Induced Lentiginosis With Use of Topical Calcineurin Inhibitors

Acquired lentiginosis at sites of inflammatory skin disease may occur at the sites where topical tacrolimus or pimecrolimus was applied.\(^1\)

Methods. Patients who developed acquired lentiginosis at sites of long-term use of topical tacrolimus ointment or pimecrolimus cream were identified by retrospective chart review. Age at onset of lentigines, duration of exposure to topical tacrolimus and pimecrolimus, and time to regression were recorded. Biopsies were performed in 2 of 12 patients, and specimens showed increased numbers of epidermal melanocytes and mild pigment incontinence consistent with the diagnosis of lentigo. Approval by the institutional review board was waived.

Results. The anatomic sites involved in our 12 patients included the relatively sun-protected areas of the antecubital fossa, dorsal hands, popliteal fossa, and wrists with chronic dermatitis (Figure 1 and Figure 2). Patients with atopic dermatitis (8 of 12), psoriasis (2 of 12), Netherton syndrome (1 of 12), and perioral dermatitis (1 of

12) used topical pimecrolimus and tacrolimus from 1 month to 7 years with infrequent breaks (Table).

Biopsies were performed in 2 of 12 patients, and specimens showed increased numbers of epidermal melanocytes and mild pigment incontinence consistent with the diagnosis of lentigo. No evidence of background actinic damage was seen on biopsy specimens. After treatment with topical medications was discontinued, lentigines at least partially regressed in 4 of 12 patients but were still present in 3 patients even 3 years following discontinuation.

Comment. Tacrolimus is a macroclide lactone antibiotic that inhibits the phosphatase activity of calcineurin by binding to an intracellular receptor found in T lymphocytes called FK binding protein (FKBP). It has been reported that tacrolimus promotes cell migration and tyrosinase activation of human melanocytes. Pimecrolimus is a 33-epichloro derivative of the macrolactam ascomycin. It also inhibits the production of cytokines in T cells, but knowledge of its effects on nonimmune cells is limited. Taken together, these facts may explain why topical calcineurin inhibitors are effective in treating vitiligo and may also account for the phenomenon of acquired lentiginosis we describe herein.

Hickey et al1 describe 3 patients with atopic dermatitis who developed lentiginosis following the use of topical tacrolimus. These patients were treated for a minimum of 9 months. Histologic findings were consistent with simple lentigines. As with our patients, lentigines persisted for at least a year after discontinuation of treatment with the topical medication.

Lentigines typically occur on sun-exposed areas and can be markers of UV radiation damage. While systemic immunosuppressants can cause increased melanocyte activity, there are no reports of acquired lentigines in patients taking oral tacrolimus. Our observations suggest that tacrolimus and pimecrolimus may induce lentigines. However, we have observed an additional 3 patients who did not recall use of either tacrolimus or pimecrolimus and developed lentigines in areas of chronic eczematous dermatitis. These patients were treated with long-term topical steroids for at least 5 years. This suggests that chronic inflammation may predispose to lentigines, but the use of tacrolimus or pimecrolimus topically might make the appearance of lentigines more likely. We propose the term ILIAD phenomenon (induction of lentiginosis in assorted dermatoses) to describe acquired lentiginosis among patients treated with topical calcineurin inhibitors.

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4. Lan CC, Kao YH, Huang SM, Yu HS, Chen GS. FK506 independently upregu-


VIGNETTES

Complete Clearance of Reticular Erythematous Mucinosis With Quinacrine Monotherapy

Reticular erythematous mucinosis (REM) syndrome is a rare skin disease that predominantly affects the chest area of middle-aged women. The clinical and histopathologic features of REM syndrome suggest a close association with cutaneous lupus erythematosus (CLE). Antimalarial drugs are the first-line systemic treatment for CLE, and many patients with REM also show improvement or clearing of their skin lesions after treatment with antimalarial agents. However, in a small proportion of patients, conventional antimalarial agents such as chloroquine or hydroxychloroquine might be unsuitable, for example in patients with certain eye diseases. We herein report a case of REM syndrome with a contraindication for conventional antimalarial agents that completely cleared with quinacrine hydrochloride monotherapy.

Report of a Case. A 42-year-old woman with a 10-month history of a symmetrical reticular erythema on the central chest area was referred to our institution (Figure, A). Previous treatment with topical corticosteroids for a total of 8 weeks had been unsuccessful. A punch biopsy specimen revealed dense mid-dermal, perivascular, lymphocytic infiltrates and focal areas of dermal mucin deposition, features consistent with REM syndrome. Her other medical background was unremarkable, except for a history of macular degeneration. Ophthalmologic examination including funduscopy showed signs of central geographic retinal atrophy suggestive for dry macular degeneration. Facing this contraindication for conventional antimalarial agents, we initiated treatment with medium-dose UV-A1 phototherapy at 60 J/cm2 for a total of 40 irradiations, resulting only in a minor improvement of skin lesions. After consideration of further treatment options, we decided to start monotherapy with quinacrine hydrochloride at a dose of 100 mg/d. Ten weeks after the initiation of quinacrine treatment, all skin lesions had completely resolved (Figure, B).

Comment. As with CLE, most patients with REM usually respond well to conventional antimalarial agents. It has been demonstrated that in patients with CLE who respond incompletely to treatment, adding quinacrine to either the chloroquine or hydroxychloroquine regimen might significantly improve residual skin lesions.

To our knowledge, few reports exist on quinacrine monotherapy in CLE, and no data are available on its use in REM syndrome as a single agent. In contrast to chloroquine and hydroxychloroquine, quinacrine seems to have no ophthalmologic adverse effects such as retinopathy or corneal deposits. Therefore, as in the present case, quinacrine monotherapy might be considered a therapeutic alternative for patients with contraindications for conventional antimalarial agents. Among the adverse events of quinacrine, gastrointestinal complaints, headache, and yellow discoloration of the skin are most frequent, but these quickly resolve after the quinacrine treatment is complete.

Interestingly, a complete response to UV-A1 phototherapy in REM syndrome was reported in a patient who had refused treatment with chloroquine. In contrast, our patient experienced only minor improvement following UV-A1 phototherapy. This discrepancy of response might be explained by the different doses of UV-A1 phototherapy that were used (high-dose vs medium-dose UV-A1). In conclusion, physicians should consider using quinacrine in REM cases with contraindications for conventional antimalarial agents before initiating other experimental treatments.

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Figure. Clinical images of our 42-year-old female patient. A, Reticular erythematous mucinosis at first presentation in our department; symmetrical reticular erythema is present on the central chest area. B, After 3 months of quinacrine hydrochloride monotherapy, all former skin lesions have completely cleared.