中文題目：案例報告：運用免疫抑制劑 mycophenolic acid 治療周邊動脈阻塞併發之皮膚血管炎引起罕見支甲溝炎副作用

英文題目：Mycophenolic acid induced Onychomadesis in treating Thromboangiitis Obliterans related cutaneous vasculitis

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Case report:

A 34-year-old woman presented at our clinic with unhealed cutaneous ulcers that had persisted for six months on her lower legs bilaterally (Fig. 1). Since adolescence, she had experienced recurrent ulcers on all distal limbs. However, these ulcers usually resolved spontaneously within a month. She did not have medical problems but used to smoke two packs of cigarettes per day since high school. She is an engineer with no history of chemical exposure or illicit drug use. On admission, physical examinations showed normal bilateral palpable dorsalis pedis pulsation and a negative Allen test. Contrast computed tomography revealed a bilateral occlusion of her posterior tibialis arteries with collateral circulation in the lower limbs (Fig. 2). Laboratory evaluations showed normal white cell count, erythrocyte sedimentation rate, and C-reactive protein level, and did not show the presence of autoantibodies. Culture of the unhealed wound revealed no microorganism growth. Histological examination of her unhealed wounds indicated mixed acute and chronic inflammation with granulation tissue formation, and focal neutrophilic infiltration of the vascular wall.

Thromboangiitis obliterans (TAO) complicated with cutaneous vasculitis was diagnosed. She received a silver-containing foam dressing, daily medications with colchicine 0.5 mg, and mycophenolic acid (MPA) 360 mg. Onychomadesis developed bilaterally in proximal finger nails one month after MPA (Fig. 3). Nail lesions went into remission gradually after withdrawing MPA (Fig. 4).

Discussion:

TAO, a nonatherosclerotic segmental occlusive vasculitis involving medium and small vessels, is often noted in young adults and diagnosed based on unhealed cutaneous ulcers on their distal lower limbs, a history of tobacco use, exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus[1-5]. Although cigarette smoking is the most important predisposing factor for TAO, the pathogenesis of TAO remains unclear. Recent cutaneous infection, genetic polymorphism, and endothelial dysfunction have been noted to be key factors in pathogenesis. The histological findings of TAO reveal that T lymphocytes

outnumber B lymphocyte infiltration in the thrombi and intima. Immunoglobulins and complement factors are deposited in a linear manner along the elastic lamina[6]. Smoking cessation is the only definitive therapy for TAO[7].

Mycophenolic acid (MPA), a noncompetitive inhibitor of eukaryotic inosine monophosphate dehydrogenase, interferes with synthesis of RNA in T and B lymphocytes and has been used to prevent allograft rejection after organ transplantation[8-9]. Adverse effects of MPA include vomiting, diarrhea, bone marrow suppression, infectious diseases, neurological problems, carcinogenicity, and teratogenicity[10]. Nonetheless, nail disorder is rarely reported to be an adverse effect of MPA.

Because T and B lymphocytes are involved in the pathogenesis of TAO, and mycophenolate mofetil has been prescribed to cure refractory ulcerative cutaneous polyarteritis nordosa[11], we prescribed MPA in this patient showing characteristics of TAO and refractory cutaneous vasculitis. The formation of nails is a process of proliferation and keratinization[14]. The average rate of normal growth of a nail is 0.1 mm per day[12-13]. The nail plate is formed by keratinocytes of the stratum basale and becomes a hardened cell filled with protein, comprising a structurally and functionally distinct keratin, and containing a surface layer such as stratum corneum. The basal cells in the nail root form the nail matrix, and proliferation of the stratum basale makes the nail elongate continuously. Onychomadesis appears as a whole thickness sulcus that separates the nail into two parts and is caused by a temporary nail matrix arrest (NMA).

Borowczyk and colleagues showed that MPA was able to influence the proliferation and differentiation of keratinocytes through the interference of *de novo* purine synthesis[15]. □-Glucuronidase in human dermis contributes to the activation of MPA, which may enhance MPA-mediated interference of *de novo* purine synthesis[11]. The suppression may lead to temporary NMA, which may cause onychomadesis. Thus, we consider that the onychomadesis in the present case was associated with the use of MPA.

Drug-related onychomadesis should be considered when proximal nail lesions develop within two weeks of new medication[12-13]. In the present case, two weeks' exposure to MPA was followed by the onset of nail lesions. Therefore, the progression of onychomadesis corresponded with the nail growth rate and MPA exposure time. To our knowledge, this is the first report of an MPA-related onychomadesis. Physicians should be aware of the cutaneous adverse effects of MPA and adjust medications accordingly.

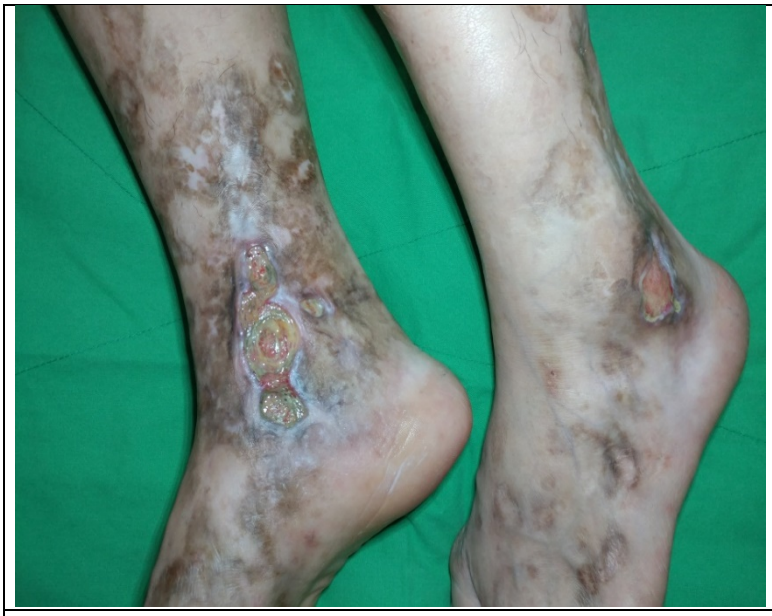

Fig. 1

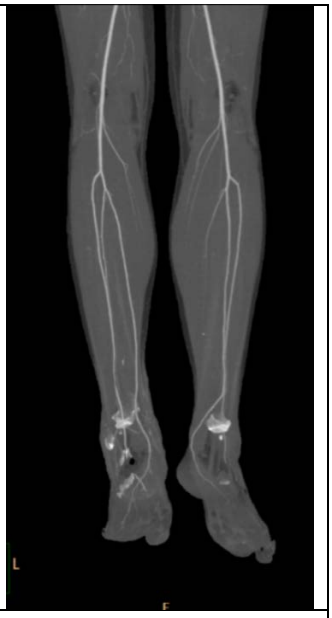

Fig. 2

Fig. 3

Fig. 4