Anais Brasileiros de Dermatologia 2023;98(5):689–714

SOCIEDADE BRASILEIRA DE DERMATOLOGIA

Anais Brasileiros de Dermatologia

www.anaisdedermatologia.org.br

LETTER - CLINICAL

Bullous pemphigoid developed after dramatic improvement of severe prurigo nodularis☆

Dear Editor,

A 40-year-old female with oral allergy syndrome visited us, complaining of itchy eruptions which appeared one year previously. Physical examination showed a number of firm nodules on the trunk and extremities (Fig. 1). Moreover, subungual hyperkeratosis was observed. Histological examination revealed irregular epidermal proliferation, mild infiltration of mononuclear cells, and fibrosis of the upper dermis (Fig. 2). Laboratory examination showed a white blood cell count of 9700 μL (12% eosinophils), and elevated AST (63 IU/L) and ALT (62 IU/L). The serum level of IgE was over 5,000 IU/mL, whereas anti-BP180 NC16A Ig was within normal range. The patient was treated with various therapies, all of which were disappointing. However, the nodular lesions dramatically improved when she visited our hospital two years later (Fig. 3). She stated that she experienced divorce, which was suspected to release mental stress and led to favorable effects on her skin conditions. Serum IgE level remained elevated (3614 IU/mL). Three and half years after the complete resolution, she revisited our department, complaining of itchy erythema and a number of bullous lesions. Physical examination showed tense blisters, erosions, and edematous erythema on the upper extremities and back (Fig. 4). Laboratory tests showed

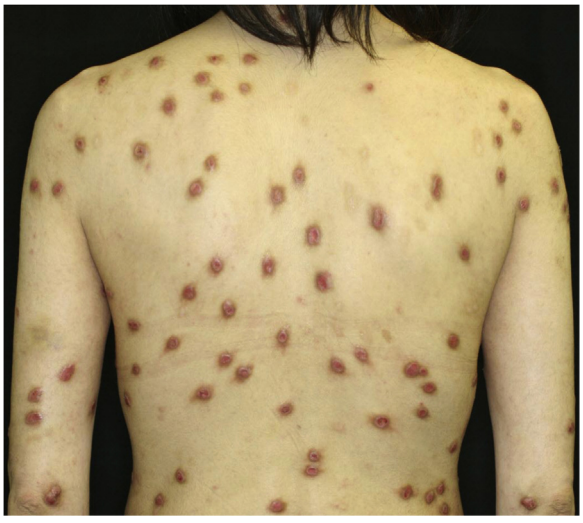

Figure 1 A number of nodular prurigo on the back

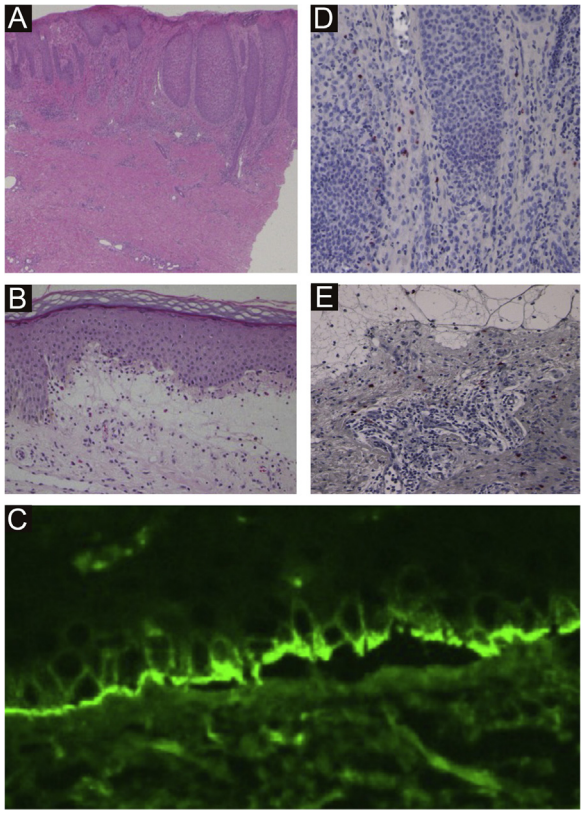

Figure 2 (A) Histological features from nodular prurigo showed irregular acanthosis of the epidermis, inflammatory cell infiltration in the upper dermis, and dermal fibrosis (×40). (B) Histological features from bullous lesion showed subepidermal bulla with eosinophil infiltration (×100). (C) and direct immunofluorescence showed linear deposition of IgG at the basement membrane zon e. BB.1 staining positive basophils in the lesional skin of prurigo nodularis (×200) (D) and BP (×200) (E)

☆ Study conducted at the Department of Dermatology, Fukushima Medical University, Fukushima, Japan.

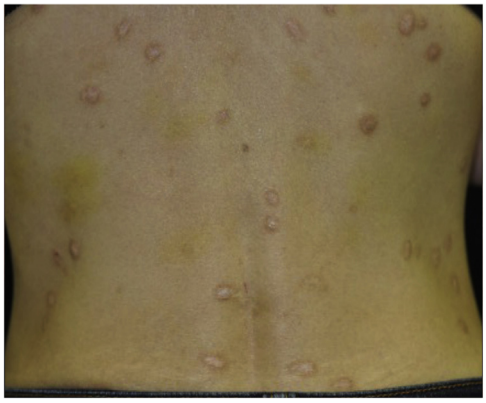

Figure 3 Nodular lesions are dramatically improved after 2 years

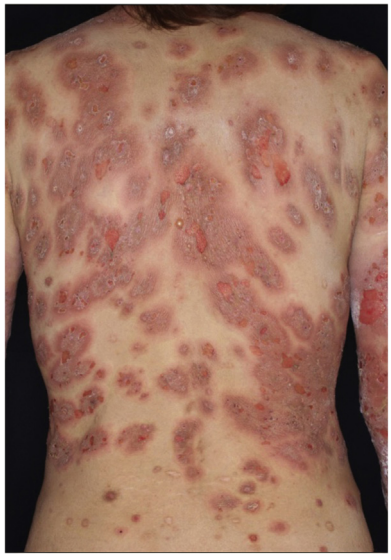

Figure 4 Bullous lesions and erythematous plaques on the trunk

an increased number of eosinophils (10%) in the peripheral blood, and serum titer of the anti-BP180 NC16A Ig antibody was over 10,000 U/mL (cut-off < 10). A biopsy from one of the blisters revealed subepidermal blister formation with prominent eosinophil infiltration (Fig. 2). Direct immunofluorescence showed linear deposition of IgG and C3 at the basement membrane zone (Fig. 2), and 1M NaCl-split skin indirect immunofluorescence revealed circulating IgG antibodies reacting on the roof of the cleavage. She was treated with methylprednisolone pulse therapy (1,000 mg for three consecutive days) followed by oral prednisolone, methotrexate, cyclosporine, and plasma exchange therapy. Immunohistological examination revealed BB1-positive basophils in both Prurigo Nodularis (PN) and Bullous Pemphigoid (BP) lesions (Fig. 2). Immunostained cells were counted in random 10 fields under high magnification (×400) of a light microscope, which showed 13.8 ± 5.2 in prurigo nodularis versus 15.2 ± 5.0 in BP lesions.

We reported herein a case of BP occurring after the complete resolution of severe PN. A similar case was reported by Yoshimoto et al.,[1] and their case developed BP 10 months after improvement of PN. They speculated that scratching and local inflammation in PN led to the exposure of neo-epitopes at the basement membrane, resulting in the production of pemphigoid antibodies.[2] Chen et al.[2] suggested that the Basement Membrane Zone (BMZ) injuries may have exposed the ''hidden'' antigens to the immune system, and induced an autoimmune response against the BMZ components. This ''epitope spreading'' phenomenon may have occurred in our case during the long course.

Recent studies have shown that basophilic infiltration was observed in PN and BP in the activated states.[3,4] Basophils are one of the major sources of producing Th2-type cytokines leading to increased IgE levels.

In conclusion, basophil was increased in number in both BP and PN lesions and may play an important role in the induction of BP and PN in the present case.

Financial support

None declared.

Authors' contributions

Tomoko Hiraiwa: The study concept and design; data collection, or analysis and interpretation of data; statistical analysis; writing of the manuscript or critical review of important intellectual content; data collection, analysis and interpretation; effective participation in the research guidance; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Natsuko Matsumura: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Tatsuhiko Mori: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Nobuyuki Kikuchi: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Toshiyuki Yamamoto: The study concept and design; statistical analysis; effective participation in the research guidance; critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

Acknowledgment

The authors thank Ms. Chiyako Miyagishi (Department of Dermatology, Tokyo Medical, and Dental University) for a special stain using an anti-BB-1 antibody.

References

1. Yoshimoto N, Ujiie H, Hirata Y, Izumi K, Nishie W, Shimizu H. Bullous pemphigoid developed in a patient with prurigo nodularis. J Eur Acad Dermatol Venereol. 2017;31:e187–189.
2. Chen LS, Vanderlught CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, et al. Epitope Spreading: lessons from autoimmune skin disease. J Invest Dermatol. 1998;110:103–9.
3. Ugajin T, Takahashi M, Miyagishi C, Takayama K, Yokozeki H. A case of bullous pemphigoid associated with infiltration and activation of basophils. Br J Dermatol. 2015;173:1095–8.
4. Inui K, Ugajin T, Namiki T, Yokozeki H. Chronic prurigo: a retrospective study of 168 cases. J Dermatol. 2020;47:283–9.

Tomoko Hiraiwa *, Natsuko Matsumura, Tatsuhiko Mori, Nobuyuki Kikuchi, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima, Japan

* Corresponding author.
E-mail: toishi@fmu.ac.jp (T. Hiraiwa).

Received 26 September 2022; accepted 28 November 2022
Available online 22 May 2023

https://doi.org/10.1016/j.abd.2022.11.003

Case for diagnosis. Disseminated erythematous and scaly plaques: chronic mucocutaneous candidiasis☆

Dear Editor,

A four-year-old male patient from a rural area had disseminated erythematous scaling plaques, some with thick adhered vegetative crusts since he was three years old (Fig. 1–2). There was no deterioration in the general health status or relevant family history. The mother reported multiple previous hospitalizations due to pericarditis, pneumonia, and skin infections, in addition to episodes of oral and genital candidiasis.

Direct mycological examinations of the skin lesions on the trunk and scalp disclosed the presence of hyphae, pseudohyphae, and yeasts – later identified as *Microsporum gypseum* and *Candida albicans* by MALDI-TOF (Matrix-assisted laser desorption ionization time-of-flight) mass spectrometry. Histopathology revealed irregular acanthosis, spongiosis, keratotic crust, and dermal edema, in addition to numerous hyphae and spores restricted to the stratum corneum (Fig. 3). The genome analysis identified a rare heterozygous mutation in exon 7 of the signal transducer and activator of transcription 1 (*STAT1*) gene; variant c.501A→C; p.Gln167His.

What's your diagnosis?

a) Acquired Immunodeficiency Syndrome (AIDS)
b) Severe Combined Immunodeficiency (SCID)
c) Chronic Mucocutaneous Candidiasis (CMCC)
d) Hyper-IgE Syndrome (HIES)

☆ Study conducted at the Department of Dermatology, Hospital Infantil João Paulo II and Hospital Eduardo de Menezes, Belo Horizonte, MG, Brazil.

Discussion

Based on the clinical-laboratory correlation, the diagnosis of chronic mucocutaneous candidiasis (CMCC) was established due to the *STAT1* gene mutation, in addition to extensive dermatophytosis. Complementary exams, including indirect Coombs, thyroid function, anti-HIV I and II serology, autoantibodies, immunoglobulin measurement and lymphocyte immunophenotyping were normal. Oral fluconazole was started with partial regression of the lesions (Fig. 4).

CMCC is a heterogeneous group of rare syndromes characterized by persistent, non-invasive *Candida spp* infections of the skin, nails, and mucous membranes caused by primary immunological defects.[1] *STAT1* gain-of-function mutations underlie the autosomal dominant form of the disease and result in defective Th1 and Th17 cell responses, characterized by reduced production of interferon-γ, interleukin-17, and interleukin-22 cytokines, crucial for antifungal defense of the skin and mucous membranes.[2–4] To the best of our knowledge, this is the first report in which the detected *STAT1* variant was documented in association with CMCC.

Typically, this form of the disease manifests as erythematous scaling crusted, hyperkeratotic generalized plaques before the age of five, sometimes accompanied by paronychia, hyperkeratosis and nail dystrophy. The oral mucosa is the most frequently affected, although the esophageal, genital and laryngeal mucosa can be affected as well. In addition to chronic *Candida* infection, there is also increased susceptibility to dermatophyte and bacterial infections, and up to 50% of the patients have associated hypothyroidism, inflammatory bowel disease, or associated autoimmune cytopenias.[5,6]

The analysis of relevant genes, such as *STAT1*, *AIRE* and *CARD9*, is the only definitive laboratory test for the diagnosis of CMCC. Other immunodeficiencies, including SCID, HIES, and AIDS, can result in chronic candidiasis, but almost invariably course with invasive *Candida* infections and additional clinical-laboratory characteristics. In SCID, severe disturbances in T-, B-, and sometimes natural killer-cell