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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This work was partly supported by Health and Labour Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labour and Welfare of Japan (H22-nanchi-ippan-003).

Disclosure: Dr Okamoto reports receiving grants and honoraria from Novartis and Bristol-Myers Squibb and receiving grants, honoraria, and residency or fellowship program from Kyowa Kirin. Drs Iriki, Adachi, Mori, Tanese, Funakoshi, Karigane, Shimizu, and Nagao have no conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.jaad.2014.07.013

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: $7\text{-}15 \times 10^9$/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

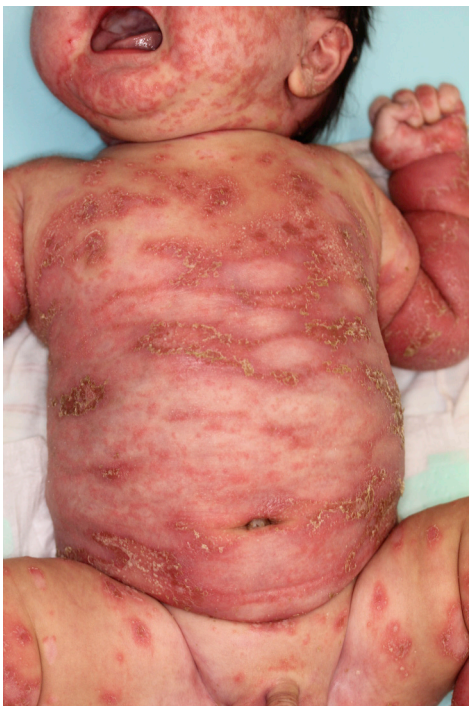

Fig 1. Varicella zoster virus–induced generalized pustular psoriasis in an infant. Pustulosis and crusts on the face, trunk, and limbs are seen.

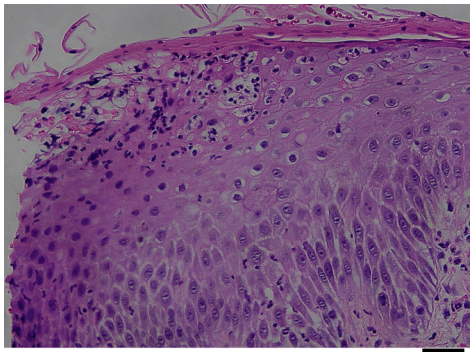

Fig 2. Varicella zoster virus–induced generalized pustular psoriasis: hematoxylin and eosin staining of the pustules; Bar: 40 μm.

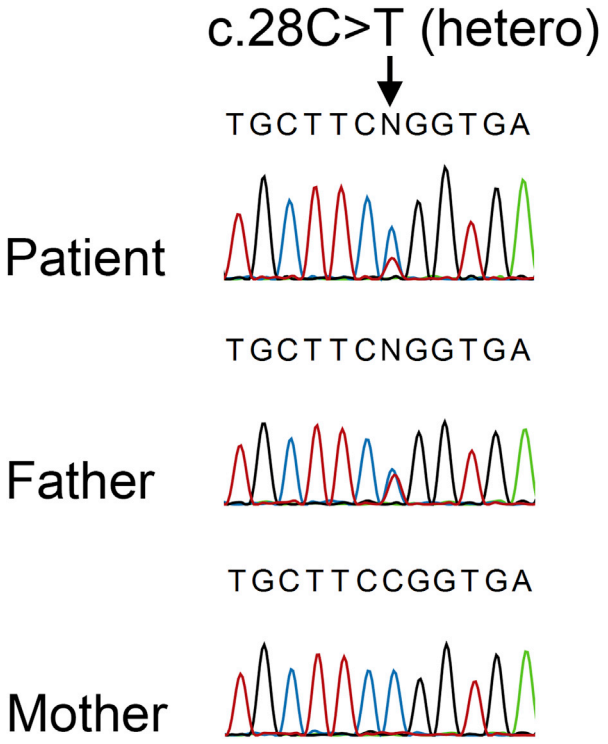

Fig 3. Varicella zoster virus–induced generalized pustular psoriasis: IL36RN sequence data of the patient and the parents. Arrow indicates the heterozygous c.28C>T mutation.

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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Funding sources: Grant-in-Aid for Scientific Research (C) 23591617 (KS) and a Grant-in-Aid for Scientific Research (A) 23249058 (MA), both from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Conflicts of interest: None declared.

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http://dx.doi.org/10.1016/j.jaad.2014.07.015

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,

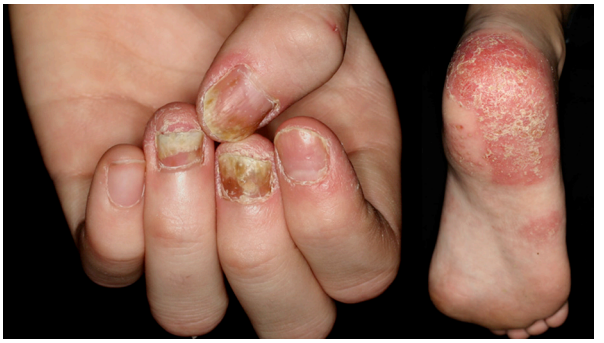

Fig 1. Chronic recurrent multifocal osteomyelitis. Onycholysis, nail pits, oil spots, and discoloration of the nails as well as erythema, hyperkeratosis, pustules on the sole of our 9-year-old female patient.

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