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Acute myeloid leukemia cutis with KMT2A::MLLT3 fusion presenting with leonine facies

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ABSTRACT

A 63-year-old woman presented with plaques covering 60 % body-surface-area and leonine facies. Blood work showed no diagnostic aberrancies. Skin biopsy contained a malignant CD4+/CD56+ mononuclear cell population concerning for blastic plasmacytoid dendritic cell neoplasm. A later bone marrow biopsy confirmed AML with *KMT2A::MLLT10* fusion detected by next-generation sequencing (NGS). This patient's LC preceded blood and marrow based symptoms of AML. NGS of the initial skin biopsy should be considered as part of diagnostic guidelines in cases with LC in the differential as this may have led to earlier diagnosis in this case and future cases.

1. Introduction

We present a case of a patient with rapidly progressive pruritic cutaneous plaques and leonine facies. The differential included cutaneous sarcoidosis, blastic plasmacytoid dendritic cell neoplasm (BPDCN), NK/T-Cell Lymphoma, or adult T-cell leukemia lymphoma. The rash developed several months prior to diagnosis of acute myeloid leukemia (AML) with *KMT2A*::*MLLT3* fusion confirmed by bone marrow biopsy. Leonine facies is a rare presentation for AML, though it has been reported in the literature [1].

Leukemia Cutis (LC) is a neoplastic leukocyte infiltration of the skin that may manifest as papules, nodules, infiltrative plaques, macules, ecchymoses, purpura or ulcerated lesions. Typically LC develops at the time of a new leukemia diagnosis or shortly thereafter (82–95 %), and rarely precedes the more typical symptoms of blood/marrow involvement. These cases are referred to as aleukemic LC or myeloid sarcoma [2]. There are few guidelines for the diagnostic workup of aleukemic LC.

2. Case

A 63-year-old woman presented with scattered, pruritic papules reminiscent of mosquito-bites on her back. She was treated with triamcinolone cream but the lesions progressed in size and quantity. She also developed alopecia of the forearms, eyebrows, and underarms, along with headaches, nausea, and vertigo. Over four months the lesions became confluent, covering the face, neck, back, chest, abdomen, proximal arms, and legs.

She had a history of psoriasis and colon cancer, treated seven years prior with subtotal colectomy, adjuvant 5-Fluorouracil, leucovorin and oxaliplatin, and radiation therapy. She was on medication for hypertension and hyperlipidemia. The physical exam showed coalescing blanching red smooth infiltrative papules in the distribution described above. Collectively the lesions covered about 60 % of her body-surface-area (Fig. 1).

Initial bloodwork was significant for WBC 3.1 × 10^3/μL (55 % neutrophils, 38 % lymphocytes, 5 % monocytes, 2 % eosinophils), Hgb 14 g/dL, and LDH of 227 U/L. No blasts were in peripheral circulation, and the blood film lacked microscopic abnormalities. Punch biopsies of lower back and medial breast lesions showed dense, monomorphous dermal infiltrates composed of immature, mononuclear cells in a myxoid stroma. The cells expressed CD4, CD45, CD56, CD68, and lysozyme and were negative for myeloperoxidase, CD2, CD3, CD20, CD34, CD117, and

Abbreviations: LC, Leukemia Cutis; AML, Acute Myeloid Leukemia; BPDCN, Blastic Plasmacytoid Dendritic Cell Neoplasm; NGS, Next Generation Sequencing.

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CD123 (Fig. 2). A subsequent PET/CT scan showed that the diffuse nodular dermal thickening was FDG avid, and also diffusely increased marrow activity. The initial bone marrow biopsy was nondiagnostic due to inadequate sampling. A repeat bone marrow sample was collected two weeks later. The blood still lacked leukemic blasts, the aspirate was aparticulate, but the core biopsy was adequate and showed atypical leukocytes that expressed CD4, CD33, CD43, CD45, CD56, CD68, and lysozyme. FLT3 testing on marrow aspirate returned indeterminate. Next-generation sequencing (NGS) was subsequently performed on the skin biopsy as there were insufficient neoplastic cells in the blood and aspirate, which identified a *KMT2A*::*MLLT10* fusion. The WHO and ICC groups both recognize *KMT2A* rearrangement as a defining genetic abnormality permitting a diagnosis of AML with *KMT2A* rearrangement, an AML subtype that usually has myelomonocytic or monoblastic features. Lumbar puncture was negative for any signs of CNS disease.

The patient was hospitalized and treated with 7 + 3 six months after the initial onset of the rash. She had a prolonged pancytopenia, with repeat bone marrow biopsies at day +17 and +26 showing hypocellularity (<5 % hematopoietic elements) and no abnormal blasts. There was an immense improvement in the patient's rash without complete resolution. A bone marrow biopsy on day +34 showed increased cellularity (40–50 %) with elevated blasts at 5–10 %. A repeat skin biopsy on day +41 showed persistent LC. A day +52 bone marrow biopsy was relatively hypercellular at ~60 %, but lacked morphologic evidence of involvement by leukemia. Due to persistent LC she was started on decitabine and venetoclax, which produced a durable remission in another case of recurrent extramedullary AML/LC [3]. The rash continued to progress, she received total skin electron beam therapy (TSEB) for a total dose of 2400 cGy [4]. A follow up skin biopsy showed subtle features of persistent LC. The bone marrow biopsy procured after the completion of TSEB showed 33 % blasts consistent with a frank AML relapse. *FLT3*-ITD remained negative, and no clonal evolution was identified.

167 days after the first induction, she underwent another re-induction with fludarabine, idarubicin, cytarabine and venetoclax (FLAG-IDA + Ven) [5]. This attempt was complicated by a neutropenic MSSA bacteremia, as well as respiratory failure. Nodular opacities were noted in the lung, but workup with a bronchial-alveolar lavage failed to detect a bacterial or fungal cause. The nodules were presumed to be malignant. The day +21 bone marrow following this reinduction showed 10 % cellularity and a persistence of an aberrant CD56+ monocytoid population, consistent with residual disease. The marrow collected day +32 of re-induction was ~40–45 % cellular, and the abnormal myelomonocytic cells represented 55 % of the cellular elements. The situation was discussed with the patient and her family on day +34, and she decided to transition to hospice care. She subsequently passed on day +36.

3. Discussion

This rare presentation of cutaneous plaques, ambiguous skin biopsy findings and a relatively normal CBC, initially led to a broad differential. Rapidly progressive erythematous plaques and leonine facies are classically associated with lepromatous leprosy, but may also be seen in mycosis fungoides, cutaneous sarcoidosis, blastic plasmacytoid dendritic cell neoplasm, NK/T-Cell Lymphoma, adult T-cell leukemia lymphoma, and leukemia cutis [1].

This patient's skin findings preceded any hemogram or bone marrow abnormalities, markedly reducing suspicion for an AML diagnosis. In one retrospective review of 50 LC cases, AML was not the favored diagnosis 65 % of the time, and was not included in the differential prior to biopsy 35 % of the time. Facial rash was observed in 28 % of cases [6]. Our patient's diagnosis was further delayed by an initial non-diagnostic bone marrow sample. If relevant genetic profiling had been obtained from initial skin biopsy samples, an AML diagnosis could have been rendered earlier.

Skin and bone marrow biopsies taken concurrently in myeloid LC patients may sometimes show discrepant immunophenotypic profiles. Some schemas for an algorithmic immunophenotypic workup of skin samples in aleukemic LC cases have been proposed [7,8]; however, skin biopsy-based diagnosis is still difficult, and depends on a multifaceted combination of morphologic and immunophenotypic findings. The most common infiltrative patterns are a periadnexal and perivascular distribution of the neoplastic mononuclear cells, which sometimes resembles more common dermatologic illnesses. Cytologic features of cutaneous AML infiltrates include blastic chromatin, large cleaved nuclei, small nucleoli, and amphiphilic cytoplasm; however, these findings may not be readily discernible on biopsies showing a relatively sparse or polymorphous inflammatory infiltrate [8]. For these reasons, definitive AML classification requires knowledge of the underlying genetic drivers, and molecular studies should be considered whenever the histopathology findings are ambiguous or there is greater clinical suspicion for leukemia cutis than the histopathologic findings seem to substantiate. In our case, the skin findings were so compelling that we suspected neoplasia, albeit definitive categorization was difficult in light of the discordant immunophenotypes.

Immunohistochemistry for AMML includes MPO, lysozyme, CD56, CD68 positive, CD34 and TdT negative [5]. Given our patient's CD4+ and CD56+ skin biopsy and clinical presentation of extensive cutaneous findings BPCDN was initially top on the differential. CD123, CD303, and TCL1 are additional markers that should be evaluated when considering a BPCDN diagnosis [9]. In our case the absence of CD123 expression and

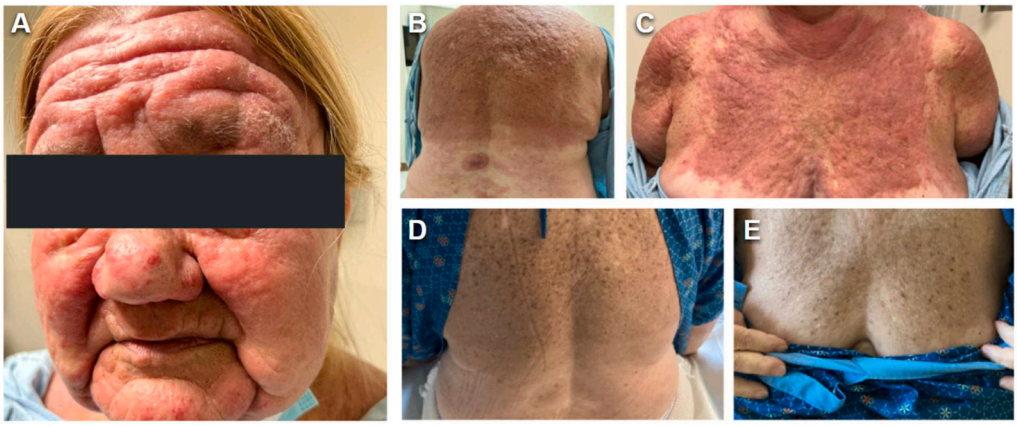

Fig. 1. Extensive pink to red smooth infiltrative papules coalescing into plaques on face, (A) back, (B) and chest (C). Interval improvement of erythematous plaques on back (D) and chest (E) the week after 7 + 3 induction chemotherapy.

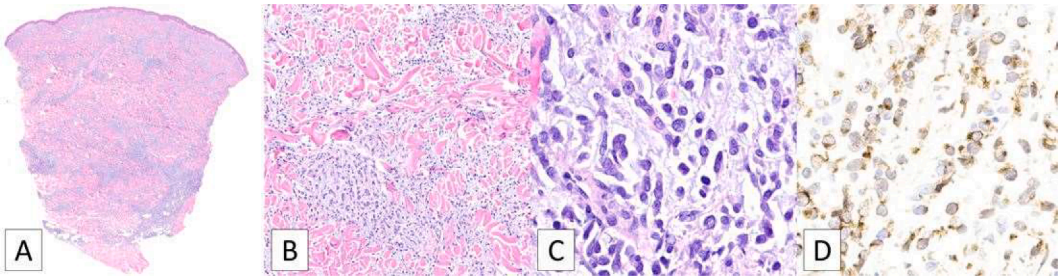

Fig. 2. Skin punch biopsy revealing a dense interstitial infiltrate extending from the superficial dermis to the deep reticular dermis (A, H&E 10x). The infiltrate involved the dermal interstitium in a manner often seen in leukemia cutis (B, H&E 100x). Atypical mononuclear cells exhibiting enlarged, slightly irregular nuclei with nucleoli (C, H&E 400x). Lesional cells stained with lysozyme (D, 400x).

presence of lysozyme argued against BPCDN and increased suspicion for AML/LC. NGS of skin biopsy samples may have aided in earlier diagnosis. This case was a rare presentation of a rare malignancy, possibly with relationship to treatment of prior colon adenocarcinoma. The case demonstrates a possible benefit of management guidelines with earlier assessment of genetics in LC which precedes peripheral or medullary findings.

4. Conclusion

Our patient's aleukemic presentation, extensive cutaneous plaques, and CD4(+), CD56(+), MPO(-) immunophenotype led to greater suspicion for BPCDN than AML/LC. Further IHC staining of skin biopsy samples demonstrated negative CD123(-) and lysozyme(+) which excluded BPCDN and favored monocytoid LC.

NGS has been used to diagnose myelodysplasia cutis [10]. Our patient was found to have a driving KMT2A gene rearrangement at 11q23. NGS of skin biopsy can expedite a diagnosis in LC and negate the shortcomings of immunophenotype based diagnosis. NGS of initial skin biopsy should be considered as part of diagnostic guidelines for cases with suspicion of LC.

Declaration of consent

The patient detailed in this case report was aware of in advance and consented in writing to publication of a case report with inclusion of photographs understanding the risks that details surrounding the case or images could reveal her identity. Her family and surrogate decision maker was also aware and agreed with her decision. The data and images are anonymized to protect her privacy to the best of our ability. The images are important to include due to the chief complaint at presentation of rash. Care was taken in presentation of the images to not be seen as denigrating. Identifying data throughout has been limited and the report is devoid of name, initials, social security numbers, birth date or other identifying information. An image of the patients face was altered to protect anonymity but we do not believe this alters or distorts the scientific meaning of the photograph. She was aware that the images we took of her were in part for publication in this case report.

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Declaration of Competing Interest

The authors have no competing financial or personal interests.

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