

CORRESPONDENCE

Development of papulonodular eruptions in a patient with granulocyte colony-stimulating factor-induced leukocytoclastic vasculitis: A case report

We report herein the case of a 62-year-old woman who had been suffering from multiple myeloma for 4 years. The patient was started on subcutaneous injection of lenograstim, a recombinant granulocyte-colony-stimulating factor (G-CSF), for chemotherapy-induced neutropenia (leukocyte count: 760/ μ l; absolute neutrophil count (ANC): 661/ μ l). Despite the treatment, the ANC decreased to 12/ μ l on day 6. On day 12, she developed a reddish papule with mild tenderness on the right cheek, followed by the appearance of similar lesions on the face and extremities, without any apparent preceding skin lesions. She was referred to the dermatology division

on day 20. Physical examination revealed discrete or grouped, light or bright red, hemispherical hard papules and nodules up to 8 mm in size on the face and extremities (Figure 1A-C). Some of the nodules were ulcerated. Purpura was not observed. At this point, the ANC was 888/ μ l. The immunoglobulin G level was 4688 mg/dl (normal: 800–1800 mg/dl) 15 days before the first lenograstim injection, and it remained high at 3787 mg/dl 10 days after the cessation of lenograstim. Anti-neutrophil cytoplasmic antibodies were not tested. Skin biopsy showed a dense neutrophilic infiltrate with few lymphocytes in the upper dermis accompanied by a large amount of nuclear

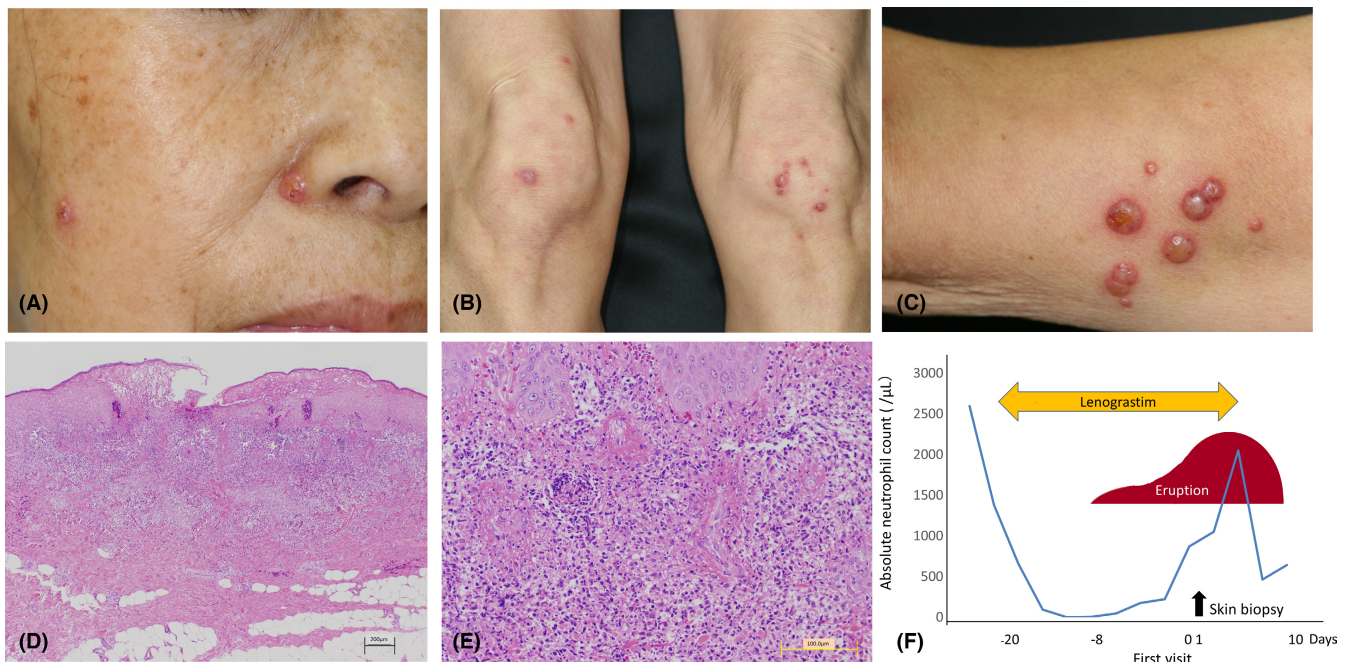


FIGURE 1 (A) Bright red small nodules on the right cheek and ala nasi. (B) Light or bright red papules and nodules scattered on the bilateral knee. (C) Bright red hemispherical hard papules and nodules of various sizes on the back of the left upper arm. (D) A skin biopsy from the left arm showing a dense neutrophilic infiltrate with few lymphocytes in the upper dermis accompanied by necrotic and ulcerated overlying epidermis. No fibrotic changes were observed (hematoxylin-eosin stain, original magnification 40 \times). (E) Blood vessels within the dense cellular infiltrate showing fibrinoid degeneration (hematoxylin-eosin stain, original magnification 200 \times). Direct immunofluorescence studies were not performed. (F) Clinical course of the present case. The skin biopsy was performed the day after the first visit

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debris. Blood vessels within the cellular infiltrate showed fibrinoid degeneration (Figure 1D-E). These findings were consistent with leukocytoclastic vasculitis (LV). The patient was thus suspected of having drug-induced vasculitis. After the cessation of lenograstim, the skin lesions spontaneously disappeared without any treatment.

A variety of adverse events have been reported in patients during treatment with G-CSF, including cutaneous adverse reactions, such as erythematous rash, urticaria, pyoderma gangrenosum, Sweet's syndrome, erythema nodosum, and vasculitis.¹⁻²

G-CSF-induced vasculitis can affect small to large vessels. The development or exacerbation of various types of vasculitis, such as cutaneous LV,³ lupus mesenteric vasculitis,⁴ polyarteritis nodosa,⁵ and aortitis,⁶ have been reported. In the initial clinical trials of G-CSF for severe chronic neutropenia, there was a 3% incidence of some form of cutaneous vasculitis.⁷

The role of neutrophils and neutrophil extracellular traps in small vessel vasculitis is fairly well established.⁸ Therefore, the pathogenesis of G-CSF-induced LV appears to be due to the upregulation of neutrophil function rather than an allergic reaction. Symptoms of vasculitis usually occur as the ANC increases, and they decrease as the ANC decreases. Consistent with this trend, the skin lesions of the present case appeared in parallel with the elevated ANC, and disappeared after the cessation of lenograstim (Figure 1F).

A cutaneous manifestation, such as papulonodular eruptions, is unusual for LV, with the exception of erythema elevatum diutinum, which may occur in association with hematologic diseases and malignancies.⁹ However, multiple nodules associated with LV have been reported in a multiple myeloma patient receiving G-CSF,¹⁰ and the spontaneous healing after the cessation of lenograstim indicated that erythema elevatum diutinum could be excluded. A high immunoglobulin level was regarded as one of the predisposing factors for LV.³ Administration of G-CSF should be undertaken with caution, especially in patients with predisposing factors for LV.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: N/A as no human participants were involved in this study.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

¹Division of Dermatology, Asahikawa City Hospital, Asahikawa,

Japan

²Nomura Dermatology and ENT Clinic, Hirakata, Japan

Correspondence

Hiroyuki Sakai, Division of Dermatology, Asahikawa City Hospital, 1-1-65 Kinsei-cho, Asahikawa, Hokkaido 070-8610, Japan.

Email: h_sakai@ach.hokkaido.jp

ORCID

Hiroyuki Sakai  <https://orcid.org/0000-0002-5231-164X>

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Hiroyuki Sakai MD, PhD¹ 

Wakana Nomura MD²