LETTER TO THE EDITOR

Successful treatment with infliximab of sibling cases with generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist

Editor

Tumour necrosis factor-α (TNF-α) inhibitors often lead to rapid resolution of generalized pustular psoriasis (GPP).[1] However, the agents' mechanism of action against GPP remains to be elucidated, because the aetiology of the disease had been unknown. Recently, we reported that the majority of GPP cases that are not preceded by psoriasis vulgaris (PV; GPP alone) are caused by deficiency of interleukin-36 receptor antagonist (DITRA) due to homozygous or compound heterozygous *IL36RN* mutations.[2]

The patients were three Japanese siblings and their mother: a 39-year-old woman (Patient 1), a 36-year-old man (Patient 2), a 29-year-old man (Patient 3) and a 65-year-old woman (Patient 4). The parents are non-consanguineous. Patient 4 had been suffering from GPP preceded by PV since she was 53-years-old (Fig. 1a). The disease onset was at 10 years of age for Patients 1 and 2 and at 6 years of age for Patient 3. Patients 1, 2 and 3 had not had any previous PV lesions. They had recurrent erythema with pustules on the whole body and a fever of over 38°C. At exacerbation of the disease, blood examinations revealed elevated white blood cell count and C-reactive protein concentration. Bacterial cultures of the pustules were negative. They had pathological findings of spongiform pustules of Kogoj by skin biopsies from pustular eruptions. The siblings were diagnosed with GPP alone.

Following ethical approval, informed consent was obtained from the patients in compliance with the Declaration of Helsinki principles. All the coding regions of *IL36RN*, including the exon/intron boundaries, were sequenced using genomic DNA samples from the patients.[2] Patients 1, 2 and 3 were found to have the homozygous mutation c.115 + T > C (p.Arg10ArgfsX1) in *IL36RN*, which is one of the GPP-causing founder mutations in Japanese[2] (Fig 2). Patient 4 had heterozygous mutation c.115 + T > C (Fig. 2). The siblings were diagnosed with GPP caused by DITRA.

Satisfactory treatment results had not been obtained with various drugs, including oral cyclosporine A. Then, Patients 1, 3 and 4 were treated with 5 mg/kg of infliximab on the first treatment day, 2 weeks later and 4 weeks later as the initial treatment, and thereafter once every 8 weeks for maintenance therapy. The GPP lesions of Patients 1 and 3 rapidly resolved during the initial treatment period and have not relapsed for 3 years (Fig. 1b–e). The GPP lesions of Patient 4 have largely resolved. There are no apparent adverse effects. Infliximab therapy was recently started also in Patient 2.

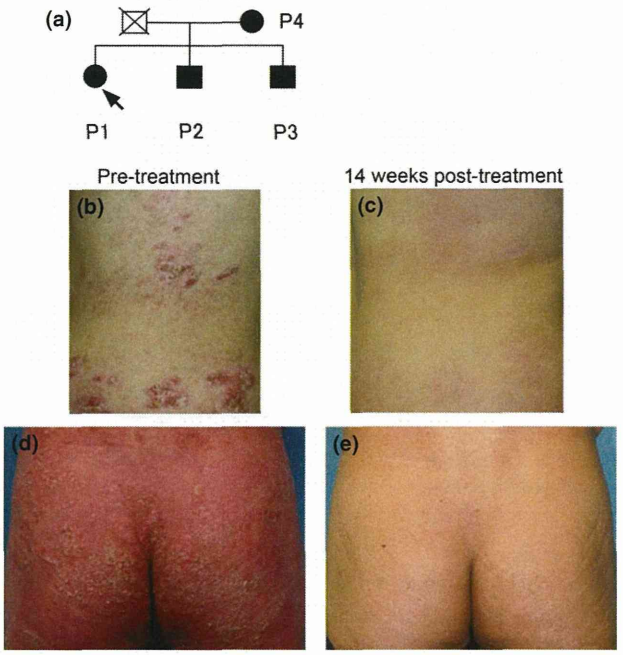

Figure 1 Pedigree of the patients' family and skin manifestations of Patients 1 and 3 before and after treatment with infliximab (a) Pedigree of the patients' family. The mother (Patient 4) was suffering from GPP preceded by PV. (b) Pustules in the background of erythema were observed on trunk in Patient 1 before treatment with infliximab. (c) The skin eruptions largely resolved by the 14th week of treatment with infliximab. Skin eruptions on the buttocks of Patient 3 before (d) and after 14 weeks (e) of treatment with infliximab.

Interleukin-36 (IL-36) is considered to play a major role in the immunopathogenesis of GPP caused by DITRA.[3,4] Carrier *et al.* reported that IL-36 expression in keratinocytes is enhanced by IL-1α, TNF-α and IL-17 *in vitro*.[5] Thus, we consider that the infliximab down-regulated IL-36 production and resolved the GPP lesions in Patients 1 and 3.

Viguier *et al.*[1] reported infliximab to be effective for two cases of GPP caused by DITRA, but both patients had severe adverse

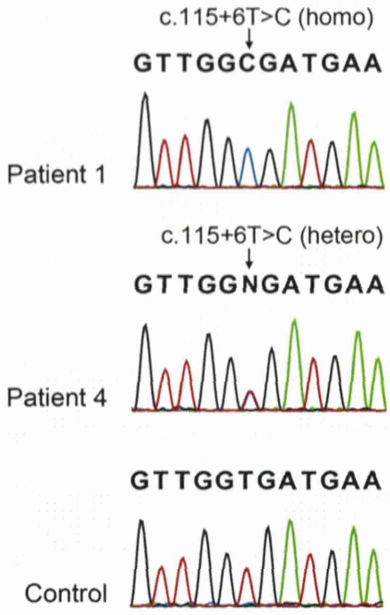

Figure 2 Sequence data of *IL36RN*. Sequence data of *IL36RN* are shown for Patient 1, Patient 4 and a control.

effects, including vomiting, fever and culture-negative pneumonia. Both patients were successfully treated by switching them from infliximab to adalimumab or etanercept, which are alternative TNF-α inhibitors.[1] Herein, we clearly demonstrated that infliximab was effective without any serious side-effects for two sibling cases of GPP caused by DITRA. Given that the majority of GPP alone cases are caused by DITRA, we think that most cases of GPP alone could be successfully treated with TNF-α inhibitors such as infliximab, because TNF-α plays a major role in the immunopathogenesis of GPP caused by DITRA.

In conclusion, Viguier's cases and our cases suggest that TNF-α inhibitors are powerful tools for treating GPP caused by DITRA.

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References

1 Viguier M, Aubin F, Delaporte E *et al.* Efficacy and safety of tumor necrosis factor inhibitors in acute generalized pustular psoriasis. *Arch Dermatol* 2012; **148**: 1423–1425.
2 Sugiura K, Takemoto A, Yamaguchi M *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**: 2514–2521.
3 Marrakchi S, Guigue P, Renshaw BR *et al.* Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011; **365**: 620–628.
4 Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? *Arch Dermatol* 2012; **148**: 381–384.
5 Carrier Y, Ma HL, Ramon HE *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**: 2428–2437.

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LETTER TO THE EDITOR

Disappearance of circulating autoantibodies to RNA polymerase III in a patient with systemic sclerosis successfully treated with corticosteroid and methotrexate

Editor

Although the titres of anti-RNAP III often change in association with total thickness skin score (TSS), it is extremely rare for anti-RNAP III to become negative after treatment in patients with SSc.[1,2]

A 66-year-old man exhibited Raynaud's phenomenon in the fingers. Four months later, oedema of the bilateral hands and feet and polyarthralgia occurred. A half-year after the initial episode of Raynaud's phenomenon, the patient was admitted to our hospital with severe joint pain and the inability to walk unaided. He had no particular past history.

Echocardiography, chest computer tomography, upper gastrointestinal endoscopy and colonoscopy revealed no remarkable finding for heart, lungs and abdomen. His fingers, hands and forearms were swollen with redness, and sclerodermatous skin change was present in the fingers (Fig. 1a). Pitting oedema was observed in the feet (Fig. 1b). The modified Rodnan TSS was 16. The laboratory data were as follows: ESR of 37 mm/h, WBC count of 3740/μL, platelets of 37 300/mm, total protein of 7.1 g/dL, albumin of 2.9 g/dL, blood urea nitrogen of 10 mg/dL, creatinine of 0.59 mg/dL and UA of 3.6 mg/dL, CRP of 5.07 mg/dL, MMP-3 of 39.2 ng/mL (normal range: 36.9–121.0 ng/mL) and plasma renin activity of 3.1 ng/mL/h (normal range: 0.2–3.9 ng/mL/h). Antinuclear antibody (ANA) was positive (1:80; nuclear speckled staining), and anti-RNAP III was detected by enzyme-linked immunosorbent assay (ELISA) with a high index of 104 and 77 at two points (normal range: < 28).[3] Rheumatoid factor, anticyclic citrullinated peptide, anti-SSA/Ro, anti-U1-RNP, anti-Scl-70 and anticentromere antibodies were negative.

A skin biopsy sample obtained from the extensor surface of the forearm showed oedema of the upper and mid dermis (data not shown). Neither bone erosion/destruction nor calcification was seen in the bilateral wrists (Fig. 1c), and there was bone marrow oedema in the carpal bones (Fig. 1d). In light of the above-mentioned findings, the patient was diagnosed as having SSc with anti-RNAP III associated with synovitis.

We administrated systemic prednisolone (PSL) at 30 mg/day, while carefully watching for signs of scleroderma kidney. This achieved almost complete remission of all symptoms, except discomfort of the metacarpophalangeal joints. After tapering the PSL dose by 2.5 mg every 2–3 weeks, the TSS fell to 0 and CRP and ESR levels normalized. When the PSL tapering reached 20 mg/day, the oedema and arthralgia relapsed and the CRP rebounded. After 3 months of PSL treatment, methotrexate (MTX) at 6 mg/week and later at 8 mg/week was added, and the joint symptoms were relieved and the CRP level decreased again. PSL has been tapered to 9 mg, and MTX at 8 mg/week has been continued; however, no recurrence of skin sclerosis or arthralgia,

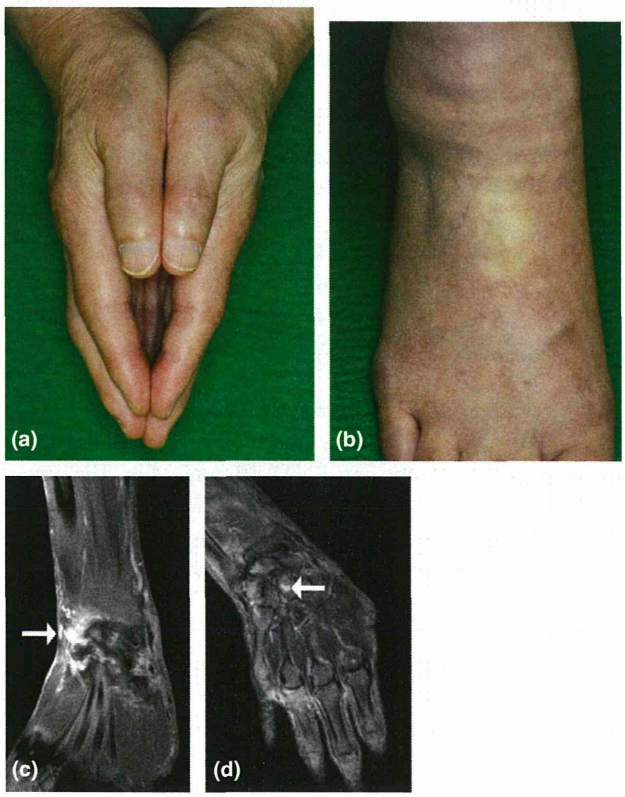

Figure 1 Clinical features of the patient before treatment. (a) The fingers and hands are red and swollen. (b) Pitting oedema is observed in the foot. (c, d) Enhanced MRI on the right hand shows synovitis (c: fat-suppressed images with gadolinium contrast agent) and bone oedema (d: high signal intensity on short tau inversion recovery).

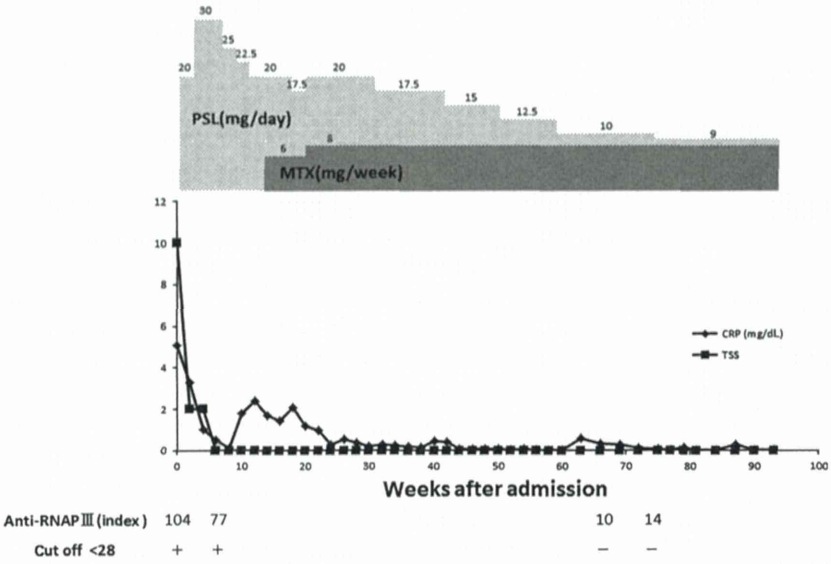

Figure 2 The treatment, course and circulating anti-RNAP III antibody titres of the patient.

or even of Raynaud's phenomenon has occurred for 2 years. Surprisingly, anti-RNAP III became negative (index value: 10) with ELISA about 1 year after PSL was started (Fig. 2). ANA also became negative.

We do not know the exact mechanism of how the antibodies disappeared in this case, although we assume that the extremely positive response to the treatments for SSc, to the extent of completely resolving the Raynaud's phenomenon, might be related to the disappearance of anti-RNAP III. The disappearance of anti-MDA-5 autoantibodies in clinically amyopathic dermatomyositis/interstitial lung disease during disease remission is another example of the disappearance of autoantibodies in a rheumatic disease.[4]

In conclusion, this is the first clear demonstration that anti-RNAP III can become negative after successful treatments in SSc patients with circulating anti-RNAP III antibodies. The present case gives us useful information that disappearance of anti-RNAP III autoantibodies might be a marker for disease remission in SSc patients with anti-RNAP III antibodies.

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References

1 Kuwana M, Okano Y, Pandey JP *et al.* Enzyme-linked immunosorbent assay for detection of anti-RNA polymerase III antibody: analytical accuracy and clinical associations in systemic sclerosis. *Arth Rheum* 2005; **52**: 2425–2432.
2 Nihtyanova SI, Parker JC, Black CM, Bunn CC, Denton CP. A longitudinal study of anti-RNA polymerase III antibody levels in systemic sclerosis. *Rheumatology (Oxford)* 2009; **48**: 1218–1221.
3 Satoh T, Ishikawa O, Ihn H *et al.* Clinical usefulness of anti-RNA polymerase III antibody measurement by enzyme-linked immunosorbent assay. *Rheumatology (Oxford)* 2009; **48**: 1570–1574.
4 Muro Y, Sugiura K, Hoshino K, Akiyama M. Disappearance of anti-MDA-5 autoantibodies in clinically amyopathic DM/interstitial lung disease during disease remission. *Rheumatology (Oxford)* 2012; **51**: 800–804.

DOI: 10.1111/jdv.12512

4 Kahofer P, Aberer E. Psoriasis vulgaris als Köbner-Phänomen in einem Erythema migrans. *Hautarzt* 2002; **53**: 805–807.
5 De D, Dogra S, Kanwar AJ. Ismorphic respons of Koebner in a patient with cutaneous small vessel vasculitis. *J Eur Acad Dermatol Venereol* 2008; **22**: 1125.
6 de Cid R, Riveira-Munoz E, Zeeuwen PL *et al.* Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet* 2009; **41**: 211–215.
7 Riveira-Munoz E, He SM, Escaramis G *et al.* Meta-analysis confirms the LCE3C_LCE3B deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with HLA- Cw6. *J Invest Dermatol* 2011; **131**: 1105–1109.
8 Bergboer JGM, Oostveen AM, de Jager MEA *et al.* Koebner Phenomenon in Psoriasis Is Not Associated with Deletion of Late Cornified Envelope Genes LCE3B and LCE3C. *J Invest Dermatol* 2012; **132**: 475–476.

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Generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist successfully treated with granulocyte and monocyte adsorption apheresis

Generalized pustular psoriasis (GPP) is a subtype of psoriasis, a rare potentially life-threatening inflammatory skin disease. GPP is often refractory to pharmacologic intervention.

We recently reported that the majority of cases of GPP without a history of psoriasis vulgaris (PV) ('GPP alone') are caused by homozygous or compound heterozygous mutations of *IL36RN*, although only a few cases of GPP preceded or accompanied by PV were found to have *IL36RN* mutations.[1]

Granulocyte and monocyte adsorption apheresis (GMA) is a therapy that is conducted using a column containing cellulose acetate beads that trap activated granulocytes and monocytes, which are effector cells that modulate inflammation in inflammatory diseases. Thus, GMA is effective against some inflammatory diseases, including GPP.[2,3] However, to our knowledge, there are no reports on whether GMA is effective against GPP caused by deficiency of interleukin-36 receptor antagonist (DITRA).[4,5] Here, we report a case of GPP caused by DITRA that was successfully treated by GMA.

The case is a previously reported patient.[2,3] Briefly, a 65-year-old woman complicated with diabetes, hypertension and hyperlipidemia showed generalized erythema with pustules on her trunk and fever. The erythema improved after oral administration of betamethasone at 0.5 mg/day and etretinate at 20 mg/day. However, the erythematous, pustular lesions reappeared on the extremities and the trunk, and the body temperature was 37.8°C (Fig. 1a). A skin biopsy from a pustular eruption on the left forearm revealed a spongiform pustule of Kogoj in the epidermis (Fig. 1c). Laboratory findings showed an increase in the white blood cell count to 17 900/μL, with elevation of the serum CRP level to 28.6 mg/dL. From these findings, the patient was diagnosed with GPP. GMA produced dramatic improvement of the symptoms associated with the GPP lesions (e.g. oedema, erythema and elevated body temperature), and the numbers of sterile pustules on the skin lesions in the patient decreased immediately after the first session of GMA therapy [2,3] (Fig. 2). Almost complete resolution of the erythema with pustules on the trunk and oedema on the legs was noted after the fifth session of GMA therapy[2,3] (Fig. 1b).

Following ethical approval, informed consent was obtained in compliance with the Declaration of Helsinki guidelines. The entire coding regions of *IL36RN* including the exon/intron boundaries were sequenced using gDNA samples from the patient.[1] The patient was found to have the homozygous mutation c.28C>T (p.Arg10X) in *IL36RN*, which is one of the GPP-causing founder mutations in Japanese (Fig. 1d).[1] She was diagnosed with GPP caused by DITRA.

The aetiology of GPP was unknown until 2011, when Marrakchi *et al.* reported that familial GPP is caused by DITRA.[4]

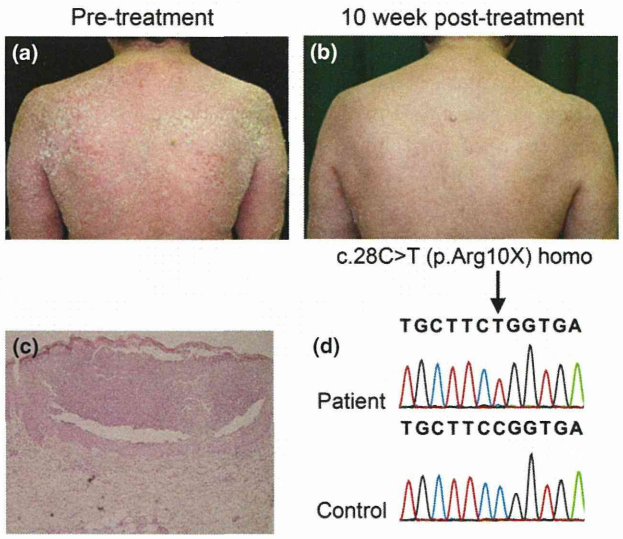

Figure 1 Clinical features, pathological findings of the pustular erythematous lesions and sequence analysis of *IL36RN* of the patient. (a) Pustules on background erythema are seen on the trunk at pretreatment. (b) The skin lesions were dramatically improved at 10 weeks post treatment of five sessions of granulocyte and monocyte adsorption apheresis. (c) Spongiosis of Kogoj and acanthosis are observed in the epidermis of the pustular erythematous lesions on the left forearm (Original magnification ×40). (d) Direct sequencing revealed the homozygous mutation c.28C>T in the patient.

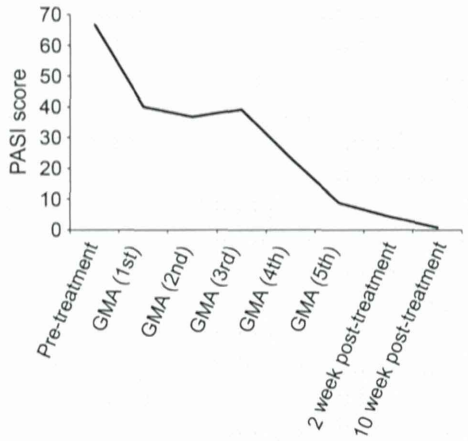

Figure 2 Clinical course of the patient. The psoriasis area and severity index score are dramatically reduced in the patient after five sessions of granulocyte and monocyte adsorption apheresis.

Recently, we reported that the majority of cases of GPP alone are caused by DITRA.[1] However, treatments for GPP caused by DITRA and their efficacy have not been well documented. Herein, we clearly demonstrated that GMA was effective for a case of GPP caused by DITRA and we suggest that granulocytes/monocytes play a major role in the immunopathogenesis of GPP caused by DITRA.

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References

1 Sugiura K, Takemoto A, Yamaguchi M *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**: 2514–2521.
2 Suzuki A, Haruna K, Mizuno Y *et al.* Successful treatment of three cases of generalized pustular psoriasis with granulocyte and monocyte adsorption apheresis. *Ther Apher Dial* 2012; **16**: 445–448.
3 Ikeda S, Takahashi H, Suga Y, Eto H, Etoh T, Okuma K, *et al.* Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. *J Am Acad Dermatol* 2013; **68**: 609–617.
4 Marrakchi S, Guigue P, Renshaw BR *et al.* Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011; **365**: 620–628.
5 Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? *Arch Dermatol* 2012; **148**: 381–384.

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T_{RM} then initiated cytotoxic responses against keratinocytes that resulted in epidermal necrolysis. Further analyses are needed to reveal the precise mechanisms.

This case shows that TEN can be evoked even in the absence of circulating T cells, and emphasizes the importance of T_{RM} during skin inflammation including drug hypersensitivity.

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REFERENCES

1. Nassif A, Bensussan A, Dorothée G, Mami-Chouaib F, Bachot N, Bagot M, et al. Drug-specific cytotoxic T cells in the skin lesions of a patient with toxic epidermal necrolysis. J Invest Dermatol 2002;118:728-33.
2. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. J Am Acad Dermatol 2007;56:181-200.
3. Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka K, Dowgiert RK, et al. The vast majority of CLA^+ T cells are resident in normal skin. J Immunol 2006;176:4431-9.
4. Sathaliyawala T, Kubota M, Yudanin N, Turner D, Camp P, Thome JJ, et al. Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. Immunity 2013;38:187-97.
5. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci U S A 2012;109:9959-64.

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Varicella zoster virus–associated generalized pustular psoriasis in a baby with heterozygous IL36RN mutation

To the Editor: A 2-month-old otherwise healthy boy presented with erythema and pustules without vesicles on the face, trunk, and all limbs. There was no improvement following treatment with oral antibiotics 3 weeks earlier. On admission to our hospital he had a slight fever and a generalized crusted pustular eruption (Fig 1). Laboratory data showed the following abnormal values: white blood cell count 19.14 × 10^9/L (normal range: 7-15 × 10^9/L); C-reactive protein level 108.5 mg/L (normal range: <3 mg/L). Bacterial culture of the pustules and microscopy for fungal infection were negative. Histopathologic examination of a skin biopsy specimen revealed spongiosis with neutrophil infiltration in the upper epidermis (Fig 2).

The pustulosis did not improve with application of a potent topical steroid and vitamin D_3-containing ointment. Oral cyclosporine was started and gradually increased to 4 mg/kg at 64 days from the disease onset. One week later, the pustules had almost cleared. Administration of 4 mg/kg cyclosporine was continued for more than 9 months. Extensive pustules reappeared with development of an upper respiratory tract infection

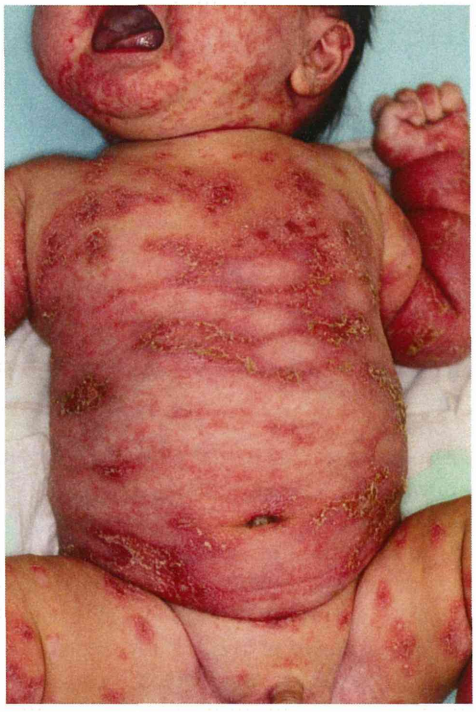

Fig 1. Varicella zoster virus–induced generalized pustular psoriasis in an infant. Pustulosis and crusts on the face, trunk, and limbs are seen.

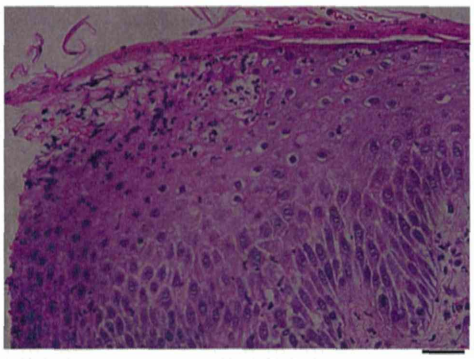

Fig 2. Varicella zoster virus–induced generalized pustular psoriasis: hematoxylin and eosin staining of the pustules; Bar: 40 μm.

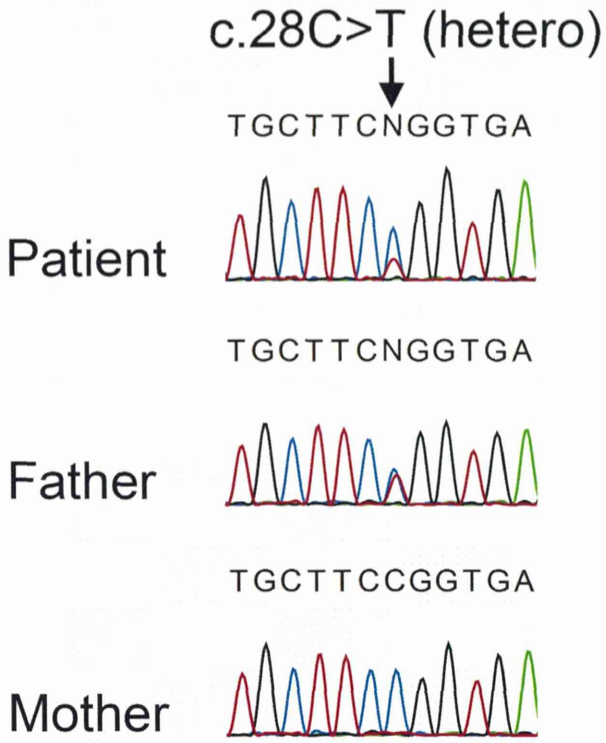

Fig 3. Varicella zoster virus–induced generalized pustular psoriasis: IL36RN sequence data of the patient and the parents. Arrow indicates the heterozygous c.28C>T mutation.

but subsequently regressed without a change in cyclosporine dosage.

There was no family history of a similar eruption. Before the skin manifestations developed, chickenpox was diagnosed in the patient's brother. Serum anti-varicella zoster virus (anti-VZV) immunoglobulin M tested negative in the baby initially but was positive 46 days after the disease onset. Anti-VZV immunoglobulin G antibodies were positive and thought to be derived from the baby's mother. There was no serologic evidence of herpes simplex virus infection.

After ethical approval was granted, written informed consent was obtained from the baby's parents in compliance with the Declaration of Helsinki. The entire coding regions of *IL36RN* including the exon/intron boundaries were sequenced using genome DNA samples from the patient and his parents. The patient and his father had a heterozygous c.28C>T (p.Arg10X) mutation in *IL36RN*, one of the generalized pustular psoriasis (GPP)-causing founder mutations in the Japanese cohort, whereas his mother did not have an *IL36RN* mutation (Fig 3).[1]

Diagnosis was VZV-induced GPP, a rare type of psoriasis that periodically recurs. Infection is one of its triggers. Mutation of *IL36RN*, which encodes interleukin-36 receptor antagonist (IL-36RN), has been associated with GPP in both its heterozygous and homozygous forms.[1-3] IL-36 is not present in normal skin but is induced by inflammatory cytokines including tumor necrosis factor-α (TNF-α).[4] When functional IL-36RN is underproduced, IL-36 can induce neutrophil-rich infiltration. TNF-α is elevated in the blood of VZV-infected individuals.[5] It is possible that this patient could not produce enough IL-36RN to antagonize the excessive IL-36 induced by VZV infection, an imbalance that resulted in GPP.

To our knowledge, this is the first report of VZV-induced GPP and of GPP triggered by infection in a patient with a heterozygous *IL36RN* mutation. Clinicians should consider IL-36RN deficiency in the setting of prolonged viral-induced generalized pustulosis.

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REFERENCES

1. 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.
2. Navarini AA, Valeyrie-Allanore L, Setta-Kaffetzi N, Barker JN, Capon F, Creamer D, et al. Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis. J Invest Dermatol 2013;133:1904-7.
3. 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.
4. 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.
5. Torigo S, Ihara T, Kamiya H. IL-12, IFN-gamma, and TNF-alpha released from mononuclear cells inhibit the spread of varicella-zoster virus at an early stage of varicella. Microbiol Immunol 2000;44:1027-31.

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Skin manifestations associated with chronic recurrent multifocal osteomyelitis in a 9-year-old girl

To the Editor: A 9-year-old girl presented with a 15-month history of severe joint pain limited to the right ankle. She had been treated for fatigue fracture and epiphysitis, but continued to require the use of crutches. The patient had pronounced muscular atrophy of the right leg, swelling and hyperthermia at the heel, and plantar pustulosis. She had mild paronychia on most fingers of the right hand and progressive changes in the fingernails, which were characteristic of nail psoriasis (Fig 1). Thus, psoriatic arthritis or osteitis was suspected, and oral naproxen (200 mg twice daily) therapy was prescribed. Whole-body magnetic resonance imaging (MRI) was performed and demonstrated inflammatory bone lesions, osteolysis, and sclerotic lesions (Fig 2). Laboratory parameters were within normal ranges. Her family history was unremarkable for similar cutaneous or musculoskeletal pathology. Chronic recurrent multifocal osteomyelitis (CRMO) with multifocal bone lesions, plantar pustulosis, and nail involvement was diagnosed. Oral methotrexate therapy (15 mg/week) was initiated and naproxen was continued. After 6 months, the joint pain resolved, and muscular atrophy, palmar pustulosis, and nail lesions improved.

CRMO is an acquired aseptic autoinflammatory bone disease that presents predominantly in girls and is characterized by pain that is worse at night, with or without fever. Typically there is a discrepancy between the mild symptoms and extensive bone inflammation. Sedimentation rate and C-reactive protein (CRP) values may be elevated,

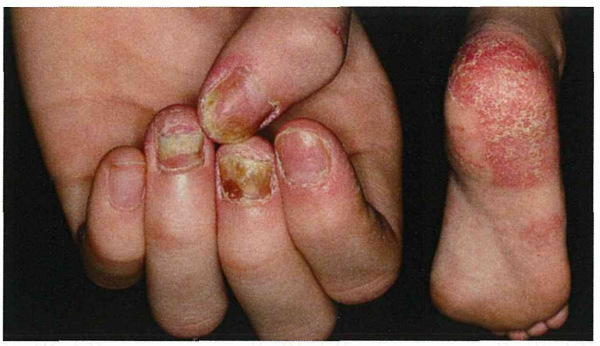

Fig 1. Chronic recurrent multifocal osteomyelitis. Onycholysis, nail pits, oil spots, and discoloration of the nails as well as erythema, hyperkeratosis, pustules on the sole of our 9-year-old female patient.

while the white blood cell count and other laboratory parameters are usually normal. The diagnosis of CRMO is mainly reliant on imaging studies. Conventional radiography initially shows osteolytic bone lesions with development of peripheral sclerosis in the course of the disease. MRI may show early lesions such as edema of bone marrow and inflammation of soft tissue. In order to diagnose CRMO, two major or one major and three minor criteria must be fulfilled.[1-3] Major criteria are osteolytic or sclerotic bone lesions, multifocal bone lesions, palmoplantar pustulosis or psoriasis, and sterile bone biopsy with signs of inflammation, fibrosis, or both. Minor criteria are normal blood cell count, good general health, slightly to moderately elevated CRP and erythrocyte sedimentation rate, clinical course of at least 6 months, hyperostosis, association with autoinflammatory diseases other than palmoplantar pustulosis or psoriasis, and a first- or second-degree relative with nonbacterial osteitis, or autoimmune or autoinflammatory disorders.

Some authors believe CRMO to be a juvenile variant of the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis). However, to what extent CRMO and SAPHO present a spectrum of one disease or separate entities remains controversial.[2]

There is no standard therapy of CRMO; however, nonsteroidal antiinflammatory drugs (NSAIDs) are considered to be first-line treatment with a favorable response rate in up to 80% of patients. Patients may require therapy to control skin and bone lesions, and NSAIDs can be used during attacks or to prevent attacks.[5] NSAID therapy is usually continued until patients are symptom-free for at least 3 months. When NSAID therapy is inadequate, primary treatment options are bisphosphonates and tumor necrosis factor antagonists,[5] and strong data

17 遺伝性の炎症性角化症

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Key words：遺伝性，炎症性角化症，汎発性膿疱性乾癬，CARD14遺伝子，IL36RN遺伝子

Abstract
炎症性角化症の病型には乾癬，毛孔性紅色粃糠疹などがある。従来炎症性角化症のほとんどは後天性の疾患と考えられていたが，近年その一部は遺伝性であることが明らかになった。「尋常性乾癬を伴わない汎発性膿疱性乾癬は大半がIL36RN遺伝子変異による遺伝性疾患である」ことが，また，基本的には常染色体劣性型式であるが，ときにはヘテロ接合体変異でも発症することが筆者らにより解明された。その他の遺伝性の炎症性角化症にCARD14遺伝子変異による常染色体優性遺伝疾患の家族性尋常性乾癬と家族性毛孔性紅色粃糠疹がある。

はじめに

炎症性角化症とは文字通り炎症を伴った角質の肥厚を呈する疾患であり，乾癬，類乾癬，扁平苔癬，毛孔性紅色粃糠疹，線状苔癬，光沢苔癬，Gibertばら色粃糠疹からなる疾患群である。従来炎症性角化症は一部を除いて後天性の疾患と考えられていた。しかし近年，後天性と考えられていた炎症性角化症の一部にも遺伝性の疾患があることが解明された。乾癬の1つの病型である，「尋常性乾癬（PsV）を伴わない汎発性膿疱性乾癬（GPP）」の大半はIL36N遺伝子が病因である常染色体劣性の疾患であることが筆者らにより解明され，疾患概念そのものが後天性の疾患から遺伝性の疾患に改められた。その他に，CARD14遺伝子が病因の常染色体優性遺伝性の炎症性角化症として，家族性尋常性乾癬と家族性毛孔性紅色粃糠疹がある。

1．汎発性膿疱性乾癬

乾癬の病型は大きくわけてPsV，滴状乾癬，膿疱性乾癬，乾癬性紅皮症，乾癬性関節炎の5つに分類される。膿疱性乾癬は汎発型と限局型に分類される。さらに，汎発型はGPPと疱疹状膿痂疹（IH）に分類される[1]。

GPPは我が国で2,000人弱の患者が登録されている難病である（http://www.nanbyou.or.jp/entry/168）。女性にやや多く（男：女＝1：1.2），小児期と30歳代に発症することが多い。急激な発熱とともに全身の皮膚が潮紅し，無菌性膿疱が多発する（図1）。病理組織学的に角層下の表皮の海綿状態に好中球性の膿瘍からなる，Kogoj海綿状膿疱を形成する。再発を繰り返すことが本症の特徴である。経過中に全身性炎症に伴う臨床検査異常を示し，しばしば粘膜症状，関節炎を合併するほか，まれに呼吸不全，眼症状，二次性アミロイドーシスを合併することがあり，ときに致死性である。

Genetic inflammatory keratoses : Kazumitsu Sugiura, Masashi Akiyama, Department of Dermatology, Nagoya University Graduate School of Medicine