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Leukemia Cutis – A Case Report

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Abstract

Leukemia cutis is a specific skin lesion which is characterized by diffuse infiltration of neoplastic cells and can occur in all types of leukemia. Leukemia cutis can have varied cutaneous presentations such as papules, macules, nodules, plaques and ulcers. We report a case of 52-year-old woman who presented with erythematous macules and papules over her trunk, thighs and upper arms. A skin punch biopsy showed monomorphic, perivascular and periadnexal infiltration by the cells positive for CD45, CD15, CD68 and lysozyme. According to the subsequent bone marrow biopsy and immunophenotypic analysis of peripheral blood cells, the diagnosis of acute monocytic leukemia (FAB AML-M5b) was made. In our case, the first clinical sign suggestive of the diagnosis of leukemia was the presence of erythematous macules and papules. Therefore, we believe that leukemia cutis should be taken into consideration in the differential diagnosis of maculopapular rush on the trunk, upper arms and leg

Key words: Leukemia, Monocytic, Acute; Skin Neoplasms; Exanthema; Diagnosis, Differential; Case Reports

Introduction

Leukemia cutis is defined as an infiltration of the skin by neoplastic leukocytes causing specific skin lesions (1-3). Specific skin changes include all lesions that are characterized by a leukemic infiltrate and which may be diagnosed as leukemia cutis by histopathology examination, irrespective of the clinical morphology (4). The frequency of leukemia cutis and age distribution of patients suffering from it depend on the leukemia subtype and can occur in all types of leukemia (2). The clinical and morphological findings have a wide range of cutaneous manifestations (papules, macules, nodules, plaques, ulcers) (2, 4-6). In addition, patients with leukemia can develop unspecific skin changes which on biopsy do not contain leukemic cells. These changes are mostly dermatological diseases associated with abnormal hematopoiesis such as thrombocytopenic purpura and opportunistic, often severe infections (generalized herpes zoster, furunculosis, fungal abscess) (2, 4). Here, we report a case of leukemia cutis presenting with a maculopapular eruption disseminated on the trunk, thighs and upper arms.

Case Report

A 52-year-old woman presented to our clinic with a history of low grade fever, and a skin rash, which was present for 2 months. On examination, erythematous macules and papules measuring up to 1 cm were present over her trunk, thighs and upper arms (Figure 1). A punch biopsy of the skin rash was performed. She was diagnosed with pneumonia and hypothyroidism four months before.

At the first presentation, the laboratory results were as follows: red blood cell (RBC) count 3,77 x10^{12}/L, hemoglobin 117 g/L, platelet count 226 $\times$ 10^9/L, total white blood cell (WBC) count 4.62 $\times$ 10^9/L (neutrophil 28.5%, large unstained cells - LUC 25%). The peripheral blood smear showed 22% neutrophils and 27% monocytoid cells, some with lobulated nuclei. Urea, creatinine and transaminases were within normal range. A skin punch biopsy showed monomorphic, perivascular

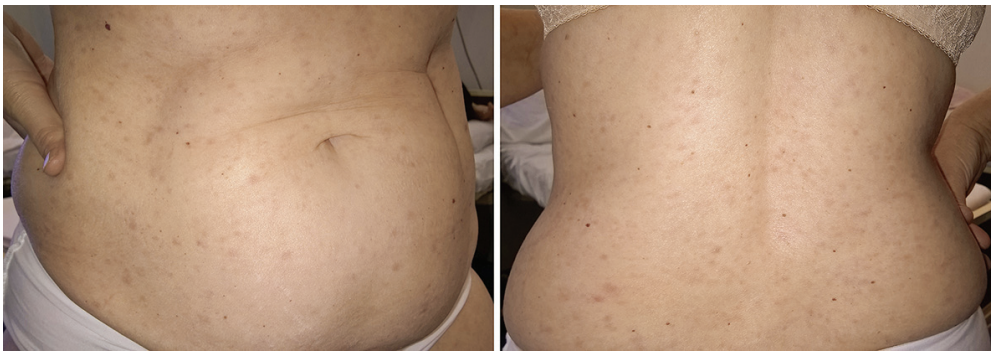

Figure 1. Maculopapular rash on the trunk.

and periadnexal infiltration of the hemopoietic cells in the dermis, without the involvement of the epidermis. The cells had scant, basophilic cytoplasm and euchromatic nuclei without prominent nucleoli. Some of the nuclei had convoluted nuclear membranes. Further immunohistochemical evaluation showed that these cells expressed CD45, CD15, CD68 and lysozyme. The cells were negative for CD3, CD5, CD20, CD34, Pax-5, TdT, CD117, myeloperoxidase (MPO) and mast cell tryptase. The immunohistochemical features indicated dermal infiltration by acute leukemia of monocytic lineage by cells with a monocytic differentiation (Figure 2). Following the histology of the skin biopsy, she was referred to a hematologist and a complete hematological work-up including a bone marrow biopsy was planned.

A bone marrow biopsy showed marked hypercellularity and hematopoiesis was largely impaired. The majority of the cells were blasts (70%) which contained scanty nongranular, basophilic cytoplasm, with oval or lobular nuclei without nucleoli. These blast cells expressed lysozyme, CD68+/- and CD15+/-, but not CD3, CD20, CD34, CD61, CD117, TdT or MPO. There was no increase in CD34 positive blasts. The genetic analysis of bone marrow cells revealed a normal karyo-

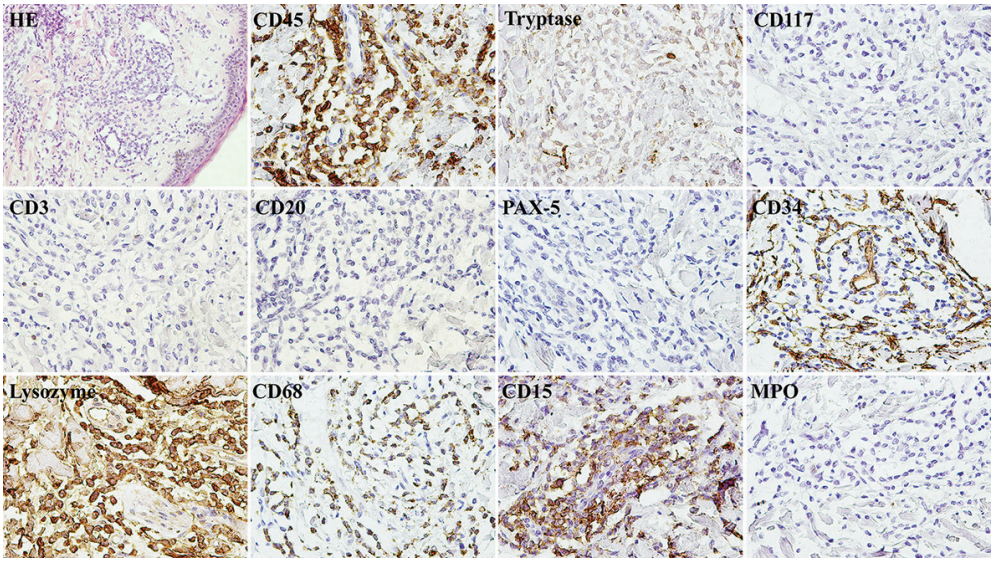

Figure 2. The skin biopsy specimen of the lesion showed perivascular, monomorphous infiltrates of atypical monocytic cells in the dermis (hematoxylin-eosin stain, HEx200). Immunohistochemical features: the cells were positive for CD45, CD15, CD68 and lysozyme and negative for CD3, CD20, CD34, Pax-5, CD117, myeloperoxidase (MPO) and mast cell tryptase (x400).

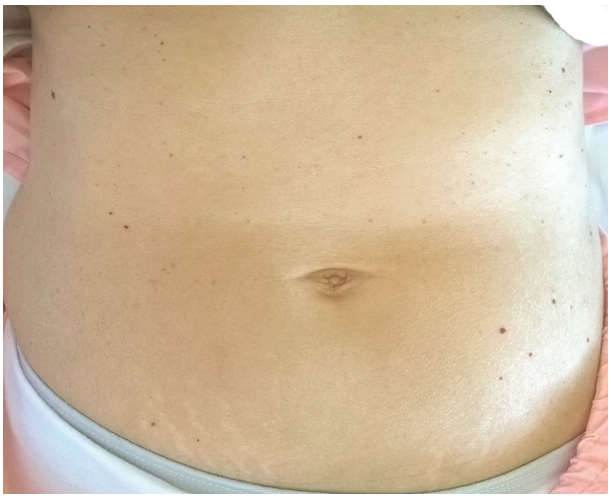

Figure 3. Skin lesions completely disappeared after induction and consolidation chemotherapy.

type, 46XX and FLT3/ITD gene mutations were not detected.

Immunophenotypic analysis of peripheral blood by flow cytometry detected 25% monocytoid cells within CD45 positive population (leukocytes). The cells expressed CD4, CD11b, CD11c (bright), CD13, CD14, CD16, CD33, CD34, CD36, CD38 and HLA-DR. These findings were compatible with acute monocytic leukemia (French-American-British (FAB) AML-M5b). Therefore, the diagnosis of acute monocytic leukemia (FAB AML-M5b) was made.

The patient received the standard 3 + 7 induction chemotherapy for acute monocytic leukemia including cytarabine 100 mg/m2 daily on days 1–7 and daunorubicin 50 mg/m2 daily on days 1–3 and, subsequently, high-dose cytarabine (HiDAC) consolidation therapy. Her skin lesions completely disappeared during chemotherapy (Figure 3).

Discussion

Leukemia cutis is the term used for cutaneous manifestations of leukemia, which can have varied clinical presentations. Epidemiological data on the prevalence and incidence of leukemia cutis are scarce (4). Overall, leukemia cutis occurs in 2.1% to 30% of leukemia patients depending on the underlying form of leukemia (4). Most frequently leukemia cutis has been described in patients with acute myeloid leukemia. The analysis of the data from 381 patients with acute myeloid leukemia was performed by Agis et al (2002). They showed that the prevalence of leukemia cutis was 3.7% (14 patients). The majority of patients with leukemia cutis (71.4% or 10/14 cases) had FAB M4 and M5 subtypes. Similar results have been reported by other authors (50% and 72.2%) (7, 8). Skin involvement can also be seen in patients with chronic myeloproliferative disease, including myelodysplastic syndrome, chronic lymphocytic leukemia, and chronic myeloid leukemia (4, 6, 9). Our patient was diagnosed with acute monocytic leukemia (FAB-M5b). Therefore, FAB4 and FAB5 are of particular interest to dermatologists because skin changes are most commonly seen in these forms of leukemia (4). The age and sex distribution of patients with leukemia cutis do not differ from leukemia patients without cutaneous involvement (4, 8, 10).

Leukemia cutis displays a variety of clinical appearances. Patients with leukemia cutis may have single or multiple skin lesions (6, 11). The lesions are usually described as violaceous, erythematous, or hemorrhagic nodules, papules, vesicles, bullae and plaques (6, 12). In terms of size, the lesions may be several millimeters or as large as the palm of the hand (4). In the retrospective study of 75 patients with leukemia cutis performed by Kang et al. (2013), the three most common types of leukemia cutis lesions were nodules (33%), papules (30%), and plaques (17%). Vesicles, ulcer, and swelling were uncommon findings of leukemia cutis. Nodules were the most common lesion in acute granulocytic leukemia, acute myelomonocytic leukemia and acute lymphocytic leukemia, whereas papules were most frequently seen in acute monocytic leukemia and chronic myeloid leukemia (2). A particular type of leukemia can produce different skin lesions during the course of the disease, even in the same patient (6, 11). The skin lesions are located most commonly in extremities, followed by trunk, scalp, and face (2, 4, 6, 9). Some studies have shown that there are no predilection sites of leukemia cutis according to leukemia type (2, 4, 11, 13). In contrast, Kang et al. (2013) reported that acute monocytic leukemia, chronic myeloid leukemia and acute granulocytic leukemia lesions were most frequently found on the extremities (63%, 44%, 42%, respectively); however, acute lymphocytic leukemia

occurred mainly on the trunk (44%). In addition, leukemia cutis can occur at the sites of previous or concomitant inflammation such as herpetic lesions, trauma, intravenous catheters, recent surgical sites, and so forth (3, 6, 14, 15). Our patient had erythematous macules and papules distributed on the trunk, thighs and upper arms.

The time between diagnosing the systemic leukemia and the occurrence of leukemia cutis varies (4). It has been reported that in the most patients (55-77%) leukemia cutis develops after leukemia has been diagnosed and, sometimes, it may be the first sign of relapse (2, 4). Concurrent cutaneous and systemic manifestation of leukemia have been observed in about one third (23-38%) of the patients (2, 4). In less than 10% of cases, leukemia cutis may occur several months or years before bone marrow or peripheral blood involvement and without systemic symptoms (2, 4, 16, 17). This type of leukemia cutis is termed “aleukemic leukemia cutis” or “primary extramedullary leukemia”. In our case, leukemia cutis was a presenting sign of acute monocytic leukemia.

The diagnosis of leukemia cutis is based on the evaluation of the morphologic pattern of skin infiltration, cytologic findings, and, most importantly, the immunohistochemical characteristics of the tumor cells (4, 6). The correlation with clinical data and hematologic results from the peripheral blood and bone marrow is often helpful to make the conclusive diagnosis. In general, most types of leukemic skin infiltrates show a perivascular and/or periadnexal distribution with well-defined boundary, as in our patient, or dense diffuse infiltrate involving the dermis and subcutis. It is impossible to determine the type of underlying leukemia based on histologic findings alone. In addition, in the absence of systemic leukemia, leukemia cutis can be difficult to distinguish from other malignant conditions, such as non-Hodgkin lymphoma (9). Therefore, immunohistochemistry is very important for establishing a specific, clinically useful diagnosis (6, 18, 19). It may be helpful to use myeloid, T-cell and B-cell markers such as MPO, lysozyme, CD68, CD34, CD117, TdT, CD10, CD15, PAX-5, CD3, CD4, CD8, CD1a, CD5, CD19, CD20 to the cell of origin and confirm the diagnosis (6, 18). However, it is not possible to classify the different forms of leukemia by skin biopsy alone; additional immunophenotyping and molecular genetic examinations (e.g., peripheral blood, bone marrow biopsy) are needed (4). In our case leukemic cells in cutis expressed CD45, CD15, CD68 and lysozyme which corresponded to myeloid differentiation. However, we confirmed the diagnosis by immunophenotypic analysis of peripheral blood and microscopic examination of bone marrow biopsy.

Conclusion

The clinical appearances of leukemia cutis are highly variable and include nodules, papules, maculae, and plaques. Leukemia cutis may occur after, before or at the same time as the diagnosis of leukemia. In the present case, the maculopapular rash was the first clinical sign pointing to the diagnosis of leukemia. Therefore, a skin biopsy with subsequent histopathological and immunohistochemical examination is the method of choice for early diagnosis. We suggest that leukemia cutis may be considered in the differential diagnosis of maculopapular rash on the trunk and legs. In addition, interdisciplinary dermatologic and hematologic follow-up is very important, even for patients in remission with underlying leukemic disease for prompt identification of cutaneous recurrences.

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Leukemija kože – prikaz slučaja

Sažetak

Leukemiju kože karakteriše difuzna infiltracija kože neoplastičnim ćelijama. Može se javiti kod svih vrsta leukemija u vidu različitih kožnih promena kao što su makule, papule, noduli, plakovi i ulkusi. U ovom radu je prikazana bolesnica starosti 52 godine, sa eritematoznim makulama i papulama na trupu, natkolenicama i nadlakticama. Biopsija kože je pokazala monomorfnu, perivaskularnu i periadneksalnu infiltraciju ćelijama koje su pozitivne na CD45, CD15, CD68 i lizozim. Naknadnom biopsijom koštane srži i imunofenotipskom analizom ćelija periferne krvi postavljena je dijagnoza akutne monocitne leukemije (FAB AML-M5b). Kod ove bolesnice, prvi klinički znak leukemije bio je makulopapularni osip. Stoga predlažemo da se leukemija kože može razmotriti u diferencijalnoj dijagnozi makulopapularne ospe na trupu i ekstremitetima.

Ključne reči: Akutna monocitna leukemija; Kožne neoplazme; Egzantem; Diferencijalna dijagnoza; Prikazi slučajeva

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