Aleukemic Leukemia Cutis: A Rare Case Report with Review of Literature

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Summary

Acute myeloid leukemia can present as an extramedullary disease without bone marrow involvement. There are two extramedullary manifestations of acute myeloid leukemia: (1) Myeloid sarcoma and (2) Leukemia cutis. It is a very unusual presentation and is mostly associated with acute myeloid leukemia. Very rarely it presents with primary skin lesions without bone marrow involvement in such a case it is called aleukemic leukemia cutis. Here we report a 57-year-old male patient who presented with skin lesions and was diagnosed with the help of excisional skin biopsy and immunohistochemistry. Bone marrow examination was normal. He was treated with standard induction chemotherapy "7+3" followed by remission documentation followed by consolidation with intermediate-dose cytarabine.

Keywords: aleukemic leukemia cutis, myeloid sarcoma, acute myeloid leukemia, chemotherapy, primary skin lesions

Introduction

Extramedullary (EM) presentation of acute myeloid leukemia (AML) is unusual. Myeloid sarcoma (MS) and leukemia cutis (LC) represent two well-known EM manifestations.[1] LC presenting before bone marrow involvement of leukemia is very rare. We hereby present a middle-aged male presented with biopsy-proven isolated skin involvement.

Case Report

A 57-year-old male without any comorbidities, ECOG performance status 1 presented with a chief complaint of skin lesions all over the body for 2 months. Skin lesions were nonpruritic nontender, erythematous to violaceous maculopapular, and nodular of varying size scattered all over the trunk, abdomen, upper back, proximal arm, and thigh. The largest lesion over the trunk was approximately 3x3cm. (Figure 1) Lesions were gradually increasing in size and pigmentation. There was no history of fever, weight loss, easy fatigabilitys and cough. On examination, there were multiple erythematous to violaceous macular patches, papules, and nodules over the trunk, abdomen, upper back, proximal arm, and thigh. The remaining general and systemic examinations were within normal limits. On laboratory evaluation, his complete blood count and bone marrow examination were within normal limits.

This patient underwent excision biopsy from skin lesion over trunk which on morphological examination showed basket wave hyperkeratosis and slight irregular acanthosis in the epidermis. There was a dense pan dermal infiltrate composed of medium to large atypical cells displaying a high N/C ratio, round to irregularly contoured nuclei, finely dispersed chromatin, conspicuous nucleoli, and scant cytoplasm. Atypical cell infiltration into the subcutis was consistent with leukemia cutis. (Figure 2)

Immunohistochemical (IHC) staining was suggestive of atypical cells that were diffusely positive for CD34 and MPO (patchy). (Figure 3 and 4) Ki67 was 70-75%. LCA showed weak patchy positivity among atypical cells. Minor populations of reactive lymphoid cell population were seen in the background showing positivity for CD3 CD20 CD4 CD8 CD5 and negative for TDT CK CD30 CD56 CD68 CD117 consistent with LC.

Bone marrow culture metaphase karyotype showed balanced reciprocal translocation between the long arm of the chromosome 16 and 22 between the regions q23 and q13 respectively {karyotype 46 XY, t16;22) (q23; q13)}. (Figure 5) Fluorescent in situ hybridization (FISH) inv16, t(4;11), t(9;11), t(8;21), t(15;17), t(9;22) were not detected. So the diagnosis of aleukemic LC was made. The patient was treated with 7+3 (cytarabine 7 days plus daunorubicin 3 days) AML-specific chemotherapy. Post-chemotherapy on day 21 there was a significant reduction in size, induration, and pigmentation of the skin lesions. (Figure 6)

To document remission whole-body ^{18}FDG PET CT was done, which was suggestive of low-grade FDG avid ill-defined soft tissue thickening along the subcutaneous plane of the right anterior chest wall in the infraclavicular region (SUVmax 2.4), and left lower anterior chest wall (SUVmax 2.5) possibility of neoplastic etiology. Low-grade FDG avid ill-defined soft tissue thickening involving the subcutaneous plane of the sole of right foot at the level of 1st toe inflammatory etiology likely. No evidence of

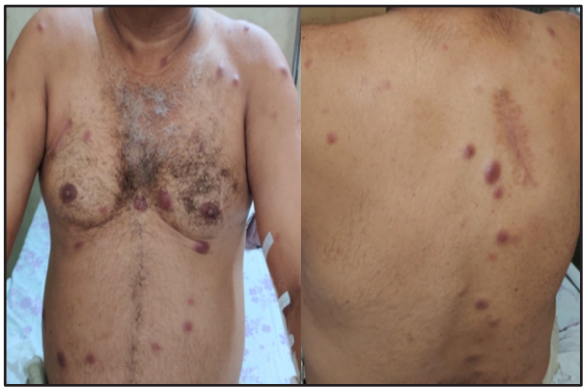

Figure 1: Erythematous to violaceous maculopapular and nodular lesions of varying size over trunk, abdomen, upper and lower back seen at the time of presentation

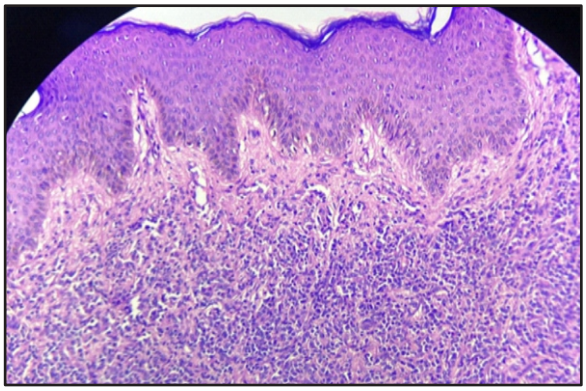

Figure 2: Skin excisional biopsy Hematoxylin and Eosin stain-Dermis showing diffuse infiltration of malignant tumor cells of varying sizes. The tumor cells are medium to large with an increased N:C ratio and irregular nuclear contour. (magnification 200x)

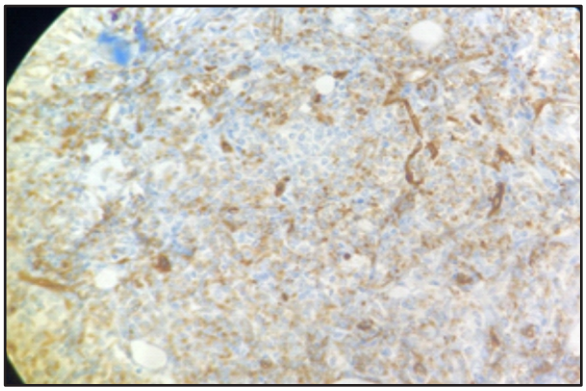

Figure 3: Immunohistochemistry staining-CD 34 positive staining (magnification 100x)

metabolically active disease elsewhere in the body. Repeat biopsy was done from the left anterior chest wall, suggestive of no residual tumor evidence. His Lumbar puncture was negative for malignant cells. After remission documentation cytarabine consolidation was started. The patient has received 2 dosages of intermediate-dose cytarabine as a consolidation therapy till date currently he is clinically well and shows no evidence of disease. The patient has been counselled for the potential role of

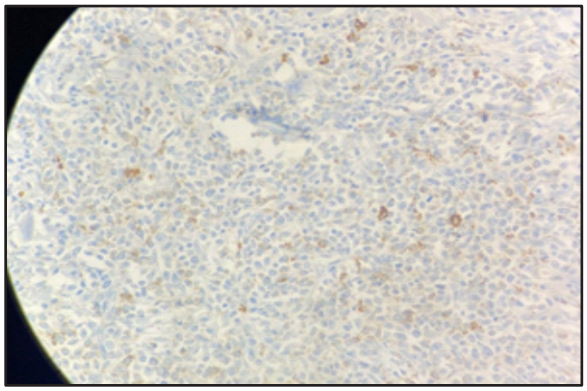

Figure 4: Scattered cells with cytoplasmic MPO positive (magnification 100x)

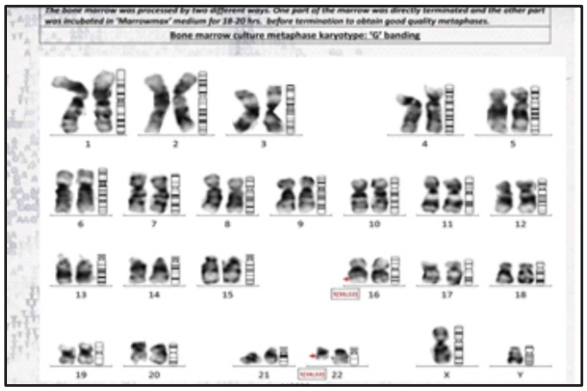

Figure 5: Cytogenetics -46XY, t(16;22)(q23;q13)

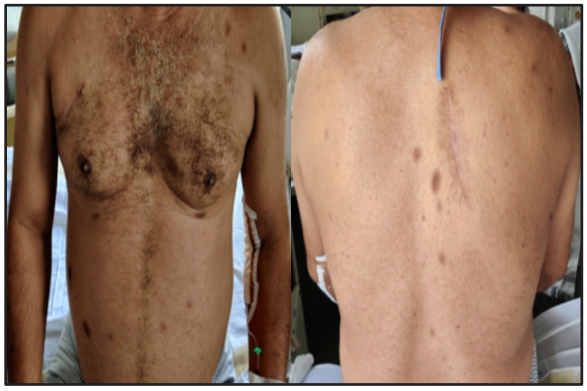

Figure 6: Significant reduction in size, induration, and pigmentation of lesions seen on post-induction chemotherapy day 21

allogeneic hematopoietic stem cell transplantation (HSCT).

Discussion

AML can present as an EM disease without bone marrow disease.[1] EM presentation is a very rare scenario and presents diagnostic challenges. There are two EM manifestations of acute leukemia (1) MS and (2) LC.

MS is a rare EM tumor of immature myeloid cells.[1] The term was first coined in 1811[2] and later called "chloroma" by King[3] in 1853 due to its green color caused by the presence of myeloperoxidase.[3]

LC occurs due to infiltration of the skin by the leukemic myeloid cells resulting in a nodular rash which is also known as cutaneous granulocytic sarcoma.[1] It is seen with higher frequency in children than adults. Approximately 25-30% of infants with congenital leukemia presents with skin involvement,[4] two-third of which are AML.[5] LC is seen in approximately 3% of patients with AML and uncommonly in chronic myeloproliferative diseases.[6] Approximately 50% of cases are of acute myelomonocytic leukemia or acute monocytic leukemia, also known as FAB subtypes AML M4 and M5 respectively.[6]

The usual mode of presentation of LC is as a diffuse papulonodular rash that is more common on the lower limbs followed by upper limbs and then the trunk.[1] AML can also presents with wide range of non-specific skin lesions such as are macules, papules, vesicles, pyoderma gangrenosum, vasculitis, neutrophilic dermatitis (Sweet syndrome), cutis verticis gyrata, and erythema multiforme or nodosum.[7] LC can present with, following, or very seldomly preceding systemic leukemia.[8] When it precedes systemic leukemia it is called "aleukemic leukemia cutis"(ALC).[8] Due to the non-specific presentation of the disease, the skin biopsy can be extremely helpful in the diagnostic work-up,[9] which on histopathology appears as diffuse infiltration of large cells with large nuclei and plentiful cytoplasm (myeloblast).[1] For confirmation of the diagnosis IHC stains, flow cytometry, FISH, and molecular analysis plays a crucial role.[1] Isolated EM AML is considered as a forerunner of medullary AML. Median time to progress to medullary AML ranges from 5-12 months.[1]

In our case, the patient has consulted a dermatologist at a private hospital and took treatment for around 1 month. After not seeing any improvement dermatologist advised to do a biopsy of the skin lesion, which was suggestive of atypical myeloid cell infiltration. He was referred to a private oncology hospital for further treatment, where IHC was done, suggestive of leukemia cutis. After that, patient has consulted our hospital for further treatment. ALC must be differentiated from other lymphoproliferative disorders by doing the IHC test.[7] In our case, the IHC report demonstrated positivity for CD34 and MPO, which was confirmative of the diagnosis of LC.

The management of isolated EM AML is similar to medullary AML with remission induction therapy. The goal is to eradicate EM leukemia and any clinically obscure disease in the marrow.[10] There is no predefined consolidation approach but chemotherapy-based consolidation can be considered in fit patients.[10] The role of allogeneic HSCT has not been evaluated very well in this setting but it is an option for fit patients who can tolerate the procedure. The aim should be eradicating the systemic disease with intensive chemotherapy and/or HSCT.[10] At present, the recommendation is to consider treatment similar to that of patients with the medullary disease.[10] When HSCT is not planned, a patient needs to be treated like conventional AML-type chemotherapy according to standard age, cytogenetic, and molecular-based risk stratifications.[11] LC in patients with AML is associated with decreased overall survival and leukemia-specific survival suggestive of poor prognosis.[12]

Conclusion

Aleukemic leukemia cutis is a very rare presentation of AML. High suspicion, early diagnosis, and treatment can have good outcomes. At present, there are very few case reports of this rare entity so large randomized studies comparing various treatment modalities are the need of the hour.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

References

1. Solh M, Solomon S, Morris L, Holland K, Bashey A: Extramedullary acute myelogenous leukemia. Blood Rev 2016; 30:333-339
2. Burns A: Observations of Surgical Anatomy in Head and Neck. Edinburgh, United Kingdom Thomas Royce & co 1811;364-366
3. King A: A case of chloroma. Monthly J Med 1853; 8:97-104
4. Resnik KS, Brod BB: Leukemia-cutis in congenital leukemia analysis and review of the world literature. Arch Dermatol 1993; 129:1301-1306
5. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F: Leukemia cutis. Am J Clin Pathol 2008; 129:130-142
6. Agis H, Weltermann A, Fonatsch C et al: A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. Ann Hematol 2002; 81:90-95
7. Yonal I, Hindilerdenc F, Coskun R, Doganb O I, Nalcaci M: Aleukemic Leukemia Cutis manifesting with disseminated nodular eruptions and a plaque preceding acute monocytic

leukemia: A Case Report. Case Rep Oncol 2011; 4:547–554
8. Su WP: Clinical, histopathologic, and immunohistochemical correlations in leukemia cutis. Sem in Dermatol 1994; 13:223-230
9. Du X A, Hung T, Surmanowicz P, Gniadecki R: Diagnostic challenge of aleukemic leukemia cutis preceding acute myelogenous leukemia: A case report. JCMS Case Reports 2020; 8: 1–4
10. Dohner H, Estey EH, Amadori S et al: Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European Leukemia Net. Blood 2010; 115:453–74
11. Burnett A, Wetzler M, Lowenberg B: Therapeutic advances in acute myeloid leukemia. J Clin Oncol 2011; 29:487-494
12. Wang CX, Pusic I, Anadkat MJ: Association of leukemia cutis with survival in acute myeloid leukemia. JAMA Dermatol 2019; 155:826-832