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LETTER TO THE EDITOR

Granular C3 dermatosis-like immunological manifestation found in a case of acute generalized exanthematous pustulosis: Implication for the mechanism in C3 deposition to the epidermal basement membrane zone

Dear Editor,

We recently proposed a novel autoinflammatory-like bullous disease entity, granular C3 dermatosis (GCD), which shows dermatitis herpetiformis-like granular deposition of C3 and C5b-9, but not of any immunoglobulins (Ig) or other complement components, to the epidermal basement membrane zone (BMZ) by direct immunofluorescence (IF).[1] The mechanism for the granular C3 deposition in GCD is unknown.

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction. AGEP patients show clinically numerous small sterile pustules on the entire body, and histopathologically subcorneal neutrophilic pustules in the epidermis.[2] AGEP is considered to occur through type IVd delayed hypersensitivity reaction, which involves $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells, as well as various neutrophil-directed cytokines, such as granulocyte macrophage colony-stimulating factor, interleukin (IL)-8, and IL-17.[3]

In addition, recent studies reported development of AGEP in patients with mutations in the *IL36RN* gene.[4] *IL36RN* encodes IL-36 receptor antagonist, which blocks pro-inflammatory actions of IL-36 cytokines on keratinocytes.[4] To date, a positive result by direct IF was reported only in one AGEP patient, who showed slight IgM deposition to the BMZ.[5]

In this study, we report a case of AGEP showing GCD-like granular C3 deposition by direct IF.

An 83-year-old Japanese woman presented with a history of chronic lumbago and pain on the right shoulder which no longer responded to loxoprofen sodium, paracetamol, or celecoxib. One day after the patient underwent the trigger point injection of carbocysteine and cinchocaine/salicylic acid, lumbar epidural block with mepivacaine, Neurotropin® (Nippon Zoki Pharmaceutical Co., Ltd, Osaka, Japan), and dexamethasone, intramuscular injections of vitamin C and chondroitin, and continuous oral celecoxib, she developed rashes on the skin.

Physical examination revealed exudative erythemas and small pustules on the erythemas on the trunk and lower limbs (Figure 1a), with fever of 38.1°C. Laboratory tests revealed elevated levels of neutrophils and C-reactive protein, and decreased levels of hematocrit, epidermal growth factor receptor, and serum albumin. Drug lymphocyte-stimulating test and skin patch test for celecoxib were negative.

Histopathological examination revealed subcorneal neutrophilic pustule and edema with infiltrates of neutrophils, lymphocytes, and eosinophils in the upper dermis (Figure 1b). Direct IF for the perilesional skin biopsy showed granular deposition of C3 (Figure 1c), but not IgG, IgA (Figure 1d), IgM, or C4, along the BMZ. Indirect IF using 1 mol/L NaCl-split normal human skin, immunoblot, and enzyme-linked immunosorbent assay analyses using various antigen sources also showed negative results for both IgG and IgA antibodies.

The diagnosis of AGEP was made. After cessation of all drugs, the skin lesions quickly disappeared upon oral prednisolone 20 mg/day.

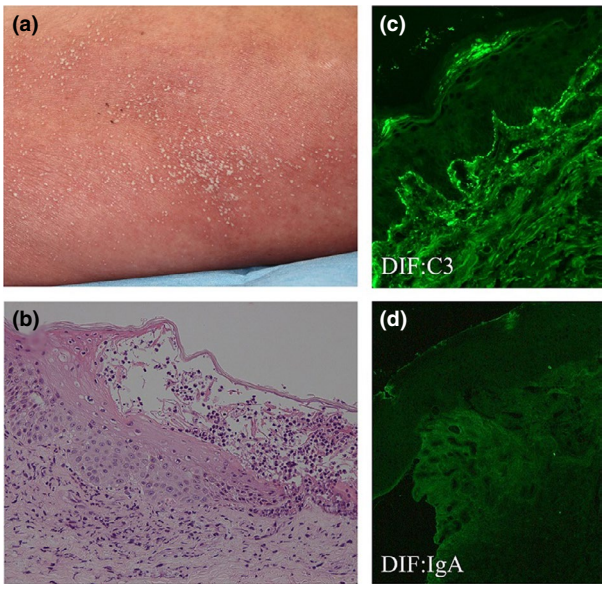

FIGURE 1 Clinical, histopathological and direct immunofluorescence (DIF) features of the present case. (a) Clinical features of the skin lesions on the right thigh. (b) Histopathological features (hematoxylin–eosin staining, original magnification ×200). (c,d) The result of DIF for (c) positive granular deposition of C3 to the BMZ (×400) and (d) negative result for immunoglobulin (Ig)A deposition (×400) [Color figure can be viewed at wileyonlinelibrary.com]

The present case showed typical clinical and histopathological features of AGEP. However, interestingly, direct IF showed granular BMZ deposition of only C3, but not of any Ig or C4, and no circulating autoantibodies to any BMZ antigens were detected by various immunological studies. These immunological patterns fall under the category of GCD.[1]

The findings in this case may indicate that AGEP and GCD are caused by the same pathomechanisms; such as *IL36RN* gene mutation[4] or type IV delayed hypersensitivity reaction to certain drugs, which involves $CD4^+$ and $CD8^+$ T cells and various neutrophil-directed cytokines.[3]

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CONFLICT OF INTEREST

None declared.

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