

A Case of Leukemia Cutis in A 43-Year-Old Male with Chronic Myelogenous Leukemia

Keywords: Leukemia Cutis; Chronic Myeloid Leukemia; Chronic Myelogenous Leukemia

Abstract

Leukemia cutis is a dermatological condition characterized by the infiltration of leukemic cells into the skin. It manifests as various skin lesions such as macules, papules, plaques, or nodules, commonly appearing on the trunk, extremities, or head. The condition is uncommon in chronic myelogenous leukemia (CML), occurring far less frequently than in acute myelogenous leukemia (AML), where it is reported in about 10–15% of cases. In this report, we present a compelling case of a 43-year-old male with chronic myelogenous leukemia who developed leukemia cutis. The emergence of leukemia cutis serves as an indicator of disease progression and is associated with a generally poor prognosis. Our objectives are to report a case of leukemia cutis in a CML patient and to compare this patient to the existing literature on the clinical manifestations, management strategies, and disease outcomes specific to leukemia cutis in the context of CML. By reviewing the available information, we aim to enhance our understanding of this condition and provide valuable insights into its diagnosis and treatment.

Introduction

Leukemia cutis refers to the infiltration of leukemic cells into the skin.[1] It commonly manifests on the trunk, extremities, and head as solitary or multiple macules, papules, plaques, and nodules. [2,3] In rare cases, the lesions present as blisters and ulcers.[3] This condition can occur in various types of leukemia, more commonly in acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).[2] In chronic myelogenous leukemia (CML), leukemia cutis is a relatively rare manifestation. It is estimated that leukemia cutis develops in 10–15% of patients with AML and is less frequent in CML. [2,3] Leukemia cutis can occur at different stages of CML, including the chronic phase, accelerated phase, or blast phase. However, it is more commonly observed in the blast phase, which is characterized by more aggressive disease features and increased infiltration of leukemic cells into extramedullary sites.[4] Certain factors may increase the likelihood of developing leukemia cutis in CML. These include a higher disease burden, advanced disease phase, specific genetic mutations, and resistance to tyrosine kinase inhibitors commonly used in CML treatment.[5]

This report will present a case of leukemia cutis which rarely presents in chronic myelogenous leukemia.

Case Report

A 43-year-old, male, married, Filipino security guard, known case of CML, presented to the clinic with an 8-week history of gradually increasing non-pruritic, non-painful, erythematous papules and plaques on the trunk and bilateral upper and lower extremities. There was no associated discharge or bleeding. He denied history of trauma or manipulation. There was no change in personal products used. No medications were applied.



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Two years prior, the patient was diagnosed with CML at another institution through bone marrow aspiration and core biopsy. He was initially managed with imatinib mesylate 400 mg once daily for 11 months with good response. No drug sensitivity testing was performed prior to initiation of imatinib, as this is not readily available in our setting. One year prior, he was admitted due to anemia and thrombocytopenia which were attributed as complications of imatinib. Hence, imatinib was decreased to 100 mg once daily. He was also maintained on prednisone 20 mg once daily, ferrous sulfate 325 mg once daily, and folic acid 5 mg once daily. Upon initial consultation at the dermatology clinic, he reported discontinuation of imatinib intake for two months due to the lack of funds.

The patient has no known history of other comorbidities nor prior surgeries. He has a family history of hypertension on the paternal side and asthma on the maternal side. He has no family members with the same lesions. The review of systems was unremarkable.

On dermatologic examination, the patient presented with multiple, discrete, round, firm, erythematous to violaceous papules and plaques on the chest, back, and bilateral upper and lower extremities (Figure 1). The initial clinical differential diagnoses were leukemia cutis, erythema nodosum, fixed drug eruption, arthropod bite reaction, and allergic contact dermatitis. He underwent a 4 mm skin punch biopsy on the chest. Haematoxylin and Eosin-stained sections revealed orthokeratosis, and an acanthotic epidermis that was slightly papillomatous with basal layer hyperpigmentation. In the dermis are diffuse infiltrates of atypical leukemic and myeloblastic cells in between thickened collagen bundles as well as surrounding adnexal structures and neurovascular bundles. (Figure 2). The specimen was negative for CD3, CD20, Myeloperoxidase (MPO), and CD117 (Figure 3A, Figure 3B, Figure 3C, Figure 3D). Meanwhile, it was positive for CD34 and CD68 (Figure 3E, Figure 3F). The histopathologic examination and immunohistochemical staining were consistent with leukemia cutis.

He was advised to continue his intake of imatinib 100 mg once daily. He then reported a decrease in the number of the lesions and

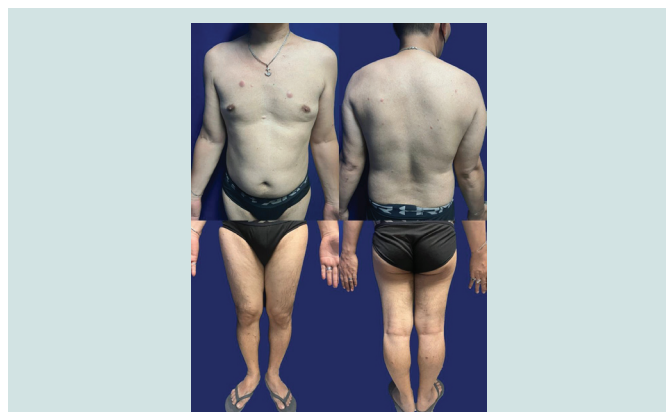


Figure 1: Dermatologic examination upon initial consultation revealed multiple, discrete, round, firm, erythematous to violaceous papules and plaques on the chest, back, and bilateral upper and lower extremities.

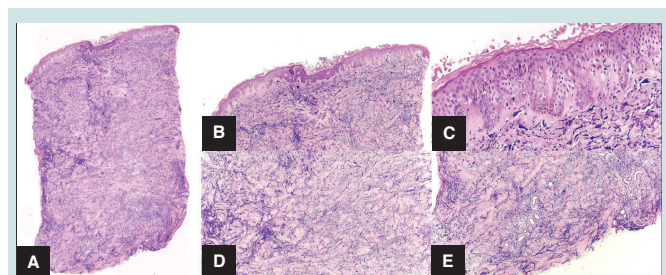


Figure 2: Haematoxylin and Eosin-stained sections. A. Pathology in the entire dermis (scanning magnification). B. The epidermis is acanthotic and slightly papillomatous with basal layer hyperpigmentation (10X magnification). C. The stratum corneum is orthokeratotic. Grenz zone is noted (40X magnification). D. In the dermis are diffuse infiltrates of atypical leukemic and myeloblastic cells in between thickened collagen bundles (10x magnification). E. Surrounding adnexal structures and neurovascular bundles are appreciated (10x magnification).

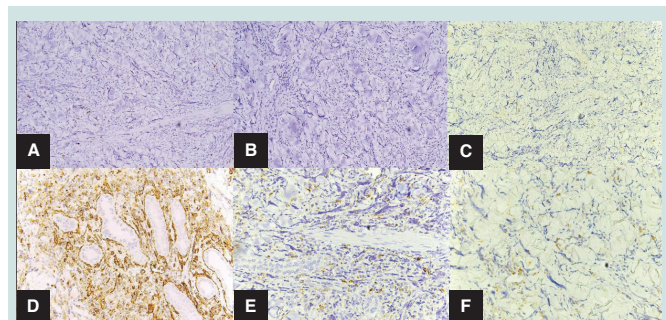


Figure 3: Immunohistochemistry Staining. A. CD3 negative. B. CD20 negative. C. MPO negative. D. CD117 negative. E. CD34 positive. F. CD68 positive.

flattening of the remaining lesions. However, two months after, he was admitted due to easy fatigability. There was an increase in the number of lesions, especially on the back and lower extremities (Figure 4). Complete blood count showed anemia, leukocytosis, and thrombocytopenia. Thoracic ultrasound revealed bilateral pleural effusion. One day after referral to the dermatology service, the patient expired due to hypovolemic shock secondary to massive blood loss. The main service was not able to rule out a cerebrovascular bleed since cranial imaging was not done.



Figure 4: Dermatologic examination upon admission exhibited an increase in the number of lesions on the chest and bilateral lower extremities.

Discussion

Leukemia cutis is defined as the cutaneous invasion of malignant hematopoietic cells. The clinical lesions are usually multiple and asymptomatic. [6,7,8] These may appear violaceous, red-brown, or hemorrhagic.[2] The lesions more commonly present as macules, papules, plaques, and nodules. [2,3] Rarely, these may also manifest as erythema, erythroderma, ulcers, and blisters. [6,7] The usual sites of predilection include the trunk, extremities, and head. When present in the face, nodular and plaque lesions may resemble leonine facies.[3] When the predominant lesions are nodules and papules, these are more frequently firm, dome-shaped lesions.[8] The lesions of leukemia cutis have a predilection to erupt at sites of previous or current inflammation.[2] It is also worth noting that, even in the same patient, leukemia cutis may produce various lesions during the course of the disease. [2] The patient in this report manifested with a common presentation of the disease, specifically multiple, papules and plaques on the trunk and extremities. However, if the patient was not initially diagnosed with CML, leukemia cutis would not be the initial impression in this case as the lesions of leukemia cutis mimic multiple disease entities. This highlights the importance of completely examining the patient even during the initial consultation.

A review of the literature revealed 11 CML patients with leukemia cutis (Appendix A). Most of the patients were elderly male patients. Five of the patients were diagnosed with leukemia cutis more than one year from the initial diagnosis of CML. Meanwhile, one patient was diagnosed with leukemia cutis concurrently with CML. Majority had lesions on the head, trunk, and extremities. Two patients had generalized lesions. One patient only presented with lesions on the buttocks; meanwhile, one patient had lesions on the glans penis aside from the trunk. Multiple macules, papules, and nodules were the most common primary lesions. All patients received chemotherapy and two of them also had resection since they both had solitary nodule. Seven of the patients expired with five of them expiring within two years from the diagnosis of leukemia cutis. Only two patients had recurrence of cutaneous lesions.

Review of the records at the Jose R. Reyes Memorial Medical Center Department of Dermatology revealed two cases of leukemia cutis, diagnosed in 2014 and 2016. Meanwhile, records of the Philippine Dermatological Society – Health Information System showed only two cases of leukemia cutis, diagnosed in 2015 and 2016. [9] The low incidence of leukemia cutis from the records may not be reflective of the true incidence of the illness in the country. This is because only hospitals accredited with the Philippine Dermatological Society are able to input to the database.

Table 1: APPENDIX A: Review of the demographic profile, duration before the diagnosis of leukemia cutis, clinical presentation, management, and complications of CML patients with leukemia cutis.

Author (Year)	Origin	Age/Sex	Duration before Diagnosis (mo)	Location	Clinical Presentation	Treatment	Follow-up	Recurrence/Complications
Kaddu, S., et al (1999)	Austria [11]	22/F	N/K	Chest	Solitary nodule	Resection, Chemotherapy	Lost to follow-up	None
		79/M	N/K	Head and trunk	Multiple nodules	Chemotherapy	Died in 3 mo	None
		45/F	N/K	Face and thigh	Multiple papules, plaques, and nodules; Infiltration of orbit	Chemotherapy	Lost to follow-up	1 recurrence
		63/M	72	Buttocks	Multiple papules	Chemotherapy	Died in 1 mo	None
		63/M	60	Trunk and glans penis	Multiple reddish papules, nodules	Chemotherapy	Died in 17 mo	1 recurrence
		67/M	N/K	Trunk	Multiple papules, plaques, and nodules	Chemotherapy	Lost to follow-up	None
		55/M	40	Generalized	Macules and papules	Chemotherapy	Died in 15 mo	None
		85/M	N/K	Head	Solitary nodule	Resection, Chemotherapy	Lost to follow-up	None
		67/M	36	Generalized	Macules and papules	Chemotherapy	Died in 11 mo	None
Watson, K. M. T., (2006)	UK [5]	72/M	At initial presentation	Face, scalp, trunk	Pruritic violaceous infiltrated nodules	Chemotherapy	Died	N/K
		83/F	28	Trunk, limbs	Violaceous macules and papules	Chemotherapy	Died	N/K

In most cases, the diagnosis of leukemia cutis is established after the diagnosis of systemic leukemia.[3] There are few cases, however, that the diagnosis is confirmed the same time as the systemic leukemia or even before it – also known as aleukemic leukemia cutis.[2] Most studies revealed that the mean interval from the diagnosis of systemic leukemia to skin eruption is about one to two years.[10] Similarly, our patient presented with cutaneous lesions two years after the initial diagnosis of CML.

The diagnosis of leukemia cutis can be particularly complex. In some cases, patients may exhibit macular and papular eruptions that resemble drug or viral exanthem, while others may only present with a single nodule that shares clinical similarities with various conditions. Additionally, there are instances where patients manifest with aleukemic leukemia cutis. These scenarios underscore the critical significance of obtaining a histopathologic diagnosis to accurately identify and differentiate the condition.[11] Additionally, whenever appropriate, immunohistochemical staining would greatly help in the final diagnosis.

The histopathologic manifestation of leukemia cutis is characterized by nodular infiltration of neoplastic leukocytes with a perivascular-periadnexal distribution, or it may be interstitial and diffuse. Epidermotropism is not common. The predominant cell components are myeloblasts and granulocytic precursors. The characteristics of neoplastic cells are large, with abundance of eosinophilic cytoplasm, large nuclei with finely dispersed chromatin, and occasional small nucleoli. There is also the presence of mitotic figures as well as scattered macrophages and mature granulocytes. The nerves, sebaceous glands, and muscle bundles are usually focally destroyed.[2]

Based on the algorithm proposed by Cronin, et al. for diagnosing myeloid leukemia cutis, the initial immunohistochemical stains to

be performed are CD3 and CD20 [12]. These markers are typically negative in myeloid leukemia cutis, which aligns with the findings in this patient’s case. The subsequent recommended stain is CD43, which tends to be positive in nearly all cases of myeloid leukemia cutis. However, this stain was not conducted in this case. The status of MPO staining can vary, being either positive or negative in myeloid leukemia cutis. In instances where it is negative, as observed in this patient, CD68 may be requested. CD68 is generally positive in cases of myeloid leukemia cutis. In line with this, the CD68 result in this patient was indeed positive. Subsequently, CD56 may have been considered. Similar to MPO, CD56 can be positive or negative. When CD56 is negative, CD117 might be requested, and a negative result would be indicative of myeloid leukemia cutis. Notably, this pattern is consistent with the results in this case. It is worth mentioning that the algorithm does not include CD34. A positive CD34 result suggests the presence of myeloid or monocytoid leukemia cutis, specifically granulocytic sarcoma. This outcome aligns with the observations in this patient’s case.

The mechanism by which leukemic cells invade the skin remains poorly understood. Cho-Vega, et al. proposed that leukemic cells migrate into the skin tissue based on the skin’s affinity to attract memory T-cells.[2] This theory emphasizes the potential involvement of adhesion molecules, chemokines, and integrins in the process of cell migration. Additionally, certain environmental factors such as benzene exposure, chemotherapy drugs with alkylating agents, ionizing radiation, and viral infections (e.g., HTLV-I infection causing ATLL) pose similar risk factors for both systemic leukemia and the development of leukemia cutis.[2]

Leukemia cutis is a manifestation of a systemic disease; hence, the treatment of the underlying leukemia using systemic chemotherapy is the main goal.[2,7] Kaddu, et al. demonstrated that patients who started chemotherapy showed remission of leukemia cutis and

absence of recurrences.[11] However, they noted that most of the patients died within 12 months due to leukemia-related causes.[11] On the other hand, Watson, et al. noted that leukemia cutis was refractory to therapy and the benefits are usually short-lived.[5] In the case of the patient in this report, he noted an initial improvement of the lesions when he was restarted on imatinib. However, he reported progression of the lesions as he developed complications of CML.

Patients with leukemia cutis usually develop various complications. However, these complications are commonly due to the underlying leukemia instead of cutaneous lesions. Patients with leukemia have pancytopenia so they are at risk for opportunistic infections. They are also prone to bleeding due to thrombocytopenia or, in some cases, due to the erosion of the skin lesions. Close monitoring of systemic symptoms and serial laboratory examination specifically complete blood count, bleeding parameters, and chest radiographs are invaluable in detecting these complications. Other complications include drug reaction to chemotherapy and mass effect if the leukemia cutis presents as a tumor. [13] The patient in this case developed easy fatigability most likely due to the anemia. He also presented with leukocytosis hinting at a concomitant infection as well as a probable cerebrovascular bleed due to thrombocytopenia. All these complications are attributable to the patient's CML.

The presence of leukemia cutis in CML is generally associated with an unfavorable prognosis. It may indicate disease progression, resistance to therapy, or transformation to a more aggressive form of leukemia. [2,3] The survival of patients with leukemia cutis is short. Chang, et al. observed that the mean interval between the diagnosis of leukemia cutis and death was around eight months.[10] Meanwhile, Su, et al. noted that 88% of patients die within one year of diagnosis. [13] Watson, et al. reported that some patients with CML die within three months from the eruption of the lesions.[5] Development of leukemia cutis in CML is associated with transformation into the blast phase, suggesting disease progression.[14] According to the World Health Organization, one of the defining criteria for the blast phase of CML is the presence of extramedullary blastic infiltration in any organ or tissue, including the skin, where it manifests as leukemia cutis. This occurs because of the presence of at least 20% blasts in the peripheral blood and/or bone marrow, some of which may infiltrate the skin.[15] In this report, the patient expired due to hypovolemic shock secondary to massive blood loss with a possible cerebrovascular bleed in a span of two months from the development of the lesions.

Conclusion

Leukemia cutis is a relatively rare manifestation of CML. It typically appears as macules, papules, plaques, or nodules on the trunk, extremities, or head. The diverse range of possible morphologies can often make it challenging to differentiate from other diseases. Therefore, a comprehensive investigation is crucial to accurately diagnose this condition. Histopathologic examination and immunohistochemical staining are valuable techniques used to aid in the diagnosis. It is important to note that the development of these skin lesions indicates disease progression and is associated with a poor prognosis.

While chemotherapy can lead to the resolution of leukemia cutis, it is unfortunate that many patients still experience a shortened lifespan due to the complications associated with CML. These complications contribute to a reduced survival outcome for the affected individuals. Regardless of the aggressive treatment of the complications of CML, the diagnosis of leukemia cutis would inevitably lead to death. Hence, an extensive dermatologic examination of patients with CML is significant for an early diagnosis of leukemia cutis and prompt treatment of the underlying leukemia.

Ethical Considerations

The patient's legal guardian in this manuscript have given written informed consent to publication of his case details.

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