

CONCISE COMMUNICATION

Atopic dermatitis without serum immunoglobulin E elevation or loss-of-function filaggrin gene mutation in a patient with X-linked agammaglobulinemia

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ABSTRACT

A case of atopic dermatitis (AD) with X-linked agammaglobulinemia (XLA), which is one of the primary immunodeficiency diseases, is reported. A 12-year-old boy had suffered from dry skin and recurrent itchy eruptions since he was 2 years old, and he was diagnosed as having XLA at the age of 4 years. His total immunoglobulin (Ig)E level was 7 IU/mL, even with regular Ig replacement therapy. Furthermore, filaggrin (FLG) mutations known in the Japanese population were not found. His skin lesions were well controlled by the application of a mild-class topical steroid and a moisturizer, though he developed folliculitis due to *Staphylococcus aureus* infection during treatment with a strong-class topical steroid. This case suggests that the FLG mutation and IgE-mediated sensitization are not necessary to induce AD skin manifestation.

Key words: atopic dermatitis (eczema), filaggrin gene mutations, immunoglobulin E, primary immunodeficiency disease, X-linked agammaglobulinemia.

INTRODUCTION

X-linked agammaglobulinemia (XLA), also called Bruton's agammaglobulinemia, was reported by Bruton in 1952.¹ In XLA patients, B-cell differentiation stops in the initial stage due to dysfunction of Bruton's tyrosine kinase, which results in the failure of B lymphocytes to mature and the subsequent absence of or very low levels of serum immunoglobulins (Ig). Patients develop severe bacterial infections during infancy. On the other hand, the function of T lymphocytes is normal. Thus, most fungi and viruses are completely eliminated, but patients are susceptible to bacterial infections, especially *Streptococcus pneumoniae* and *Hemophilus influenzae*.² The incidence is 1/300 000 in Japan and 1/900 000–1 400 000 in Europe.^{3,4} Here, we report a case of atopic dermatitis (AD) with XLA.

CASE REPORT

A 12-year-old Japanese boy had suffered from dry skin and repeated itchy eczema since he was 2 years old. He had repeated respiratory infection and was then diagnosed with XLA based on a frame-shift mutation of 186delGAAA of the *BTK* gene at the age of 4 years. He received regular i.v. Ig replacement therapy. Regarding his family history, his mother

had allergic rhinitis. He was referred to our department for his refractory eczema. Physical examination revealed extensive dry skin with mild erythema on the trunk and extremities. White dermographism was noted. Erythema with mild lichenification was noted on the popliteal and cubital fossae (Fig. 1).

His laboratory tests showed a white blood cell count of 7200/μL, of which eosinophils comprised 650/μL. The levels of all serum Ig were decreased and Ig values 26 days after Ig replacement therapy were: IgG, 572 mg/dL; IgA, 23 mg/dL; IgM, 8 mg/dL; and IgE, 7 mg/dL. The percentages of lymphocyte subsets were: CD3, 90.9%; CD4, 63.8% (elevated); CD8, 23.0% (normal); CD19, 0.2%; and CD56⁺CD16, 3.4% (decreased). In peripheral blood, T-helper (Th)1/Th2 analysis showed: Th1 (interferon [IFN]-γ⁺/interleukin [IL]-4⁻), 9.1% (normal, 11–44%); Th2 (IFN-γ⁻/IL-4⁺), 2.3% (normal, ≤5.0%); Th0 (IFN-γ⁺/IL-4⁺), 0.7% (normal, ≤3.0%); Th0 (IFN-γ⁻/IL-4⁻), 88.0%; and Th1/Th2 ratio (CD4), 4.0% (normal, 3.8–25%). His serum thymus and activation-regulated chemokine (TARC) level was increased to 2570 pg/mL. Filaggrin (FLG) analysis revealed the absence of the following mutations: p.Arg501X, c.3321delA, p.Ser1695X, p.Gln1701X, p.Ser2554X, p.Ser2889X, p.Ser3296X, p.Lys4022X, p.Gln1790X and c.441–442delAG.

The skin prick test with the mite antigen *Dermatophagoides farina* (Torii Pharmaceutical, Tokyo, Japan) was negative,

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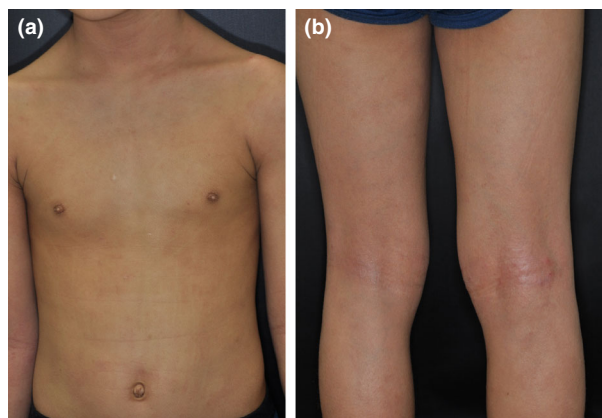


Figure 1. Clinical symptoms at the first visit to our department. (a) Diffuse erythema, dry skin and white dermographism were noted on the trunk. (b) Erythema with mild lichenification was noted on the popliteal fossa.

whereas a 7 mm × 7 mm wheal and 20 mm × 20 mm erythema were noted with 1% histamine dihydrochloride. The scratch patch test with mite antigen (*D. farina*) was positive (+) at 48 and 72 h based on the International Contact Dermatitis Research Group standard. The diagnosis was AD according to the typical skin symptoms, elevated serum TARC level and his family history.

After he was treated with the strong-class topical steroid beclomethasone propionate (Propaderm[®], Kyowa Kirin Co., Ltd., Tokyo, Japan) ointment twice daily, red papules, nodules and pustules appeared on the forearm and the abdomen (Fig. 2). Methicillin-susceptible *Staphylococcus aureus* was identified from the lesion, suggesting that most of these newly developed lesions were staphylococcal folliculitis. Those lesions improved after treatment with fusidic acid (Fucidine Leo[®], Daiichi Sankyo Company, Tokyo, Japan) ointment. We changed the topical steroid to medium-class hydrocortisone butyrate (Locoid[®], Torii Pharmaceutical Co., Ltd., Tokyo, Japan) ointment, and then new pustules did not occur. Four months after his first visit to our department, his serum TARC level dropped to 488 pg/mL. His skin symptoms remained in remission with treatment with a topical steroid and a moisturizer.

DISCUSSION

Primary immunodeficiency disease (PID) is a group of chronic disorders in which certain components of the immune system are missing or dysfunctional due to congenital problems. Other than infectious skin lesions such as abscesses, some PID have specific skin symptoms, namely AD-like symptoms in hyper-IgE syndrome and Wiskott–Aldrich syndrome, erythroderma with diffuse alopecia in Omenn syndrome, urticaria and angioedema in complement deficiency, and albinism in Chediak–Higashi syndrome.⁵

Peterson *et al.*⁶ reported typical AD in four of 23 patients with XLA. In these patients, skin tests of more than 200 antigens, including *Ascaris lumbricoides*, were all negative for an



Figure 2. Folliculitis on the forearm after treatment with a strong-class topical steroid.

immediate type of wheal/erythema reaction, whereas the delayed response to *A. lumbricoides* antigens was positive. The skin test result with the mite antigen in our case is similar to these observations. Afterwards, there were no reports that described AD in XLA, as far as we know.

In AD, barrier dysfunction, the colonization of *S. aureus*, house dust mite on the skin and environmental pollutant induce epidermal expression of thymic stromal lymphopoietin, IL-25 or IL-33. These cytokines stimulate innate lymphoid cell 2 and Langerhans cells leading to the activation of Th2 cell-dominant immune response.⁷ FLG is an important protein that constitutes the stratum corneum barrier.⁸ Some AD patients carry a loss-of-function *FLG* mutation, which is considered to be a risk factor for AD development, because it causes the barrier disruption. The prevalence of *FLG* mutations in AD patients varies depending on the climate of the study area, namely approximately 20–55% in Europe and the USA,⁸ and 7.9–27.0% in Japan. Eight mutations (p.Arg501X, c.3321delA, p.Ser1695X, p.Gln1701X, p.Ser2554X, p.Ser2889X, p.Ser3296X, p.Lys4022X) have been identified in the Japanese population, whereas c.2282del4 has been identified in European patients. In the present case, no such mutation was identified.

Similarly, although many patients with AD, particularly those with severe disease, show IgE-mediated sensitization to common allergens,⁹ this patient could not produce IgE. This observation is consistent with recent evidence suggesting that IgE-mediated sensitization is a secondary phenomenon that can amplify existing inflammatory lesions.¹⁰ Therefore, our case strongly suggests that the lack of *FLG* mutation and IgE-mediated sensitization are not necessary to induce skin manifestation of AD. This notion is supported by the observation that the intrinsic AD which lacks *FLG* mutation or IgE-mediated sensitization shows skin manifestation indistinguishable from the extrinsic AD.¹¹

On the other hand, this patient showed two specific findings, probably related to the induction of AD skin manifestation: the reduction of IFN- γ -producing T cells in the peripheral blood and increased plasma TARC levels. These findings suggest that his peripheral immune response was shifted toward a Th2 response. To our knowledge, the role of Bruton's tyrosine kinase in the development of Th2 cells is not known. Because XLA patients in general are susceptible to bacterial infection, it is conceivable that this patient had skin microbial dysbiosis, which induces Th2-dominant immune response. Recently, Byrd *et al.*¹² reported that AD skin shows microbial dysbiosis with the dominant colonization of *S. aureus* and that this tendency increases according to the severity of the skin lesions. Moreover, application of *S. aureus* obtained from the skin of severe AD patients to mice skin elicited a Th2-type immune response.¹² Although analysis of the skin microbiome was not performed in our patient, *S. aureus*-dominant microbiome induced by XLA might have played a role in the development of AD in this patient.

CONFLICT OF INTEREST: None declared.

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