

## A Case of Aleukemic Leukemia Cutis

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Aleukemic leukemia cutis is a rare condition characterized by invasion of leukemic cells in the skin before their appearance in the peripheral blood or bone marrow. We report a case of a 24-year-old man who presented with a 2-month history of nodules on his chin and left thigh. His medical history included acute myelocytic leukemia which had been in complete remission for 13 years and seminoma of the right testis which had been treated with orchiectomy 1 year before. Biopsy of the cutaneous lesions revealed infiltrating cells characterized by irregular shaped or kidney bean-shaped nuclei with abundant pale, slightly eosinophilic cytoplasm. These atypical cells stained positive for leukocyte common antigen, lysozyme and myeloperoxidase. His peripheral blood examination and bone marrow biopsy failed to demonstrate leukemic changes. With these results, a diagnosis of aleukemic leukemia cutis was made. We then performed another immunohistochemical stain for lysozyme and myeloperoxidase on the testicular specimen which had been diagnosed as seminoma 1 year previously. The tumor cells of seminoma were lysozyme- and myeloperoxidase-positive. We were also able to diagnose seminoma as isolated granulocytic sarcoma. A complete remission of the cutaneous lesion was achieved with chemotherapy, but recurrent leukemia cutis reappeared six months later. He underwent a bone marrow transplant but died 3 months later. (*Ann Dermatol (Seoul)* 18(2) 86~90, 2006)

*Key Words:* Aleukemic leukemia cutis, Granulocytic sarcoma

### INTRODUCTION

Aleukemic leukemia cutis is an extremely rare condition characterized by the appearance of specific cutaneous infiltrates in the absence of other signs of leukemia. Granulocytic sarcoma is an extramedullary tumor composed of granulocytic precursor cells and is rarely recognized as an isolated tumor without any evidence of leukemia. These primary cutaneous

lesions and tumors with normal blood and bone marrow can be used as a sign to forecast the development or relapse of leukemia. We report a case of aleukemic leukemia cutis and isolated granulocytic sarcoma, which was initially diagnosed as seminoma, in a patient with acute myelocytic leukemia in complete remission.

### CASE REPORT

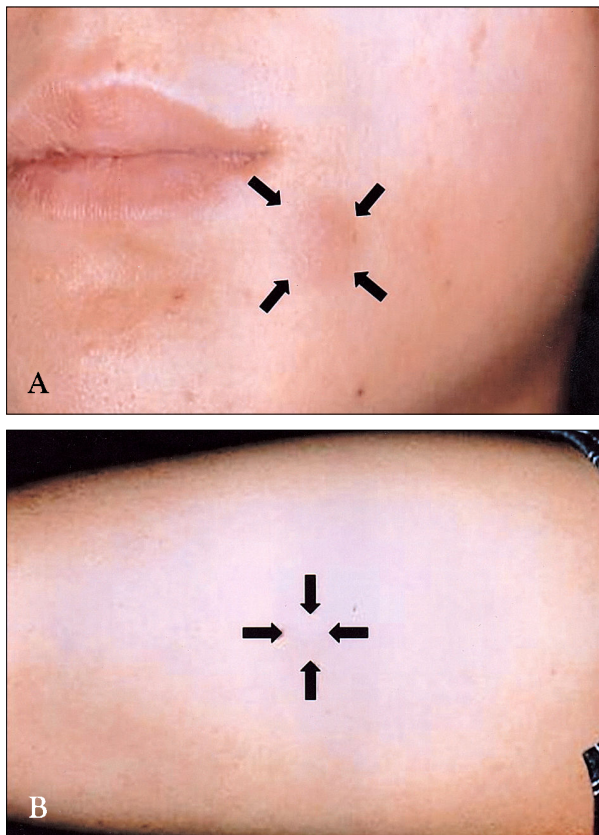
A 24-year-old male presented with a 2-month history of nodules on his chin and left thigh. His medical history included acute myelocytic leukemia which had been in complete remission for 13 years and a mass on the right testis which had been treated with radical orchiectomy and radiotherapy 1 year before. The initial diagnosis on the right testis was seminoma. Clinical examination revealed asymptomatic, 1.0 × 1.5 cm sized, skin to plum-colored nodules on the chin and left thigh (Fig. 1). There

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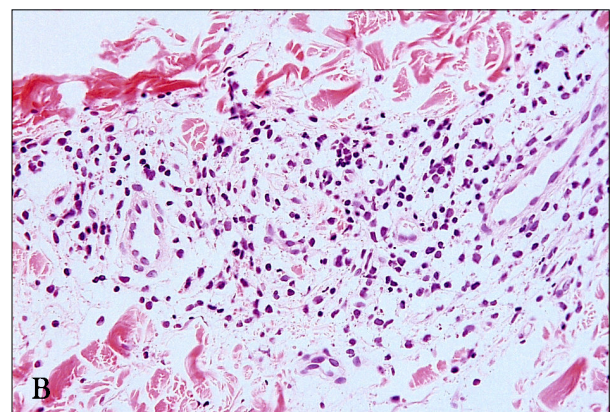
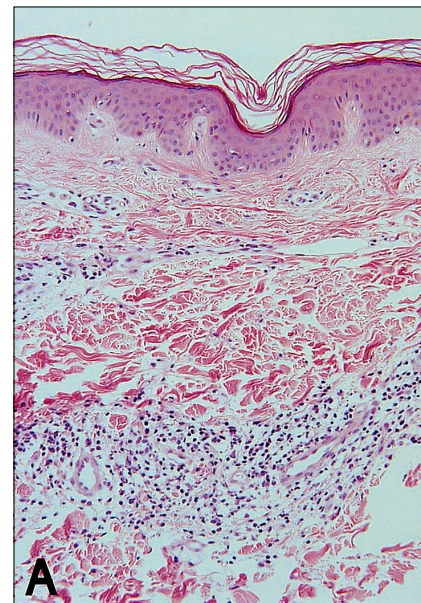
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**Fig. 1.** An erythematous nodule on the chin (A) and skin-colored nodule on the left thigh (B).

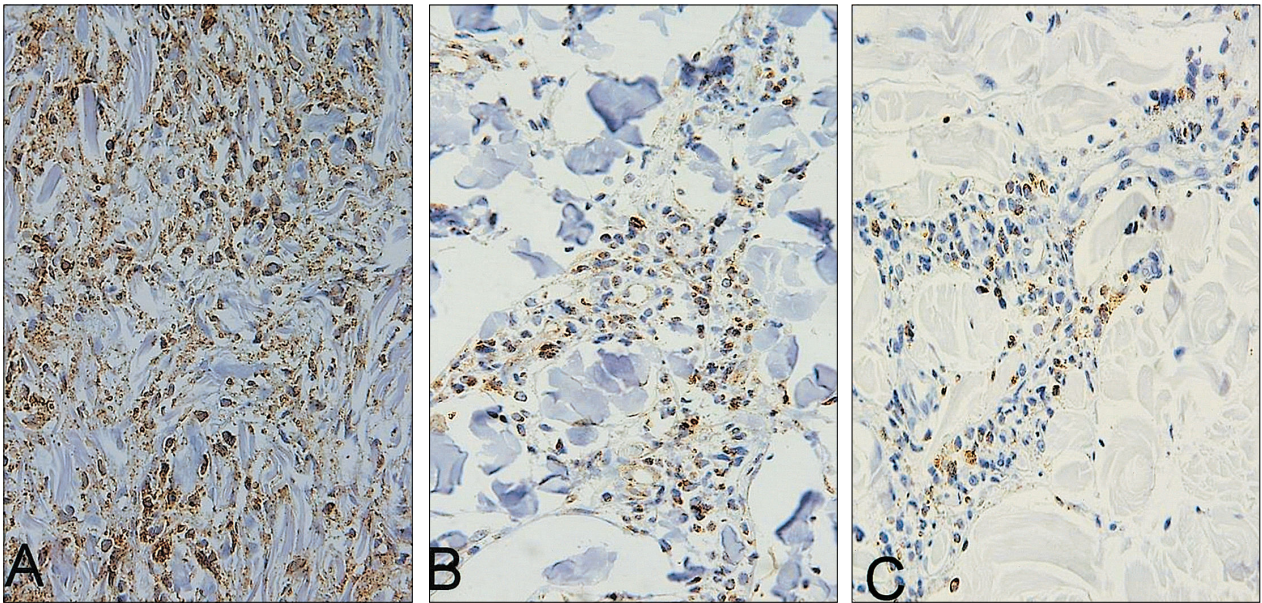
was no gum hypertrophy, lymphadenopathy or organomegaly on physical examination. A complete blood cell count revealed the following values: hemoglobin, 14.1g/dL; hematocrit, 40%; white blood cell count, 4500/ $\mu$ L with 77% segmented forms, 13% lymphocytes, 8% monocytes, and 2% eosinophils; platelet count, 179000/ $\mu$ L; and reticulocyte, 1.6%. A peripheral blood smear showed only mild thrombocytopenia. Bleeding time, prothrombin time, partial thromboplastin time, and urine analysis were within normal limits. There were no abnormal findings with the chest X-ray or abdominopelvic CT. Punch biopsies were performed at each site. On microscopic examination, the nodules disclosed dense, linear and diffuse infiltrate involving the entire dermis and impinging the subcutis while sparing the epidermis. The infiltrate surrounded vascular and adnexal structures (Fig. 2A). At higher magnification, most of the infiltrating cells were characterized by irregular-shaped or kidney bean-shaped nuclei with abundant pale, slightly eosino-



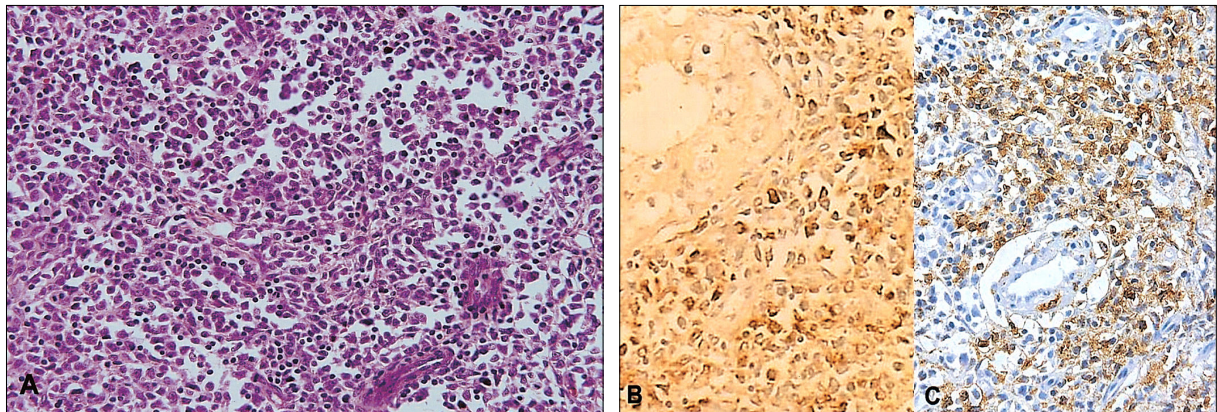
**Fig. 2.** The histopathologic findings show perivascular infiltration composed of pleomorphic cells in the dermis (H & E,  $\times 100$ , A). Higher magnification of Fig. 2-A showing atypical cells characterized by irregular shaped or kidney bean-shaped nuclei with abundant pale, slightly eosinophilic cytoplasm (H & E,  $\times 200$ , B).

philic cytoplasm (Fig. 2B). Immunohistochemical staining identified that the atypical cells stained positive for leukocyte common antigen (Fig. 3A), lysozyme (Fig. 3B) and myeloperoxidase (Fig. 3C), but not for B-cell-specific or T-cell-specific antigens. Results of the bone marrow aspiration and biopsy revealed that erythroid precursors and granulocytic precursors were normal in number and in distribution, and leukemic blasts had not increased. Chromosomal analysis failed to demonstrate an





**Fig. 3.** The infiltrative tumor cells show positive response to immunohistochemical staining with leukocyte common antigen ( $\times 200$ , A), lysozyme ( $\times 200$ , B), and myeloperoxidase ( $\times 200$ , C).



**Fig. 4.** The testicular specimen showing infiltration of the neoplastic cells with oval or folded nuclei, inconspicuous nucleoli (H & E,  $\times 100$ , A). The infiltrative tumor cells show positive response to myeloperoxidase ( $\times 200$ , B), and lysozyme ( $\times 200$ , C).

abnormal karyotype (46, XY). These observations indicated the diagnosis of aleukemic leukemia cutis. We then performed another immunohistochemical stain for lysozyme and myeloperoxidase on the testicular specimen which had been diagnosed as seminoma 1 year before. The tumor cells of seminoma were lysozyme and myeloperoxidase-positive. We were also able to diagnose seminoma as isolated granulocytic sarcoma. Antileukemic therapy was initiated with cytosine arabinoside and daunorubicin,

and a complete remission of the cutaneous lesions was achieved with induction chemotherapy. Two months later, the patient was re-hospitalized for consolidation chemotherapy. Results from the complete blood cell count were normal, and the patient was felt to be in complete clinical remission. But recurrent leukemia cutis on his left thigh was confirmed by a skin biopsy specimen six months later. He underwent a successful bone marrow transplant, but died from sepsis 3 months after the

treatment.

## DISCUSSION

Leukemia is associated with a wide variety of specific and nonspecific cutaneous manifestations, including pruritus, pallor of anemia, purpura, hyperpigmentation, vasculitis, exfoliative erythroderma, pyoderma gangrenosum, prurigo-like papules, erythema multiforme, urticaria, panniculitis, bullous eruptions, ichthyosis, acute febrile neutrophilic dermatosis, and a variety of recurrent bacterial, viral, and fungal dermatoses<sup>1-4</sup>. The specific eruptions, termed leukemia cutis, are much less common than nonspecific manifestations and result from skin infiltration by neoplastic cells or their precursors.

Ratnam et al.<sup>5</sup> reported that the most common presentation of leukemia cutis was multiple papules, nodules or infiltrated plaques, and the lesions varied from flesh-colored to red-brown or plum colored. Leukemia cutis represents dissemination of systemic disease to the skin and is confirmed by histopathological analysis of the tissue biopsy specimen. Leukemia cutis usually develops several months after the diagnosis of systemic leukemia, although it occasionally preceded it (aleukemic form)<sup>2</sup>. Aleukemic leukemia cutis is an extremely rare condition characterized by the appearance of specific cutaneous infiltrates in the absence of other signs of leukemia. The distinction between leukemic and aleukemic is important from the therapeutic and the prognostic standpoints. The presence of leukemic infiltrates of the skin has been associated with a high likelihood of systemic and dermal relapse after standard induction chemotherapy in patients with leukemia<sup>6,7</sup>. The prognosis of patients with leukemia with skin infiltrates was generally grave: Su et al.<sup>2</sup> reported that 88% of patients in the series died, most within one year of diagnosis.

The incidence of leukemia cutis varies greatly according to the type of leukemia. In analysis of 877 cases, Baer et al.<sup>6</sup> reported that eighteen patients (2%) seen with AML over 17 years had skin involvement, all occurring with FAB (French-American-British) types and two of these had skin disease preceding bone marrow involvement by up to 6 months. There was a strong association of extramedullary disease into other sites, particularly the CNS, which involved six patients (33%). There were no consis-

tent cytogenetic findings.

Granulocytic sarcoma, also known as chloroma, is an extramedullary tumor composed of granulocytic precursor cells and may precede the appearance of circulating blasts in acute non-lymphocytic leukemia and, as such, represent a form of aleukemic leukemia cutis<sup>8</sup>. Granulocytic sarcoma occur most commonly in lymph nodes, skin, bone, and soft tissue, but they can affect almost any anatomic site. They may be found in patients with known acute myeloid leukemia, with a chronic myeloproliferative disorder, with a myelodysplastic syndrome, or with no prior hematologic disease. In patients with myelodysplasia, granulocytic sarcoma often heralds the development of acute myeloid leukemia, and even patients with no prior hematologic disease usually develop acute leukemia unless they are treated aggressively upon discovery of the granulocytic sarcoma<sup>9,10</sup>. In some series, the majority of cases of granulocytic sarcoma were initially misinterpreted<sup>11</sup>, and this has been the experience in the testis as well<sup>11</sup>. In our case, the proper diagnosis was initially missed and a correct diagnosis was made when skin lesion developed, and first relapse occurred in the testis, without abnormality of peripheral blood. Testicular involvement is also seen in ALL and the testicles are a frequent site of relapse. In AML, collections of leukemic blast cells, often referred to as myeloblastomas, can appear as rubbery, fast-growing masses<sup>12</sup>.

The diagnosis of aleukemic leukemia cutis may be difficult, because most patients present with asymptomatic clinical manifestations ranging from a single nodule to erythroderma. To confirm the diagnosis of aleukemic leukemia cutis, immunohistochemistry of the skin lesions as well as a complete staging procedure is necessary. Both acute and chronic forms of myeloid leukemia are derived from myeloid progenitors in the bone marrow, therefore, cells are histochemically positive for myeloperoxidase, Sudan black B, chloroacetate esterase, and naphthol-AS-D-chloroacetate esterase (Leder) stains. Myeloid cells do not express B-lineage (CD19, CD20, CD22, CD19a) or T-lineage (CD2, CD3, CD5, CD7) markers, but may show immunohistochemical staining for the myeloid markers CD13, CD33 (My-9), CD15, CD117, or megakaryoblastic antigens C41 and CD61<sup>13</sup>.

The mechanism of extramedullary invasion of leukemic cells is still unknown. CD56 has been implicated as a possible risk factor of developing extramedullary infiltration in AML. Also, coexpres-



sion of CD56 and CD4 on tumor cells, or a synergistic role between CD56 and t (8;21) (q22;q22), has been speculated to be involved<sup>14,15</sup>.

There is no consensus regarding the treatment of choice for aleukemic leukemia cutis. Most reports demonstrated that local irradiation alone is ineffective in preventing subsequent development of overt leukemia and the outcome is dismal. On the other hand, systemic chemotherapy is suggested as a curative intent therapy<sup>15</sup>. Byrd et al<sup>16</sup> stated that extramedullary leukemia showed a different behavior depending on the type of therapy employed and the accuracy of the initial diagnosis. Patients who had received only local therapy (i.e. surgery and/or radiation) were at risk of developing AML within a median time of 7 months and had a median survival time of 14 months from extramedullary leukemia. By contrast, only 33% of the patients who had initially received AML induction chemotherapy developed overt leukemia: in these patients local therapy did not affect the course of the disease.

In conclusion, the diagnosis of leukemia cutis in the absence of peripheral blood and bone marrow disease is difficult. The application of immunohistochemical methods enables easy differentiation. Its recognition is important, because early diagnosis should lead to more appropriate chemotherapy, and a better prognosis.

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