SKIN

BRIEF ARTICLE

Leukemia Cutis in An Adult Patient with Acute Lymphoblastic Leukemia: A Review of Histopathology and Immunohistochemistry in Diagnosis

Alessandro Alfieri, MD[1], Satiti Retno Pudjiati, MD[1], Ery Kus Dwianingsih, MD[2]

[1] Department of Dermatology and Venereology, Faculty of Medicine, Nursing, and Public Health, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia
[2] Department of Anatomical Pathology, Faculty of Medicine, Nursing, and Public Health, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

ABSTRACT

Leukemia Cutis (LC) is a condition of cutaneous infiltration by neoplastic leukocytes. It can manifest in any leukemia, but LC caused by acute lymphoblastic leukemia (ALL) has the rarest incidence compared to other types of leukemia. The examination of histopathological morphology supported by immunohistochemical examination and its correlation with peripheral blood morphology and bone marrow is important in the final diagnosis of LC. We present a LC case of a 35-year-old male patient with ALL, using histopathological and immunohistochemistry examinations to diagnose. This case report aims to help clinicians establish the diagnosis for cutaneous manifestations in patients with ALL by using histopathological and immunohistochemical examinations.

INTRODUCTION

Leukemia cutis (LC) is cutaneous infiltration by neoplastic (myeloid or lymphoid) leukocytes, which can be identified clinically in cutaneous lesions. The subtypes of leukemia with cutaneous involvement can be divided into two broad groups, namely myeloid disorders and lymphoproliferative disorders.[1] The prevalence of LC has been reported in 2-3% of patients with systemic leukemia.[2] Among that, acute lymphoblastic leukemia (ALL) has the rarest incidence for the occurrence of LC, which is less than 1%.[3] Hereby we report a case of a 35-year-old man with ALL diagnosed with LC. The discussion in this paper will emphasize the diagnosis by histopathology and immunohistochemistry. This paper aims to help clinicians establish the diagnosis for LC in patients with ALL using histopathological and immunohistochemical examinations.

CASE REPORT

A 35-year-old man came to the emergency department complaining of general weakness and fever. These complaints had been felt for three months after the patient had undergone surgery for a lump in his neck. The patient also complained of red patches that appeared on his face, trunk, and extremities, which turned into black patches within three days.

The physical examination showed that the blood pressure was 106/59, the pulse rate was 122 beats per minute, and the respiratory rate was 20 times per minute with a temperature of 38°C. The patient's conjunctiva was anemic, and enlarged lymph nodes were found in the bilateral cervical, supraclavicular, and mandibular regions. On the skin lesion examination, hyperpigmented plaques were found on both cheeks and the temporal region of the face, chest, abdomen, back, arms, and proximal legs (**Figure 1**).

The laboratory examination revealed anemia (haemoglobin 3.4 g/dL), leukocytosis (white blood cells 23.24 × 10^3/µL with 93.3% lymphocytes), and thrombocytopenia (platelets 12 × 10^3/µL). Peripheral blood morphology showed abnormal erythrocyte morphology, 90% lymphoid blast-like cells, and decreased platelets. The result of bone marrow puncture (BMP) supported the diagnosis of acute lymphoblastic leukemia (ALL)-L1. The skin biopsy from the patient's cheek showed an atrophic epidermis with flattened rete ridges. The epidermis was free of tumor cell infiltration, with a grenz zone in the upper dermis. A diffuse cellular tumor infiltrate extended from the dermis to the subcutaneous tissue. The tumor cells were monotonous, medium-sized with scant cytoplasm. The nuclei showed single or multiple daughter nuclei, with evident mitotic figures (**Figure 2**). Immunohistochemical (IHC) staining revealed (**Figure 3**):

1. CD45 : Strong membrane and cytoplasmic expression
2. TdT : Strong nuclear expression in most tumor cells
3. CD3 : Partial membrane and cytoplasmic expression
4. CD20 : Negative membrane and cytoplasmic expression
5. CD117 : Negative membrane expression
6. Ki67 : Strong nuclear expression in 60% of tumor cells

From the histopathology and IHC profile, the diagnosis of leukemia cutis in a patient with ALL, with the subtype T-cell ALL, was concluded. With this diagnosis, the patient received a protocol of chemotherapy administration with daunorubicin, vincristine, cyclophosphamide, L-asparaginase, and prednisone.

DISCUSSION

The pathogenesis of the appearance of leukemic cell infiltration in the skin is still not well elucidated. A hypothesis about migrating leukemic cells to skin tissue is based on specific adhesion molecules in the skin tissue to memory T cells. Adhesion molecules, chemokines, and integrins may be essential in migrating these cells.[1]

In the histopathological appearance of ALL lesions, there may be diffuse, interstitial, or nodular infiltration, with or without peri-adnexal or perivascular involvement. The involvement of the epidermis is infrequent, and usually, there will be a zone of tumor-cell-free area at the dermo-epidermal junction (Grenz zone).[4] The cell morphology usually gives a monotonous appearance, moderate in size, and has a rounded nuclear contour and blastic chromatin.[5]

Leukemia cutis in ALL is difficult to distinguish morphologically from other malignancies, especially non-Hodgkin lymphoma (NHL).[6] Lymphoblastic lymphoma, a type of NHL, and lymphoblastic leukemia can be differentiated based on bone marrow involvement. If lymphoid blast cells replace less than 25% of bone marrow tissue, the diagnosis is lymphoma; if they replace more than 25%, the diagnosis is leukemia.[7]

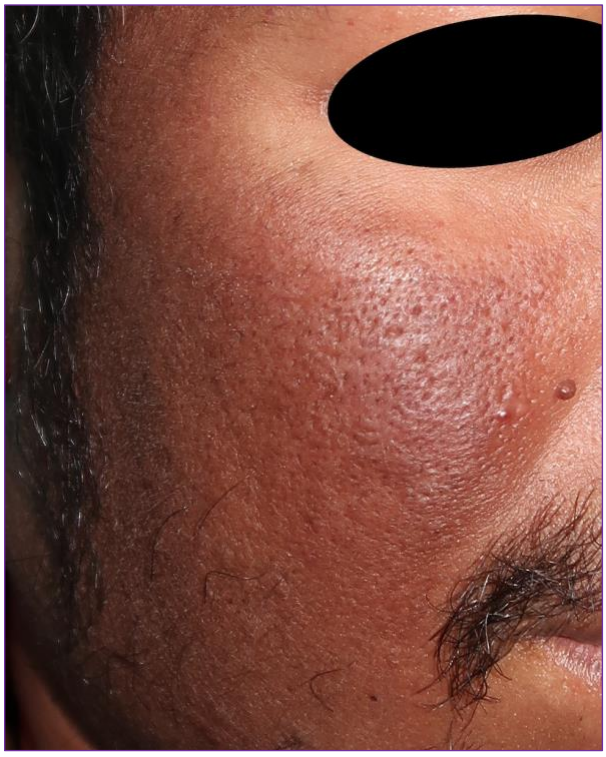

Figure 1. Hyperpigmented plaques present on the left and right cheek

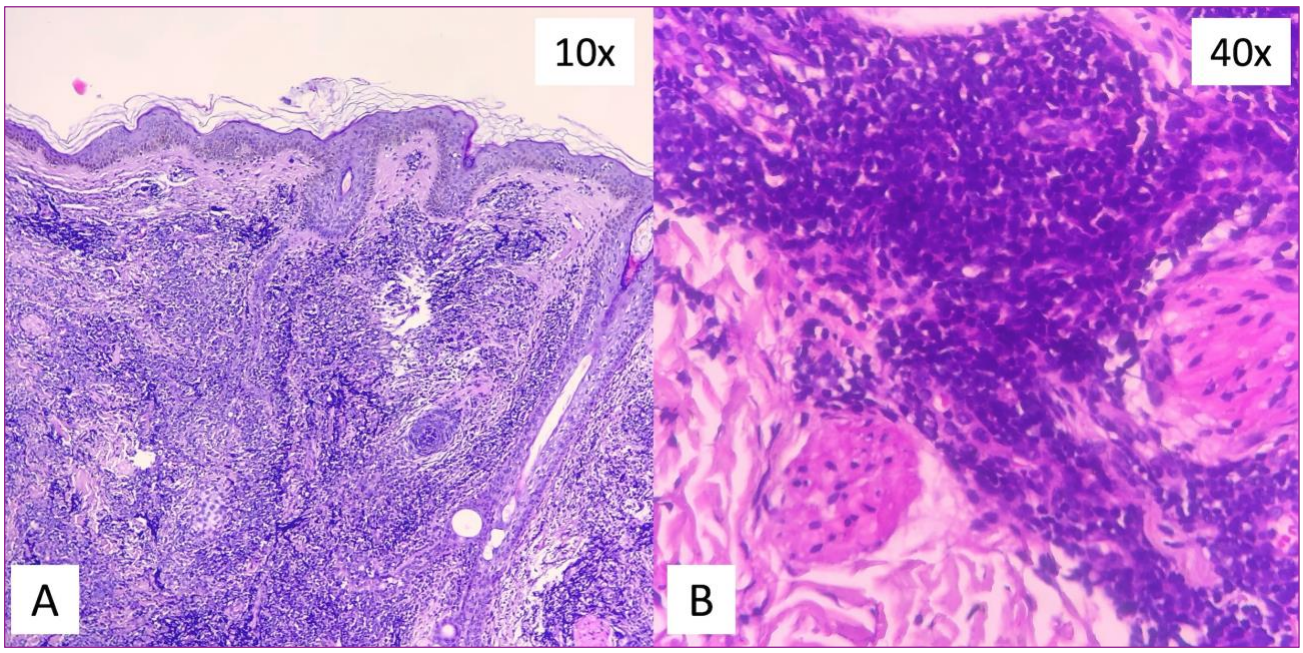

Figure 2. (A) The epidermis showed no tumor cell infiltration, and a Grenz zone was observed in the upper dermis. The tumor cells were diffusely arranged throughout the dermis. (B) These lymphoid tumor cells displayed monotonous morphology and were moderate in size with scanty cytoplasm. Each cell contained a single nucleus with a single daughter nucleus.

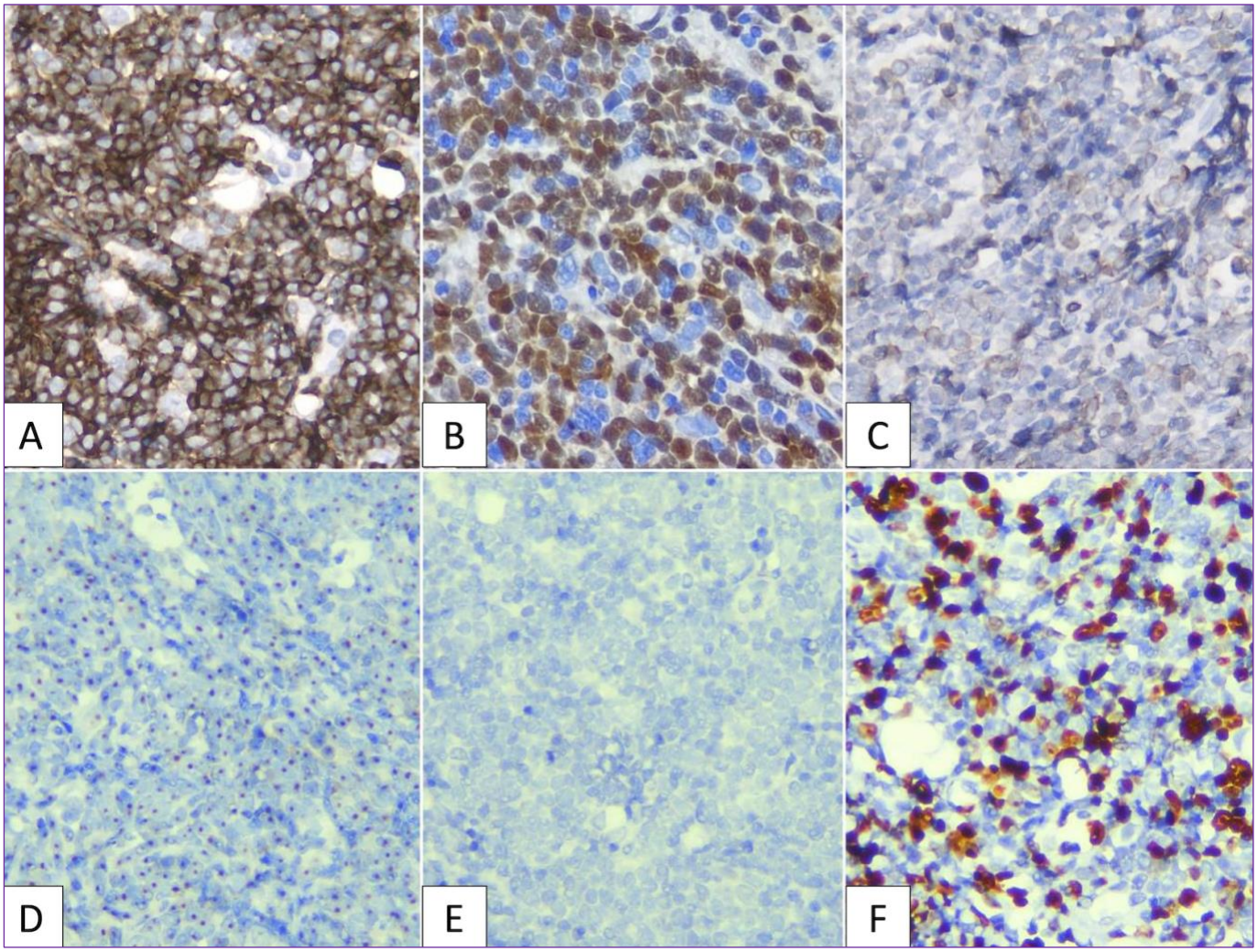

Figure 3. (A) CD45: Strong membrane and cytoplasmic expression; (B) TdT: Strong nuclear expression in most tumor cells; (C) CD3: Partial membrane and cytoplasmic expression; (D) CD20: Negative membrane and cytoplasmic expression; (E) CD117: Negative membrane expression; (F) Ki67: Strong nuclear expression in 60% of tumor cells

Immunohistochemistry (IHC) staining remains the primary ancillary examination for establishing the diagnosis and characterizing neoplastic cells.

Terminal deoxynucleotidyl Transferase (TdT) is a DNA polymerase marker commonly expressed in immature, pre-B, and pre-T lymphoid cells that helps to differentiate ALL from mature lymphoid malignancies.[8] In situations with overlapping histopathological features, TdT can also help differentiate between ALL and other conditions, such as mycosis fungoides or Sézary syndrome.[9] Furthermore, combining CD3, the most sensitive and reliable T-cell marker[10], with TdT is a specific marker for identifying T-cell lymphoblastic leukemia/lymphoma. A study by Madakshira et al. (2020)[11] reported that IHC examination in patients with T-ALL showed positive results for both TdT and CD3 staining.

The immunohistochemistry stains in this case were positive for CD45, TdT, and CD3, but negative for CD20 and CD117. CD45 positivity confirms hematopoietic origin.[12] TdT positivity indicates immature tumor cells,

suggesting cutaneous infiltration of systemic ALL.[8] CD3 positivity and CD20 negativity implies a T-cell lineage for the ALL.[13] Negativity for CD117 rules out myeloid derivation.[14] In summary, the profile (CD45+/TdT+/CD3+/CD20-/CD117-) demonstrates the skin lesion represents leukemia cutis, a cutaneous manifestation of the patient's T-cell acute lymphoblastic leukemia.

The management of leukemia cutis is primarily focused on treating the underlying leukemia condition through systemic chemotherapy. As the blood disorder improves, skin lesions typically show either full or partial healing. While chemotherapy is the standard treatment approach, doctors may recommend radiation therapy for refractory or palliative cases.[15]

CONCLUSION

Although the incidence of LC in ALL is rare, dermatologists and dermatopathologists should consider LC as a differential diagnosis if a patient with ALL complains of new lesions in any area of the body. A thorough physical examination, supported by histopathological examination and IHC, will help establish the diagnosis of LC.

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Corresponding Author:
Alessandro Alfieri
Universitas Gadjah Mada
Gd. Radiopoetro, lt. 3, Sekip, Yogyakarta 55281
Email: andro.alfieri@mail.ugm.ac.id

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