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Case Report

Leukemia cutis as an initial presentation in a case of mixed phenotype acute leukemia: a double jeopardy

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Abstract: Leukemia cutis (LC) is defined as infiltration of the skin by leukemic cells resulting in clinically recognizable cutaneous lesions. The lesions range from violaceous papules, plaques, nodules, blisters, maculopapular rash and as erythroderma. LC can precede or happen after the presentation of leukemia. Here, we report a case of Mixed phenotype Acute leukemia (MPAL) presenting as LC (erythematous & violaceous nodules) which is a rare as well as a grave combination as it carries a worse prognosis. Here, we present a case of MPAL which presented as Leukemia Cutis proven on biopsy. The paper discusses the importance of identifying LC both in a clinical and a pathological pretext as it is important to start the Chemotherapy for MPAL at the earliest for a better outcome.

Keywords: Leukemia cutis, mixed phenotype acute leukemia, nodules

Introduction

Leukemia cutis (LC) is defined as infiltration of the skin by leukemic cells resulting in clinically recognizable cutaneous lesions. Leukemia cutis is commonly associated with myeloid leukemias like congenital leukemia and acute myeloid leukemia (M4 and M5). Among lymphoid leukemias it is usually seen with Adult T cell leukemia/lymphoma, T cell prolymphocytic leukaemia and rarely with acute lymphoblastic leukemia (ALL). LC is considered to be a rare extramedullary manifestation of acute Leukemias. It has rarely been reported with mixed phenotypic acute leukemias (MPAL) with occasional case reports in literature. Mixed phenotype acute leukemia (MPAL) refers to acute leukemia that displays an ambiguous pattern of antigen expression (i.e., reflecting more than one hematopoietic lineage), to a degree that it cannot be unequivocally assigned to one lineage. MPAL carries a worse prognosis and is difficult to treat. In addition, this case presented as cutaneous lesions (Leukemia cutis), which made us suspect Leukemia with further detailed work-up to confirm the diagnosis. We report the case of a MPAL of the B/myeloid with monocytic differentiation lineage presenting as leukemia cutis.

Case report

A 50-year-old female presented with multiple erythematous to violaceous infiltrated plaques and nodules over her chest wall occurring for the three weeks. There was no evidence of any lymphadenopathy or organomegaly. A Complete blood count revealed leucocytosis with thrombocytopenia which prompted a peripheral blood film revealing the presence of 62% blasts. Simultaneously, a skin biopsy of the lesion and a bone marrow aspirate were performed. The skin biopsy confirmed cutaneous and intravascular blast infiltration. These blast cells were positive for CD45 (leukocyte common antigen), CD34 and CD20 on immunohistochemistry. Bone marrow aspirate revealed 93% blasts with two distinct blast populations (**Figure 1**).

Immunophenotyping with the bone marrow sample showed blasts which were positive for

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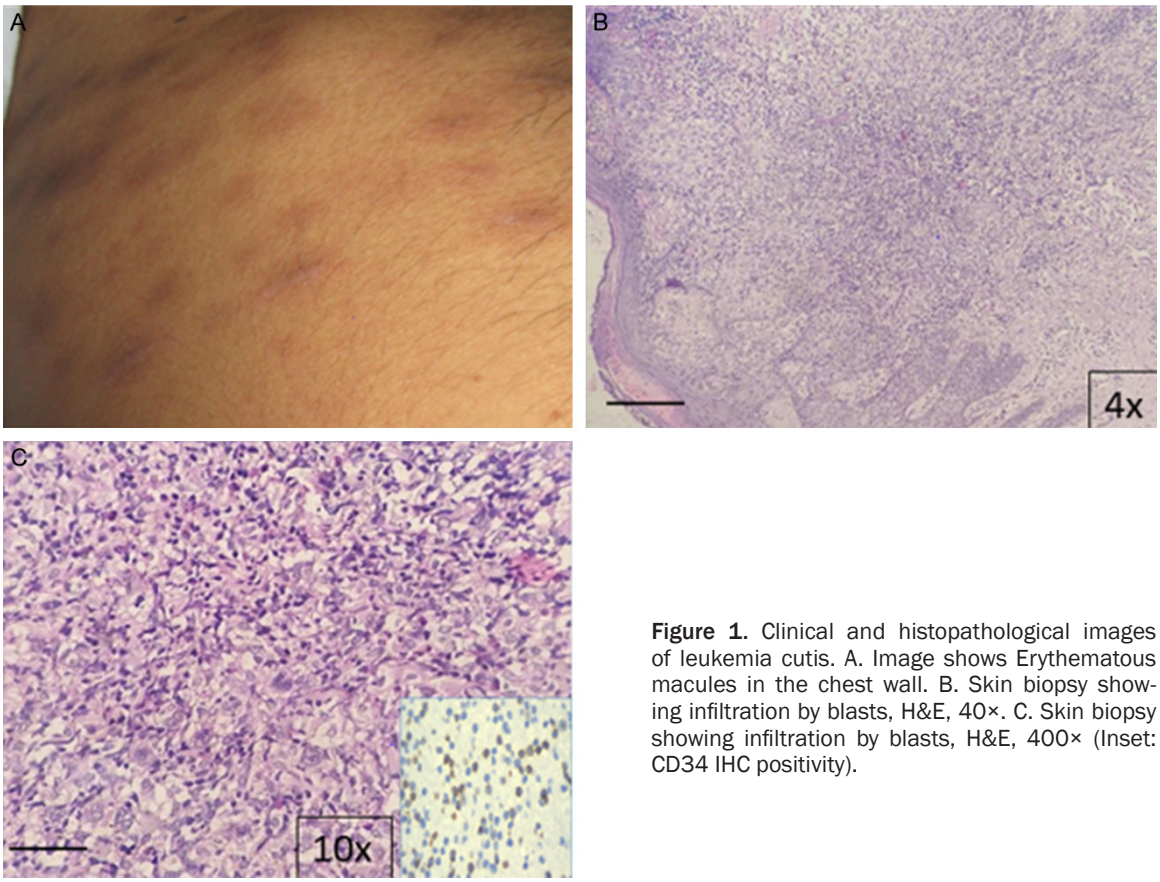

Figure 1. Clinical and histopathological images of leukemia cutis. A. Image shows Erythematous macules in the chest wall. B. Skin biopsy showing infiltration by blasts, H&E, 40×. C. Skin biopsy showing infiltration by blasts, H&E, 400× (Inset: CD34 IHC positivity).

Myeloid markers like CD34, HLA-DR, MPO, CD33, CD117. In addition, the blasts were positive for Monocytic markers like CD64 and CD11c and B lymphoid markers like CD19 and CD79a.

The blasts were negative for T cell markers like CD3 and CD7. As per the European group of the immunological classification of Leukemia (EGIL), the diagnosis was given as Mixed phenotypic acute leukemia - Acute Myeloid leukemia (Monocytic)/B lymphoid phenotype (**Figure 2**).

The patient was started on hyper CVAD regimen (cyclophosphamide, vincristine, doxorubicin, dexamethasone). The cutaneous lesions resolved with the Chemotherapy. However, a follow up bone marrow was not performed as the patient continued the further treatment in a different hospital.

Discussion

Leukaemia cutis, or skin infiltration by leukemic cells, is an uncommon phenomenon that may precede the development of systemic leukaemia, while acute leukaemia of ambiguous lineage NOS is rare and its exact incidence in association with LC is unknown. Both represent a diagnostic challenge with a poor overall prognosis [2].

The classification of acute leukemias is based on a combination of morphology, cytochemical staining as well as Immunophenotypic studies [3]. Acute leukemia of ambiguous lineage (ALAL) and mixed phenotype acute leukaemia (MPAL) are grouped under a single category in view of their overlapping clinical and immunophenotypic features, which in recent studies have been shown to also share common molecular pathogenic mechanisms. Here too, a framework for a molecular classification is laid by separating ALAL/MPAL with defining genetic abnormalities from those that are defined based on immunophenotyping only [4]. According to the WHO 5th edition our case was diagnosed as MPAL of the B/myeloid with monocytic differentiation lineage.

The percentage of LC with Acute Myeloid leukemia is 10-15%, Acute lymphoblastic leukemia is

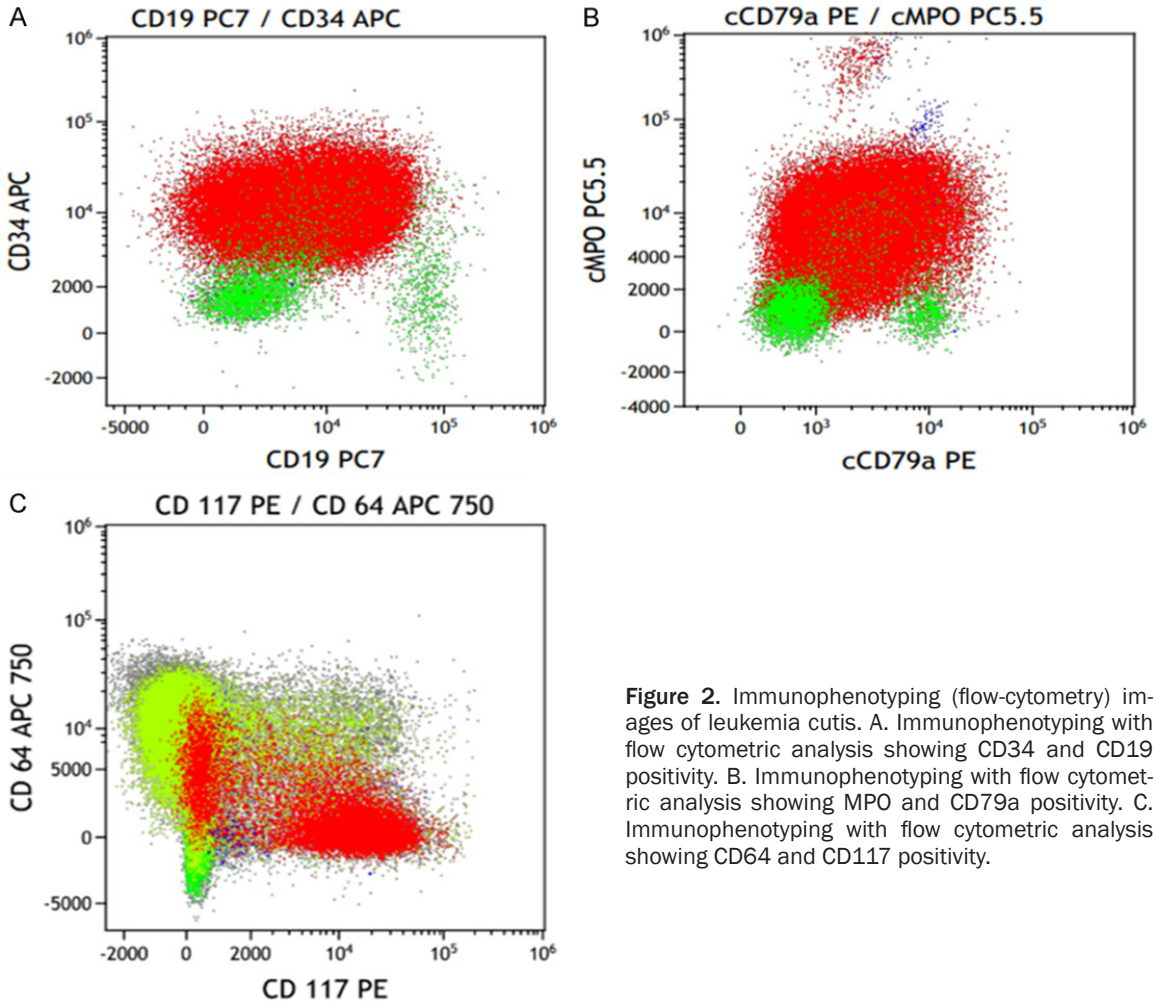

Figure 2. Immunophenotyping (flow-cytometry) images of leukemia cutis. A. Immunophenotyping with flow cytometric analysis showing CD34 and CD19 positivity. B. Immunophenotyping with flow cytometric analysis showing MPO and CD79a positivity. C. Immunophenotyping with flow cytometric analysis showing CD64 and CD117 positivity.

1-3% [5, 6]. LC with MPAL is not well documented with only a few reports in literature. LC may follow, precede or occur concomitantly with Systemic leukemias. Narayanan et al., described a case of MPAL presenting as leukemia cutis similar to our case [1]. LC can also present as aleukemic leukemias which accounts for 7% of cases [7].

The exact pathophysiology of the specific migration of leukemic cells to the skin is not well understood. It has been proposed that chemokine integrin and other adhesion molecules like intercellular adhesion molecule 1 (ICAM 1) may play a role in skin specific homing of T and B leukemic cells [8].

LC in Myeloid leukemias tends to be more severe in those with mutated NPM1 [9]. In our case, molecular testing was not performed. In addition, the presence of LC in Myeloid leukemias confers a poor prognosis with increased chances of extramedullary crises in other sites especially in CNS [10]. However, there were no other areas of extramedullary blast crises in our case.

Leukemia cutis frequently presents as erythematous or violaceous nodules. It can also have a myriad of clinical presentations like papules, plaques, vesicles, blisters, ulcers, maculopapular rash and erythroderma. The sites involved are in the extremities (41%), torso (40%) or in the head and neck region (16%). In our case, LC was involving the chest wall presenting as violaceous plaques and nodules. Rarely, it can also affect previous herpes infected regions, intravenous or surgery sites (i.e., prior inflammation and trauma) [11].

Clinically, leukemia cutis can mimic panniculitis, cellulitis, sweet syndrome, pseudolympho-

ma and vasculitis [11]. However, on histopathological examination, these can be ruled out. Panniculitis will have a subcutaneous inflammation, sweets and cellulitis have a predominant neutrophilic population. Pseudo lymphomas can be ruled out by the absence of clonality in the lymphocytic population and vasculitis can also be easily ruled outby the absence of the transmural neutrophilic debris, endothelial swelling and the absence of fibrinoid necrosis [12].

Due to the rarity, the exact treatment for MPAL is not very well defined and it depends on the predominant lineage that is established through Immunophenotyping. The current data suggests an ALL-based induction regimen followed by Allogenic stem cell transplant in complete remission 1 (CR1), which stands the greatest chance of benefit. However, if the patient fails induction, treatment can be switched to an AML-like regimen followed by Allogenic stem cell transplant in CR1 [13]. In our case, the patient was started on induction therapy (hyper CVAD) regimen but the patient went to a different center for further treatment.

Conclusion

It is imminent that the pathologist picks up cases of leukemia cutis especially in an undiagnosed case of leukemia as they carry an overall worse prognosis. Very few cases of leukemia cutis in MPAL have been reported, the incidence of which is unknown. A thorough clinical assessment especially in an undiagnosed case as well as vigilant pathological assessment are vital for a prompt diagnosis.

Disclosure of conflict of interest

None.

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