Leukemia Cutis in Relapsed Acute Myeloid Leukemia: A Call for Distinct Classification

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Patient: Female, 56-year-old
Final Diagnosis: Leukemia cutis in the setting of relapsed acute myeloid leukemia
Symptoms: Anemia • lethargy • shortness of breath • thrombocytopenia
Clinical Procedure: —
Specialty: Oncology

Objective: Rare coexistence of disease or pathology
Background: Acute myeloid leukemia is characterized by dysregulated proliferation and maturation arrest of myeloid precursors, precipitating a spectrum of complications. Among these, leukemia cutis refers specifically to ectopic deposition and proliferation of malignant myeloid cells within the skin. This infiltration pathogenesis remains unclear. Although there are numerous reports of leukemia cutis in the setting of acute myeloid leukemia or primary acute myeloid leukemia, there are no specific reports of leukemia cutis in the setting of relapsed acute myeloid leukemia.

Case Report: A 59-year-old woman, with a history of remission from poor-risk acute myeloid leukemia, previously treated with chemotherapy and allogenic bone marrow transplant, presented with shortness of breath, lethargy, anemia, thrombocytopenia, and subcutaneous nodules on lower extremities. Leukemia cutis was diagnosed, in the setting of relapsed acute myeloid leukemia. After unsuccessful salvage chemotherapy and being deemed unsuitable for further treatment, she pursued palliative care and died a month later.

Conclusions: Our case highlights a lack of reporting or making a distinction of those patients with relapsed acute myeloid leukemia and leukemia cutis. Consequently, it can be deduced that patients who simultaneously have relapsed acute myeloid leukemia and leukemia cutis are expected to fare worse in terms of clinical outcomes than those with primary acute myeloid leukemia and leukemia cutis. Relapsed acute myeloid leukemia patients with leukemia cutis should be classified as a distinct group, warranting further research into aggressive therapeutic targets and survival rates, while emphasizing the need for more vigilant follow-up and lower biopsy thresholds for cutaneous lesions in patients with treated hematologic malignancies.

Keywords: Recurrence • Leukemia, Myeloid, Acute • Leukemia • Skin Manifestations

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Introduction

Acute myeloid leukemia (AML) is an uncompromising disease of clonal hematopoiesis and progenitor cells, where these hematopoietic forerunners are halted in an early stage of development. As such, this arrested development leads to diminished production of normal blood cells, resulting in anemia, neutropenia, and thrombocytopenia. Leukemia cutis (LC) is the manifestation of the infiltration of these neoplastic leukocytes to the cutaneous surface. The pathogenesis of specific migration of leukemic cells to the skin is unclear. Some suggested mechanisms involve the expression of intercellular adhesion molecule 1, CD56 expression, and cutaneous lymphocyte-associated antigen expression [1-3].

Also, AML displaying monocytic characteristics exhibit a higher prevalence of nucleophosmin (NPM1) mutations than do AML without monocytic features (36% vs 20%, P<0.0001) [4]. In the monocytic AML cohort, 74% of patients with LC have NPM1 mutations, whereas only 32% of patients without LC have these mutations [4]. These findings suggest there is a significant association between the presence of mutated NPM1 and the development of LC within the monocytic AML subgroup [4]. Although there are numerous reports of LC in the setting of AML or primary AML, there are no reports of LC with specifically relapsed AML [5]. Herein, we report a case of LC in a setting of relapsed AML.

Case Report

A 59-year-old woman presented with shortness of breath, lethargy, anemia, and thrombocytopenia. She also developed subcutaneous nodules over both lower extremities over a month. The lesions continued to develop from small papules to tender violaceous hyperpigmented nodules, with some ulcerations on both lower extremities (Figure 1A, 1B). The tissue culture grew fungal elements but no bacteria or acid-fast bacillus.

Three years ago, she was diagnosed with poor-risk AML with translocation (3;3)(q21;q26.2) with 36% myeloblasts by bone marrow biopsy. Molecular studies revealed negativity for NPM1 Exon 12 frameshift mutation, FLT3/ITD mutation, and FLT3 D835 mutation. She was started with induction chemotherapy with idarubicin and cytarabine (7+3) with no response, followed by FLAG (fludarabine, cytarabine, and G-CSF) reinduction with complete remission, followed by reduced-intensity conditioning with intravenous fludarabine, busulfan, and rabbit ATG, followed by a full match unrelated allogeneic bone marrow transplant. She did well after allogeneic stem cell transplant, was off immunosuppressive medications, and stayed in remission for 3 years. At her first diagnosis of AML and treatment, she never developed cutaneous lesions.

After her relapse of AML, she was given decitabine and venetoclax for salvage chemotherapy. As stated before, she was noted on treatment to have new skin lesions. A skin biopsy specimen from the lower extremities revealed an acute myelogenous leukemia cutis with myelomonocytic differentiation (Figure 1C). She was given a French-American-British classification of M4 (acute myelomonocytic leukemia). Immunoperoxidase studies revealed atypical mononuclear cells that expressed CD43, but not CD3 or CD20. The atypical cells were also variably immunoreactive for myeloperoxidase (Figure 1D), lysozyme, and CD69. Ki-67 revealed a proliferation fraction of approximately 40%. The aspirate from a bone marrow biopsy revealed a hypercellular marrow for age, featuring left-shifted myeloid lineage with decreased erythropoiesis and increased megakaryocytes with dyspoietic features, such as clustering. CD34 immunostain highlighted 2% to 3% myeloblasts. The concurrent flow cytometric analysis revealed 3.6% medium to large cells with the following aberrant immunophenotype: CD45(moderately+), CD13(+), CD33(+), CD34(+) CD117(+), HLA-DR(-), CD38(-), CD15(+), CD4(subset dim+), CD14, CD64(-), and CD56(-). These findings were consistent with a persistent AML. Cytogenetic studies demonstrated a consistent presence of the (3;3)(q21;q26.2) translocation. DNA and RNA extracted from her bone marrow specimen revealed no specific mutations, including the NPM1 mutation. Despite several cycles of decitabine and venetoclax for 6 months, her disease had progressed. Following a multidisciplinary discussion, she was determined not to be a candidate for further chemotherapy. She pursued palliative home hospice care and eventually died.

Discussion

AML relapses can take place in all patients who achieve remission after initial treatment and can occur months to years after treatment. Commonly, relapsed or refractory AML has amplified therapeutic resistance and abysmal long-term survival rates [6]. The acquisition of clones with additional mutations has been proposed as a mechanism of resistance in targeted therapy [7]. Moreover, patients with LC in the setting of AML have greater extramedullary involvement and decreased overall survival than do those patients with AML and the absence of LC [5]. In a comparative analysis of survival rates, the 5-year survival rate among the 62 patients presenting with AML accompanied by LC was found to be 8.6%. In contrast, the rate was significantly higher at 28.3% for the 186 matched patients diagnosed with AML without the presence of LC [5].

Our patient presented with LC in a setting of a relapsed AML and had a poor outcome. Patients with AML who present with LC exhibit a poorer prognosis than those without this cutaneous manifestation [5]. Additionally, individuals with relapsed AML tend to experience worse survival rates than those with primary AML [6]. Consequently, it can be deduced that patients who simultaneously have relapsed AML and LC are expected to fare worse in terms of clinical outcomes than those with
primary AML and LC. In the literature, many cases of LC do not distinguish its source between relapsed or primary AML [5,8]. However, since LC is a poor prognostic sign for AML and other leukemias [5], treatments of relapsed AML may need more therapeutic targets than primary AML [9,10]. Early treatment initiation for patients with AML predicts survival outcomes [11-13].

Conclusions

We suggest that patients with relapsed AML who have LC may have beneficial utility in their disease state being classified as a distinct group. With this recognition of a distinctive class, reporting of cases of LC with relapsed AML will be further delineated. Moreover, research should look at the overall survival rates of AML patients and LC, compared with those with relapsed AML and LC. The acknowledgment of this distinction may provide the impetus for evaluating even more aggressive therapeutic targets in patients with LC with relapsed AML or other relapsed leukemias.

Declaration of Figures’ Authenticity

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