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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

REFERENCES

Fuchs-Telem D, Sarig O, van Steensel MA *et al.* (2012) Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet* 91:163–70

Jordan CT, Cao L, Roberson ED *et al.* (2012a) Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet* 90:796–808

Jordan CT, Cao L, Roberson ED *et al.* (2012b) PSORS2 is due to mutations in CARD14. *Am J Hum Genet* 90:784–95

Scudiero I, Zotti T, Ferravante A *et al.* (2011) Alternative splicing of CARMA2/CARD14 transcripts generates protein variants with differential effect on NF-kappaB activation and endoplasmic reticulum stress-induced cell death. *J Cell Physiol* 226: 3121–31

Sugiura K, Takemoto A, Yamaguchi M *et al.* (2013) The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor Antagonist. *J Invest Dermatol* 133: 2514–21

Tsoi LC, Spain SL, Knight J *et al.* (2012) Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet* 44:1341–8

Epidermal Growth Factor–Functionalized Polymeric Multilayer Films: Interplay between Spatial Location and Bioavailability of EGF

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TO THE EDITOR

Wound healing is a complex process involving cell–cell and cell–matrix interactions modulated by the surrounding microenvironment. One of the key events in this process is re-epithelialization: the directed migration and proliferation of epithelial cells to resurface the wound. Numerous studies have documented that the migration of cells into the wound site is regulated by autocrine and paracrine signaling of growth factors (Gurtner *et al.*, 2008). Epidermal growth factor (EGF) is an extensively investigated growth factor, which is implicated in keratinocyte adhesion and migration, as well as fibroblast function, and granulation tissue formation (Hardwicke *et al.*, 2008). Conflicting reports exist regarding the ability of EGF alone to modulate wound healing (Brown *et al.*, 1989; Cohen *et al.*, 1995). A systematic review concluded that EGF is effective as an adjuvant but not as monotherapy for diabetic foot ulcers (Buchberger *et al.*, 2011). The reason for this lack of efficacy of EGF in healing wounds may be derived from the mechanism of delivery, in that it needs to be intimately associated with the extracellular matrix to limit proteolysis (Macri and Clark, 2009).

Various approaches for delivering EGF to the wound have been attempted with the goal of maximizing therapeutic effects with minimal dose (to minimize potential adverse effects). EGF conjugated to copolymers composed of poly(ε-caprolactone) (PCL) and poly (ethyleneglycol) (PEG) improved healing in diabetic mouse wounds, compared with treatment with the copolymers alone or no treatment (Choi *et al.*, 2008). Recent advances in materials science have led to the development of engineered systems such as polymeric microparticles for controlled release of cytoactive factors (CFs; Lee *et al.*, 2011). Another method that has received limited attention is the covalent immobilization of CFs within polyelectrolyte multilayer (PEM) films. PEM films, which are formed by the layer-by-layer deposition of polyelectrolytes, provide numerous advantages for biomedical applications, such as ease of preparation, biocompatibility, tunable mechanical properties, spatio-temporal control over film organization, and most importantly, the sustained and controlled contact of embedded factors with tissue (Guthrie *et al.*, 2013). In particular, we speculate that the nanoscopic thickness of PEMs enables their intimate contact with the tissue surface upon application. When CFs are conjugated to the PEMs, it also limits, if not eliminates, the systemic release of embedded CFs and the associated potential for systemic toxicity (Agarwal *et al.*, 2010). Another key advantage of the PEM films is that they can also be easily immobilized to complex geometries such as wound bed (Jain *et al.*, 2013). However, the efficacy, bioavailability, and bioactivity of CFs such as growth factors, when conjugated to PEMs, have not been reported.

To address the question of the bioavailability of growth factors within PEMs, we fabricated PEM films with EGF that was covalently immobilized at varying depths within the PEMs. The accessibility and bioactivity of EGF immobilized within the PEM films was determined by measuring the migratory and proliferative responses of

Abbreviations: CF, cytoactive factor; EGF, epidermal growth factor; HKGS, human keratinocyte growth supplement; NHK, neonatal human keratinocyte; PAA, poly(acrylic acid); PAH, poly(allylamine hydrochloride); PEM, polyelectrolyte multilayer

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SHORT COMMUNICATION

Annular Erythema Associated with Sjögren's Syndrome Preceding Overlap Syndrome of Rheumatoid Arthritis and Polymyositis with Anti-PL-12 Autoantibodies

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Anti-PL-12 are among the anti-aminoacyl tRNA synthetase autoantibodies (1). Anti-PL-12 has been recently found in overlap syndrome of rheumatoid arthritis (RA) and polymyositis (PM)/dermatomyositis (DM), as well as in antisynthetase syndrome (2, 3). However, no skin manifestations preceding overlap syndrome with anti-PL-12 have been described.

CASE REPORT

A 44-year-old woman exhibited swelling with erythema on the bilateral upper eyelids. She was treated with prednisolone 20 mg/day at a different hospital. However, after the prednisolone was discontinued, the lesions relapsed. Four months after onset, the patient came to our clinic. A lip biopsy to investigate possible Sjögren's syndrome (SS) confirmed lymphocytic infiltration of the minor salivary glands. Circulating autoantibodies to SS-A (anti-SS-A) were positive, but anti-SS-B antibodies were negative. She had no muscle weakness at any site of the body. Serum levels of creatinine kinase were not elevated. She was diagnosed with SS according to the Japanese Ministry of Health revised criteria for the diagnosis of SS (4). The lesions resolved with oral prednisolone 30 mg/day.

When the prednisolone dose was reduced to 22.5 mg/day, several lesions of annular erythema (AE) appeared on the lower back (Fig. 1A). A biopsy of the AE lesion showed sleeve-like perivascular and periappendigeal lymphocytic infiltration, which was consistent with AE with SS (AESS) (Fig. 1B, C). The lesions resolved with oral prednisolone 30 mg/day and azathioprine 50 mg/day.

Sixteen months after the onset of SS, arthralgia on the bilateral hip, knee, and ankle joints occurred. Oral prednisolone had been tapered to 10 mg/day, and oral azathioprine 50 mg/day had been maintained. Physical examinations found swelling of the bilateral knee and ankle joints. Circulating anti-CCP antibodies were 453 U/ml (normal value <15 U/ml). Serum levels of c-reactive protein and matrix metalloproteinase-3

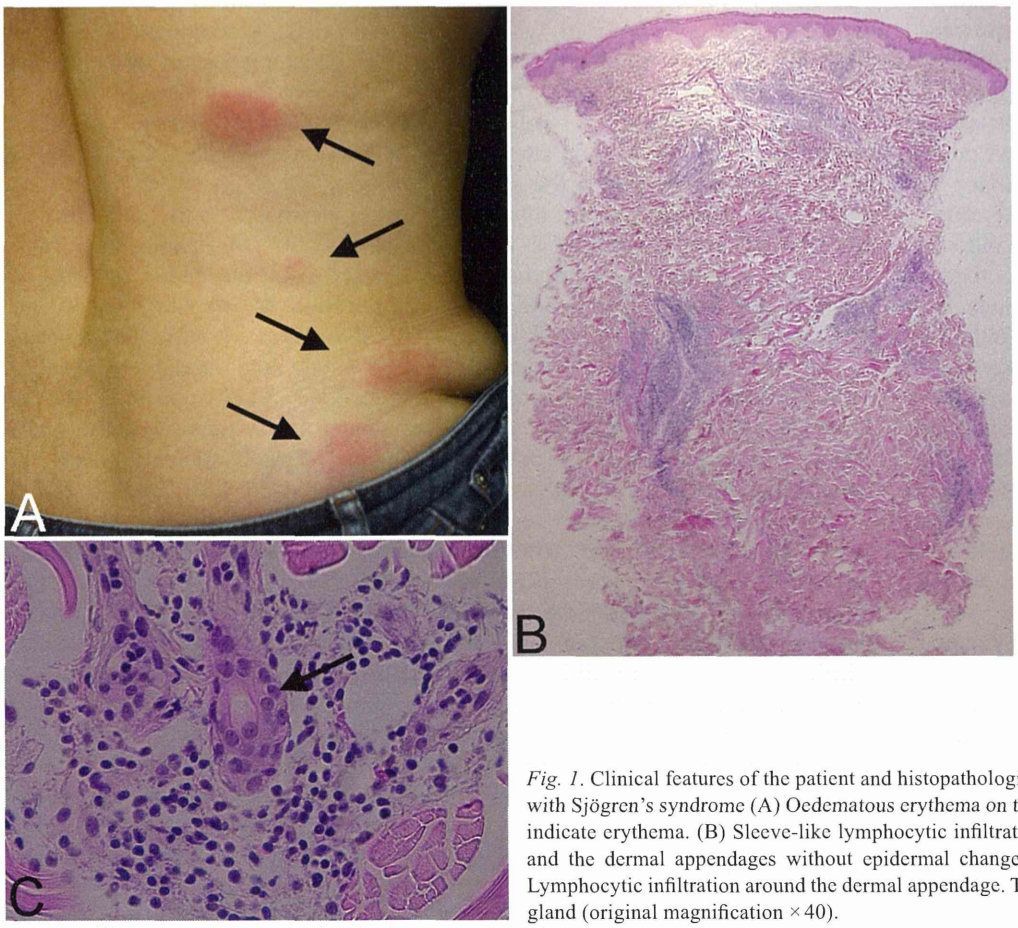

Fig. 1. Clinical features of the patient and histopathological features of the annular erythema with Sjögren's syndrome (A) Oedematous erythema on the lower back of the patient. Arrows indicate erythema. (B) Sleeve-like lymphocytic infiltrates are prominent around the vessels and the dermal appendages without epidermal changes (Original magnification ×2). (C) Lymphocytic infiltration around the dermal appendage. The arrow indicates the eccrine sweat gland (original magnification ×40).

were elevated. The arthritis continued for >6 weeks. From these clinical features, she was diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA (5). DAS28-ESR was 4.83 (moderate activity). In addition to oral prednisolone 7.5 mg/day and azathioprine 50 mg/day, salazosulfapyridine (SASP) 500 mg/day was started and, 7 months later, methotrexate 6 mg/week was substituted for the SASP. Thereafter, the RA disease activity was controlled. azathioprine was administered for a total of 28 months.

Thirty-one months after the onset of SS, she had symptoms of refractory cough and muscle weakness in the proximal limbs. She was admitted to our hospital. The serum level of myoglobin was 546 ng/ml (normal value <60 ng/ml), creatinine kinase was 683 IU/l (<163 IU/l), aldolase was 18.5 IU/l (<5.9 IU/l), and KL-6 was 917 U/ml (<500 U/ml). Interstitial lung disease (ILD) was identified by computer tomography. Myositis in the proximal limbs was suggested by magnetic resonance imaging. Circulating anti-PL-12 was positive by ELISA, using a system developed by us. The titre of anti-PL-12 of the patient was 830 units (normal value <4 units). She was diagnosed as having PM with ILD and was treated with systemic prednisolone 50 mg/day and tacrolimus 4 mg/day. The Bohan & Peter 1975 PM/DM Criteria was used for diagnosis of PM (6, 7). PM and ILD were improved. The patient had difficulty in raising her arms and going up stairs when the creatinine kinase was 683 IU/l. After the creatinine kinase fell within the normal range, she was gradually able to extend her arms and go up the stairs. The patient has been treated with prednisolone 10 mg/day and tacrolimus 3 mg/day. We have carefully tapered prednisolone and tacrolimus, because patients with anti-PL-12 sometimes experience worsening ILD and develop pulmonary hypertension (8). prednisolone was administered for a total of 51 months.

DISCUSSION

Three clinical types of AESS have been characterised: isolated doughnut-ring-like erythema mimicking Sweet's disease with an elevated border (type I), SCLE-like marginally scaled polycyclic erythema (type II), and papular insect bite-like erythema (type III) (9). The patient had type III. According to a review of 120 cases with AESS by Katayama et al. (9), AESS can be controlled in most patients with prednisolone 5–15 mg/day, but among the patients receiving >20 mg/day of prednisolone there is a minor subset of recurrent AESS patients. The present case is categorised as the latter subset of AESS, because AESS occurred while prednisolone 22.5 mg/day was administered.

Bernacchi et al. (10) recently reported a patient with primary SS positive for anti-SS-A and anti-SS-B, who developed chronic relapsing PM and subacute cutaneous lupus erythematosus (SCLE). The present case and the previously reported case suggest a common spectrum of annular lesions of AESS and SCLE that can occur in patient with PM. When we reviewed the clinical course of the present patient, the differential diagnosis of skin manifestations of DM at the first visit could have been considered for the swelling with erythema on the bilateral upper eyelids.

In conclusion, this is the first report of annular autoimmune lesions of SS with PM and also with anti-PL-12. When we see a patient whose AESS requires >20 mg/day of prednisolone to manage, the differential diagnosis of overlap syndrome of RA and PM with anti-PL-12 should be considered.

ACKNOWLEDGEMENT

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The authors declare no conflict of interest.

REFERENCES

1. Bunn CC, Bernstein RM, Mathews MB. Autoantibodies against alanyl-tRNA synthetase and tRNAAla coexist and are associated with myositis. J Exp Med 1986; 163: 1281–1291.
2. Nakajima A, Yoshino K, Soejima M, Kawaguchi Y, Satoh T, Kuwana M, et al. High frequencies and co-existing of myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies overlapped to rheumatoid arthritis. Rheumatol Int 2012; 32: 2057–2061.
3. Ishikawa Y, Yukawa N, Kawabata D, Ohmura K, Fujii T, Usui T, et al. A case of antisynthetase syndrome in a rheumatoid arthritis patient with anti-PL-12 antibody following treatment with etanercept. Clin Rheumatol 2011; 30: 429–432.
4. Tsuboi H, Hagiwara S, Asashima H, Umehara H, Kawakami A, Nakamura H, et al. Validation of different sets of criteria for the diagnosis of Sjogren's syndrome in Japanese patients. Mod Rheumatol 2013; 23: 219–225.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569–2581.
6. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975; 292: 344–347.
7. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975; 292: 403–407.
8. Hervier B, Wallaert B, Hachulla E, Adoue D, Lauque D, Audrain M, et al. Clinical manifestations of anti-synthetase syndrome positive for anti-alanyl-tRNA synthetase (anti-PL12) antibodies: a retrospective study of 17 cases. Rheumatology 2010; 49: 972–976.
9. Katayama I, Kotobuki Y, Kiyohara E, Murota H. Annular erythema associated with Sjogren's syndrome: review of the literature on the management and clinical analysis of skin lesions. Mod Rheumatol 2010; 20: 123–129.
10. Bernacchi E, Neri R, Caproni M, Loggini B, Fabbri P, Bombardieri S. Annular subacute cutaneous lupus erythematosus lesions and polymyositis onset in a patient with primary Sjogren's syndrome: how should this unusual association be classified? Lupus 2013; 22: 312–315.

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SHORT COMMUNICATION

Symmetrical Giant Facial Plaque-type Juvenile Xanthogranuloma Persisting Beyond 10 years of Age

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Juvenile xanthogranuloma (JXG) is a non-Langerhans histiocytosis occurring predominantly in infancy and early childhood. Resolution usually occurs over a period of months to several years, and it is rare for the condition to persist beyond late childhood (1). The symmetrical giant facial plaque variant of JXG (SGFP-JXG) is very rare. It was originally reported by Gunson & Birchall. (2). Herein we report a case of SGFP-JXG that persisted beyond 10 years of age.

CASE REPORT

A 10-year-old Japanese boy was referred to our clinic with facial yellowish papules. He was a fraternal twin, the result of a normal pregnancy and delivery, and was otherwise completely healthy and taking no regular medications. The twin brother showed no skin lesions. There was no particular family history, such as neurofibromatosis. The plaques were first noticed as red macules at approximately 6 months of age, which slowly evolved during the first year of life. He had also had yellowish nodules on the bilateral arms. He had come to a nearby dermatology clinic at 2 years of age (Fig. 1A). At that time, a biopsy from a skin lesion on the left arm showed mixed inflammatory cell infiltration containing small lymphocytes and histiocytes from the superficial dermis, extending into the deep dermis. Touton giant cells and numerous foam cells were present (Fig. 2). The nodules on the arms had been diagnosed as JXG. Although the JXG on the arms gradually decreased in size and mostly resolved, the facial lesions did not improve. Physical examination at the age of 10 revealed symmetrical yellowish indurated

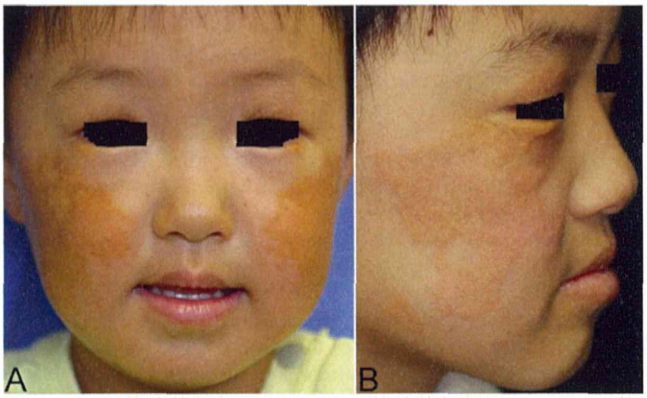

Fig. 1. Multiple yellowish plaques are distributed symmetrically on the upper and lower eyelids and on the cheeks. (A) At 2 years of age. (B) At 10 years of age.

plaques with smooth surface on the bilateral upper and lower eyelids and on the cheeks (Fig. 1B). Similar yellowish nodules were also seen on the left elbow. There was neither ophthalmic or oral mucosal involvement, or palpable hepatosplenomegaly nor lymphadenopathy. Pathological findings following a skin biopsy at the age of 10 from the lesion on the right cheek were consistent with JXG (Fig. 3A). In addition, CD68 was positive (Fig. 3B), but S-100, CD1a, and langerin were negative (data not shown) by immunohistochemistry, which is also consistent with JXG. Hence, the patient was diagnosed with SGFP-JXG.

DISCUSSION

JXG usually manifests as an asymptomatic, reddish-brown nodule which slowly grows to a diameter of 1–2

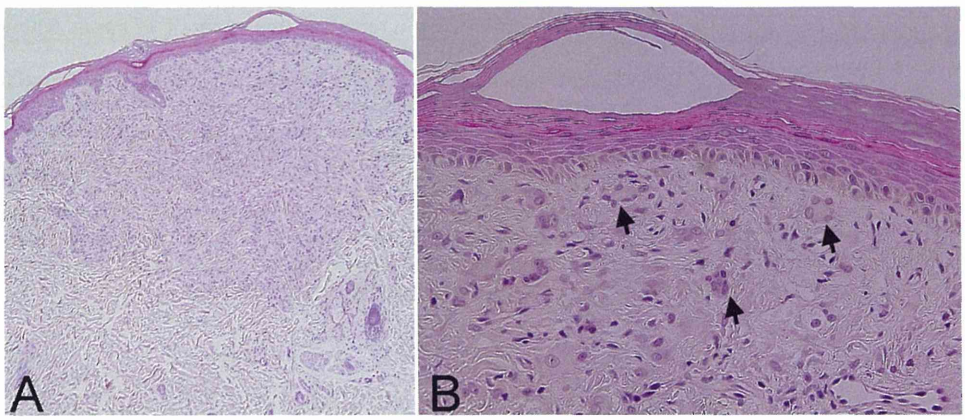

Fig. 2. Haematoxylin-eosin staining of the yellowish nodule on the left arm at 2 years of age. Numerous foam cells are seen throughout the dermis (original magnification ×4) (A). Giant cells and numerous foam cells are seen. Arrows indicate Touton giant cells (original magnification ×20) (B).

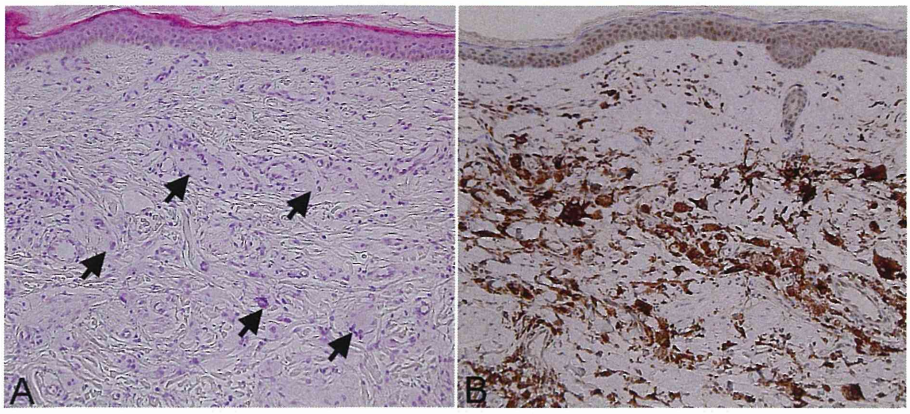

Fig. 3. Haematoxylin-eosin staining of the yellowish plaque on the right cheek at 10 years of age. Many foam cells are seen in the dermis (A). Immunohistochemistry of CD68 on the lesion of the right cheek. The histiocytes are CD68 positive (B) (original magnification × 10). Arrows: Indicates gaint cells and foam cells.

cm. Evolution into a yellowish-brown papule, plaque or nodule often occurs, followed by spontaneous resolution that may leave an atrophic scar.

Plaque and clustered types of JXG at extrafacial sites have been reported (3, 4). However, despite the atypically large lesions, these types of JXG usually reduce with scarring and pigmentation within a year.

SGFP-JXG was first reported by Gunson & Birchall. (2) in 2008. To the best of our knowledge, our report is the second reported case of SGFP-JXG. Gunson & Birchall described SGFP-JXG lesions as multiple large, flat, symmetrically distributed plaques of over 2 cm in diameter (2). The case in the literature had facial lesions, without any JXG lesions on other body sites. The lesions had been present for >6 years and had shown no sign of spontaneous resolution. The present case has also had the facial lesions for 10 years without any noticeable tendency of spontaneous resolution. Interestingly, he had also had JXG on the arms, and it tended to spontaneously resolve. Disseminated JXG, which has multiple cutaneous lesions, is sometimes associated with visceral JXG in infancy (5, 6). Both the present SGFP-JXG case and the patient in the literature showed no involvement of internal organs. Unfortunately, the therapeutic options are limited given the large and cosmetically sensitive area involved.

In conclusion, we report herein the second case of SGFP-JXG, and both cases suggest that this type of JXG may persist beyond the age of 10 years but that it is not associated with visceral lesions.

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The authors declare no conflicts of interst.

REFERENCES

1. Chang MW. Update on juvenile xanthogranuloma: unusual cutaneous and systemic variants. Semin Cutan Med Surg 1999; 18: 195–205.
2. Gunson TH, Birchall NM. Symmetrical giant facial plaque-type juvenile xanthogranuloma. J Am Acad Dermatol 2008; 59(2 Suppl 1): S56–57.
3. Yazganoglu KD, Erdem Y, Buyukbabani N, Baykal C. A giant congenital plaque. Pediatr Dermatol 2012; 29: 217–218.
4. Kaur MR, Brundler MA, Stevenson O, Moss C. Disseminated clustered juvenile xanthogranuloma: an unusual morphological variant of a common condition. Clin Exp Dermatol 2008; 33: 575–577.
5. Haughton AM, Horii KA, Shao L, Daniel J, Nopper AJ. Disseminated juvenile xanthogranulomatosis in a newborn resulting in liver transplantation. J Am Acad Dermatol 2008; 58(2 Suppl): S12–15.
6. Patel P, Vyas R, Blickman J, Katzman P. Multi-modality imaging findings of disseminated juvenile xanthogranuloma with renal involvement in an infant. Pediatr Radiol 2010; 40 Suppl 1: S6–10.

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Invited Review Article

The genetic background of generalized pustular psoriasis: *IL36RN* mutations and *CARD14* gain-of-function variants

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Pityriasis rubra pilaris

ABSTRACT

Generalized pustular psoriasis (GPP) is often present in patients with existing or prior psoriasis vulgaris (PV; "GPP with PV"). However, cases of GPP have been known to arise without a history of PV ("GPP alone"). There has long been debate over whether GPP alone and GPP with PV are distinct subtypes that are etiologically different from each other. We recently reported that the majority of GPP alone cases is caused by recessive mutations of *IL36RN*. In contrast, only a few exceptional cases of GPP with PV were found to have recessive *IL36RN* mutations. Very recently, we also reported that *CARD14* p.Asp176His, a gain-of-function variant, is a predisposing factor for GPP with PV; in contrast, the variant is not associated with GPP alone in the Japanese population. These results suggest that GPP alone is genetically different from GPP with PV. *IL36RN* mutations are also found in some patients with severe acute generalized exanthematous pustulosis, palmar-plantar pustulosis, and acrodermatitis continua of hallopeau. *CARD14* mutations and variants are causal or disease susceptibility factors of PV, GPP, or pityriasis rubra pilaris, depending on the mutation or variant position of *CARD14*. It is clinically important to analyze *IL36RN* mutations in patients with sterile pustulosis. For example, identifying recessive *IL36RN* mutations leads to early diagnosis of GPP, even at the first episode of pustulosis. In addition, individuals with *IL36RN* mutations are very susceptible to GPP or GPP-related generalized pustulosis induced by drugs (e.g., amoxicillin), infections, pregnancy, or menstruation.

Contents

Abbreviations: ACH, acrodermatitis continua of hallopeau; AGEP, acute generalized exanthematous pustulosis; CARD14, caspase recruitment domain family, member 14; DITRA, deficiency of IL-36 receptor antagonist; FGPP, familial generalized pustular psoriasis; GPP, generalized pustular psoriasis; GPP with PV, generalized pustular psoriasis often presents in patients with existing or prior psoriasis vulgaris; GPP alone, generalized pustular psoriasis have been known to arise without a history of psoriasis vulgaris; GMA, I granulocyte monocyte plasma apheresis; IL-36RN, L-36 receptor antagonist; IL-36A, interleukin-36α; IL-36B, interleukin-36β; IL-36G, interleukin-36γ; KC, keratinocyte; PPP, palmoplantar pustulosis; PRP, pityriasis rubra pilaris; PV, psoriasis vulgaris.

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0923-1811/

1. Introduction

von Zumbusch described the first documented case of generalized pustular psoriasis (GPP) in 1910 [1]. GPP is an uncommon variant of psoriasis, with an acute, subacute, or occasionally chronic eruption, with sterile pustulosis as its central feature. Fever and other systemic symptoms are common, and the disease can be life-threatening. It can appear with or without a previous psoriasis vulgaris (PV) condition or history and can reoccur in periodic episodes. GPP can present at any age. Provocative factors include infection, pregnancy, hypocalcaemia associated with hypothyroidism, and drugs [2].

About a century after von Zumbusch's description of the first case of GPP, the cause of the disease remained completely unknown. The pathogenesis of GPP was not considered to be monogenic skin diseases until 2011. However, after Marrakchi et al. first reported the causative gene of familial GPP in 2011, there has been increasing knowledge of the genetic background of GPP [3]. Currently, two genes, *IL36RN* and *CARD14*, which encode proteins secreted by keratinocyte (KC) or KC-localized proteins, are thought to be the causative or susceptibility genes in GPP (Table 1).

This review discusses recent findings on causal or predisposing factors of GPP, acute generalized exanthematous pustulosis (AGEP), palmoplantar pustulosis (PPP), and acrodermatitis continua of hallopeau (ACH). In addition, it discusses the clinical relevance of identifying *IL36RN* mutations in GPP and GPP-related pustular skin diseases.

2. Clinical and histological features of GPP

2.1. Epidemiology of GPP

GPP occurs repeatedly at any age in both sexes. In 2004 and 2005, 83–84 GPP patients were registered per year with the Japan Intractable Diseases Information Center (http://www.nanbyou.or.jp/entry/168). Thus, GPP occurs with a frequency of about 0.6–0.7 cases per million people each year in Japan, which is similar to the frequency estimated by a recent survey in France [4]. The male to female ratio was 1:1.2 in both Japan and France [4,5].

2.2. Clinical features of GPP

GPP presents as pustules and plaques over a wide area of the body; it differs from the localized form of pustular psoriasis, in that the patients are often febrile and systemically ill [6]. However, the most prominent symptom is sheeted, pinhead-sized, sterile, subcorneal pustules [7]. The International Psoriasis Council adds that these pustules often occur either at the edges of expanding, intensely inflamed plaques or within erythrodermic skin (Fig. 1A) [8].

2.3. Histopathlogical features of GPP

A spongiform pustule of Kogoj is an epidermal pustule formed by infiltration of neutrophils into necrotic epidermis, in which the cell walls persist as a sponge-like network; these pustules are common to lesions in both the skin and mucosa (Fig. 1B).

3. Familial generalized pustular psoriasis

Landry et al. provided the first description of familial generalized pustular psoriasis (FGPP), specifically accounting for 2 sibling GPP cases among 12 siblings [9]. Hubler reported 3 sibling GPP cases among 9 siblings [10]. Juvenile GPP in a pair of monozygotic twins was reported in Japan [11]. However, FGPP was not considered to have a monogenic genetic background until 2011. In 2011, Marrakchi et al. reported that homozygous mutations of *IL36RN* underlie FGPP in Tunisian patients [3]. This report is very striking because it was the first to indicate that Tunisian FGPP is an autosomal recessive inherited background skin disease, as well as to identify the causative gene of the disease. *IL36RN* encodes the IL-36 receptor antagonist (IL-36RN; Table 1). Autosomal recessive FGPP has also been referred to as the deficiency of IL-36 receptor antagonist (DITRA) [3].

4. IL36RN

4.1. Interleukin-36 receptor antagonist

IL-36RN is primarily expressed in the skin [12] (Table 1) and is an antagonist to 3 cytokines that belong to the interleukin-1 family: interleukin-36α (IL-36A), interleukin-36β (IL-36B), and interleukin-36γ (IL-36G), which are also known as interleukin-1F6, interleukin-1F8, and interleukin-1F9, respectively [13–16]. IL-36A, B, and C are absent in normal skin but are induced by inflammatory cytokines such as TNF-α, IL-17A, and IL-22 [17]. IL-36s activate several pro-inflammatory signaling pathways such as the nuclear factor-κ-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase pathways [18,19] (Fig. 2). *Il1f6* is the mouse ortholog of *IL36A*. Abnormal IL-36 receptor signaling results in transient skin inflammation characterized by acanthosis, hyperkeratosis, and neutrophil-dominant mixed-cell infiltration in *Il1f6* transgenic mice [20], which resembles human GPP, as well as PV. *Il1f5* is the mouse ortholog of *IL36RN*. When *Il1f6* transgenic mice are crossed with *Il1f5* knockout mice, the skin phenotype is more similar to human GPP than that of the *Il1f6* transgenic mice [20]. These findings strongly suggest that IL-36RN deficiency is associated with the pathogenesis of GPP.

Table 1
GPP and GPP-related diseases associated with *IL36RN* mutations or *CARD14* mutations/variants.

Gene	Protein	Localization	Disease
IL36RN	Interleukin-36 receptor antagonist	Secreted by KC	GPP, AGEP, ACH, PPP
CARD14	Caspase recruitment domain family, member 14	Localized in KC	PV, GPP, PRP

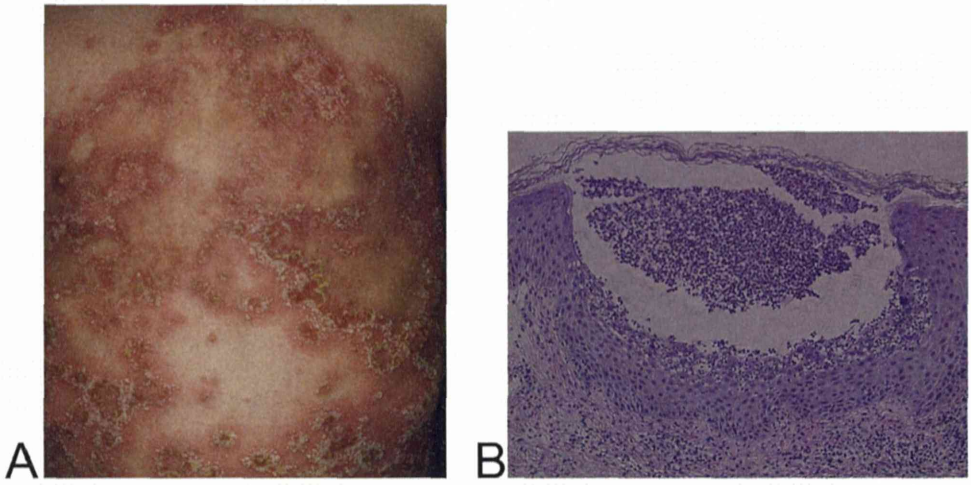

Fig. 1. Clinical features and pathological findings of pustules of generalized pustular psoriasis.
(A) The clinical features of GPP. Pustules on background erythema are visible on the trunk. (B) The pathology of the pustules of GPP. Spongiosis of Kogoj and acanthosis are observed in the epidermis of the pustular erythematous. Scale bar: 100 μm.

4.2. IL36RN *mutations and generalized pustular psoriasis*

Concurrent with the report by Marrakchi et al. that *IL36RN* is the causative gene of autosomal recessive FGPP, Onoufriadis et al. reported that *IL36RN* mutations can cause sporadic GPP, by using a challenging exome-sequencing strategy on only 5 GPP patients [21]. They prioritized analysis of the exome variant profiles with a model of rare autosomal recessive inheritance because 1 of the 5 patients used for the exome-sequencing strategy was a child of consanguineous parents. Onoufriadis's report was very important because it showed that *IL36* mutations underlie sporadic European GPP, as well as Tunisian autosomal recessive FGPP. Indeed, we reported the first Asian case of GPP associated with *IL36RN* mutations in 2012, and we subsequently realized that *IL36RN* mutations would be the common cause of some GPP cases worldwide [22]. Thus, DITRA is also included in some sporadic GPP cases, as well as in Tunisian cases of FGPP (Table 1).

The next interest of the field's researchers was directed toward the frequency of *IL36RN* mutations in all GPP patients. We searched

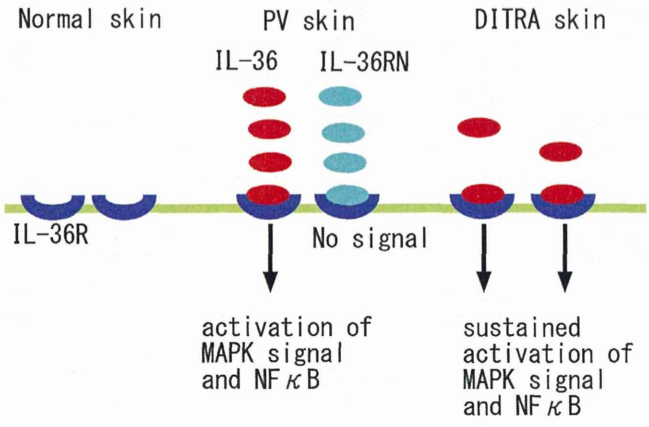

Fig. 2. Signaling pathway activated by interleukin-36s in psoriasis vulgaris and generalized pustular psoriasis.
IL-36A, IL-36B, and IL-36G exert their actions by binding to the IL-36 receptor (IL-36R). Ligand binding to this receptor leads to signal transduction involving the activation of NF-κB and mitogen-activated protein (MAP) kinases. IL-36RN also binds to the IL-36R, which blocks binding by agonist ligands but fails to activate downstream inflammatory signaling (NF-κB and MAP kinases), avoiding exacerbated inflammatory responses. In PV, IL-36RN antagonizes IL-36 to some extent. In DITRA, functional IL-36RN is absent. Therefore, the sustained inflammatory signaling activated by IL-36 results in GPP.

for *IL36RN* mutations in 2 groups of GPP patients in the Japanese population: GPP not associated with psoriasis vulgaris (PV) and GPP preceded or associated with PV. Eleven cases of GPP not associated with PV ("GPP alone") and 20 cases of GPP preceded or accompanied by PV ("GPP with PV") were analyzed. Nine out of 11 cases of GPP alone (82%) had homozygous or compound heterozygous mutations in *IL36RN*. In contrast, only 2 of 20 cases of GPP with PV (10%) had compound heterozygous mutations in *IL36RN*. Thus, we concluded that the majority of cases of GPP alone are caused by homozygous or compound heterozygous mutations of *IL36RN* [23]. In contrast, only a few exceptional cases of GPP with PV were found to have *IL36RN* mutations. A similar trend was observed in a study by Korber et al. who reported recessive *IL36RN* mutations in 6 of 13 patients with GPP alone (46%) but in only 1 of 6 patients with GPP with PV (17%) [24]. Li et al. reported that 18 of 30 cases of pediatric-onset GPP (combined cases of GPP alone and GPP with PV) had the homozygous pathogenic *IL36RN* c.115 + 6T > C (p.Arg10ArgfsX1) mutation, and 9 of 38 cases of adult-onset GPP had the same homozygous mutation [25].

Taken together, the 3 reports discussed above indicate that the majority of cases of GPP alone are caused by homozygous or compound heterozygous mutations of *IL36RN*. We consider GPP alone to be more frequent in pediatric-onset GPP than in adult-onset GPP, based on an epidemiological study by Ohkawara et al. [5].

More than 10 GPP patients carrying a single *IL36RN* mutation have been reported by 4 groups, including our group [23–26]. The pathomechanism of how individuals with the heterozygous *IL36RN* mutation are affected by GPP is uncertain. However, Capon suggested that mutations at a second gene locus may account for disease onset because of the low recurrence rate of GPP within sibships that might have the heterozygous *IL36RN* mutation [27].

4.3. IL36RN *mutations and GPP-related diseases*

AGEP follows infection and/or drug ingestion. It presents with acute generalized, nonfollicular, pinpoint pustules on a background of erythema, and it is easily confused with other entities, especially GPP. Pathologically, there is marked dermal vasculitis with nonfollicular subcorneal pustules [28]. The levels of Th17 cells and the cytokine they produce, IL-22, were elevated in the peripheral blood of patients with AGEP [29]. As IL-17 and IL-22 cooperatively stimulate KCs to produce IL-8, IL-8 may contribute to the accumulation of neutrophils in the lesional epidermis of AGEP.

A recent report suggested that homozygous or heterozygous *IL36RN* mutations may be found in severe cases (Table 1) [30]. In light of the finding that IL-36 is induced by pre-inflammatory cytokines, including IL-17 and IL-22, it is not surprising that IL-36RN insufficiency results in a severe form of AGEP with a sustained activated inflammatory signal downstream of IL-36 [17]. We recently reported the detection of compound heterozygous *IL36RN* mutations in monozygous twins who were diagnosed with amoxicillin-triggered GPP alone [31]. Thus, severe AGEP is similar to GPP alone in that the diseases are caused by the same *IL36RN* mutations. Amoxicillin, clindamycin/rifampicin, and piroxicam have been reported as the triggering drugs for AGEP with *IL36RN* mutations [30,31]. In addition, GPP linked to *IL36RN* mutations, which is triggered by infections, pregnancy, or menstruation, has also been reported [3,24].

PPP and ACH are 2 acral forms of pustular psoriasis that have been historically grouped with GPP. Setta-Kaffetzi et al. showed that some cases of ACH and PPP, as well as GPP, had homozygous, compound heterozygous, and single heterozygous *IL36RN* mutations [26]. In other words, *IL36RN* mutations are sometimes related to localized pustular psoriasis.

4.4. IL36RN *mutations reported*

Fig. 3 summarizes the *IL36RN* mutant alleles reported thus far to be associated with GPP and related pustular diseases (Fig. 3). The c.28C > T (p.Arg10X) and c.115 + 6T > C (p.Arg10ArgfsX1) transitions are known to be founder mutations in cases reported in Japan [23]. The c.115 + 6T > C transition is also recurrently found in Chinese and Malaysian patients [25,26]. The c.80C > T (p.Leu27Pro) transition is a recurrent mutation in Africa [3], and the c.338C > T (p.Ser113Leu) transition is a recurrent mutation in Europe [21,26,30]. In contrast, the c.368C > T and c.368C > G transitions have been reported in 1 case in Japan [32,33]. c.104A > G (p.Lys35Arg), c.142C > T (p.Arg48Trp), and c.304C > T (p.Arg102Trp) have been reported in 1 or 2 cases in Europe [21,26,30].

4.5. *Therapy for DITRA*

The majority of cases of GPP alone are associated with DITRA. Many DITRA patients can be treated by therapy for GPP alone, including steroid ointment, active vitamin D3 ointment, systematic cyclosporine A, systematic etretinate, systemic methotrexate, systemic corticosteroid, oral PUVA, narrow band UVB, biological therapies, and granulocyte monocyte plasma apheresis (GMA) [34,35].

Hüffmeier et al. and Rossi-Semerano et al. reported that anakinra, a recombinant IL-1 receptor antagonist, was effective against a case of DITRA [36,37]. We have reported that GMA was also very effective against a case of DITRA [38]. The question of whether there are differences in therapeutic strategy between DITRA and GPP without *IL36RN* mutations should be answered in the near future. In addition, new therapeutic strategies for DITRA are expected. For example, recombinant IL-36RN is one of the most promising therapies for DITRA.

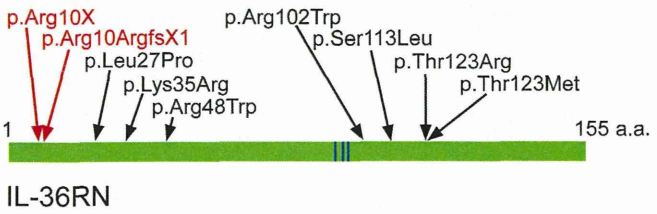

Fig. 3. The secondary structure of IL-36RN and location of all reported *IL36RN* mutations.
All reported *IL36RN* mutations are shown. The red characters indicate truncating mutations, and the black characters indicate missense mutations. Blue lines show critical residues such as Tyr89, Glu94, and Lys96 that mediate receptor interaction with IL36-RN.

5. CARD14

5.1. *Caspase recruitment domain family, member 14*

CARD14 encodes caspase recruitment domain family, member 14 (CARD14; Table 1) [39]. The caspase recruitment domain (CARD) is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-κB signaling complexes. CARD proteins include NOD1, NOD2, RIG-I, MDA5, and CARD9 [40]. Some CARD proteins are related to chronic inflammatory skin diseases; e.g., *NOD2* mutations cause Blau syndrome/early-onset sarcoidosis, and MDA5 is an autoantigen of amyopathic dermatomyositis, often accompanied by life-threatening acute interstitial lung disease [41–45]. CARD14, found to be specifically expressed in the skin, is a known activator of NF-κB signaling, and is predominantly localized in KCs [46,47] (Table 1). When the activity of CARD14 is up-regulated from mutations or variations, the KCs easily activate NF-κB signaling, which presumably results in psoriatic diseases (Fig. 4).

5.2. CARD14 *and psoriasis vulgaris and pityriasis rubra pilaris*

Jordan et al. identified rare gain-of-function variants and mutations in *CARD14*, including p.Gly117Ser, in 2 large multiplex families affected by Mendelian forms of psoriasis and psoriatic arthritis [47,48]. They also found 5 rare *CARD14* gain-of-function variants in large PV cohorts. The group used luciferase reporter assays to test the effects of the substitutions on the NF-kB-inducing activity of the abundant CARD14 protein isoform. The NF-kB assay revealed that compared with wild-type CARD14, 5 substitutions, including p.Gly117Ser, p.Glu138Ala, and p.Asp176His, lead to increased levels of the luciferase reporter [48]. Thus, they considered the 5 variants to be gain-of-function variants. Autosomal-dominant pityriasis rubra pilaris, which is phenotypically related to psoriasis, was also reportedly caused by mutations in *CARD14* [46], including p.Glu138del and p.Leu156Pro. Moreover, *CARD14* p.Arg820Trp (rs11652075) was found to be a PV-susceptible variant in a large psoriasis cohort [48,49]. Therefore, *CARD14* variants and mutations are closely related to various types of psoriasis and psoriasis-related diseases (Table 1, Fig. 5).

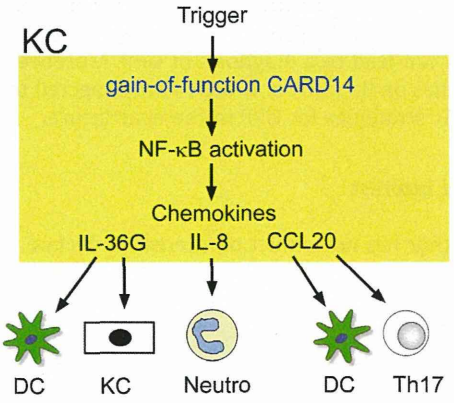

Fig. 4. Signaling pathway activated through gain-of-function CARD14 in generalized pustular psoriasis or autosominal dominant psoriasis vulgaris.
Triggers outside the KCactivate NF-κB through gain-of-function CARD14. Activated NF-κB induces chemokines, including IL-36G, IL-8, and CCL20. The chemokines recruit inflammatory cells, leading to GPP. DC: dendritic cell, Neutro: neutrophil, Th17: T helper 17 cell

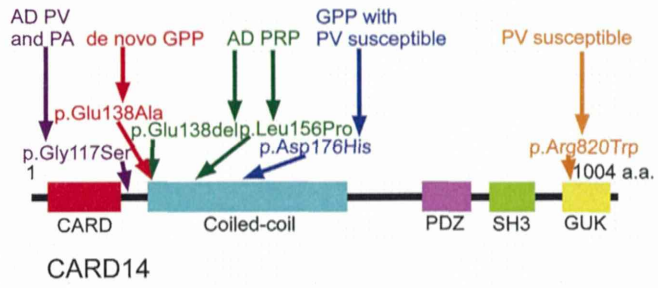

Fig. 5. CARD14 protein domain structure, locations of amino acid substitutions and deletions, and related psoriatic diseases.
CARD and coiled-coil domains are essential for NF-kB activation. The PDZ, SH3, and GUK domains are proposed as essential for membrane localization and lipid raft recruitment of CARD14 protein. Rare and common variants and mutations are indicated. AD: autosomal dominant; CARD: caspase recruitment domain; PA: psoriatic arthritis; PDZ: a domain from the initial letters of the PSD-95, Dlg, and ZO-1 proteins; PRP: pityriasis rubra pilaris; SH3: src homology 3; GUK: guanylate kinase

5.3. CARD14 *and generalized pustular psoriasis*

Jordan et al. identified the rare *de novo CARD14* gain-of-function variant p.Glu138Ala in a child with severe early-onset GPP (Fig. 5) [47]. There was no association of the gain-of-function variant p.Asp176His with PV because the rare variant was found not only in the large PV cohorts but also in the large control cohorts. However, we recently reported that the *CARD14* variant p.Asp176His is an important predisposing factor for GPP with PV in the Japanese population (Fig. 5) [50]. Although the underlying reason is not clear, we found that the carrier rate of p.Asp176His in the Japanese individuals examined in the present study was significantly higher than that in the European cohort [50]. In contrast, the variant is not associated with PV or with GPP alone. These findings suggest that the genetic background of GPP with PV differs from that of simple PV or GPP alone.

6. Concluding remarks

GPP alone is associated with mutations in *IL36RN*. These mutations can also be associated with PPP, ACH, and severe types of AGEP. However, the gain-of-function *CARD14* p.Asp176His variant is related to GPP with PV in the Japanese cohort. The above knowledge will be useful to consider when a patient with sterile pustulosis is seen in a clinical setting. For instance, even during a first episode of pustulosis, identification of recessive *IL36RN* mutations can lead to a diagnosis of GPP. Moreover, molecular-based studies on IL-36RN or CARD14 are expected to lead to new therapeutic strategies for GPP in the near future.

Conflict of interest

The author has no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2014.02.006.

References

[1] von Zumbusch L. Psoriasis und pustulosis Exanthem. Arch Dermatol Syphilol 1910;99:335–46.
[2] Posso-De Los Rios CJ, Pope E. New insights into pustular dermatoses in pediatric patients. J Am Acad Dermatol 2013.
[3] Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011;365:620–8.
[4] Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol: EJD 2006;16:669–73.
[5] Ohkawara A, Yasuda H, Kobayashi H, Inaba Y, Ogawa H, Hashimoto I, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol 1996;76:68–71.
[6] Murphy FR, Stolman LP. Generalized pustular psoriasis. Arch Dermatol 1979;115:1215–6.
[7] Khan SA, Peterkin GA, Mitchell PC. Juvenile generalized pustular psoriasis. A report of five cases and a review of the literature. Arch Dermatol 1972;105:67–72.
[8] Griffiths CE, Christophers E, Barker JN, Chalmers RJ, Chimenti S, Krueger GG, et al. A classification of psoriasis vulgaris according to phenotype. Br J Dermatol 2007;156:258–62.
[9] Landry M, Muller SA. Generalized pustular psoriasis. Observations on the course of the disease in a familial occurrence. Arch Dermatol 1972;105:711–6.
[10] Hubler Jr WR. Familial juvenile generalized pustular psoriasis. Arch Dermatol 1984;120:1174–8.
[11] Takematsu H, Rokugo M, Takahashi K, Tagami H. Juvenile generalized pustular psoriasis in a pair of monozygotic twins presenting strikingly similar clinical courses. Acta Derm Venereol 1992;72:443–4.
[12] Mulero JJ, Pace AM, Nelken ST, Loeb DB, Correa TR, Drmanac R, et al. IL1HY1: A novel interleukin-1 receptor antagonist gene. Biochem Biophys Res Commun 1999;263:702–6.
[13] Kumar S, McDonnell PC, Lehr R, Tierney L, Tzimas MN, Griswold DE, et al. Identification and initial characterization of four novel members of the interleukin-1 family. J Biol Chem 2000;275:10308–14.
[14] Smith DE, Renshaw BR, Ketchem RR, Kubin M, Garka KE, Sims JE. Four new members expand the interleukin-1 superfamily. J Biol Chem 2000;275:1169–75.
[15] Blumberg H, Dinh H, Dean Jr C, Trueblood ES, Bailey K, Shows D, et al. IL-1RL2 and its ligands contribute to the cytokine network in psoriasis. J Immunol 2010;185:4354–62.
[16] Dinarello C, Arend W, Sims J, Smith D, Blumberg H, O'Neill L, et al. IL-1 family nomenclature. Nat Immunol 2010;11:973.
[17] Carrier Y, Ma HL, Ramon HE, Napierata L, Small C, O'Toole M, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. J Invest Dermatol 2011;131:2428–37.
[18] Debets R, Timans JC, Homey B, Zurawski S, Sana TR, Lo S, et al. Two novel IL-1 family members, IL-1 delta and IL-1 epsilon, function as an antagonist and agonist of NF-kappa B activation through the orphan IL-1 receptor-related protein 2. J Immunol 2001;167:1440–6.
[19] Towne JE, Garka KE, Renshaw BR, Virca GD, Sims JE. Interleukin (IL)-1F6, IL-1F8, and IL-1F9 signal through IL-1Rrp2 and IL-1RAcP to activate the pathway leading to NF-kappaB and MAPKs. J Biol Chem 2004;279:13677–88.
[20] Blumberg H, Dinh H, Trueblood ES, Pretorius J, Kugler D, Weng N, et al. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J Exp Med 2007;204:2603–14.
[21] Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89:432–7.
[22] Sugiura K, Takeichi T, Kono M, Ogawa Y, Shimoyama Y, Muro Y, et al. A novel IL36RN/IL1F5 homozygous nonsense mutation, p.Arg10X, in a Japanese patient with adult-onset generalized pustular psoriasis. Br J Dermatol 2012;167:699–701.
[23] Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuma T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. J Invest Dermatol 2013;133:2514–21.
[24] Korber A, Mossner R, Renner R, Sticht H, Wilsmann-Theis D, Schulz P, et al. Mutations in IL36RN in patients with generalized pustular psoriasis. J Invest Dermatol 2013;133:2634–7.
[25] Li M, Han J, Lu Z, Li H, Zhu K, Cheng R, et al. Prevalent and rare mutations in IL-36RN gene in Chinese patients with generalized pustular psoriasis and psoriasis vulgaris. J Invest Dermatol 2013;133:2637–9.
[26] Setta-Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon SE, et al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. J Invest Dermatol 2013;133:1366–9.