

A rare manifestation of chronic lymphocytic leukaemia – leukaemia cutis treated with ibrutinib

Białaczka skóry w przebiegu przewlekłej białaczki limfocytowej leczona ibrutinibem

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Abstract

Skin infiltration by leukaemia (leukaemia cutis – LC) in chronic lymphocytic leukaemia (CLL) occurs in less than 5% of affected patients. It is significantly less common than skin cancers complicating the course of CLL, with an incidence of up to 20%, and non-specific skin lesions. Therefore, it is crucial to perform additional diagnostic tests to establish the aetiology of skin lesions in CLL patients.

In this report, we present a case of a 60-year-old woman with CLL, in whom diffuse skin lesions were observed seven years after diagnosis, histologically confirmed as CLL infiltrates, and who responded well to treatment with ibrutinib.

Key words: chronic lymphocytic leukaemia, leukaemia cutis, ibrutinib.

Streszczenie

Naciek skóry przez białaczkę w przewlekłej białaczce limfocytowej (*chronic lymphocytic leukaemia* – CLL) występuje u ok. 5% pacjentów. Jest znacznie rzadziej obserwowany niż nowotwory skóry komplikujące przebieg CLL z częstością do 20% czy niespecyficzne zmiany skórne. Dlatego kluczowe jest przeprowadzenie diagnostyki zmian w celu ustalenia ich etiologii u pacjentów z CLL.

W pracy przedstawiono przypadek 60-letniej kobiety z CLL, u której 7 lat po ustaleniu rozpoznania zaobserwowano rozlane zmiany skórne, potwierdzone histologicznie jako naciek CLL, z dobrą odpowiedzią na leczenie ibrutinibem.

Słowa kluczowe: przewlekła białaczka limfocytowa, białaczka skóry, ibrutinib.

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INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in western countries with an incidence of 4.2 : 100,000 per year. The median age of diagnosis is 72 years with 10% of patients diagnosed under 55 years old [1]. Skin infiltration by leukaemia (leukaemia cutis – LC) [2] in CLL is rare and occurs in less than 5% of affected patients [3]. It is significantly less common than skin cancers com-

plicating course of CLL with an incidence of up to 20% [4], and non-specific skin lesions. Therefore, it is crucial to perform additional diagnostic tests to establish the aetiology of the skin lesions in CLL patients.

In this report, we present a case of a 60-year-old woman with CLL, in whom diffuse skin lesions were observed seven years after diagnosis, histologically confirmed as CLL infiltrates, and who responded well to the treatment with ibrutinib.

CASE REPORT

We present a case of a 60-year-old female patient with CLL, diagnosed eight years earlier in 11/2011. The diagnosis was made according to standard criteria: the presence of monoclonal B-lymphocytes with characteristic phenotype in the peripheral blood, confirmed by flow cytometry. At the time of diagnosis, the disease was in stage II according to Rai [5] classification (peripheral blood lymphocytes $70 \times 10^9/l$, peripheral lymphadenopathy, splenomegaly). There was no del(17p) on the cytogenetic examination [6]. The following treatment regimens were used over the years: from 1/2012 fludarabine and cyclophosphamide (FC), 1/2013 rituximab, fludarabine and cyclophosphamide (R-FC), and 11/2015 rituximab and bendamustine (R-B). In 4/2017, rising lymphocytosis with intra-abdominal lymphadenopathy (aorto-caval lymph nodes with a transverse dimension of 125 mm showed on computed tomography) was found. The patient was subsequently treated with six cycles of bendamustine (B).

Due to lack of response and suspicion of Richter's transformation, on 03/2018 a surgical biopsy of the left iliac lymph node was performed. The histopathological evaluation revealed infiltration of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) with large, merging proliferation centres and an increased mitotic index of up to 50-60%, histologically aggressive form of the disease, characterised in WHO 2017 classification as an intermediate stage between the typical CLL/SLL and Richter syndrome. In repeated cytogenetic examination, there was no del(17p) and no mutation in TP53 gene in the molecular examination using the Sanger method [7].

Due to the aggressive form of CLL, three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) were introduced, (3/2018-6/2018). During the control visit in 6/2018, the patient reported the appearance of follicular lesions on the skin of the forearms and shins (Fig. 1). A performed skin biopsy revealed CLL infiltration (Fig. 2). Computed tomography (CT) revealed progression of lymphadenopathy (aorto-caval lymph nodes with a transverse dimension of 135 mm), which corresponded to disease progression (PD) (Fig. 3A). Skin infiltrations with CLL might have indicated an aggressive, refractory disease. It was decided to initiate treatment with a targeted therapy with Bruton's tyrosine kinase inhibitor – ibrutinib. After eight months of treatment the patient achieved complete response with incomplete marrow recovery [8] (CRi), according to response criteria. The laboratory results were as follows: peripheral blood lymphocytes count 3.5 G/l, neutrophil count 1.4 G/l, haemoglobin concentration 14.1 g/dl, and platelet count 80 G/l. Thrombocytopenia was considered to be unrelated to CLL

but related to drug toxicity. There was a spectacular response of lymphadenopathy, with the decrease of the intra-abdominal lymph nodes, aorto-caval to 11 mm in the transverse dimension (Fig. 3B).

Skin lesions

Diffuse papillary lesions and nodules on erythematous ground with central necrosis, with a particular intensity on the skin of the upper and lower limbs were observed (Fig. 1). Skin changes were accompanied by severe pruritus, and according to the patient's report, appeared suddenly. Due to the sudden appearance of non-specific skin lesions, a skin biopsy was taken for histopathological examination with immunohistochemistry (Fig. 3): in the dermis, mainly around the blood vessels and skin appendages, infiltrates composed mostly of reactive T lymphocytes (CD3+, CD5+) were found, with small groups of small B cells with immunophenotype typical for CLL: CD79+, PAX5+, CD23+, CD5+, CD3–, but without CD20 expression, (prior to the examination, chemotherapy with anti-CD20 monoclonal antibody was used in the treatment). The skin lesions disappeared during ibrutinib therapy.

Histopathology

The microscopic presentation of leukaemia cutis can be very diverse. Cerroni *et al.* described three main histological patterns based on a series of 42 cases of patients with skin leukaemia in CLL [9]. They distinguished three main subtypes: with lymphocytic infiltration around the vessels and skin appendages – perivascular and periadnexal pattern, nodu-



Fig. 1. Skin lesions with particular intensity on upper and lower limbs

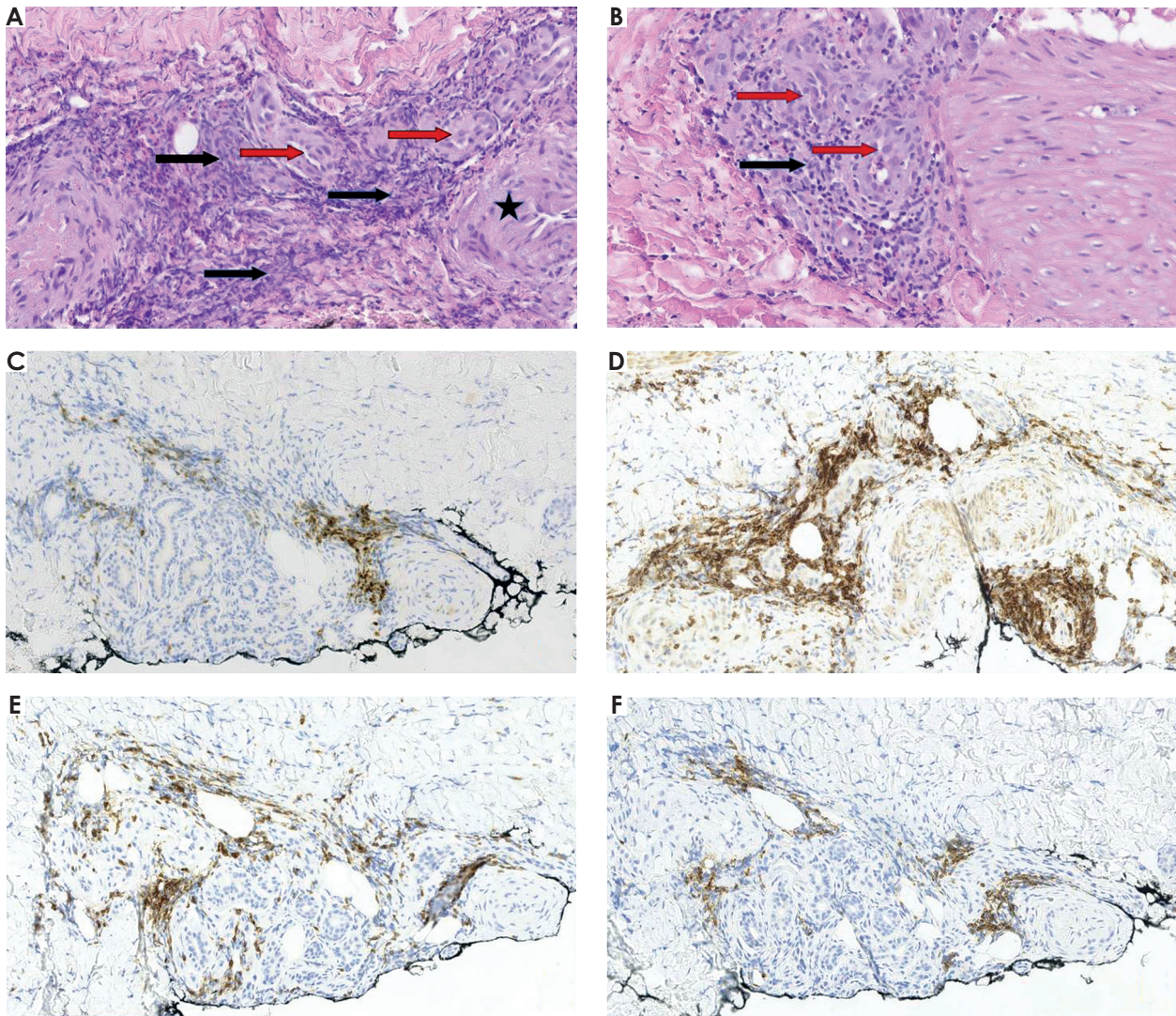


Fig. 2. Pathological examination and immunohistochemical staining. **A, B** Infiltration of the dermis by small B lymphocytes (black arrows) with a tendency to localisation around blood vessels (asterix) and appendages (red arrow) of the skin. Haematoxylin and eosin staining, magnification 300×. **C**) Anti-PAX staining, magnification 200×. **D**) Anti-CD5 staining, magnification 200× **E**) Anti-CD3 staining, magnification 200× **F**) Anti-CD23 staining, magnification 200×

lar and diffuse pattern, and band-like pattern. Monoclonal B lymphocytes most often coexpress CD20, CD43, CD23, and CD5 molecules. In the presented case, the first subtype – perivascular and periadnexal – was present (Fig. 2).

DISCUSSION

The infiltration of skin by leukaemic cells is a rare manifestation of CLL with an unclear prognostic significance. In the described case, the changes occurred seven years after the diagnosis, after multiple lines of chemotherapy, with the latter being a R-CHOP regimen. Therefore, it can be concluded that the infiltrations of the skin indicated an aggressive and refractory disease.

The prognosis of LC in the course of CLL remains controversial. LC according to Raufi *et al.* did not

worsen the prognosis of patients with CLL [10]. Other authors suggested worse prognosis in LC after the initiation of CLL systemic therapy and in Richter syndrome [11]. Colburn *et al.* suggested better prognosis in the appearance of LC [12]. In the latest study by Thiesen *et al.*, it was shown that nearly half (33/70) of LC lesions were located in close proximity to, or overlapped with, other skin lesions observed in non-melanoma skin tumours, precancerous states (actinic keratosis, Bowen's disease), and reactive inflammatory dermatoses (such as arthropod bites). The authors hypothesised that damage to the epidermal barrier may be a factor provoking the occurrence of LC [13].

In CLL patients, primary skin cancers are also common. In the study presented by Kleinstern *et al.*, in which a group of 846 CLL patients were analysed, 20% developed skin cancer. Squamous cell carcinoma was the most common (59%) [4]. Therefore, skin

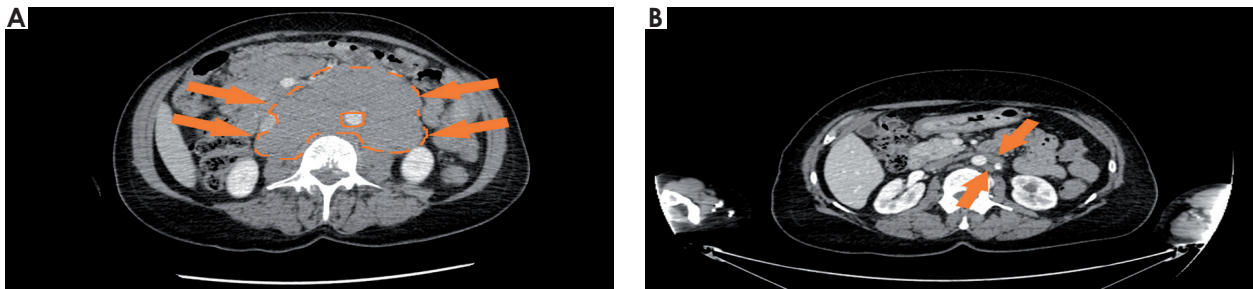


Fig. 3. Response to the treatment with ibrutinib in computed tomography. Aorto-caval lymph nodes with a transverse dimension of 135 mm at baseline (**A**) in September 2018 and after 8 months of ibrutinib (**B**), aorto-caval lymph nodes with a transverse dimension of 11 mm in June 2019. Aorto-caval lymph nodes are indicated with arrows

cancers should always be considered in the differential diagnosis of skin lesions in patients with CLL.

In the case of LC, various therapeutic options seem to be beneficial in symptomatic treatment. Authors of individual clinical case reports described therapeutic successes after using locoregional treatment [14-16]. In our case, however, systemic treatment of the underlying disease with ibrutinib was crucial.

Ibrutinib has demonstrated marked efficacy in CLL patients in clinical trials [17-19] and is approved by the US Food and Drug Administration for the therapy of CLL in any line of therapy. Its use has become a standard of care for relapsed CLL patients as well as for frontline high-risk patients with TP53 mutation and/or del(17p) [1, 8].

Usage of ibrutinib in CLL patients is relatively safe; the most serious adverse events include atrial fibrillation, bleeding, and infection [20]. The risk of complications during ibrutinib treatment increases with patient's age and coexisting comorbidities. In the presented case, the patient tolerated treatment very well; only temporary grade 2 thrombocytopenia according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 was noted, which did not require dose modification.

In conclusion, ibrutinib is a highly effective therapy for patients with relapse-refractory CLL, and it shows efficacy in the treatment of leukaemia cutis in the course of CLL.

The authors declare no conflict of interest.

REFERENCES

- Eichhorst B, Robak T, Montserrat E i wsp. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26 (Suppl 5): v78-v84.
- Siegel RS, Gartenhaus RB, Kuzel TM. Human T-cell lymphotropic-I-associated leukemia/lymphoma. *Curr Treat Options Oncol* 2001; 2: 291-300.
- Hurt MA, Weedon D. Weedon's skin pathology. 3rd ed. Churchill Livingstone Elsevier, London 2010.
- Kleinstern G, Rishi A, Achenbach SJ i wsp. Factors associated with non-melanoma skin cancer (NMSC) among chronic lymphocytic leukemia (CLL) patients. *Blood* 2017; 130 (Suppl 1).
- Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46(2):219-234. *Blood* 2016; 128: 2109.
- Pflug N, Bahlo J, Shanafelt TD i wsp. Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. *Blood* 2014; 124: 49-62.
- Catherwood M, Gonzalez D, Donaldson D i wsp. Relevance of TP53 for CLL diagnostics. *J Clin Pathol* 2019; 72: e343-e346.
- Hallek M, Cheson BD, Catovsky D i wsp. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018; 131: 2745-2760.
- Cerroni L, Zenahlik P, Höfler G i wsp. 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.
- Raufi A, Alsharedi M, Khelfa Y i wsp. Leukemia cutis in a patient with chronic lymphocytic leukemia presenting as bilateral helical nodules. *SAGE Open Med Case Reports* 2016; 4: 2050313X1668362.
- Ratnam KV, Khor CJ, Su WP. Leukemia cutis. *Dermatol Clin* 1994; 12: 419-431.
- Colburn DE, Welch MA, Giles FJ. Skin infiltration with chronic lymphocytic leukemia is consistent with a good prognosis. *Hematology* 2002; 7: 187-188.
- Thiesen I, Wehkamp U, Bruggemann M, Ritgen M. Skin involvement by chronic lymphocytic leukemia is frequently associated with unrelated neoplastic or inflammatory cutaneous disease and is not indicative of general disease progression. *Br J Dermatol* 2019; 180: 227-228.
- Bakst R, Yahalom J. Radiation therapy for leukemia cutis. *Pract Radiat Oncol* 2011; 1: 182-187.
- Porter WM, Sidwell RU, Catovsky D i wsp. Cutaneous presentation of chronic lymphatic leukaemia and response to ultraviolet B phototherapy. *Br J Dermatol* 2001; 144: 1092-1094.
- Sainsbury DC, Allison KP, Muir T. Electrochemotherapy treatment of a recalcitrant earlobe keloid scar with chronic lymphocytic leukaemia infiltration. *J Plast Reconstr Aesthet Surg* 2010; 63: e733-e736.
- Brown JR, Hillmen P, O'Brien S i wsp. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. *Leukemia* 2018; 32: 83-91.
- Burger JA, Tedeschi A, Barr PM i wsp. RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med* 2015; 373: 2425-2437.
- Byrd JC, Brown JR, O'Brien S i wsp. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; 371: 213-223.
- Maddocks KJ, Ruppert AS, Lozanski G i wsp. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol* 2015; 1, 80-87.