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Review

Leukemia Cutis as an Early Presentation or Relapsing Manifestation of Chronic Lymphocytic Leukemia (CLL)

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Summary: *Background and Objective:* Cutaneous infiltration by Chronic Lymphocytic Leukemia (CLL) is a rare complication. The clinical presentation, impact of it on disease prognosis, and the proper treatment choice are not clear. Here in our review, we try to answer these questions. *Acquisition of evidences:* A systematic search of PubMed, and Google Scholar for English language articles published from Jan 2000 to June 2019. *Synthesis of evidences:* A total of 56 cases were identified, with a median age of 66 years. Of these cases 43 were males and 12 were females, and one missing data, with a ratio of 3,6:1. Head and neck were most commonly involved. The commonest clinical presentation was papulonodular lesions, and the majority were diagnosed at an early stage. CLL skin involvement at the site of old herpetic lesions was common. Because of the rarity of the disease, treatment modalities varied widely, and there are no consensus on treatment. The majority were treated with chemotherapy. In general, 35 (77.8% - of the non-missing data) patients responded to treatment (25 patients had a complete remission and 10 a partial remission). All patients ≤60 years had an early-stage disease, on the other hand, all patients with advanced-stage were >60 years. *Conclusion:* Patients with early-stage and localized leukemia cutis can benefit from observation alone strategy, while intervention in young patients with advanced disease is warranted. Skin infiltration by CLL does not affect prognosis, as most patients attained complete or partial remission with a very low progression rate.

Keywords: Chronic lymphocytic leukemia, small lymphocytic lymphoma, leukemia cutis, cutaneous infiltration, skin involvement.

Background

With more than 15,000 new cases diagnosed every year in the United States, Chronic lymphocytic leukemia (CLL) is the most frequent form of indolent lymphoma in the Western world (1). CLL is characterized by the clonal proliferation of neoplastic B lymphocytes in the blood, bone marrow, and lymphatic system (2). Most patients are asymptomatic at diagnosis, 10% present with B symptoms, on examination most patients have palpable lymphadenopathy, while 20 to 50% of the patients have hepatosplenomegaly (3). Cutaneous infiltration (Leukemia cutis) by CLL is regarded as a specific sign of skin involvement, usually consists of papules, nodules, or tumors (4,5). On the other hand, skin lesions, in general, can be seen in 25% of patients with CLL (6). It is unclear what is the impact of cutaneous infiltration by CLL on prognosis, mainly because most cases are sporadic, either in case reports or series, with no consistent modality of treatment.

We reviewed published data from January 2000 to June 2019, from case reports, series, and reviews. To get a better understanding of the vast scale of presentations, prognosis, and the best treatment modality of CLL skin infiltration.

Acquisition of evidences

A systematic search of the Medline database (PubMed), Google Scholar was performed to identify English language articles published from January 2000 to June 2019 with the following search terms: Leukemia cutis - CLL, cutaneous - CLL, skin - CLL, cutaneous - chronic lymphocytic leukemia, skin - chronic lymphocytic leukemia. Only patients with histopathologically confirmed CLL

Leukemia cutis was included in this analysis, cases with concomitant diagnoses of other neoplasms in the same biopsy were excluded. Also, Richter transformation was excluded. Where available, the following patients' characteristics were extracted from each study: sex, age at diagnosis of CLL, specific location and type of skin CLL involvement, systemic disease setting at the time of CLL skin involvement, type of treatment used for skin involvement, reported outcome, and follow-up period.

Synthesis of evidences

A total of 56 cases were identified as shown in Table 1, with a median age of 66 years (range 39-90), of these cases 43 (76.8%) were males and 12 (21.4%) were females, and one missing data with a ratio of 3,6: 1.

Head and neck were the most common involved sites, as seen in 19 (33.9%) cases, followed by trunk and extremities with 15 (26.8%) cases, the most common clinical presentation was in the picture of papulonodular skin lesions in 28 (50%) cases, while erythematous patches were seen in 15 (26.8%) cases, ulceration was uncommon (5.4%), 5 cases had CLL skin involvement at the site of old herpetic lesions. In 27 cases, (55.1% - of the non-missing data) leukemia cutis was the initial presentation of CLL, while 22 cases (44.9% - of the non-missing data) had their skin lesions as a relapse, and data were missing for 7 patients.

The median time before relapse with skin involvement was 5.5 years (range 1 to 21 years). 17 patients (70.8% - of the non-missing data) were diagnosed on early-stage (11 with Rai 0,1,2 and 6 Binet A, B), on the other hand, 7 patients (29.2% - of the non-missing data) were diagnosed in advanced stage (2 with Rai 3, 4 and 5 with Binet C), and data were missing for 32 patients.

The majority of the patients were treated with chemotherapy alone, (11 patients) where most of the cutaneous involvement responded to treatment [7 Complete Remission (CR)], 3 Partial Response (PR) and 1 stable disease), others managed by observation strategy alone (10 patients), five of the patients who were observed had stable disease over the follow-up period, and 2 had spontaneous cutaneous CR. An-

Table 1. Patients Demographics N = 56

Data I	
Age, Median (Range)	66 (39-90)
Gender, N (%)	
Male	43 (76.8)
Female	2 (21.4)
Missing data	*1 (1.8)*
Follow up time in months, Median (Range)	*12 (2-132), data were missin for 28 patients.*
Site of involvement, N (%)	
Head and Neck	19 (33.9)
Trunk and Extremities	15 (26.8)
lsolated Extremities	11 (19.6)
Head, Neck and extremities	5 (8.9)
Genitalia	2 (3.6)
Generalized	4 (7.1)
Type of skin lesions, N (%)	
Papulonodular	28 (50)
Erythematous patch	15 (26.8)
Erosive/Ulceration	3 (5.4)
Others	10 (17.9)
Stage, N (%)	
Rai 0,1,2	11 (19.6)
Rai 3,4	2 (3.6)
Binet A, B	6 (10.7)
BinetC	5 (8.9)
Early Stage (Rai 0,1,2 and Binet A, B)	*17 (30.4)*
Advanced Stage (Rai 3,4 and Binet C)	*7 (12.5)*
Missing_ Data	*32 (75.1)*
Time of diagnosis, N (%)	
Initial	27 (48.2)
Relapse	22 (39.3)
MissinK Data	*7 (12.5)*

other 10 patients treated with local radiotherapy (7 CR and 3 PR), 6 patients were treated with chemo-immunotherapy (chemotherapy with immunotherapy like Rituximab), all of them responded to treatment (5 CR and 1 PR). Data were not available for 11 patients, other treatment modalities like local, surgical, and others were seen in 8 patients. In general, 35 patients (77.8% - of the non-missing data) responded to treatment (25 CR and 10 PR) as shown in Table 2 (7-56).

Patients were followed for a median duration of 12 months (range 2-132 months), at the time of reporting the cases, 8 patients (24.2% - of the non-missing data) had disease progression, 3 of those 8 patients died, 25 patients (75.8% - of the non-missing data) had stable disease over the follow-up period, while data for 23 patients were missing. More treatment details are shown in Table 3.

Table 2. Treatment approaches used (*) , N = 56

Type of treatment	N (%)	Cutaneous Response, N
Observation	10 (17.9) [Ref.7-16]	2 CR 5 Stable Disease *3* Missing Data
Chemotherapy alone	11 (19.6) [Ref.17-26]	7 CR 3 PR 1 Stable Disease
Chemoimmunotherapy	6 (10.7) [Ref. 27-32]	5 CR 1 PR
Radiotherapy	10 (17.9) (1 received rituximab with RT and had CR) [Ref.7,20,21,33-39]	7 CR 3 PR
Local treatment	2 (3.6) [Ref.9,40]	1 CR 1 Stable Disease
Surgical removal	2 (3.6) (1 received alemtuzumab with surgical excision and had CR) [Ref.20,41]	2 CR
Others	4 (7.1) [Ref.42-45]	1 CR 3 PR
Missing Data	11 (19.6) [Ref.46-56]	N/A

(*) Because of the rarity of the disease, and the vast variety in the treatment options only the last regimen used in each case was considered in table 2 (some regimens were changed after recurrence or after treatment failure, some regimens were repeated in the same cases after recurrence).

Discussion

Dermatological manifestations of CLL previously discussed in several studies, including primary CLL skin infiltrations (Leukemia cutis) and secondary skin reactions (infectious or hemorrhagic origin, others like vasculitis, purpura.) that is associated with CLL (57), these findings can vary in presentations as they can be localized or generalized in the form of erythematous patches, plaques, nodules, and large tumors, however, ulceration is uncommon (5).

Some reviews analyzed skin lesions in CLL, that included both malignant and non-malignant skin changes (57,58), others reviewed cutaneous changes in all B cell lymphomas in general (59), and finally a review of 42 patients with specific cutaneous infiltrates of CLL, showed M:F ratio of 1,3 : 1 with 24 males and 18 females, with a median age at skin lesions diagnosis of 68 years (range 42-83), the duration of CLL before the skin involvement ranged from 0 to 142 months, with mean of 39 months. In seven patients (16.7%), skin lesions represented the first sign of disease. Generalized lesions were seen in 17 cases, and limited lesions were seen in 25 cases (head and neck 10, and trunk and extremities in 15 cases), In six patients, lesions were seen at the sites of scars from previous herpes zoster (4 patients) or herpes simplex (2 patients) eruptions. Follow up data were available for 31 patients, the two patients with Richter's syndrome died after 5 and 8 months, the 5-year survival of patients with cutaneous B-CLL was 66.6%. Patients with generalized disease were treated with chemotherapy, and those with solitary or localized disease were treated with radiotherapy (5).

In another review for specific cutaneous infiltrates of CLL at sites typical for Borrelia burgdorferi infection, six patients with CLL were described with M:F ratio of 4 : 2 and mean age of 67.8, the skin lesions located on the nipple in 4 cases and scrotum in two cases, in the form of solitary erythematous plaques or nodules. Histology confirmed the diagnosis of B-CLL skin infiltration in all the cases. Polymerase chain reaction (PCR) analysis showed the presence of deoxyribonucleic acid (DNA) sequences specific for B.burgdorferi in 4 cases (60). CLL skin infiltration was not uncommon, but it was not well described in the literature.

Table 3. Treatment Regimens

	Age (years)	Sex	Stage	Cutaneous outcome
Chemotherapy alone				
1. Cladribine 0.12 mg/kg daily for five days for 4 cycles [17].	79	M	Rai II	CR
2. Fludarabine 40 mg/m2 daily for five days for 4 cycles [18].	63	M	Rai III	CR
3. Chlorambucil 0.1 mg/kg daily for 2 cycles [19].	75	M	Binet B	PR
4.Vincristine and dexamethasone (treated initially with rituximab without response then fludarabine for 3 cycles with some improvement) [20].	70	F	MD	SD
5. Chlorambucil and Prednisolone [21].	67	F	MD	CR
6. Chlorambucil for 4 months [22].	63	F	MD	CR
7. Chlorambucil for 6 months [22].	75	F	MD	PR
8.Chlorambucil and methylprednisolone [23].	84	M	Binet C	PR
9. Fludarabine, first 2 cycles 25 mg/m2, then reduced to 18.75 mg/m2 for 2 cycles, due to hematological toxicity [24].	66	M	Binet C/Rai IV	CR
10. Fludarabine [25].	68	M	MD	CR
11. Chlorambucil and IVIG [26].	77	F	MD	CR
Chemoimmunotherapy				
1. Obinutuzumab and chlorambucil for 6 cycles [27].	45	M	Rai I	CR
2. Rituximab and bendamustine for 8 cycles[28].	84	M	Binet C	CR
3. Rituximab, fludarabine, and cyclophosphamide for 2 cycles [29].	62	M	Binet C	CR
4. Ofatumumab, pentostatin, and cyclophosphamide, for 3 months, then consolidation with ofatumumab [30].	58	M	MD	PR to initial treatment and CR to consolidation.
5. CHOP for 5 cycles and rituximab for 4 cycles, then fludarabine and cyclophosphamide were added to rituximab [31].	67	F	MD	Mild to RCHOP and CR to second regimen.
6. Rituximab, fludarabine, and cyclophosphamide [32].	55	M	MD	PR
Radiotherapy				
1. Local RT (preceded with intralesional steroid injections, with minimal response) [7].	61	M	Rai I	CR
2. Local RT [20].	60	M	Rai 0/Binet A	CR
3. Local RT and rituximab [21].	74	M	MD	CR
4. Local RT 36 Gy in 18 fractions [33].	65	F	Binet A	CR
5. Local RT 4 Gy in 2 fractions for each ear (lesion) [34].	39	M	Binet A	PR
6. Local RT 20 Gy (preceded by cyclophosphamide and prednisolone, with no response) [35].	63	M	Binet C	CR
7. Local RT [36].	74	M	MD	PR
8.Local RT 30 Gy in 15 fractions [37].	66	F	MD	PR
9. Local RT 24 Gy in 12 fractions then 16 Gy in 8 fractions after two months, after recurrence prednisolone followed by RT 4 Gy in 2 fractions [38].	45	M	MD	CR to initial and second regimen.
10. Local RT 20 Gy in 10 fractions [39].	73	M	MD	CR

Table 3. Treatment Regimens

	Age (years)	Sex	Stage	Cutaneous outcome
Local treatment				
1. Intralesional methotrexate every 2 weeks for 2 doses [9].	72	M	Binet A	CR
2. Triamcinolone 0.1% cream [40].	72	M	Rai I-II	SD
Others				
1. Broad-band ultraviolet B [42].	59	M	MD	PR
2. Local imiquimod 3 times/week, increased to once per day after 8 weeks of no response [43].	71	M	Rai 0	CR after 6 weeks of high dose.
3. Idelalisib 150 mg twice daily [44].	60s	M	MD	CR
4. Prednisolone 60 mg daily (due to patient's preference) [45].	90	F	MD	PR

Legend: M, Male; F, Female; RT, Radiotherapy; CR, Complete remission; PR, Partial remission; SD, Stable disease; MD, Missing data; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

In our search, for better understanding of the impact of CLL skin infiltration on the disease prognosis, and outcomes, and to discuss the treatment modalities that were used, and the outcome after treatment, we focused our attention on leukemia cutis rather than general secondary skin manifestations in CLL. The most common clinical presentations were papulonodular skin lesions, and erythematous patches, while ulceration was seen in a minority of cases. Five cases had CLL skin involvement at the site of old herpetic lesions. It has been hypothesized that CLL skin infiltration is a recruitment to an antigenic response, rather than a true metastasis. A hypothesis explains these findings by a breach of the blood-skin barrier caused by an inflammatory or malignant disease as the underlying cause of skin involvement by CLL (7,61). This can also explain the leukemia cutis at the sites of herpetic lesions, Borrelia burgdorferi infection, trauma sites, and foreign body sites.

In most of the patients the skin involvement was the first presentation of CLL patients, and most of them had skin involvement in the early disease stage. All patients ≤ 60 years old have early-stage disease, while the 7 patients with advanced disease were older than 60 years, and all of those with advanced-stage disease had received treatment with complete disappearance of their skin lesions except one patient. It was also observed that skin infiltration by CLL did not affect prognosis, as most patients attained complete or partial cutaneous remission (35; 77.8 % - of the non-missing data).

Because of the rarity of the disease, treatment modalities varied widely, and there is not yet a consensus. All treatment modalities (i.e. local radiotherapy, chemotherapy alone, chemoimmunotherapy) resulted in complete or partial cutaneous response. Observation alone resulted in stable disease in 5 out of 10 patients, all of them had early disease with rather localized skin involvement. A spontaneous resolution was seen in 2 patients in the same group. The best modality of treatment in cutaneous CLL is based on the staging and the patient's co-morbidities. Chemoimmunotherapy (used more often in reported cases after the approval of rituximab in 2010 as a treatment for CLL), was used in 7 cases (5 with rituximab, 1 with obinutuzumab, and 1 with ofatumumab), while rituximab in monotherapy was used only once before 2010 with no response. These results point out to the importance of rituximab, in the treatment of CLL related leukemia cutis, mainly in combination. A total of 10 patients (17.9%) were treated with local radiotherapy (RT), mainly in localized skin involvement with CR in 7 out of 10 as shown in Tables 2 and 3.

Conclusion

Leukemia cutis is rare but rather a recognized complication of CLL, most likely presents as papulonodular lesions as the initial sign or early stage of the disease. All patients ≤60 years had an early-stage disease, on the other hand, all patients with advanced-stage were >60 years. Patients with early-stage and localized leukemia cutis can benefit from observation alone strategy, while intervention in young patients with advanced disease is warranted. Skin infiltration by CLL does not affect prognosis, as most patients attained complete or partial remission with a very low progression rate.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethical Statement
Our study did not require an ethical board approval because all patients' information was taken from published case reports and/or series. And we do not have direct access to participants of the primary studies included in this review.

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