

Graham-Little-Piccardi-Lassueur Syndrome

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PRACTICE POINTS

- Graham-Little-Piccardi-Lassueur syndrome (GLPL) is characterized by a triad of cicatricial alopecia of the scalp, nonscarring alopecia of the axillae and/or groin, and a rough follicular eruption on the body and/or scalp.
- Graham-Little-Piccardi-Lassueur syndrome is considered one of the 3 clinical variants of lichen planopilaris.
- Potential therapies for GLPL include hydroxychloroquine, cyclosporine, tetracyclines, and pioglitazone.

To the Editor:

A 56-year-old white woman with a history of melanoma and hypertension presented for evaluation of progressive hair loss of more than 1 year's duration with associated pruritis. Scalp examination revealed diffuse erythema and scarring alopecia of the bilateral parietal and temporal regions. Physical examination also revealed nonscarring alopecia of the bilateral axillae, with associated thinning of the pubic hair, eyebrows, and eyelashes, as well as keratosis pilaris on the upper arms. Biopsy of the parietal scalp revealed mild scarring alopecia with isthmic fibroplasia consistent with early lichen planopilaris (LPP) (Figure). These histologic features combined with the patient's clinical presentation were consistent with a diagnosis of Graham-Little-Piccardi-Lassueur syndrome (GLPL).

Graham-Little-Piccardi-Lassueur syndrome was first described by Piccardi in 1913. A second case was then described by Graham-Little in 1915 in a patient referred

by Lassueur, resulting in the name it bears today.^{1,2} The condition presents most commonly in middle-aged white women and is characterized by a triad of cicatricial alopecia of the scalp, nonscarring alopecia of the axillae and/or groin, and a rough follicular eruption on the body and/or scalp. Symptoms may not be present simultaneously. In GLPL, scarring alopecia of the scalp often precedes follicular eruptions of the trunk, arms, and legs by as much as years,² and the inverse also has been reported.¹ The inflammatory lesions of the scalp eventually resolve spontaneously, but the hair loss is by definition irreversible.

This rare condition is considered one of the 3 clinical variants of LPP. Other variants include classic LPP, also known as follicular lichen planus, and frontal fibrosing alopecia.³ More recently, fibrosing alopecia in a pattern distribution has gained some popularity as a fourth variant of LPP.⁴ All variants of LPP, including GLPL, result in a scarring alopecia. The classic scalp finding is an erythematous to violaceous, perifollicular, hyperkeratotic scale at the base of the terminal hairs. The population of inflamed follicles spreads outward, leaving behind a round to oval, central, atrophic scar that often is devoid of follicles. Few hairs may persist within zones of alopecia at presentation; however, these hairs are affected by inflammation and also will likely shed. A hair pull test will be positive at the margins during active disease, consisting of mostly anagen hairs on trichogram examination.^{1,5} Patients may develop only a single foci of hair loss, but much more commonly, a patchy multifocal alopecia is noted.⁶ Sites often will coalesce. Onset of scalp alopecia may be insidious or fulminant.

The nonscarring alopecia of the axillae and groin may be described as subtle thinning to complete hair loss with

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The authors report no conflict of interest.

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no signs of atrophy or inflammation. Although not commonly reported, a case of nonscarring alopecia located on the shoulders has been seen.⁷

The follicular eruption that can be present on the trunk, arms, or legs in GLPL is most often but not limited to keratosis pilaris, as was seen in our patient. One reported case also described lichen spinulosus as a potential variant.⁸ Lichen planopilaris is separate from lichen planus (LP) because of its selective follicular involvement vs the nonselective mucocutaneous distribution of LP. The 2 processes also are histologically distinct; however, estimations have shown that more than 50% of patients with GLPL experience at least 1 episode of mucosal or cutaneous LP in their lifetime.⁹ Rarely, coexistence of GLPL and LP lesions has been described. One reported case of GLPL and concomitant hypertrophic LP could represent a severe form of the disease.⁹ Additionally, lichen planus pigmentosus, an uncommon variant of LP

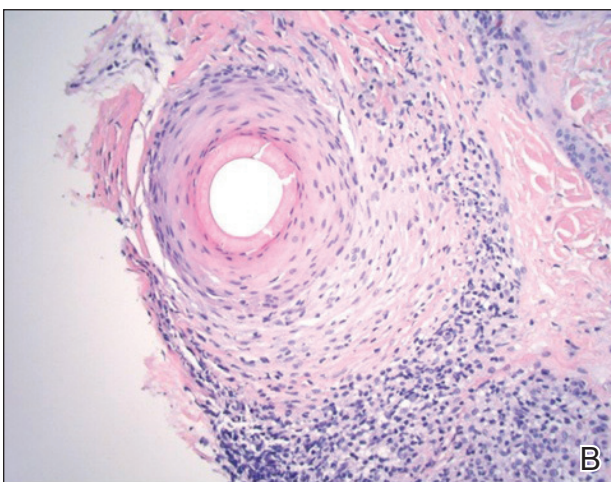
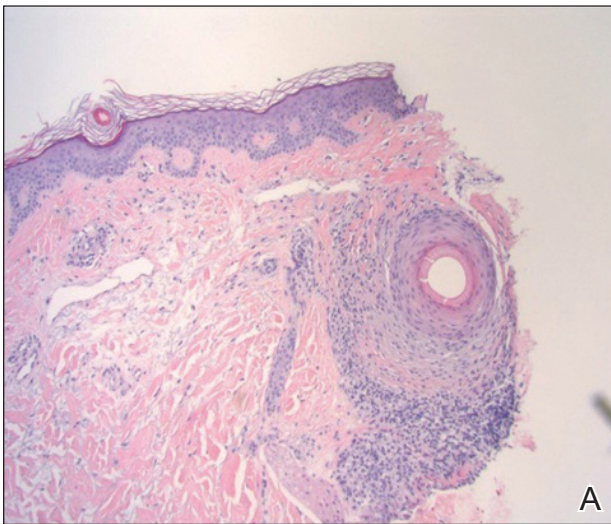
characterized by hyperpigmented brown macules in sun-exposed areas and flexural folds, was identified in a case report of an Asian woman with GLPL.¹⁰

As a general rule, the variants of LPP most commonly are seen in postmenopausal women aged 40 to 60 years; however, rare cases in a child and a teenager have been reported.¹¹ The GLPL variant of LPP is reported up to 4 times more frequently in females.⁵ Pruritus and pain are inconsistent findings, and there are no systemic signs of illness. A case of androgen insensitivity syndrome associated with GLPL suggested a potential influence of hormones in LPP.¹² Stress, vitamin A deficiency, and autoimmunity also have been proposed as triggers of GLPL.¹³ Furthermore, familial GLPL was described in a mother and daughter, though the association was uncertain.¹⁴ Our patient had no relevant family history.

Workups to reveal the etiology of GLPL have been inconclusive. Reports of laboratory testing including complete blood cell count, basic metabolic panel, liver function tests, testosterone and dehydroepiandrosterone levels, and chest radiograph have been normal.² Additional workup for viral triggers also has been negative.¹⁵ A case series of 29 patients with LPP and its variants, including GLPL, revealed positive antinuclear antibodies in 10% of patients and a thyroid disorder in 24% of patients, with Hashimoto thyroiditis being the most prevalent in 7% of cases.¹⁶ There may be a strong association between the comorbidities of thyroid dysfunction and GLPL, as documented in other studies.^{10,17} A case-control study by Mesinkovska et al¹⁷ revealed a considerable increase in the prevalence of thyroid gland disease among patients with LPP vs controls. Human leukocyte antigen DR1 was found in a familial case of GLPL,⁴ and a case of GLPL following hepatitis B vaccination also has been described.¹⁸

Graham-Little-Piccardi-Lassueur syndrome most likely is a T-cell mediated autoimmune condition associated with one or multiple unknown keratinocyte antigens. Autoantibodies to the inner centromere protein were identified in a case that was positive on direct immunofluorescence, which may provide more insight into the disease pathophysiology.¹³ Interestingly, a study comparing the concentrations of inflammatory cells in LPP and traction alopecia found an elevation in the ratio of Langerhans cells to T lymphocytes within the follicular inflammatory infiltrate of LPP.¹⁹

Histologically, cicatricial alopecia of the scalp is characterized by an interface dermatitis and a lichenoid lymphocytic infiltrate of the isthmus and infundibulum of the hair follicle sparing the bulb (Figure). A follicular plug is present in the active border. The increased pressure from the keratinous plug from above and the pressure from the infiltrate from the sides has been proposed to decrease the blood supply to the follicle and result in its death.² Late-stage disease is notable for fibrotic longitudinal tracks of the hair follicle, perifollicular lamellar fibrosis, and adjacent epidermal atrophy.²⁰ Direct immunofluorescence



A and B, Mild scarring alopecia with isthmic fibroplasia consistent with early lichen planopilaris in a patient with Graham-Little-Piccardi-Lassueur syndrome (H&E, original magnifications $\times 10$ and $\times 40$).

in GLPL generally is negative. A trichogram performed in a 29-year-old woman with GLPL was normal, with 84% anagen, 2% catagen, and 14% telogen hairs. It was noted that 10% of the sampled hairs were classified as dystrophical dysplastic hairs.¹² Despite the lack of fibrosis on physical examination in patients with GLPL, nonscarring alopecia of the axilla and groin may show follicular destruction on microscopic examination.¹ The pathology of the papules present on the trunk and extremities—whether that of keratosis pilaris or lichen spinulosus—demonstrates similar hyperkeratosis, hypergranulosis, and follicular plugging with a possible superficial, perivascular, lymphocytic infiltrate.

The differential diagnosis of GLPL includes other variants of LPP as well as discoid lupus erythematosus (DLE), pseudopelade of Brocq, pityriasis rubra pilaris, sarcoidosis, acne keloidalis, central centrifugal scarring alopecia, follicular mucinosis, and folliculitis decalvans.¹⁴ Differentiation of LPP from DLE is difficult. Clinical clues include lack of central erythema and telangiectases within the lesions. Histologically, the lymphocytic dermatitis and folliculitis can be indistinguishable, but subtle findings suggesting DLE may be present, such as increased mucin in the reticular dermis, a focally thinned epidermis, and less severe dermal sclerosis when compared to cases of LPP.² Direct immunofluorescence with IgG and C3 revealing linear granular deposits at the dermoepidermal junction is characteristic of DLE.²⁰ Pseudopelade of Brocq is best thought of as an end-stage clinical pattern of hair loss in LPP rather than a separate condition. It is considered to be the end point of GLPL as well as DLE and others when the inflammation has subsided and the cicatricial alopecia is stable. For the duration of active disease, GLPL is classified as an unstable cicatricial alopecia that has a tendency to progress and recur periodically.²⁰ Folliculitis decalvans also can mimic GLPL during a period when the pustules have resolved; however, a neutrophilic infiltrate will be present.

The goal of treatment in GLPL as well as other scarring alopecias is to stop the progression of hair loss. Early diagnosis is imperative if control is to be gained before considerable hair loss has occurred. Once follicular destruction has occurred as a result of the inflammation, there is minimal potential for hair rejuvenation.²¹ To date, treatment has been mostly fruitless, except in the management of keratosis pilaris that accompanies GLPL. First-line therapy often includes topical corticosteroids with or without intralesional corticosteroids. Systemic corticosteroids, retinoids, and psoralen plus UVA therapy also are frequently employed.^{1,2} Success in treating GLPL with cyclosporine A at a dosage of 4 mg/kg daily was described in several studies.^{1,2,15} Treatment resulted in reduction of perifollicular erythema and follicular hyperkeratotic papules as well as mild hair regrowth within the scarring patches.¹⁵ Nonetheless, cyclosporine A may prove useful in the initial inflammatory phase of GLPL.

Consequently, cyclosporine A also is associated with a high relapse rate.^{1,2}

Because the number of patients with GLPL is so few, therapy should mirror advances being made in treatments for other variants of LPP. More recent studies of LPP treatment with hydroxychloroquine showed opposing results, though the safety profile of this agent makes it an enticing treatment option.^{22,23} Tetracyclines showed improvement in 4 of 15 (26.7%) patients in a retrospective study by Spencer et al.²⁴ Another retrospective study showed promising results with the potent 5-alpha reductase inhibitor dutasteride with 7 of 10 (70%) postmenopausal patients reporting stabilization over a mean duration of 28 months with no reported side effects.²⁵ Antimalarial medications also have been implemented as adjunct therapies with mixed results.⁵ A case of a 26-year-old man with GLPL from South India showed systemic disease improvement following treatment with pulsed systemic steroids, isotretinoin, and anxiolytics.⁷ Chloroquine phosphate at a daily dose of 150 mg for 3 to 9 months yielded a transient response in one postmenopausal patient with frontal fibrosing alopecia.⁶ Stabilization of hair loss was achieved with a combination of hydroxychloroquine and doxycycline in a woman with GLPL who was previously unresponsive to tacrolimus ointment.¹⁰ Thalidomide showed early promise in an isolated report claiming successful treatment of LPP,²⁶ but there is contradictory evidence, as thalidomide showed no benefit in a series of 4 patients with LPP.²⁷

Peroxisome proliferator-activated receptor gamma (PPAR- γ), a transcription factor that regulates genes, is downregulated in LPP.²⁸ Deletion of PPAR- γ within follicular stem cells in mice results in a phenotype similar to cicatricial alopecia. Data have supported the role of PPAR- γ in maintaining the pilosebaceous unit. A case report of pioglitazone (PPAR- γ agonist) therapy used at 15 mg daily for 8 months was successful in treating a patient with LPP.²⁸ Further investigation must be conducted to evaluate these treatments since early attenuation of the disease process is crucial to the reduction of permanent hair loss.

Advances in the early recognition and successful treatment of GLPL are dependent on continued research in all variants of LPP. Randomized controlled trials are necessary to establish standard of care. Further studies should target the association of GLPL and other autoimmune phenomena. Moreover, research into the etiology will provide direction in understanding disease progression and outcome.

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