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CASE REPORT

Severe Nail Fold Psoriasis Extending from Nail Psoriasis Resolved with Ustekinumab: Suggestion of a Cytokine Overflow Theory in the Nail Unit

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Because nail psoriasis is difficult to treat, therapy with many biological drugs has been attempted. Ustekinumab is approved for chronic plaque psoriasis and psoriatic arthritis (PsA), with some trials reporting nail improvement using this agent. A 51-year-old man with severe chronic plaque psoriasis had severe involvement of all fingernails and toenails, with accompanying nail fold psoriasis. He also had PsA of the small joints of the fingers. Despite multiple conventional therapies, the nail lesions did not improve, and his nail psoriasis severity index score was 97. After a fourth ustekinumab injection, most of the fingernail psoriasis was resolved, and only hyperkeratosis remained on both large toenails. Because the nail plate, nail fold, and small joints of the fingers are closely apposed structures within a small area, cytokines produced from the nail units overflow to the nail fold and small joints and can induce nail fold psoriasis and PsA. **(Ann Dermatol 28(1) 94～97, 2016)**

-Keywords-
Arthritis, Nail diseases, Psoriasis, Psoriatic, Severity of illness index, Ustekinumab

INTRODUCTION

Psoriasis is a chronic inflammatory disease, with typical skin lesions represented by erythematous scaly plaques. Although the lesions predominately occur on the knees, elbows, and scalp, the lifetime incidence of nail involvement is reported to be as high as 90%[1]. Patients with nail psoriasis have severe physical and psychological issues, but nail involvement is very difficult to treat with conventional modalities such as topical steroid, calcipotriol, or intralesional triamcinolone injections for chronic plaque psoriasis (CPP)[2].

Biologics for psoriasis such as adalimumab, etanercept, infliximab, and ustekinumab have recently emerged as treatments for moderate to severe plaque psoriasis. However, relevant data on nail psoriasis improvement are limited. Phase III clinical trials of infliximab[3], ustekinumab[4], and adalimumab[5] have reported nail psoriasis improvements. The clinical manifestations of nail psoriasis are mainly classified into nail matrix and nail bed lesions[6]. Nail fold psoriasis is currently regarded as a clinical sign of nail psoriasis[7]. It has usually been disregarded because the lesion is limited to a very small area of skin, in contrast to CPP in other regions. In this report, severe nail psoriasis extending to the nail fold and affecting all 20 nails improved dramatically with ustekinumab treatment.

CASE REPORT

A 51-year-old man with CPP for 15 years had been treated with narrow-band ultraviolet B phototherapy, topical steroids, and systemic agents such as acitretin, methotrexate, and cyclosporine A. His nail and nail fold psoriasis developed 3 years previously. On gross inspection, entire nail plate leukonychia on all toes, nail plate crumbling, Beau's

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lines, and subungual hyperkeratosis were observed. Triamcinolone acetonide was injected into his fingernail folds, and topical betamethasone dipropionate/calcipotriol ointment was applied to the fingernails and toenails. Despite these treatments, only minimal improvement was observed on his fingernails, and nail fold atrophy was observed in the fingernail folds (Fig. 1). He also had symptoms of psoriatic arthritis (PsA), such as swelling and pain in the distal (DIP) and proximal interphalangeal (PIP) finger joints.

The patient was socially and psychologically stressed, especially because of his nail psoriasis. He was treated with 45 mg of ustekinumab at weeks 0 and 4, and then every 12 weeks thereafter. His initial psoriasis area and severity index score was 17.0, the involved body surface area was 20%, and the initial nail psoriasis severity index (NAPSI) score was 98. After the second injection of ustekinumab, dramatic recovery in his nail and nail fold psoriasis was observed. A complete disappearance of nail fold psoriasis was seen at week 28 and was maintained thereafter. Swelling and pain of the DIP and PIP joints due to PsA was reduced. Psoriasis was almost completely resolved, and the NAPSI score decreased to 7 at week 40 (Fig. 2). After the termination of ustekinumab treatment at week 64 at the patient's request, his nail psoriasis relapsed.

DISCUSSION

Nail involvement in psoriasis is reported in up to 50% of patients, with a lifetime incidence of up to 90%[1]. Nail psoriasis usually follows a chronic course and causes ongoing social, psychological, and physical problems. Consequently, patients with severe nail psoriasis have decreased quality of life[8,9]. Surprisingly, patients with nail psoriasis have greater physical and psychological problems than those with other chronic diseases, including arthritis, lung disease, heart failure, and diabetes[1]. Nail fold involvement is a relatively common but disregarded nail psoriasis pattern. The incidence of nail fold psoriasis, with scaling of the nail fold, was as high as 25% in a previous report[7]. However, severe nail fold psoriasis, as in the present case, is relatively uncommon.

There are limited therapeutic options for the treatment of nail psoriasis. Most conventional medications have been used for nail psoriasis, but their effects are limited and can cause a number of side effects[10]. Treatment with emerging antipsoriatic biologics has been attempted for the management of intractable nail psoriasis refractory to conventional treatment. Antitumor necrosis factor α agents were investigated for nail psoriasis treatment. In a large, phase III, multicenter, double-blind, placebo-controlled trial of infliximab for nail psoriasis, the results showed a sig-

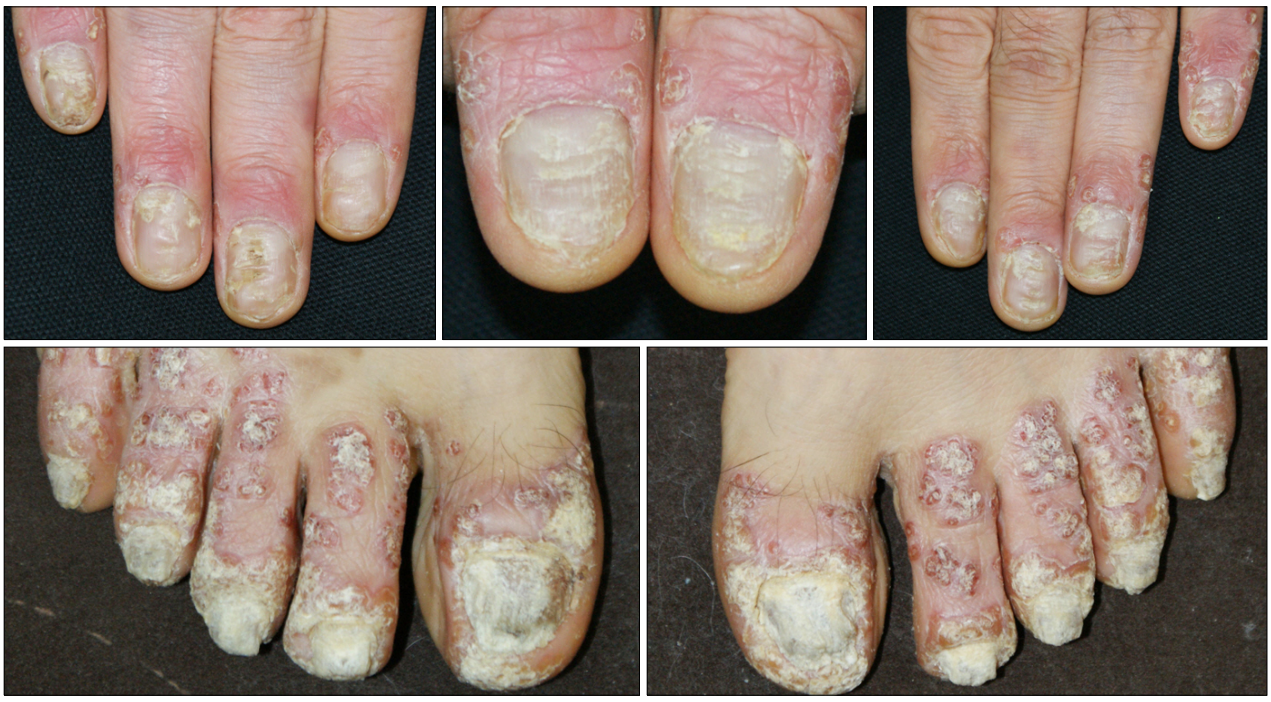

Fig. 1. Severe 20-nail and nail fold psoriasis before ustekinumab treatment. Fingernails showing relatively less change than the toenails because of the effect of repetitive triamcinolone intralesional injections. Proximal nail fold atrophy caused by steroid injection can be seen.

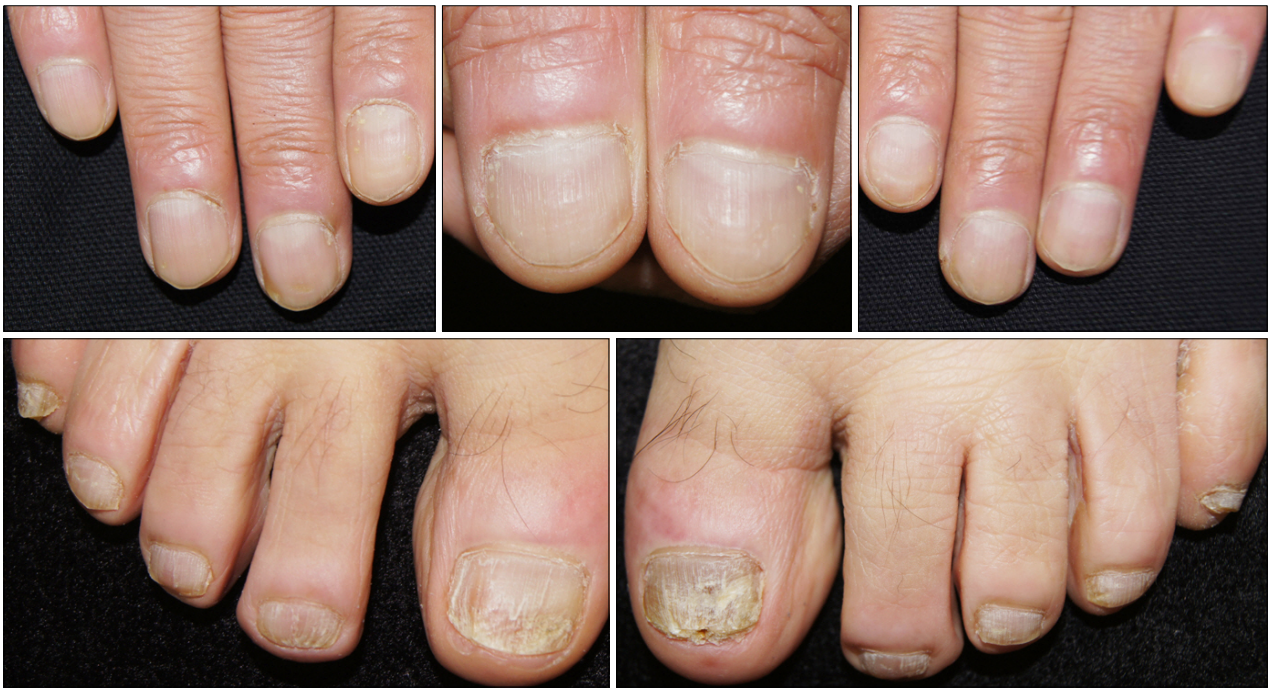

Fig. 2. Improvement in nail psoriasis after the fourth injection of ustekinumab. There is complete remission of fingernail psoriasis. Both large toenails show subungual hyperkeratosis, which was completely resolved after treatment.

nificant effect on NAPSI scores by week 10, with sustained improvement through week 50[3]. The mean improvement in NAPSI scores from baseline to week 50 was 78%～80%. Adalimumab achieved an average reduction of 57% in NAPSI scores at week 12, with sustained improvement to week 20, in a study of 164 patients with nail psoriasis and concurrent PsA[11]. In another study of 562 patients with nail psoriasis, the mean NAPSI score improvement was 51% after 54 weeks of therapy with etanercept[12].

Ustekinumab is another biologic drug used for psoriasis by blocking the p40 subunit, which is shared by interleukins (IL)-12/23[13]. Ustekinumab also has high efficacy and safety for the treatment of nail psoriasis[14]. In clinical trials, 45 mg of ustekinumab for nail psoriasis improved mean NAPSI scores by 46.5% within 24 weeks[4]. However, nail fold psoriasis has not been discussed in any trials of biologics. Nail fold psoriasis is rarely reported because the nail fold has not been included in the standardized NAPSI evaluation. In most cases of nail fold psoriasis, the lesion mainly shows mild erythema, with or without thin scales, and does not interest clinicians and patients. In the present case, the nail fold skin showed severe erythema with silvery-white, scaly psoriatic papules.

When considering the relationship between nail psoriasis and PsA, the anatomical structure between the nail and the DIP joint is the main source of the relationship between these structures[15]. The nail is anchored to bone via entheses, and causative cytokines affect these structures via the entheses. Nail fold skin lies between the nail and DIP, and the primary effector cytokines such as IL-17 and IL-22 flow from nail to joint, or vice versa. We named this hypothesis the cytokine overflow theory: the overproduction of psoriasis-inducing cytokines that leads to overflow from their origin to nearby tissue. This patient's nail psoriasis was extremely severe, causing almost complete deformation of the nail, thereby inducing nail fold psoriasis, and ultimately PsA of the DIP joint.

His nail fold psoriasis and joint symptoms were improved first by soft-tissue relief, and then nail psoriasis was improved because of slow growth of the nails. This phenomenon therefore occurred because of unique nail unit structure and growing rate rather than cytokine overflow theory.

In conclusion, we present a case of severe nail and nail fold psoriasis, which improved with ustekinumab. Symptoms of PsA were also improved. This case gives us new insight into psoriatic disease development around the nail unit and joint. Ustekinumab could be a new therapeutic option for severe nail psoriasis and PsA.

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