

Graham-Little Syndrome — a rare entity of both scarring and non-scarring alopecia concomitance

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ABSTRACT

Graham Little-Piccardi-Lassueur syndrome also called in a shorter form as Graham-Little syndrome, is a rare clinical entity characterized by the symptomatic triad including multifocal progressive cicatricial alopecia on the scalp, non-scarring hair loss of axillae and pubic areas and presence of keratosis pilaris-like eruption on the trunk and extremities. The etiology of the disease remains unknown with some hypotheses proposed. The condition is diagnosed based on clinical presentation, trichoscopic characteristic findings and histopathological analysis. The treatment of the syndrome is challenging. The therapeutic strategy includes topical or systemic corticosteroids, retinoids and PUVA therapy with different efficacy. We present the case of this rare syndrome and discuss it from the practical point of view in terms of diagnosis and treatment approach.

Forum Derm. 2019; 5, 1: 6–10

Key words: lichen planopilaris, alopecia, Graham-Little syndrome

INTRODUCTION

Graham-Little syndrome (also known as Graham Little-Piccardi-Lassueur syndrome, GLS or GLPLS) is a rare subtype of lichen planopilaris characterized by the distinctive triad of symptoms, including coexistence of multifocal progressive scarring alopecia on the scalp, non-scarring hair loss of axillar and inguinal areas and the presence of follicular skin lesions on the trunk and extremities with lichenoid vellus hairs inflammation histopathologically, called keratosis spinulosa [1, 2]. Graham-Little syndrome is a chronic disease characterized by flare-ups and remissions leading to scalp permanent hair loss when left untreated. It more often affects white women in their early fifties [3].

CASE REPORT

61-year old woman was admitted to the outpatient clinic with a two year history of lichen planopilaris on her scalp with vertex and frontal involvement (Fig. 1). Her concomitant diseases included hypothyroidism due to subtotal strumectomy performed in the past and treated squamous cell dysplasia of the vulva. At the time of examination she presented with scarring hair loss of her scalp, complaining about severe itching and burning of this particular area of the skin showing inflammation and scaling of periauricular

and occipital regions (Fig. 2). The presence of lichenoid, pigmented lesions of her armpits was also noticed (Fig. 3). The face and neck were covered with scattered palpable pinkish, inflamed, hyperkeratotic papules, previously also detected on her oral mucosa. Trichoscopy examination images per-

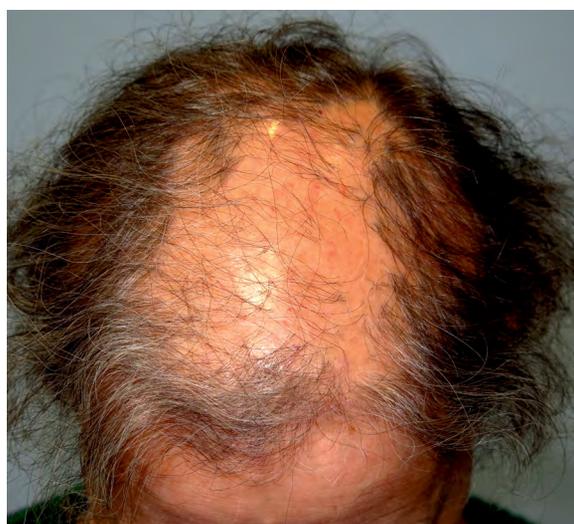


Figure 1. Scarring alopecia in the process of lichen planopilaris on the vertex and frontal region of the patient scalp

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Figure 2. The periauricular area of the patient scalp giving her itching and burning sensation with noticeable perifollicular inflammation around the hairs at the periphery of the scarred area



Figure 3. The armpit presented decreased hair density with brown red discoloration of the skin

formed by Fotofinder digital dermoscope at 20× and 50× fold magnification, either dry or with immersion fluid, revealed the features of lichen planopilaris of the scalp with characteristic irregular white dots coalescing into white or reddish areas of the skin, dystrophic hairs and perifollicular scaling (Fig. 4 A–C). In her armpit, trichoscopy examination revealed non-scarring alopecia of the armpit (Fig. 5).

Trichoscopy guided scalp biopsy of the involved lonely hair presented on Fig. 4C, revealed terminal hair with lichenoid lymphocytic infiltrate in its upper part with vacuolar degeneration of the hair epithelium, features of the scarring alopecia with loss of terminal and vellus hair follicles replaced by fibrous tracts, preserved arrector pili muscles with dilated blood vessels (Fig. 6, H and E, 40 × magnification).

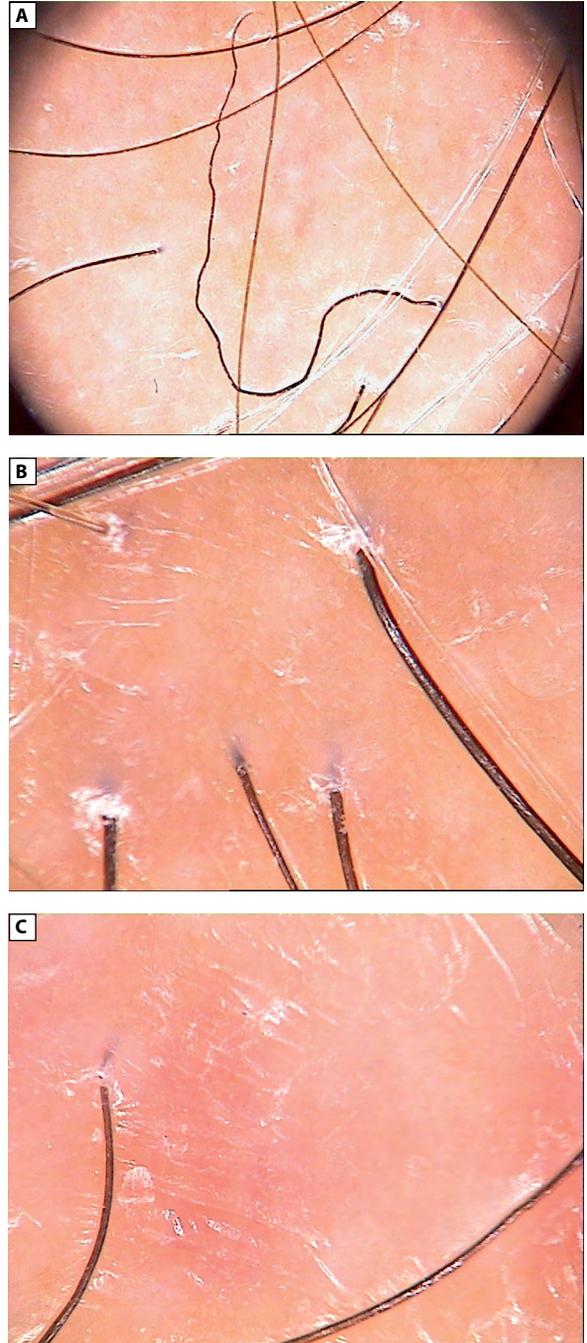


Figure 4. Trichoscopic characteristic findings of the lichen planopilaris on the patient scalp included A. dystrophic hairs and irregular white dots coalescing into white or reddish areas of the skin (20×); B. perifollicular scaling (50×); and C. peripilar erythema with dilated blood vessels and milky red areas (50×)

The biopsy from the involved armpit skin showed interface lichenoid inflammation of the epidermis with pigment incontinence in the papillary dermis (Fig. 7A) coexisting with terminal hair affected by lichenoid lymphocytic infiltrate of the hair epithelium with lymphocytic exocytosis and dyskeratotic and necrotic keratinocytes in the epithelium leading to disturbed maturation of the inner root sheath

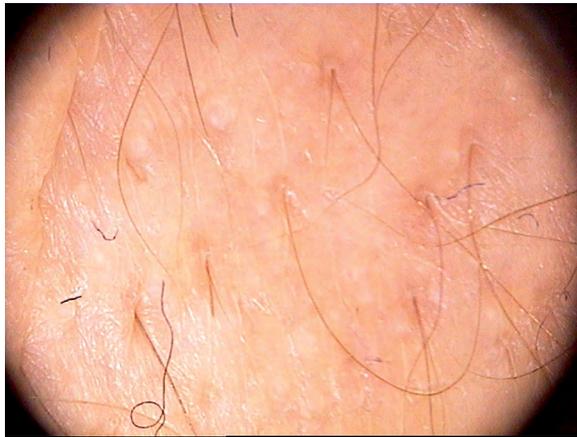


Figure 5. Trichoscopy of the armpit revealed sparse, thin and long hair shafts with faint yellow dots

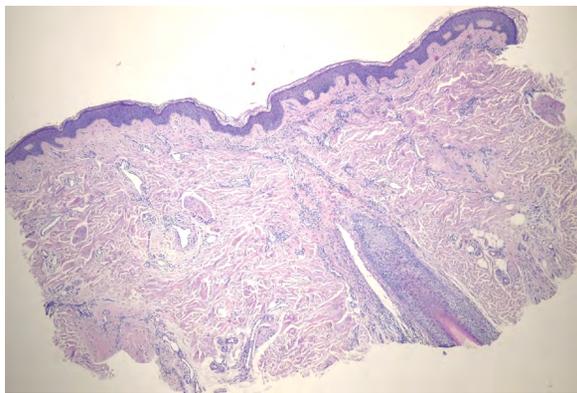


Figure 6. The biopsy from the involved scalp with selected terminal hair presented on Fig. 4C revealed terminal hair with lichenoid lymphocytic infiltrate in its upper part with vacuolar degeneration of the hair epithelium, features of the scarring alopecia with loss of terminal and vellus hair follicles replaced by fibrous tracts, preserved arrector pili muscles with dilated blood vessels in reticular dermis (H and E, 40×)

(Fig. 7B). The patient was diagnosed with Graham-Little syndrome.

The patient was implemented with oral acitretin 10 mg/day, topical 0.1% tacrolimus ointment for her skin lesions and topical bethametasone in solution once per day for her sensation of itching and burning. She was also given three courses of intralesional injections with triamcinolone acetonide on her most severe and inflamed scalp lesions every six weeks. Her complaints resolved soon after combined treatment introduction, but scalp hairs regrowth was not obtained. The inflammatory pigmented plaques in the armpits resolved and follicular hyperkeratotic papules of the face and neck disappeared leaving normal looking skin.

DISCUSSION

Graham-Little syndrome (GLS) was for the first time described by Piccardi in 1914, and a year later by Ernst Graham-

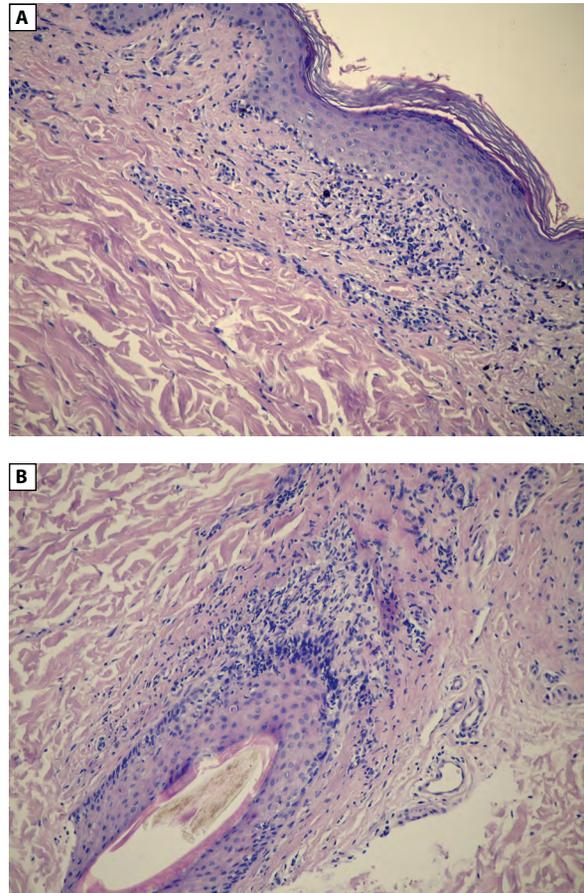


Figure 7. The biopsy from the armpit showed interface lichenoid inflammation of the epidermis with pigment incontinence in the papillary dermis (A) and terminal hair with lichenoid lymphocytic infiltrate of the hair epithelium with lymphocytes exocytosis and dyskeratotic and necrotic keratinocytes in the epithelium leading to disturbed maturation of the inner root sheath (B)

-Little [2]. The origin of GLS has been elucidated with some hypotheses, but still remains unexplained. Most authors consider the condition as a form of lichen planopilaris, the subtype of lichen planus with hair involvement and destruction [3–6]. The development of the disease depends on the hair follicle condition, which at the beginning is filled with keratotic plug, then becomes surrounded by lymphocytic inflammatory infiltrate generating lichenoid-interface reaction leading to epithelium destruction ending up with hair loss with concomitant scarring. Bardazzi et al. raised a hypothesis of potential viral etiology since he described the development of both Graham-Little syndrome and lichen planus after hepatitis B virus (HBV) vaccination [7]. There are also reports suggesting a potential autoimmune connection related to autoantibodies against INCENP protein, which is responsible for mitosis regulation and chromosome segregation [8] as well as familial predispositions to GLS connected to HLA-DR1 (human leukocyte antigen) inheritance, according to Viglizzo et al., who described familial case of

Graham-Little syndrome in both mother and daughter [9]. The association with hormonal dysregulation, such as androgen insensitivity syndrome, has also been reported [1].

This condition the most often affects middle-aged caucasian women in their perimenopausal age, but racial prevalence has not been confirmed. The syndrome usually develops slowly within months or years [10]. According to its hypothesized correlation with lichen planus, pruritus remains common but not constant feature among patients with GLS [9]. As mentioned before, the disease hallmark triad contains: i) multifocal cicatricial alopecia of the scalp, ii) hair decrement in the axillae and/or groins with no signs of scarring and also iii) presence of skin lesions typical for lichen planopilaris with vellus hairs involvement, which manifest as small disseminated keratotic reddish-brown acuminate or spinous follicular papules localized on the trunk or/and extremities, which can coalesce into larger plaques [2, 11]. The components of the triad do not have to occur simultaneously. However, non-scarring alopecia of the eyebrows and follicular papules of the face have also been reported as features of the syndrome [6]. Disease activity can be evaluated by the clinical hair examination and the positive pull test indicating the active stage of the process [12].

Trichoscopic findings of lichen planopilaris depend on the activity and severity of the disease. Active lesions are characterized by the presence of silver-white perifollicular, collar-like scaling (peripilar casts) around the hair shafts, protruding few millimeters above the skin surface (which is considered a hallmark of lichen planopilaris, especially observed with dry trichoscopy), as well as perifollicular inflammation, violaceous (blue-violet) areas surrounding empty hair follicles sometimes associated with pigment incontinence, elongated linear blood vessels, honeycomb pattern hyperpigmentation and tufted hairs (5 or more hairs growing out of the one hair opening). The interfollicular epidermis is usually spared in contrast to discoid lupus erythematosus, which is the main differential diagnosis for lichen planopilaris [11, 13, 14].

The inactive phase of lichen planopilaris is characterized by predominance of irregular white dots fusing into white or milky-red areas on the skin, which correlate with perifollicular fibrosis, characteristic for folliculocentric cicatricial alopecia. These features may occur in other examples of cicatricial alopecia, but also need a differentiation from eccrine gland excretory ducts visible on sun-exposed skin, which can visually mimic fibrotic white dots. Late stage of LPP may manifest by the presence of hair tufts containing between 5 up to 9 hairs.

Skin lesions detected in patients with Graham-Little syndrome show no difference in comparison to classic lichen planopilaris and result from body vellus hairs involvement and present as erythematous, rough follicular papules. The

examination of pubic and axillary areas reveals hypopigmented, thin, degenerative terminal hairs without signs of fibrotic process such as white dots. Yellow dots can be present [15].

The target of inflammation and destruction in the hair epithelium is localized in the upper half of pilosebaceous unit, such as infundibulum and isthmus [16]. Histopathological examination reveals band-like, lichenoid inflammatory lymphocytic infiltrate between follicular epithelium and the dermis. The absence of sebaceous glands is also noticeable, especially in the early onset of the disease [17]. The epithelium-directed lymphocytic exocytosis is also noticeable. Keratinocyte dyskeratosis varies in its severity (from mild to severe) and is localized usually next to the epithelial-dermal junction. Hair follicle orifices are usually affected by inflammation around infundibulum, which lead to hypergranulosis and hyperkeratosis inside infundibulum. Direct immunofluorescence of the involved tissue may show the deposits of globular IgM cytooid bodies in follicular epithelium. Hypergranulosis, acanthosis, Civatte bodies and pigment incontinence may also be seen [18, 19].

The advanced stage of the disease manifests with concentric, lamellar fibroplasia or compact fibrosis around the openings of affected hair follicles leading finally to hair follicle contraction and decapitation. As the final result, the longitudinal scar so called fibrous tract, replacing pre-existing hair follicle in the dermis is formed. Fusion of the follicles and inner root sheath degeneration can also be noticed. The specimens taken from axillary areas and groins show no signs of atrophy [3, 18, 19].

Differential diagnosis of Graham-Little syndrome should include other causes of cicatricial alopecia, such as discoid lupus erythematosus, pseudopelade of Brocq, frontal fibrosing alopecia, pityriasis rubra pilaris, sarcoidosis, follicular mucinosis, folliculitis decalvans or keratosis pilaris atrophicans [7, 12]. In ambiguous cases with inconclusive trichoscopic findings, the trichoscopy guided biopsy is recommended for histopathological evaluation.

Treatment of Graham-Little syndrome includes topical, intralesional or systemic corticosteroids with different efficacy [3, 6], topical tacrolimus, retinoids or PUVA therapy, but some cases prove cyclosporine A effectiveness, as an example of drug succeeding in hair growth induction and the hypothesis has been stated, that it could be administered in early stage of the condition, before the fibrosis develops [20]. Hydroxychloroquine has been reported as an useful drug in lichen planopilaris and frontal fibrosing alopecia cases, resulting in decreasing the signs and symptoms of the disease, according to LPPAI (Lichen Planopilaris Activity Index) [21], but we do not share this observation. In our hands the administration of systemic retinoids, such as isotretinoin and acitretin is beneficial for the stabilization

of lichen planopilaris type such as frontal fibrosing alopecia [22], therefore small dose of acitretin was introduced to our patient with Graham-Little syndrome with a good tolerance and clinical efficacy. The presence of progressive fibrosis and concomitant inflammation is responsible for the complex and challenging treatment of the disease [2, 3]. The choice and duration of the therapy is guided by the response and relapse rate of Graham-Little entity.

CONCLUSIONS

Graham-Little syndrome is relatively rare, distinctive disorder requesting a consideration while differentiating common cicatricial alopecia entities. Early diagnosis of subtle lesions of GLS followed by adequate treatment may prevent patients from permanent hair scalp alopecia and disease progression. The condition has a chronic course. The advanced stage of the disease has a noticeable esthetic impact on the patient life. Thorough examination of the scalp and hormone-dependent body areas with the knowledge of the characteristic hair-loss patterns and lichenoid follicular skin eruptions with well described trichoscopic findings [23] are crucial to make the diagnosis of Graham-Little syndrome, entity described over 100 years ago.

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