Review

Leukemia Cutis—the Current View on Pathogenesis, Diagnosis and Treatment

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Review

Leukemia Cutis—the Current View on Pathogenesis, Diagnosis and Treatment

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Simple Summary: Leukemia cutis occurs in different types of leukemia, most commonly in chronic lymphocytic leukemia and acute myeloid leukemia. Its varied clinical appearance makes it difficult to differentiate from other skin lesions. The leukemic skin changes are localized or disseminated and can be located in any site of the body. The diagnosis is mainly based on the clinical characteristics and histopathologic, as well as immunophenotypic features of the skin lesions. The treatment of leukemia cutis depends on the specific diagnosis of hematologic malignancy and is aimed at eradicating the primary underlying disease. Local irradiation for skin lesions is sometimes useful for palliative treatment.

Abstract: Leukemia cutis (LC) is defined as leukemic infiltration of the epidermis, the dermis, and the subcutaneous tissue. Leukemia cutis may follow or occur simultaneously with the diagnosis of systemic leukemia. However, cutaneous lesions are occasionally diagnosed as the primary manifestation of leukemia. Leukemic skin infiltrations demonstrate considerable variation regarding number of changes, distribution, and morphology. The highest incidence of LC is observed in chronic lymphocytic leukemia, monocytic and myelomonocytic acute myeloid leukemia, and in T-cell lineage leukemia. Although the pathogenic mechanism of the invasion of leukemic cells into the skin is not well understood, chemokine receptors and adhesion molecules as well as genetic characteristics of leukemia are thought to play a role. Leukemic skin lesions may be localized or disseminated and may occur alone or in combination on any site of the skin, most frequently in the trunk and extremities. The most common clinical presentations of leukemia cutis are papules, nodules, macules, plaques, and ulcers. In most patients, complete or partial resolution of cutaneous infiltrations occurs simultaneously with hematologic remission. However, in patients with resistant disease or recurrent skin infiltration, local radiotherapy can be used. This review presents recent data on the pathogenesis, diagnosis and treatment of leukemic skin involvement in different types of leukemia

Keywords: acute leukemia; chronic leukemia; cutis; diagnosis; pathogenesis; prolympchocytic leukemia; Richter transformation; skin lesions; treatment

1. Introduction

Leukemia cutis (LC) is manifested as clinically-demonstrated skin infiltration by neoplastic leukocytes or their precursors into the epidermis, dermis or subcutaneous tissue [1-4]. It is a relatively rare symptom observed usually in more advanced stages of the disease. The frequency of LC varies from 2 % to 30%, depending on the diagnosis of primary leukemia [2,5-8]. Leukemia cutis may follow or occur simultaneously with the diagnosis of systemic leukemia. However, LC is occasionally diagnosed as the primary manifestation of leukemia. All subtypes of leukemia can infiltrate the skin. However, LC is most commonly observed in children with congenital leukemia, ranging from 25% to 30% of cases [9]. Generally, the highest incidence of LC has been noted in chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML) of monocytic and myelomonocytic FAB (French, American, British)

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subtypes and in the T-cell leukemias [6,10,11]. Leukemia cutis frequently indicates an advanced disease with additional sites of extramedullary involvement, which is strongly associated with poor prognosis. Larger studies of leukemia cutis are presented in Table 1.

Table 1. Selected large studies of leukemia cutis.

Authors/Reference	No. of patients						Clinical characteristics	Time from leukemia diagnosis to LC development	Survival from LC diagnosis
	Total	AML	ALL	CML	CLL	Other			
Su et al 1984 [1]	42	20	3	3	16	0	Multiple papules and nodules (60%), infiltrative plaques (26%), macules, nodules, ulcers	LC after systemic leukemia – 23 mo. (55%), before - 3 mo. (7%), concomitant 16 mo. (38%)	10-60 mo. (range)
Yook et al 2022 [3]	56	40	8	3	2	MDS-3	Plaques (28%), papules (27%), patches (18%), nodules (16%)	12.3 mo. (mean)	5.4 mo. (mean)
Kaddu et al. 1999 [4]	26	17	0	9	0	0	Solitary or multiple reddish to violaceous papules, plaques, and nodules (17 pts.), generalized erythematous maculopapular eruption (9 pts.)	0 to 13 mo. in AML pts. (range), 36 -72 months (mean of 52.4 mo.) in CML pts.	AML 1-25 mo. (range), CML 3-17 mo. (range)
Chang et al. 2021 [5]	42	24	3	1	1	MDS-8, ALL-5	Papules (38%), nodules (29%), plaques (16%), ulcers (10%)	16.3 mo. (mean)	7.2 mo. (median)
Kang et al 2013 [18]	75	49	18	7	0	MDS-1	Nodules (33%), papules (30%), and plaques (17%)	16.2 mo. (mean) in 58 pts. after systemic leukemia diagnosis, 2.3 mo. (mean) in 4 pts. LC before systemic leukemia diagnosis, 13 pts. concurrent diagnosis with	8.3 mo. (median)

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								systemic leukemia	
Martinez-Leborans et al 2016 [22]	17	12	0	4	1	0	Nodules (7 pts.), papules (5 pts.), erythematous-violaceous plaques (4 pts.)	aleukemic LC – 5 pts.	7 pts. died during the first year
Li et al 2018 [22]	10	9	0	0	0	CMML-1	Generalized papules or nodules (5 pts), localized masses (5 pts).	4-72 mo. in 7 pts. after systemic leukemia diagnosis	6 pts. died within 2 - 12 mo.
Watson et al. 2006 [88]	8	5	0	2	1	0	Erythematous papules (75%), nodules and plaques	2-114 mo. (range); 2 pts. at presentation	14 mo. (median) and 3 - 39 mo. (range)

Abbreviations: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, ATLL – adult T-cell leukemia lymphoma, CLL – chronic lymphocytic leukemia, CML – chronic myeloid leukemia; CMML – chronic myelomonocytic leukemia, Hb-hemoglobin; LC – leukemia cutis, MDS – myelodysplastic syndrome, mo. – month, pts. – patients.

In 55% to 77% of cases with LC, skin lesions occur in patients already diagnosed with leukemia [7,8]. However, leukemic skin infiltrations are seen at leukemia diagnosis in 23% to 44% of cases, and can precede diagnosis in peripheral blood (PB) and/or bone marrow (BM) by several months or years in 2% to 3% of cases [2]. Cutaneous involvement usually indicates advanced disease, and extramedullary involvement in other sites is common.

Risk factors for the development of LC are generally the same as those for systemic leukemia, including exposure to benzene, ionizing radiation, alkylating agents and viruses. In patients with LC, prognosis is generally poor [3,12,13]. However, it can be improved by appropriate treatment with novel drugs.

This review provides an overview of the pathogenesis, diagnosis and treatment of leukemic skin involvement in different types of leukemia.

1. Pathogenesis

The pathogenic mechanism of leukemic skin involvement is not well known. However, chemokine receptors and adhesion molecules as well as genetic characteristics of leukemia are believed to play a role [7]. In particular, adhesion molecules such as chemokine integrin may be involved in the migration of leukemic cells into the skin via skin-selective homing processes [7,14-16]. In addition, important roles may be played by chemokine receptors and adhesion molecules. For example, the cutaneous leucocyte-associated antigen (CLA) receptor and CC chemokine *receptor* 4 (*CCR4*) on the leukemic cells may interact with E-selectin and/or TARC (thymus- and activation-regulated chemokine /CCL17 (CC chemokine ligand 17) on the dermal post-capillary venules. This process may stimulate the movement and binding of leukemic cells into the dermis; in addition, such migration of leukemic cells into the dermis may also be stimulated by the interaction between integrins and endothelial-bound chemokines. Some observations indicate that the infiltration of leukemic cells is more likely to occur in places with previous skin infection or inflammation [17].

2. Diagnosis

A diagnosis of LC requires an evaluation of clinical features, morphology, histopathology, and immunophenotyping [7,8,17]. While LC is most commonly characterized as nodules, plaques, ulcers,

vesicles, and swellings [2,14,15,18], unusual clinical manifestations are occasionally observed, including erosions, ulcerations and desquamation [2,19,20]. Moreover, leukemic vasculitis has also been noted as a unusual manifestation of LC, while it occurs mostly in patients with acute leukemia with myelomonocytic or monocytic features [19,21,22]. Skin changes are mainly located in the trunk, extremities and face [15,17,18]. Widespread petechiae-like eruptions secondary to LC have also been rarely described [23]. Although skin lesions are usually generalized, some solitary, clustered, or dispersed lesions have also been observed [2]. In rare cases, the distributions of LC can include sites of herpetic lesions, intravenous catheters, lips, trauma and recent surgeries [7,24,25].

Some authors indicate that generalized LC occurs mainly in acute leukemias, and single lesions are observed mainly in less aggressive hematologic malignancies [2]. However, most studies have found no correlation between the location and distribution of skin leukemic infiltration with regard to the specific type of disease [26,27]. Leukemic lesions can be violaceous or brick-red to skin colored. Leukemia cutis may also exist as diffuse purpura, particular in infants, as blueberry muffin syndrome. In most patients, the skin lesions are asymptomatic, but occasionally pain or pruritus may be present [5,28]. The development of LC is more likely to be rapid in acute leukemias, but more gradual in chronic leukemias [29]. The appearance of the skin lesions in LC is nonspecific, which makes it difficult to clinically differentiate from other skin lesions [18,30,31] .

The diagnosis of LC requires evaluation of biopsy specimens with immunohistochemical staining, with the diagnosis confirmed by determining the expression of characteristic cell surface markers [32]. Immunohistochemical staining remains essential for distinguishing reactive from neoplastic infiltrates, as LC can mimic clinically the reactive lesions. Skin biopsy shows nodular or diffuse infiltrations with leukemic cells in the dermis and/or subcutaneous tissue. In most cases, the leukemic infiltrations do not involve the epidermis and upper dermis, known as the “grenz zone”. However in T-cell leukemias, epidermotropism is a common event.

The differential diagnosis of LC includes neoplastic, inflammatory, and infectious skin lesions [33,34]. Cutaneous paraneoplastic disorders are defined as nonleukemic cutaneous features of leukemia. They are more common than LC, as more than 40% of leukemia patients can develop skin changes. The cutaneous findings include petechiae/purpura as a result of thrombocytopenia, leukocytoclastic vasculitis, neutrophilic dermatoses such as pyoderma gangrenosum and Sweet’s syndrome [5,35]. In addition, opportunistic infections such as disseminated candidiasis and disseminated herpes zoster may also occur. Any erythematous bright-red, or red-brown plaques in LC should be differentiated with erythema exudativum multiforme, panniculitis, or mycosis fungoides [2,7]. Infiltrated erythema and flat nodules should be distinguished from erythema nodosum. Hemorrhagic or purpuric nodules and plaques on the trunk or the lower legs, should be differentiated with vasculitis allergica and Kaposi sarcoma. Macular or maculopapular exanthems may resemble pityriasis rosea, viral exanthems or drug eruptions.

3. Prognosis

In patients with LC, prognosis depends on the leukemia type, and advancement of the disease. As LC coexists with systemic leukemic involvement, the prognosis is rather poor, especially in patients with other extramedullary infiltrations and in cases when LC is diagnosed in advanced leukemia, resistant to previous therapies. Worse prognosis is also observed in AML, T-cell prolymphocytic leukemia (T-PLL) and Richter’s syndrome (RS) [6,36,37,38]. In a recent study, the median survival time of patients with LC was 7.2 months, with no statistically significant difference between different types of leukemia [5,18]. In other study by Yook et al, 93% of patients died within 10 months after diagnosis [3]. Similar results were reported by Su et al., where 88% of patients with LC died within one year from diagnosis of LC in acute lymphoblastic leukemia (ALL), AML, CLL and other leukaemias [1].

4. Treatment

Leukemia cutis is a local manifestation of an underlying systemic disease and should be treated with systemic therapy appropriate to the specific subtype of leukemia. In most patients, hematologic

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remission occurs simultaneously with complete or partial response of cutaneous infiltrations. However, in patients with resistant LC or recurrent skin infiltration, local radiotherapy can be used [33,39]. Recently, simultaneous integrated boost with helical arc radiotherapy of total skin (HEARTS) is proposed to treat cutaneous manifestations in treatment of refractory cutaneous leukemia [40].

5. Characteristics of leukemia cutis in different subtypes of leukemia

5.1. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), is the most common adult leukemia in the western countries, with an estimated 20050 new cases in 2022 in the United States [41,42]. It is a clinically and biologically heterogeneous disease with a variable clinical course. Only a minority of patients has an aggressive disease at diagnosis requiring treatment. Most patients have indolent disease and rarely require intervention [43].

Cutaneous symptoms in CLL have been described in 4%–20% of CLL [44]. Most commonly, skin changes are secondary, nonmalignant lesions such as purpura, pruritus, urticaria, erythroderma, pyoderma gangrenosum, cutaneous vasculitis and Sweet's syndrome [2]. However, histologicaly confirmed LC is a rare event in CLL and most frequently occurs in patients with Richter transformation. Typically, skin LC occurs late in the natural history of the disease, most commonly after multiple lines of treatment and relapses. In contrast, CLL infiltration in the skin is only occasionally the first manifestation of the disease [37,45-52]. In some cases, leukemic skin infiltrations develop at the previously affected healed sites of *Borrelia burgdorferi*, herpes zoster or herpes simplex [50,53,54]._

Skin infiltration with B-CLL/SLL can manifest as solitary, grouped, or generalized papules, plaques, nodules, or large tumors (Figure 1). The most common skin site manifestations are the head and neck (34% of lesions), and trunk or extremities (27%) [55]. Immunohistochemistry and genetic studies are useful in proper diagnosis. In CLL leukemic cells are small, mature-appearing cells that that show perivascular, periadnexal, or nodular distribution. Skin infiltrates by CLL/SLL most commonly exhibit a classic immunophetype: CD20+ , CD3-, CD5+, CD23+, cyclin D1-. Three main histologic patterns of CLL skin infiltrations have been reported, including perivascular and periadnexal lymphoid infiltration around vessels/adnexal structures, with a nodular, diffuse and band-like pattern [37].

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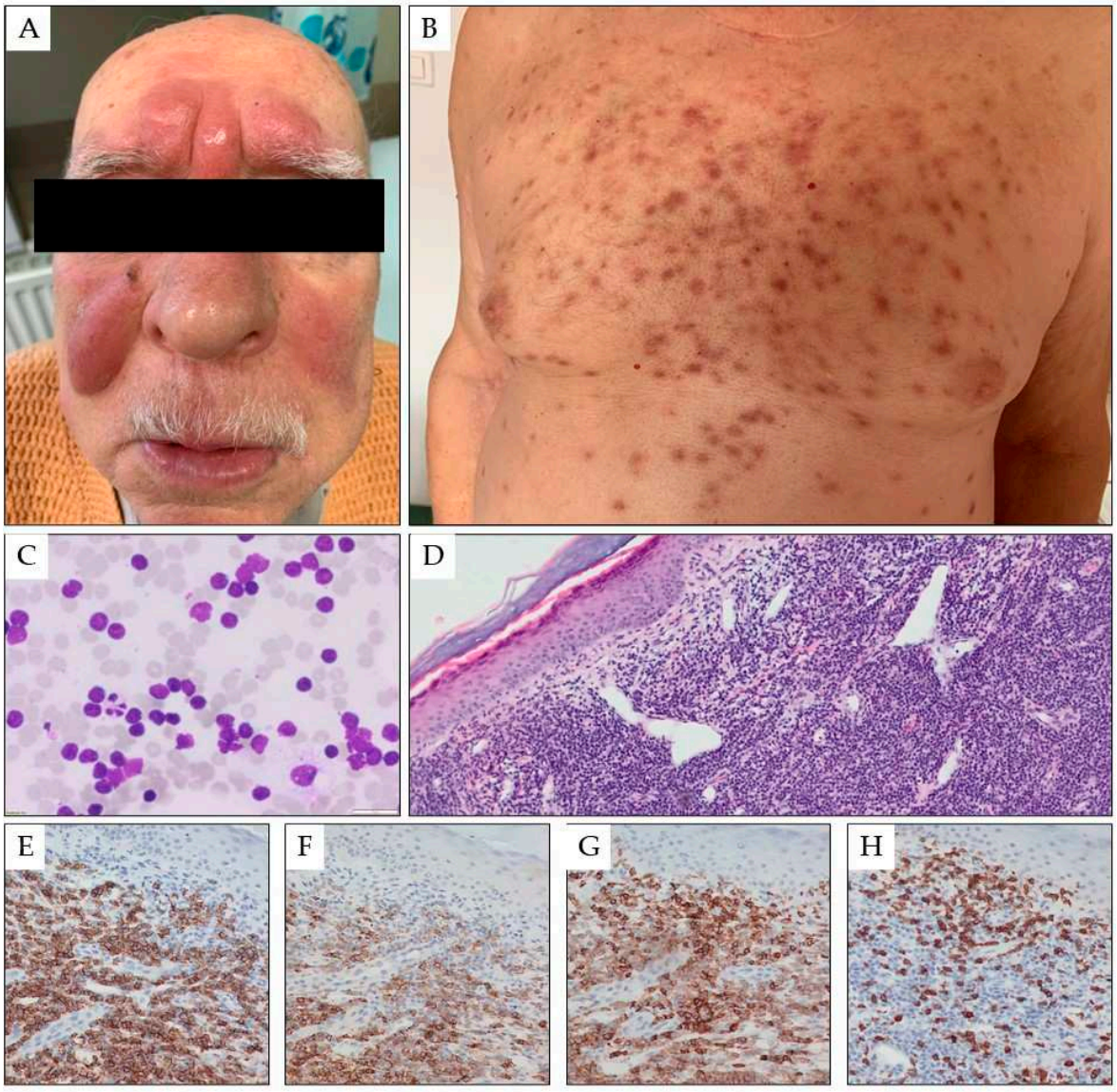

Figure 1. Multiple red-brown tumors and nodules on the skin of the central surface of the forehead and the cheeks of a 78-year-old male patient with CLL; there are in the form of symmetrical nodular infiltrates (A). Moreover, numerous, scattered red-blue papules and nodules with a hemorrhagic reaction are present on the torso (B). Fine needle biopsy of the forehead tumor (C) and biopsy of the skin torso infiltration in Haematoxillin&eosin staining (25X magnification, panel D), and in immunohistochemistry for: CD20 (200X magnification, panel E), CD23 (200X magnification, panel F), CD5 (200X magnification, panel G), and CD3 (200X magnification, panel H).

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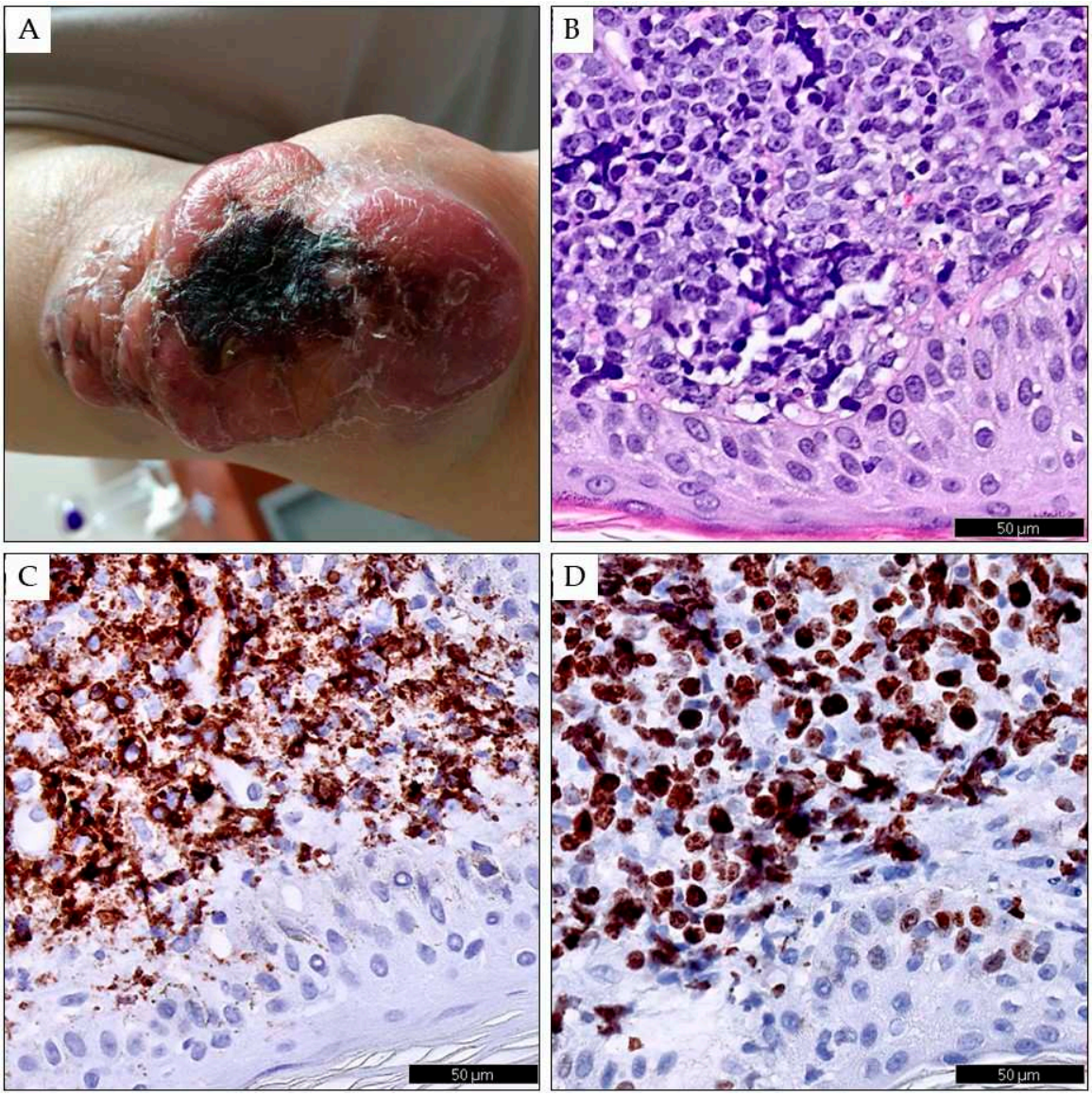

Figure 2. Richter transformation in the skin of the left upper limb in a 78-year-old female patient with CLL lasting four years. The skin shows a conglomerate of merging red-blue tumors of various sizes with a necrotic scab in the center (A). Skin biopsy showing infiltration by diffuse large B-cell lymphoma in Haematoxillin&eosin staining (B), in immunohistochemistry for: CD20 (C), and Ki67 (D). Digital scans were obtained Phillips IntelliSite UltraFast Scanner.

In contrast to other leukemias, prognosis in most CLL/SLL patients is not affected by skin involvement [37,44]. However, it is unfavorable in the RT of CLL with specific infiltration of the skin, and if LC is diagnosed later in the disease course (Figure 2) [49,56,57]. Cerroni et al analyzed the clinical, histopathologic, immunophenotypic, and molecular features from 42 patients with SLL/CLL skin involvement [37]. The mean duration of CLL before skin manifestations was 39 months (range 0 to 142 months). In seven patients (16.7%), the skin lesions represented the first sign of CLL. Follow-up data could be obtained from 31 patients. Two patients with RT died after five and eight months. The five-year survival rate of the patients was 66.6%.

Leukemia cutis of CLL can be treated with conventional immunochemotherapy and more recently, with Bruton's tyrosine kinase inhibitors (ibrutinib, acalabrutinib and zanubrutinib) or B cell lymphoma – 2 (BCL-2) inhibitor venetoclax [58-60]. However, local therapy, including radiation therapy, excision, intralesional steroids, ultraviolet light B and electrochemotherapy can be useful in local control of the skin lesions [61,62].

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5.2. Hairy cell leukemia

Hairy cell leukemia (HCL) is a subtype of B-cell indolent lymphoid leukemia characterized by infiltration of mature lymphocytes with typical hairy projections in various organs including the peripheral blood (PB), bone marrow (BM) and spleen, resulting in splenomegaly, pancytopenia and susceptibility to infection [63]. HCL cells are positive for B cell antigens including CD19, CD20, and CD22 and the HCL-specific antigens CD11c, CD25, CD103, CD123, TRAP. In addition, intense expression of CD200 is observed [64]. Recently, the *BRAF*-V600E mutation has been reported as a specific oncogenic mutation for classic HCL [65].

Skin lesions have been observed in about 10% of HCL patients, and are mostly related to autoimmune processes, infections or secondary cutaneous neoplasms [66]. However, leukemic infiltration of the skin by HCL cells is reported only extremely rarely [67-69]. In a larger study of 600 HCL patients, LC was reported in 48 (8%) patients, but histologic confirmation was available only in eight (1.6%) [70]. In most HCL cases, LC was diagnosed at presentation of HCL, while in the remainder it was noted in the course of disease [70-75]. Clinical appearances of LC infiltration in HCL include papules, plaques, or nodules ranging from violaceous to red-brown or flesh-colored nodules. Skin lesions may be localized on one side or generalized in many places [8]. Skin biopsy and immunophenotyping is recommended in all patients with suspicion of leukemic skin infiltraton. Skin changes should be correlated with clinical and laboratory symptoms of HCL, including BM and PB immunophenotyping and molecular characteristics. [7,8,60].

In HCL patients, LC responds well to antileukemic treatment with purine analogs. Leukemia cutis in HCL patients can be successfully treated with cladribine or pentostatin. In most cases, cutaneous infiltrates disappeared with a complete resolution of the skin lesions following treatment with cladribine. Recently, refractory or relapsed patients have been treated with BRAF inhibitors, including vemurafenib and dabrafenib [76].

5.3. T cell prolymphocytic leukemia

T-cell prolymphocytic leukemia (T-PLL) is the most common type of mature T-cell leukaemia, however its prevalence is low – T-PLL accounts for only 2% of small lymphocytic leukaemias in adults [77]. Most patients with T-PLL are resistant to conventional chemotherapy. In suitable patients, the most effective treatment currently consists of anti CD52 monoclonal antibody alemtuzumab followed by consolidation with allogeneic hematopoietic stem cell transplantation. However, the median survival ranges from 17 to 33 months in patients treated with alemtuzumab alone and 48 months in those receiving allogeneic stem cell transplantation [78,79]. Cutaneous involvement is a common symptom of T-PLL, and appears in 25–30% of patients, most commonly at presentation [80-83]. Skin lesions present mainly as retiform hyperpigmented macules and patches; however they can also be found as skin nodules, erythroderma, symmetrical distributed petechia or purpura and facial eruption (Figure 3) [81,82,84,85]. Conjunctival involvement and periorbital petechiae have also been reported in some patients with T-PLL (Figure 3) [82,84,86,87].

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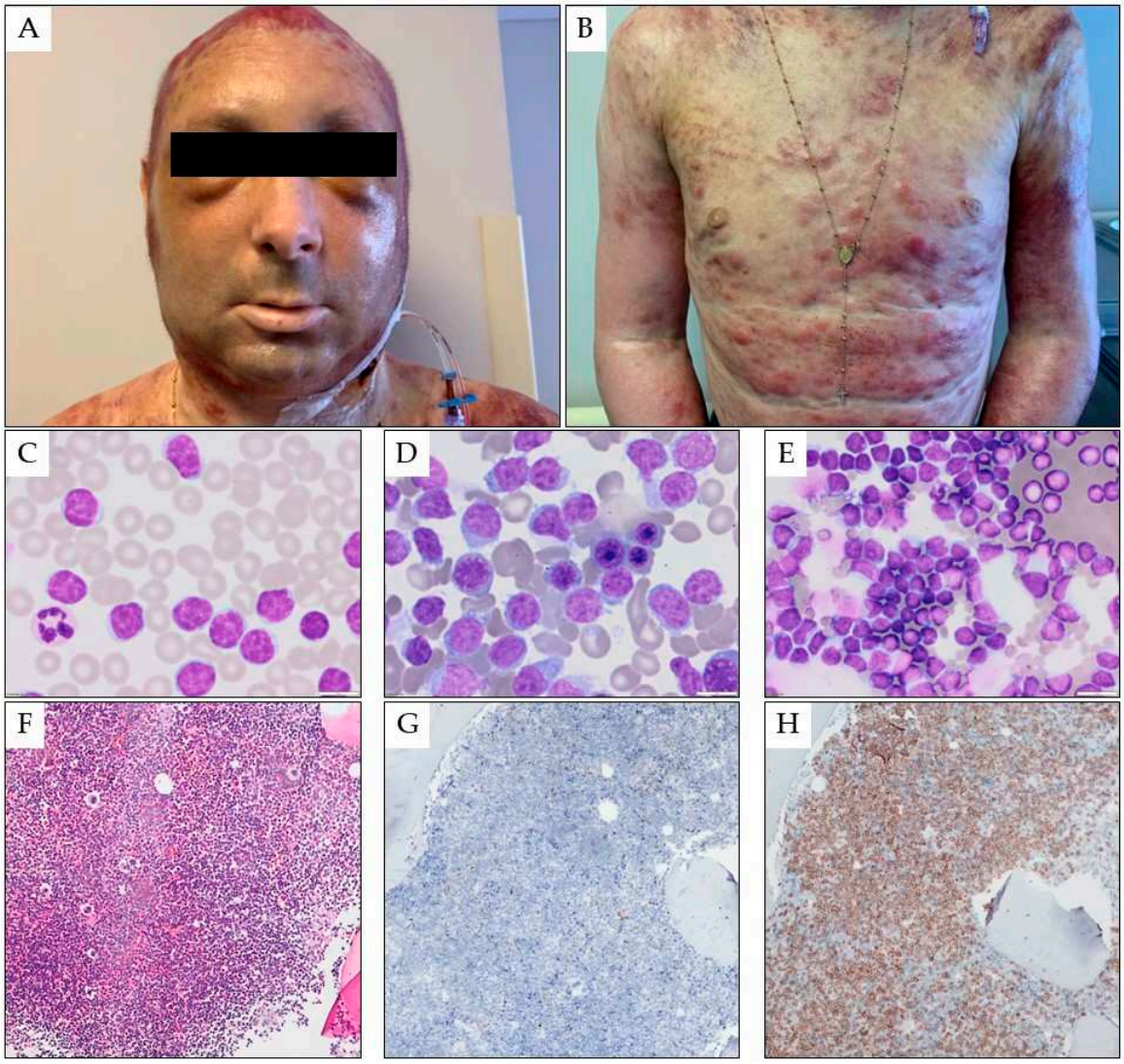

Figure 3. Pink-red papules, nodules and tumors scattered on the face torso and upper limbs in a 32-year-old male with T-PLL. A confluent erythema with a hemorrhagic reaction is also visible in the area of the scalp. Generalized skin edema, scattered petechiae and conjunctivitis are also visible (A-B). Peripheral blood (C) and bone marrow (D) smears, and fine-needle skin aspiration (E) show numerous atypical prolymphocytes. In bone marrow trephine, a homogenous infiltrate by CD3-positive, TdT-negative prolymphocytes is seen; Haematoxillin&eosin staining image under 100X magnification (F), and in immunohistochemistry for: TDT (100X magnification, G), and CD3 (100X magnification, H).

Other manifestations include diffuse infiltrative erythema and nodules, and exfoliative dermatitis over the whole body**.** The most common facial involvement of LC is edema [82,86-89]. In most patients, skin biopsy shows extensive monotonous infiltration of prolymphocytes positive for T-cell immunohistochemic markers including CD2, CD3, CD5 and CD7, while negative for TdT, CD1a and variably positive for CD4 and CD8 (Figure 3) [90].

In a study of 25 TPLL patients by Hsi et al., eight (32%) demonstrated cutaneous manifestations, presenting as rash, purpura, papules, and ulcers; the skin biopsies showed leukemic lesions with small to medium-sized, irregular, perivascular and periadnexal lymphoid infiltrates without epidermotropism. Cutaneous involvement by T-PLL was often associated with significant peripheral blood involvement [91]. Shumilov et al observed three relapsed patients with T-PLL including one with skin manifestations [92]. Only one of these patients relapsed with skin manifestations.

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Wasitudin et al. described another patient with diffuse generalized skin lesions, rash and anasarca [81], and Matutes et al noted the presence of skin lesions in 27% of 78 patients with T-PLL [93].

5.4. Acute lymphoblastic leukemia

Acute lymphoblastic leukemia is the second most common acute leukemia in adults, with an estimated 6660 new cases in 2022 in the United States [41]. Acute lymphoblastic leukemia most commonly affects children younger than 15 years old and adults older than 50 years old [94,95]. In adults, ALL contains 20% of all leukemias [96]. The disease is divided into two main types: B-cell ALL and T-cell ALL. The T-cell ALL subtype is less common than B-cell ALL and is observed in around 20-25% of all ALL cases. Dose-intensification systemic treatment have led to a significant progress in outcomes for children with ALL. However, prognosis for the elderly remains very poor with only 30–40% long-term remission in adult patients with ALL [97].

Leukemia cutis rarely presents in patients with ALL and may be seen in only 1% of cases [7]. Skin involvement has been reported in 1% to 3% of ALL patients [13,98,99]. In most patients with ALL, LC appears as single or multiple red-to-violaceous papules, nodules, and plaques [1,23,24,99,100-102]. Occasional oval or annular scaling red patches on buttocks, thighs, and back waist are observed. Systemic chemotherapy and stem cell transplant can be the primary treatment in some patients. However, radiation therapy can be used in patients with the limited lesions, especially, if they are not candidates for chemotherapy and stem cell transplant. Leukemia cutis is usually associated with T-ALL but occurs only occasionally in B-ALL [103].

Only three cases of LC associated with B-ALL have been reported previously [103-105]. In one patient, an asymptomatic, solitary, dome-shaped, indurated nodule on his left cheek was observed [104]. The second patient presented with an erythematous, indurated, purplish nodule on his nose, with larger, erythematous nodules on the forehead and forearm [105]. The third patient presented with a non-healing leg ulcer and patches on the face, left arm, and bilateral legs [103]. In all patients, immunohistochemical staining found the infiltrations involving the skin to be consistent with B-ALL.

More cases of LC were reported in T-ALL [106-112]. Leukemia cutis in T-ALL may present with erythematous papules and annular plaques and petechiae-like eruption [102,109,113]. In T-ALL, leukemic infiltration appears in the dermis and in the subcutaneous tissue; however, in contrast to primary cutaneous T-cell lymphoma, the epidermis is uninvolved. Leukemic cells typically display T lineage-specific antigens including CD3, CD4, or CD8 and one or more precursor immature T-cell antigens including TdT, CD99, CD34, and CD1a [114]. The prognosis of LC in ALL is rather poor. However, in rare cases, longer survival was observed, especially after treatment with combination chemotherapy and allogeneic stem cell transplantation [109,112,115].

5.5. Acute myeloid leukemia

Acute myeloid leukemia is the second most common leukemia in adults, with 20,050 new cases in 2022 in the United States [41]. 10–15% AML cases were reported to have involvement of skin; this was most commonly observed in the myelomonocytic (AMML) and monocytic (MoAML) subtypes and with a higher prevalence in congenital leukemia (25–30%) [2,7,14,26,116,117]. Aleukemic LC is observed in 7% of cases with AML [118]. While LC most commonly develops in patients with an established diagnosis of AML, it is occasionally seen before a diagnosis of systemic AML [119]. AML LC can be associated with extra medullary leukemic involvement at other sites, most commonly the central nervous system (17%) [33]. In addition, gingival hyperplasia can be observed, particularly in AMML (42%) and MoAL (55%) [120]. Some gene abnormalities are associated with LC presentation of AML, including numerical abnormalities of chromosome 8, translocation (8;21)(q22;q22), and inversion (16)(p13;q22) [118, 121-125].

The most frequent lesions in AML LC are erythematous or violaceous papules and nodules, which are observed in 60% of AML LC patients (Figure 4). Infiltrated plaques, a generalized cutaneous eruption, and erythroderma are also noted [117]. Myeloid leukemia cells also involve the dermis and subcutis in a diffuse pattern. A skin biopsy serves as the gold standard for diagnosis. Histopathologically, infiltrates of blasts with varying intensity, positive for at least two myeloid

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markers, are essential criteria for establishing the diagnosis. An extensive immunophenotyping is clinically important to differentiate AML LC from blastic plasmacytoid dendritic cell neoplasm—the latter being positive specifically for TCF4, CD303, TCL1, and less specifically strongly positive for CD4, CD56, and CD123, while negative for CD34, CD117, CD15, and myeloperoxidase.

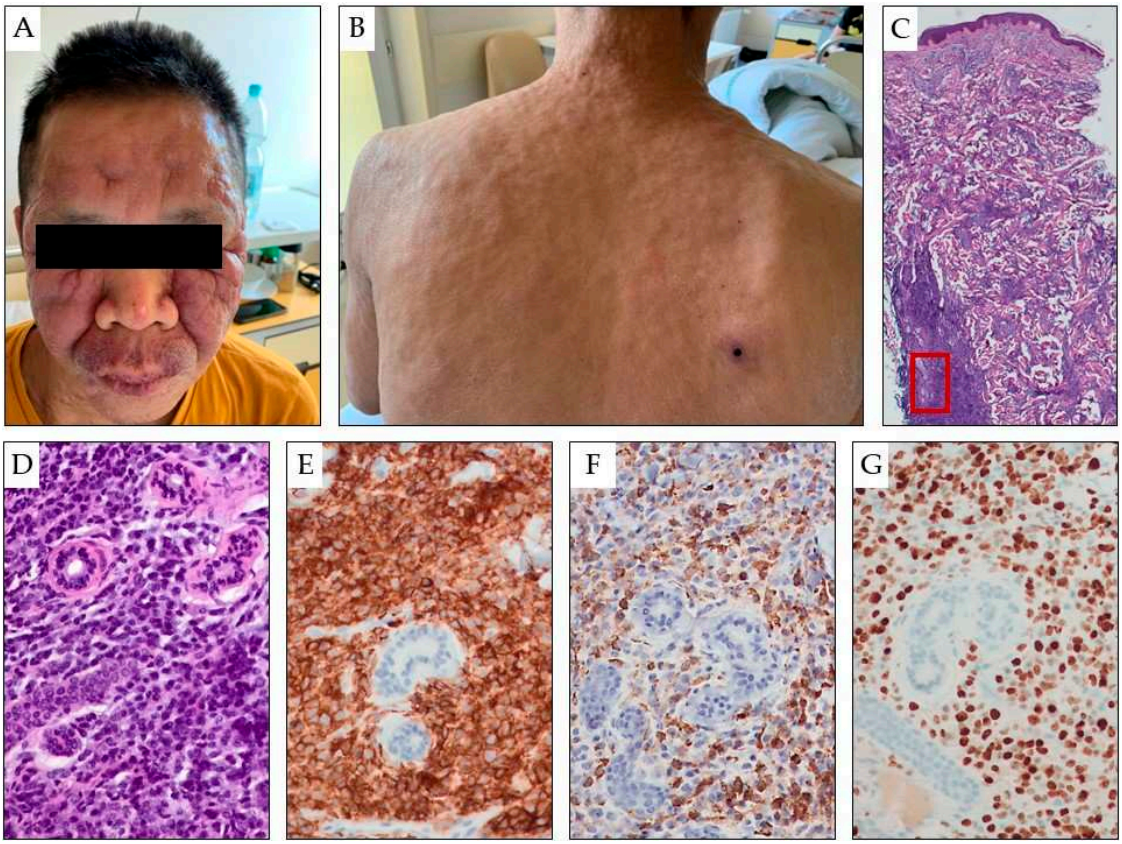

Figure 4. Asymptomatic, multiple, variable-sized, erythematous tumors and papules are present on the face (A) and torso (B) of a 49-year-old patient with AML. The entire skin was thickened and infiltrated, with numerous red-blue tumors and nodules scattered over the entire surface. A particularly large, hard infiltrate is visible on the facial skin, where erythematous and exfoliative foci are also present on the basis of the nodular infiltrate (A-B). Biopsy of the skin showing infiltration by myeloblasts (Haematoxillin&eosin staining in panels C and D under 25X, and 200X magnification, respectively), which are positive for CD45 (LCA, 200X magnification, panel E), myeloperoxidase (200X magnification, panel F), and Ki-67 proliferation marker (200X magnification, panel G).

There are no specific treatment options for patients with AML LC. Initial treatment is determined by factors such as age, performance status, cytogenetics, and molecular markers [126-130]. The standard induction regimen for younger, fit patients is based on a combination of cytarabine and anthracycline, known as the 7+3 regimen. Various molecular markers, including mutations in *FLT3*, *NPM1*, *CEBPA*, and *IDH* mutations, can influence treatment decisions. The incorporation of targeted drugs, such as midostaurin, in *FLT3*-mutated patients has shown improved prognosis, but its impact on LC in AML patients remains unknown.

Simultaneous integrated boost (SIB)–helical arc radiotherapy of total skin (HEARTS), a modified version of helical irradiation of total skin (HITS) therapy, has been used to treat AML in some patients with disseminated LC [40]. Wang et al. reported a 5-year survival rate of 8.6% among 62 patients with AML and LC; this value was significantly lower than that observed for 186 matched AML patients without LC (28.3%) [126]. In addition to conventional chemotherapy, allogeneic stem cell transplantation can improve the outcome [118,127-130].

5.6. Chronic neutrophilic leukemia

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Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative *BCR-ABL* negative leukemia with numerous mature neutrophils [131]. It occurs mainly in older adults and is characterized by marked leukocytosis with neutrophilia and splenomegaly. However, the clinical presentation of CNL may vary from asymptomatic to highly symptomatic with large spleen and constitutional symptoms [132].

The prognosis of CNL is poor, with a median survival of approximately two years [133,134]. Recently, colony stimulating factor 3 receptor (*CSF3R*) mutation was identified to drive the disease, and this mutation has been indicated as a criterion for diagnosis of CNL [135]. Very few cases of LC with CNL have been reported in the literature [131,136,137]. Typical manifestations of LC in CNL include erythematous to violaceous papules on varying parts of the body, leukemic vasculitis, gingival hypertrophy and purpura. Leukemia cutis in CNL should be differentiated from other skin lesions, especially with Sweet syndrome, based on clinical and histological similarities [133,138,139]. However, it can be difficult to differentiate these two diseases due to their clinical and histopathological similarities.

In LC, immature leukocytes infiltrate the skin without significant dermal edema, and skin lesions do not improve with steroids. Although biopsy of Sweet syndrome reveals almost exclusively mature leukocytes, morphology alone may not be sufficient for proper diagnosis in some cases [131]. In some patients, multiple violaceous papules and excoriations have been reported [136]. Nevertheless, it is important to obtain a correct diagnosis of LC as it is associated with a worse prognosis than Sweet syndrome and the two conditions require different treatments. In Sweet syndrome, improvement is observed after treatment with steroids. In CNL available therapies include conventional therapy with hydroxyurea as the conventional frontline option and targeted JAK inhibitors. Ruxolitinib has shown significant responses in patients with CNL, but allogeneic stem cell transplantation is the only curative treatment [139]. In patients with LC, CNL is characterized by an aggressive course and short survival [131,140]. However, due to the low prevalence of CNL, the influence of LC remains unclear.

5.7. Chronic myelomonocytic leukaemia

Chronic myelomonocytic leukemia (CMML) is a hematological malignancy with the characteristics of myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), and whose incidence has been found to be approximately four cases per 100,000 persons per year [141]. Diagnosis requires the presence of sustained peripheral blood monocytosis (≥1 × 10^9 /L) and bone marrow dysplasia, and exclusion of both myeloproliferative, and myelodysplastic neoplasms. In 15-20% of patients, leukemic transformation is observed over three to five years.

Leukaemia cutis is a rare event in patients with CMML, with only 89 such cases being recorded thus far in English language publications [142]. In most patients (63%) LC developed after a diagnosis of CMML; however, in one-third of the patients, skin lesions were observed simultaneously with the diagnosis of CMML, and in five (6%), skin lesions were observed several months or years before the development of systemic symptoms. The clinical features include violaceous or red-brown nodules, papules, plaques of varying sizes and maculo-papular rash. In some cases, painful or pruritic rashes, pustules and ulcers were observed [142]. The skin changes were localized in any site of the body, most commonly on the trunk, the lower extremities and less frequently in the face, arms, scalp and neck.

Skin biopsy shows blast cells with granulocytic or monocytic differentiation [143]. Histologically, LC in CMML can include four type of changes, according to the morphological and immunophenotypic characteristics [144]. Most frequent is a myelomonocytic cell type (43%) consisting of myeloid blastic cells that are positive for CD68 and/or myeloperoxidase, and negative for dendritic cell antigens. The second type (38%) is characterized by infiltration of mature plasmacytoid dendritic cells positive for CD123, TCL1, and CD303. A less common (10%) form is blastic plasmacytoid dendritic cell LC composed of monomorphous medium-sized blast cells that are positive for CD4, CD56, CD123 and TCL-1. Finally, blastic indeterminate dendritic cell tumors (10%)

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may also occur, recognized by large blast cells positive for CD1a, CD4, CD13, CD33, CD56 and S100 antigens and for langerin, CD123 and TCL-1.

Leukaemia cutis in CMML, is associated with a poor prognosis, especially if extramedullary infiltrations coexist with LC. In several patients, LC proceeds disease progression, including AML transformation [142,145-149]. The treatment of LC in CMML requires systemic therapy that eradicates the primary underlying disease [150]. Cytoreductive therapy with hydroxyurea or other cytotoxic drugs are indicated in most patients. Treatment with hypomethylating agents such as 5-azacitidine and decitabine can yield overall response rates of 30%-40% and complete response rates of 7% to 17%. Allogeneic stem cell transplant is the only potentially curative treatment; however, it is associated with high morbidity and mortality, and is available for only a few patients. Radiotherapy, including total skin electron beam therapy, can be an important part of treatment if LC persists after systemic therapy.

5.8. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a malignant clonal disorder of the hematopoietic stem cell characterized by the t(9;22)(q34;q11) rearrangement; this generates the BCR–ABL1 fusion gene that codes for a chimeric BCR-ABL1 protein with high tyrosine kinase activity. The BCR-ABL1 protein has constitutive tyrosine kinase activity, which results in aberrant activation of oncogenic cytoplasmic signaling molecules or pathways [151]. In most patients, the disease is diagnosed at the chronic phase, but in 5% to 10% it may transform to an accelerated or blast phase. Within the United States, the incidence of CML was estimated at 8860 people in the United States in 2022 year [41]. Treatment with tyrosine kinase inhibitors such as first-generation inhibitor (imatinib), second-generation inhibitors (dasatinib, bosutinib, nilotinib) and third-generation inhibitor (ponatinib), markedly improved prognosis in CML.

Skin lesions in CML may be associated with viral or bacterial infections, treatment with tyrosine kinase inhibitors and CML leukemic infiltration [152]. However, skin infiltration of CML patients in the chronic phase is extremely rare and is observed in 2 to 8% of patients [3,153]; it more commonly occurs in the blast phase of CML [154,155]. Leukemia cutis has also been reported to be associated with the chronic stable phase of CML, preceding the blast crisis by one week [153]. The patient was treated with leukapheresis and induction chemotherapy with the improvement of skin changes. Subcutaneous nodules with overlying ecchymoses mimicking a neutrophilic panniculitis-like leukemia cutis have also been reported [125,154,155]. Kaddu et al. reported five CML patients with skin infiltration [125]. They identified a variable mixture of mature and immature cells of the granulocytic series (myelocytes, metamyelocytes, eosinophilic metamyelocytes, and neutrophils) or a monomorphous mononuclear cells. In other reports, patients with CML developed blastic transformation in the skin [126,156,157].

Singhal et al described a patient with CML who developed extensive cutaneous manifestations during a second lymphoblastic blast crisis [156]. He presented with multiple subcutaneous skin nodules, and extensive violaceous papules and plaques over the limbs and the trunk. The diagnosis was confirmed by fine needle aspiration from the skin nodules which showed blast with lymphoblastoid characteristics.

Naher et al describe a patient with CML and AML blastic transformation with multiple cutaneous lesions, diagnosed as LC; the patient had multiple papules, nodules and plaques of reddish-brown colored on his head, neck, back and chest [157]. In another report, Qi et al presented the case of a CML patient who developed a skin nodule in the right calf [154]. The diagnosis of CML in the chronic phase was confirmed by PB and BM analysis, whereas the biopsy specimen obtained from the right calf showed extramedullary myeloid blast crisis of CML despite the chronic phase in the bone marrow.

6. Conclusions

Leukemia cutis (LC) is a dermatological manifestation of leukemia, characterized by the infiltration of the skin by leukemic cells, which may originate from either myeloid or lymphoid

lineages. In most cases, cutaneous lesions manifest after a systemic leukemia diagnosis. However, in some instances, LC is identified concurrently with the detection of generalized leukemia, and occasionally even before the hematological diagnosis. The highest incidence of LC is observed in chronic lymphocytic leukemia, monocytic and myelomonocytic acute myeloid leukemia, and in T-cell lineage leukemia. Clinical presentations vary in terms of appearance, location, and quantity of leukemic skin infiltrations. A skin biopsy is imperative for distinguishing between malignant infiltration and non-specific changes. Prognosis for patients with LC is contingent on the type of leukemia, involvement of other organs, and response to specific treatments.

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