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Case Report

Leukemia Cutis in a Patient with Acute Myeloid Leukemia Undergoing Azacitidine-Venetoclax: Case Presentation and Review of the Literature

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Abstract. Leukemia Cutis (LC) in acute myeloid leukemia (AML) is typically managed within the context of systemic AML therapy, namely intensive chemotherapy (IC). In frail patients, though, viable options are hypomethylating agents (HMAs) associated with Venetoclax (VEN), but data on the efficacy of this approach in this specific setting is scarce. Here, we report our experience and provide a short review of the previous cases of LC treated with HMAs plus VEN to underline the efficacy of such treatment in LC patients who are unsuitable for IC.

Keywords: Leukemia cutis; Acute myeloid leukemia; Demethylating agents; Venetoclax.

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Introduction. The term leukemia cutis (LC) refers to the cutaneous infiltration of neoplastic leukocytes and encompasses a wide range of manifestations, including papules, nodules, plaques, erythema, and ulcers.[1]

Cutaneous involvement in hematologic malignancies, especially in leukemia, generally carries an unfavorable prognosis,[2] but opinions are conflicting.[3,4]

Commonly observed in chronic lymphocytic leukemia[1] and chronic myeloid leukemia (4-27%),[5] it is the most frequent extramedullary localization in AML and considered a sanctuary for leukemic cells, it occurs in 3-6% of acute myeloid leukemia (AML); but some reports show an incidence of up to 50% in myelomonocytic and monocytic types.[6,7] When associated with AML, LC is typically managed according to standard protocols; however, the efficacy of novel agents in this specific patient population remains largely unknown.

Herein, we report a case of a 58-years-old female patient with AML who was admitted to our Hospital in January 2024 because of skin lesions consistent with leukemic infiltrates and was consequently treated with Azacitidine plus Venetoclax (AZA-VEN).

Case presentation. In January 2024, a 58-year-old female patient underwent a hematological examination because of cutaneous nodules previously biopsied at another center whose histopathological findings were

consistent with leukemic infiltrates. The lesions primarily appeared on the arms and then spread extensively to the chest area. The patient reported no constitutional symptoms (e.g., fever, night sweats, or weight loss). Medical history was remarkable for chronic obstructive pulmonary disease (COPD) due to a 30-year smoking habit requiring triple inhalation therapy. Furthermore, she was previously affected by De Quervain disease, for which she underwent surgery. Physical examination revealed generalized violaceous and hard nodules on the entire body except the face (**Figure 1**). Laboratory tests showed a reduced leukocyte count (WBC = $2.92x10^6$/L), normal platelet (PLT) count ($264x10^9$/L) and hemoglobin (Hb) level (12.2 g/dl), a prolonged activated partial thromboplastin time of 50.9 sec and elevated D-dimer (>20.000 ng/ml), low level of fibrinogen (89 mg/dl), and elevated lactate dehydrogenase (1054 U/L). Total Body Computed Tomography scan showed no involvement of other organs, whereas pulmonary function testing was consistent with a very severe COPD.

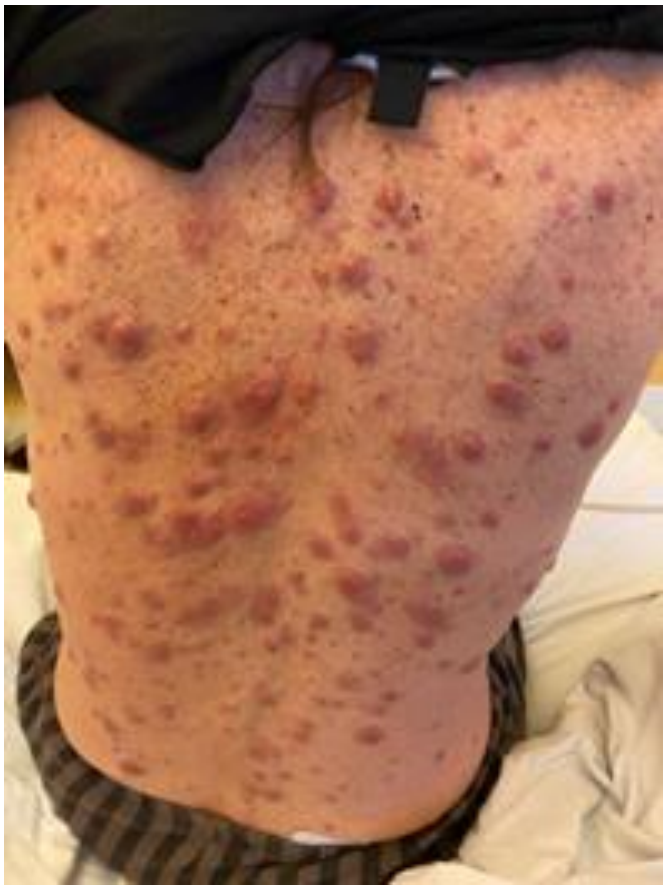

Figure 1. Before treatment.

The bone marrow (BM) morphologic examination revealed a 70% blast infiltrate. Flow cytometry (FCM) evaluation resulted in the following pattern: CD45+, CD34-, CD33+, CD117-, CD13+, CD56+, CD15+, CD64+, MPO+, CD4+. The molecular genetic analysis revealed mutations in nucleophosmin1 (*NPM1*) and isocitrate dehydrogenase1(*IDH1*) genes. Cytogenetics analysis failed because of the absence of metaphases in the examined sample, and FISH showed no aberrations involving chromosomes 5, 7, 8, 11, and 20. To exclude a possible central nervous system (CNS) involvement, we performed a lumbar puncture and then examined cerebrospinal fluid (CSF) using conventional cytology and FCM, both of which resulted in negative.

According to the AML-Composite Model (AML-CM),[8] the patient was considered unsuitable for intensive chemotherapy (IC); hence, she received treatment with Azacytidine (given at 75 mg/m^2 intravenously on days 1–7) plus Venetoclax (given at 100 mg on day 1, 200 mg on day 2 and 400 mg on day 3-28). At the end of the first cycle, the patient showed a peripheral hematologic recovery (WBC $1.79x10^6$/L, neutrophils $1.03x10^6$/L; Hb 8.9 g/dl, PLT $330x10^9$/L). Concomitant to the hematologic recovery, the skin lesions were reduced in size, number, and consistency. BM examination demonstrated a complete morphological remission (CR).

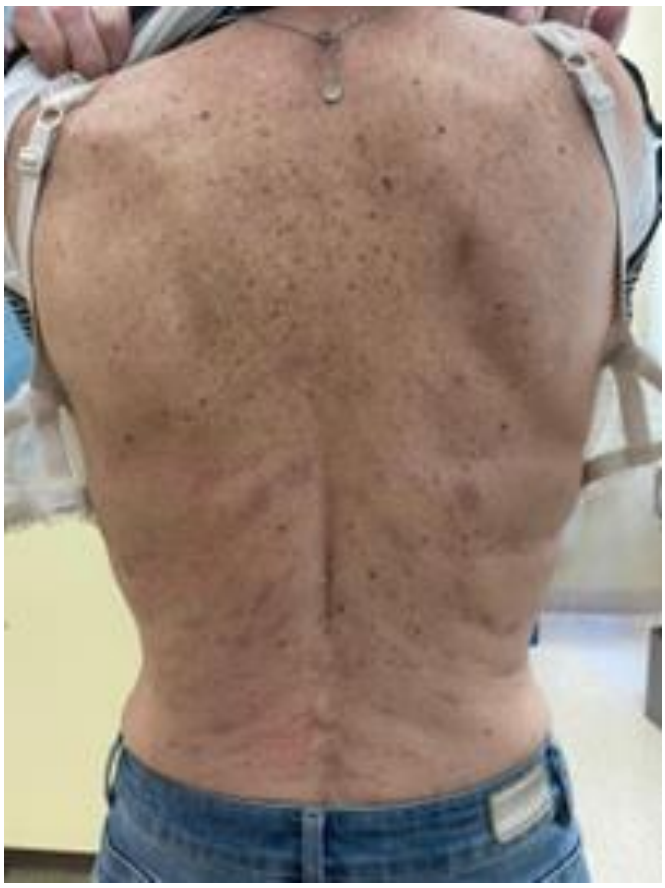

Figure 2. After 6 cycles of AZA-VEN

At this stage, the *NPM1* copy number was 123.2333/10.000 of ABL in BM and 24.876/10.000 of ABL in the peripheral blood. The therapy was continued, and by cycle no. 6, a complete resolution of the skin lesions was achieved with a persistent condition of BM morphologic CR and positive, measurable residual disease (MRD) (**Figure 2**). No temporary or permanent

interruptions due to toxicity were reported. Since LC is prone to be associated with CNS infiltration and little is known about the attitude of VEN to cross the blood-brain barrier, we decided on a monthly schedule of medicated lumbar punctures. The patient is still alive at eleven months from therapy starting, in MRD positive CR, and receiving her IX cycle.

Discussion. The recommended treatment for patients with AML and LC is conventional IC followed by a consolidation program defined according to NCCN or ELN risk allocation.[9] In this context, skin infiltration is not recognized as having a specific prognostic role. Some have reported approaches for LC like modulatory therapy,[10] radiotherapy,[11] and total skin electron beam.[12]

The therapeutic decision is usually determined by factors such as age, performance status, cytogenetics, and molecular markers,[13] but it is also essential to consider the patient's comorbidities. To decide the best treatment, the use of AML-CM, a risk-stratifying model incorporating comorbidities, age, cytogenetic, and molecular risks, allows patients to be divided into four groups based on mortality risk. Our patient, with a score of 8, belonged to the 3rd group, namely moderate-high risk of mortality. Consequently, our purpose was to deliver a therapy as effective as possible with the lowest amount of toxicity.

Currently, in the landscape of new target drugs, the addition of VEN to hypomethylating agents (HMAs) has proven to be effective in both newly diagnosed and relapsed/refractory AML,[14,15] with a good safety profile.[16] Then, it is increasingly recognized as the preferred treatment option for patients deemed unfit for IC. Moreover, VEN has demonstrated efficacy in addressing extramedullary involvement of AML[17,18] and in patients with chronic lymphocytic leukemia with skin infiltrates.[19] However, in the context of this specific AML extramedullary disease localization, the impact of demethylating agents associated with VEN remains largely unknown.

Pubmed research using a Boolean combination of the words "leukemia cutis", "cutaneous extramedullary leukemia", "cutaneous myeloid sarcoma", and "venetoclax" showed only eight previous reports of LC treated with HMAs associated with VEN (HMAs-VEN) (**Table 1**).[18,20–23] In 62% of them, skin involvement was concomitant to AML diagnosis; instead, 25% of the cases were relapsed/refractory AML. *NPM1* was the most frequent molecular alteration in this setting (50%). The preferred hypomethylated agent was decitabine, used in 62% of the cases. In half of the reported patients and in our experience, the association was effective and led to a complete response. In our case, AZA-VEN was well-tolerated, with an improvement in the patient's quality of life.

Therefore, HMAs-VEN appears to be a viable combination for AML with skin involvement in patients ineligible for IC. However, randomized studies are needed to establish the appropriate dosage and duration schedule. The question remains as to whether the association will be capable of maintaining a sustained remission in both BM and skin.

Finally, extramedullary disease is known to be associated with CNS spreading,[6,24,25] and intensive chemotherapy protocols are able to sterilize CSF to improve prognosis and prevent CNS seeding. However, in the context of non-intensive treatment, the ability to overcome the blood-brain barrier is still a matter of debate. Thus, even if reports suggest that VEN might reach a therapeutic concentration in CSF,[26,27] we decided to apply CNS prophylaxis with medicated lumbar punctures.

Conclusions. Skin has always been considered a sanctuary for leukemic cells, therefore the optimal management of AML with LC is not established yet. Our case showed the positive effect of HMAs-VEN on LC despite the short follow-up. This association has proven to be a promising treatment for patients unable to undergo IC, even though accumulating experience and further studies are needed to establish HMAs-VEN as a reliable treatment option in this category of patients.

Data availability. All relevant data are included in this article. For additional data inquiries, an additional request can be directed to the corresponding author.

Table 1. Review of the literature.

Author	Age and sex	AML setting	HMA type	Treatment response	Karyotype or molecular abnormalities
Otoukesh et al 2020	M 74 y	Newly diagnosed AML	Decitabine	CR	46 XY, del(11)(q23), *FLT3-TKD*
	F 78 y	Newly diagnosed AML	Decitabine	Refractory	*NPM1*
	M 50 y	R/R AML	Decitabine	CR	Complex karyotype
	M 76 y	Newly diagnosed AML	Decitabine	Refractory	46 XY, del(12)(p11q13), *FLT3-ITD*
Wang et al 2020	M 58 y	R/R AML	Azacitidine	Refractory	*IDH1*
Maravalle et al 2022	F 74 y	Post remission AML	Decitabine	CR	*NPM1, FLT3-TKD*
Selan et al 2023	M 70 y	Newly diagnosed AML	Azacitidine	Early death	*NPM1*
Niscola et al 2023	M 81 y	Newly diagnosed AML	Azacitidine	CR	*NPM1*

AML: acute myeloid leukemia; HMA: hypomethylating agents; M: male; F: female; CR: complete remission; R/R: relapsed/refractory.

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