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## Title

Comorbid conditions in lichen planopilaris: A retrospective data analysis of 334 patients

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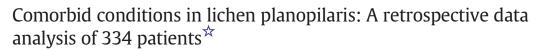
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### ABSTRACT

*Background:* Lichen planopilaris (LPP) is a rare, cicatricial, lymphocyte-mediated alopecia that is thought to have an autoimmune pathogenesis and possibly related to other autoimmune diseases. However, data are limited and studies that examine comorbid conditions are lacking.

*Objectives:* We sought to determine the prevalence of systemic comorbid conditions, nutritional deficiencies, psychological problems, and skin cancers in patients with LPP.

*Methods:* We identified 334 patients with LPP who were seen in the Department of Dermatology at the Cleveland Clinic Foundation between 2000 and 2016. Patients with LPP were compared with 78 control patients with a diagnosis of seborrheic dermatitis.

*Results*: There were more female patients with LPP compared with the controls (93.1% vs. 79.5%; p < .001) but the average age did not differ ( $54.77 \pm 12.83$  vs.  $52.19 \pm 15.37$ ; p = .12). Conditions positively associated with LPP were Hashimoto's thyroiditis (6.3% vs. 0%; p = .023), hypothyroidism (24.3% vs. 12.8%; p = .028), and hirsutism (11.4% vs. 1.3%; p = .006). Negatively associated conditions were allergic rhinitis (15% vs. 24.4%; p = .046), diabetes mellitus type II (11.7% vs. 21.8%; p = .019), hyperlipidemia (38.6% vs. 52.6%; p = .024), vitamin D deficiency (50% vs. 65.4%; p = .014), depression (15.6% vs. 28.9%; p = .018), and sleep problems (7.5% vs. 29.5%; p < .001).

*Conclusions:* Our study further emphasizes that dermatologists should screen patients with LPP for autoimmune disorders that are associated with LPP and complete a full metabolic workup to avoid missing other abnormalities. The importance of atopy, autoimmune disorders, endocrine disorders, nutritional deficiencies, psychological problems, and skin cancers in patients with scarring alopecia should be better understood.

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#### Introduction

Lichen planopilaris (LPP) is a rare, lymphocyte-mediated, scarring form of alopecia (Assouly and Reygagne, 2009). According to Ochoa et al. (2008), the annual incidence rate of LPP across four medical centers varied from 1.15% to 7.59%. The age of onset for LPP is between 25 and 70 years and the most common reported symptoms of LPP are increase in shedding, pruritus, scale, and scalp tenderness

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(Tan et al., 2004). Clinically, LPP presents on the scalp as scaly, erythematous plaques of alopecia, sometimes with ulceration and atrophy, and with perifollicular erythema, follicular hyperkeratosis, and permanent hair loss (Tan et al., 2004). With regard to the distribution of LPP alopecia plaques on the scalp, a retrospective study of 80 cases revealed that 58.75% of patients had random plaques scattered on the scalp and 36.25% had frontotemporal hair region involvement (Soares et al., 2015).

The pathophysiologic mechanism is based on a T-lymphocytic inflammation within the stem cell area of the hair follicle, which is also known as the infundibuloisthmic or bulge region (Pozdnyakova and Mahalingam, 2008). The body's repair mechanisms attempt to recover from the inflammatory response; however, there is permanent damage to the infundibuloisthmic region, which

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results in follicular scarring and irreversible hair loss (Lavker et al., 2003; Mobini et al., 2005). This pathophysiologic mechanism is thought to be similar to lichen planus (LP), which LPP is believed to be a follicular variant of (Bolduc et al., 2016). Although there are known associations of LP with autoimmune disorders, hyperlipidemia, metabolic syndrome, hypothyroidism, anxiety, and depression, the relationship between LPP and other diseases has been largely unexplored (Garcia-Pola et al., 2016; Hirota et al., 2013; Lai et al., 2016; López-Jornet et al., 2014).

Only two prior reports on the association between LPP and hypothyroidism exist and one small study that examined the comorbidities in patients with LPP but without comparison with controls (Atanaskova-Mesinkovska et al., 2014; Cevasco et al., 2007; Meinhard et al., 2014). Therefore, this study aims to examine the prevalence of atopic conditions, autoimmune disorders, thyroid conditions, metabolic disorders, endocrine disorders, nutritional deficiencies, psychological problems, and sun-induced skin cancers in patients with a diagnosis of LPP. To our knowledge, this is the second-largest retrospective study to be conducted on patients with LPP.

#### Methods and materials

A retrospective case-control study of patient medical records was conducted and approved by the Cleveland Clinic Foundation institutional review board (No. 10-160). All patients were evaluated at the Cleveland Clinic Department of Dermatology between 2000 and 2016. A clinical presentation in combination with a scalp biopsy was used to confirm the diagnosis of LPP. We identified 334 patients with LPP and 78 age- and race-matched controls who were diagnosed with seborrheic dermatitis and no clinical evidence of concomitant hair loss (n = 78).

The electronic health records were reviewed for demographic factors such as age, sex, and race, medical comorbidities, and skin malignancies. Medical comorbidities included atopic conditions (e.g., allergic rhinitis, eczema, and asthma), autoimmune disorders (e.g., Hashimoto's thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, sarcoidosis, celiac disease, ulcerative colitis, vitiligo, Sjogren's syndrome, and limited scleroderma/systemic sclerosis), thyroid gland disease (e.g., hypothyroidism, hyperthyroidism, goiter, nodules, and subacute thyroiditis), metabolic conditions (e.g., diabetes mellitus type II, hyperlipidemia, and obesity), endocrine conditions (e.g., hirsutism and hyperparathyroidism), nutritional deficiencies (e.g., vitamin D deficiency, anemia, and iron deficiency), psychological problems (e.g., anxiety, depression and sleep problems), and sun-induced skin cancers (e.g., nonmelanoma skin cancer subdivided into basal cell carcinoma [BCC] and squamous cell carcinoma [SCC] and melanoma). In addition, we evaluated laboratory positive results for antinuclear antibody (ANA) and recorded the number of patients who received an ANA test to determine the percentage of patients who were positive. The prevalence of comorbidities and skin cancers was compared with that of the control patients.

Study data were collected and managed using Research Electronic Data Capture, which is a secure, web-based application. Categorical factors were summarized as frequency and percentage. The statistical relationships between these study groups and associated parameters were tested using  $\chi^2$  and two-sample t-tests as appropriate. Pearson's  $\chi^2$  test was employed to compare the prevalence of various systemic medical comorbidities. All tests were conducted at a significance level of p < .05 using SPSS software version 20 (IBM, Armonk, NY).

### Results

A total of 334 patients were identified (Table 1). There was a female predominance (n = 311; 93.1% female vs. n = 23; 6.9%

#### Table 1

Demographic data	of patients with	LPP and controls
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Category	Control (n = 78) n (%)	LPP (n = 334) n (%)	p-value
Sex			< .001
Female	62 (79.50)	311 (93.10)	
Male	16 (20.50)	23 (6.90)	
Age at time of diagnosis (mean, SD)	$52.19 \pm 15.37$	$54.77 \pm 12.83$	.12
Race			.75
White	55 (70.50)	221 (66.20)	
African-American	17 (21.80)	86 (25.70)	
Other	6 (7.70)	27 (8.10%)	

LPP, lichen planopilaris; SD, standard deviation.

male patients). The mean age at the time of LPP diagnosis was 54.77 years (Range, 18-90). The majority of patients with LPP were Caucasian (n = 221; 66.2%) and the next most prevalent group was African-American women (n = 86; 25.7%).

The common comorbid conditions in patients with LPP are presented in Table 2 and include atopic conditions (allergic rhinitis, atopic dermatitis, and asthma), autoimmune disorders (Hashimoto's thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, sarcoidosis, celiac disease, ulcerative colitis, vitiligo, Sjogren's syndrome, and limited scleroderma/systemic sclerosis), thyroid gland disease (hypothyroidism and other thyroid gland disease), metabolic conditions (diabetes mellitus type II, hyperlipidemia, and obesity), endocrine disorders (hirsutism and hyperparathyroidism), nutritional deficiencies (vitamin D deficiency, anemia, and iron deficiency), and psychological problems (anxiety, depression, and sleep problems). The comorbid conditions that resulted in statistically significant associations with LPP were sleep problems, hirsutism, vitamin D deficiency, depression, diabetes mellitus type II, Hashimoto's thyroiditis, hyperlipidemia, hypothyroidism, and allergic rhinitis (Fig. 1).

Of the 334 patients with LPP, 145 patients had laboratory testing for ANA and 22.10% of the test results (n = 32) were positive. There was no statistical significance between ANA positivity and the diagnosis of LPP.

There seems to be a lower rate of sun-induced skin cancers in patients with LPP; however, this was not statistically significant.

### Discussion

LPP was initially described by Pringle in 1895 and can also be termed follicular lichen or follicular lichen planus (Assouly and Reygagne, 2009). The etiology of LPP is not well understood and has a higher incidence among Caucasian women (Kang et al., 2008). We report a significant association between LPP and sleep problems, hirsutism, vitamin D deficiency, depression, diabetes mellitus type II, Hashimoto's thyroiditis, hyperlipidemia, hypothyroidism, and allergic rhinitis. Although the correlation between metabolic conditions (diabetes and hyperlipidemia), vitamin D deficiency, and psychological problems with nonscarring alopecia is well known, this has not been studied in scarring alopecia.

The only prior studies that examined comorbidities in LPP focused on thyroid disease and hormonal balance. First, several studies that revealed increased rates of thyroid disease among patients with LPP have been published (Atanaskova-Mesinkovska et al., 2014; Rosina et al., 2002), In addition, Hashimoto's thyroiditis has been described as significantly associated with LPP (Atanaskova-Mesinkovska et al., 2014; Khurana et al., 2015). Patients with oral LP also demonstrated higher rates of thyroid disorders (Lo Muzio et al., 2013; Siponen et al., 2010). Our results add to the current literature and confirm this association in a larger patient population.

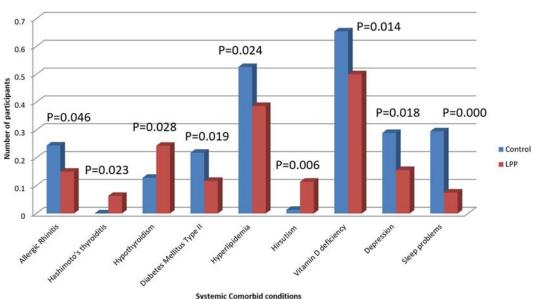
#### Table 2

Summary of systemic comorbid conditions in patients with LPP and controls

Characteristic	$\begin{array}{c} \text{Control} \\ (n = 78) \end{array}$	LPP (n = 334)	<i>p</i> -value	OR (95% CI)
	n (%)	n (%)		
Atopy				
Allergic rhinitis	19 (24.40)	50 (15.00)	.046*	0.55 (0.30-0.99
Atopic dermatitis	10 (12.80)	42 (12.60)	.953	0.98 (0.46-2.05)
Asthma	12 (15.40)	33 (9.90)	.161	0.60 (0.29-1.23)
Autoimmune disorders				
Hashimoto's thyroiditis	0	21 (6.30)	.023*	0.80 (0.76-0.84)
Systemic lupus erythematosus	1 (1.30)	5 (1.50)	.887	1.17 (0.14-10.16)
Rheumatoid arthritis	1 (1.30)	4 (1.20)	.951	0.93 (0.10-8.47)
Psoriasis	1 (1.30)	7 (2.10)	.639	1.65 (0.20-13.59)
Sarcoidosis	1 (1.30)	4 (1.20)	.951	0.93 (0.10-8.47)
Celiac disease	2 (2.60)	4 (1.20)	.364	0.46 (0.08-2.56)
Ulcerative colitis	2 (2.60)	4 (1.20)	.364	0.46 (0.83-2.56)
Vitiligo	1 (1.30)	2 (0.60)	.523	0.46 (0.04-5.18)
Sjogren's syndrome	1 (1.30)	2 (0.60)	.523	0.46 (0.04-5.18)
Limited scleroderma and systemic sclerosis	0	3 (0.90)	.401	0.80 (0.77-0.85)
Thyroid gland disease				
Hypothyroidism	10 (12.80)	81 (24.30)	.028*	2.18 (1.07-4.43)
Other thyroid disease	6 (7.70)	25 (7.50)	.950	0.97 (0.38-2.45)
Hyperthyroid	1 (1.30)	4 (1.20)	.951	0.93 (0.10-8.47)
Goiter	3 (3.80)	10 (3.00)	.698	0.77 (0.21-2.87)
Nodule (s)	1 (1.30)	3 (0.90)	.756	0.69 (0.07-6.80)
Subacute thyroiditis	0	1 (0.30)	.628	0.81 (0.77-0.85)
Metabolic conditions				× ,
Diabetes mellitus type II	17 (21.80)	39 (11.70)	.019*	0.47 (0.25-0.89)
Hyperlipidemia	41 (52.60)	129 (38.60)	.024*	0.57 (0.35-0.93)
Obesity (BMI > 30)	27 (34.60)	109 (32.60)	.738	0.92 (0.54-1.54)
Endocrine disorders				× ,
Hirsutism	1 (1.30)	38 (11.40)	.006*	9.88 (1.34-73.14)
Hyperparathyroidism	3 (3.80)	3 (0.90)	.050	0.23 (0.05-1.15)
Deficiency				× ,
Vitamin D	51 (65.40)	167 (50.00)	.014*	0.53 (0.32-0.88)
Anemia	17 (21.80)	60 (18.00)	.435	0.79 (0.43-1.44)
Iron	5 (6.40)	27 (8.10)	.619	1.29 (0.48-3.45)
Psychological problems				(
Anxiety	10 (12.80)	35 (10.50)	.551	0.79 (0.38-1.69)
Depression	21 (28.90)	52 (15.60)	.018*	0.50 (0.28-0.89)
Sleep problems	23 (29.50)	25 (7.50)	.000*	0.19 (0.10-0.36)

BMI, body mass index; CI, confidence interval; LPP, lichen planopilaris; OR, odds ratio.

\* Statistically significant at p = .05.



Systemic Comorbid conditions



In addition, a single prior study by Ranasinghe et al. (2017) described 168 women from a total of 413 patients with LPP, of which 20 women (11.9%) had comorbid clinical evidence of hirsutism. Our study further supported these findings with a statistical significance of hirsutism in 11.4% of our population with LPP.

In the literature on LP, several studies have been performed on comorbidities. The largest study was performed by Chung et al. (2015) who reviewed 12,427 patients to investigate autoimmune comorbid diseases in patients with LP. The researchers found higher rates of systemic lupus erythematosus, Sjogren's syndrome, dermato-myositis, vitiligo, and alopecia areata (AA). However, another study disagreed with these findings. In our study we did not find a significant association with autoimmune diseases except for thyroid disease (López-Jornet et al., 2014). A meta-analysis of patients with LP found that they are at an increased risk for hyperlipidemia (Lai et al., 2016). Interestingly in our study, we found a lower risk of dyslipidemia compared with controls and further investigation is necessary to determine the true risk.

Systemic comorbidities have also been described in nonscarring alopecia and particularly in AA. One retrospective study showed a significant association between AA and thyroid disease but not with allergic rhinitis or diabetes (Thomas and Kadyan, 2008). Another retrospective study of 584 patients with AA revealed a significant association between AA and eczema, thyroid conditions, vitamin D deficiency, and anemia (Miller et al., 2015). An association between AA and metabolic syndrome has been reported in a case report that highlighted the need for full laboratory assessments of patients with AA (Ishak and Piliang, 2013).

Vitamin D deficiency and its relationship with alopecia has been studied for years. A deficiency of vitamin D has been reported as associated with AA (Aksu Cerman et al., 2014; Mahamid et al., 2014; Miller et al., 2015). In our literature review, there was no published association between vitamin D deficiency and LPP and to a magnitude whereby 50% of our patients with LPP were deficient (p = .014). An unpublished Cleveland Clinic Foundation review of vitamin D deficiency and alopecia in 2012 revealed that the odds of being vitamin D deficient for patients with LPP was estimated at 3.693 times that of the control group (p = .0031) after adjusting for age and race.

Additionally, existing data support the prevalence of psychological conditions. A retrospective case-control study by Sellami et al. (2014) reported a high prevalence of symptoms of anxiety and depression in patients with nonscarring AA. Our study adds a new finding to the literature with a significant association between depression and sleep problems in patients with scarring LPP alopecia.

In this cohort, BCC was present in 4.50% and SCC in 1.80% of patients with LPP; however, this was not statistically different from the control group. Few reports exist on sun-induced skin cancers that were found concomitantly with LPP. In one report from 2015, a patient with basal cell nevus syndrome developed LPP on the same site of the scalp that had been previously treated with two cycles of imiquimod for multiple BCCs (Drummond et al., 2015). Epidermal stem cells are well-known to be damaged by chronic inflammation and cicatrization that is localized in the hair follicle bulb and basal layer of the interfollicular epidermis in patients with cicatricial alopecia and deemed precursors of SCC (Kamstrup et al., 2007; Ohyama, 2012; Ratushny et al., 2012). One published case studied three SCCs that were found concomitantly with LPP in a patient with 18 years of LPP duration (Garrido Colmenero et al., 2013).

The national statistics to develop BCC or SCC at least once by the age of 65 years consists of at least 40% to 50% of the American population (UV Exposure and Sun Protective Practices, 2016). The most common type of skin cancer is BCC and >4 million cases are diagnosed per year in the United States (Bleyer et al., 2006; Rogers et al., 2015). Still, the higher absolute rates in our cohort suggest

that close a follow up of patients with a long history of LPP for skin cancers is needed and further studies are needed to explore this issue.

The strength of our study is the high numbers for this rare condition and our study population was selected from patients who were evaluated at a single institution. The accuracy of the LPP diagnosis is high because most patients were seen by Cleveland Clinic hair disorder specialists and the diagnosis was confirmed with a scalp biopsy examination.

This study also has some limitations: the retrospective study design as well as the potential recall bias in the epidemiologic data and potential bias in the measuring predictors.

#### Conclusions

To our knowledge, this is the second largest series of patients with a diagnosis of LPP in the literature to date. Hashimoto's thyroiditis, hypothyroidism, and hirsutism were positively associated with LPP and allergic rhinitis, diabetes mellitus type II, hyperlipidemia, vitamin D deficiency, depression, and sleep problems were negatively associated.

Further larger scale studies that investigate a larger population with LPP are needed to confirm the significance of these findings. Clinicians should understand the importance of the comorbidity profile of patients with LPP to better understand the potential pathogenic mechanism and be able to optimize the laboratory work up.

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