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Diagnostic challenge of aleukemic leukemia cutis preceding acute myelogenous leukemia: A case report

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Abstract

Aleukemic leukemia cutis is a rare condition in which malignant white cells invade the skin before they appear in the peripheral blood or bone marrow. It is often associated with a poor prognosis. The condition presents a diagnostic challenge as its manifestations are quite variable terms of lesion type. It can manifest as papules, nodules, and/or plaques, and in rare cases erythematous macules, blisters, and ulcers. The most commonly affected areas of the body are the lower extremities, followed by the upper extremities, back, trunk, and face. Due to the non-specific presentation of the disease, skin biopsy and comprehensive immunohistochemical testing can be extremely helpful in the diagnostic work-up. We describe a case of leukemia cutis presenting prior to acute myelogenous leukemia that was initially misdiagnosed as hyper-IgG4 disease.

Keywords

Aleukemic leukemia cutis, acute myelogenous leukemia

Introduction

Leukemia cutis (LC) refers to the cutaneous manifestations of blood-borne or bone marrow–borne cancer cells. LC can present itself in up to 50% of patients with acute myelogenous leukemias (AMLs) and less commonly in patients with chronic myeloproliferative disease. Skin involvement with acute lymphocytic leukemia (ALL) can be seen in 1.3%–3% of patients and 6%–10% of patients with chronic lymphocytic leukemia (CLL).[1] Clinically significant skin lesions appear as a result of epidermal, dermal, or subcutaneous infiltration by neoplastic white cells.[2] Patients with LC often present with concurrent systemic leukemia, but occasionally cutaneous involvement precedes peripheral blood or bone marrow involvement. This rare presentation is known as aleukemic leukemia cutis (ALC) and is only seen in approximately 5%–7% cases of LC.[3,4] As such, a positive skin biopsy can be the first indication of malignancy in this population of patients.

The clinical presentation of LC is quite variable in terms of lesion type. It can manifest as papules, nodules, and/or plaques, and in rare cases erythematous macules, blisters, and ulcers.[5] The most commonly affected areas of the body are the lower extremities, followed by the upper extremities, back, trunk, and face. Due to the non-specific presentation of the disease, the skin biopsy can be extremely helpful in the diagnostic work-up.

Case report

A 40-year-old male patient presented to our clinic in January of 2017 with a 6-month history of dozens of painful nodules throughout his body (Figure 1), and progressive severe pain in his abdomen and joints. The patient self-reported pain as being 20/10 on a scale from 0 to 10. He had a past medical history of lymphocytic vasculitis and rotator cuff injury.

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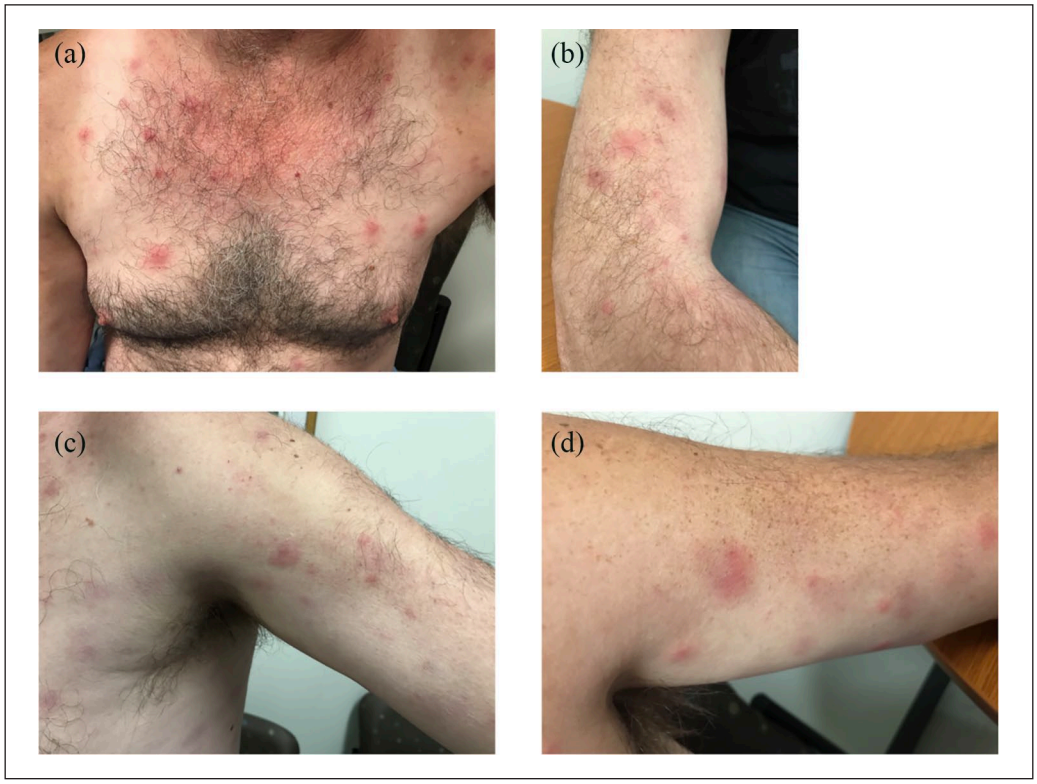

Figure 1. Multiple erythematous nodules of aleukemic leukemia cutis on the patient's (A) chest, (B) left forearm, (C) left upper arm, and (D) left inner arm.

There was no past surgical history on file. His current medication list included azathioprine 100 mg q.d., prednisone 10 mg q.d., and intravenous immunoglobulin therapy.

Physical examination revealed erythematous and painful papules with poorly demarcated borders located bilaterally on the forearms, upper arms, and shoulders. The largest papule measured approximately 1.5 cm in diameter. A punch biopsy performed in 2017 showed a moderate superficial and deep lymphocytic perivascular infiltrate that was interpreted as a vasculopathic reaction. The lymphoid cells were small and showed minimal cytologic atypia (Figure 2).

The patient presented for further follow-up 10 months later with approximately 12 erythematous and painful nodules measuring 2–3 cm in diameter on the arms and chest. The lesions did not show necrosis, macular or retiform purpura, or petechiae.

A second punch biopsy was performed in 2018 with a clinical concern of potential hyper-IgG4 disease. This biopsy showed similar histologic features to the 2017 sampling. Again, a moderate superficial and deep perivascular lymphoid infiltrate was present with minimal cytologic atypia. However, because of the cellularity of the infiltrate and the clinical history of persistent lesions, additional immunohistochemical stains were performed to further investigate the nature of the dermal cells (Figure 3). The lesional cells were positive for CD4, CD45, CD43, CD123, and MPO stains. CD56, CD3, CD61, CD99, CD34, CD138, CD8, CD117, IgG4, and TdT stains were negative. From the skin biopsy, a diagnosis of extramedullary myeloid cell tumor was given. A subsequent bone marrow biopsy showed myelodysplasia, resulting in a diagnosis of acute myelogenous leukemia.

Discussion

ALC is a rare condition in which malignant white cells invade the skin before they appear in the peripheral blood or bone marrow. It is often associated with a poor prognosis, with a mean survival of 3–30 months after cells migrate from the skin to the peripheral blood and bone marrow.[6] Therapy is generally directed at treating the underlying systemic disease. Our case highlights both the clinical and histologic challenges of diagnosing LC, particularly when it precedes the diagnosis of systemic leukemia. The clinical differential diagnosis in our patient included autoinflammatory disease, hyper-IgG4 disease, and urticarial vasculitis. Histologically, because of the superficial and deep perivascular nature of the infiltrate, and the very subtle cytologic atypia, a vasculopathic reaction was initially favored.

The accurate diagnosis LC relies heavily on correlation between clinical, histological, and pathological findings. Leukemic skin infiltrates may be seen as dermal or subcutaneous nodules, or as a densely diffuse interstitial pattern. In patients who have or go on to develop AML, as in the case of our patient, there will typically be invasion of the vasculature and adnexal structures with leukemic cells.[7] Immunohistochemical staining is of utmost importance when there is any clinical suspicion of LC. Co-expression

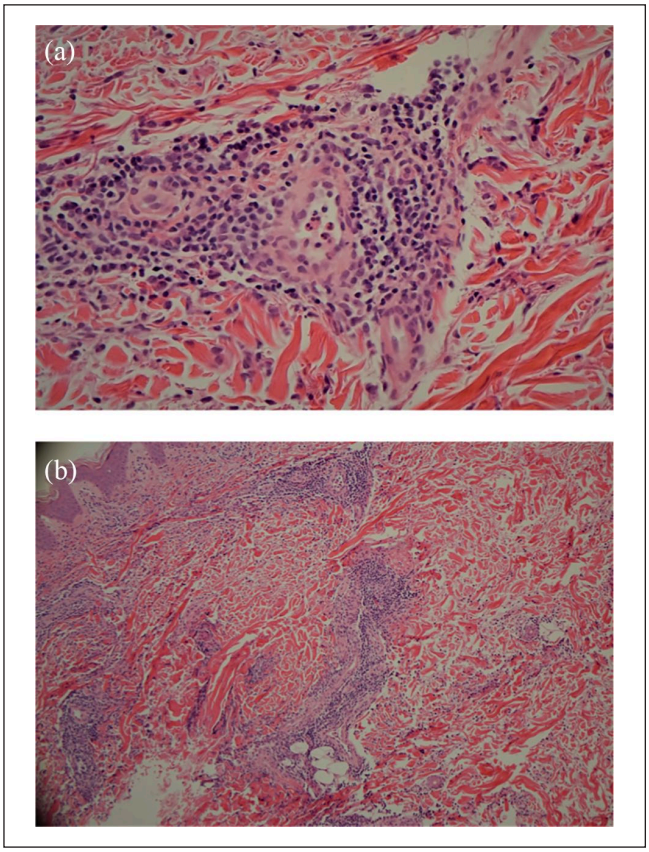

Figure 2. (A) Medium power image highlighting the lack of significant atypia in the small lymphocytes. No mitoses or apoptoses are present. These lymphocytes could be mistaken as a normal reactive perivascular infiltrate. (B) Low power image showing a mild to moderate lymphocytic perivascular infiltrate with minimal cytologic atypia. This is a common pattern for reactive lymphocytic infiltrates.

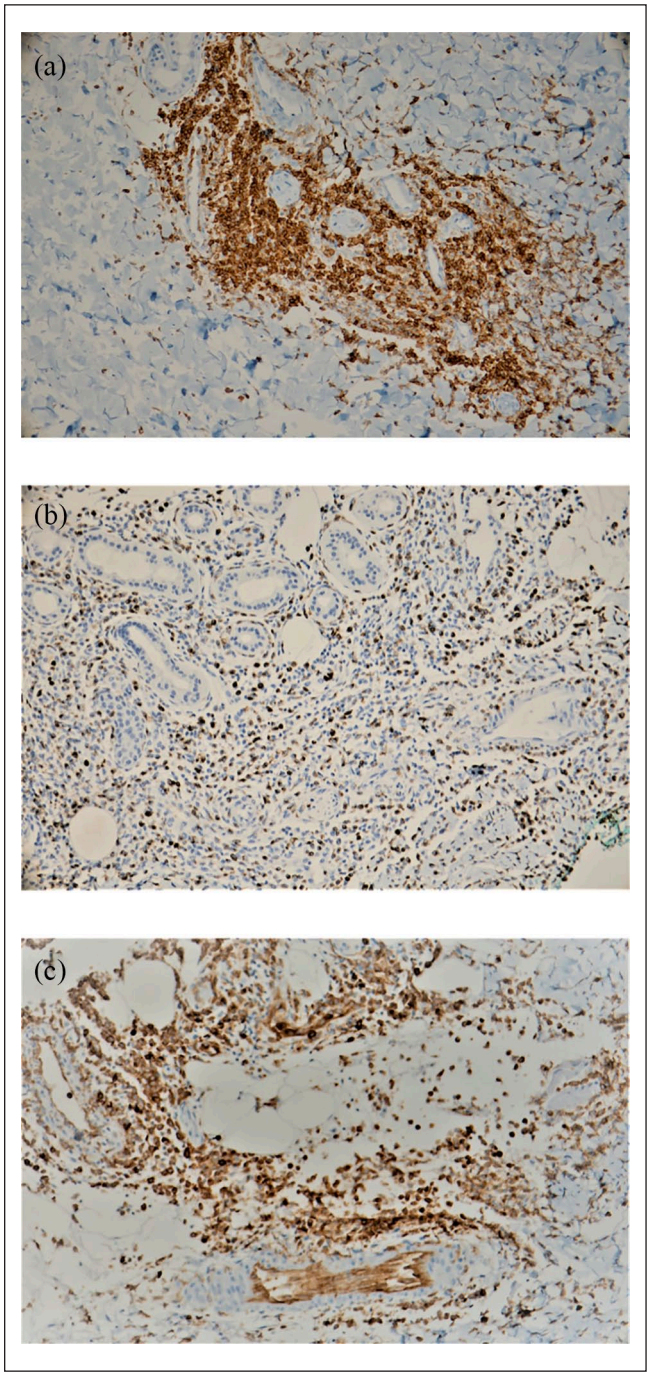

Figure 3. Immunohistochemical stains highlighting the perivascular malignant cells: (a) CD43, (b) MPO, and (c) CD68.

of the hematopoietic markers CD34 and CD117 denotes the presence of blast cells in bone marrow; however, these same markers cannot be used reliably in the setting of LC because of their decreased expression in the skin.[8] A reliable marker expressed in both the bone and the skin is CD43. Positive expression of this marker has been shown to correspond with the presence of myeloid cells in both areas.[9] In addition, antibodies against MPO have also been shown to be specific for myeloid cells, specifically for granulocytic neoplasms.[10] A retrospective immunohistochemical study of 33 cases of myeloid LC diagnosed at the Stanford University Medical Center found that, regardless of leukemic phenotype or flow cytometric expression profile, a panel of antibodies including MPO, CD3, CD20, CD43, CD56, CD68, and CD117 would correctly identify myeloid LC in the majority of cases.[9]

In our case of ALC, the focal clusters of small lymphocytes surrounding the superficial and deep vessels on the second biopsy was a diagnostic clue that led to further immunohistochemical staining. Additional staining was ultimately necessary to confirm the final diagnosis of AML. We emphasize that a high level of suspicion and clinical correlation are necessary to avoid a misdiagnosis, especially given the poor outcomes associated with this disease and the necessity of urgent treatment. Our patient underwent two cycles of standard induction chemotherapy as well as allogeneic hematopoietic stem cell transplantation with some complications of post-transplant infection and graft-versus-host disease. Fortunately, at 4 months post-allogeneic transplant, his engraftment and disease status are excellent with only mild anemia.

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Informed consent

Explicit verbal consent was obtained from the patient in using their data.

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