

## Granulocyte Colony-Stimulating Factor (G-CSF) Induced Disseminated Erythema with CD68 Positive Histiocytes

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Sir,

Granulocyte colony-stimulating factor (G-CSF) is used in the haematological treatment of neutropenia following cytotoxic chemotherapy and haematological disorders; it encourages proliferation and differentiation of granulocytes. G-CSF therapy is occasionally known to be associated with skin rash, including neutrophilic dermatosis (1), widespread folliculitis (2) and cutaneous vasculitis (3), associated with neutrophil infiltration in the skin. We describe a patient with a cutaneous reaction who had received G-CSF treatment for myelodysplastic syndrome. In our case, numerous CD68-positive mononuclear cells were seen infiltrating the lesional skin.

### CASE REPORT

An 80-year-old Japanese male had received human recombinant G-CSF (Lenograstim®) for his myelodysplastic syndrome-related leucocytopenia. After 5 weeks of G-CSF therapy at a daily dose of 100 µg, numerous infiltrated erythemas, ranging from 1 to 6 cm in diameter, developed on his face, neck and chest (Fig. 1). The erythematous areas sometimes formed vesicles with crusts on the surface. Laboratory examinations revealed pancytopenia, liver dysfunction and a slight elevation of CRP. After the development of more severe cutaneous eruptions, G-CSF treatment was stopped for 2 weeks and the erythema started gradually to subside. However, when daily administration of G-CSF 100 µg was re-started due to the leucocytopenia, the skin eruption recurred. The dosage of G-CSF was then decreased to 100–200 µg weekly and the skin eruption improved. No recurrence was noted after that.

During this time period, we performed 3 skin biopsies at different time points and from different sites. All the skin specimens were found to be histologically similar. The biopsy from the infiltrated erythema on the face revealed a perivascular and perifollicular mononuclear cell infiltration in the upper to middle dermis. Mature neutrophil infiltration was not observed, although there were extravagated erythrocytes and nuclear debris. No clear signs of vasculitis were noted. Interestingly, an immunohistochemical examination revealed that many of the perivascular-infiltrated cells were CD68-positive (Fig. 2) and myeloperoxidase-positive; only a few were CD3-positive. The majority of infiltrated mononuclear cells in the dermis were therefore identified as histiocytes.

### DISCUSSION

It is well known that neutrophilic dermatosis and leucocytoclastic vasculitis occur as a result of G-CSF treatment (4). However, dominant mononuclear cell infiltration was observed in our case associated with the administration of G-CSF, and matured neutrophils were hardly apparent at all in the skin lesions. Paul et al. (4) examined the cutaneous effects of

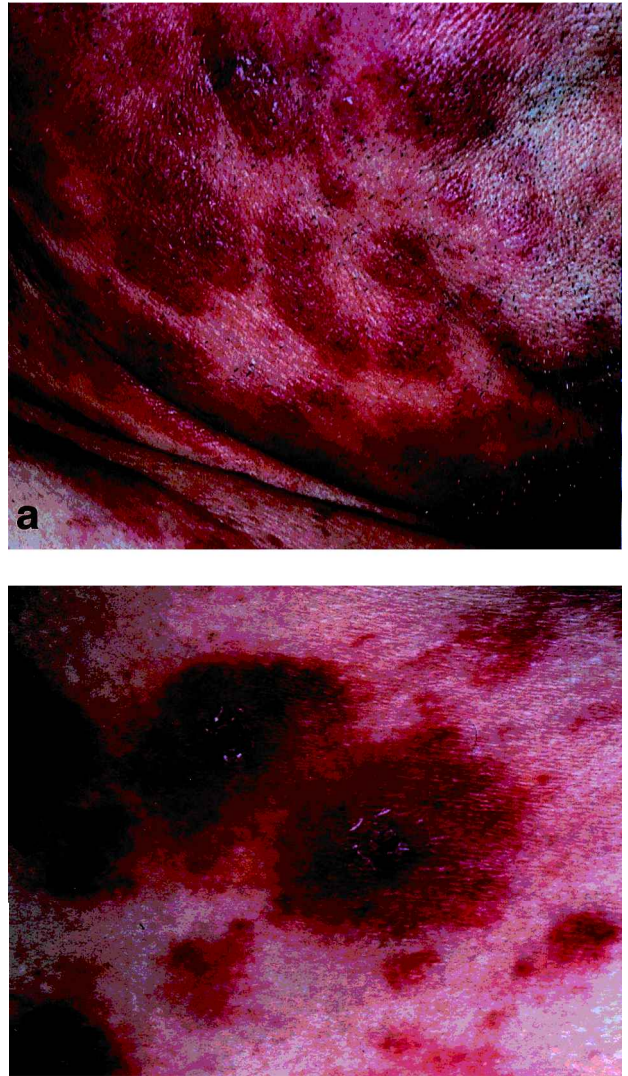


Fig. 1. Well-demarcated dark reddish infiltrated erythemas on the cheek and neck (a) and chest (b). Some of the lesions formed crusted vesicles on the surface.

G-CSF in healthy volunteers. In their report, 2 out of 8 volunteers developed maculopapular eruptions. Findings from the histologic examinations showed lymphocytes and large CD68-positive histiocytes within the dermis, but the presence of neutrophils was rare. It is known that G-CSF has an effect similar to that of granulocyte-macrophage colony-stimulating factor (GM-CSF) on myelomonocytic precursors (1). Although G-CSF is more selective for granulocytic lines, GM-CSF also enhances the function of mature cells, such as neutrophils and monocytes. It is likely that G-CSF, like

GM-CSF, stimulates tissue macrophages, causing an increased abundance in the skin. It is also speculated that high levels of G-CSF produce many inflammatory cytokines in the skin, which leads to a greater mononuclear cell infiltration in this tissue (4, 5).

In the literature, we found 4 cases with predominant mononuclear cell infiltration in cutaneous reactions associated with the use of G-CSF (5, 6), just as in our patient. There were 2 cases of cancer involving internal organs (5, 6), a case of acute leukemia (5), and a case of Hodgkin's disease (5). Most of the cutaneous reactions were erythematous plaques. The appearance of the cutaneous reactions started 13–42 days after the use of G-CSF. Histologically, cutaneous reactions showed dominant perivascular lymphohistiocytic infiltration with few neutrophils. The majority of infiltrated cells were CD68-positive in all biopsied cases (5, 6). Our report adds to the body of evidence showing that administration of G-CSF induces a cutaneous reaction that histopathologically shows a CD68-positive mononuclear cell infiltration into the skin.

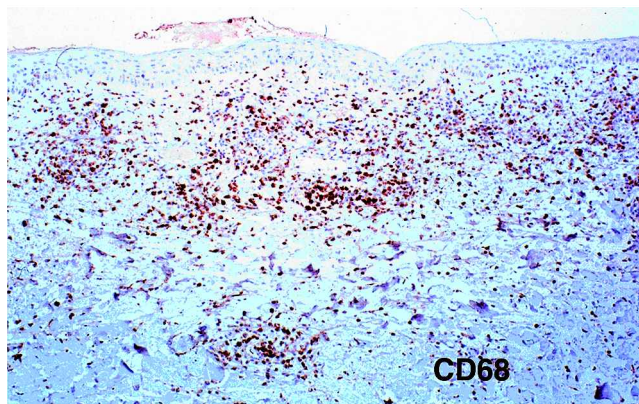


Fig. 2. Positive immunostaining with CD68 in the dermis showing perivascular and perifollicular mononuclear cell infiltrations in the dermis ( $\times 40$ ).

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## Constitutional Pompholyx Eczema Complicated by Secondary Lymphoedema

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Sir,

The aetiology of pompholyx eczema remains unknown, but an atopic diathesis, local hyperhidrosis and contact sensitivity to metals may contribute to the development of this relapsing vesicobullous disease of the palms and soles (1). Exacerbation by bacterial infection is common and the resulting inflammation potentiates the development of lymphatic damage. We describe here a patient who developed lymphoedema of all four limbs, secondary to constitutional pompholyx eczema, which proved resistant to treatment.

#### CASE REPORT

A 47-year-old woman, formerly an assistant chef, presented with a 3-year history of recurrent attacks of severe pompholyx eczema affecting her palms and soles. Pitting oedema of her hands coincided with the second attack of eczema (Fig. 1), about 2 months after the initial presentation, and was followed by oedema of her feet. The swelling extended to involve the forearms and gaiter area, being marked during an acute flare of eczema and diminishing but not clearing when the rash settled. On occasion she reported swelling of the lower abdo-



Fig. 1. Lymphoedema of the hands.

men, axillae and breasts during exacerbations. Observation of acute flares demonstrated bacterial superinfection, as evidenced by tenderness, erythema, weeping and crusting of the palms and soles associated with a neutrophil leukocytosis. Patch testing with the ICDRG standard battery, the steroid and