A Case of Suppurative Granuloma Induced by Insulin Injection

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We report a case of suppurative granuloma, which developed following local adminstration of recombinant human insulin in an elderly woman with diabetes.

CASE REPORT

A 76-year-old woman with diabetes mellitus that had been controlled for 5 years with a rapid-acting type of recombinant human insulin (Humalog Kit®, Eli Lilly and Company, Indianapolis, USA), presented with multiple deep-seated, red-to-brown, slightly pruritic, symmetrical skin nodules, which had developed over the previous few months on the flanks and thighs (Fig. 1a and b). She reported that the lesions appeared exactly at the injection sites of recombinant human insulin 2–3 days after injections. She had also been treated with local interferon injected at the antecubital fossae for hepatitis C virus infection with no skin manifestation (Fig. 1c), indicating the negativity of the pathergy test. A skin biopsy of an erythematous nodule on the thigh revealed bottom-heavy inflammation without plain fat necrosis (Fig. 2a), and granuloma formation with massive neutrophil infiltration from the deep dermis extending to the subcutaneous area (Fig. 2b). No human insulin crystal formation was detected by polarized light examination (data not shown). Haematoxylin and eosin, Grocott, Periodic acid-Schiff, and Ziehl-Neelsen stains showed no fungus or atypical mycobacterial bodies. These findings suggest that the skin lesions were consistent with suppurative granuloma secondary to the injection of recombinant human insulin. Therefore, recombinant

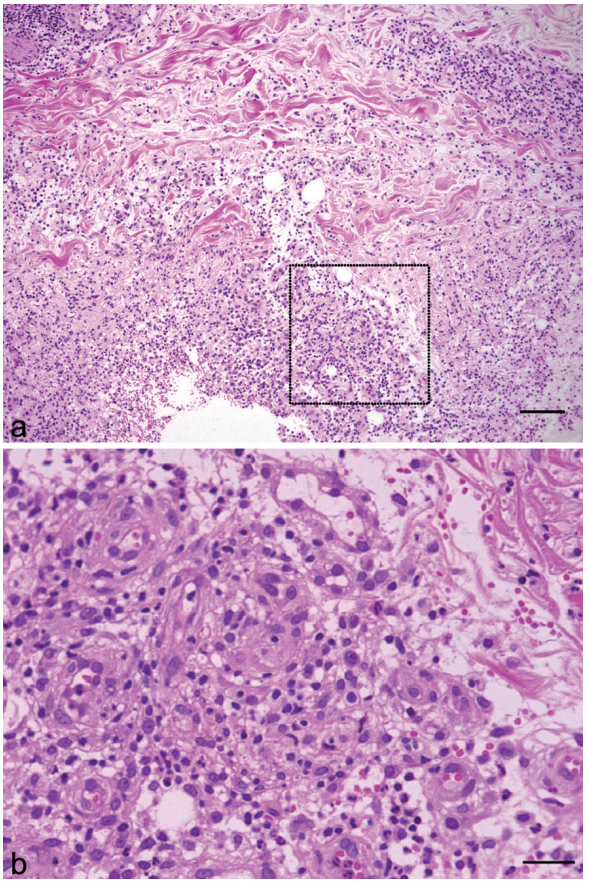

Fig. 2. Histological findings. (a) Haematoxylin and eosin stained sections of a skin nodule shows bottom-heavy inflammation without plain fat necrosis. (b) Granuloma with massive neutrophil infiltration in the deep dermis to subcutaneous tissue. Bars: (a) 100 μm; (b) 30 μm.

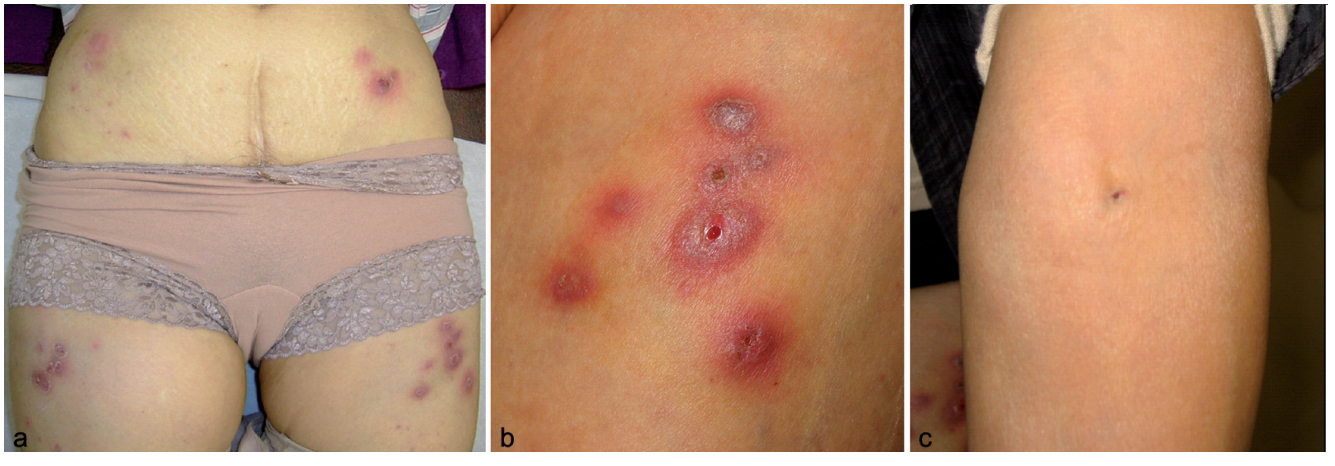

Fig. 1. Clinical appearance. (a) Multiple, deep-seated, red-to-brown nodules on both sides of the flanks and thighs at the injection sites of insulin therapy. (b) Red papules with crusts or ulcers. (c) On the skin of the left antecubital fossa, the injection site of interferon is intact.

human insulin was changed to purified human insulin (NovoPen®, Eli Lilly and Company, Indianapolis, USA), and tentative treatment with topical glucocorticoid ointment (0.05% Betamethasone butyrate propionate) was initiated. The skin lesions improved gradually with no recurrence of lesions. The patient did not agree to further skin testing or provocation.

DISCUSSION

Insulin therapy occasionally leads to skin complications, such as erythema, induration, oedema and swelling at injection sites. Among these, erythema and induration are common cutaneous adverse effects with diverse morphological and histological findings, and these reactions may be induced by insulin *per se* or by other components in the insulin preparation (1, 2). Suppurative granuloma consists of collections of epithelioid histiocytes surrounded by neutrophilic abscesses, and is usually attributable to infections with deep mycoses or mycobacterium, pyoderma gangrenosum, ruptured cysts/hair follicles, or halogenodermas. In the present case, no fungus or atypical mycobacterial body was observed by histology, and fresh sterile needles were used each time after sterilization of the injection site. Since these skin lesions were induced by injection of recombinant human insulin but not by purified human insulin or interferon, it is unlikely that the suppurative granuloma was secondary to pyoderma gangrenosum, or ruptured cysts/hair follicles. The ingredients in Humalog are insulin lispro, glycerine, dibasic sodium phosphate, meta-cresol, zinc oxide, trace amounts of phenol and water for injection. The ingredients in NovoPen are insulin aspart, glycerine, hydrochloric acid, meta-cresol, zinc oxide, sodium hydroxide, trace amounts of phenol and water for injection. Since the ingredients were not identical, we cannot rule out the possibility that the granulomatous reaction was induced by other constituent substances. In fact, it has been reported that halogenoderma can induce suppurative granuloma, but recombinant human insulin does not contain any halogen compounds. The other possible cause is the acquisition of immunogenicity by human insulin crystals due to chemical alternation of stored insulin, or aggregation or degradation of injected insulin or compounds. Anti-insulin antibody, which is known to induce skin inflammation (3, 4), was not detected by radioimmunoassay in our case.

The patient described here developed multiple skin nodules with suppurative granuloma at the injection site of recombinant human insulin. Further reports and characterization of the effects of the constituent substances in insulin therapy are required for clarification of its pathogenesis.

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