

# Lichen Amyloidosis Associated With Atopic Dermatitis

## Clinical Resolution With Cyclosporine

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

### REPORT OF A CASE

A 64-year-old Asian man with a history of refractory atopic dermatitis (AD) presented with severe generalized pruritus. Results of examination revealed erythematous, lichenified, crusted plaques and papules, mainly on the chest, abdomen, back, and extremities. In addition, numerous firm, skin-colored papules were found on the anterior shins (**Figure 1**). The patient stated that he first noticed these lesions approximately 2 years ago, after an extremely pruritic flare of his AD. They had not remitted since they first appeared. The patient reported no other medical problems and denied any family history of skin disease.

The clinical differential diagnosis of the leg lesions included lichen amyloidosis (LA), lichen simplex chronicus, and lichen planus. A punch biopsy specimen of a papule was taken from the right leg for routine microscopic examination. Results of histological examination showed hyperkeratosis, acanthosis, pigment incontinence, and amorphous material in the papillary dermis consistent with amyloid (**Figure 2**). A histological diagnosis of LA was given.



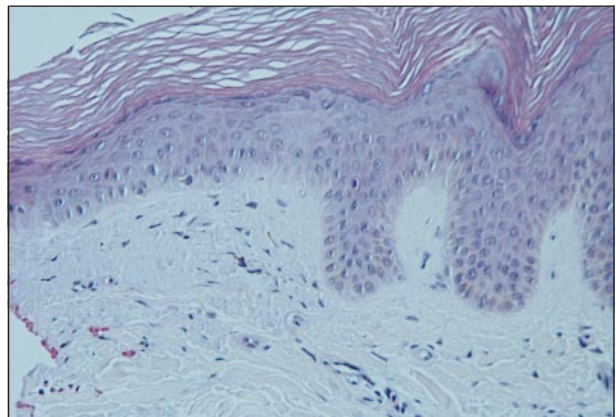
**Figure 1.** Baseline appearance of the right leg showing multiple papules in a cobblestonelike pattern.

### THERAPEUTIC CHALLENGE

Several treatment modalities have been suggested for the management of LA, but none has been uniformly effective. New and innovative treatment options are needed.

### SOLUTION

After a discussion of the possible adverse effects, the patient agreed to a trial of oral cyclosporine, 300 mg/d (approximately 4 mg/kg), for his refractory AD. He noted a decrease in pruritus approximately 2 weeks after beginning this therapy. One month later, the AD had remitted completely and the number and size of the LA lesions was dramatically reduced. The patient experienced a mild increase in blood pressure during that time, but had no other problems. During a 7-month course, the cyclosporine dose was tapered to 100 mg/d, with normalization of his blood pressure and no recurrence of the skin eruption. Results of renal function studies remained normal. Nine months after beginning cyclosporine therapy, his AD remained in remission. The LA papules had flattened completely and remained asymptomatic (**Figure 3**).



**Figure 2.** Baseline biopsy specimen showing dermal papillary deposits of amorphous eosinophilic material, characteristic of amyloid (hematoxylin-eosin, original magnification  $\times 200$ ).



**Figure 3.** Right anterior leg after 5 months of cyclosporine therapy. The papules have flattened completely.

Results of a follow-up punch biopsy of the right shin demonstrated improvement in acanthosis and hyperkeratosis, with persistence of amyloid deposits in the papillary dermis (**Figure 4**). After 12 months of therapy, the complete clinical remission continues at a dose of 100 mg/d.

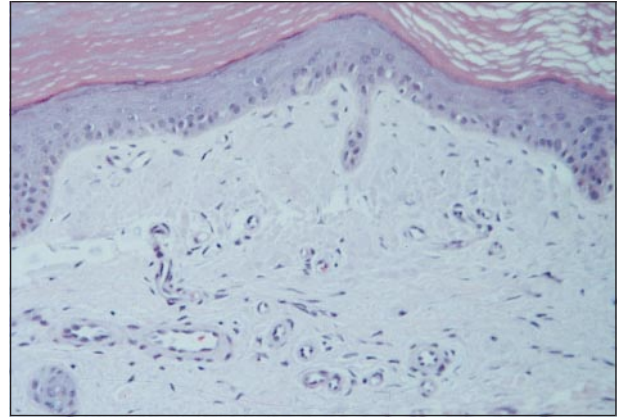
#### COMMENT

Lichen amyloidosis is a chronic pruritic skin disorder characterized by amyloid deposition in the skin without evidence of visceral involvement. First described by Gutmann in 1928,<sup>1</sup> it is seen most frequently in Southeast Asia,<sup>2</sup> China,<sup>3</sup> and South America.<sup>4</sup> Clinically, LA is characterized by discrete, intensely pruritic, hyperkeratotic papules that may coalesce into plaques. Lesions are found mainly on the anterior legs, but can occur on the back, forearms, and thighs. Results of microscopic examination show amyloid deposition in the papillary dermis and hyperkeratosis and acanthosis of the epidermis.

Lichen amyloidosis has been reported in association with several skin disorders, including AD<sup>5,6</sup> (as seen in our patient), lichen planus,<sup>7</sup> and mycosis fungoides.<sup>8</sup> Genetic<sup>9</sup> and viral<sup>10</sup> factors have been identified as possible causes, as has chronic friction.<sup>11</sup> However, the precise pathogenesis of LA is yet to be determined. Several immunohistochemical studies have demonstrated reactivity between anti-keratin antibody and cutaneous amyloid deposits in LA.<sup>12,13</sup> Amyloid deposits have also been shown to contain disulfide bonds, which are present in keratin.<sup>14</sup> Based on this finding and on those of ultrastructural studies, cutaneous amyloid deposits are thought to be derived from degenerated keratin peptides of apoptotic keratinocytes transformed into amyloid fibrils by dermal macrophages and fibroblasts.<sup>14,15</sup> A working hypothesis is that the epidermal trauma induced by long-term scratching and rubbing seen in associated chronic diseases results in keratinocyte degradation and formation of amyloid.<sup>11</sup>

Current treatments of LA are unsatisfactory, with high relapse rates, adverse effects, and treatment failures. Therapeutic options include topical<sup>16</sup> and intralesional<sup>3</sup> corticosteroids, dermabrasion,<sup>17</sup> scalpel scraping,<sup>18</sup> tretinoin,<sup>19</sup> calcipotriene,<sup>16</sup> topical dimethyl sulfoxide,<sup>20</sup> UV-B therapy,<sup>21</sup> and cyclophosphamide.<sup>22</sup>

Cyclosporine is a potent immunomodulator that is isolated from the fungus *Tolypocladium inflatum gams*. It has been used successfully for the treatment of psoriasis and has recently become a treatment alternative for other inflammatory dermatoses such as atopic dermati-



**Figure 4.** Histological findings of a biopsy specimen taken after 2 months of cyclosporine therapy, showing a reduction in hyperkeratosis and acanthosis, with persistence of amyloid deposits in the papillary dermis (hematoxylin-eosin, original magnification  $\times 200$ ).

tis,<sup>23</sup> lichen planus, pyoderma gangrenosum, and epidermolysis bullosa acquisita.<sup>24</sup> Cyclosporine affects the intracellular signal transduction pathways of cells, mainly of the lymphoid lineage. Through these pathways, cyclosporine modulates the production of key inflammatory proteins, thereby suppressing immunological activity.<sup>24</sup> Cyclosporine may also suppress the production of cytokines that cause pruritus.<sup>23</sup> Persistent scratching probably plays a major role in the etiology of cutaneous amyloidosis.<sup>11</sup> Treatment of chronic AD with cyclosporine may then indirectly improve LA clinically. Cyclosporine may also act directly to attenuate the pruritic symptoms of LA and/or modulate unknown immune mediators contributing to the formation of amyloid fibrils.

The 2 most common and serious adverse effects encountered when using low-dose cyclosporine are nephrotoxicity and hypertension. These are dose dependent and reversible with therapy discontinuation. Hypertension also can be controlled using calcium channel blockers. Other common adverse effects of low-dose cyclosporine include electrolyte disturbances (hyperkalemia, hypomagnesemia, and hyperuricemia), neurologic effects (hand tremors, paresthesias, and headache), gastrointestinal tract problems (nausea, vomiting, diarrhea, and abdominal discomfort), dental disease (gingival hyperplasia), cardiovascular problems (hyperlipidemia), liver disease (hyperbilirubinemia), hematologic changes (anemia and leukopenia), cutaneous effects (hypertrichosis, acne, and folliculitis), and severe fatigue.<sup>25</sup> At higher doses, infection and increased risk for neoplasms<sup>26</sup> are potential problems.

Our patient had refractory AD that responded well to cyclosporine. In addition, the LA on his anterior legs resolved clinically. To our knowledge, the use of oral cyclosporine in the treatment of LA has never before been published. Further experience is needed to define clearly the role of cyclosporine and its mechanism of action in the treatment of LA.

Accepted for publication January 1, 2001.

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