—Case Reports—

Atopic Dermatitis-Like Rash During Evolocumab Treatment of Familial Hypercholesterolemia

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that targets the low-density lipoprotein (LDL) receptor for lysosomal degradation. PCSK9 impedes the receptor-mediated clearance of LDL-cholesterol, thereby increasing serum LDL-cholesterol levels. Evolocumab, a human monoclonal antibody against PCSK9, effectively reduces serum LDL-cholesterol levels. We report the first known case of a patient who developed an atopic dermatitis (AD)-like rash during evolocumab therapy.

A 43-year-old Japanese man with heterozygous familial hypercholesterolemia was treated with subcutaneous injection of 140 mg evolocumab biweekly, for 16 months. The therapy was then changed to subcutaneous injection of 420 mg evolocumab monthly. A few days after the first dose, the patient experienced pruritus and rash on his extremities. The rash worsened, while the pruritus subsided, then relapsed after the second and third doses. He had erythema and excoriation on his legs, lichenification over his popliteal fossa, xerosis on his forearms, an increased serum IgE level, and a family history of AD in his siblings. We made a provisional diagnosis of AD characterized by enhanced type 2 helper T (Th2) activity and treated him with topical corticosteroids and oral anti-histamines. His rash improved and did not relapse after the fifth dose; however, his LDL-cholesterol level increased.

PCSK9 or oxidized LDL activates macrophages or dendritic cells, respectively, and enhances their activity to induce Th1 cells antagonizing Th2 cells. We hypothesized that high-dose evolocumab may suppress Th1 activity to antagonize Th2, and unmask Th2 disposition based on the patient's atopic diathesis, triggering the rash mimicking AD. Clinicians should be aware of rash development during evolocumab therapy. (J Nippon Med Sch 2019; 86: 187–190)

Key words: atopic dermatitis, evolocumab, familial hypercholesterolemia, proprotein convertase subtilisin/kexin type 9, rash

Introduction

Familial hypercholesterolemia (FH) is a genetic disease characterized by hyper-low density lipoprotein (LDL)-cholesterolemia, tendon xanthomas, and premature coronary heart disease[1]. FH is caused by an autosomal dominant mutation of the genes involved in LDL uptake and catabolism. These include the LDL receptor, apolipoprotein-B, or proprotein convertase subtilisin/kexin type 9 (PCSK9). Treatment to reduce the levels of LDL-cholesterol is required for these patients, to prevent cardiovascular diseases[1]. LDL-cholesterol comes into contact with the LDL receptor on the surface of hepatocytes, followed by the internalization of the LDL/LDL receptor complex into the endosome. Thereafter, the LDL particle undergoes degradation in the lysosome, while the LDL receptor is recycled and returned to the cell surface. This return further contributes to the lowering of LDL-cholesterol levels[2]. PCSK9 is a serine protease mainly produced in hepatocytes and secreted. PCSK9 targets the LDL receptor so that it can be degraded by extracellular and intracellular pathways[2]. Extracellular PCSK9 binds to the LDL receptor on the cell surface. The resulting PCSK

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9/LDL receptor complex is then endocytosed and degraded in the lysosome. In the intracellular pathway, newly synthesized PCSK9 in hepatocytes exits the endoplasmic reticulum and is transported to the *trans*-Golgi network. At this site, it is then able to bind and direct the LDL receptor to the lysosome, for degradation. PCSK9 thus reduces the LDL receptor density on the cell surface, thereby increasing serum LDL-cholesterol levels[2]. Evolocumab, a human monoclonal antibody against PCSK9, binds extracellular PCSK9 and suppresses its interaction with the LDL receptor. This prevents the degradation of the LDL receptor, thereby reducing serum LDL-cholesterol levels[3]. Evolocumab is an approved therapy for FH[3]. We describe the first known case of rash development that was observed to mimic atopic dermatitis (AD) during evolocumab therapy.

Case Report

A 43-year-old Japanese man visited the Department of Endocrinology, and was diagnosed with heterozygous FH based on the diagnostic criteria for FH[4], specifically: a high serum LDL-cholesterol level of 325 mg/dL (normal <139 mg/dL), Achilles tendon thickening, and a positive family history of hypercholesterolemia in his mother and younger sister. Treatment with atorvastatin calcium trihydrate, and ezetimibe failed to control the LDL-cholesterol level in this patient. Subcutaneous injection of 140 mg evolocumab biweekly was initiated, which reduced his LDL-cholesterol level. After 16 months, the therapy was changed to subcutaneous injection of 420 mg evolocumab monthly, due to financial reasons. A few days after the first dose, the patient experienced pruritus and rash on his lower legs and forearms (**Fig. 1**). The pruritus spontaneously subsided 10 days later; however, the rash persisted. A few days after the second and third doses, the pruritus relapsed and subsided between 7 and 10 days later, while the rash persisted and worsened. The patient visited the Department of Dermatology complaining about the pruritus and displayed erythema with desquamation and excoriation on the posterior surface of his lower legs and the anterior surface of his thighs, lichenification over his popliteal fossa (**Fig. 2**), and xerosis on his forearms. It is important to note that his younger sister and brother had AD, though he had no history of AD, asthma, or allergic rhinitis. The patient showed an increased serum IgE level of 1,186 IU/mL (normal <170 IU/mL), mild eosinophilia of 561/μL (normal <450/μL), 9.2% of total leukocytes (normal <7.0%), and a normal thymus and activation-regulated chemokine (TARC) level of 382 pg/mL. The IgE radioallergosorbent tests were positive against Japanese cedar, *Dermatophagoides pteronyssinus*, and house dust.

We made a provisional diagnosis of AD based on the properties of the rash and his atopic diathesis. Thus, we treated him with topical clobetasol propionate, heparinoid, and oral bilastine 20 mg. Three weeks later, his rash improved, and the rank of steroid was reduced to betamethasone butyrate propionate. Several days after the fourth dose, the pruritus relapsed at the lower level and subsided 1 week later. At month 4, his rash subsided, and neither his pruritus nor rash relapsed after the fifth dose. Though his serum IgE level slightly increased to 1,379 IU/mL at month 5, his eosinophil count and TARC levels decreased to 325/μL (5.0% of total leukocytes) and 219 pg/mL, respectively. However, his LDL-cholesterol level gradually increased to 95 mg/dL at month 5, compared to 43 mg/dL at month 0 (**Fig. 1**).

Discussion

The prescribing information for evolocumab describes the following adverse skin reactions: rash (1.0% and 0.5% for evolocumab group and placebo, respectively), eczema (0.4% and 0.2%), and erythema (0.4% and 0.2%)[5]. To date, no cases have been reported of rash being associated with evolocumab. Our patient developed a rash mimicking AD after high-dose evolocumab therapy. The temporal relationship of the rash and high-dose evolocumab therapy indicates that this therapy may have triggered the rash. Based on the diagnostic criteria for AD by the Japanese Dermatological Association[6], the patient's rash fulfilled 2 of the 3 criteria: pruritus and typical morphology and distribution of erythema/lichenification and symmetrical distribution/predilection sites (joint areas of the limbs). The third criterion, a chronic relapsing course more than 6 months, was not fulfilled since the duration of his rash was approximately 4 months. Therefore, his rash could not be diagnosed as AD, although it did mimic this condition. AD is a chronic inflammatory skin disease and its associated skin lesion is infiltrated by a large amount of type 2 helper T (Th2) cells that produce interleukin (IL)-4, IL-5, or IL-13[7]. The production of these cytokines leads to an immune response that results in elevated serum IgE levels[8]. The patient's family history of AD and high serum IgE level indicated his Th2 disposition, and the properties of his rash also indicated the involvement of Th2-mediated inflammation. It is known that Th1 cells that produce interferon-γ antagonize the development of Th2 cells and *vice versa*: interferon-γ sup-

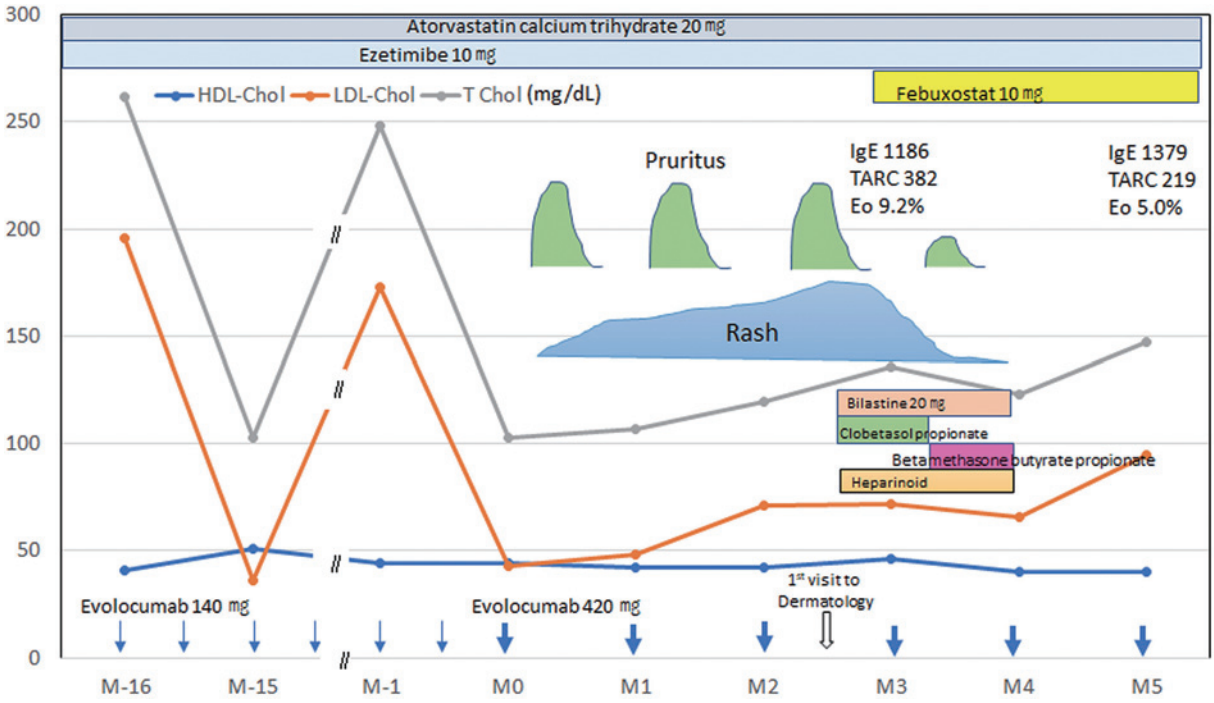

Fig. 1 The progress of rash, serum cholesterol levels, and treatment. The beginning of the 420 mg evolocumab treatment was set as month 0 (M0).

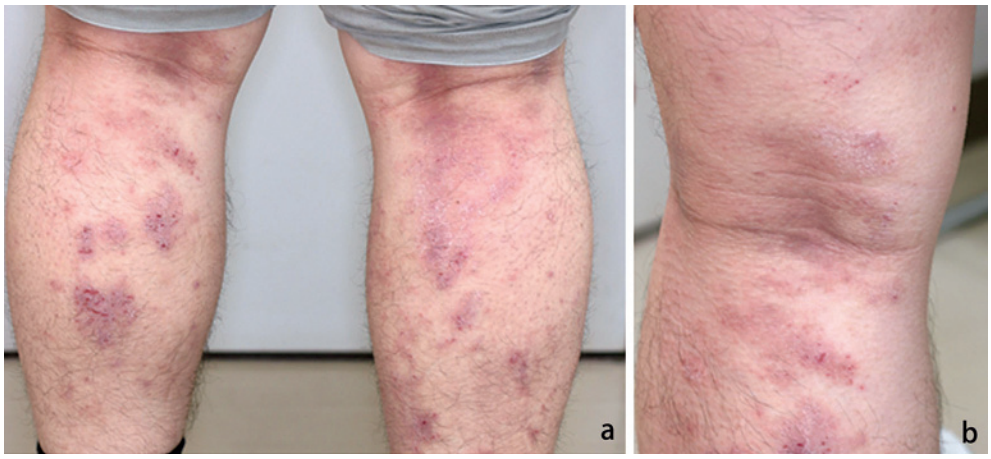

Fig. 2 Clinical photographs of the rash at 2.5 months after three doses of 420 mg evolocumab. The patient manifested erythema with desquamation and excoriation on his lower legs (a) and lichenification over his popliteal fossa (b).

presses Th2 cell proliferation, whereas Th2 cytokines, such as IL-4/IL-13, inhibit the development of Th1 cells[9,10]. Although Th2 cells antagonize the development of the Th17 cells that produce IL-17A, no lineage-specific mechanisms where Th17 cells suppress Th2 development have been elucidated[11].

Independently from increasing LDL levels, extracellular PCSK9 enhances tumor necrosis factor-α, IL-1β, and IL-6 production in macrophages[12]. Subsequently, PCSK9 polarizes these macrophages into M1 macrophages, which promote the proliferation and activation of T cells, and drive them toward Th1 and Th17 phenotypes[13]. It has also been reported that LDL is oxidized on the vessel wall[14]. The oxidized LDL acts on dendritic cells and promotes their activity to differentiate naïve T cells into Th1 and Th17 cells[15]. The anti-PCSK9 antibody, evolocumab, may directly suppress the effect of extracellular PCSK9, while indirectly affecting that of oxidized LDL via the reduction of LDL-cholesterol levels. Both actions of evolocumab may therefore lead to the inhibition of Th1 and Th17 activity. It is hypothesized that administering high-dose evolocumab therapy to our patient may have

prominently suppressed the effects of extracellular PCSK9 and the oxidized LDL to induce Th1 and Th17 activity. These actions would then reduce Th1 activity in antagonizing Th2, thereby unmasking his Th2 disposition and triggering Th2-mediated inflammation in the skin, leading to the rash mimicking AD. However, despite the continuation of high-dose evolocumab, our patient's LDL-cholesterol level gradually increased, while the rash resolved (**Fig. 1**). This could be attributed to reduced host responsiveness to evolocumab, and/or the compensatory activation of intracellular PCSK9, which evades evolocumab-binding, and targets the LDL receptor intracellularly for lysosomal degradation. This targeting thereby increases serum LDL-cholesterol[16]. The increased LDL-cholesterol may generate oxidized LDL, which drives Th1 and Th17 activity. Particularly, enhanced Th1 activity to antagonize Th2 may counteract the possible Th2-mediated inflammation in our patient's skin lesion, resulting in the resolution of the rash.

This is the first known case report on rash associated with evolocumab therapy. Clinicians should be aware of rash during evolocumab therapy, especially in patients with atopic diathesis. Such adverse reactions to evolocumab may, however, aid in dissecting the immunological effects of PCSK9.

Conflict of Interest: The authors declare no conflict of interest.

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