

Cutaneous presentation preceding acute monocytic leukemia

A CARE-compliant article

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Abstract

Rationale: Cutaneous presentation preceding acute myeloid leukemia (AML) is rare, and the prognosis is poor.

Patient concerns: We report 4 cases of AML cutis, where skin infiltration precedes any blood or bone marrow evidence of leukemia. We also reviewed 13 cases reported in English and Chinese literature. The 4 cases all presented typical cutaneous lesions without any systemic evidence of leukemia. Histopathological examination found that dense monomorphous cell infiltration involved the dermis. Some cells surrounded blood vessels and skin appendages in a concentric manner or showed single-row arrangement in the collagen fiber bundles. Uninvolved papillary dermis was found to separate normal epidermis from dermal infiltration. Minor cells had a large kidney-shaped or oval nucleus with nucleoli and slightly eosinophilic cytoplasm. Immunohistochemical analysis was positive for CD4, CD56, while CD123 was negative in all cases.

Diagnoses: AML-M5.

Interventions: 2 patients received chemotherapy, but others rejected treatment.

Outcomes: Most patients died within 1 year after the onset of skin lesions.

Lessons: These findings suggest that skin infiltration of AML may precede any systemic evidence, and typical cutaneous lesions in elderly individuals may be indicative for AML.

Abbreviations: ALC = aleukemic leukemia cutis, AML = acute myeloid leukemia, AML-M5 = acute monocytic leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm, Hb = hemoglobin, HE = hematoxylin-eosin staining, HLA-DR = human leucocyte antigen DR, LC = leukemia cutis, LCA = leukocyte common antigen, PLT = platelet, POX = myeloperoxidase, RBT = routine blood test, WBC = white blood cell.

Keywords: acute monocytic leukemia, clinical manifestations, cutis

1. Introduction

The clinical manifestation of leukemia cutis (LC) results from an infiltration of leukemic cells into the epidermis, dermis, or subcutaneous tissues. Typically, cutaneous lesions present as multiple substantial reddish or purple red (occasionally dark red or brown), firm papules, plaques, or nodules which are 0.5 to 2.0 cm in diameter and involve the trunk and extremities. In some cases, rashes can extend over the whole body. It also can present as a purpuric rash or ecchymosis.

It has been reported that an overall incidence of LC in patients with acute myeloid leukemia (AML) reached 2% to 20%.^[1] There are different frequencies of skin involvement in various

subtypes of AML. Half of patients with acute monocytic leukemia (AML-M5) may finally develop LC.^[1] The presence of LC generally suggests that there are other sites of extramedullary involvement, thereby indicating a poorer prognosis.^[2,3] Therefore, early diagnosis and treatment of LC is important for symptomatic relief and improved prognosis.

2. Case report

This Ethics Committee of the Second Hospital of Jilin University has approved this study. All procedures followed were in accordance with the ethical standards of Institutional Review Board of the Second Hospital of Jilin University and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. General characteristics of 4 patients are shown in Table 1.

Four patients were admitted to the Dermatology Department of the Second Hospital of Jilin University and were diagnosed as AML-M5-LC.

Case 1: A 68-year-old woman presented with a 2-year history of papules on the right lower limb, and over the past 2 months lesions had extended over the whole body. The patient did not have fever, pruritus, or weight loss. She was previously diagnosed with lymphomatoid papulosis. On physical examination, there were multiple various sized, skin-colored to erythematous, firm papules over the trunk, extremities, and scalp. Lesions were isolated, and there was no ulceration (Fig. 1). There was no palpable lymph node enlargement. Apart from a low platelet

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Table 1**General characteristics of 4 patients.**

Case number	Gender/age	Initial CBC	Bone marrow examination	Flow cytometry	Treatment/prognosis
1	F/68	WBC: $6.39 \times 10^9/L$, monocytes: $0.7 \times 10^9/L$; RBC: $2.91 \times 10^{12}/L$; Hb: 94 g/L, PLT: $4.8 \times 10^9/L$	Nucleated cells in bone marrow showed active proliferation; Granulocytic cells (7%) at different stages reduced and had no evident morphological abnormality; Erythrocytic cells (0%) showed reduced proliferation, erythrocytic cells at different stages reduced, and mature RBCs displayed different sizes; Monocytes showed active proliferation, monoblast and promonocytes accounted for 79.5%, had large and irregular cell body, and were rich in gray-blue cytoplasm, there were some vacuoles, small granules were found in the cytoplasm, the nuclei were thin and net-like, there were 1–3 clear nucleoli. Lymphocytes showed normal proportion and morphology; 3 megakaryocytes were found, and few platelets were found. Cells were negative for POX	R3 (1.73%) were positive for CD33, CD38, CD13, CD64, CD15, HLA-DR, but negative for CD10, CD19, CD117, CD7, CD56, CD14, and CD11b; R5 (23.49%) were mainly immature monocytes, and increased significantly	Daunorubicin, cytarabine and neomycin daunorubicin/died within 6 mo after diagnosis
2	F/74	WBC: $16.7 \times 10^9/L$, monocytes: $6.6 \times 10^9/L$, RBC: $1.9 \times 10^{12}/L$; Hb: 64 g/L, PLT: $61 \times 10^9/L$	Difficult bone marrow aspiration, active bone marrow cell proliferation, erythrocytic cells were few, some granulocytic cells showed scattered distribution, the cell bodies with diffuse distribution were large and irregular, evident nucleoli and abundant cytoplasm were found in some cells, megakaryocytes were observable. Fibroblasts were focally found	Unavailable	Treatment refusal/died within 1 mo after diagnosis
3	M/82	WBC: $4.89 \times 10^9/L$; Monocytes: $0.7 \times 10^9/L$, RBC: $4.0 \times 10^{12}/L$; Hb: 130 g/L, PLT: $174 \times 10^9/L$	Monocytes increased significantly; pronormoblast and erythroblasts were the major RBC. Bone marrow aspiration showed extremely active proliferation; a large amount of naïve cells were observed; Acute myeloid leukemia was considered	Unavailable	Low-dose cytarabine, daunorubicin, homoharringtonine/16 mo
4	M/70	WBC: $14.7 \times 10^9/L$, monocytes: $7.4 \times 10^9/L$, PLT: $51.0 \times 10^9/L$, RBC: $3.9 \times 10^{12}/L$, lymphocytes: $4.4 \times 10^9/L$	Bone marrow aspiration showed active proliferation; G = 14%; E = 15.5%, G/E = 0.9:1. granulocytic cells reduced significantly; erythrocytic cells reduced markedly, mature RBCs had different sizes, lymphocytes accounted for 14.5%; monocyte cells increased significantly and were mainly promonocytes; These promonocytes had cell body of different sizes and abundant gray-blue cytoplasm, there were granules in cytoplasm, nuclei were irregular, chromatins were meticulous, and nucleoli were occasionally found. Only 3 megakaryocytes were noted; PLT were observable. Cells were weakly positive for POX. Bone marrow aspiration showed adipose tissues reduced, there was congestion, naïve cells showed patchy distribution, had large cell body and irregular karyotype, depressed, and folded nuclei were observed with clear nucleoli, there was abundant cytoplasm, mature granulocytes reduced, and erythrocytic cells decreased and megakaryocytes reduced. Focal hyperplasia of fibrous tissues was observed. Acute leukemia with secondary partial fibrosis was diagnosed	Tumor immunophenotyping: lymphocytes: 17.9%, granulocytes: 11.2%, abnormal cells: 60%, nucleated RBC: 10.9% CD34 + cells accounted for 0.4% of nucleated RBC. Gating in CD45/SSC scatter plot showed abnormal cells in the transition area from promonocytes to monocytes accounted for 60% of nucleated cells and were positive for HLA-DR, CD4, CD11b, CD13, CD33, CD38, CD56, and CD64, and some cells expressed CD14 and CD15. These indicated acute myeloid leukemia (probably M5 type)	Treatment refusal/1 y

CBC = complete blood count, Hb = hemoglobin, HLA-DR = human leucocyte antigen-DR, PLT = platelet, POX = myeloperoxidase, RBC = red blood cell, SSC = side scattering, WBC = white blood cell.



Figure 1. Clinical features: multiple reddish, substantial papules, and plaques 0.5 to 2.0 cm in diameter involving the trunk and extremities.

(PLT) count ($4.8 \times 10^9/L$), laboratory examination results were normal. She had no evident bleeding trend (including gum bleeding). No special treatment was administered before the pathological examination of the skin lesions.

These findings combined with skin biopsy results suggested that a lymphoreticular tumor was likely. After 20 days, the patient was examined for fever: her leukocyte count was $18.5 \times 10^9/L$. Peripheral blood smearing showed promonocytes accounted for 44% and had large and irregular cell body; these cells were rich in gray-blue cytoplasm; there were vacuoles and small granules in cells; the nuclei were thin and net-like, and there were 1 to 3 clear nucleoli in each nucleus. Following bone marrow examination, she was subsequently diagnosed with AML-M5 and received 2 cycles of chemotherapy (daunorubicin, cytarabine, and neomycin daunorubicin). Following chemotherapy, her lesions were remission but there were no changes in bone marrow and blood tests. The patient died 6 months after diagnosis.

Case 2: A 74-year-old woman presented with a 2-month history of red papules and nodules on the trunk. She was admitted to our department with progressive lesions that increased in number over a 1-week period. Systemic erythrous or cuticolor rashes, substantial papules and nodules of different sizes were found (sorghum sized to broad bean sized), some lesions merged partially, and there was no superficial ulcer. Pain, itching, and no other symptoms were noted (Fig. 1). One week later, the patient was admitted to the hematology department with dizziness, lassitude, and fever. Routine blood test (RBT) showed white blood cells (WBC) count was $16.7 \times 10^9/L$, monocyte count was $6.6 \times 10^9/L$, red blood cells (RBC) count was $1.9 \times 10^{12}/L$, hemoglobin (Hb) was 64 g/L, and PLTs count was $61 \times 10^9/L$. Peripheral blood smearing showed the WBC increased significantly and granulocytes reduced, naïve granulocytes were observable, mature RBCs displayed different sizes. Among 100 WBCs counted, there were no nucleated cells, lymphocytes accounted for 4%, monocytes increased significant-

ly (86%), and promonocytes and naïve monocytes accounted for 84%. The proportion of cells weakly positive for myeloperoxidase was higher than 3%. She was diagnosed as AML-M5 based on the third bone marrow examination. The patient requested discharge and died 1 month later.

Case 3: An 82-year-old man was admitted to our department with a 2-month history of extensive kermesinus papules on the prothorax and lesions extending over the trunk, limbs, face, and scalp. Systemic dark red or cuticolor rashes and nodules of different sizes were observed (sorghum sized to broad bean sized), lesions were not merged, and there was no superficial ulcer (Fig. 1). Laboratory examination was almost normal. RBT showed that WBC count was $4.89 \times 10^9/L$, monocytes count was $0.7 \times 10^9/L$, RBC count was $4.0 \times 10^{12}/L$, Hb was 130 g/L, and PLT count was $174 \times 10^9/L$. At disease onset, the WBC count was $14.5 \times 10^9/L$ and Hb was 109 g/L. He was previously diagnosed with drug eruption. Six months later, the patient was diagnosed with AML-M5 based on bone marrow examination. Peripheral blood smearing showed promonocytes accounted for 10%, immature monocytes for 11%, lymphocytes for 17%, metagranulocytes for 4%, rod-shaped nuclear cells for 8%, and segmented cells for 35%. This patient received 1 course of chemotherapy (cytarabine, daunorubicin, and homoharringtonine). Following chemotherapy, remission of the lesions were observed, but the patient died in 8 months after therapy.

Case 4: A 70-year-old man presented to our department with a 40-day history of extensive claret papules on the anterior chest. On admission, physical examination showed no palpable superficial lymph nodes enlargement, dark purple papules were diffusely distributed at the cheeks, trunk, and limbs. Pain, itching, and other symptoms were not observed (Fig. 1). The weight loss was 10 kg in the past month. Laboratory examinations showed normal. He was diagnosed with granuloma fungoides. Ten days later, RBT showed WBC count was $14.7 \times 10^9/L$, monocytes count was $7.4 \times 10^9/L$, PLT count was $51.0 \times 10^9/L$, RBC count was $3.9 \times 10^{12}/L$, and lymphocytes count was $4.4 \times 10^9/L$. Blood

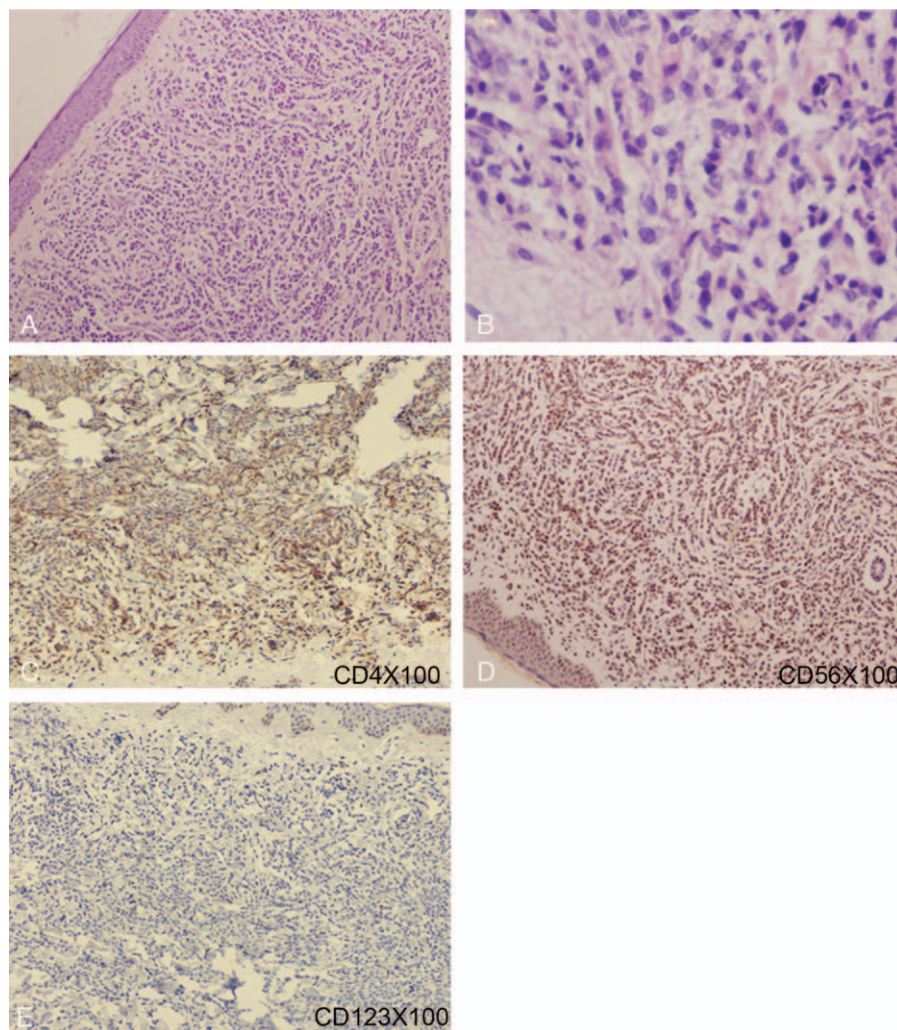


Figure 2. (A) Magnification of hematoxylin-eosin staining (HE) $\times 100$. (B) Magnification of HE $\times 400$. (C–E) The marker CD4, CD56 were positive, and CD123 was negative.

smearing showed WBCs increased significantly, granulocytes reduced, and mature RBCs showed different sizes. Among 100 WBCs counted, there were 1 proerythroblast and 3 orthochromatic erythroblasts, lymphocytes reduced significantly, monocytic cells increased markedly, but they were mature monocytes. Platelets were observable. Based on skin biopsy results, immunohistochemistry, and bone marrow examination, he was diagnosed with AML-M5. This patient rejected chemotherapy and died in the first year following diagnosis.

2.1. Pathohistologic findings

Pathohistologic changes for the 4 cases were similar. Epidermis had no significant changes. A dense monomorphous cellular infiltration involved the dermis. Some cells surrounded blood vessels and skin appendages in a concentric manner or showed single-row arrangement in the collagen fiber bundles. Uninvolved papillary dermis was found to separate normal epidermis from underlying dermal infiltration (Fig. 2A). Minor cells had a large kidney-shaped or oval nucleus with 1 or more conspicuous nucleoli, and abundant pale, slightly eosinophilic cytoplasm. Sometimes atypical mitotic figures were present (Fig. 2B). It is in accordance with literature (Tables 2 and 3).

2.2. Immunohistochemistry

Immunohistochemical results were lack of specificity. Immunohistochemical analyses for the 4 cases were similar (Fig. 2C–E). Markers for CD4, CD56, and leukocyte common antigen were positive and markers for CD20, CD34, and CD123 were negative in all cases. Marker CD68 was positive in cases 2 and 4 and CD45RO was positive in cases 1 and 2. CD3 and CD30 were negative in case 1 and CD117 was negative in cases 2, 3, and 4 (Table 4). The marker CD68 (7/9, 9 cases received immunohistochemical examination and 7 cases were positive) was positive and the markers including CD45RO(4), CD56(2), and CD4(4) were positive in all cases. The markers CD3(4), CD20(3), CD30(2), CD34(3), and CD117(2) were negative in all cases. Above all, the marker CD4 and CD56 were strongly positive; CD123 and CD20 were negative.

3. Discussion

Skin infiltration preceding any blood or bone marrow evidence of leukemia is classified as aleukemic leukemia cutis (ALC) and is very rare.^[1] All 4 of our cases are AML-M5-ALC. In the present report, the 4 patients were older than 68 years (median: 73.5 years). In previously reported 14 cases, only 2 patients were

Table 2**Summary of cases reported in the literature since 1986.**

Reference	Sex/age, y	Clinical manifestations	Pathogenic manifestations	Immunohistochemical results
Waller et al ^[3]	F/60	A persistent, tenderness, violaceous rash on scalp for 6wk	A diffuse infiltration of the dermis by atypical cells with a moderate to high nuclear to cytoplasm ratio, open chromatin, and 1 to 2 prominent nucleoli. The cells were discohesive and had a "squared off" appearance	Mild positivity for CD4 and strong positivity for CD33; CD3, CD10, CD34, CD43, CD68, CD 117, Tdt, MPO (–)
Gambichler et al ^[2]	F/43	Reddish papules and plaques gradually spread out on the face, trunk, and extremities for 6wk	An interstitial leukemic infiltrate. The so-called reticular pattern of infiltration was marked by diffuse permeation of the dermis. The myelomonocytic cells had large atypical nuclei with scant cytoplasm	CD33, CD45 (+)
Yonal et al ^[4]	M/63	Firm, extensive nodular swellings on the whole body	A diffuse neoplastic infiltration extending from the dermis to subcutaneous tissue	MPO, CD34 (+)
Hejmadi et al ^[5]	F/75	Erythematous maculopapular rash on the trunk for 8 wk	A monomorphic dermal infiltrate of hemopoietic cells with angulated nuclei and extremely convoluted nuclear membranes. The infiltrate involved the dermis and extended into the subcutaneous tissue. The hemopoietic cells were arranged in an interstitial pattern between collagen bundles. Mitotic figures were easily identified	CD45, CD43, CD4, CD68, CD163 (+), Ki-67 60%; CD34, CD117, CD2, CD3, CD5, CD7, CD8, CD30, CD56, CD57, CD20, CD138, CD79a, perforin, granzyme B, Pax5, Tdt, S100, mast cell tryptase (–)
litani et al ^[6]	M/81	Asymptomatic nodules on trunk and legs for 2 mo	A dense, nodular, diffuse infiltrate of monotonous uniform cells with round nuclei, prominent single or multiple nucleoli, and abundant pale, slightly eosinophilic cytoplasmic cells throughout the dermis and subcutaneous fat. A number of atypical mitotic figures were seen	Leukocyte common antigen, CD68, myeloperoxidase (+)
Hattori et al ^[7]	F/67	Diffuse edematous erythema distributing symmetrically on cheeks, eyelids and glabella for 1 mo	Dense infiltration of large atypical mononuclear cells in the dermis. Some cells were extended into the subcutaneous tissue, although epidermotropism was absent. The nuclei of those cells were large with irregular contours, and a few mitotic figures were observed	CD68, lysozyme (+)
Ferreira et al ^[8]	M/64	Multiple various sized, skin-colored to erythematous, psoriasis-like papules and plaques over the anterior trunk, abdominal wall and upper extremities	A diffuse infiltration involving the dermis and subcutis, with perivascular and periadnexal accentuation composed of monomorphous cells with homogeneous oval nuclei. The epidermis was not involved	Lysozyme, CD68 (+), MPO (–)
Perez et al ^[9]	F/49	An extensive eruption of rounded and ovoid dermal plaques affecting trunk and limbs for 1 y	A diffuse infiltrate of cells with bean-shaped nuclei in the upper dermis extending to the subcutis. Occasional immature myeloid blasts were seen	CD45 (+), some CD15, CD68 (–), CD3, CD20 (–)
Millard et al ^[10]	M/68	A widespread mildly pruritic eruption over the whole body for 5 wk	A Grenz zone with an underlying dense dermal infiltrate composed of large, mildly atypical mononuclear cells	Leukocyte common antigen, KP1 and PGM1 (+), MIB-1 40% (+)
Gil-Mateo et al ^[11]	F/50	Multiple puritic skin lesions for 1 mo, hundreds of erythematous nodules were located mainly on the anterior mink	A dense monomorphous cellular infiltrate involving the dermis and subcutis with perivascular and periadnexal accentuation. A zone of uninvolved papillary dermis that separated normal epidermis from the underlying dermal infiltrate was observed. The minor cells were characterized by a large kidney-shaped or oval nucleus with 1 or more conspicuous nucleoli, and abundant pale	Lysozyme, CD68, CD4, CD45Ra, CD43, CD15 (+), CD 3, CD30, CD 20 (–)

(continued)

Table 2
(continued).

Reference	Sex/age, y	Clinical manifestations	Pathogenic manifestations	Immunohistochemical results
Daoud et al ^[12]	M/67	Nodules and papules on the back, low limbs	A dense monomorphous cellular infiltrate involving the dermis and subcutis	CD43, monocyte common antigen (+)
Jiang et al ^[13]	M/81	Firm, extensive, claret nodular, papular swellings on the trunk	Gentle hyperkeratosis present in epidermis, dense infiltration of large atypical mononuclear cells in the dermis. Some cells were extended into the subcutaneous tissue. The nuclei of those cells were large with irregular contours	CD68 (+)
Wang et al ^[14]	M/47	Swelling of right testis 2 mo, extensive nodules on the whole body for 20 d	Diffuse permeation of the dermis by leukemic cells in strands between collagen bundles; The myelomonocytic cells had large atypical nuclei with scant cytoplasm	MPO, CD4, CD68, CD56 (+)
Huang et al ^[15]	M/86	Firm, extensive, claret infiltrated nodules, papules and plaques on the whole body for 1 mo	A diffuse infiltration involving the dermis and subcutis, with perivascular and periadnexal accentuation composed of monomorphous cells	None

diagnosed at about 40 years old, and the median age was 64.4 years. AML-M5-LC occurs most frequently in elderly people. The patients in our cases reports showed a similar clinical presentation to cases documented in the literature.^[2,16–19] Gingival hypertrophy is also striking and unique finding of the M4/M5 variants,^[1,20] although this feature was not reported in our patients.

Incidentally, we found that all 4 cases showed strong positive CD56 staining. Di Bona et al^[21] found that AML-M5 accounted for 37% in 37 AML cases of CD56 positivity. It was the highest proportion across the AML subtypes. Through literature review, it was thought that CD56 positivity is correlated with AML-M5-LC.^[10] Generally, CD56 may be also expressed in the normal NK cells, CD3+ cytotoxic T cells, some CD4+T cells, and monocytes. In addition, cells of neuroectodermal origin (such as nerve cells and neuroendocrine cells) may also express CD56. Tumor cells of lymphoma, pseudolymphoma, blastic plasmacytoid dendritic cell neoplasm (BPDCN), Merkel cell carcinoma, and small cell lung cancer with skin metastasis are also positive for CD56. When the

pathological examination shows changes similar to those in skin infiltration of AML and tumor cells are negative for markers of T cells and B cells, being positive for CD56 is indicative of leukemia or BPDCN. Although immunohistochemical changes lack specificities, CD4, CD56 in all 4 patients were strongly positive, and the marker CD123 was negative. Expression of CD4, CD56, and lack of CD123 may be the immunological markers for AML-M5-LC.

This disease should be differentiated from metastatic skin tumors, lymphomas, and neuroendocrine tumors according to the clinical and pathological features. Metastatic skin tumors may also manifest multiple nodules and papules clinically and the infiltration of private-like tumor cells with evident atypia in dermal collagen fibers pathologically. However, the primary cancer may be identified by systemic examination in patients with metastatic skin tumors. In addition, immunohistochemistry may display features identical to those of primary cancer, and bone and blood examination may fail to show abnormalities. Plaques or nodules and evident itching are the predominant clinical

Table 3
Treatments and the outcomes of these cases in the literature since 1986.

Reference	Treatment	Prognosis
Waller et al ^[3]	Unclear	Unclear
Gambichler et al ^[2]	Cytarabine, idarubicine, and cyclophosphamide	Died within 12 mo after diagnosis
Yonal et al ^[4]	Cytarabine 100 mg/m ² for 7 d and idarubicin 12 mg/m ² for 3 d	Died within 7 mo after diagnosis
Hejmadi et al ^[5]	Unclear	Died within 4 wk after diagnosis
litani et al ^[6]	Unclear	Died within 8 wk after diagnosis
Hattori et al ^[7]	Enocitabine and daunorubicin hydrochloride	Remission
Ferreira et al ^[8]	cytarabine, daunorubicin, and cyclosporin	Died within 3 mo after diagnosis of rash
Perez et al ^[9]	FLAG-Ida (fludarabine, cytosine arabinoside, idarubicin, granulocyte colony stimulating factor)	Died within 1 y after diagnosis of rash
Millard et al ^[10]	Symptomatic and supportive therapies	Rash disappeared within 6 wk
Gil-Mateo et al ^[11]	Cytarabine, idarubicine, and cyclophosphamide	Died within 12 mo after diagnosis
Daoud et al ^[12]	Unclear	Remission after 1 y
Jiang et al ^[13]	Cytarabine, homoharringtonine	Died within 2 wk after diagnosis
Wang et al ^[14]	MA protocol (mitoxantrone, cytarabine), IA protocol (demethoxy daunorubicin, cytarabine), VMCPV protocol (vincristine, mitoxantrone, cyclophosphamide, prednisone, etoposide), VMA protocol (vincristine, mitoxantrone, and cytarabine)	Died
Huang et al ^[15]	Symptomatic treatments	Died within 2 mo after diagnosis of skin rash

Table 4**Findings from immunohistochemistry of the skin in 4 patients.**

Antibody	Case 1	Case 2	Case 3	Case 4
CD3	–	–	No staining	–
CD4	+	+	+	+
CD20	–	–	–	–
CD30	–	No staining	No staining	No staining
CD34	–	–	–	–
CD45RO	+	+	No staining	No staining
CD56	+	+	+	+
CD68	No staining	+	No staining	+
CD117	No staining	–	–	–
CD123	–	–	–	–
CD138	No staining	No staining	+	No staining
LCA	+++	+++	+++	+++
MPO	No staining	–	–	–
Vimentin	No staining	No staining	+++	No staining
AE1/AE3	–	No staining	–	No staining

LCA = leukocyte common antigen.

characteristics of cutaneous T-cell lymphoma; pathologically, tumor cells are proepidermal, spinal lamina lymphocytes form typical Pautrier microabscess, and immunohistochemistry shows that tumor cells are positive for markers of clonal T lymphocytes (CD3 and CD4). However, tumor cells of AML have no CD3 expression. Merkel cell carcinoma is one of neuroendocrine tumors, and tumor cells are smaller than spine cells and have little cytoplasm; pathologically, Merkel cell carcinoma is similar to AML and also positive for CD56; tumor cells of Merkel cell carcinoma are also positive for other markers of neuroendocrine tumors (TTF-1, CgA, Syn, NSE, and CK20), but negative for CD4. In addition, bone marrow examination and flow cytometry does not show changes as in AML. In case 4 of present report, the disease should be differentiated from CD4+CD56+ BPDCN according to the clinical and pathological features. However, this disease was positive for CD123, and flow cytometry did not show the changes as in AML. In the present report, the case was negative for CD123, and thus CD4+CD56+ BPDCN may be excluded.

The present treatments mainly include chemotherapy in which Daunorubicin (ZHEJIANG HISUN PHARMACEUTICAL CO. LTD, Taizhou City, Zhejiang province, China), neomycin daunorubicin, cytarabine, retinoic acid, gituximab, etoposide, and methotrexate are used. Radiotherapy may also be employed if necessary. Our findings and those reported in previous studies^[3–9,11,12] showed that there is no effective treatment for this disease. Lee et al^[22] employed sorafenib in the treatment of skin infiltration of AML with internal tandem duplication, and complete remission was observed.

Skin infiltration of AML-M5 has a poor prognosis, and most patients died within 1 year after diagnosis.^[3–9,11,12] This may be explained as that tumor cells in the skin escape from the killing of chemotherapeutics because most chemotherapeutics mainly kill tumor cells in the bone marrow, tumor cells in the skin are hard to be killed, and these tumor cells may be a major cause of recurrence.^[1,20] Thus, some clinicians proposed that total skin electron beam radiation therapy may be employed simultaneously with chemotherapy in leukemia patients with skin involvement.^[1,20] There is evidence showing that increased lactate dehydrogenase in patients with skin infiltration of AML predicts a poor prognosis.^[1]

Taken together, the progression of molecular biology and the application of genetic diagnosis in skin infiltration of AML-M5

may help the development of effective treatments such as target therapy and biotherapy.

In conclusion, clinicians should pay special attention to the differential diagnosis of this disease in elderly patients. It has a higher skin infiltration rate compared with other subtypes and a poor prognosis. Skin biopsy and immunohistochemical examination, combined with routine blood analysis and bone marrow examination, are required to ensure early diagnosis and proper treatment to delay the progress of this disease. Improvements in present treatment for AML-M5-LC require further discussion.

References

- Patel LM, Maghari A, Schwartz RA, et al. Myeloid leukemia cutis in the setting of myelodysplastic syndrome: a crucial dermatological diagnosis. *Int J Dermatol* 2012;51:383–8.
- Gambichler T, Herde M, Hoffmann K, et al. Poor prognosis of acute myeloid leukaemia associated with leukaemia cutis. *J Eur Acad Dermatol Venereol* 2002;16:177–8.
- Waller WL, Hughes SR, Boh E. Leukemia cutis masquerading as a chemical burn. *J Am Acad Dermatol* 2011;64:1003–4.
- Yonal I, Hindilerden F, Coskun R, et al. Aleukemic leukemia cutis manifesting with disseminated nodular eruptions and a plaque preceding acute monocytic leukemia: a case report. *Case Rep Oncol* 2011;4:547–54.
- Hejmadi RK, Thompson D, Shah F, et al. Cutaneous presentation of aleukemic monoclastic leukemia cutis—a case report and review of literature with focus on immunohistochemistry. *J Cutan Pathol* 2008;35 (suppl 1):46–9.
- Iitani MM, Abe R, Yanagi T, et al. Aleukemic leukemia cutis with extensive bone involvement. *J Am Acad Dermatol* 2010;63:539–41.
- Hattori T, Amano H, Nagai Y, et al. Leukemia cutis in a patient with acute monocytic leukemia presenting as unique facial erythema. *J Dermatol* 2008;35:671–4.
- Ferreira M, Caetano M, Amorim I, et al. Leukemia cutis resembling a flare-up of psoriasis. *Dermatol Online J* 2006;12:13.
- Perez A, Kennedy C, Standen G, et al. A case of monocytic leukaemia cutis in a patient with myelodysplastic syndrome transforming to acute myeloid leukaemia. *Clin Exp Dermatol* 2004;29:497–8.
- Millard TP, Aitchison R, Wilkinson JD. Aleukaemic leukaemia cutis presenting as a benign-appearing eruption. *Clin Exp Dermatol* 2003;28:148–50.
- Gil-Mateo MP, Miquel FJ, Piris MA, et al. Aleukemic “leukemia cutis” of monocytic lineage. *J Am Acad Dermatol* 1997;36(5 pt 2):837–40.
- Daoud MS, Snow JL, Gibson LE, et al. Aleukemic monocytic leukemia cutis. *Mayo Clin Proc* 1996;71:166–8.
- Jiang PD, Hua HK, Li M. One case of acute myelomonocytic leukemia presenting as a benign-appearing cutaneous exanthema. *Chin J Derm Venereol* 2007;21:366–7.

- [14] Wang WW, Pan MA, Hu Y. A case report and literatures review of acute monocytic leukemia with initial manifestations of subcutaneous nodules and testicular infiltration. *China Medical Herald* 2011;8:121-3.
- [15] Huang DB, You C, Ye XY. A case report of acute monocytic leukemia. *J Clin Dermatol* 2014;43:617-9.
- [16] Kaddu S, Zenahlik P, Beham-Schmid C, et al. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. *J Am Acad Dermatol* 1999;40(6 pt 1):966-78.
- [17] Majd NK, Jain SK, Murphy MC, et al. Total skin electron beam radiation in a pediatric patient with leukemia cutis: a case report. *J Pediatr Hematol Oncol* 2012;34:556-8.
- [18] Miyoshi I, Uemura Y, Sonobe H, et al. Leukemia cutis. *Intern Med* 2007;46:65-6.
- [19] Thomas CG, Patel RM, Bergfeld WF. Cytophagic and S-100 protein immunoreactive myeloid leukemia cutis. *J Cutan Pathol* 2010;37:390-5.
- [20] Weinel S, Malone J, Jain D, et al. Leukaemia cutis in a patient treated for breast cancer. *Australas J Dermatol* 2009;50:52-5.
- [21] Di Bona E, Sartori R, Zambello R, et al. Prognostic significance of CD56 antigen expression in acute myeloid leukemia. *Haematologica* 2002;87:250-6.
- [22] Lee SH, Paietta E, Racevskis J, et al. Complete resolution of leukemia cutis with sorafenib in an acute myeloid leukemia patient with FLT3-ITD mutation. *Am J Hematol* 2009;84:701-2.