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Letter to the Editor

Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma Skin Infiltration Triggered by Borrelia Burgdorferi Infection

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Chronic lymphocytic leukaemia/small lymphocytic lymphoma is the most common adult leukaemia [1]. The disease in its initial stages mostly involves the bone marrow and lymph nodes, with other sites being infrequently affected [2]. Skin infiltration in CLL/SLL is seen in 1-2 % of cases [3]. Skin involvement is a rare initial presentation of the disease. One study showed that skin infiltration by tumour cells was the initial manifestation in 7 patients (16.7%) from a series of 42 patients with B-CLL/SLL [4]. *Borrelia burgdorferi* infection has been linked to skin manifestations of CLL/SLL [5].

A 65-year-old male patient from a rural area presented to the General Practitioner's office with a slow-growing nodule of the right nipple. The patient was referred to the Surgery Department of the "Prof. Dr. Ion Chiricuță" Oncology Institute.

In our department, the patient reported that he had noticed the lesion four months prior to the current presentation, with a progressive, slow-growing, painless evolution. The patient's family history revealed two first degree relatives with haematological diseases. One of the patient's sons was diagnosed with a form of acute leukaemia, from which he subsequently died at the age of 33. The patient's mother also suffered from a form of haematological malignancy. The patient was not able to give further details regarding the diseases of his relatives. He had been a smoker since the age of 14, with an average of one pack of cigarettes per day. He also reported occasional alcohol consumption, but denied any consumption of drugs or narcotics. There was no other significant history.

Clinical examination showed facial erythema, a good state of nutrition, a blood pressure of 160/80 mm Hg, a heart rate of 80 bpm, and a body temperature of 36.8°C. In the right nipple area, a nodular lesion with a diameter of 2 cm was present. The skin overlying the lesion was erythematous, but showed no ulceration. On palpation, the tumour had a hard consistency. Bilaterally, in the lateral cervical, submandibular and axillary areas, several enlarged lymph nodes less than one centimetre in diameter were identified. No liver or spleen enlargement was found on abdominal examination.

Histopathological, haematological, laboratory and imaging findings

An incisional biopsy was performed and submitted to the pathology department. The examination revealed a skin fragment with a diffuse full-thickness infiltration of small size lymphocyte cells, with a mature morphology (**Figure 1a**). Focally, the formation of reactive follicles was observed. Immunohistochemistry showed positivity for: CD20, CD19, CD23, CD5 (**Figure 1b**). Cyclin D1 was negative. FMC7 was not available.

The patient was referred to the Haematology Department of our Institution. The International Prognosis Index was 1. Laboratory examination revealed an increased number of white blood cells (WBC 28,000/mm^3), with a predominance of lymphocytes (86%). Flow cytometry evidenced the following immunophenotype: 80% B lymphocytes, 12% T lymphocytes and 8% natural

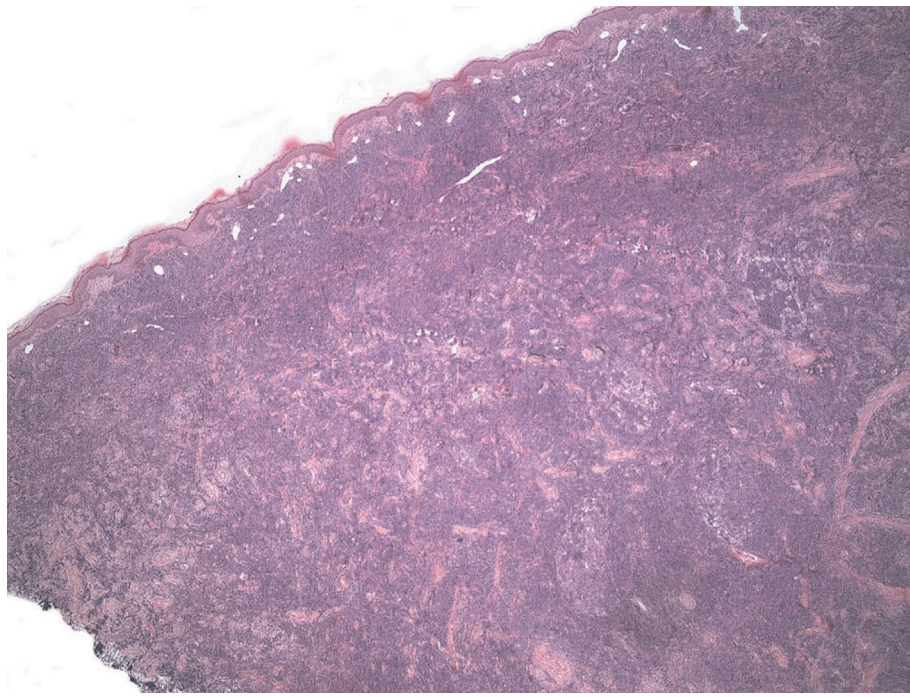

Figure 1a. Diffuse full-thickness infiltration of the skin by mature small size lymphocytes admixed with reactive follicles (HE stain, 4X).

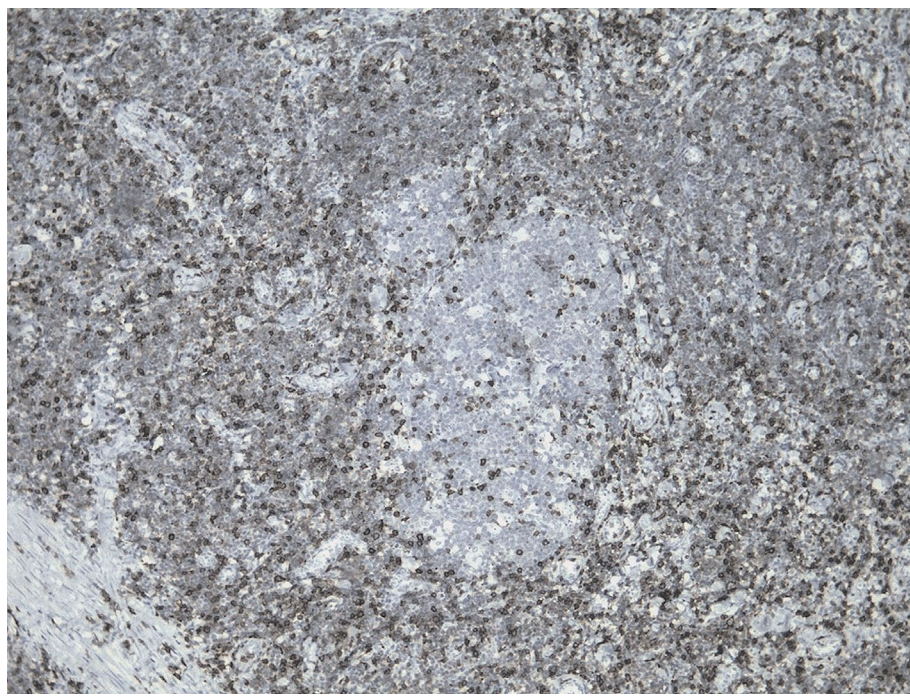

Figure 1b. Expression of CD5 by tumour cells.

killer cells. B cells were positive for CD45, CD20, CD19, CD22, CD23, CD5, HLA-DR+, FMC7 and lambda (λ) chains. CD38 and ZAP70 were negative. The peripheral blood smear revealed 86% lymphocytes, 12% neutrophils and the presence of "smudge cells". Biochemistry showed an increased total bilirubin value (2.19 mg/dl), with a direct bilirubin value of 0.91 mg/dl.

Serology (ELISA) evidenced increased levels of IgG (4.78) and IgM (0.26) for *Borrelia burgdorferi*. Western-blot analysis was positive for IgG antibodies, but negative for IgM. On computed tomography, several lymph node enlargements were identified in the lateral cervical, submandibular, axillary, paraaortic, pelvic and inguinal areas.

Diagnosis was ***skin infiltration by CLL/SLL in the nipple area,*** most likely triggered by a *Borrelia burgdorferi* infection.

Antibiotic therapy with doxycycline, 100 mg po bid for 10 days, and symptomatic relief drugs were administered. The cutaneous lesion showed a favourable evolution. Considering the incipient stage of the haematological disease (CLL/SLL), a *watch-and-wait* approach was preferred. Follow-up at 3, 6, 9 and 12 months showed a stationary disease, with a mean WBC count of 23,000/mm^3 and the persistence of lymph node enlargement.

Borrelia burgdorferi is associated with several skin manifestations. Cutaneous infiltrations by CLL/SLL have been previously described at sites that are characteristic of borrelial lymphocytoma (ear lobe, nipple, scrotum), a Borrelia burgdorferi-associated skin manifestation that involves polyclonal lymphoid hyperplasia [4,6,7]. In fact, the particular site of involvement was very suggestive of an association with the infection in our case. Although in the given circumstances the likelihood of a causative effect is very high, the definitive proof would be demonstrating monoclonality in cutaneous tissue sections (by PCR analysis of the JH gene rearrangement), and the presence of DNA sequences specific for B. burgdorferi. This is a limitation of our study.

CLL/SLL infiltration of anatomic sites affected by a benign inflammatory condition with an infectious aetiology has been described in the literature, but this etiological category is not the exclusive trigger for these events [5,6]. In our case, the presence of reactive follicles suggests a prior benign inflammatory infiltrate secondarily "colonised" by neoplastic cells. Histopathological differential diagnosis includes several entities: B-cutaneous lymphoid hyperplasia (pseudolymphoma), cutaneous marginal zone B-cell lymphoma, mantle cell lymphoma (MCL), primary cutaneous follicle centre lymphoma (PCFCL), and skin involvement by follicular lymphoma (FL) [3,5]. Lymphoid hyperplasia usually has a nodular, perivascular and periadnexal distribution, with the formation of polarised follicles and a mixed inflammatory infiltrate in the interfollicular area [2,3]. In the case of CLL/SLL, the restriction of light chain expression is a strong argument for malignancy [2]. The presence of reactive follicles and infiltration with small size lymphocytes raises the differential diagnosis of cutaneous marginal zone lymphoma, which does not express the CD5 and CD23 markers [2,5,8]. FMC7 expression evidenced by flow cytometry raises differential diagnosis problems with MCL, as this is an exception. Cyclin D1 expression is useful in differentiating CLL/SLL from MCL, although skin involvement in this case is rare [9]. PCFCL is characterised by a predominantly follicular architecture, but can sometimes show a diffuse pattern [8]. Cells usually do not express CD5 and CD43. Skin involvement in FL usually represents a secondary site and cells express, in most cases, BCL2 and CD10 [8].

The particularities of the case are represented by the initial presentation, the relatively rare skin involvement, the association with *Borrelia*

burgdorferi infection, and the familial clustering of haematological malignancies.

Consent information

The patient's informed consent was obtained.

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References:

1. Muller-Hermelink HK, Montserrat E, Catovsky D, Campo E, Harris NL, Stein H. Chronic lymphocytic leukemia/small lymphocytic lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. 4th ed. Lyon: IARC; 2008:180-2.
2. Viswanatha DS, Montgomery KD, Foucar K. Mature B-Cell Neoplasms: ChronicLymphocytic Leukemia–Small Lymphocytic Lymphoma, B-Cell Prolymphocytic Leukemia, and Lymphoplasmacytic Lymphoma. In: Jaffe ES, Lee Harris N, Vardiman JW, Campo E, Arber DA, (eds). Hematopathology. 1st ed. Philadelphia: Saunders/Elsevier; 2011:221-47. DOI: 10.1016/B978-0-7216-0040-6.00014-9.
3. Goodlad J, Calonje E. Cutaneous lymphoproliferative diseases and related disorders. In: Calonje E, Brenn T, Lazar A, McKee, PH. McKee's pathology of the skin with clinical correlations. 4th ed. Elsevier Health Sciences, 2011:1312-420.
4. Cerroni L, Zenahlik P, Höfler G, Kaddu S, Smolle J, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol. 1996 Aug;20(8):1000-10. DOI: 10.1097/00000478-199608000-00009.
5. 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 Oct;33(7):712-5. DOI: 10.1097/DAD.0b013e3181fc576f.
6. 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 Jul 1;76(1):26-31. DOI: 10.1002/1097-0142(19950701)76:1<26::AID-CNCR2820760105>3.0.CO;2-J.
7. Hill BT, Weil AC, Kalaycio M, Cook JR. Pulmonary involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma is a specific pathologic finding independent of inflammatory infiltration. Leuk Lymphoma. 2012 Apr;53(4):589-95. DOI: 10.3109/10428194.2011.623252.
8. McDivitt Duncan L. Primary Cutaneous B-Cell Lymphoma. In: Jaffe ES, Lee Harris N, Vardiman JW, Campo E, Arber DA, eds. Hematopathology. 1st ed. Philadelphia: Saunders/Elsevier; 2011:306-18. DOI: 10.1016/B978-0-7216-0040-6.00019-8 DOI: 10.1016/B978-0-7216-0040-6.00040-X.
9. Sen F, Medeiros LJ, Lu D, Jones D, Lai R, Katz R, Abruzzo LV. Mantle cell lymphoma involving skin: cutaneous lesions may be the first manifestation of disease and tumors often have blastoid cytologic features. Am J Surg Pathol. 2002 Oct;26(10):1312-8. DOI: 10.1097/00000478-200210000-00008.