Unusual cutaneous manifestations of chronic lymphocytic leukaemia with increased prolymphocytes

Klaudia Gradzka, Kamila Kruczkowska-Tarantowicz, Marzenna B. Klimiuk, Janusz Kloczko

Department of Haematology, University Hospital in Bialystok, Poland

Chronic lymphocytic leukaemia with increased prolymphocytes (CLL/PL) is an aggressive form of atypical chronic lymphocytic leukaemia (CLL). Skin lesions associated with B-cell non-Hodgkin lymphomas are rare manifestations compared to T-cell non-Hodgkin lymphomas. Cutaneous presentations are divided into specific and non-specific changes. Specific skin involvement in B-cell non-Hodgkin lymphoma represents secondary cutaneous manifestations of systemic B-cell lymphoma, primary cutaneous B-cell lymphoma (PCBCL), or any other cancer. However, the most frequently observed eruptions are the non-specific skin lesions. They can be either haemorrhagic, of infectious aetiology, or a drug-induced reaction after chemotherapy. We present a case of a 61-year-old Caucasian man who was admitted to the Department of Haematology at University Hospital in Bialystok due to an abnormal complete blood count (WBC 54 G/l, HgB 13.6 g/dl, PLT 334 000/ml, 25% of prolymphocytes in smear) and the presence of numerous tumours with a diameter of 6 cm to 35 cm, some being within the area of the skin and some within the subcutaneous tissue. This patient's case is very interesting because of the rarity of this disease as well as the presence of unusual specific skin lesions. B-cell lymphomas are a heterogeneous group of clonal lymphoproliferative disorders, and they have a wide range of skin manifestations. For this reason a comprehensive diagnostic profile is crucial as it is the key to proper diagnosis and allows for the application of an appropriate treatment.

Key words: chronic lymphocytic leukaemia, leukaemia cutis, lymphoproliferative disorder.

Contemp Oncol (Pozn) 2014; 18 special issue
DOI: 10.5114/wo.2014.50641

Introduction

Chronic lymphocytic leukaemia with increased prolymphocytes (CLL/PL) is a very rare and aggressive form of atypical CLL [1]. The average age at the time of diagnosis is 63 years [2]. The disease is characterised by the presence of prolymphocytes, which constitute 11–54% of lymphoid cells in the peripheral blood and are more pleomorphic than prolymphocytes found in the course of B-cell prolymphocytic leukaemia (B-PLL) [3].

Chronic lymphocytic leukaemia with increased prolymphocytes may appear *de novo* or evolve from chronic lymphocytic leukaemia (B-CLL) in its course [4]. It morphologically and clinically presents the features of B-CLL and B-PLL [5]. The presence of lymphadenopathy is a characteristic feature of CLL/PL [2]. This distinguishes it from B-PLL, in which the lymph nodes are increased only in about every third patient [2]. In terms of immunophenotype, CLL/PL is more like B-CLL than B-PLL [2]. Skin lesions associated with the B-cell non-Hodgkin lymphomas are rare manifestations in comparison with T-cell non-Hodgkin lymphomas [6]. Nonetheless, they can be observed in up to 25% of patients with CLL [7].

Case report

We present the case of a 61-year-old Caucasian man who reported to the Dermatology Clinic on March 2012 because of the appearance of tumours of 5 cm in diameter on the skin of his whole body. Doctors diagnosed them as lipomas, because the changes were soft, skin-coloured, painless, movable relative to the surrounding tissue, and showed no tendency to decay.

The patient was informed about the possibility of cosmetic removal of changes if pain or restriction of movement occurred. In order to confirm the diagnosis he visited an oncologist and general surgeon who confirmed the diagnosis. He made an appointment with the surgeon for September 2012 to remove the skin lesions. However, the changes gradually expanded, and by June 2012 they became blue.

The concerned patient reported to a family doctor, who recommended performing basic blood tests. Due to the abnormal complete blood count (WBC 65 G/l) the patient was admitted to the Department of Haematology at University Hospital in Bialystok for further diagnosis. During his admission he complained about general weakness. The examination revealed the presence of numerous tumours with a diameter of 6 cm to 35 cm, some being within the area of the skin and some being within the subcutaneous tissue.

The two biggest skin changes were localised on the back, having a diameter of about 35 cm and 20 cm, of grey-blue colour, connected with the subcutaneous tissue, compact, without any signs of softening or tendency to decay. Similar changes were observed on the right thigh, measuring 15 cm in diameter, and one located on the right forearm, measuring 18 cm in diameter. In ad-

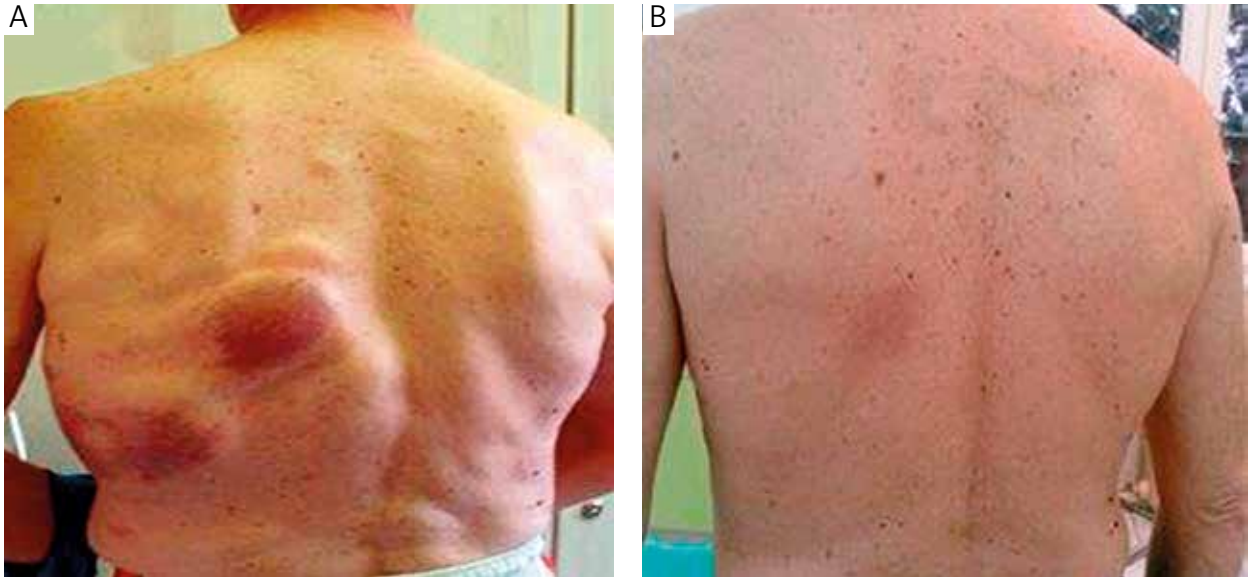

Fig. 1. Cutaneous manifestations of CLL/PL before chemotherapy and after treatment

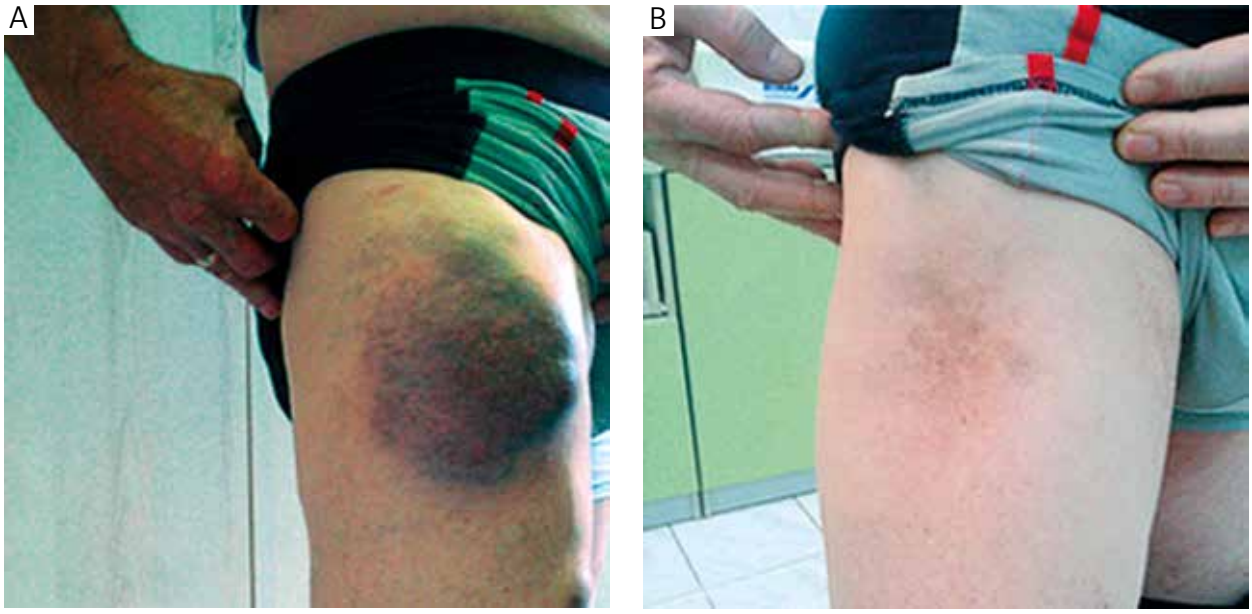

Fig. 2. Cutaneous manifestations of CLL/PL before chemotherapy and after treatment

dition, about 30 skin tumours located in the subcutaneous tissue were present within the skin area of the torso. They were skin-coloured, measuring 10 cm in diameter, cohesive, without any signs of softening or tendency to decay. In addition, physical examination revealed numerous enlarged supraclavicular and axillary lymph nodes, measuring up to about 2 cm.

On admission, the complete blood count was as follows: white blood cell count (WBC) 54.0 G/l, haemoglobin (HgB) 13.6 g/dl, platelet count (PLT) 334 000/ml, and 25% of prolymphocytes in smear. Laboratory tests revealed: LDH 593 IU/l and B2M 4.65 mg/l. The bone marrow aspirate was hypercellular, and 54% of cells were mature B-lymphocytes. The trephine biopsy showed a non-diffuse histopathological pattern of lymphatic infiltration; immunohistochemical analysis of cyclin D1 expression was negative. Peripheral blood immunophenotyping revealed an abnormal B cell population expressing CD19+, CD5–, CD23+, CD20+, CD22+, CD79b+, CD43+, CD81+, lambda+, IgM+, FMC7–, and CD38+. Cytogenetic analysis demonstrated normal karyotype. Computed tomography of neck, chest, abdomen, and pelvis revealed a group of enlarged supraclavicular and axillary lymph nodes with diameter of about 25 × 30 mm and massive lymphadenopathy in the abdomen. An incisional biopsy of the involved skin was performed and histological and immunohistochemical

studies were done. Results were consistent with chronic lymphocytic leukaemia with increased prolymphocytes.

In the treatment of the underlying disease, R-FC regimen was applied every 28 days in 6 cycles. There were no serious side effects. In November of 2012, just before the start of the third cycle of chemotherapy, complete regression of the skin lesions was observed. In February of 2012 the patient was hospitalised in the Department of Haematology, University Hospital in Bialystok, in order to evaluate his response to the therapy. A complete remission was achieved. He remains under the care of the Haematology Outpatient Clinic.

Discussion

Cutaneous manifestations of B-cell non-Hodgkin lymphoma are divided into specific and non-specific changes [8]. Specific changes are characterised by the presence of leukemic cells or other tumour infiltrations of the skin [7]. Non-specific skin lesions can be either haemorrhagic, of infectious aetiology, or a drug-induced reaction after chemotherapy [9]. Specific skin involvement in B-cell non-Hodgkin lymphoma represents secondary cutaneous manifestations of systemic B-cell lymphoma, primary cutaneous B-cell lymphoma (PCBCL), or any other cancer [6]. The differential diagnosis of skin involvement in the primary extracutaneous B-cell non-Hodgkin lymphoma should include B-CLL, mantle cell lymphoma (MCL), Burkitt lymphoma (BL), systemic diffuse large B-cell lymphoma (DLBCL), and Richter's syndrome (RS) [10].

Cutaneous lesions of B-CLL are seen in 25% of patients and tend to be diverse. The eruptions may be single, multiple, or generalised plaques, papules, nodules, and large tumours [7]. It is also believed that the occurrence of lymphoproliferative lesions within the scar area resulted from herpes zoster and herpes simplex infections [11], lesions in the area typical of Varicella zoster virus and Borrelia burgdorferi infections [12], can also be a manifestation of the underlying disease. However, the most commonly observed eruptions are non-specific skin lesions [9]. They have been observed in up to 80% of patients with CLL [13]. These include purpura, vasculitis, erythema nodosum, pyoderma gangrenosum, generalised itching, paraneoplastic pemphigus, pemphigoid, and Sweet's syndrome [14].

The eruptions associated with the skin infiltration by leukaemia cells is called leukaemia cutis (LC) [15]. The incidence of LC in patients with chronic lymphocytic leukaemia is very rare [16]. Agnew *et al*. identified only three cases of LC in 750 consecutive patients suffering from CLL [17]. However, even in the case of a correct percentage of lymphocytes in the blood and the absence of lymphadenopathy, the specific nature of the lesions should always be considered [18]. Typically CLL has an indolent clinical course. Many authors believe that the presence of specific lesions at the time of CLL diagnosis does not worsen the prognosis [19, 20]. Nonetheless, secondary occupation of the skin in CLL may indicate RS, which has a poor prognosis. RS has been reported in 3% of patients with CLL [21].

Skin involvement in MCL is very rare, occurring in just 2–6% of cases [10]. The lesions are usually located on the chest and legs and have a form of multiple erythematous macules, plaques, nodules, or papules [10]. The cutaneous manifestation of BL is extremely rare and usually accompanies another extracutaneous lesion [10]. The three distinct clinical forms of BL have different clinical presentations. In the sporadic type, BL presents itself as an extranodal mass in the abdomen, and in the endemic form it usually involves the maxilla or mandible. Immunodeficiency-associated BL is a frequent disease in AIDS patients [10].

Primary cutaneous B-cell lymphomas constitute 25% of extranodal non-Hodgkin lymphomas [22]. They are a heterogeneous group of rare clonal B-cell lymphoproliferative disorders and must be distinguished from the more common primary extracutaneous B-cell lymphomas. They are classified into three main types in the World Health Organisation – European Organisation for Research and Treatment of Cancer (WHO-EORCT) new classification for cutaneous lymphomas: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle – centre lymphoma (PCFCL), and primary diffuse large B-cell lymphoma, leg type (PCDLBCL, LT) [6]. PCMZL and PCFCL are characterised by an indolent course, a very good response to radiotherapy, and excellent prognosis. Both types commonly affect middle-aged adults with no gender predominance [22]. The most common presentations of PCFCL are solitary plaques, nodules, or tumours located on the trunk or head and neck region. However PCMZL are characterised by multifocal skin lesions in the form of red violaceous plaques or nodules on arms and legs [22]. Primary diffuse large B-cell lymphoma, leg type has an aggressive clinical course, inferior prognosis, and often spreads to extracutaneous sites. It predominantly affects elderly females and presents itself with rapidly growing tumours involving the lower legs [22]. Management of patient with PCDLBCL, LT is comparable to the treatment of patients with systemic DLBCL. Primary cutaneous lymphomas have completely distinct clinicopathological features from nodal lymphomas. Correct diagnosis of PCBCL requires skin biopsy for morphologic and immunohistochemical analysis and staging evaluation. Comprehensive lymphoma staging should include the following: history, physical examination, and laboratory studies including LDH and imaging [22]. In addition, it is appropriate to perform bone marrow aspirate and a biopsy, especially in cases of PCDLBCL, LT.

The authors declare no conflict of interest.

References

1. Muller-Hermelink HK, Catovsky D, Montserrat E, Harris NL. Chronic lymphocytic leukemia/small lymphocytic lymphoma. In: Tumours of Haemopoetic and Lymphoid Tissues. World Health Organization Classification of Tumours. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds.). IARC Press, Lyon 2001; 127-30.
2. Melo J V, Catovskv D, Galton DA. Chronic lymphocytic leukaemia and prolymphocytic leukaemia: a clinicopathologic reappraisal. Blood Cells 1987; 12: 339.
3. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of chronic (mature) B and T lymphoid malignancies. J Clin Pathol 1989; 42: 567-84.

4. Balogh Z, Reiniger L, Deák L, et al. IgVH gene mutation status and genomic imbalances in chronic lymphocytic leukaemia with increased prolymphocytes (CLL/PL). Hematol Oncol 2007; 25: 90-5.
5. Kroft SH, Finn WG, Peterson LC. The pathology of the chronic lymphoid leukaemias. Blood Rev 1995; 9: 234-50.
6. Willemze R, Jaffe ES, Burg G, et al. WHO-EORCT classification for cutaneous lymphomas. Blood 2005; 105: 3768-85.
7. Cerroni L, Zenahlik P, Hofler 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; 20: 1000-10.
8. Burg G, Kempf W, Sander CA, Wood G, Schmid U, Cogliatti S. Haematolymphoid Tumours; Lymphoid infiltrates of the skin mimicking lymphoma (cutaneous pseudolymphoma). In: Pathology and Genetics of Skin Tumours. LeBoit PE, Burg G, Weedon D, Sarasin A (eds.). IARC Press, Lyon 2006; 212-4.
9. Payne AS, Janes WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. Semin Oncol 2006; 33: 86-97.
10. Swerdlow SH, Kurrer M, Bernengo M, Buchner S. Haematolymphoid Tumours; Cutaneous involvement in primary extracutaneous B-cell lymphoma. In: Pathology and Genetics of Skin Tumours. LeBoit PE, Burg G, Weedon D, Sarasin A (eds.). IARC Press, Lyon 2006; 204-6.
11. Zimmer M, Bornkessel A, Hahnfeld S, Weyers W. "Specific" cutaneous infiltrate of B-cell chronic lymphocytic leukemia at the site of a florid herpes simplex infection. J Cutan Pathol 2005; 32: 581-4.
12. Rosen LB, Frank BL, Rywlin AM. A characteristic vesiculobullous eruption in patients with chronic lymphocytic leukemia. J Am Acad Dermatol 1986; 15: 943-50.
13. Buchner S. Specific and nonspecific skin manifestation in leukemia. Schweiz Rundsch Med Prax 2002; 12: 1071-7.
14. Bonvalet D, Foldes C, Civatte J. Cutaneous manifestations in chronic lymphocytic leukemia. J Dermatol Surg Oncol 1984; 10: 278-82.
15. Ratnam KV, Kohr CJ, Su WP. Leukemia cutis. Dermatol Clin 1994; 12: 419-31.
16. Colburn DE, Welch MA, Giles FJ. Skin infiltration with chronic lymphocytic leukemia is consistent with a good prognosis. Hematology 2002; 7: 187-8.
17. Agnew KL, Ruchlemer R, Catovsky D, et al. Cutaneous findings in chronic lymphocytic leukemia. Br J Dermatol 2004; 150: 1129-35.
18. Su WP. Clinical, histopthologic and immunohistochemical correlations in leukemia cutis. Semin Dermatol 1994; 13: 223-30.
19. Greenwood R, Barker DJ, Tring Fc, et al. Clinical and immunohistological characterization of cutaneous lesions in chronic lymphocytic leukemia. Br J Dermatol 1985; 113: 447-53.
20. Kaddu S, Smolle J, Cerroni L, Kerl H. Prognostic evaluation of specific cutaneous infiltrates in B-chronic lymphocytic leukemia. J Cutan Pathol 1996; 23: 487-94.
21. Robak T. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukemia. Hematology 2004; 9: 387-400.
22. Wilcox RA. Cutaneous B-cell lymphomas: 2013 update on diagnosis, risk-stratification, and management. Am J Hematol 2013; 88: 73-6.

Address for correspondence

Klaudia Gradzka
Department of Haematology
University Hospital in Bialystok
M. Sklodowskiej-Curie 24 A
15-276 Bialystok, Poland
tel. +48 85 746 82 30
fax +48 85 744 70 26
e-mail: kgradzka@yahoo.com

Submitted: 15.04.2013
Accepted: 1.10.2014