lentiginous nevus, is considered within the spectrum of congenital melanocytic nevi[3], due to its usual occurrence during late infancy or early childhood. Dark brown pigmented macules and papules lying on a tan lentiginous patch is the characteristic finding. Histologically, the background area resembles lentigo simplex, whereas the darker spots usually show the features of a lentiginous nevus with lentigo-like areas progressing to junctional and even small compound nevi[4]. In contrast, agminated nevi usually occur during puberty and lack background pigmentation. In our case, background pigmentation was not clinically visible, and the small amount of normal tissue surrounding the excised nevus did not reveal a lentiginous feature.

Since melanoma arising from acquired agminated melanocytic nevi has been described[5] and the patient is relatively young, long-term follow-up for any malignant change as well as development of background pigmentation is warranted.

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Successful Treatment with Tacrolimus in a Case of the Glucocorticoid-Dependent Recurrent Cutaneous Eosinophilic Vasculitis

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Dear Editor:

Recurrent cutaneous eosinophilic vasculitis (RCEV) is a rare type of necrotizing vasculitis. The cases present with inflamed small dermal vessels with eosinophilic infiltration and no systemic organ involvement. The disease is also associated with peripheral blood eosinophilia[1]. Although the systemic glucocorticoid treatment is usually effective, a relapse often occurs during the reduction of the glucocorticoid dosage. However, there are few reports of RCEV ameliorated by other immunosuppressive medications.

We report a case of RCEV in which the oral tacrolimus treatment not only improved the clinical manifestations including eosinophilia and vasculitis-induced purpura, but also decreased the corticosteroid dosage required to control eosinophilic vasculitis.

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An 80-year-old Japanese woman transferred to our department with complaints of digital pain, low grade fever, cutaneous purpura (Fig. 1) and general malaise. She had multiple purpuric patches (not palpable) on her palms, the lower extremities and trunk. She had a fever (body temperature, 37.8°C) and had lost 3 kg of body weight in the past month. She had been well until 1 month previous, when she had visited another local clinic. She had no previous history of illness or any family history of significant disease, including rheumatic disease or vasculitis syndrome. Her laboratory investigations revealed leucocytosis caused by eosinophilia. The leukocyte count in her peripheral blood was 16,000/μl, and the proportion of eosinophils was 63%; thus the absolute eosinophil count was estimated at 10,080/μl. Thrombocytopenia was not observed. The lactate dehydrogenase (LDH) levels were slightly elevated at 314 U/L (normal, 100～225 U/L). The alkaline aminotransferase levels were within the normal range. The results of the serological tests were as follows. Anti-nuclear antibody was positive (titer 1:80) with homogeneous and speckled patterns. Complement levels were not decreased. The serum levels of immunoglobulin (Ig) G, IgA and IgM were 1,290 mg/dl (normal, 870～1,818 mg/dl), 261 mg/dl (normal, 110～424 mg/dl) and 104 mg/dl (normal, 31～252 mg/dl), espectively. Serum IgE level was 4 mg/dl (normal, ＜295 mg/dl). Serum monoclonal protein was undetectable by immunoprecipitation. The results of immuno-complex (C1q), IgM-class Rheumatoid factor, Myeloperosidase and Proteinase-3 anti neutrophils cytoplasmic auto antibody (ANCA) were all negative. She was negative for the antibodies of the hepatitis B and C viruses. Bone marrow aspiration showed eosinophil-dominant cell proliferation without atypical feature or chromosomal abnormalities. She was negative for cryoglobulin, cryofibrinogen and cold agglutinin. Coagulation tests were all within the normal range, and β2-glycoprotein-dependent anti-cardiolipin antibody was not detected. Stool examination for parasitic infestation was negative. Cutaneous histopathology of purpuric patches revealed dermal vasculitis that was accompanied by the inflammatory cell infiltration, consisting largely of eosinophils and lymphocytes (Fig. 2). No other systemic organ involvement, such as pericardiac, hepatic or pulmonary leucocyte infiltration could be identified. The patient was diagnosed as RCEV, and was initially given 30 mg prednisolone daily. This resulted in a dramatic and immediate decrease in the eosinophil counts, LDH levels and digital pain. The improvement of the purpuric patches on the skin followed. The prednisolone treatment was gradually tapered over several months. After decreasing the prednisolone dosage to 15 mg daily, the patient's symptoms, including low-grade fever, digital pain and peripheral blood eosinophilia reappeared. The increased systemic corticosteroid therapy (prednisolone 30 mg/d) was very effective, and the effect was same as that of the initial treatment. Oral tacrolimus (2 mg, once daily) was combined with the corticosteroid treatment when the prednisolone dosage was decreased to 20 mg/day. After commencing with the additional treatment, the corticosteroid dosage was again gradually tapered to 2.5 mg daily, and the patient remained in remission. The trough concentrations of tacrolimus in the plasma were within 5.5～8.3 ng/ml at the beginning of the treatment. However, renal insufficiency accompanied by the elevation of serum creatinine developed when the oral tacrolimus dosage was increased to 3 mg daily. This adverse effect improved within a week after the tacrolimus dosage was decreased to 2 mg/d. No other adverse effects

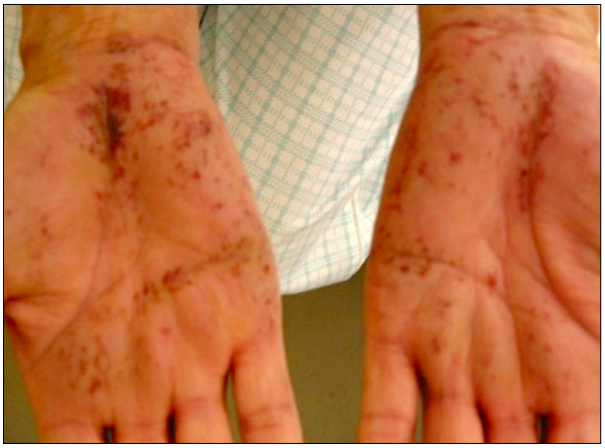

Fig. 1. Purpuric papules and plaques on the palm.

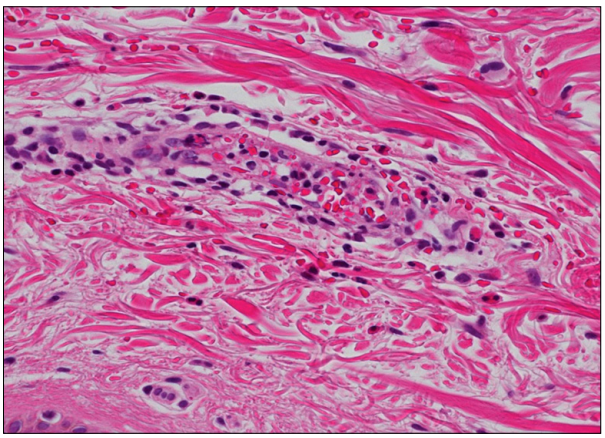

Fig. 2. Histopathological findings of purpuric papules: biopsy revealed inflamed small dermal vessels with eosinophil-predominant infiltration (H&E, ×400).

of this medication, such as hypertension, hyperkalemia, intestinal symptoms, diabetes mellitus or rashes, have been observed thus far in the patient on the 2 mg/d dosage.

Tacrolimus (FK506) is not only used for immunosuppression in the organ-replacement therapy[2], but is also prescribed for other immunological disorders, including lupus nephritis, rheumatoid arthritis, atopic eczema and the inflammatory bowel disease[3,4]. Tacrolimus binds to the FK-binding proteins in the cytoplasm, and the complex then associates with the calcium-dependent calcineurin/calmodulin complexes to impede the calcium-dependent signal transduction in lymphocytes. This causes the expression of the transcription factors related to the cytokine gene activation to be decreased. We predicted that tacrolimus might be useful as an alternative immunomodulation therapy for RECV.

Sakuma-Oyama et al.[5] reported that a case of RCEV subsided with a treatment of suplatast tosilate, considered an effective treatment for various atopic conditions. However, to our knowledge, there is no other report concerning the use of the immunosuppressive therapy other than corticosteroids in RCEV.

The pathological findings of vasculitis in RCEV include fibrinoid necrosis with leucocyte infiltration, which can be described as being similar to Churg-Strauss syndrome (CSS) and hypereosinophilic syndrome (HES)[6]. The differential diagnosis among these vasculitis syndromes is often difficult, as they have common clinical manifestations. Therefore, any treatment which could ameliorate HES and CSS might also improve the clinical manifestations in RCEV.

Furthermore, eosinophilia in RCEV is dependent on the concentrations of serum interleukin (IL)-5, a Th2 cytokine which is released from CD4 T-lymphocytes[1]. As a result, the anti-IL-5 treatment may decrease the number of eosinophils in such illness. Tacrolimus decreases the production of cytokines, including IL-5, by T-lymphocytes as CsA[7,8]. In addition, FK506 ointment has been shown to decrease the local levels of IL-5 in the inflamed tissues in the cases of atopic dermatitis[9]. Moreover, a previous study has reported that eotaxin, C-C Chemokine Receptor type 3 (CCR3), Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) which are important in regulating eosinophil survival, recruitment, activation and proliferation are decreased with the tacrolimus application in allergic inflammation[10].

In our conclusion, we suggest that FK506 may be a reliable salvage therapy for the corticoid-dependent RCEV. However, it is noted that the therapy may sometimes lead to serious adverse effects.

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