IJD | 5352 | B
Journal Name | Manuscript No.
Dispatch: 15.10.11 | Journal: IJD | CE: GeethaPriya P.
Author Received: | No. of pages: 3 | PE: Prasanna
International Journal of Dermatology

Correspondence

Sweet's syndrome presenting with vegetative nodules on the hands: relationship to neutrophilic dermatosis of the dorsal hands

A 22-year-old Japanese woman was referred to our department with a 3-week history of painful eruptions on her hands, extremities, face, and buttocks. Initially, a few reddish eruptions appeared on the left hand, and these gradually developed on other sites. She had experienced sore throat and mild fever (38 °C) for a week before the eruptions. Initial examination showed elevated erythematous nodules on both hands (Fig. 1). Multiple reddish papules were distributed over the extremities, buttocks, and face. Her medical history was unremarkable except for a 5-year course of antidepressants. The biopsy specimen from the nodule on the right dorsal hand revealed neutrophilic infiltration and edematous change in the dermis, and the specimen from the papule on the left thigh showed neutrophilic infiltration of the dermis (Fig. 2). Neither of the specimens showed vasculitis. Gram, periodic acid-Schiff, Grocott, and Ziehl–Neelsen stains on the biopsy specimen, culture of skin tissue, and polymerase chain reaction analyses failed to indicate any infectious diseases. Laboratory examinations detected weakly positive antinuclear autoantibody (1 : 80), but they were negative for rheumatoid factor. Neither anti-PR3-ANCA nor anti-MPO-ANCA antibodies were detected. Complete blood counts showed increased leukocytes (11 000/μl) and slightly elevated eosinophil fraction (10%). Cytopenia, abnormal granules in the cells, and abnormal nuclear shape were not observed. Systemic examinations, including X-ray and endoscopy, detected neither internal malignancies nor inflammatory bowel diseases. To summarize the clinicopathological features and laboratory findings, the patient had: (i) abrupt onset of painful nodules; (ii) histopathological evidence of dense neutrophilic infiltration without leukocytoclastic vasculitis; and (iii) previous upper respiratory tract infection and pyrexia. These fulfilled the diagnostic criteria of Sweet's syndrome (SS).[1] Two weeks after our initial examination, the lesion resolved itself without any systemic and topical therapies, leaving residual pigmentation. No recurrence has been observed for 2 years (Fig. 1e–h).

Neutrophilic dermatosis of the dorsal hands (NDDH) was first described by Strutton *et al.*[2] In 2006, Walling *et al.*[3] reviewed 52 reported cases and proposed the concept of NDDH as a distributional variant of SS; this

COLOR

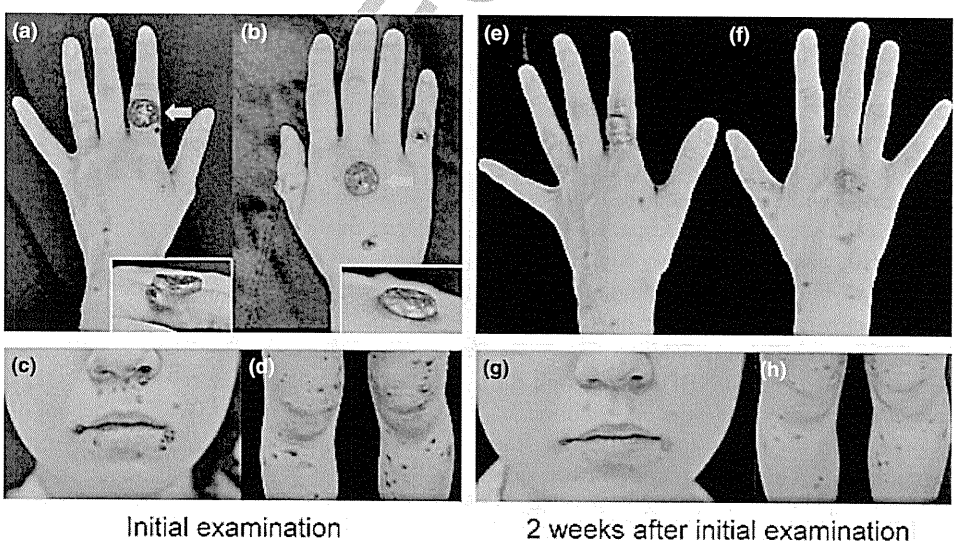
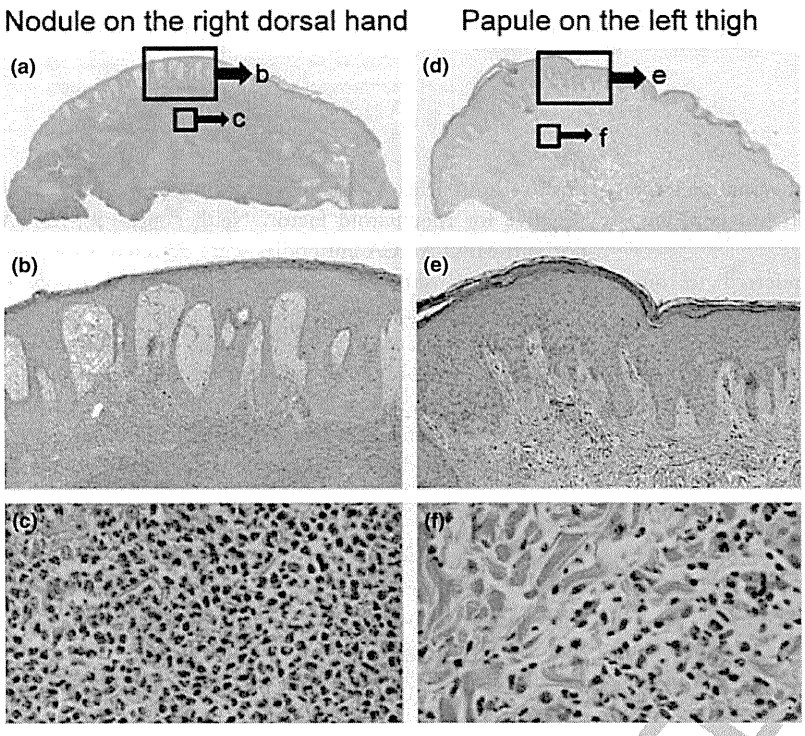


Figure 1 (a, b) Painful nodules and papules on both hands. A broad-based erythematous vegetative nodule elevated from the violaceous margin and 25 mm in diameter is observed on the left index finger (a, inset). An erythematous vegetative nodule 20 mm in diameter is noted on the right dorsal hand (b, inset). (c, d) Multiple dark red papules with partial scales and crusts on the surface ranging in size from 2 to 10 mm are observed on the face (c) and thighs (d). (e–h) Two weeks after our first examination, the lesions resolved without systemic and topical therapies, leaving residual pigmentation



COLOR

Figure 2 Histopathological observation. (a–c) The biopsy specimen from the nodule of the right dorsal hand shows edematous change in the superficial dermis (b) and dense neutrophilic infiltration throughout the dermis (c). (d–f) The specimen from the papule on the left thigh reveals perivascular infiltration of neutrophils and lymphocytes (e, f). Neither of the specimens shows apparent leukocytoclastic vasculitis. (Hematoxylin–eosin stain, original magnification; a, d: ×4; b, e: ×100, c, f: ×400)

concept has been followed by several studies.[4–6] Recently, Takahama and Kanbe[7] reported a patient with NDDH with HLA-B51, the marker for SS, which suggests a strong relationship between NDDH and SS. Our case showed typical NDDH vegetative nodules and definitively fulfilled the criteria for SS, which also supports the disease concept of NDDH proposed by Walling *et al.*[3] NDDH lesions are usually limited to the dorsal hands; however, some patients with NDDH also have lesions at other sites.[1,3,4,8] As far as we have surveyed, there have been no NDDH cases with skin lesions distributed as widely as our patient's. From the histopathology, we speculate that the pathogenesis of all the skin lesions is similar, with lesion severity depending on the affected body site. It is not known why eruptions on the dorsal hands tended to develop vegetative nodules.

Although the patient had typical NDDH lesions on the hands, our case is unique for the wide distribution of lesions at sites other than the hands and for fulfilling the diagnostic criteria for SS. The present case further supports the notion that NDDH is a clinical variant of SS and highlights the diversity of cutaneous manifestations of SS.

Osamu Mizuno, ????
Teruki Yanagi, MD, PhD
Keiko Baba, ????
Naoko Yamane, ????
Daisuke Inokuma, ????
Kei Ito, ????
Masashi Akiyama, ????
Hiroshi Shimizu, ????
Department of Dermatology
Hokkaido University Graduate School of Medicine
Sapporo
Japan

Masashi Akiyama, ????
Department of Dermatology
Nagoya University Graduate School of Medicine
Nagoya
Japan

Teruki Yanagi, MD, PhD
Hokkaido University Graduate School of Medicine
N15 W7 Kita-ku
Sapporo
Japan
E-mail: yanagi@med.hokudai.ac.jp

Conflicts of interest: None.

doi: 10.1111/j.1365-4632.2011.05352.x

References

1 Cohen PR. Sweet's syndrome – a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; 2: 34–62.

2 Strutton G, Weedon D, Robertson I. Pustular vasculitis of the hands. *J Am Acad Dermatol* 1995; 32: 192–198.

3 Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol* 2006; 142: 57–63.

4 Abbas O, Kibbi AG, Rubeiz N. Sweet's syndrome: retrospective study of clinical and histologic features of 44 cases from a tertiary care center. *Int J Dermatol* 2010; 49: 1244–1249.

5 Kung EF, Arora A, Petronic-Rosic V, Tsoukas MM. Clinicopathologic challenge. Neutrophilic dermatosis of the dorsal hands – a variant of localized Sweet's syndrome. *Int J Dermatol* 2009; 48: 555–557.

6 Duquia RP, Almeida HL Jr, Vettorato G, *et al.* Neutrophilic dermatosis of the dorsal of the hands: acral sweet syndrome? *Int J Dermatol* 2006; 45: 51–52.

7 Takahama H, Kanbe T. Neutrophilic dermatosis of the dorsal hands: a case showing HLA B54, the marker of Sweet's syndrome. *Int J Dermatol* 2010; 49: 1079–1080.

8 DiCaudo DJ, Connolly SM. Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands: a report of 7 cases and review of the literature. *Arch Dermatol* 2002; 138: 361–365.

Erythema Annulare Centrifugum-like Neutrophilic Dermatosis: Effects of Potassium Iodide

Hanako Koguchi, Ken Arita*, Naoko Yamane, Satoru Shinkuma and Hiroshi Shimizu
*Department of Dermatology, Hokkaido University Graduate School of Medicine, N15, W7, Sapporo 060-8638, Japan. *E-mail: ariken@med.hokudai.ac.jp*
Accepted October 16, 2011.

Figurate erythema can be seen in various dermatological backgrounds, including erythema annulare centrifugum (EAC) and collagen diseases. Neutrophilic dermatoses clinically demonstrating figurate erythema, however, are relatively rare. We describe here a case of a 76-year-old Japanese man who presented with figurate erythema histologically characterized by neutrophilic infiltration, which was treated successfully with potassium iodide.

CASE REPORT

A 76-year-old man presented to our outpatient clinic with a one-year history of recurrent annular erythematous lesions. The eruptions had usually disappeared spontaneously within 2–4 weeks, with new lesions occurring after a few months.

On physical examination, annular oedematous erythemas were found spread over the extremities, back and gluteal regions (Fig. 1a). Some of the lesions were more than 10 cm in diameter. The lesions had elevated borders and central resolution. Scaling, vesicles and crusts were absent. The patient reported slight itching. His general condition was good, and he had not been taking any medications. The initial diagnosis was EAC, and differential diagnoses were erythema gyratum repens and Sjögren's syndrome.

Laboratory data showed slightly elevated C-reactive protein (0.48 mg/dl) and immunoglobulin E (658 IU/l). Anti-nuclear antibody was positive at a titre of 1:80, although anti-Sjögren's syndrome A (SS-A) and B (SS-B) antibodies were negative. Otherwise, the results were normal, including blood cell count, rheumatoid factor, tumour markers and serum complement. Whole-body computed tomography (CT) scanning showed only fatty liver and gallbladder stones.

Histological examination of a skin biopsy taken from the active border of an annular lesion on the left thigh showed perivascular and interstitial cell infiltration without remarkable epidermal changes. The dermal infiltrate consisted mostly of neutrophils in association with small numbers of eosinophils and rare lymphocytes (Fig. 2). Vasculitis was not detected. The case was finally diagnosed as neutrophilic figurate erythema.

Initial treatments with oral anti-histamine and topical steroid were unsuccessful. Based on the diagnosis of neutrophilic dermatosis, oral potassium iodide at 0.9 g/day was started, and the lesions disappeared completely within 2 weeks (Fig. 1b). The eruptions have been almost completely suppressed for 2 months under the potassium iodide treatment.

DISCUSSION

The eruptions had the characteristic annular figurate pattern. Figurate erythema is typically seen in EAC, erythema gyratum repens, Sjögren's syndrome and certain other disorders. However, our case showed typical histological features of neutrophilic dermatosis. A search of the English literature found only two cases described as "neutrophilic figurate erythema" in adults (1, 2): one with Hodgkin's lymphoma showed a paraneoplastic clinical course, and the other had no associated diseases or laboratory abnormalities. In children, we found three cases described as "neutrophilic figurate erythema of infancy", characterized by annular and arciform lesions with centrifugal growth and central clearing, without associated diseases and significant laboratory abnormalities (3–5).

From the viewpoint of neutrophilic dermatoses, Christensen et al. (6) described two cases of patients with chronic and recurrent outbreaks of generalized annular erythematous, oedematous cutaneous plaques, with histopathological findings suggestive of Sweet's syndrome, but without fever or general symptoms. They used the term "chronic recurrent neutrophilic dermatosis", and Cabanillas et al. (7) also reported a case of this entity. Clinicopathologically, our case can also be included in this entity, although most of the annular eruptions seen in neutrophilic dermatoses were not as large as those in our case. Our case suggests that neutrophilic dermatoses can rarely show large annular figurate erythema mimicking EAC.

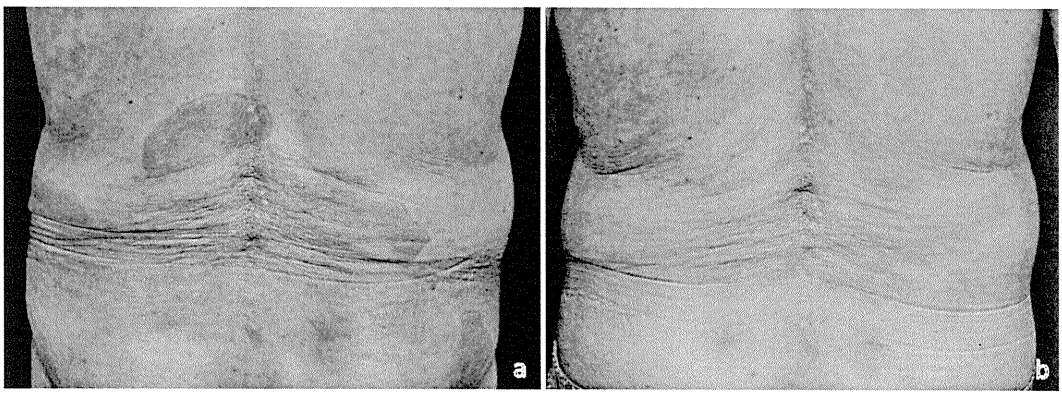


Fig. 1. (a) Annular erythematous plaques with central clearing on the back. (b) Healing after one month of potassium iodide treatment.

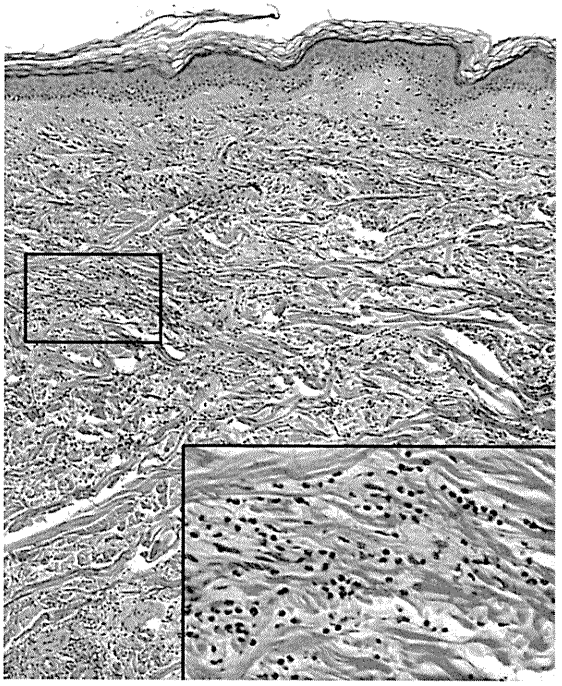


Fig. 2. Superficial and deep perivascular and interstitial dermatitis without epidermal changes (haematoxylin & eosin (H&E) ×40). Inset: the perivascular and interstitial infiltrate consists mostly of neutrophils (H&E ×200).

Treatment of neutrophilic figurate erythema includes oral prednisolone (1, 6, 7), colchicine (2), antihistamines (2, 4) and topical therapy (mild corticosteroid cream, miconazole nitrate ointment, etc.) (4, 5), although one paediatric patient presented a complete resolution with no drug treatment (3). Potassium iodide, which inhibits neutrophil chemotaxis, often has clinical benefit for neutrophilic dermatoses, and our case also showed a prompt and favourable response. We report here the first case of potassium iodide treatment for neutrophilic figurate erythema showing annulare centrifugum-like lesions.

REFERENCES

1. Trébol I, González-Pérez R, García-Rio I, Arregui MA, Saracibar N, Carnero L, et al. Paraneoplastic neutrophilic figurate erythema. Br J Dermatol 2007; 156: 396–398.
2. Ozdemir M, Engin B, Toy H, Demirkesen C. Neutrophilic figurate erythema. Int J Dermatol 2008; 47: 262–264.
3. Annessi G, Signoretti S, Angelo C I. Neutrophilic figurate erythema of infancy. Am J Dermatopathol 1997; 19: 403–406.
4. Cox NH, McQueen A, Evans TJ, Morley WN. An annular erythema of infancy. Arch Dermatol 1987; 123: 510–513.
5. Patrizi A, Savoia F, Varotti E, Gaspari V, Passarini B, Neri I. Neutrophilic figurate erythema of infancy. Pediatr Dermatol 2008; 25: 255–260.
6. Christensen OB, Holst R, Svensson A. Chronic recurrent neutrophilic dermatosis. Acta Derm Venereol 1989; 69: 415–418.
7. Cabanillas M, Suárez-Amor O, Sánchez-Aguilar D, Pereiro MM, Toribio J. Chronic recurrent neutrophilic dermatosis: a possible variant in the spectrum of neutrophilic dermatoses. Actas Dermosifiliogr 2008; 99: 61–63.

IJD 51391 B
Journal Name Manuscript No.
Dispatch: 5.7.11 Journal: IJD CE: GeethaPriya P.
Author Received: No. of pages: 2 PE: Prasanna
International Journal of Dermatology

Correspondence

Intractable erythematous plaques on the hands: palmoplantar eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF) is an inflammatory disease characterized by plaques studded with numerous papules and sterile pustules.[1] The lesions are usually located on the face, trunk, and arms, and much less commonly on the palms and soles.[2,3] Palmoplantar EPF lesions have been reported as grouped papules and pustules on the palms and soles, resembling palmoplantar pustulosis.[4–6] Herein, we report a case of EPF that was unique in that the affected region was limited to the hands.

The present case is a 44-year-old Japanese woman with a 2-year history of itchy eruptions on her hands. Initial presentation was at a local dermatology clinic, where she was diagnosed as having hand eczema and treated with topical steroid. However, the treatment did not improve her skin lesions. The patient was referred to our department for further consultation. Upon initial examination, pruritic erythematous plaques with papules that spread centrifugally were observed on both hands, including on dorsal hands, palms and fingers (Fig. 1). Potassium hydroxide examination of the scales was negative. There were no eruptions on the face, trunk, arms, legs, or soles. General laboratory examinations revealed no apparent abnormalities except for an elevated eosinophil count (570/μl, eosinophil fraction of total white blood cells = 11.4%). Human immunodeficiency virus antibody was negative in the serum. At first, we suspected skin lesions of being dyshidrotic eczema of the hands. Treatment with antihistamine medication (bepotastine besilate) and topical steroid ointment (clobetasol propionate) slightly improved the lesions, although they relapsed soon after withdrawal of medication. The medical history revealed that the patient had received metal dental fixtures for the restoration of three teeth 1 year before. Metal patch tests on her back showed positive cutaneous reactions to palladium, nickel, and platinum at 48 h (+; ICDRG criteria). However, removal of the palladium-containing dental implants failed to improve her skin condition. As her skin lesions were intractable, we performed a skin biopsy to obtain pathological findings. Skin biopsy specimens from the left dorsal hand showed psoriasiform acanthosis of the epidermis and perivascular infiltration of eosinophils in the superficial dermis (Fig. 2). No spongiosis was observed. These histopathological observations were consistent with palmoplantar EPF.[5] We finally diagnosed her skin lesions as EPF of the hands, and we started administration of indomethacin (200 mg/day). Two weeks later, the erythematous plaques had subsided,

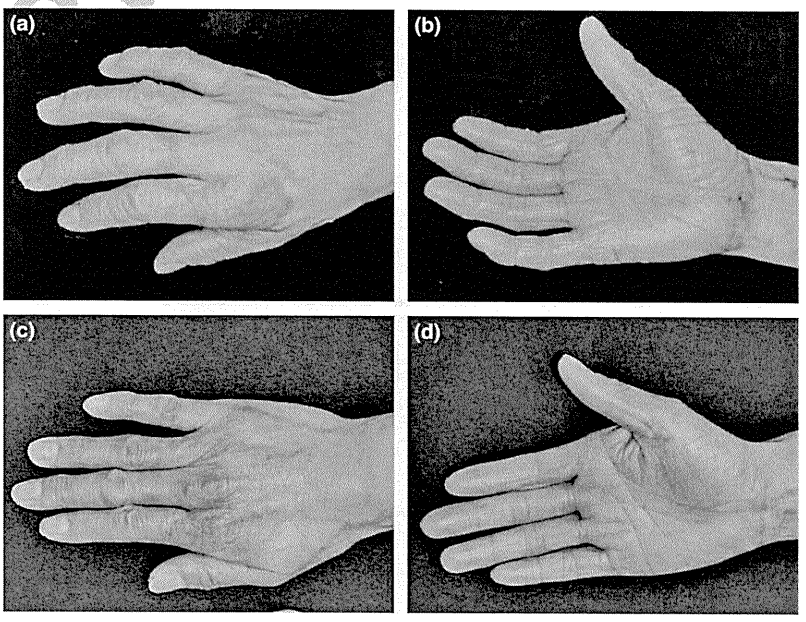


Figure 1 (a,b) Before oral indomethacin treatment. Pruritic plaques with centrifugally spreading papules are seen on the right hand. (c,d) After oral indomethacin treatment. The erythematous plaques have subsided, leaving only pigmentation

LOW RESOLUTION COLOR FIG

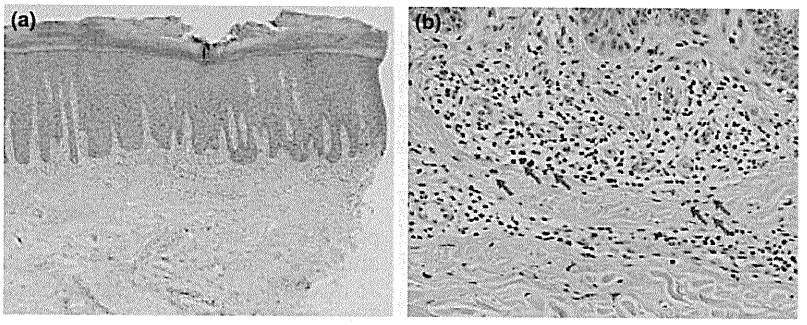


Figure 2 (a) A skin biopsy specimen was taken from the left dorsal hand. The epidermis shows psoriasiform acanthosis and parakeratosis (hematoxylin–eosin stain, original magnification ×10). (b) In the superficial dermis, perivascular inflammatory cell infiltration with eosinophils is recognized. Arrows indicate eosinophils (hematoxylin–eosin stain, original magnification ×40)

leaving residual pigmentation (Fig. 1c,d). The eosinophil count decreased from 570 to 382/μL (eosinophil fraction of total white blood cells = 7.8%) after systemic indomethacin treatment. The indomethacin dosage was decreased, and no recurrence has been observed for the following 2 years.

There have only been a few reports of palmoplantar EPF.[4–6] Aoyama and Tagami reported that palmoplantar lesions were noted in 18% of patients with EPF and that the initial skin lesions of 8% of patients with EPF were restricted to the palms or soles.[5] They described palmoplantar EPF lesions as having three characteristics: (i) palmoplantar pustulosis-like skin manifestation; (ii) poor response to topical steroids; and (iii) favorable response to indomathacin.[5] Concerning histopathology, they reported that the specimens from palmoplantar EPF lesions showed psoriasiform acanthosis and infiltration of eosinophils.[5] From the histopathological findings, we finally diagnosed the skin lesions as hand-restricted EPF, and we were able to easily manage the lesions with oral indomethacin as previously reported.[5,6] A review of the literature found no other reported cases of EPF patients with hand-restricted involvement for the entire disease course.

Our case suggests we should consider palmoplantar EPF as a candidate diagnosis when intractable erythematous plaques occur on the hands.

Kentaro Izumi, MD
Teruki Yanagi, MD, PhD
Masashi Akiyama, MD, PhD
Reine Moriuchi, MD
Ken Arita, MD, PhD
Hiroshi Shimizu, MD, PhD
Department of Dermatology
Hokkaido University Graduate School of Medicine
Sapporo
Japan

Masashi Akiyama, MD, Phd
Department of Dermatology
Nagoya University Graduate School of Medicine
Nagoya
Japan
E-mail: yanagi@med.hokudai.ac.jp

Conflicts of interest: None.

doi: 10.1111/j.1365-4632.2011.05139.x

References

1 Ofuji S, Ogino A, Horio T, *et al.* Eosinophilic pustular folliculitis. *Acta Derm Venereol* 1970; 50: 195–203.
2 Takematsu H, Nakamura K, Igarashi M, *et al.* Eosinophilic pustular folliculitis: report of two cases with a review of the Japanese literature. *Arch Dermatol* 1985; 121: 917–920.
3 Ofuji S. Eosinophilic pustular folliculitis. *Dermatologica* 1987; 174: 53–56.
4 Saruta T, Nakamizo Y. Eosinophilic pustular folliculitis particularly with reference to lesions on the palm of the hand and sole of the foot. *J Dermatol* 1980; 7: 239–246.
5 Aoyama H, Tagami H. Eosinophilic pustular folliculitis starting initially only with palmoplantar pustular lesions. *Dermatology* 1992; 185: 276–280.
6 Tsuboi H, Niiyama S, Katsuoka K. Eosinophilic pustular folliculitis (Ofuji disease) manifested as pustules on the palms and soles. *Cutis* 2004; 74: 107–110.

CORRESPONDENCE

Intraepidermal neutrophilic IgA pemphigus successfully treated with dapsone

A 25-year-old woman presented with a 2-month history of erythematous, intensely itchy macules and vesicles on the extremities and trunk. Before onset, she was in good health and took no medication. Physical examination revealed pinkish or reddish, edematous, well-demarcated erythema *(figure 1A)*. The lesions tended to coalesce, forming annular patterns, some of which had vesicles around the margins, forming a sunflower-like configuration. The oral cavity and genital area were unaffected. Histopathological findings of a pustule revealed intraepidermal blisters with neutrophil infiltrates without prominent acantholysis *(figure 1B)*. Laboratory examinations, including serum immunoglobulins, and ELISA for anti-desmoglein 1 and 3 were within normal ranges. Chest X-ray, electrocardiogram, and blood tests revealed no other related diseases and monoclonal gammopathy. DIF of the erythematous lesion revealed IgA deposition in the intercellular space throughout the epidermis *(figure 1C)*. IIF revealed circulating IgA autoantibodies binding to the cell surfaces of the entire epidermis of normal human skin (titer: 64×). Immunoblot analysis using epidermal extracts from normal human skin and recombinant desmocollin 3 showed no specific bands for either IgA or IgG antibodies. These findings led to the diagnosis of IEN-type IgA pemphigus. Treatment was initiated with topical corticosteroids, achieving only a slight effect; dapsone (50 mg per day) was therefore started. The pruritus and lesions improved but the symptoms recurred after four weeks. For that reason the dose was raised to 75 mg dapsone and the itchness subsided within a few days. Two weeks later, only pigmented macules with no active lesions were observed. The titer of IIF also decreased from 64× to 16×.

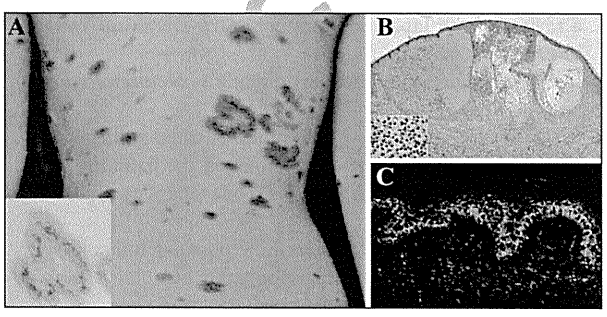


Figure 1. A) Pinkish and reddish edematous erythema with vesicles around the margins are scattered on the trunk. **B)** Histopathological findings of a pustule reveal intraepidermal blisters with neutrophil infiltrates. **C)** Direct immunofluorescence of the perilesional skin biopsy specimen reveals IgA deposits on the keratinocyte cell surfaces.

IgA pemphigus is a distinct group of auto-immune intraepidermal blistering diseases that present with vesiculopustular eruption, neutrophil infiltration with or without acantholysis. IgA autoantibodies that target keratinocyte cell surfaces and desmosomal components in the epidermis have been detected in DIF and IIF [1]. IgA pemphigus is divided into two major subtypes: the IEN type, and the SPD type. While SPD-type IgA pemphigus shows subcorneal pustules, the IEN type is characterized by pustule formation, mainly in the middle or lower epidermis.

In DIF, SPD-type IgA pemphigus involves cell surface IgA binding only in the upper epidermis, whereas IEN-type IgA pemphigus shows binding throughout the epidermis [2]. Desmocollin 1 has been identified as an autoantigen in SPD-type IgA pemphigus, suggesting that it plays an important role in the pathogenesis of this disease subtype [3]. Although autoantibodies against desmogleins [4] and desmocollins [5] have been reported in some cases of IEN-type IgA pemphigus, the specific autoantigen remains unidentified. In our case, we were also unable to detect specific autoantibodies using immunoblot analysis. Interestingly, a case with clinical and histological features compatible with SPD-type IgA pemphigus, but for which anti-desmocollins antibodies were not detected, was diagnosed as IEN-type IgA pemphigus [6]. That report suggested that the subtypes of IgA pemphigus might be considered to be divided by autoantigens.

In contrast to the common types of pemphigus, like pemphigus vulgaris, treatment for some cases of IgA pemphigus does not require corticosteroid or other immunosuppressive therapy. These cases of IgA pemphigus are well controlled using only anti-inflammatory treatments, such as dapsone, colchicine or isotretinoin [1]. Dapsone may be useful in treating IgA pemphigus due to its effect in suppressing neutrophilic infiltration. However refractory cases require plasmapheresis or cyclophosphamide. In the present case, oral administration of dapsone quickly caused the symptoms to subside. In IgA pemphigus, it is important to make the correct diagnosis and to choose a suitable therapy to avoid the side effects by the prolonged use of systemic corticosteroids. ■

Disclosure. *Financial support: none. Conflict of interest: none.*

doi:10.1684/ejd.2012.1662

To cite this article: Hirata Y, Abe R, Kikuchi K, Hamasaka A, Shinkuma S, Nomura T, Nishie W, Arita K, Shimizu H. Intraepidermal neutrophilic IgA pemphigus successfully treated with dapsone. *Eur J Dermatol* 2012 (epub ahead of print) doi:10.1684/ejd.2012.1662

Department of Dermatology,
Hokkaido University Graduate
School of Medicine
N15 W7,
Sapporo 060-8638, Japan
<aberi@med.hokudai.ac.jp>

Yu HIRATA
Riichiro ABE
Kazuhiro KIKUCHI
Asuka HAMASAKA
Satoru SHINKUMA
Toshifumi NOMURA
Wataru NISHIE
Ken ARITA
Hiroshi SHIMIZU

1. Hashimoto T. Immunopathology of IgA pemphigus. *Clinics in dermatology* 2001; 19: 683-689.

2. Hashimoto T, Ebihara T, Nishikawa T. Studies of autoantigens recognized by IgA anti-keratinocyte cell surface antibodies. *Journal of dermatological science* 1996; 12: 10-17.

3. Hashimoto T, Kiyokawa C, Mori O, *et al.* Human desmocollin 1 (Dsc1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. *The Journal of Investigative Dermatology* 1997; 109: 127-131.

4. Karpati S, Amagai M, Liu WL, *et al.* Identification of desmoglein 1 as autoantigen in a patient with intraepidermal neutrophilic IgA dermatosis type of IgA pemphigus. *Experimental Dermatology* 2000; 9: 224-228.

5. Yasuda H, Kobayashi H, Hashimoto T, et al. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *The British journal of Dermatology* 2000; 143: 144-148.

6. Iida K, Sueki H, Ohyama B, *et al.* A unique case of intraepidermal neutrophilic dermatosis-type IgA pemphigus presenting with subcorneal pustules. *Dermatology* 2011; 222: 15-19.

doi:10.1684/ejd.2012.1662

British Journal of Dermatology

Case report

Title: Mucous membrane pemphigoid with generalized blisters: IgA and IgG autoantibodies target both laminin-332 and type XVII collagen

Running head: Mucous membrane pemphigoid with IgA/G reacting with laminin-332 and type XVII collagen

I. Hayashi, S. Shinkuma*, S. Shimizu, K. Natsuga*, H. Ujiie*, C. Yasui, K. Tsuchiya, W. Nishie*, H. Shimizu*

Department of Dermatology, Sapporo City General Hospital, Sapporo, Japan

*Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence and reprint requests to:

Satoru Shinkuma, M.D., Ph.D.

Department of Dermatology,

Hokkaido University Graduate School of Medicine,

N15 W7, Sapporo 060-8638, Japan

TEL: +81-11-716-1161, ext. 5962

FAX: +81-11-706-7820

E-mail: qxfjc346@ybb.ne.jp

Conflicts of interest: None

Manuscript word count: 1526

Table count: 0

Figure count: 3

What's already known about this topic?

- IgA and IgG class autoantibodies directed against type XVII collagen (COL17) or laminin-332 in patients with mucous membrane pemphigoid (MMP) have been well documented.
- MMP with IgA autoantibodies that react with both laminin-332 and COL17 has not been reported.

What does this study add?

- This is the first MMP case in which circulating IgA and IgG class autoantibodies against both laminin-332 and COL17 were detected.

Abstract

Mucous membrane pemphigoid (MMP) is a mucous membrane-dominated, subepidermal autoimmune blistering disease in which autoantibodies usually react with the C-terminal domain of type XVII collagen (COL17) or with laminin-332. Only a few cases of MMP with widespread blisters have been reported. Serologically, IgA and IgG class autoantibodies directed against COL17 or IgG autoantibodies directed against laminin-332 in patients with MMP have been well documented. MMP cases in which IgA reacts with laminin-332, however, are extremely rare. We report a case of MMP in a 67-year-old man. Clinical examination revealed extensive mucosal lesions as well as generalized blisters and erosions that healed with scar formation. He was intractable with systemic steroid treatment. Interestingly, in addition to IgG directed against laminin-332 and the noncollagenous 16A (NC16A) and C-terminal domains of COL17, circulating IgA reacted with laminin-332 and with the NC16A domain of COL17 were also detected. This is the first MMP case with circulating IgA and IgG autoantibodies against both laminin-332 and COL17.

Keywords: cicatrical pemphigoid, autoimmune blistering disease, scar

Introduction

Mucous membrane pemphigoid (MMP) is characterized by blistering and erosive lesions that occur mostly in the oral cavity and conjunctivae, leaving scarring [1]. C-terminal portions of type XVII collagen (COL17) and laminin-332 are known as major autoantigens of MMP [2,3]. IgA and IgG autoantibodies directed against COL17 or IgG autoantibodies directed against laminin-332 in MMP patients have been well described [4,5], and clarified using *in vivo* mouse models [6-9]. In contrast, MMP cases whose IgA autoantibodies react with laminin-332 are extremely rare [5].

We report a case of MMP with extensive mucosal lesions as well as generalized blisters and erosions resulting in scar formation. Interestingly, both IgA and IgG autoantibodies directed against COL17 and laminin-332 were detected.

Case report

A 67-year-old Japanese male had a three-week history of pruritic tense blisters on the hands and feet that gradually spread to entire body. On physical examination, numerous disseminated vesicles, erosions and excoriated papules were observed on the whole body (Fig. 1a, b). In addition, erosions and ulcers were found on the lower lip and the buccal and perianal area (Fig. 1d). The conjunctivae were normal. He also had a sore throat, and endoscopic examination revealed multiple erosions and ulcers on the pharyngeal, laryngeal and esophageal mucosae (Fig. 1c). A biopsy specimen taken from the edge of blister on the back showed subepidermal blister formation with eosinophilic, lymphocytic and neutrophilic infiltrates (Fig. 1h). Enzyme-linked immunosorbent assay (ELISA, MBL, Nagoya, Japan) was positive for IgG antibodies to the NC16A domain of COL17 (index value: 1074; cutoff: 9).

He was initially treated with intravenous prednisolone (1.5 mg/kg per day), followed by oral prednisolone (1 mg/kg per day) for more than a month; however, this failed to sufficiently improve the clinical condition. Since 100 mg of oral azathioprine and 50 mg of diaphenylsulfone daily were added, cutaneous and mucosal lesions started to improve slowly leaving post-inflammatory hyperpigmentation and scar formation (Fig. 1e, f, g).

Material and methods

Immunofluorescence analysis

Direct immunofluorescence (IF) for detecting deposits of IgG, IgA, IgM, C3 and C1q was performed on perilesional skin biopsy specimens from the patient. Indirect IF was performed on normal human skin and 1M NaCl-split normal human skin as described previously [10].

Immunoblot analysis

Epidermal and dermal extracts of normal human skin, supernatants of cultured HaCaT cells and recombinant proteins (NC16A and the C-terminal (BP915) domains of COL17) were prepared as described previously [11-14]. Purified laminin-332 was supplied as a gift from Dr. S. Amano of Shiseido Life Science Research Center, Yokohama, Japan [15,16]. Immunoblotting was performed as described previously [5]. For IgG detection, nitrocellulose membranes were incubated with 1 : 20 diluted serum overnight at 4℃. Bound antibodies were visualized enzymatically using 1 : 100 diluted HRP-conjugated rabbit antihuman IgG for 3 h at room temperature. For IgA detection, membranes were incubated with 1 : 20 diluted serum overnight at 37℃, then incubated in 1 : 50 diluted HRP-conjugated rabbit antihuman IgA for 3 h at room temperature. Colour was

developed with 4-chloro-1-naphthol in the presence of H_2O_2 [5].

Results

Immunofluorescence analysis

Direct IF microscopy showed linear deposition of IgG (Fig. 2a), IgA (Fig. 2b) and C3 (data not shown) at the basement membrane zone (BMZ). Indirect IF of normal human skin demonstrated circulating IgG (titre 1 : 320) and IgA (titre 1 : 32) reacting with the BMZ (data not shown). Indirect IF using 1M NaCl-split normal human skin revealed linear deposition of IgG (Fig. 2c) (titres of 1 : 320 and 1 : 80, epidermal and dermal sides, respectively) and IgA (Fig. 2d) (titres of 1 : 32 and 1 : 16, epidermal and dermal sides, respectively).

Immunoblot analysis

Immunoblot analysis using epidermal and dermal extracts from normal human skin, the recombinant NC16A and C-terminal domains of COL17, purified laminin-332 and a cell culture supernatant of HaCaT cells, from which the 120-kDa soluble ectodomain (LAD-1) of COL17 was isolated[17], were performed. We found circulating IgG autoantibodies against the NC16A domain (Fig. 3a), the C-terminal domain (Fig. 3b) and the 120-kDa soluble ectodomain (Fig. 3c) of COL17, and the γ2 subunit of laminin-332 (Fig. 3d).

Further immunoblotting revealed that IgA autoantibodies reacted with the γ2 subunit of laminin-332 (Fig. 3d) and faint reactivity with the NC16A domain and the 120-kDa soluble ectodomain of COL17 (data not shown). IgA autoantibody against the C-terminal domain of COL17 was negative.

Neither IgG nor IgA against BP230, type VII collagen or p200 protein were detected in epidermal and dermal extracts (data not shown).

Discussion

We describe an uncommon case of MMP with multiple mucosal involvement as well as generalized blisters, which predominantly healed with scar formation. Initially, the widespread bullae and circulating IgG against the NC16A domain of COL17 led us to diagnose bullous pemphigoid (BP). Detailed immunohistochemical examination, however, showed that both IgA and IgG reacted with laminin-332 as well as with COL17. From these results, the patient's disease could be diagnosed as MMP with generalized blisters, BP with extensive mucosal involvement or subepidermal autoimmune blistering disease with overlapping features of MMP and BP. In this case, because of multiple mucosal lesions and the unusual scar formation, we finally made the diagnosis of MMP with generalized blisters.

A variety of different autoantigens are recognized by circulating autoantibodies from patients with MMP and it is possible that the unusual autoimmune profile developed as a result of epitope spreading. In this case, in addition to IgG directed against laminin-332 and the noncollagenous 16A (NC16A) and C-terminal domains of COL17, circulating IgA reacted with laminin-332 and with the NC16A domain of COL17 were also detected. Previously, antibodies against laminin-332 are found in about 10% to 20%