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The Koebner phenomenon seen in a case of drug-induced granular C3 dermatosis

Running title: Koebner phenomenon in drug-induced GCD

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Granular C3 dermatosis (GCD), first described by Hashimoto et al. in 2016, is characterised by granular deposition of C3 and C5b-9, but not immunoglobulin (Ig)A, IgG or IgM, at the epidermal basement membrane zone (BMZ) by direct immunofluorescence (DIF).^{1,2} GCD clinically manifests as vesicles or tense blisters with erythema. Histopathologically, GCD presents mainly subepidermal blisters, at times with oedematous and spongiotic changes, without apparent intraepidermal blister, in the epidermis.^{1,2} Neutrophils, lymphocytes and eosinophils infiltrate in both the dermis and epidermis. Although epidermal keratinocytes stimulated by inflammatory cytokines may produce C3,¹ the pathogenesis behind GCD remains unclear.

Some drugs can induce autoimmune bullous diseases and sometimes result in the Koebner phenomenon (KP)^{3,4}. There is no previous report of GCD, which showed the KP. Herein, we present a case of GCD, considered to be induced by Chinese herbal medicine demonstrating the KP.

A 72-year-old woman presented with a one-year history of multiple vesicles and tense blisters annularly arranged with erythema on the lower extremities and trunk (Fig. a, b). She noticed these symptoms 8 months after the administration of Choreitou, a Chinese herbal medicine to treat cystitis. Mucosal erosion was absent. Laboratory examinations revealed no abnormal findings, but the drug lymphocyte stimulation test (DLST) was positive for Choreitou (266%, cut-off >180). Histopathological examination showed subepidermal blisters and neutrophilic, eosinophilic, and lymphocytic infiltration in the upper dermis and intraepidermal spongiosis (Fig. d, e). DIF revealed granular deposition of C3 (Fig. f), but not IgG and IgA (Fig. g, h) at the BMZ. Serological test for Dsg1, Dsg3, BP180 antibodies was negative. Thus, GCD diagnosis was determined. Interestingly, vesicles and erythema was noticed at the biopsy site corresponding to the dressing plaster. (Fig. c). Treatment with topical steroids improved skin lesions. After discontinuing Choreitou, the symptoms did not recur.

We would like to highlight this drug Choreitou as a causative agent for GCD and supported with a positive DLST. Cessation of the drug resulted in remission. GCD may be associated with the Koebner phenomenon as demonstrated in our patient, which is observed as the emergence of new skin lesions on preexisting skin diseases, as seen in psoriasis, vitiligo, lichen planus and pemphigus.³ We are not aware of other reports of KP in GCD.

Although the GCD pathomechanisms are unknown, certain cytokines are likely involved.^{1,2} Histopathological examination of this case showed neutrophilic and eosinophilic infiltration. Neutrophils release inflammatory cytokines, including TNF- α , IL-1, IL-6, and IL-7.⁵ Furthermore, epidermal keratinocytes, stimulated by inflammatory cytokines are reported to produce C3.¹ Therefore, a possible GCD pathogenesis is the cascade of keratinocytes stimulation by neutrophil-derived cytokines and over-production of C3. In our case, a systemic drug allergy or mechanical stress from skin biopsy might have increased inflammatory cytokines, followed by triggering granular C3 deposition at the BMZ. Further studies are required to unravel GCD pathogenesis.

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Figure legend

Figure. Clinical and histopathological features of the patient

(a, b) Multiple vesicles and tense blisters with erythema on the lower extremities. **(b, c)** Skin lesions on the right thigh before (b) and after (c) the application of tape (the Koebner Phenomenon). **(d, e)** Histopathological features showing subepidermal blisters and spongiosis (d), and infiltration of neutrophils, eosinophils, and lymphocytes in the upper dermis (e). Hematoxylin and eosin (H&E) staining, original magnification: $\times 100$; scale bar = 100 μm (d) and $\times 200$; scale bar = 50 μm (e). **(f, g, h)** The results of direct immunofluorescence of C3 (f), IgG (g), and IgA (h).

Figure1, Onata et al.

