Review paper

Leukaemia cutis for clinicians, a literature review

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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].

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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 erythematosus 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.

In another retrospective observational study, the incidence rate of LC in children diagnosed with AML was 5.5% (24/438). The authors demonstrated that children presenting LC associated with AML were usually younger and had worse overall survival rates than the ones without skin involvement. In the light of these findings leukaemia cutis could be a negative prognostic factor in childhood AML [21].

Leukaemia cutis is reported to be the initial presenting sign in 50% of neonates with leukaemia [22]. The most common clinical manifestation present at birth are multiple randomly distributed bluish subcutaneous nodules with a predilection to the trunk and face, described in the literature as blueberry muffin rash. Other causes of blueberry muffin rash include congenital infections, congenital vascular lesions and other malignancies [22].

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-

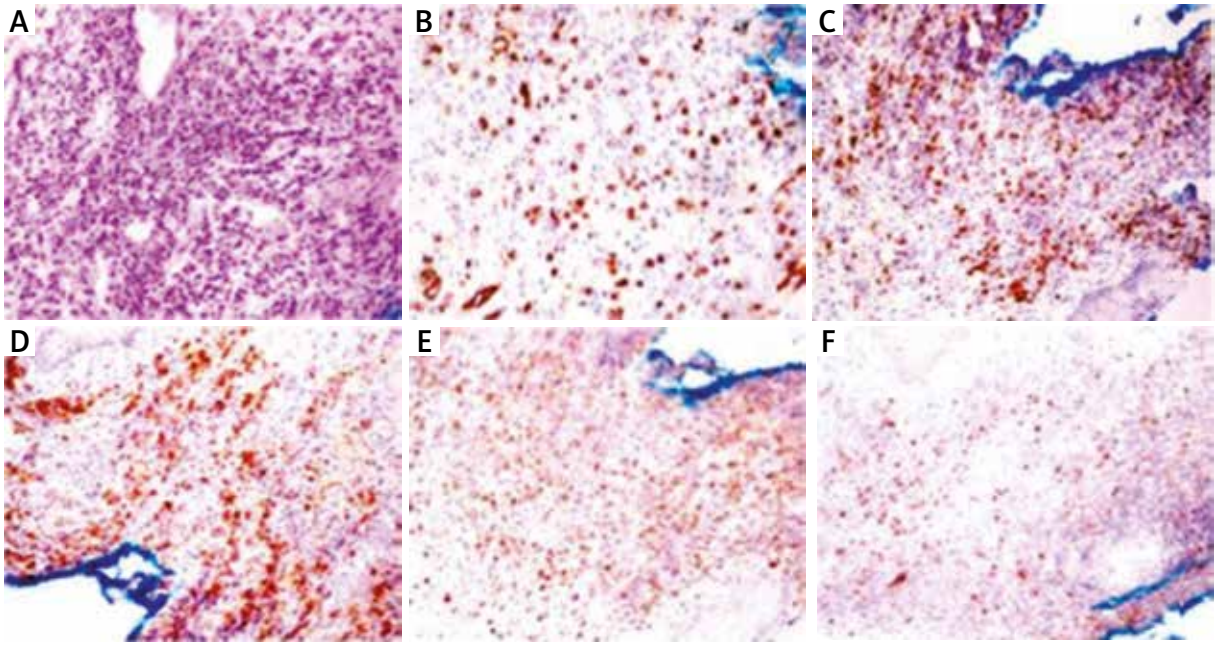

Figure 1. Skin with acute myelomonocytic leukaemia infiltration. **A** – H&E (200× magnification). **B** – Positive CD34 stain in blasts (200× magnification). **C** – Positive CD117 stain in blasts (100× magnification). **D** – Positive CD56 stain in neoplastic cells of monocytic differentiation (100× magnification). **E** – Positive CD68 stain in neoplastic cells of monocytic differentiation (100× magnification). **F** – Positive MPO stain in neoplastic cells of granulocytic differentiation (100× magnification)

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-α 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

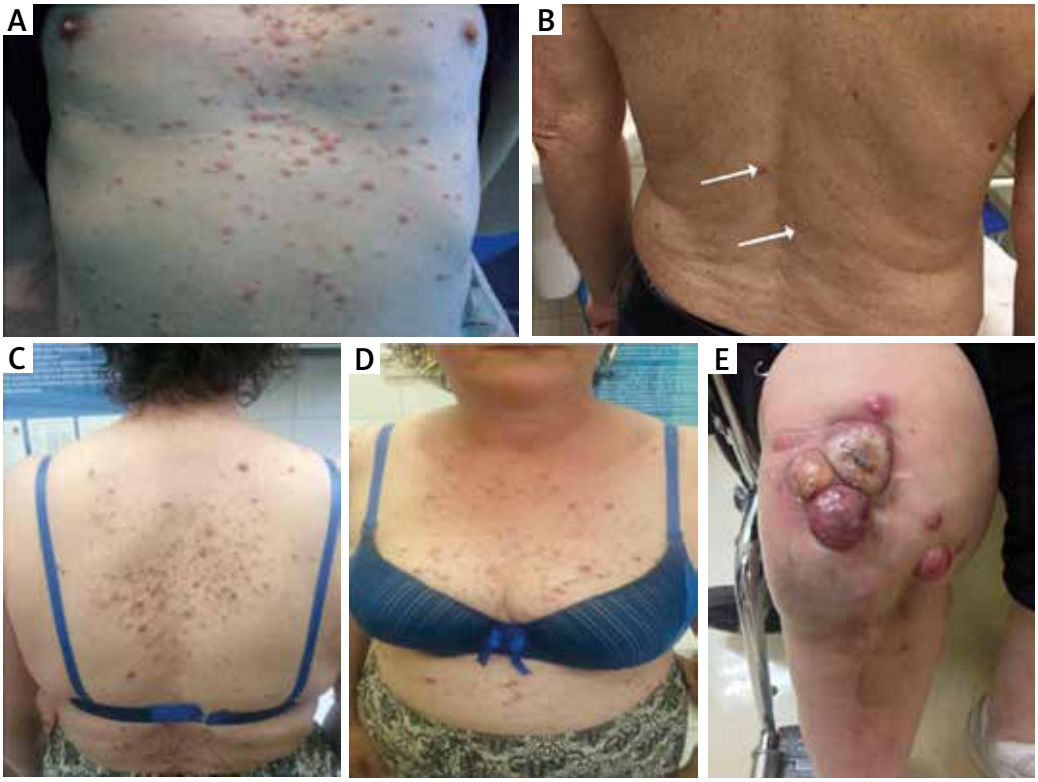

Figure 2. Clinical presentation of leukaemia cutis. **A** – Diffused erythematosus infiltrated papules often coalescing into small plaques on the trunk; LC in monocytic leukaemia (M5 according to FAB classification) in a 30-year-old male patient. **B** – Single infiltrated erythematosus papules and nodules 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 erythematosus papules and nodules on the trunk (**C, D**). **E** – Grouped erythematosus 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

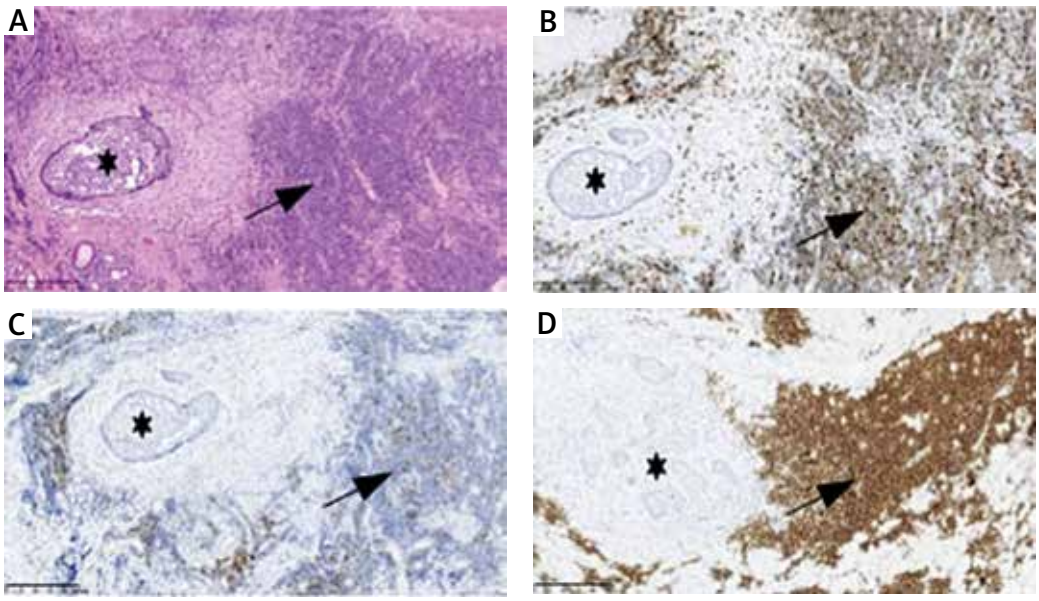

Figure 3. Skin with basal cell carcinoma (BCC) (asterisk) and chronic lymphocytic leukaemia (CLL/SLL) (arrow) coexistence. **A** – H&E (100× magnification). **B** – Positive CD5 stain in CLL/SLL cells (100× magnification). **C** – Positive CD23 stain in CLL/SLL cells (100× magnification). **D** – Positive PAX-5/BSAP stain in CLL/SLL cells (100× magnification)

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 few cases of LC were described worldwide [46], 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).

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 side. 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 erythematosus papules and nodules or erythematosus 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 molecule showed a significantly frequent cutaneous 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.

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