

Lichen Planopilaris Treated With a Peroxisome Proliferator–Activated Receptor γ Agonist

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

Primary cicatricial alopecias (PCAs), rare disorders that lead to permanent hair loss, have been poorly understood and are difficult to treat. Lichen planopilaris (LPP) is a prototypical PCA; patients often present with sudden onset of hair loss and clinically significant symptoms of itching, burning, and pain of the scalp. Examination reveals patchy alopecia or a more diffuse thinning of the scalp with characteristic perifollicular erythema and perifollicular scale at the margins of the areas of alopecia. Treatment typically includes use of anti-inflammatory medications; although symptoms may improve, hair loss is often progressive.

REPORT OF A CASE

The patient, a 47-year-old white man, had sudden onset of scalp irritation, redness, and itching with rapid hair loss. Although he had long-standing male-pattern hair loss with thinning hair on the top of the scalp, he observed new hair loss involving the entire scalp. The patient had no other significant medical problems; he was taking finasteride, 1 mg/d orally. On examination, he had frontal and vertex pattern hair loss with miniaturization. Along the temporal and occipital rim he had scattered areas of patchy hair loss 1 to 2 cm in diameter, with absence of follicular markings (**Figure 1A**). At the active border of the patches, there was perifollicular scaling and erythema. A pull test was positive for anagen hair. A scalp biopsy specimen showed decreased numbers of anagen follicles, a dense perifollicular lymphocytic infiltrate at the level of the isthmus, and decreased sebaceous glands (**Figure 2A**), confirming a histologic diagnosis of lymphocytic PCA, and consistent with the clinical findings of LPP. At the initial evaluation, the severity of his disease was scored using a previously described cicatricial alopecia flowchart that records 3 main end points at each patient visit: severity of symptoms; clinical disease activity, including the anagen positive pull test; and progression of hair loss.¹ Treatment regimens over the subsequent 1.5 years included oral prednisone, hydroxychloroquine sulfate, 200 mg twice daily, oral antibiotics (doxycycline hyclate, 100 mg twice daily), my-

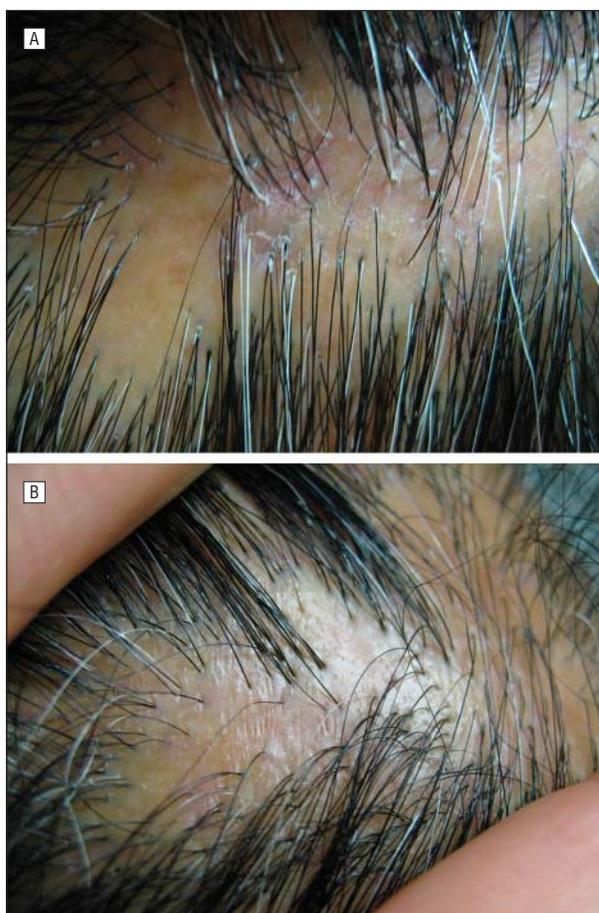


Figure 1. Patient with patchy areas of alopecia throughout the temporal and occipital rim. A, The scalp showed loss of follicular markings; the residual hair at the margins showed perifollicular scaling and erythema. B, Photograph of the scalp after treatment with pioglitazone hydrochloride showing persistent patchy alopecia with loss of follicular markings but no evidence of inflammation at the border.

cophenolate mofetil hydrochloride, 1 g twice daily, intralesional corticosteroid injections, high-potency topical corticosteroid solution and shampoo, topical tacrolimus, and antiseborrheic shampoo (ketoconazole). The patient declined a trial of oral cyclosporine because of



Figure 2. Hematoxylin-eosin–stained scalp biopsy specimens from the active border. A, Scalp biopsy specimen taken prior to any treatment (original magnification $\times 20$). There is a dense perifollicular lymphocytic infiltrate at the level of the isthmus, decreased follicular density, and diminished sebaceous glands. B, Scalp biopsy specimen taken after 18 months of various anti-inflammatory treatments (original magnification $\times 20$). There is a persistently dense lymphocytic infiltrate at the level of the isthmus with fibrotic tracts and loss of sebaceous glands. C, Scalp biopsy specimen taken after 6 months of treatment with oral pioglitazone hydrochloride (original magnification $\times 40$). There is minimal superficial perivascular inflammatory infiltrate, but no perifollicular inflammation was noted.

concerns of adverse effects. Although he experienced some improvement in clinical symptoms and clinical signs, his scalp itching persisted, as did his perifollicular scaling and erythema. A scalp biopsy specimen taken after treatment showed a decreased but persistent inflammatory infiltrate (Figure 2B).

THERAPEUTIC CHALLENGE

Treatment recommendations and strategies for lymphocytic cicatricial alopecias include immunosuppressive and anti-inflammatory regimens. The goal of treatment is to alleviate symptoms and signs and arrest the progression of hair loss; hair regrowth is not possible after destruction of the follicles has occurred. In LPP, as in other lymphocytic PCAs, the choice of treatment is based on the extent of symptoms, clinical activity, and progression of hair loss.^{2,3} First-line treatment for active disease includes topical and intralesional corticosteroids, oral antibiotics, and hydroxychloroquine sulfate. For more symptomatic, active, and rapidly advancing disease, or disease that is resistant to treatment, medications such as oral prednisone, mycophenolate mofetil, and cyclosporine have been advocated.^{4,5}

The patient had ongoing disease activity despite a trial of multiple medications aimed at decreasing or suppressing his scalp inflammation. The therapeutic challenge was to find a treatment that was effective in controlling or halting the patient's symptoms, inflammation, and the progression of hair loss with an acceptable adverse-effect profile.

SOLUTION

Although PCAs have traditionally been considered “inflammatory” scalp disorders that lead to irreversible destruction of the regenerative capacity of the hair follicle, the target or the trigger of this inflammation has been unclear. A recent study⁶ of LPP suggests that the initial trigger of inflammation in LPP is abnormal functioning of the peroxisome proliferator–activated receptor γ (PPAR- γ), which then leads to aberrant lipid metabolism in the sebaceous gland, a toxic build-up of lipids, and a subsequent inflammatory response.

Accordingly, the patient was prescribed an oral PPAR- γ agonist, pioglitazone hydrochloride, 15 mg/d orally; he con-

tinued to use his antiseborrheic shampoo. He tolerated the oral medication without adverse effects and reported almost no scalp itching in the first month of treatment. A follow-up examination after 2 months revealed a decrease in the patient's recorded treatment outcomes of symptoms and clinical examination. A scalp biopsy performed after 6 months of therapy (Figure 2C) showed a dramatic decrease in the inflammatory infiltrate. The patient continued taking oral pioglitazone for 8 months, after which he stopped all treatment. To date, 1 year later, he remains symptom-free and without evidence of inflammation or further hair loss on examination (Figure 1B).

COMMENT

Primary cicatricial alopecias are rare disorders that are poorly understood, difficult to treat, and lead to permanent hair loss.⁷ The various types of cicatricial alopecias are provisionally classified based on the predominant cellular infiltrate in active disease (lymphocytic, neutrophilic, mixed).⁸ Lichen planopilaris is a prototypic lymphocytic cicatricial alopecia, with patients often presenting with sudden-onset hair loss and clinically significant symptoms of itching, burning, and pain of the scalp.

We have performed gene expression profiling studies that have shown that the expression of genes required for lipid metabolism and peroxisome biogenesis are decreased in LPP.⁶ Specifically, the expression of PPAR- γ , a transcription factor that regulates both inflammatory and lipid metabolic genes, was dramatically downregulated in LPP.⁶

Peroxisome proliferator–activated receptor γ belongs to the nuclear receptor superfamily and initiates gene transcription by forming a heterodimer with the retinoid receptor RXR. Targeted deletion of PPAR- γ in the follicular stem cells in mice causes a skin and hair phenotype closely resembling scarring alopecia.⁶ In addition, targeted deletion of maternal hematopoietic PPAR- γ in mice results in transient alopecia in the nursing neonates.⁹ These data support the concept that PPAR- γ is essential for healthy pilosebaceous units. Thus, a new model for the pathogenesis of cicatricial alopecia has emerged in which a loss of PPAR- γ function leads to decreased peroxisome biogenesis and lipid homeostasis, causing tissue damage (lipotoxic effects) of the pilosebaceous unit. This tissue damage then triggers

chemokine and cytokine expression in the form of leukotrienes and prostaglandins that recruit lymphocytes and macrophages and activate a lipid-mediated programmed cell death (lipoapoptosis), contributing to permanent hair loss. One may speculate that a combination of genetic factors (such as peroxisomal polymorphisms) or environmental triggers (toxins) may lead to this localized and acquired PPAR- γ dysfunction. Based on these new data, it was proposed that PPAR- γ agonist therapy represents a new strategy in the treatment of cicatricial alopecias.⁶

Thiazolidinediones or glitazones are medications widely used for the treatment of type 2 diabetes mellitus (DM) and were originally identified as regulators of adipogenesis and glucose homeostasis. They exert their action by increasing the activity of the nuclear receptor PPAR- γ . Thiazolidinediones have been shown to have anti-inflammatory, antiproliferative, and immunomodulatory effects, including downregulation of proinflammatory nuclear transcription factors (nuclear factor- κ B, nuclear factor of activated T-lymphocytes), proteolytic enzymes (matrix metalloproteinase-9), and inflammatory interleukins (interleukin 1 β [IL-1 β], IL-2, and IL-6) and other inflammatory molecules (TNF).^{10,11} Because thiazolidinediones can affect signaling pathways involved in lipid homeostasis in sebocytes, regulation of the epidermal barrier, and inflammatory pathways, their use has been advocated in various inflammatory skin disorders, including atopic dermatitis, psoriasis, and acne.¹²

In this patient, a number of anti-inflammatory medications had failed to arrest the ongoing symptoms, signs, and perifollicular lymphocytic infiltration seen on histologic findings. In contrast, after initiation of pioglitazone therapy, the patient experienced rapid resolution of his symptoms and a decrease in inflammation on biopsy, suggesting that pioglitazone was responsible for his improvement, even though this cannot be definitively concluded from this single case report.

Rosiglitazone maleate and pioglitazone are the thiazolidinediones currently available in the United States. Because these medications lower blood glucose levels by improving insulin sensitivity, circulating insulin concentrations are not affected, and they can be safely used in patients without DM. The thiazolidinediones can cause dosage-dependent weight gain owing to fat accumulation and fluid retention or peripheral edema as a result of renal sodium reabsorption.¹³ The rate of peripheral edema is reported to be 5% in patients not prescribed insulin. This fluid retention, however, may pose a cardiovascular risk in patients predisposed to congestive heart failure.¹⁴ Recent data suggest an increase in relative risk of myocardial infarction among patients with type 2 DM treated with rosiglitazone.¹⁵ Although the myocardial risk patients without DM is unknown, the use of thiazolidinediones in patients with cardiac risk factors should proceed with caution. It has also been suggested that liver function tests should be obtained before initiating therapy with these medications and periodically thereafter because they are similar in structure to another thiazolidinedione, troglitazone, which was removed from the market owing to severe idiosyncratic hepatotoxic effects. Pioglitazone also induces cytochrome P450 isoform CYP3A4, raising the possibility of drug interactions, for

example, with oral contraceptives.¹⁶ When compared with other oral medications used for treatment of LPP and other cicatricial alopecias, the thiazolidinediones have an acceptable adverse effect and safety profile. Another consideration for drug delivery is the topical administration of thiazolidinediones. Of interest, new proprietary PPAR- γ agonists optimized for topical administration are reportedly under development.¹⁷

A recent publication¹⁸ showed the relative rarity of LPP, which has an incidence rate of only 1.15% to 7.59% in all new patients with hair loss seen annually in 4 tertiary hair research centers in the United States. Thus, any drug having an indication for LPP would be eligible for orphan drug status by the US Food and Drug Administration. Given the experimental evidence for the role of PPAR- γ in LPP and the positive clinical and histologic effects of pioglitazone in this patient, studies evaluating the efficacy of thiazolidinediones, either orally or topically, may be advocated for LPP.

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