Aleukemic Monocytic Leukemia Cutis

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Aleukemic leukemia cutis is a rare condition in which leukemic cells invade the skin before they appear in peripheral blood or bone marrow specimens. The condition frequently is misdiagnosed as atypical lymphoma. Generally, the diagnosis is made retrospectively, after the leukemic cells appear in peripheral blood or bone marrow samples. Immunohistochemical studies are the primary methods for diagnosis. Prognosis is usually poor. We describe the case of a 75-year-old woman with acute aleukemic monocytic leukemia cutis who developed systemic disease 1 1/2 years after skin involvement.

The occurrence of leukemic infiltrates or cells in the skin before their appearance in blood or bone marrow specimens is referred to as *aleukemic leukemia cutis*. The condition usually has a poor prognosis. To our knowledge, less than 15 cases of aleukemic monocytic leukemia cutis are reported in the English literature. We present a typical case of this rare skin manifestation of leukemia.

Case Report

A 75-year-old woman underwent assessment because of a pruritic maculopapular eruption on her lower extremities. The lesions first appeared a few months before hospital admission and gradually increased in number. The patient's medical history included hypertension and paroxysmal atrial fibrillation. Findings from the physical examination were unremarkable. The dermatologic examination revealed erythematous macules and papules, mainly on her shins. Results from the laboratory tests (complete blood count and erythrocyte sedimentation rate) were normal. Blood chemistry was within reference range, except for elevated lactate dehydrogenase (LDH) values (334 U/L, reference range 100–260 U/L). Results from a skin biopsy showed superficial perivascular and interstitial dermatitis with many eosinophils and were interpreted as a reaction to an insect bite. Two months later, the patient developed night sweats and multiple new skin lesions. Dermatologic examination showed multiple erythematous, violaceous, and flesh-colored infiltrated plaques and nodules, located mainly on her extremities (Figure 1). Findings from the physical examination were normal, except for mild hepatomegaly.

Results of routine laboratory tests showed the following: hemoglobin, 11.4 g/dL; mean cell volume, 83; mean cell hemoglobin, 32; white blood cell count, 3.2×10^9/L (segmented forms, 32%; lymphocytes, 45%; and monocytes, 11%). Serum chemistry results revealed an elevated LDH of 494 U/L. Other test results, including serology for hepatitis, purified protein derivative (tuberculin), and markers for malignancy (carcinoembryonic antigen, cancer antigen [CA] 125, CA19-9, and α-fetoprotein), were all negative. Thorough imaging procedures, including chest radiography, abdominal ultrasonography, total body computed tomography, and bone scan, were normal. Results from a biopsy of a cutaneous nodule revealed diffuse infiltrate composed of large cells with abundant amphophilic cytoplasm and few mitotic figures (Figure 2). Most cells were negative for T-cell and B-cell markers. Bone marrow biopsy results revealed one tiny granuloma and slight fibrosis. No malignancy was found, and results of special stains for microorganisms were negative.

During the following months, the patient developed multiple skin nodules on her trunk, face, and extremities. Thus, with the presumptive diagnosis of primary cutaneous lymphoma, the patient initially was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). This treatment resulted only in partial and temporary regression of some skin nodules.

Revision of the results from the skin biopsy was done, and additional immunohistochemical stains were performed. Examination of the stains showed that the cells were positive for CD68 (Figure 3)

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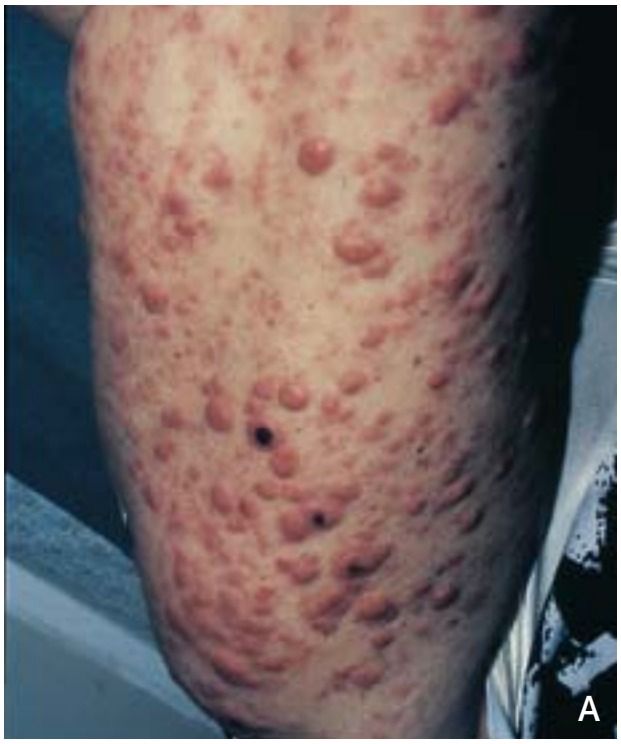

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B

Figure 1. Multiple erythematous, violaceous, and flesh-colored plaques and nodules of aleukemic monocytic leukemia cutis on the leg (A) and face (B).

and CD43, a typical phenotype of monocytes. After the monocytic origin of the skin infiltrates was established both morphologically and immunophenotypically, a second biopsy of the bone marrow was performed and was again free of tumor cells. Thus, in the absence of peripheral blood and bone marrow involvement, a diagnosis of aleukemic monocytic leukemia cutis was made.

After failure of the CHOP treatment, total skin electron-beam therapy was initiated. This caused partial regression of some lesions, but multiple new lesions appeared. Within a few months, and exactly 18 months after the nodular eruption had appeared, the patient's general condition deteriorated and pancytopenia developed. Results of another bone marrow biopsy showed monocytic infiltrate. The patient received chemotherapy with cysplatin and dexamethasone. Despite therapy, the patient died 2 months later from disseminated disease.

Comment

Various rashes may appear in patients with leukemia. Generally, these are divided into 2 groups: leukemid or nonspecific lesions (with no leukemic cells) and leukemia cutis or specific lesions (where leukemic cell infiltrate is present). Clinical differentiation between the 2 groups can be difficult. Nonspecific lesions occur in about 30% of patients with leukemia and are much more common than leukemia cutis.[1,2] The causes of these lesions can be divided broadly into 3 groups: (1) reactive or paraneoplastic lesions and results of either, (2) bone marrow failure, or (3) cytotoxic chemotherapy.[2] The incidence of leukemia cutis varies from 1.3% to 20% in patients with lymphocytic and granulocytic leukemia and from 10% to 50% in patients with monocytic leukemia.[3] The clinical appearance of leukemia cutis includes papules, nodules, plaques, macules, purpura, ecchymoses, palpable purpuric lesions, ulcers, nodular ulcerative lesions, and, often, a combination of them. The lesions are typically flesh colored, pink, erythematous, or red-brown to purple. Gingival hypertrophy is seen in acute myelogenic and acute myelomonocytic leukemias.[4] Erythroderma and bullous lesions are observed more often in chronic lymphocytic leukemia.[3] Erythema annulare centrifugum–like, urticaria pigmentosa–like, and erythema nodosum–like lesions also were described.[2] Lesions may grow rapidly and rarely show spontaneous involution. They are usually multiple and appear in a widespread distribution. However, they can be localized at the sites of trauma.[5,6]

Most specific infiltrates occur in the setting of established leukemia or concomitantly with the appearance of systemic leukemia. Except for chronic

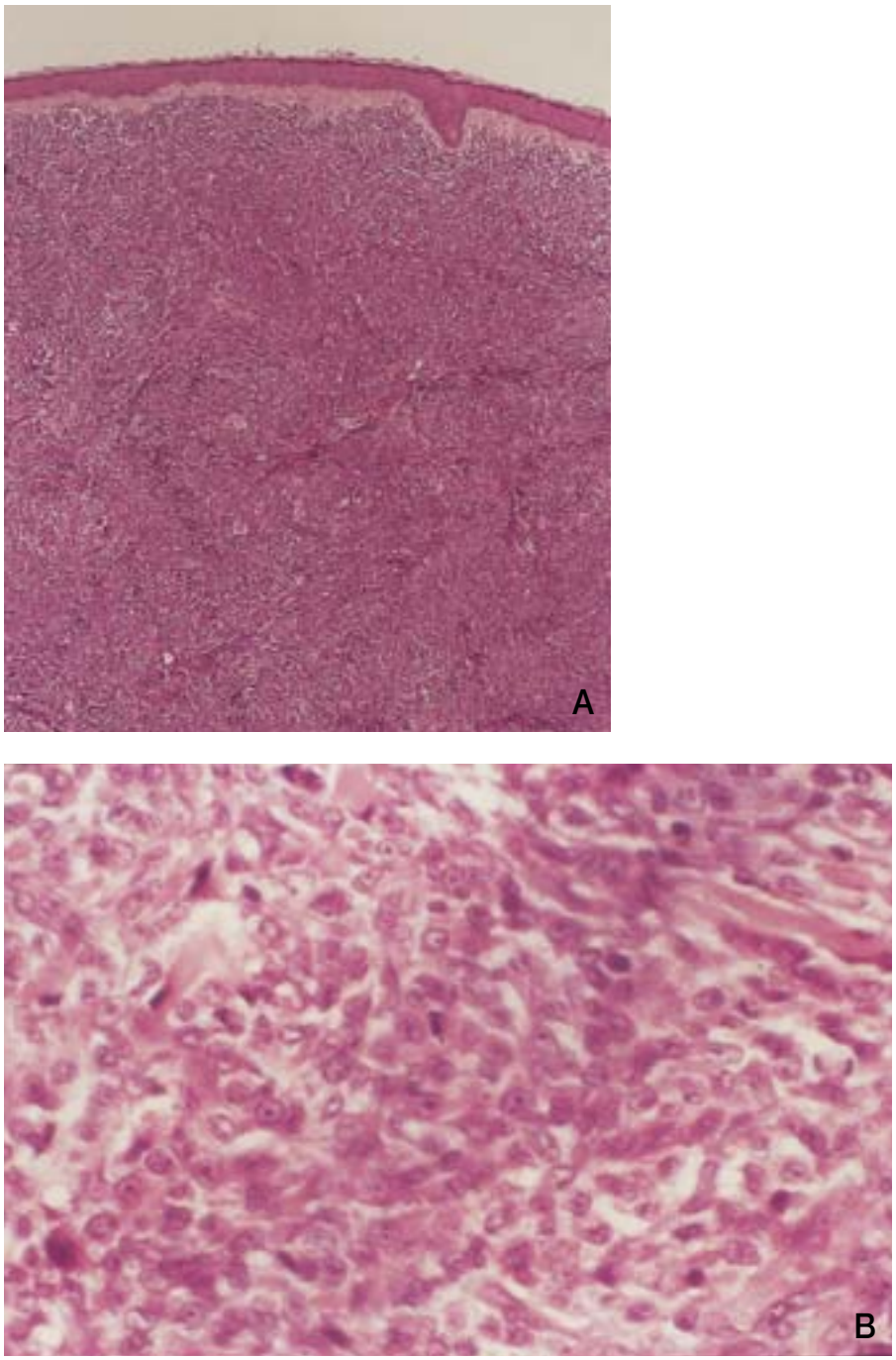

Figure 2. Diffuse infiltrate of large cells with amphophilic cytoplasm (A). Higher magnification (B) shows few mitotic figures (H&E, original magnifications ×40 and ×400).

lymphocytic leukemia,[7] skin involvement indicates advanced disease with poor prognosis.[2-4,8,9]

Aleukemic leukemia cutis is a rare condition characterized by the presence of leukemic cell infiltrates in the skin in the absence of peripheral blood or bone marrow involvement.[2,8] Our patient complies with the stringent definition (ie, both peripheral blood and bone marrow were uninvolved). Whether the leukemic clone originates in the bone marrow—with early seeding to extramedullary sites—or whether its origin is extramedullary—with hematogenous spread to bone marrow and other sites—is unknown.[1,8] The diagnosis of leukemia cutis is based on the recognition of the preponderant cell type and pattern of infiltration in the skin and on correlation with clinical and hematologic findings.[10] Immunohistochemistry is most important in identifying the leukemic cells and establishing the diagnosis, especially in cases of aleukemic leukemia cutis.[8] The present case

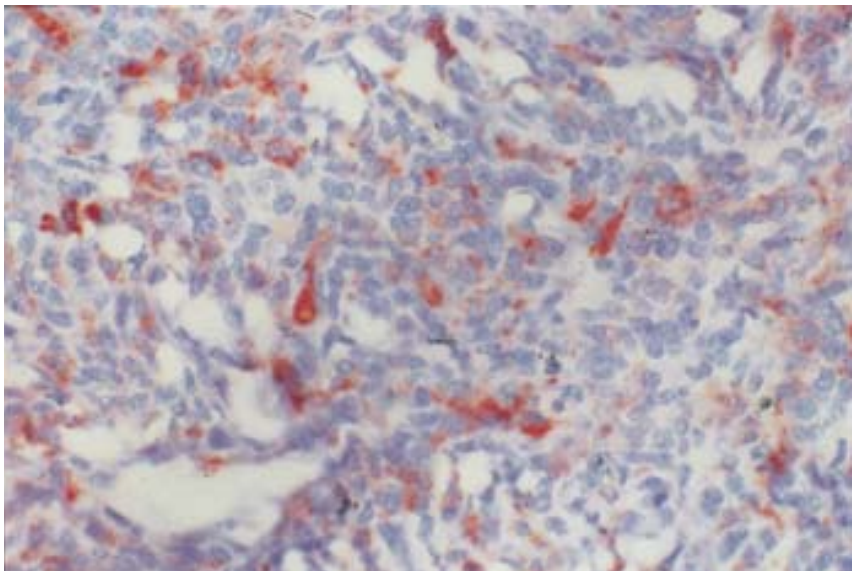

Figure 3. Cell positivity for the monocytic marker CD68 (streptavidin-biotin technique, original magnification ×200).

further stresses the difficulty in diagnosing aleukemic leukemia cutis, particularly the aleukemic monocytic or myelomonocytic leukemias, where clinical manifestations and histology may simulate cutaneous large cell lymphoma. Therefore, it is not surprising that many of these tumors initially were diagnosed as lymphoma.[8] Negativity of tumor cells for both pan-T and pan-B cell markers (CD45RO, CD3, and CD20) and positivity for monocyte (CD68) or granulocyte (myeloperoxidase and chloracetate esterase) markers are the key diagnostic features.

Generally, the prognosis of patients with aleukemic monocytic leukemia cutis is poor, and most patients die within one year.[9] One patient remained free of disease for one year after a vigorous chemotherapy regimen.[1] However, the follow-up period in this report may be too short, because systemic involvement can occur more than one year after the initial diagnosis.[9] Although skin infiltrates may respond better to electron-beam radiation than to systemic chemotherapy,[8,9] even a combination of both modalities does not prevent disease progression and its fatal outcome. Bone marrow transplantation may be the sole hope for these patients.

The patient presented demonstrates the diagnostic difficulties of aleukemic monocytic leukemia cutis, as well as its grave prognosis. This case is unusual in that the development of systemic disease occurred relatively late—$1^1/_2$ years after the initial skin involvement. Indeed, an insect bite–like reaction may precede the development of hematologic malignancies and can be considered a nonspecific phenomenon.[11,12]

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