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Research letter

Acrodermatitis continua of Hallopeau with dense infiltration of IgG_4-positive cells in the lesional dermis

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DEAR EDITOR, Acrodermatitis continua of Hallopeau (ACH) is a rare acropustular subtype of psoriasis[1]. The characteristic feature of ACH is chronic, painful and destructive disease affecting the hands and feet, especially the fingertips and toes[2]. The pathogenic mechanisms of ACH have not been fully elucidated. We report a case of ACH whose skin lesions showed dense infiltration of IgG_4-positive cells in the dermis.

An 80-year-old Japanese man consulted our hospital complaining of chronic persistent pustules and erosions on the fingers, toes and right upper arm, and severe nail deformities (Fig. 1a-c). The symptoms had developed almost simultaneously and had persisted for four years. The nail symptoms had been treated with oral antibiotics and topical and oral antifungal agents, to no effect. The patient did not have any other medical or drug history. Bacterial cultures from the pustules on the fingertips and toes were negative. A skin biopsy was taken from a plaque on the upper arm. Histologically, a large number of neutrophils in the stratum corneum and psoriasiform dermatitis with parakeratosis (Fig. 1e, f), the elongation of thick epidermal rete ridges were observed. In addition, dense perivascular infiltration of lymphocytes and plasma cells forming small was seen in the superficial and mid dermis (Fig. 1e). Lymphocytes formed small lymph follicles, and plasma cells infiltrated

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diffusely in the dermis independently from lymph follicles. Immunohistochemically, the lymphocytic infiltration was composed of CD20- positive B- cells and CD3 CD3-positive T-cells. Plasma cells expressed CD138 and IgG, and most of the IgG- positive cells were IgG4-positive. The IgG_4-positive cell count per high-power field (HPF) was 231 (Fig. 1g).

Laboratory tests revealed elevated serum IgG_4 at 168 mg/dl, with a normal level of total serum IgG of 1241 mg/dl. The serum IgE concentration was slightly elevated, but IgM and IgA serum levels were within normal ranges, respectively. Serum C-reactive protein was not elevated.

White blood cell counts and serum lactate dehydrogenase concentration were within normal ranges. Secondary syphilis was excluded by blood tests. Serum angiotensin converting enzyme was normal. Antinuclear antibody and rheumatoid factor were negative. Internal malignancies were screened by total body contrast-enhanced computerized tomography imaging and with measurements of serum cancer markers. No signs of malignancy were found. There were no IgG_4-related disease (IgG_4-RD) organ symptoms. He had no other skin symptoms, such as atopic dermatitis or pemphigus.

The present study was approved by the Ethics Committee of the Nagoya University Graduate

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School of Medicine. Written informed consent was obtained from the patient. We performed Sanger sequencing using genomic DNA samples from the patient, but neither *IL36RN* mutation nor *CARD14* mutation/variant was detected (data not shown).

The patient was treated with a very strong topical steroid. At three weeks later, the scales on the upper arm were decreased and the fingers and toes showed significant improvement. After four months, the erythema and pustules still remained, but he had no pain from normal daily activity (Fig. 1d).

This case showed moderately elevated serum IgG_4 (168 mg/dl), which fulfilled the comprehensive diagnostic criteria of serum IgG_4 concentration (>135 mg/dl) for IgG_4-RD.[3] The pathological diagnostic guidelines for IgG_4-RD set strict pathological cutoffs: The skin should have a dense IgG_4-positive plasma cell infiltration of more than 200 cells in HPF[4]. Our case fulfilled these histological criteria. However, the clinical features were quite different from the known skin symptoms of IgG_4-RD. Tokura *et al.*[5] divided skin symptoms into two groups: primary symptoms, caused by direct IgG_4-positive plasma cell-infiltration, and secondary symptoms, caused by IgG_4-positive plasma cell and/or serum IgG_4. Our case fit none of the primary subtypes. It showed rather typical clinical and histological features of

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ACH, and we made the diagnosis of ACH with dense infiltration of IgG_4-positive cells.

ACH cases related to IL36RN mutations are considered to be "autoinflammatory keratinization disease" (AIKD),[6] although the present patient had neither IL36RN mutation nor CARD14 mutation and might be a non-AIKD case of ACH. AIKDs have a mixed autoinflammatory- and autoimmunity-driven pathogenesis. In contrast, IgG_4 is an immunoglobulin subtype associated with allergic responses related to T-helper 2 (Th2)[7], and it has been hypothesized that Th2 plays a role in the pathogenesis of IgG_4-RD.[5] Interestingly, in cases of generalized pustular psoriasis, IgG_4-RDs were reported as complications.[8] In light of this, the present case suggests that Th2 mechanisms might be involved in the pathogenesis of pustular psoriasis and related pustular skin diseases, although we were unable to find fully reasonable explanations for the correlation between the Th2 reaction and pathogenic mechanisms of the present subtype of pustular psoriasis.

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Figure legends

Fig 1. (a) Pustules and erosions on the left forefinger. (b) Pustules and erosions on the right big toe. (c) Pustules and erosions on the right upper arm. (d) The skin lesion on the forefinger tip improved after topical steroid treatment, although pustules and erosions remained. (e) Histological features of a skin biopsy from the upper arm. Dense infiltration of lymphocytes and plasma cells is observed in the superficial and mid dermis (haematoxylin and eosin, original magnification x40) (f) The epidermis and the superficial dermis show neutrophilic infiltration and psoriasiform dermatitis with parakeratosis (haematoxylin and eosin, original magnification x200). (g) The IgG_4-positive cell count per high-power field (HPF) is 231 (immunohistochemical staining for IgG_4, original magnification x400).

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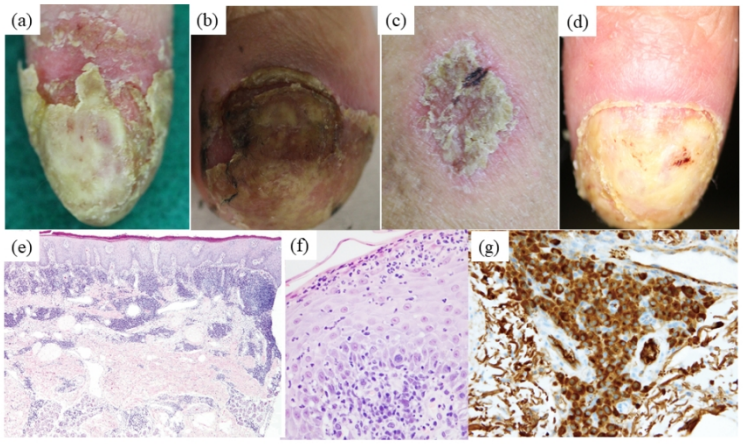

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