Leukaemia cutis for clinicians, a literature review

Małgorzata Osmola¹, Beata Gierej², Agata Kłosowicz¹, Anna Waszczuk-Gajda⁴, Grzegorz W. Basak⁴, Wiesław W. Jędrezejczak⁴, Artur Jurczyszyn¹, Bogna Ziarkiewicz-Wróblewska¹

¹Department of Haematology, Oncology and Internal Diseases, University Clinical Centre, Medical University of Warsaw, Warsaw, Poland
²Department of Pathomorphology, Medical University of Warsaw, Warsaw, Poland
³Department of Dermatology, University Hospital, Jagiellonian University Medical College, Krakow, Poland
⁴Department of Haematology, Oncology and Internal Diseases, University Clinical Centre, Medical University of Warsaw, Warsaw, Poland
⁵Department of Haematology, Jagiellonian University Medical College, Krakow, Poland

Adv Dermatol Allergol 2021; XXXVIII (3): 359–365
DOI: https://doi.org/10.5114/ada.2021.107923

Abstract
Leukaemia cutis (LC) describes infiltration of the skin by leukaemia cells, resulting in clinically identifiable cutaneous lesions. LC has a wide range of clinical manifestations, which can make it difficult to distinguish LC from other skin changes. In a group of patients, LC can be the first manifestation of leukaemia, therefore skin biopsy is crucial for the diagnosis. In this mini review, we discuss various types of leukaemia most frequently represented in leukaemia cutis, in both children and adults and skin changes in multiple myeloma, focusing on the clinical presentation of LC and prognosis in patients.

Key words: leukaemia cutis, clinical presentation, chronic lymphocytic leukaemia, acute myeloid leukaemia, multiple myeloma.

Definition
Leukaemia cutis (LC) describes the infiltration of the epidermis, dermis, or subcutis by neoplastic leukocytes, myeloid or lymphoid, resulting in clinically identifiable cutaneous lesions [1, 2].

Leukaemia cutis has been described in patients with acute myeloid leukaemia, chronic myeloproliferative disease, including chronic myelogenous leukaemia (CML), myelodysplastic syndromes, and myelodysplastic/lymphoproliferative diseases including chronic myelomonocytic leukaemia (CMML). LC may also occur in lymphocytic leukaemia such as acute lymphoblastic leukaemia B or T (B-ALL, T-ALL), precursor B- or T-cell lymphoblastic leukaemia/lymphoma (pre-B ALL, pre-T ALL) and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) [3, 4].

Clinical presentation of LC
Cutaneous manifestations of leukaemia can be classified as specific (infiltrates of leukemic cells) or nonspecific (inflammatory, related to marrow failure). The specific lesions called LC are considered as malignant lesions associated with localized or disseminated infiltrations of the skin by leukemic cells [4]. The time between the diagnosis of leukaemia and the development of leukaemia cutis varies. In the study of Kang et al., the vast majority (95%) of LC lesions developed after the diagnosis of leukaemia or showed concurrent involvement [5]. The clinical findings of LC often involve asymptomatic nodular lesions, tumours, and plaques. The nodules and papules are usually dome-shaped, firm in consistency and erythematous [6, 7]. In a retrospective study of 75 cases of LC, nodules (33%), papules (30%), and plaques (17%) were the three most common types of LC lesions [5]. The skin lesions were usually multiple (84%). These findings are consistent with the data presented by Li et al. who demonstrated that multiple nodules and papules were most commonly seen clinical features in patients with myeloid LC [8]. Leukaemia cutis may rarely present as other clinical manifestations like erythema, macules, blisters, and ulcers [9].
These rare clinical manifestations may occur simultaneously. There is no apparent site of predilection for LC. Skin lesions usually appear in the area of the trunk, extremities and head [10]. On the face, the transition from erythema to nodular and plaque stage may resemble leonine facies [10]. LC rarely affects palmoplantar surface and oral mucosa. Individual lesions’ morphology and distribution are not characteristic of specific forms of leukaemia; however, the different growth dynamics of cutaneous lesions may indicate acute or chronic forms of the disease. Rapid and disseminated growth is usually seen in the course of acute leukaemia while gradual, stepwise dynamics is more characteristic in chronic forms [9]. The cutaneous lesions produced by different leukaemia subtypes have remarkable uniformity; however, a patient may develop different morphologies over the course of the disease [11, 12]. Localized in the sites of the scars, herpetic lesions, trauma, and recent surgical procedures [13].

Nonspecific cutaneous lesions in the course of leukaemia occur in 30–40% of patients suffering from the disease [14]. The most common nonspecific signs include haemorrhagic skin lesions such as petechiae or purpura. Patients with leukaemia cutis are at higher risk of developing infectious diseases due to bone marrow failure. The list of conditions associated with infections include varicella-zoster virus, herpes simplex virus, or cutaneous mycoses. There is also an increased incidence of reactive and paraneoplastic lesions: generalized pruritus, Sweet’s syndrome, or pyoderma gangrenosum [15]. In the course of other malignant conditions, such as lymphoma, metastases of visceral tumours, skin cancers or Kaposi sarcoma, skin lesions in the form of papules and nodules on the trunk and extremities may also appear [14, 16]. Those entities should be taken into consideration in differential diagnoses. Sudden, exanthematous spread of skin lesions may occur in the course of papular drug eruptions, leukocytoclastic vasculitis or infectious diseases [9, 17].

The frequency of leukaemia cutis seems to be higher among children than adults, 25% to 30% of infants with congenital leukaemia develop skin involvement [7, 9, 18]. Acute lymphoblastic leukaemia/lymphoblastic lymphoma (ALL/LBL) accounts for approximately one-quarter of all childhood malignancies and is the most common form of cancer in children; ALL/LBL is five times more common in children than acute myeloid leukaemia (AML) [19]. Similar to the adult population, LC in children may manifest as papules, macules, patches, plaques and purpura. Leukaemia cutis has been described in children with both ALL/LBL and AML.

Andriescu et al. investigated clinical presentations and outcomes in thirty-one paediatric patients with leukaemia cutis [20]. The most common type of leukaemia associated with LC was AML (74%), followed by ALL (16%). The authors of the study did not note any significant differences in the clinical manifestation between two subtypes. The head and lower extremities were the two main sites of predilection. The skin lesions usually presented as erythematous and/or violaceous nodules and papules. In more than half of the patients, more than one morphology of skin lesions was present. In the majority of cases, LC presented concomitantly with systemic leukaemia.

Myelogenous leukaemia

LC occurs in about 4% of patients with AML and less frequently in CML [2]. Certain subtypes of AML are more commonly associated with skin infiltrations. The most frequent association occurs with acute myelomonocytic and monocytic differentiation [3], (former M4 and M5 according to FAB classification) [23], with skin involvement in up to 50% of patients [1, 19–22]. Those who were treated previously with chemotherapy are prone to develop secondary leukaemia cutis [24, 25].

Leukemic skin infiltrates usually show diffuse involvement of the dermis and subcutis, sparing the upper papillary dermis. Perivascular and periadnexal infiltrations are common. The nature of neoplastic cells depends on the type of leukaemia. Neoplasms can be composed of myeloblasts with or without features of promyelocytic or neutrophilic maturation, cells with monocytic or monoblastic morphology. Erythroid precursors or megakaryoblasts are rare. Immunohistochemistry is essential for the diagnosis. In Figure 1, we present a case from the author’s practice: skin with acute myelomonocytic leukaemia infiltrations (Figures 1 A–F). Figure 2 shows the clinical presentation of LC in monocytic leukaemia (Figure 2 A).

Besides LC in acute myeloid leukaemia, we can distinguish another form of extramedullary leukaemia (EML), namely myeloid sarcoma, also known as granulocytic sarcoma or chloroma. It is a rare EML tumour of immature myeloid cells, reported in 2.5–9.1% of patients with AML [11]. It was historically named “chloroma” because of its green colour caused by the presence of myeloperoxidase (MPO) [6]. The site of EML may be the central nervous system, skin, ovary, orbits, gums, lymph nodes, soft tis-
sues and other organs [7]. The prognosis in the case of the presence of EML has been suggested to be a marker of an aggressive disease, difficult to control and patients prone to extramedullary relapses after an intensive chemotherapy regimen [21, 22].

Extramedullary disease has been also reported in acute promyelocytic leukaemia (APL), a distinct subtype of acute myeloblastic leukaemia with specific clinical, morphologic and genetic features. Acute promyelocytic leukaemia is characterized by a 15;17 chromosome translocation, associated with the PML/RAR-\(\alpha\) gene rearrangement [24, 25].

EML is affecting around 3% of APL patients, mostly at the time of relapse, and has poor prognosis [26, 27]. The largest number of reports regarding EML in APL was associated with previous treatment with all-trans retinoic acid (ATRA) [28, 29]. The most common site of EML was the central nervous system and skin [27, 29–32].

A special form of LC is aleukemic leukaemia cutis. This term describes cases when skin infiltrations by leukaemia cells occurs before bone marrow or peripheral blood involvement and in the absence of systemic symptoms. It is uncommon and occurs predominantly in patients with AML [33–36].

**Lymphocytic leukaemia**

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukaemia in Western countries with an incidence of 4.2 : 100,000 per year [37]. LC in CLL is relatively rare and occurs in less than 5% of affected patients [4]. It is significantly less common than skin cancers complicating the course of CLL with an incidence up to 20% [38], and non-specific skin lesions.

There are three main histopathological types of skin involvement of LC in CLL, (1) perivascular and periadnexal pattern with lymphocytic infiltration around the vessels and skin appendages, (2) nodular and diffuse pattern, and (3) band-like pattern [39]. In tissue sections, small B lymphocytes with scant cytoplasm are seen, usually with a round nucleus with clumped chromatin, occasionally a small nucleus is present. Monoclonal B lymphocytes most often coexpress CD20, CD5, CD23, CD43 and LEF1 molecules (Figure 3).

In patients with CLL, the incidence of non-melanoma skin cancers (NMSC) is significantly higher compared to controls [38]. The most frequent NMSC was squamous cell carcinoma (63%), followed by basal cell carcinoma (55%), and Merkel cell carcinoma (1%). The authors suggest that screening for NMSC is important in CLL patients particularly among patients with aggressive CLL receiving T-cell immunosuppressive treatments as well as those who have a prior history of NMSC, or history of severe sunburn [38]. Therefore, differential diagnosis of skin cancers in patients with CLL should always be taken into consideration. In the study of Thiesen et al., it was shown that nearly half (33/70) of LC lesions were located in close proximity 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. It is hypothesized that damage to the epidermal barrier may be a factor provoking the occurrence of LC [40]. In the author’s experience, LC may coexist with skin cancers, such as basal cell carcinoma as it is presented in our case (Figures 3 A–D).

The prognosis of LC in the course of CLL remains controversial. According to Raufi et al., LC did not worsen the prognosis of patients with CLL [41]. Other authors suggested better prognosis in the case of LC in Richter’s syndrome and in CLL patients [42, 43].

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 [44], but systemic treatment of the underlying disease is crucial [44]. Figure 2 shows the clinical presentation of LC in CLL (Figure 2 B).

In patients with acute lymphoblastic leukaemia (ALL), LC is rarely reported and affects 1–3% of ALL patients [45, 46]. In patients with precursor-B-cell ALL (Pre-B-ALL) only a few cases of LC were described worldwide [45], presenting as asymptomatic firm erythematous nodules, but a case of pre-B-ALL associated LC presenting as soft, lipoma-like mounds was also reported [46].

Microscopically neoplastic cells diffusely infiltrate the dermis, surrounding a blood vessel but sparing the epidermis. The morphological features of B-ALL/LBL and T-ALL/LBL are indistinguishable [47]. Specific immunohistochemistry must be applied. The B- and T-lymphoblasts are almost always positive for terminal deoxynucleotidyl transferase (TdT).

![Figure 2](https://example.com/figure2)

**Figure 2.** Clinical presentation of leukaemia cutis. A – Diffused erythematous infiltrated papules often coalescing into small plaques on the trunk; LC in monocytic leukaemia (MS according to FAB classification) in a 30-year-old male patient. B – Single infiltrated erythematous papules and nodules in the lumbar area, confirmed as skin infiltrations of chronic lymphocytic leukaemia (CLL/SLL) in a 65-year-old male patient (arrows). C–E – Skin involvement in multiple myeloma (MM). Diffuse erythematous papules and nodules on the trunk (C, D). E – Grouped erythematous firm tumours on the right thigh, certain with central necrosis, appearing in proximity of a scar after orthopaedic surgery of the knee in the same MM patient.
In a study performed by Kata et al. and analysing patients with relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT), 62 of 324 patients relapsed at any site. 11.3% of patients had extramedullary relapse, including leukaemia cutis (2 ALL and 2 pre-B-ALL, 3 AML patients). Despite the treatment, all the patients died after a median time of 10 months due to resistant systemic relapse. According to the author's experience and the literature, EM relapse following alloHSCT is associated with poor prognosis and the optimal therapy remains a challenge [48].

Multiple myeloma

Cutaneous involvement of multiple myeloma (MM) is uncommon, typically occurs in the late stage of the disease, and is a poor prognostic indicator. In the study performed by Jurczyszyn et al. [49], there is an overrepresentation of MM with immunoglobulin class A (IgA) and light chain in skin involvement. Patients with skin MM and skin involvement presented in all MM International Staging System (ISS) stages, from I to III, and there was no preferential cytogenetic abnormality. Those patients carry a very poor prognosis with a median overall survival (OS) of 8.5 months [49, 50]. Clinical presentation of cutaneous involvement of MM can be erythematous papules and nodules or erythematous firm tumours (Figure 2 C–E).

Molecular pathogenesis

The molecular background responsible for the invasion of leukemic cells into the skin is not fully understood. Homing to specific tissues is controlled by expression of different chemokine receptors and adhesion molecules. Blast neural cell adhesion molecule (CD56) has long been implicated in EM pathogenesis [35, 50, 51]. In a study performed by Kuwabara, AML expressing CD56 involvement compared to CD56-negative cases [52]. Concerning cytogenetic abnormalities in AML, trisomy and tetrasomy of chromosome 8 are more common in patients with AML with leukaemia cutis than in patients with AML without leukaemia cutis [53, 54]. The 8;21 chromosome translocation is common in patients with myeloid sarcoma [55].

Conclusions

The diagnosis of leukaemia cutis is based on the morphologic pattern of skin infiltration, cytologic features, and the immunophenotype of the tumour cells. Patients presenting with leukaemia, or a history of leukaemia, especially AML patients with skin infiltrations, should undergo a skin biopsy. Histopathological examination of the tissue sample should include: haematoxylin and eosin staining, immunohistochemistry and, when feasible, flow cytometry,
fluorescence in situ hybridization and molecular analysis [4]. If a diagnosis of leukaemia is not already established, a bone marrow biopsy should be performed [6]. The correlation of clinical data, bone marrow and peripheral blood findings is often helpful to confirm the diagnosis.

Clinically, the presence of LC varies and is not specific for leukaemia subtype and has been suggested to be a marker of an aggressive disease, difficult to control and patients are prone to relapse after an intensive chemotherapy regimen.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

1. Agis H, Weltermann A, Fonatsch C, et al. A comparative study on demographic, hematological and cytogenetic findings and prognosis in acute myeloid leukaemia with and without leukaemia cutis. Ann Hematol 2002; 81: 90-5.

2. Cho-Vega JH, Medeiros LJ, Prieto VG, et al. Leukemia cutis: a review. J Am Acad Dermatol 2002; 46: 553-62.

3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-90.

4. Michel G, Boulad F, Small TN, et al. Risk of extramedullary relapse following allogeneic bone marrow transplantation for acute myelogenous leukaemia with leukaemia cutis. Bone Marrow Transplant 1997; 20: 306-12.

5. Vega-Ruiz A, Faderl S, Estrov Z, et al. Incidence of extramedullary involvement in patients with acute promyelocytic leukaemia: a single-institution experience. Int J Hematol 2009; 89: 489-96.

6. Li YP, Andersen J, Zelent A, et al. PML-RARA protein expression in acute promyelocytic leukemia cells: a molecular and laboratory-clinical correlative study. Blood 1997; 90: 306-12.

7. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia: analysis and review of the world literature with report of an additional case. Arch Dermatol 1993; 129: 1301-6.

8. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukaemia. Pediatr Clin North Am 2015; 62: 47-60.

9. Weinel S, Malone J, Jain D, et al. Therapy-related leukaemia cutis: a review. Australas J Dermatol 2008; 49: 187-90.

10. Li L, Lian CG, Jin H, et al. Clinical and pathological features of leukemia cutis: a review. Australas J Dermatol 2008; 49: 187-90.

11. Sw WP. Clinical, histopathologic, and immunohistochemical correlations in leukemia cutis. Semin Dermatol 1994; 13: 223-30.

12. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. British Journal of Haematology 1999; 104: 11-32.

13. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of acute leukaemias. British Journal of Haematology 1997; 97: 549-72.

14. Gouache E, Greze V, Strullu M, et al. Specific cutaneous infiltrates in patients with myelogenous leukaemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. J Am Acad Dermatol 1999; 40: 966-78.

15. Resnick KS, Brod BB. Leukemia cutis in congenital leukemia: analysis and review of the world literature with report of an additional case. Arch Dermatol 1993; 129: 1301-6.

16. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukaemia. Pediatr Clin North Am 2015; 62: 47-60.

17. Martinez-Escanamé M, Zuriel D, Tee SI, et al. Cutaneous infiltrates of acute myelogenous leukaemia simulating inflammatory dermatoses. Am J Dermatopathology 2013; 35: 419-24.

18. Driggers WE, Lichtman MA. Leukemia cutis and extramedullary leukaemia: a clinicopathologic study of 14 patients. Am J Dermatopathol 1992; 14: 75-80.

19. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia: analysis and review of the world literature with report of an additional case. Arch Dermatol 1993; 129: 1301-6.

20. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukaemia. Pediatr Clin North Am 2015; 62: 47-60.

21. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia: analysis and review of the world literature with report of an additional case. Arch Dermatol 1993; 129: 1301-6.
36. Annessi G, Signoretti S, Simon R. Minimally differentiated acute myeloid leukaemia revealed by specific cutaneous lesions. Br J Dermatol 1996; 135: 119-23.
37. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 (Suppl 5): v78-84.
38. Kleinestern G, Rishi A, Achenbach S, et al. Factors associated with non-melanoma skin cancer (NMSC) among chronic lymphocytic leukaemia (CLL) patients. Blood 2017; 130 (Suppl 1): 2158.
39. Cerroni L, Zenaahlik P, Höfler G, et al. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukaemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol 1996; 20: 1000-10.
40. Thiesen I, Wehkamp U, Brüggemann M, et al. Skin involvement by chronic lymphocytic leukaemia is frequently associated with unrelated neoplastic or inflammatory cutaneous disease and is not indicative of general disease progression. Br J Dermatol 2019; 180: 227-8.
41. Raufl A, Alsharedi M, Khelfa Y, et al. Leukaemia cutis in a patient with chronic lymphocytic leukaemia presenting as bilateral helical nodules. SAGE Open Med Case Reports 2016; 4: 2050313X16683622.
42. Kluk J, Moonirn M, Duran A, et al. Cutaneous Richter syndrome: a better place to transform? Br J Dermatol 2015; 172: 513-21.
43. Colburn DE, Welch MA, Giles FJ. Skin infiltration with chronic lymphocytic leukemia is consistent with a good prognosis. Hematology 2002; 7: 187-8.
44. Osmola M, Girej B, Waszczyk-Gajda A, et al. A rare manifestation of chronic lymphocytic leukaemia – leukaemia cutis treated with ibrutinib. Palliat Med 2019; 11: 180-3.
45. Obizozor C, Ganguly S, Fraga GR. Leukemia cutis with lymphoglandular bodies: a clue to acute lymphoblastic leukaemia cutis. Dermatol Online J 2017; 23: 13030/qt6bs2d542.
46. Mansoori P, Taheri A, O’Neill SS, et al. T-lymphoblastic leukemia/lymphoma with annular skin rash and epidermotropism. Am J Dermatopathol 2018; 40: 676-8.
47. Kata D, Kycz-Krzemien S, Czerw T, et al. Incidence, treatment and outcome of isolated extramedullary relapses after allogeneic hematopoietic stem cell transplantation for acute lymphoblastic and myeloid leukemias: single-center experience with 324 patients. Blood 2008; 112: 4302.
48. Jurczyszyn A, Olszewska-Szopa M, Hungria V, et al. Cutaneous involvement in multiple myeloma: a multi-institutional retrospective study of 53 patients. Leuk Lymphoma 2016; 57: 2071-6.
49. Jurczyszyn A, Olszewska-Szopa M. Nietypowe objawy kliniczne szpiczaka plazmocytowego. Acta Haematol Pol 2017; 48: 189-94.
50. Chang H, Brandwein J, Yi QL, et al. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. Leuk Res 2004; 28: 1007-11.
51. Kuwabara H, Nagai M, Yamaoka G, et al. Specific skin manifestations in CD56 positive acute myeloid leukemia. J Cutan Pathol 1999; 26: 1-5.
52. Şen F, Zhang XX, Prieto VG, et al. Increased incidence of trisomy 8 in acute myeloid leukemia with skin infiltration (leukemia cutis). Diagnostic Mol Pathol 2000; 9: 190-4.
53. Ferrara F, Cancemi D, Friso P, et al. Tetrasomy 8 and t(1;11) (p32;q24) in acute myelo-monocytic leukemia with extensive leukemic cutaneous involvement. Leuk Lymphoma 1996; 20: 513-5.
54. Tallman MS, Hakimian D, Shaw JM, et al. Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. J Clin Oncol 1993; 11: 690-7.