Clinical Case Report

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Acute myeloid leukemia presenting as erythema nodosum

A case report

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Abstract

Rationale: Erythema nodosum (EN), a type of septal panniculitis, could be a rare nonspecific cutaneous presentation of acute myeloid leukemia (AML).

Patient Concerns: A 58-year-old Chinese female was admitted for a 4-week history of painful cutaneous lesions, accompanied by a sternal pain and fever. The lesions once resolved spontaneously but then recurred. Physical examination revealed warm, tender, indurated, rounded, erythematous to violaceous nodules in bilateral lower extremities, ranging in diameter from 1 to 6 cm. Blood marrow examination was compatible with AML-M2.

Diagnoses: AML-M2 presenting as EN.

Interventions: Daunorubicin and cytarabine were used in induction chemotherapy. The patient achieved complete remission and her skin lesions disappeared simultaneously. Six courses of consolidation chemotherapy were conducted in the following 6 months.

Outcomes: The patient died due to AML relapse.

Lessons: The case strengthens the awareness of cutaneous involvement of AML and raises oncological vigilance in patients with EN.

Abbreviations: AML = acute myeloid leukemia, EN = erythema nodosum.

Keywords: acute myeloid leukemia, cutaneous involvement, erythema nodosum

1. Introduction

Cutaneous eruptions of acute myeloid leukemia (AML) could be specific or nonspecific. The specific cutaneous involvement, which is also called as leukemia cutis, has been defined as infiltration of leukemic cells into skin, while other conditions with various histopathologic features fall into the category of nonspecific cutaneous involvement.[1] Specific cutaneous involvement has been observed in more than 10% of AML patients and its frequency is especially higher in subtype M4 and M5.[2] Nonspecific cutaneous involvement occurs in approximately 30% cases of AML,[1] with a wide spectrum of etiologies, including graft versus host disease, drug rash, infection, purpura, the Sweet syndrome, vasculitis, and intraepidermal blistering disorder.[3] Additionally, erythema nodosum (EN) is a rare one on this list. To the best of our knowledge, only 9 cases of EN associated with AML have been reported in English literature in the recent 50 years (Table 1).[4–11] We describe herein a Chinese adult with AML-M2 presenting as EN.

2. Case report

A 58-year-old Chinese female was admitted to our hospital with a 4-week history of painful cutaneous lesions in lower extremities, accompanied by a sternal pain and intermittent fever. The lesions once resolved spontaneously within 2 weeks, without ulceration or scarring, but recurred several days later. Careful inquiry failed to discover any history of recently acquired infections, autoimmune diseases, allergies and drug consumption. Physical examination revealed warm, tender, indurated, rounded, erythematous to violaceous, slightly raised nodules in bilateral extensor and flexor surface of lower extremities, ranging in diameter from 1 to 6 cm (Fig. 1). No other abnormalities were observed.

Peripheral blood count was as follows: hemoglobin 78 g/L, leucocyte 55.52×10^9/L, neutrophil 13.64×10^9/L, monocyte 16.53×10^9/L, lymphocyte 25.10×10^9/L, platelet 71×10^9/L. Blood marrow examination showed myeloblast 59%, monoblast 1%, promonocyte 10% with immunophenotype HLA-DR, CD 34, CD13, CD33, and CD 15 (+). No chromosomal abnormalities or fusion genes were detected. Purified protein derivative skin test, T cell-spot. tuberculosis test, antistreptolysin O test, hepatitis

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Table 1

Reports of erythema nodosum associated acute myeloid leukemia.

	Gender /Age	Type	Duration before diagnosis	Location	Histological feature	Laboratory findings (besides CBC)	Responses to treatment
1[4]	65/F	M4	7 months	Upper and lower extremities, face abdomen	Superficial and deep perivascular histiolymphocytic infiltration with multi-nucleated giant cell and epithelioid granuloma	Elevated serum TNF-α and IL-1β	EN disappeared after PSL treatment or chemotherapy but relapsed later
2[5]	35/M	NA	1 month	Lower extremities	Dense infiltration of immature myeloid precursors in the subcutaneous fat and interlobular septa, with reactive T lymphocytes scattered among them; MPO (+), CD117 (+)	Elevated LDH	AML relapsed repeatedly and were resistant to chemotherapy.
3[5]	50/F	NA	10 days	Upper and lower extremities	infiltrating cells were mostly reactive T lymphocytes, with the presence of immature cells with a myelogenous aspect; MPO(+), CD117 (+)	Elevated CRP, ESR and LDH	AML relapsed repeatedly and were resistant to chemotherapy.
4[6]	3/M	NA	5 months	Upper and lower extremities, forehead	Fibrocytes in the lower portion of the dermis were plump. The perivascular spaces and fat tissues contained a sparse infiltrate of atypical mononuclear cells, some of which had reniform nuclei and a sprinkling of lymphocytes. Septa in the subcutaneous fat were edematous.	PPD test (+)	EN self-resolved and recurred; the patient developed infection during chemotherapy and died.
5[7]	58/F	NA	About 1 week	Lower extremities	NA	Elevated ESR	EN faded during chemotherapy but the patient died of infection.
6[8]	26/M	NA	NA (EN appeared later than diagnosis)	Upper and lower extremities	Edematous thickened fat septa containing scattered neutrophils and a few lymphocytes	NA	EN resolved after PSL treatment.
7[9]	5/F	NA	2 weeks	Lower extremities	NA	NA	EN resolved during chemotherapy and the patient received CR.
8[10]	23/F	M4	2 weeks	Lower extremities and hands	The vessels were occluded with fibrin and surrounded by dense infiltration of cells with large, deeply staining nuclei, probably the abnormal monocytes	NA	EN was responsive to PSL treatment.
9[11]	57/F	NA	About 1 week	Upper and lower extremities	Acute inflammatory lesion confined to the lower dermis and subcutaneous tissue	NA	EN was responsive to PSL treatment, but AML was resistant to chemotherapy.
Present case	58/F	M2	4 weeks	Lower extremities	NA	NA	EN self-resolved and recurred; then resolved again during chemotherapy but recurred with AML relapse.

AML = acute myeloid leukemia; CBC = complete blood counts; CR = complete remission; EN = erythema nodosum; IL-1β = interleukine-1 beta; MPO = myeloperoxidase; PPD = purified protein derivative; PSL = prednisolone; TNF-α = tumor necrosis factor-alpha.

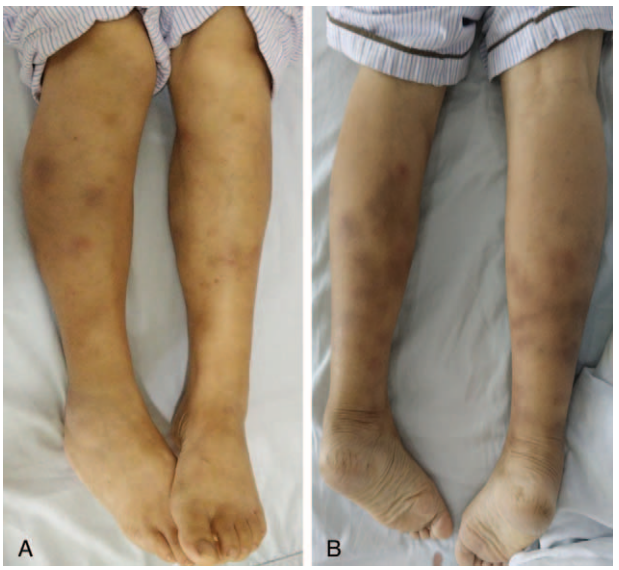

Figure 1. Clinical photos of lower extremities (A: extensor surface; B: flexor surface) of the patient. There are rounded, erythematous to violaceous, slightly raised nodules, ranging in diameter from 1 to 6 cm.

B surface antigen, and hepatitis C antibody were all negative. Serological screening for auto-antibodies and skin prick test were negative as well. Skin biopsy was not performed out of concern for the high risk of infection and hemorrhage.

The diagnosis of AML subtype M2 was made. According to National Comprehensive Cancer Network Guidelines,[12] induction chemotherapy with daunorubicin and cytarabine was initiated. Since then, the cutaneous lesions gradually faded within 3 weeks, leaving merely light brown pigmentation. The patient achieved complete remission 4 weeks after induction chemotherapy and refused to receive blood marrow transplantation due to economic factors. Six courses of consolidation chemotherapy were conducted in the following 6 months, during which time no recurrence of cutaneous lesions was observed.

Two months after the last course, the skin lesions appeared again, whose morphology and distribution were similar with the first onset. A relapse of the leukemia was confirmed based on blood marrow biopsy. The patient died before the start of salvage chemotherapy.

3. Discussion

EN is a type of septal panniculitis, which denotes inflammation of subcutaneous fat tissue. It is 5 to 6 times more likely to occur in females than males and has a peak incidence in population aged 20 to 30.[13,14] EN typically appears as painful, symmetric, erythematous nodules, symmetrically located in pretibial area, varying from 1 to 10 cm in diameter. The lesions tend to become bruise-like and resolve without atrophy, ulceration or scaring in 2 to 8 weeks.[14] Prodromal symptoms, such as fever, fatigue, malaise, cough, and arthralgia may precede cutaneous manifestations. Laboratory investigations often demonstrate markedly increased leucocyte count, C-reactive protein, and erythrocyte sedimentation rate.[14]

The skin lesions of this patient were clinically compatible with EN, yet rigorous differential diagnosis is still required due to the absence of histologic evidences. First, leukemia cutis could mimic the morphologic features of EN.[1] Nevertheless, it is commonly painless and rarely self-limiting before the remission of AML,[5,7] which is inconsistent with what happened in this case. Admittedly, leukemia cutis and nonspecific EN cannot be easily distinguished merely based on clinical manifestations. Among the 9 previously reported cases (Table 1) of AML associated EN, two were actually leukemia cutis confirmed by the presence of immature myeloid precursors in skin biopsy.[5] Second, the Sweet syndrome should be considered as well. It is an entity characterized by acute onset of febrile leukocytosis and tender erythematous plaques or nodules infiltrated by neutrophils. However, upper extremities, face and neck are more frequently affected in the Sweet syndrome than lower extremities. Besides, its lesions often have a transparent, edematous, and vesicular appearance, rather than the indurated ones in this case.[15] Finally, vasculitis might also occur in AML patients, but its classic presentation should involve purpura, necrosis or ulceration, which was not observed in this patient.[16]

Around 17% to 72% of EN is believed to be idiopathic, while the remaining might be caused by a variety of underlying disorders. Streptococcal infection is the commonest (28%-48%) trigger, followed by sarcoidosis, other infection (mainly Yersinia and mycobacterium tuberculosis), drugs, auto-immune disease, pregnancy and inflammatory bowel disease. Malignancies attribute to less than 1% of EN, among which the Hodgkin lymphoma is the predominance and AML is extremely rare.[12,17] It is reasonable to speculate that EN in this case was possibly associated with AML, as its regression and progression was parallel to the remission and relapse of AML, respectively. Furthermore, there were no findings suggestive of other common etiological factors.

Whether there is a causal relationship between AML and EN remains unclear. One hypothesis is that EN is resulted from hypersensitive reaction to leukemic cells, which may serve as foreign antigens.[7] It has been also purposed that tumor necrosis factor-α and interleukin 1-β released by myelomonocytic cells might participate in the inflammation of EN.[4] Further research aimed to evaluate the role of cytokines in AML and EN would be helpful for the investigation of their pathogenic relevance.

Cases of AML presenting as EN would shed light on both clinical work and research in the future. According to the previously published cases, EN might be the initial presentation of AML.[4,7] Therefore, it is necessary to perform a thorough work-up and keep close surveillance for leukemia in patients with EN, although there is no sign for hematological abnormalities. Furthermore, our case provides support for the hypothesis that recurrence of EN may reflect AML relapse. Prompt and accurate identification of recurred EN is crucial for timely management. Finally, an expanded understanding of the simultaneous occurrence of AML and EN suggests us to explore their common underlying mechanism of pathogenesis.

4. Conclusion

In conclusion, we presented a rare case of AML-associated EN, which strengthens the awareness of cutaneous involvement of AML and raises oncological vigilance in patients with EN.

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