Dermatopathol*. 2011;33:712–715.
- Plaza JA, Comfere NI, Gibson LE, et al. Unusual cutaneous manifestations of B-cell chronic lymphocytic leukemia. *J Am Acad Dermatol*. 2009;60:772–780.
- Bonvalet D, Foldes C, Civatte J. Cutaneous manifestations in chronic lymphocytic leukemia. *J Dermatol Surg Oncol*. 1984;10:278–282.
- Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. *J Cutan Pathol*. 1993;20:407–410.
- Cerroni L, Zenahlik P, Hoffer G, et al. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. *Am J Surg Pathol*. 1996;20:1000–1010.
- Buechner SA, Li CY, Su WP. Leukemia cutis. A histopathologic study of 42 cases. *Am J Dermatopathol*. 1985;7:109–119.
- Kazakov DV, Belousova IE, Michaelis S, et al. Unusual manifestation of specific cutaneous involvement by B-cell chronic lymphocytic leukemia: spontaneous regression with scar formation. *Dermatology*. 2003;207:111–115.
- Wilson ML, Elston DM, Tyler WB, et al. Dense lymphocytic infiltrates associated with non-melanoma skin cancer in patients with chronic lymphocytic leukemia. *Dermatol Online J*. 2010;16:4.
- Dueber JC, Coffin CM. Collision of chronic lymphocytic leukemia/small lymphocytic lymphoma and melanoma. *Blood*. 2013;121:4819.
- Maughan C, Kolker S, Markus B, et al. Leukemia cutis coexisting with dermatofibroma as the initial presentation of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma. *Am J Dermatopathol*. 2014;36:e14–e15.
- Walther BS, Gibbons G, Chan EF, et al. Leukemia cutis (involving chronic lymphocytic leukemia) within excisional specimens: a series of 6 cases. *Am J Dermatopathol*. 2009;31:162–165.
- Brewer JD, Shanafelt TD, Otley CC, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol*. 2012;30:843–849.
- Barzilai A, Trau H, David M, et al. Mycosis fungoides associated with B-cell malignancies. *Br J Dermatol*. 2006;155:379–386.
- Chang MB, Weaver AL, Brewer JD. Cutaneous T-cell lymphoma in patients with chronic lymphocytic leukemia: clinical characteristics, temporal relationships, and survival data in a series of 14 patients at Mayo Clinic. *Int J Dermatol*. 2014;53:966–970.
- Metzman MS, Stevens SR, Griffiths CE, et al. A clinical and histologic mycosis fungoides simulant occurring as a T-cell infiltrate coexisting with B-cell leukemia cutis. *J Am Acad Dermatol*. 1995;33:341–345.
- Hapgood G, Mooney E, Dinh HV, et al. Leukaemia cutis in chronic lymphocytic leukaemia following varicella zoster virus reactivation. *Intern Med J*. 2012;42:1355–1358.
- Boudova L, Kazakov DV, Sima R, et al. Cutaneous lymphoid hyperplasia and other lymphoid infiltrates of the breast nipple: a retrospective clinicopathologic study of fifty-six patients. *Am J Dermatopathol*. 2005;27:375–386.
- Belousova IE, Nemcova J, Kacerovska D, et al. Atypical histopathologic features in cutaneous lymphoid hyperplasia of the scrotum. *Am J Dermatopathol*. 2008;30:407–408.
- Boer A, Bresch M, Dayrit J, et al. Erythema migrans: a reassessment of diagnostic criteria for early cutaneous manifestations of borreliosis with particular emphasis on clonality investigations. *Br J Dermatol*. 2007;156:1263–1271.
- Tee SI, Martinez-Escaname M, Zuriel D, et al. Acrodermatitis chronica atrophicans with pseudolymphomatous infiltrates. *Am J Dermatopathol*. 2013;35:338–342.
- Kempf W, Kazakov DV, Kutzner H. Lobular panniculitis due to *Borrelia burgdorferi* infection mimicking subcutaneous panniculitis-like T-cell lymphoma. *Am J Dermatopathol*. 2013;35:e30–e33.
- Lopez C, Delgado J, Costa D, et al. Clonal evolution in chronic lymphocytic leukemia: analysis of correlations with IGHV mutational status, NOTCH1 mutations and clinical significance. *Genes Chromosomes Cancer*. 2013;52:920–927.
- Lu G, Kong Y, Yue C. Genetic and immunophenotypic profile of IGH@ rearrangement detected by fluorescence in situ hybridization in 149 cases of B-cell chronic lymphocytic leukemia. *Cancer Genet Cytogenet*. 2010;196:56–63.
- Mitteldorf C, Tronnier M, Merz H, et al. Insect bite-like reactions in a patient with B-cell chronic lymphocytic leukaemia: fluorescence in situ hybridization analysis revealed neoplastic B cells within the skin infiltrate. *Br J Dermatol*. 2012;167:944–946.
- Tang G, Banks HE, Sargent RL, et al. Chronic lymphocytic leukemia with t(14;18)(q32;q21). *Hum Pathol*. 2013;44:598–605.