Leukemia Cutis

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Leukemia cutis (LC) is defined as the 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 a number of changes, distribution, and morphology. The highest incidence of LC is observed in chronic lymphocytic leukemia, monocytic and myelomonocytic acute myeloid leukemia, and T-cell lineage leukemia. 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, the 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.

cutis diagnosis pathogenesis leukemia cutis

1. Introduction

Leukemia cutis (LC) is manifested as clinically demonstrated skin infiltration via neoplastic leukocytes or their precursors into the epidermis, dermis, or subcutaneous tissue [1][2][3][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][6][7][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 acute myeloid leukemia (AML) of, monocytic and myelomonocytic FAB (French, American, British) subtypes, chronic lymphocytic leukemia (CLL), chronic lymphocytic leukemia (CLL), and 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 [12]	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 [13]	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)

Authors/Reference	No. of Patients						Clinical Characteristics	Time from Leukemia Diagnosis to LC Development	Survival from LC Diagnosis
	Total	AML	ALL	CML	CLL	Other			
								systemic leukemia	[7][8]
Martinez-Leborans et al., 2016 [14]	17	12	0	4	1	0	Nodules (7 pts.), papules (5 pts.), erythematous-violaceous plaques (4 pts.)	aleukemic LC—5 pts.	7 pts.[2] died during the first year
Li et al., 2018 [15]	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 [16]	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.

However, ...agnosis in ...utaneous ...n. ...exposure ...poor [3][16][17] ...ptors and ...particular, ...e skin via skin-selective homing processes [7][18][19][20]. 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 via 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 infections or inflammation [21].

3. Diagnosis

A diagnosis of LC requires an evaluation of clinical features, morphology, histopathology, and immunophenotyping [7][8][21]. While LC is most commonly characterized as nodules, plaques, ulcers, vesicles, and swellings [2][13][18][19], unusual clinical manifestations are occasionally observed, including erosions, ulcerations, and desquamation [2][22][23]. Moreover, leukemic vasculitis has also been noted as an unusual manifestation of LC, while it occurs mostly in patients with acute leukemia with myelomonocytic or monocytic features [14][22][24]. Skin changes are mainly located in the trunk, extremities, and face [13][19][21]. Widespread petechiae-like eruptions secondary to LC have also been rarely described [25]. 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][26][27].

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 [15][28]. Leukemic lesions can be violaceous or brick-red to skin colored. Leukemia cutis may also exist as diffuse purpura, particularly in infants, such as blueberry muffin syndrome. In most patients, the skin lesions are asymptomatic, but occasionally, pain or pruritus may be present [5][29]. The development of LC is more likely to be rapid in acute leukemias but more gradual in chronic leukemias [30]. The appearance of the skin lesions in LC is nonspecific, which makes it difficult to clinically differentiate from other skin lesions [13][31][32].

The diagnosis of LC requires the evaluation of biopsy specimens with immunohistochemical staining, with the diagnosis confirmed by determining the expression of characteristic cell surface markers [33]. Immunohistochemical staining remains essential for distinguishing reactive from neoplastic infiltrates, as LC can clinically mimic 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 [34][35]. Cutaneous paraneoplastic disorders are defined as one group of nonleukemic cutaneous leukemias that comprise the cutaneous paraneoplastic disorders. Such skin changes have been noted in more than 40% of leukemia patients and are more common than LC. The condition manifests as petechiae/purpura caused by thrombocytopenia, neutrophilic dermatoses such as pyoderma gangrenosum and Sweet’s syndrome, as well as leukocytoclastic vasculitis [5][36]. Other studies have also reported the occurrence of opportunistic infections, including disseminated candidiasis and herpes zoster. 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.

4. 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 with advanced leukemia, resistant to previous therapies. A worse prognosis is also observed in AML, T-cell prolymphocytic leukemia (T-PLL), and Richter’s syndrome (RS) [6][37][38][39]. 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][13]. In another 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 leukemias [1].

5. 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 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 [34][40]. Recently, simultaneous integrated boost with helical arc radiotherapy of total skin (HEARTS) has been proposed to treat cutaneous manifestations in the treatment of refractory cutaneous leukemia [41].

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