

Lichenoid Cutaneous Drug Reaction at Injection Sites of Granulocyte Colony-Stimulating Factor (Filgrastim)

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Key Words

Lichen planus • Lichenoid drug reaction • Growth factor • Granulocyte colony-stimulating factor

Abstract

Colony-stimulating factors are widely used for bone marrow recovery after chemotherapy. Various cutaneous side-effects have been described in most cases involving neutrophils. We report the first case of lichenoid reaction at injection sites of granulocyte colony-stimulating factor (G-CSF) in a 40-year-old patient treated for breast cancer. The eruption cleared after drug withdrawal, no recurrence was observed after drug replacement by granulocyte-macrophage colony-stimulating factor. Mainly lymphocyte-mediated lichenoid eruption to G-CSF was shown. Cutaneous side-effects to G-CSF do not share unequivocal pathogeny based on stimulation of neutrophils.

Colony-stimulating factors (CSFs) are glycoproteins that have a distinct action on bone marrow progenitor cells. Among them, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are particularly used in patients with neutropenia induced by chemotherapy for cancer. Their action includes promotion of proliferation of progenitor cells, induction of differentiation into

specific lines, promotion of final cell maturation, improvement in cell survivability and enhancement of mature cell function [1]. Various cutaneous side-effects, localized or generalized, have resulted from such treatment. To the best of our knowledge, we report the first case of lichenoid cutaneous reaction at injection sites of filgrastim (G-CSF, Neupogen[®]) in a patient with breast cancer.

Case Report

A 40-year-old woman receiving chemotherapy for breast cancer was seen with localized eruption at injection sites of G-CSF therapy. Because of a familial history of breast cancers, she had a regular follow-up in gynaecology. A multifocal adenocarcinoma of the right breast with metastatic axillary lymph nodes was discovered in 1996. Despite 6 courses of chemotherapy, liver metastasis appeared 1 year later. Treatment with taxotere, together with steroids (Medrol[®]) and granisetron (Kytril[®]) was then started. Because of induced neutropenia after the first course, monthly G-CSF therapy (Neupogen) was added starting from the second cycle. These subcutaneous injections (5 mg/kg/day) were made during 12 days after each cycle by the patient herself after instruction. After the fifth course of G-CSF treatment, the patient presented a pruritic rash at G-CSF injection sites and was referred to us.

Physical examination showed erythematous, indurated, inflammatory plaques, on the anterior sides of both thighs. The patient decided not to change the injection sites; thus,

nearly all subsequent G-CSF injections were done into the right thigh, explaining the asymmetrical lesions (fig. 1). A punch skin biopsy specimen for histopathological examination was taken (fig. 2). It revealed orthokeratotic hyperkeratosis, damages of the granular layer with necrotic keratinocytes and large particles of keratohyalin in some cells. A dense lymphocytic infiltrate at the interface and in the papillary dermis with perivascular reinforcement was found. Blood vessels did not present any signs of vasculitis, and direct immunofluorescence was negative.

Based on clinical and histopathological data, our diagnosis was localized lichenoid cutaneous reaction induced by G-CSF (Neupogen) at the injection site. Under topical steroid treatment and after withdrawal of the medication, the lesions healed progressively with residual pigmentation. G-CSF (Neupogen) was then replaced by GM-CSF (Leucomax[®]). No other treatment change occurred. No cutaneous reaction was noted at the injection sites of this drug during the following courses. The patient died 3 months later from polymetastatic evolution of her breast carcinoma.

Discussion

The role of G-CSF (Neupogen) is evident in this observation considering the signs localized at the site of injection, the recurrence of lesions after each drug injection and the recovery after drug withdrawal. To the best of our knowledge, this is the first report of a cutaneous lichenoid reaction at injection sites of this drug.



Fig. 1. Erythematous, indurated, inflammatory plaques involving both thighs.

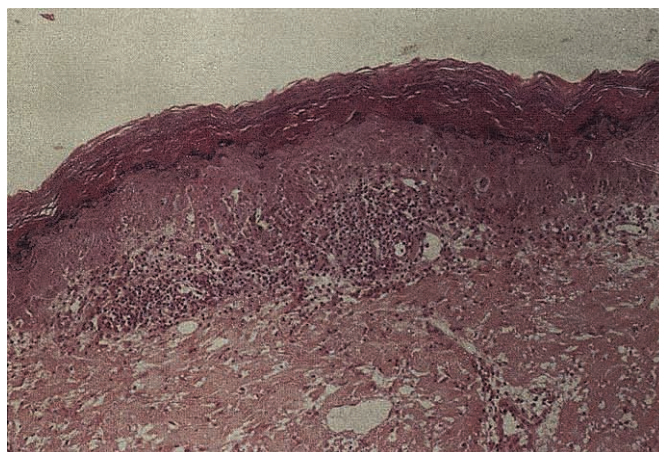


Fig. 2. Biopsy specimen showing a dense lymphocytic infiltrate in the superficial dermis under necrotic keratinocytes of granular stratum in the dermis. Absence of neutrophilic or eosinophilic infiltrate. No signs of vasculitis. HES. $\times 200$.

Many other cutaneous side-effects have been reported with G-CSF therapy. The first group is constituted by skin diseases associated with accumulation of neutrophils in the skin, such as pyoderma gangraenosum [2, 3], Sweet's syndrome [4, 5] and cutaneous leukocytoclastic vasculitis. The latter usually occurs as an adverse drug reaction in 6% of patients with chronic benign neutropenias treated with G-CSF but rarely in patients with neutropenia associated with malignancy and cytostatic therapy. The onset of cutaneous vasculitis could be prevented in most patients if the ANC was kept below $800/\text{mm}^3$. The reaction usually resolved spontaneously after discontinuation or dose reduction of G-CSF; corticosteroids have been found to be useful in the treatment of some patients [6]. Exacerbation of psoriasis [7] and widespread recurrent folliculitis [8] might be linked with these neutrophil-linked disorders. The second group of cutaneous side-effects concerns rashes: in a review about filgrastim, Frampton et al. [9] noted mild generalized rash or itch in 8% of the patients. Glass et al. [10] described 3 patients with indurated, well-demarcated, occasionally annular, erythematous papules and plaques that became generalized, then cleared after withdrawal of the medication. Distinctive histological features consisted of mild epidermal spongiosis overlying a dermal infiltrate of enlarged, plump macrophages. Increased expression of the vascular adhesion molecules ELAM-1 and VCAM-1, as well as the keratinocyte-produced ICAM-1, was

noted. These results suggested that CSF could also play a role in modulating adhesion molecule expression in the skin [10].

No lichenoid generalized eruptions have been reported in the literature. Few local reactions at injection sites of G-CSF have been reported. Subcutaneous nodules infiltrated by leukaemic blast cells at the site of injection in a 54-year-old woman with acute myelomonocytic leukaemia have been described [11]. Samlaska and Noyes [12] presented a patient with erythematous oedematous plaques at three injection sites with pruritus. The clinical presentation was very similar to our case; however, the pathology was different: biopsy specimens were remarkable for focal acanthosis, focal parakeratosis, vacuolar alteration, spongiosis and intra-epidermal microabscesses composed of eosinophils. The involved sites slowly resolved with local care and application of triamcinolone cream, while the patient continued to receive G-CSF without complications over the following 2 months [12].

It is interesting to note that in our case, eruption did not reappear under GM-CSF (molgramostim, Leucomax). This suggests that there was no cross-reaction between these two drugs. This finding is a little surprising because the incidence of localized cutaneous reaction with subcutaneous G-CSF is lower than with GM-CSF. However, a skin eruption appeared after 5 months of treatment with G-CSF and molgramostim has only been used during 3 months.

The pathogeny is unknown. Samlaska and Noyes [12] suggest that local reactions may be related to impurities within specific drug batches. For this reason, monitoring of batch numbers could be interesting [12]. At last, CSF production by keratinocytes and dermal fibroblasts has been reported, but their contribution to skin homeostasis and skin disease remains to be determined [1]. Cutaneous adverse effects could be mediated through up-regulation of neutrophil function and the secondary release of cytokines, but it is interesting to notice that in contrast to previously reported cases, there was no increase in neutrophils or eosinophils in the infiltrate.

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