

Drug Eruption Caused by Recombinant Human G-CSF

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Two types of recombinant human granulocyte colony-stimulating factor (rhG-CSF) are available, and equally used for mitigation of neutropenia. One is a glycosylated natural product from mammalian cells, and the other a non-glycosylated form from *Escherichia coli*. Though only minimal adverse effects have been reported for both, we treated two patients with rhG-CSF-induced systemic eruption. Based on these patients, the following should be noted: 1) drug eruption may occur in both types of rhG-CSF without detectable antibodies, 2) intradermal test is useful for determination of the causal drug, and 3) if one rhG-CSF product causes eruption, the alternative one may possibly be safe and effective.

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Introduction

Recently, a large scale of production of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was established by expression in bacterial or mammalian cells (1, 2). The former product of rhG-CSF is deglycosylated (filgrastim), and the latter is the glycosylated natural type (lenograstim). Since the effect of both rhG-CSF products is considered identical (3), both are usually used for mitigation of neutropenia due to cancer chemotherapy (1, 2, 4–6). rhG-CSF in general has been associated with only minimal subjective discomfort, essentially limited to bone pain (1, 2, 4, 5). We treated two cases of rhG-CSF-induced severe eruption; here we describe these patients and discuss the possible mechanism.

Case Report

Case 1

A 37-year-old patient with lung cancer (stage IV) was admitted to our hospital. He had a history of cured seminoma of testis at age of 26. His mother, an uncle, and an aunt died from cancer. The diagnosis of lung cancer with multiple lung metastasis was made and a combined chemotherapy (etoposide, mitomycin-C, vindesine and cisplatin) was started on July 23, 1993. During the second cycle of the chemotherapy, he developed systemic eruption on the third day (September 10) of filgrastim administration (subcutaneously, 75µg once a day;

same as the first cycle) for the neutropenia. The causal drug was considered to be filgrastim by the result of intradermal tests (Table 1). Since lenograstim was negative for intradermal test, we used lenograstim in place of filgrastim. His eruption disappeared promptly, and the same beneficial effect of rhG-CSF on his neutropenia was observed.

Case 2

A 71-year-old patient with lung cancer (stage IIb) was treated with a combined chemotherapy (the same regimen of case 1). After 9 days administration of lenograstim (subcutaneously, 100µg once a day) for the chemotherapy-induced neutropenia, recovery of the number of neutrophils was observed. However, since the number of peripheral blood neutrophils was again decreased, lenograstim was re-administered in the same way. He developed severe systemic eruption (Fig. 1) on July 27, 1993, the sixth day of re-administration. Intradermal tests of both rhG-CSF (lenograstim and filgrastim) were positive, although the wheal of lenograstim was much bigger than that of filgrastim. rhG-CSF was then discontinued, as the number of neutrophils had already recovered. The eruption disappeared quickly.

In both patients, anti-G-CSF antibodies were not detected and lymphocyte stimulation tests (LST) were also negative (Table 1). In the first patient, total serum IgE was transiently increased 4 days after his eruption appeared.

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Table 1. Immunological Examination

	Patient 1	Patient 2
Age (yr), Gender	37, M	71, M
Histology/Stage	Adenocarcinoma/IV	Squamous cell carcinoma/IIIb
Date of eruption appearance	9/10/93	7/27/93
Causal G-CSF	Filgrastim	Lenograstim
Intradermal reaction* (mm)	9/11 Filgrastim (70×50) Lenograstim (9×9) Vehicle (7×7)	8/3 Lenograstim (120×70) Filgrastim (15×15)
LST** (SI)	Filgrastim (82)	Lenograstim (159)
Anti-G-CSF Antibody	IgG: (-), IgM: (-), IgA: (-) IgG: (-), IgM: (-), IgA: (-)	
Concentration of total IgE (IU/ml)	9/11 18 9/14 166 9/17 <9	7/28 <9

*Therapeutic concentration of rhG-CSF (0.02 ml) was applied intradermally to the skin of forearm. Erythematous lesions were measured in 20 minutes.

**LST (Lymphocyte stimulation test) expressed as SI (stimulation index) (%) (negative <200).

Discussion

According to the initial post-market surveillance of filgrastim (Kirin Brewery/Sankyo Pharmaceutical) and lenograstim (Chugai Pharmaceutical) in Japan, adverse effects were reported in 8.9% and 4.5%, respectively. Most of them were fever and bone-related pain. Skin disorders have been documented (5, 6), but most were minor disorders, although details were not available. Systemic eruption observed in the present patients seemed to be very rare.

Since intradermal test for rhG-CSF but not for vehicle was positive in the two patients, the eruption was considered to be due to rhG-CSF. The mechanism of the eruption is unknown, but at the least type I allergic reaction may be involved because intradermal reaction occurred within less than 15 minutes and the serum IgE level transiently increased when the eruption appeared (Case 1). Like usual drug-induced eruptions, the eruption was developed following latent time, which would be needed to give sensitization. It is interesting that intradermal reaction was strongly positive for one rhG-CSF product which had been used, but weakly positive or negative for the alternative one. Such a difference indicates that the small structural difference between them, a minute contamination of protein(s), from *E. coli* or Chinese hamster ovary cells, would be responsible. If we can not use one product of rhG-CSF due to adverse effects, the other product may possibly be applicable under mandatory careful observation, as demonstrated in case 1. This notion could be supported by the fact that no antibodies to G-CSF were detectable.

Recently, Gribben et al (7) reported the development of

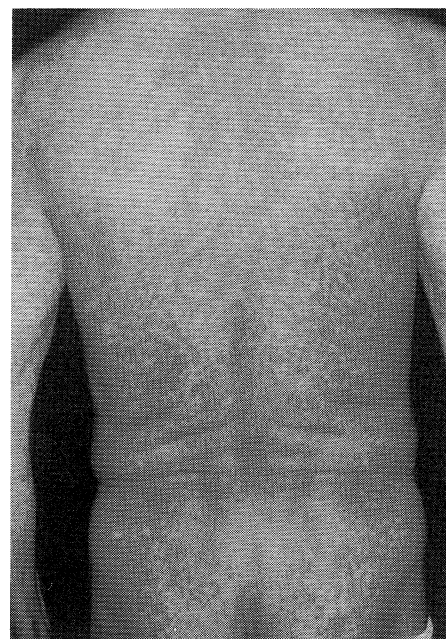


Fig. 1. Severe systemic eruption appeared on the sixth day of readministration of lenograstim in case 2.

antibodies to rhGM-CSF (granulocyte-macrophage colony-stimulating factor). They noted that the clinical effect of antibody formation might not be obvious, but the antibody seemed to accelerate plasma clearance of rhGM-CSF in some cases. Antibody has also been reported in the case of recombinant human growth hormone derived from *E. coli* (8). These antibodies react with sites on the protein backbone which are normally protected by glycosylation but which are exposed in the non-glycosylated form. No antibody against G-CSF has been reported even in the non-glycosylated form. Antibodies of IgG, A, and M class were not detected, but specific IgE antibody may be involved in the pathogenesis of the eruption.

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