Leukemia Cutis from CD56 Positive, Myeloperoxidase Negative Acute Myeloid Leukemia

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SUMMARY Acute myeloid leukemia (AML) is a clonal expansion of myeloid blasts in peripheral blood, bone marrow, or other tissues. Cutaneous manifestations of leukemia are either specific or nonspecific. Specific lesions result from direct infiltration of the skin by leukemic cells. We present a case of myeloid leukemia cutis manifested by erythematous asymptomatic nodules and plaques distributed on the chest, abdomen and back. The clinical and histopathologic features of the cutaneous infiltrate were suggestive of hematolymphoid malignancy, more towards lymphoma. However, the immunohistochemical features were against the diagnosis of lymphoma and were highly suspicious of myeloid leukemia, which were concomitantly confirmed by bone marrow biopsy and blood smear. In any poorly differentiated malignant skin infiltrate of confirmed hematopoietic lineage, myeloid differentiation should be considered and excluded by an appropriate panel. CD56+ AML is a rare type of AML that has special features like the great liability of extramedullary involvement including skin, monocytic characteristic of leukemia cells, and absence of myeloperoxidase expression.

KEY WORDS: leukemia cutis, acute myeloid leukemia, CD56, CD68, myeloperoxidase

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal expansion of myeloid blasts in peripheral blood, bone marrow, and other tissues (1). It is a heterogeneous disease clinically, morphologically and genetically, and it may involve one or all myeloid lineages (myeloblast, monoblast/promonocyte, megakaryoblast). The diagnosis requires the presence of more than 20% of blasts in peripheral blood or bone marrow. Myeloid leukemia cutis is a described entity that refers to cutaneous involvement by leukemic cells, consisting of myeloblasts and myeloid cells in varying stages of differentiation (2).

Skin lesions are rare in AML and may be nonspecific or specific due to direct skin infiltration by leukemic cells. The rate of skin involvement in AML has been reported to be 5%-15% in adults and 30% in children (3). The most commonly described specific lesions are erythematous or violaceous plaques, papules or nodules. Less common appearances include maculae, maculopapules or plaques (3). Other lesions may be present like gingival hypertrophy or leonine face (4). There are no predilection sites for skin involvement, but lower extremities followed by upper extremities, trunk and face are the most commonly reported sites

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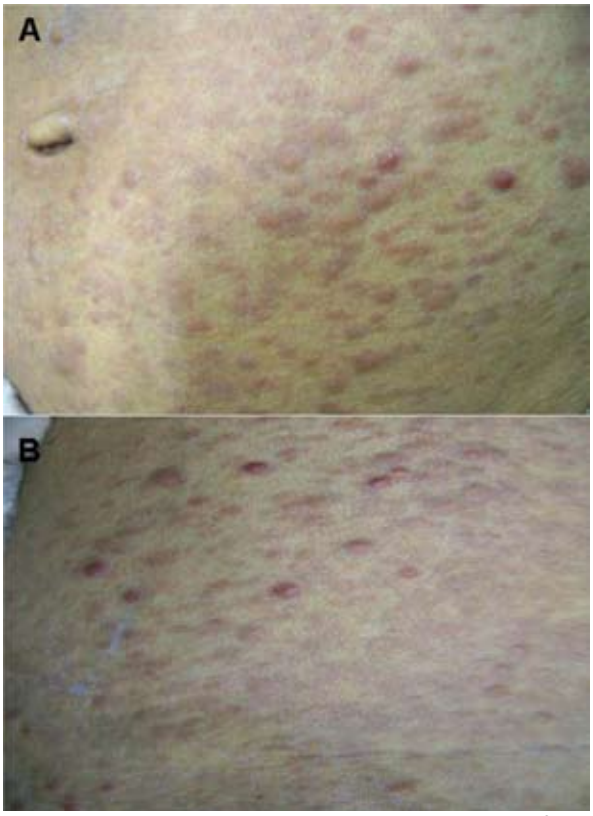

Figure 1. Erythematous nodules and plaques affecting (A) the abdomen and (B) back of the trunk.

(3,5). In adults with AML, leukemia cutis represents a higher tumor burden and tends to be predictive of a prolonged and less favorable course (6).

In this report, we describe a rare and special entity of myeloid leukemia cutis that simulates cutaneous lymphoma clinically and histopathologically, shows co-expression of CD56 and CD68, and lacks myeloperoxidase expression.

CASE REPORT

We report a case of a 64-year-old male presenting with erythematous asymptomatic nodules and plaques of two-week duration. Lesions were distributed on the chest, abdomen (Fig. 1a) and back of the trunk (Fig. 1b). Generally, the patient had marked pallor, fever and hepatosplenomegaly. Clinically, the picture was highly suggestive of lymphoma.

Biopsy was obtained from one of the representative skin nodules, which was then submitted to routine tissue processing in Pathology Department, Faculty of Medicine. Hematoxylin and eosin stained sections revealed dermal infiltration by neoplastic monomorphous cells invading collagen bundles and separated from the overlying epidermis by a grenz zone (Fig. 2a). The neoplastic infiltrate was formed of intermediate to large cells showing scanty and deeply basophilic cytoplasm, large vesicular nuclei, prominent nucleoli and frequent mitoses (Fig. 2b). Immunophenotypically, the tumor cells showed diffuse and strong positivity for LCA (Fig. 2c), CD56 (Fig. 3a) and CD68 (Fig. 3b), but they were negative for myeloperoxidase (Fig. 2d), CD34 (Fig. 3c), CD3, CD20, CD30, CD123, LMP1, chromogranin, HMB-45 and pancytokeratin.

These histopathologic and immunohistochemical features of the neoplastic infiltrate in cutaneous nodules necessitated further clinical investigations to clarify their nature. Therefore, complete blood picture was performed and showed increased total leukocyte count (18.2x106/mm^3) with myeloid blast cells in peripheral blood smear. Bone marrow biopsy was also done and showed 90% infiltration by myeloblasts, which confirmed the diagnosis of AML. Abdominopelvic ultrasonography showed hepatosplenomegaly and enlarged para-aortic lymph nodes.

DISCUSSION

When leukemia cutis occurs in the course of the disease, it is usually concomitant with the diagnosis of systemic leukemia, as in our case, or it may precede the diagnosis of systemic leukemia, which is then called aleukemic leukemia (5).

The main differential diagnosis in the case we studied is cutaneous lymphoma. However, the histopathologic picture of the cutaneous infiltrate was not compatible with the clinical features of mycosis fungoides, since the infiltrate was confined to the dermis with the absence of epidermotropism together with the absence of nuclear characteristics of T cell lymphoma that featured marked irregular nuclear membrane and complete negativity for CD3. The possibility of non-Hodgkin's lymphoma of B cell origin was suspected, especially with the presence of neoplastic infiltrate in the dermis, but the neoplasm was completely negative for CD20. Additional examinations using CD30, chromogranin, CK and HMB-45 were performed to reveal the absence of their expression, thus excluding anaplastic lymphoma, Merkel cell carcinoma, other epithelial tumors and melanoma, respectively. The positivity for LCA (CD45) was an important finding because it raises suspicion of leukemic infiltration. LCA positivity has been reported in 90% of myeloid leukemia cutis (7). Therefore, the patient underwent bone marrow biopsy and complete blood count, which confirmed the diagnosis of AML.

On the other hand, the neoplastic cells were diffusely positive for CD56 and CD68. CD56 is an isoform of neural adhesion molecule (N-CAM). It is considered a natural killer cell marker, but it is also expressed by

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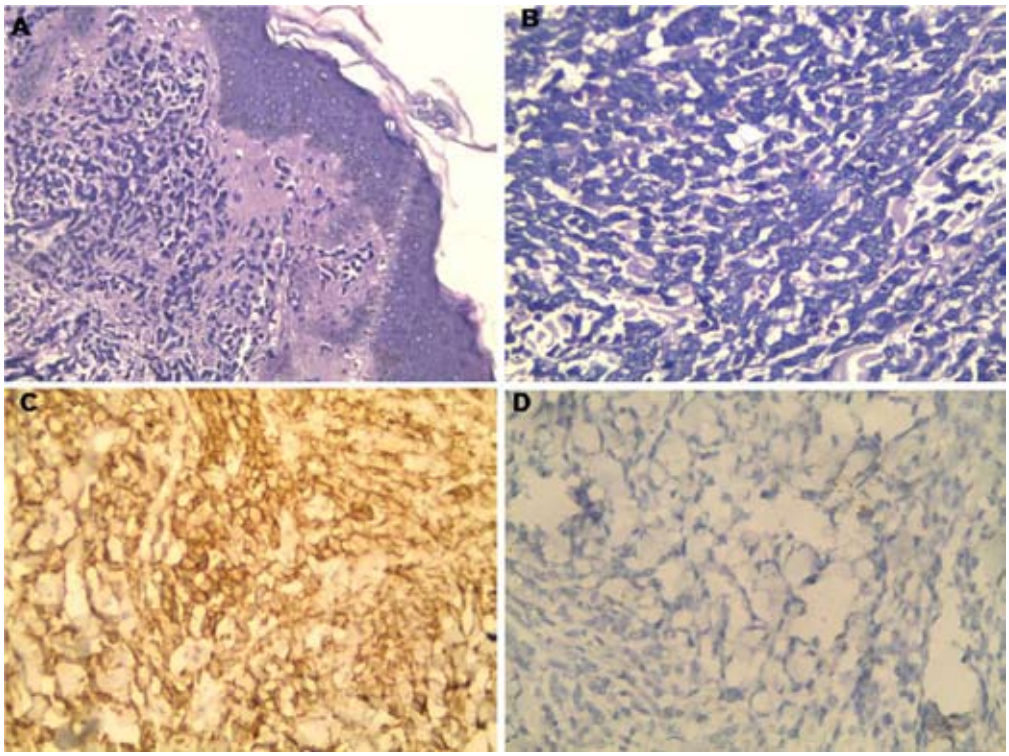

Figure 2. The dermis is infiltrated by a population of monomorphous cells that leave grenz zone from the overlying epidermis (A); neoplastic cells are large, with scanty and deeply basophilic cytoplasm, large vesicular nuclei, prominent nucleoli and frequent mitoses (H&E staining, X100 for A, X400 for B) (B); positive and diffuse immunohistochemical staining for LCA in the neoplastic cells (C); negative immunoreactivity for myeloperoxidase (immunohistochemical staining, X400 for C and D) (D).

normal T lymphocytes and some myeloid cells (8). There is a group of rare lymphoproliferative cutaneous lesions characterized by CD56 positivity, which include hematodermic neoplasm/blastic NK-cell lymphomas/blastic plasmacytoid dendritic cell neoplasm, CD56+ acute myeloid leukemia, nasal-type extranodal natural killer/T-cell lymphoma and 'classic' cases of cutaneous T-cell lymphoma (CTCL) with co-expression of the CD56 molecule (9).

Absence of angio-invasion, necrosis and angio-destruction together with the lack of LMP1 expression exclude nasal-type extranodal natural killer/T-cell lymphoma. Absence of T cell marker expression excludes 'classic' cases of cutaneous T-cell lymphoma (CTCL) with co-expression of the CD56 molecule. Diffuse positivity for CD68 with absence of CD123 expression excludes hematodermic neoplasms/blastic NK-cell lymphomas (9). Therefore, the picture was highly suggestive of myeloid leukemia cutis, which was concomitantly accompanied by systemic leukemia.

Skin involvement may reach up to 20%-30% in AML, which is more common in myelomonocytic and monoblastic/monocytic differentiation (10). In the case described, several lines of evidence referred to this differentiation, starting with monomorphous morphology, absence of cytoplasmic granularity and diffuse expression of CD68. Some authors recommend the use of CD68 in the diagnostic panel for myeloid leukemia cutis in challenging cases (11). The lack of myeloperoxidase and CD34 expression goes with this monocytic differentiation. CD56+ myeloid leukemia displays more frequently an extramedullary involvement (skin, lymph node) at initial presentation (12), together with monocytic differentiation of leukemic cells (13).

Myeloperoxidase is a microbicidal protein, which is present in the primary granules of myeloid cells and takes part in the defense of the body. It is synthesized in promyelocytes, where it is packed into azurophilic granules (14). Detection of myeloperoxidase indicates myeloid differentiation, but its absence does not exclude a myeloid lineage because early myeloblasts as well as monoblasts may lack myeloperoxidase (15). Our case showed negative myeloperoxidase expression, which was considered as one of the challenging results to reach an accurate diagnosis. This negativity may be explained by the loss of cellular differentiation or maturation. It has been reported that decreased myeloperoxidase activity in polymorphonuclear leukocytes in AML may contribute to the increased susceptibility to infections (16).

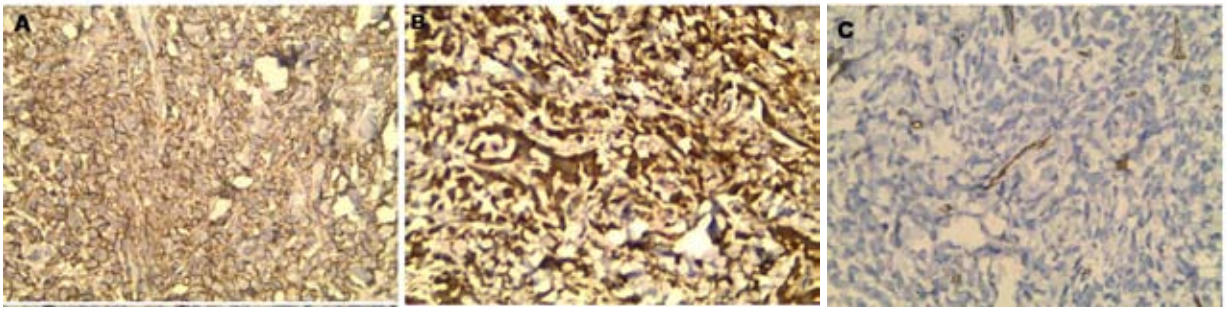

Figure 3. The neoplastic infiltrate shows diffuse and strong positivity for CD56 (A) and CD68 (B), but lacks expression of CD34 (immunohistochemical staining, X400).

CONCLUSION

Involvement of skin in case of AML may be the first presentation that sometimes simulates cutaneous lymphoma clinically. The histopathologic features, immunophenotyping, and bone marrow biopsy are greatly helpful in reaching an accurate diagnosis. In any poorly differentiated malignant skin infiltrate of confirmed hematopoietic lineage, myeloid differentiation should be considered and excluded by an appropriate panel. CD56+ AML is a rare type of AML that has special features like the great liability for extramedullary involvement including skin, monocytic characteristic of leukemia cells, and absence of myeloperoxidase expression.

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