Leukemia Cutis in a Patient With Acute Myelogenous Leukemia: A Case Report and Review of the Literature

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The estimated time to complete this activity is 1 hour.

GOAL

To understand leukemia cutis and acute myelogenous leukemia (AML) to better manage patients with these conditions

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Recognize the clinical presentation of AML.
2. Discuss the classification of AML based on the French-American-British system and the World Health Organization system.
3. Manage the induction of remission and prevention of relapse of leukemia cutis in patients with AML.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 12.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: December 2009.

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Leukemia cutis is an infiltration of malignant neoplastic leukocytes or their precursors into the epidermis, dermis, or subcutis. These neoplastic cells are derived from abnormal leukocytes in the bone marrow where maturation aberrations occur. Acute myelogenous leukemia (AML) is the second most common cause of leukemia cutis and the most common leukemia among adults. In the elderly population, AML presents a challenge to the medical community because of the number of preexisting comorbid conditions and the safety profile of useful chemotherapeutic agents.

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Leukemia cutis is one of many manifestations of marrow-based neoplasms. Although they share clinical similarities, there are morphologic, immunophenotypic, and cytogenetic differences among these neoplasms. In most cases of leukemia cutis the presence of systemic disease precedes the evolution of skin lesions.

The pathogenesis of acute myelogenous leukemia (AML) is unclear; however, there is strong evidence in epidemiologic studies suggesting that environmental, occupational, and genetic factors play an important role in its development.[1,2] The malignant cell in AML is a blast that most often expresses myeloid or monocytic differentiation; however, blasts also may express erythroid or megakaryocytic differentiation. Cytogenetic analysis has demonstrated that as much as 50% of patients with AML subtypes M4 (acute myelomonocytic leukemia) and M5 (acute monocytic leukemia) develop leukemia cutis. Karyotypic analysis of these subtypes demonstrates t(8;21)(translocation of chromosomes 8 and 21). Although the precise molecular basis for developing leukemia cutis is still not defined, this knowledge will assist in defining the factors responsible for its manifestation.[3]

Case Report

A 78-year-old man with no remarkable medical history presented to his primary care physician with numerous asymptomatic subcutaneous nodules that appeared abruptly 3 months prior to his visit. The first lesion appeared on his neck and was believed to be an enlarged lymph node. The number of lesions steadily increased; at the time of presentation to dermatology, approximately 30% of his body surface area was covered. Other symptoms began to manifest, such as extreme fatigability and loss of appetite. During dermatologic evaluation, multiple nontender, indurated, violaceous, subcutaneous papules and nodules of various sizes were noted (Figure 1).

The clinical differential diagnosis included benign lymphocytoma cutis, sarcoidosis, Sweet disease, urticarial vasculitis, hypereosinophilic syndrome, cutaneous metastatic carcinoma, neutrophilic eccrine hidradenitis, drug eruptions, drug-induced gingival hyperplasia, erythema nodosum, and pyoderma gangrenosum.

A 3-mm punch biopsy was performed and revealed a diffuse dermal infiltrate of atypical mononuclear cells with little epidermal involvement, destruction of adnexal structures, and an underlying grenz zone (Figure 2). Immunoperoxidase staining was positive for lysozyme and negative for myeloperoxidase (Figure 3). A diagnosis of leukemia cutis was rendered consistent with either AML subtype M4 (acute myelomonocytic leukemia) or M5 (acute monocytic leukemia). Bone marrow biopsies and peripheral blood smears confirmed the diagnosis of AML subtype M5. The patient was evaluated by a hematologist/oncologist and treated with subcutaneous cytarabine 20 mg every 12 hours for 10 days. This regimen decreased the number of leukemic cells seen on the peripheral blood smear and increased the patient's vitality but had no effect on the skin lesions. The patient later developed pancytopenia related to chemotherapy for which 2 units of blood were transfused to alleviate this adverse reaction. For 2 months after the transfusion, most of the lesions involuted and resolved with only postinflammatory hyperpigmentation. However, this phenomenon was ephemeral and lesions reappeared soon thereafter, covering more than 40% of the patient's body surface area. The patient then decided to stop chemotherapy and go to a hospice for end-of-life care.

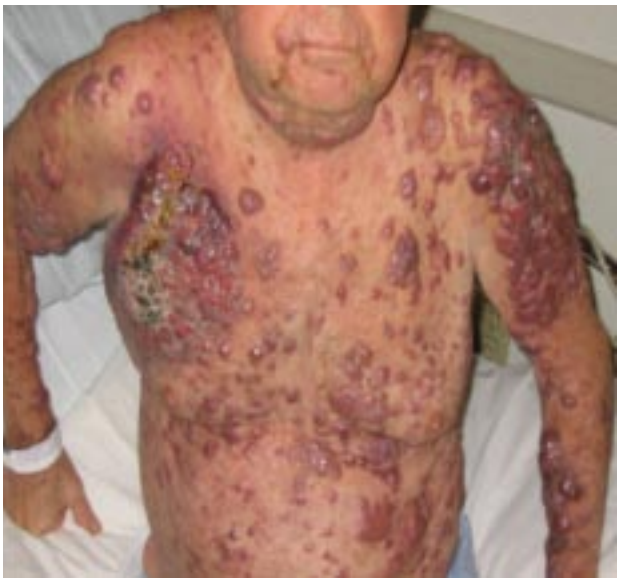

Figure 1. Multiple nontender, indurated, violaceous, subcutaneous papules and nodules of various sizes on the trunk and upper extremities.

Comment

Leukemia cutis is the infiltration of malignant neoplastic leukocytes or their precursors into the epidermis, dermis, or subcutis that most commonly results in red to purple papules, nodules, or hemorrhagic ulcers. Although lesions of leukemia cutis can occur in any location, the areas most commonly involved are the head, neck, and trunk.[4]

There are several types of leukemia, each with its own epidemiologic characteristics. Acute lymphoblastic leukemia most commonly is seen in children,

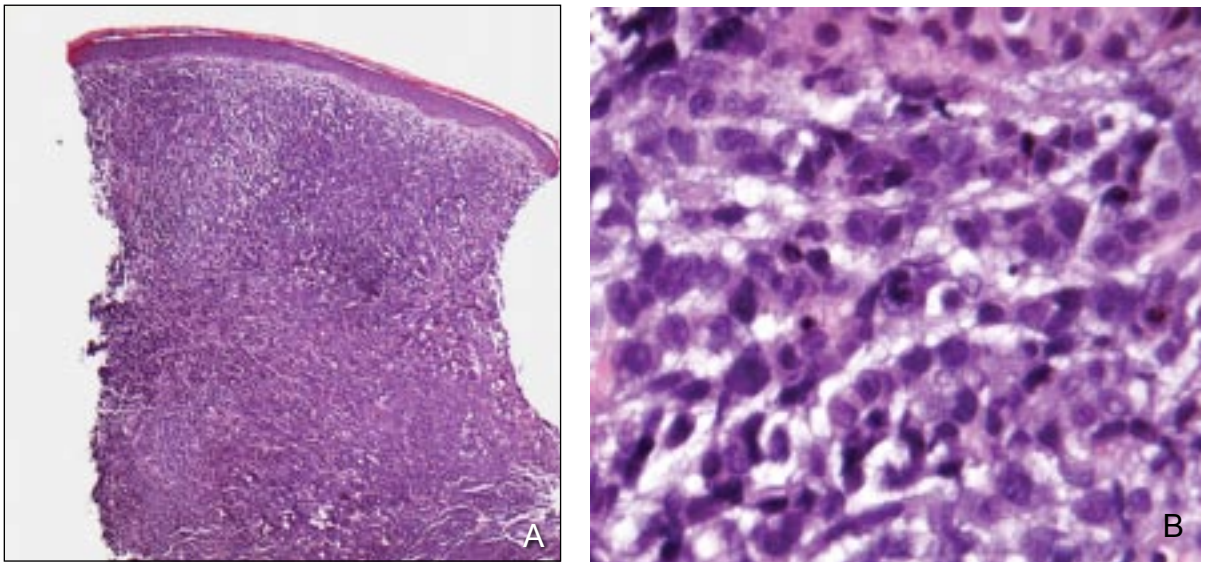

Figure 2. A diffuse dermal infiltrate of atypical mononuclear cells with destruction of adnexal structures (A)(H&E, original magnification ×2.5). The nuclei are round to oval with scant cytoplasm (B)(H&E, original magnification ×40).

AML and chronic myelogenous leukemia primarily are seen in adults, and chronic lymphocytic leukemia and hairy cell leukemia characteristically are seen in elderly patients.[4] Accurate diagnosis has tremendous prognostic importance, especially in cases of aleukemic leukemia cutis in which skin lesions present prior to any systemic leukemic process.

Acute myelogenous leukemia is characterized by an increased number of atypical myeloid cells in the bone marrow with arrested maturation that frequently results in granulocytopenia, thrombocytopenia, and/or anemia with or without leukocytosis. A variety of defects promote the clonal expansion of leukemic cells, including abnormal proliferative potential, defective terminal differentiation, and defective apoptosis. Activation by oncogenes and/or inactivation of tumor suppressor genes directly causes an increase in proliferative potential.[5]

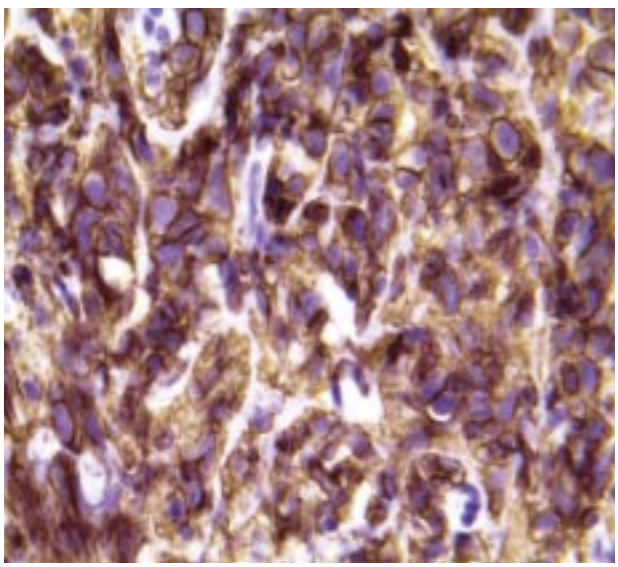

Figure 3. Cells within the infiltrate stained positive for lysozyme (original magnification ×40).

In the United States the annual incidence of AML is approximately 2.4 per 100,000 individuals and increases progressively with age to a peak of 12.6 per 100,000 individuals in those 65 years or older. The survival rate among patients younger than 65 years is only 40%.[6] Likewise, histologically proven leukemia cutis has a poor prognosis in acute nonlymphocytic leukemias.[7]

The clinical signs and symptoms of AML are nonspecific and diverse; however, they usually are the result of bone marrow failure or organ infiltration with leukemic cells, or both. Typically, patients present with fatigue, hemorrhage, dyspnea, pallor, fever, infection, hepatosplenomegaly, lymphadenopathy, skin lesions, bone pain, and gingival infiltration.

The primary diagnosis of AML is obtained by identification of leukemic myeloblasts in preparation of peripheral blood smears, bone marrow aspiration, biopsy, and flow cytometry. These cells have round to irregular nuclei, distinct nucleoli, and very little cytoplasm. Within the cytoplasm, fine azurophilic granules and a variable number of Auer rods usually are visible.

Once a diagnosis of AML is established, the morphologic, immunologic, and genetic subtype must be identified. The specific therapeutic protocol is initiated based on the sensitivity of biologically defined subtypes. Previously, the most common method of classification used, the French-American-British (FAB)

classification of AML, divided acute myelogenous leukemia into subtypes (M0–M7) differing in morphology and reactivity with a variety of histochemical stains (Table 1).[8]

This classification has been revised by a group of pathologists, clinicians, and scientists for the World Health Organization (WHO). While elements of the FAB classification have been retained, the WHO classification also includes discoveries regarding immunophenotypic, cytogenic, and clinical features to create a classification that is universally applicable and prognostically valid (Table 2). The most notable difference between the FAB and WHO classifications is the blast threshold for the diagnosis of AML. The WHO recommends a requisite blast percentage of at least 20% in the blood or bone marrow for the diagnosis of AML in contrast to the FAB classification that requires a blast percentage of at least 30%.[9]

Acute monocytic leukemia (FAB subtypes M5a and M5b) accounts for 2% to 10% of cases of AML. French-American-British subtype M5 is divided into 2 subgroups: M5a, which is poorly differentiated with predominant monoblasts and promonocytes, and M5b, which is well-differentiated and composed of mostly mature monocytes.[10] Monocytic precursors are recognized by fluoride-inhibitable nonspecific esterase positivity and expression of CD14 and CD4 but not CD2. Staining with antibodies to lysozyme and CD68 can identify monoblasts. Although the cytogenetic abnormalities in FAB subtype M5 are not specific, they often consist of translocations of chromosomes 11, 9, or 19. Patients with FAB subtype M5a tend to be younger than those with FAB subtype M5b; approximately 75% of patients are younger than 25 years. Also more common in FAB subtype M5 versus other subtypes is extramedullary involvement characterized by a prominent infiltration of the skin, gingiva, and central nervous system. In addition, this type of leukemia is associated with poor prognostic factors and has a shorter duration of response to treatment.[2]

Environmental factors also have been implicated in the pathogenesis of AML. The most common factors include solvents (eg, benzene), smoking, ionizing radiation (eg, atomic bomb, nuclear power, therapeutic radiation), nonionizing radiation, chemotherapy (alkylating agents, topoisomerase II inhibitors), and drugs such as chloramphenicol and phenylbutazone.[2]

The clinical differential diagnosis of leukemia cutis includes benign lymphocytoma cutis, sarcoidosis, Sweet disease, urticarial vasculitis, hypereosinophilic syndrome, cutaneous metastatic carcinoma, neutrophilic eccrine hidradenitis, drug eruptions, drug-induced gingival hyperplasia, erythema nodosum, and pyoderma gangrenosum.

Table 1.

French-American-British Classification of Acute Myelogenous Leukemia

Subtype	Morphology
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5a	Acute monoblastic leukemia without differentiation
M5b	Acute monocytic leukemia with differentiation
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Data from Bloomfield and Brunning.[8]

Table 2.

WHO Classification of AML

Classification	Subgroup
AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22)—AML1-ETO fusion protein
	AML with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22)—CBFβ-MYH11 fusion protein
	Acute promyelocytic leukemia with t(15;17)(q22;q12)—PML-RARα fusion protein—and variants
	AML with 11q23—MLL protein—abnormalities
AML with multilineage dysplasia	Following MDS or MDS/MPD
	Without antecedent MDS or MDS/MPD but with dysplasia in at least 50% of cells in 2 or more myeloid lineages
AML and MDSs, therapy related	Alkylating agent/radiation-related type
	Topoisomerase II inhibitor–related type (some may be lymphoid)
	Other types
AML, not otherwise categorized	AML, minimally differentiated
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/acute monocytic leukemia
	Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
	Myeloid sarcoma

Abbreviations: WHO, World Health Organization; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease.

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Leukemia cutis is a local manifestation of an underlying systemic process; therefore, treatment should be directed at eradicating the leukemic clone by using systemic chemotherapy. Treatment should be tailored according to AML subtype and by the patient's ability to tolerate the treatment. Induction of remission and prevention of relapse are the primary objectives of treatment. Remission is defined by the presence of less than 5% of blasts in bone marrow as well as recovery of peripheral blood counts.[11]

The treatment is divided into 2 phases: induction and postinduction. Induction of remission can be achieved using chemical agents such as cytarabine, daunorubicin, idarubicin hydrochloride, or mitoxantrone hydrochloride. Complete remission can be induced routinely using these agents in 70% to 80% of patients younger than 60 years, and approximately 50% of older patients.[12] Administration of cytarabine, usually in conjunction with an anthracycline, has been the cornerstone therapy for AML for the last 30 years. Brief spontaneous

remissions rarely have occurred without therapy. Once remission is induced, further intense treatment is essential to prevent relapse. Currently, there are 3 postinduction treatment options available: allogenic bone marrow transplant from a related or unrelated HLA-matched donor (allograft), autologous bone marrow transplant (autograft), or chemotherapy.

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