C A S E R E P O R T S

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Granulomatous rosacea – like leukemid in a patient with acute myeloid leukemia

Leukemid sličan granulomatoznoj rozacei kod bolesnika sa akutnom mijeloidnom leukemijom

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Abstract

Introduction. Skin findings in leukemias may be divided into specific lesions (leukemia cutis) and non-specific lesions (leukemids) which may be found in up to 80% of all patients with leukemias. The leukemids vary clinically and they are usually a manifestation of bone marrow or immunologic impairment, but also Sweet syndrome, pyoderma gangrenosum, erythroderma, maculopapular exanthema, prurigo-like papules, generalized pigmentation, follicular mucinosis, generalized pruritus may be found during the course of leukemia. **Case report.** We report a 70-year-old male with a 3-month history of erythema, papules and pustules on the face, ears and neck and over a month history of refractory anemia, anorexia, weight loss, malaise, and fever. Physical examination revealed symmetric erythematous, violaceous papules, papulo-nodules and plaques with slate scale and sparse, small pustules on the face, earlobes and neck. Histopathologic findings of involved skin showed diffuse mixed inflammatory cell infiltrate with perifollicular accentuation and focal granulomatous inflammation in the papillary and upper reticular dermis. Extensive check-up revealed the presence of acute myeloid leukemia French-American-British (FAB) classification subtype M2, with signs of three-lineage dysplasia. The patient was treated by L6 protocol which led to complete remission, both in bone marrow and skin, but after seven months he had relapse of leukemia with the fatal outcome. **Conclusion.** This case indicates the importance of skin eruptions in the context of hematological malignancies.

Key words:
rosacea; skin manifestations; leukemia, myeloid; diagnosis; treatment outcome.

Apstrakt

Uvod. Kutane lezije kod bolesnika sa leukemijama mogu se podeliti na specifične (*leukemia cutis*) i nespecifične (leukemidi), koje se mogu naći kod čak do 80% bolesnika sa leukemijama. Leukemidi imaju različita klinička ispoljavanja i uobičajena su manifestacija zahvaćenosti koštane srži i imunskog sistema, ali se takođe mogu manifestovati kao *Sweet* sindrom, *pyoderma gangrenosum*, folikulska mucinoza, kao generalizovani svrab mogu pratiti klinički tok leukemije. **Prikaz bolesnika.** Prikazan je bolesnik muškog pola, star 70 godina, sa simetrično raspoređenim lividno eritematoznim papulama, papulonodulusima i plakovima sa oskudnom skvamom i retkim sitnim pustulama na licu, ušnim školjkama i vratu, kao i refrakternom anemijom, gubitkom telesne mase, malaksalošću i febrilnošću. Patohistološki nalaz isečka kože ukazao je na prisustvo difuznog mešovitog inflamacijskog infiltrata sa perifolikularnom akcentuacijom i fokalnom granulomskom inflamacijom. Ekstenzivnom evaluacijom dokazano je prisustvo akutne mijeloidne leukemije podtipa M2 po Francusko-američko-britanskoj (FAB) klasifikaciji, sa znacima displazije sve tri linije. Bolesnik je primio L6 terapijski protokol nakon čega je nastupila kompletna remisija i u kostnoj srži i na koži. Međutim, nakon sedam meseci došlo je do relapsa leukemije koji je doveo do smrtnog ishoda. **Zaključak.** Prikazani bolesnik ukazuje na značaj prisustva kutanih erupcija u kontekstu hematoloških maligniteta.

Ključne reči:
rozacea; koža, manifestacije; leukemija, mijeloidna; dijagnoza; lečenje, ishod.

Introduction

Skin findings in leukemias are very diverse and conventionally divided into specific lesions (leukemia cutis) and nonspecific lesions (leukemids) which may be found in up to 80% of all patients with leukemias [1]. The leukemids vary clinically and they are usually a manifestation of bone marrow or immunologic impairment (hemorrhagic diathesis and

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different skin infections), but also Sweet syndrome, *pyoderma gangrenosum*, erythroderma, maculopapular exanthema, prurigo-like papules, generalized pigmentation, follicular mucinosis, generalized pruritus may be found during the course of leukemia [2, 3]. Histopathologic findings in leukemids are as variable as clinical picture. Granulomatous skin infiltrates are reported in the context of various forms of lymphomas and leukemias, clinically they are mostly widespread eruptions consisting of papules and nodules with sarcoidal histology. Sherertz et al. [4] reported a granulomatous rosacea-like leukemid in a patient with poorly differentiated lymphocytic lymphoma.

Case report

A 70-year-old Caucasian male was referred to our Institute for a 3-month history of erythema, papules and pustules in the face with wax-and-wane course. Family history was unremarkable, in personal history there were tuberculous orchiepididymitis 35 years ago and the patient had vitiligo for 20 years. Two month before the admittance to the Institute the patient developed unexplained fever, weight loss (7 kg in one month, approx. 10% of body mass), malaise and anemia irresponsive to iron supplements.

On examination, there were disseminated symmetric erythematous and violaceous papules, papulo-nodules and plaques with slate scale on the face, ears and neck; there were sparse pustules, too (Figure 1). The mucous membranes showed no lesions; there were no lymphadenopathy, hepatomegaly or splenomegaly.

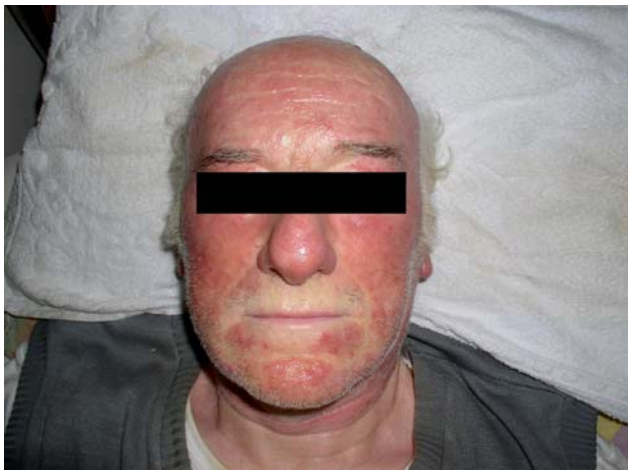

Fig. 1 – Symmetric disseminated closely grouped erythematous papules, papulonoudules and plaques on the face with sparse pustules

Histopathologic examination of lesional skin revealed hyperkeratosis and acanthosis of epidermis and follicular and perifollicular diffuse mixed infiltrate with granuloma formation and multinucleate giant cells of foreign body type (Figure 2). There were no acid fast bacteria or mucin deposition. No Demodex was seen.

Routine laboratory evaluation discovered high erythrocyte sedimentation rate (12 mm in the first hour) and severe

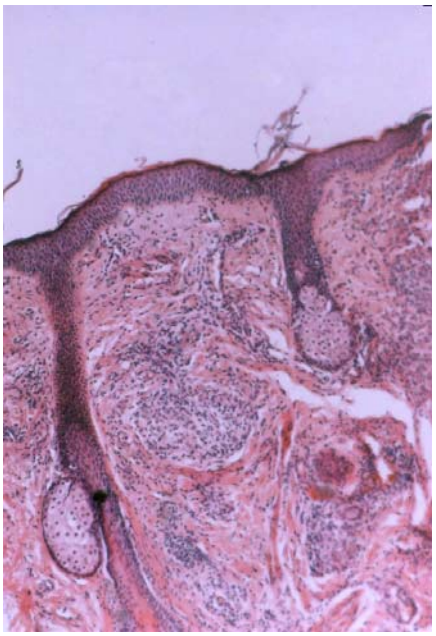

Fig. 2 – Follicular and perifollicular diffuse mixed infiltrate with granuloma formation and giant cells of foreign body type (H&E, 40×)

macrocytic anemia (hemoglobin 80 g/l and erythrocytes 2.28×1012/l) with normal leukocyte and platelet count. Feritine was very high – 641 μg/l. Lactate dehydrogenase was slightly elevated (358 U/l), C-reactive protein was highly elevated (45 mg/l). Other tests – biochemistry (serum glucose, urea, creatinine, cholesterol, triglycerides, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma glutamil transpherase), immunology (antinuclear antibodies, anti parietal antibodies), urinanalysis, chest radiography, echosonography of the abdomen, HIV – were all within normal limits, or negative.

Direct immunofluorescence test from the involved skin and lupus band test from nonlesional skin were negative. Colonoscopy showed no abnormalities. Purified protein derivative (PPD) test was positive, 21 mm. Electrophoresis of the serum proteins demonstrated relative increase in alpha 1 (5.3%), alpha 2 (14.7%) and gamma fraction (16.7%) with decrease in albumin (50.1%).

Hematological exploration (cytological findings from bone marrow aspirate) showed findings consistent with acute myeloid leukemia (AML), French-American-British (FAB) subtype M2 with signs of three lineage dysplasia, with underlying myelodysplastic syndrome. Cytochemical staining showed that 78% of blasts were peroxidase positive with Auer rods. Cytogenetic analysis showed normal male kariotype 46 XY.

The patient was referred to the Institute of Hematology and received L6 protocol (cytarabine with mercaptopurine). After the induction the patient had entered the remission in his bone marrow status and peripheral blood and the consolidation treatment was introduced. Hematological remission was followed by clinical remission of cutaneous findings – infiltration of lesions relatively rapidly diminished and erythema gradually decreased; in several weeks most of lesions completely resolved (Figure 3).

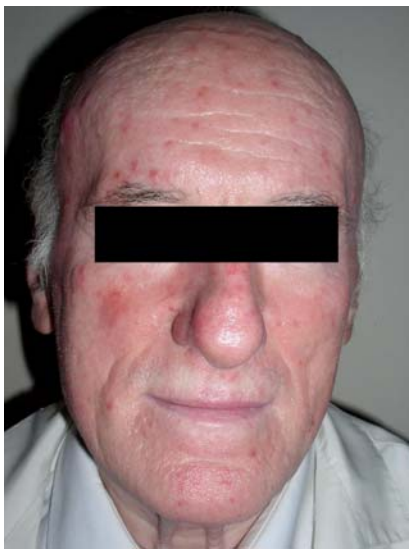

Fig. 3 – Clinical remission of facial lesions after the treatment of underlying acute myeloid leukemia

Unfortunately, after a 7-month remission the patient had relapse of leukemia with disease progression which had fatal outcome. During the relapse several new infiltrated papules and plaques were noted.

Discussion

Nonspecific skin findings in leukemias are frequent and very variable. Most of them are the result of impairment function of bone marrow and include purpura, hemorrhage or ecchymoses or they are a manifestation of impaired immunity and include various skin infections, e.g. disseminated or severe herpes zoster, warts, fungal infections [1–3, 5]. Other cutaneous findings in leukemias include Sweet syndrome, including bullous Sweet syndrome, pyoderma gangrenosum, severe necrotic arthropod bite, erythroderma, maculopapular exanthema, prurigo-like papules, generalized pigmentation, follicular mucinosis, and generalized pruritus [1–3, 6]. Frequent skin findings in myelodysplastic syndromes and myelogenic leukemias include neutrophilic dermatoses, namely Sweet syndrome, pyoderma gangrenosum, subcorneal pustular dermatosis and erythema elevatum diutinum [7–10]. Skin eruptions in myelodysplastic syndromes may be a sign of transition to acute myeloid leukemia and are associated with poor prognosis [11].

Histopathologic findings in cutaneous leukemias and leukemids are as diverse as clinical picture. Granulomatous skin infiltrates have been reported in the context of myelodysplasia [12, 13], acute myelomonocytic leukemia [14], Sezary syndrome [15, 16], acute myeloid leukemia [13], immunocytoma [17], poorly differentiated lymphocytic lymphoma [4], adult T-cell leukemia/lymphoma [18]. Most of granulomatous infiltrates had sarcoidal histology, true leukemic infiltration have been rarely reported [15–18]. Sarcoidal tissue reaction have been proposed to be a host response to leukemia progression [18, 19]; tumor necrosis factor-alpha and interleukin-1 beta are considered to be crucial for granuloma formation [14].

Rosacea-like facial eruptions have only been sporadically reported as specific or nonspecific skin findings in leukemias and lymphomas [4, 17, 20, 21]. Sherertz et al. [4] reported a granulomatous rosacea-like leukemid in a patient with poorly differentiated lymphocytic lymphoma. The patient had rosaceiform eruption along with subcutaneous nodules on the face, both had sarcoidal histology, skin lesions followed the course of lymphoma. Colvin et al. [17] reported a patient with cutaneous lymphoplasmocytoid lymphoma (immunocytoma) with facial lesions consistent with rosacea, the skin lesions are proved to be actual immunocytoma. Thomson and Cochran [20] reported a patient with chronic lymphatic leukemia presenting as atypical rosacea, the review of biopsy specimens revealed the presence of follicular mucinosis.

Apart from unusual and rare skin eruption in association with acute myeloid leukemia, another interesting fact is that the skin lesions preceded the development of myelodysplasia and leukemia. Since there are several reports of connection between granulomatous skin lesions, including granulomatous rosacea, with various forms of leukemias, in our opinion, it is appropriate to investigate every suddenly developed rosacea (especially granulomatous) which does not respond to standard therapy.

Conclusion

This case indicates the importance of skin eruptions in the context of hematological malignancies.

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