SARS-CoV-2 protein on vascular endothelial cells were observed (*figure 1N, P, Q*). The immune response to infection can lead to activation of Langerhans cells, resulting in vasodilation [6], consistent with finger purpura. We speculate that COVID-19-associated abnormal coagulation causes livedo, and that accumulation of microthrombus at these sites impairs skin circulation, resulting in necrosis of keratinocytes and sweat gland cells.

Our case showed positivity for C3d, SARS-CoV-2 envelope and spike protein, and MXA protein (*figure 1O*), and this is consistent with both COVID-19-induced thrombogenic vasculopathy and COVID-19-induced increased type I interferon (IFN) response [7]. Recently, biopsies from livedo/retiform purpura in severe COVID-19 patients were shown to exhibit pauci-inflammatory vascular thrombosis without any MXA, and blood vessels exhibited extensive complement deposition with SARS-CoV-2 protein [8]. Furthermore, it has reported that at least 3.5% of patients with life-threatening COVID-19 pneumonia had genetic defects at eight of the 13 candidate loci involved in Toll-like receptor 3- and interferon regulatory factor 7-dependent induction and amplification of type I IFNs [8]. Thus, cutaneous disease in patients with severe COVID-19 may be linked to a decreased type I IFN response. However, there are some studies reporting a high type I IFN response in severe COVID-19 [9, 10]. Therefore, it remains to be determined whether MXA expression correlates with disease severity.

Although the patient's general condition did not improve, the livedo and finger purpura finally disappeared after three weeks; cutaneous manifestations, therefore, did not correlate with COVID-19 disease activity. Such a correlation remains to be determined, and a large number of Japanese cases would be required to investigate this further. ■

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Linear porokeratosis with severe itch accompanied by lesional upregulation of interleukin 31, thymic stromal lymphopoietin, and periostin

Porokeratoses are heterogeneous keratotic disorders encompassing at least six subtypes: porokeratosis of Mibelli; punctate porokeratosis; porokeratosis palmaris et plantaris disseminata; disseminated superficial porokeratosis (DSP); disseminated superficial actinic porokeratosis; and linear porokeratosis (LP). Itch is a rare symptom in porokeratosis, but sometimes occurs in DSP once inflammation develops against DSP lesions; this condition is termed "eruptive pruritic papular porokeratosis" [1]. In addition, patients with hypertrophic lesions occasionally complain of itch [2]. We report a case of LP with hypertrophic lesions and severe itch that was accompanied by local upregulation of thymic stromal lymphopoietin (TSLP), periostin, and interleukin (IL)-31.

A 32-year-old Japanese man presented with a history of pruritic keratotic lesions on the left posterior upper limb since childhood. His medical history included well-controlled atopic dermatitis, but no contributory familial history was elicited. Physical examination revealed well-demarcated, irregularly shaped, hyperkeratotic white-reddish plaques with a raised peripheral ridge and slightly atrophic centre. These lesions were arranged along Blaschko's lines (*figure 1A, B*). Numerical Rating Scale (NRS) score for itch was 9 out of 10. Histological examination showed psoriasiform epidermal hyperplasia accompanied by vertical columns of tightly packed parakeratotic cells within a keratin-filled epidermal invagination, known as "cornoid lamella" (*figure 1C*). Perivascular lymphocytic infiltration in the upper dermis was also apparent, but neither eosinophils nor lichenoid tissue reaction was noted. LP was diagnosed. Administration of oral antihistamines, topical corticosteroid, and 10% salicylic acid for one month did not improve symptoms. Conversely, topical maxacalcitol, a vitamin D3 analogue (VDA), dramatically improved pruritus within two months (NRS score of 1) with ameliorated inflammation, redness, and excoriation (*figure 1D*).

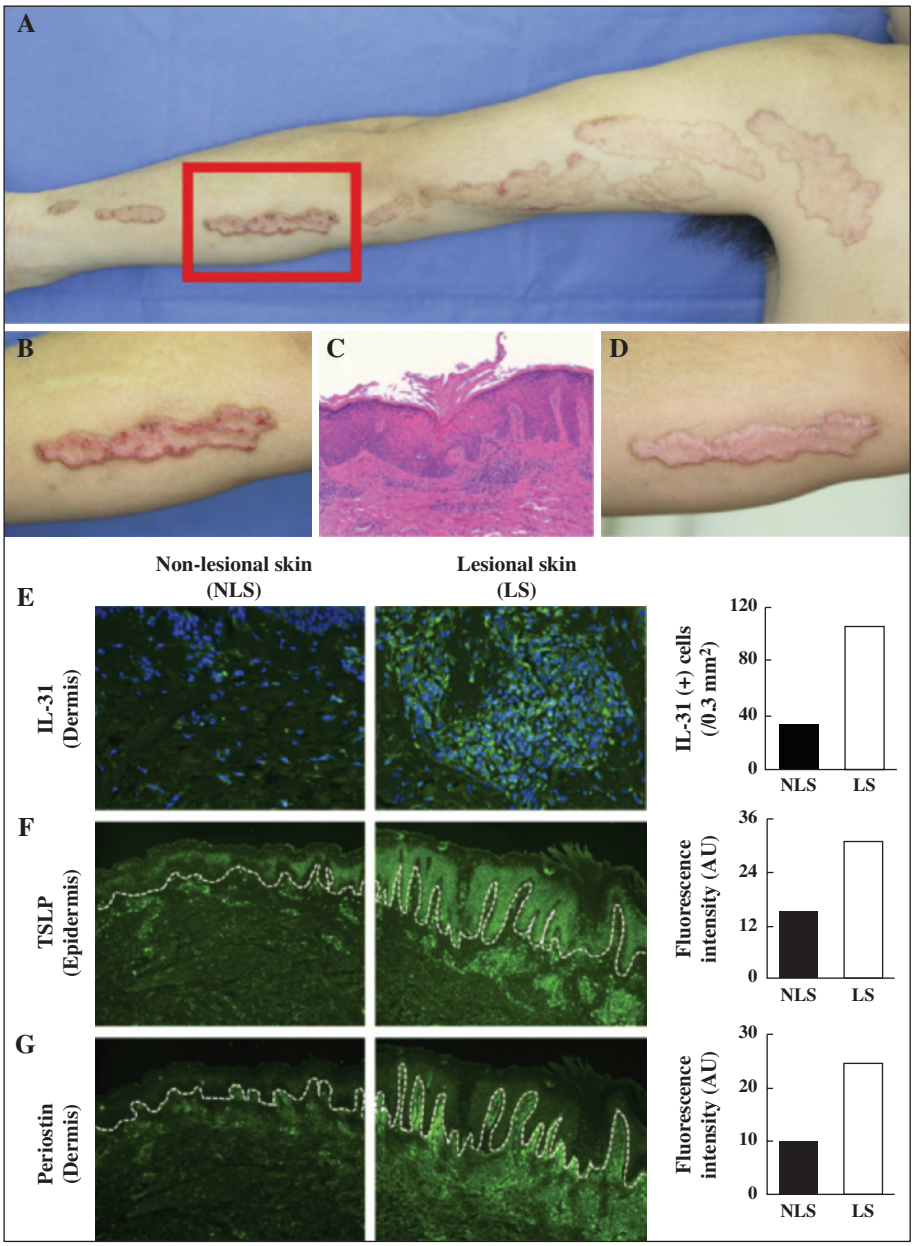

Figure 1. Clinical and histopathological features and immunofluorescence. **A**, **B**) Initial presentation showing irregularly shaped hyperkeratotic plaques arranged along the lines of Blaschko (**A**); the red box corresponds to (**B**). Each lesion has a raised peripheral ridge and slightly atrophic centre. **C**) Histopathological findings showing soriasiform epidermal hyperplasia with cornoid lamella and lymphocytic infiltration in the upper dermis (haematoxylin and eosin; original magnification: ×4). **D**) Skin lesions improved after two months of topical maxacalcitol. **E**-**G**) Immunofluorescence showing dermal IL-31-expressing cells (green indicates IL-31 and blue indicates nuclei; DAPI staining) (**E**), epidermal expression of TSLP (green) (**F**), and dermal deposition of periostin (green) (**G**). Expression of TSLP and periostin is measured as fluorescence intensity in arbitrary units (AU), normalized by fluorescence area and background using Image J software (NIH, Bethesda, MD, USA). Dotted lines indicate the dermo-epidermal junction.

Itch involves various mediators that include not only histamines, but also non-histaminergic mediators such as IL-31, periostin, and TSLP [3, 4]. We conducted immunofluorescence staining to investigate the expression of itch mediators in the present case. We detected a significant number of IL-31-positive cells in the lesional skin compared with non-lesional skin (*figure 1E*). Enhanced epidermal expression of TSLP and dermal deposition of periostin were also noted (*figure 1F, G*). In contrast, the number of mast cells, as major cellular sources of histamine in the skin, was not increased in the lesion (data not shown). Given these findings and the fact that antihistamines did not improve symptoms, non-histaminergic itch appears to have been predominant in the present case. TSLP is an epithelium-derived master regulator of Th2 immunity [5]. Periostin is a Th2-related protein that amplifies Th2 inflammation [4]. IL-31 is a pruritogenic cytokine produced preferentially under Th2-dominant circumstances [6]. Taken

together, proliferated abnormal keratinocytes in lesional skin presumably secrete a significant amount of TSLP, triggered by as-yet unknown stimuli, in turn, promoting Th2 immune responses. This would result in upregulation of periostin and IL-31, which could have been major contributors to the intractable itch in this case. Factors that might have initially triggered the allergic inflammation remain to be determined, although contribution of atopic predisposition needs to be considered. In addition, this hypothesis may not be generalizable to other cases of itchy porokeratosis. We are not aware of any prior reports discussing Th2 immunity and itch mechanisms of porokeratosis.

VDAs can modulate epidermal proliferation and differentiation in addition to inflammation [7]. Based on the assumption that proliferation of abnormal keratinocytes is an important aspect of pathogenesis of severe itch, topical maxacalcitol in our case possibly exerted anti-pruritic effects by modulating the functions of epidermal cells. This can be supported by the fact that topical VDAs are also capable of improving prurigo nodularis, another hyperkeratotic dermatosis associated with severe itch [7]. Topical VDAs may warrant consideration as a first-line therapeutic option for porokeratosis with severe itch.

Recent findings have reported that most cases of porokeratosis have heterozygous germline mutations in mevalonate biosynthesis pathway genes. In addition, somatic second-hit genetic changes in the embryonic period can be involved in the pathogenesis of LP [8, 9]. In this regard, it may be rational to rephrase the term "linear porokeratosis" with "superimposed linear porokeratosis" considering the concept of superimposed segmental manifestation of polygenic skin disorders proposed by Dr. Happle [10]. Lastly, we were unable to perform the genetic analyses, and the patient needs to be carefully followed in order to see whether late-onset sporadic disseminated porokeratotic lesions develop or not. ■

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A case of cutaneous colonization of *Bipolaris spicifera* associated with radiation dermatitis

A 59-year-old man noted a cutaneous, brownish area on his right elbow. The patient had been previously found to have an abnormal shunt between the left pulmonary artery and the systemic circulation, which could cause abnormal blood flow and rupture of vessels or cerebral infarction. Embolization of the shunt was therefore performed at three months and one month before the onset of the change in skin. He was a farmer, but had never injured his right elbow. The cutaneous lesion had been expanding gradually, and about eight months later, he was referred to our department. At his first visit to our department, pigmentation was found on his right elbow (*figure 1A*). The skin biopsy showed post interface dermatitis-like change (*figure 1B*). Additional examinations were considered, but he visited another local clinic instead. In the clinic, he was given some antibiotics and topical steroid treatments with some oral prednisolone, and his cutaneous lesion showed repeated exacerbation and remission. Two years later, he was again referred to our department, showing dark erythema on his right elbow with an ulcer and necrotic tissue (*figure 1C*). The biopsy showed a cutaneous ulcer with dermal fibrosis containing puffed star-like fibroblasts (*figure 1D, E*), consistent with radiation dermatitis due to the former embolization therapy. In fact, his right elbow was the part of his body that was closest to the radiation source. The cutaneous lesion seemed to be intractable, and it was decided to excise the lesion and cover it with a pedicled flap. After the operation, the flap showed successful adhesion.

Histopathology of the excised specimen showed fungal material, septate, and branched fungal hyphae in the dermis of the ulcer (*figure 1F*), positive on periodic acid-Schiff (*figure 1G*) and Grocott staining (*figure 1H*). Sequence analysis based on polymerase chain reaction using a paraffin specimen from the excised lesion [1] showed that the internal transcribed spacer region, with an amplified size of 531 bp, matched that of *Bipolaris spicifera*, Centraalbureau voor Schimmelcultures (CBS), Baarn, The Netherlands (CBS 315.64, 100%).