Dermatology Practical & Conceptual

Association Between Periostin Expression and Disease Progression in Lichen Planopilaris: Insights Into Pathophysiology

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ABSTRACT

Introduction: Lichen planopilaris (LPP) is the most prevalent form of scarring alopecia and lymphocytic infiltration that affects the infundibulum and isthmus, perifollicular melanophages, and perifollicular constrictive fibrosis

Objective: We aimed to assess the contribution of periostin tissue levels to the pathogenesis of LPP and its association with disease severity.

Methods: A total of 30 cases diagnosed with LPP between July 15 and October 15, 2022 were studied. Patient age, disease duration, disease severity, and periostin levels were recorded, and periostin immunohistochemistry was performed to obtain histoscores for the perifollicular area, dermoepidermal junction, fibroblasts, and inflammatory cells, and these were compared with the control group.

Results: The female sex predominated, with the majority (67%); 25 patients were classified with mild disease and five with severe LPP. Statistically significant differences were found in keratinocyte staining intensities between the mild and severe groups (P=0.023; P<0.01), with the LPP group exhibiting

a higher rate of moderate staining intensity compared to the control group. In terms of perifollicular staining intensities, the rate of non-staining was higher in the control group compared to the LPP group. Statistically significant differences were also observed in fibroblast (P=0.001) and inflammatory cell (P=0.001) staining intensities between the groups. No statistically significant difference was found between the patients with mild or severe disease in the LPP group.

Conclusion: The relationship between periostin and disease severity could not be conclusively established. The presence of periostin staining in all histopathologically-affected areas of patients with LPP suggests that periostin may serve as a promising marker in LPP.

Introduction

Lichen planopilaris (LPP) stands as the most prevalent form of scarring alopecia, characterized by lymphocytic infiltration [1, 2]. Its pathogenesis remains elusive, with a proposed autoimmune etiology mediated by T lymphocytes specific to follicular antigens [3]. The bulge region of the hair follicle, targeted by T lymphocytes, is considered a central site of antigenic stimulation. Clinically, LPP typically manifests with perifollicular erythema and scaling, progressing to irreversible scarring. Patients may describe pain, itching, and burning on the scalp. LPP profoundly impacts patients' psychosocial well-being due to its potential for permanent hair loss. Despite being regarded as a benign condition by physicians, patients tend to perceive it as a considerably more significant issue [4]. Thus, prompt diagnosis and treatment are of utmost importance [2, 4]. There is no discernible clinical or laboratory marker indicative of the disease's progression or severity in patients with LPP, yet the Lichen Planopilaris Activity Index (LLPPAI) offers an objective method for disease monitoring [2]. Periostin, an extracellular matrix protein, acts as an integrin ligand receptor on cells, triggering proliferation, migration, and differentiation. Major inducers of periostin production include interleukin (IL)-4, IL-13, and transforming growth factor beta [5]. Discovered in 1993, periostin is a soluble secreted extracellular matrix protein that has been studied in cardiac diseases, fibrosis-related disorders, cancers, and various dermatological diseases [5, 6]. Periostin expression occurs in the basal membrane, papillary dermis, and hair follicles. [7, 8]; it is believed to play a role in tissue repair. In inflammatory conditions, mast cells are considered to significantly contribute to the process by releasing histamine, triggering periostin release from fibroblasts through histamine secretion [7]. The pathology of LPP involves lichenoid lymphocytic infiltration affecting the infundibulum and isthmus, perifollicular melanophages, perifollicular constrictive fibrosis, necrotic keratinocytes, vacuolar degeneration in basal cells, sebaceous gland and erector pili muscle atrophy, hair follicle losses, and fibrous tracts [9]. Periostin, present in the papillary dermis in normal skin, has been detected in all dermal layers following injury. Thus, it is considered to facilitate the proliferation and differentiation of epithelial cells [5, 6].

Objective

This study aimed to elucidate the interaction between periostin and tissue in patients with LPP due to its implications in fibrosis, inflammation, and epidermal changes. We sought to compare periostin levels based on the LPPAI and evaluate the association between periostin and keratinocytes, dermoepidermal junction, fibroblasts, collagen in the perifollicular area, and inflammatory cells compared to a control group. We were unable to find any studies in the literature investigating periostin in hair diseases.

Methods

The study was conducted at theBaşakşehir Çam and Sakura City Hospital Dermatology and Pathology Clinics with patients aged 18 and above who were diagnosed with LPP and who provided voluntary consent after reading and signing the informed consent form. Ethical approval for the study was received from the local ethics committee. Individuals aged 18 and above who had not received treatment in the previous three months, whose LPP diagnosis was histopathologically confirmed through a biopsy and H&E staining, and who had complete clinical and pathological data were enrolled in the study. Punch biopsy tissues obtained at the time of diagnosis were used for periostin examination. Patients' age, sex, disease duration, and disease severity were recorded. Disease severity was evaluated using the classical LPPAI [10].

Immunohistochemical Staining

In this study, periostin immunohistochemistry was performed as previously reported [11], and the clinicopathological characteristics of periostin and LPP were evaluated. Both the patient and control groups were evaluated by the same pathologist blinded to patient information. The periostin

staining intensity in the perifollicular area, fibroblasts, inflammatory cells, keratinocytes, fibroblasts, collagen, and dermoepidermal junction was compared between the two groups. Immunohistochemical staining was performed using the Human POSTN/OSF-2 (Periostin) ELISA kit (Elabscience Biotechnology Inc., USA). In histopathological examination, five visual fields were randomly selected, and the percentage of positively-stained cells and staining intensity were evaluated by the pathologist. The staining was graded using a histoscore (distribution x intensity). The stained areas were scored according to the percentage of staining as follows: <25%, 0.1; 26-50%, 0.4; 51-75%, 0.6; and 76-100%, 0.9. In addition, staining intensity was scored as 0 (no staining), 0.5 (very weak staining), 1 (weak staining), 2 (moderate staining), or 3 (very strong staining) [12].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 26 (IBM SPSS, Turkey). Descriptive statistical methods, such as mean, standard deviation, median, frequency, ratio, minimum, and maximum, were used to evaluate the study data. For the comparison of the two groups in terms of quantitative data that did not exhibit a normal distribution, the Mann-Whitney U test was employed. Fisher's exact test and the Fisher-Freeman-Halton exact test were used to compare qualitative data. Significance was assessed at a minimum level of $P<0.05$.

Results

During the study period, a total of 30 cases histopathologically diagnosed with LPP were included, with 80% (N=24) being female and 20% (N=6) male. The ages of the cases ranged from 18 to 77 years. Disease duration ranged from 1 to 120 months, with a mean of 38.00 ± 36.73 months. Among the patients, five had severe disease, while 25 had mild disease. Fibrosis was absent in five cases (18%) and present in 25 cases (83.3%). Patients' biopsies for histopathological examination were obtained from active margins suspected of LPP, with no additional dermatological features present in their hair. After evaluating patients diagnosed with LPP via hematoxylin and eosin staining, they were compared with a healthy control group of 30 individuals regarding periostin. Five patients were classified as having severe LPP. Both the LPP group and the control group exhibited strong staining for periostin in the perifollicular and dermoepidermal junction areas. While the staining percentages of the patient and control groups were similar to each other (63% vs. 70%, respectively) in the evaluation performed for dermoepidermal periostin, no statistical significance was detected in the perifollicular area, despite the predominance of staining in favor of the patient group. The rate of non-staining in the control group was higher than in the LPP group. The rate of non-staining was higher in the control group compared to the LPP group. Statistically significant differences were observed between the keratinocyte histoscore measurements of the groups ($P= 0.001$; $P<0.01$), with the moderate staining intensity being higher in the LPP group than in the control group. Statistically significant differences were also found in fibroblast staining intensities between the groups ($P=0.001$), with the moderate staining intensity being higher in the LPP group than in the control group (Table 1). Statistically significant differences were observed in inflammatory cell staining intensities between the groups ($P=0.001$). Accordingly, the moderate staining intensity in the LPP group was higher than that in the control group. When inflammatory cells were evaluated using hematoxylin and eosin staining, weak staining was observed in 43% of cases, while moderate-to-strong staining was observed in the remaining cases. No statistically significant difference was found between the patients with mild and with severe disease in the LPP group (Table 2).

Conclusions

LPP is a lymphocytic hair-bearing skin disease characterized by persistent cicatrizing alopecia due to its effect on perifollicular units. Periostin is an extracellular matrix protein that has been used to investigate the relationship between the extracellular matrix and diseases of the skin. In our study, we compared the immunohistochemical staining of periostin in tissue biopsies of LPP patients with that of a control group in the perifollicular, dermoepidermal region, fibroblasts, collagen, inflammatory cells, dermoepidermal junction, and keratinocytes; significantly elevated periostin staining was detected in inflammatory cells, keratinocytes, and fibroblasts. This study explored periostin in the context of hair follicle disorders. The incidence of LPP has been reported to be between 1% and 8% [13]. In our study, 52 patients were identified as having been pathologically diagnosed with LPP over a two-year period, although only 30 patients were included in the analysis due to incomplete data. In previous reports, the mean age of patients with LPP ranged from 25 to 70 years, while in our study, the mean age was determined to be 40.37 ± 14.27 years. While 20 patients were in the 25-45 age range, only one patient was under 25 years old. LPP is more commonly observed in females. A previous study evaluating 46 patients with LPP reported a female-to-male ratio of 4.75:1 [3], which was the same as in our study. Zhang et al. [11] demonstrated elevated tissue periostin expression in oral lichen planus. Those authors compared patients' tissue levels with blood levels, revealing that patients with high tissue expression also exhibited high blood levels of periostin. Furthermore, proinflammatory cytokines IL-6 and tumor necrosis factor were found to be elevated in patients'

Table 1. Evaluation of Histoscore Measurements in the Patient and Control Groups.

	Histoscore	Total (n = 60)	Control (n = 30)	LPP (n = 30)	[a]*P*
Dermoepidermal junction	Min-max (median)	0.1-2.7 (2.7)	0.4-2.7 (2.7)	0.1-2.7 (2.7)	0.646
	Mean ± SD	1.94 ± 0.94	2.00 ± 0.94	1.89 ± 0.96	
Collagen	Min-max (median)	0.1-2.7 (1.2)	0.4-2.7 (1.8)	0.1-2.7 (1.2)	0.304
	Mean ± SD	1.39 ± 0.73	1.49 ± 0.80	1.29 ± 0.66	
Keratinocyte	Min-max (median)	0-1.8 (0.6)	0-1.8 (0.4)	0-1.8 (0.8)	0.023*
	Mean ± SD	0.79 ± 0.70	0.58 ± 0.67	0.99 ± 0.69	
Perifollicular area	Min-max (median)	0-2.7 (2.7)	0-2.7 (2.3)	0-2.7 (2.7)	0.370
	Mean ± SD	1.88 ± 1.03	1.76 ± 1.10	2.00 ± 0.95	
Fibroblast	Min-max (median)	0-1.8 (0.4)	0-1.8 (0)	0-1.8 (0.4)	0.001**
	Mean ± SD	0.57 ± 0.68	0.24 ± 0.43	0.89 ± 0.73	
Inflammatory cell (IHC)	Min-max (median)	0-1.8 (0.4)	0-1.8 (0)	0-1.8 (0.7)	0.001**
	Mean ± SD	0.56 ± 0.59	0.29 ± 0.42	0.83 ± 0.61	

[a]Independent samples t-test, **P*<0.05, ***P*<0.01

Abbreviations: IHC = immunohistochemical staining; LPP = lichen planopilaris SD = standard deviation.

Table 2. Evaluation of Staining Intensities in the Patient and Control Groups.

	Staining intensity	Total (n = 60) n (%)	Control (n = 30) n (%)	LPP (n = 30) n (%)	*P*
Dermoepidermal junction	No staining	0 (0)	0 (0)	0 (0)	[a]0.350
	Weak staining	10 (16.7)	6 (20.0)	4 (13.3)	
	Moderate staining	10 (16.7)	3 (10.0)	7 (23.3)	
	Very strong staining	40 (66.7)	21 (70.0)	19 (63.3)	
Collagen	No staining	0 (0)	0 (0)	0 (0)	[b]0.110
	Weak staining	22 (36.7)	12 (40.0)	10 (33.3)	
	Moderate staining	29 (48.3)	11 (36.7)	18 (60.0)	
	Very strong staining	9 (15.0)	7 (23.3)	2 (6.7)	
Keratinocyte	No staining	12 (20.0)	8 (26.7)	4 (13.3)	[a]0.001*
	Weak staining	19 (31.7)	15 (50.0)	4 (13.3)	
	Moderate staining	29 (48.3)	7 (23.3)	22 (73.3)	
	Very strong staining	0 (0)	0 (0)	0 (0)	
Perifollicular area	No staining	5 (8.3)	4 (13.3)	1 (3.3)	[b]0.504
	Weak staining	5 (8.3)	3 (10.0)	2 (6.7)	
	Moderate staining	14 (23.3)	7 (23.3)	7 (23.3)	
	Very strong staining	36 (60.0)	16 (53.3)	20 (66.7)	
Fibroblast	No staining	25 (41.7)	20 (66.7)	5 (16.7)	[a]0.001*
	Weak staining	20 (33.3)	8 (26.7)	12 (40.0)	
	Moderate staining	15 (25.0)	2 (6.7)	13 (43.3)	
	Very strong staining	0 (0)	0 (0)	0 (0)	
Inflammatory cell (IHC)	No staining	20 (33.3)	17 (56.7)	3 (10.0)	[a]0.001*
	Weak staining	24 (40.0)	11 (36.7)	13 (43.3)	
	Moderate staining	16 (26.7)	2 (6.7)	14 (46.7)	
	Very strong staining	0 (0)	0 (0)	0 (0)	

[a]Pearson Chi-squared test, [b]Fisher-Freeman-Halton exact test, ***P*<0.01
Abbreviation: IHC = immunohistochemical staining.

blood. Consistent with that study, we found that tissue periostin levels were higher in patients compared to the control group. Furthermore, the staining of inflammatory cells with periostin was found to be significantly high. However, due to the lack of assessment of patients' blood periostin levels, the alignment between blood and tissue periostin levels could not be evaluated in our study. While periostin secretion in oral mucosal epithelium was previously reported to be higher than in the control group, our study found greater moderate and strong staining in the perifollicular area in the patient group compared to the control group, albeit without a statistically significant difference. Although periostin expression is known in the perifollicular area, the similar rate of secretion in the LPP group may be related to the low number of cases in our sample. The association of periostin with allergic diseases is well documented. However, the relationship between mast cells and periostin remains to be fully elucidated [11]. Studies have shown that in atopic dermatitis, periostin is released from dermal fibroblasts via the influence of the cytokines IL-4 and IL-13 acting through the TH2 pathway. It has been demonstrated that periostin secretion occurs in wild-type fibroblasts, i.e., fibroblasts that are not stimulated by IL-13, and that periostin affects keratinocyte proliferation and differentiation. The autocrine effects of periostin and its role in keratinocyte proliferation and differentiation through paracrine effects involving IL-6 and IL-1β have also been suggested. In the absence of periostin secretion in the dermoepidermal region of normal skin, no pathology has been encountered in the epidermis. However, studies conducted with atopic patients and mouse models indicate that periostin affects the epidermis through autocrine and paracrine effects during inflammation and wound repair [14]. Similarly, the high rate of periostin detection in lesions in atopic patients suggests that it may play a role in chronic atopic dermatitis and skin lichenification. In our study, keratinocyte staining with periostin was higher in patients with LPP than in the control group, which is consistent with studies suggesting that periostin has an effect on keratinocytes [11]. The relationship between periostin and mycosis fungoides is being investigated [15, 16]. In a study evaluating patients with mycosis fungoides (MF), it was demonstrated that periostin staining was more prominent in early stages. A study examining patients with MF demonstrated that periostin staining was elevated during the early stages. The authors reported that in the early stages of MF lesions, macrophages stimulated by periostin were involved, while in advanced stages, macrophages produced by tumor cells replaced periostin [16]. Although our study evaluated biopsies taken from active margins, the disease duration of our patients was on average around three years. This finding suggests a continuous effect of periostin in LPP.

The involvement of periostin in fibrosis has been previously reported. Periostin staining has been observed in sclerotic and morphea lesions, showing staining in dermal fibroblasts [17]. Moreover, elevated levels of periostin have been detected in keloid tissue [18]. In localized scleroderma, significant elevations in periostin staining have been detected in the dermoepidermal junction and dermis. In our study, while significant staining was observed in fibroblasts compared to the control group, there was no difference in the dermoepidermal area, with both the patient and control groups exhibiting strong staining. Inflammation, trauma, or tumor-damaged skin triggers a physiological process involving humoral factors, mediators, cytokines, and growth factors. In addition, mast cells and T lymphocytes, which play a role in tissue repair, migrate to the damaged tissue and stimulate the production of various extracellular matrix proteins by these cells. Periostin production is considered to begin in dermal fibroblasts due to the effect of histamine released from mast cells, providing the necessary environment for fibrosis [7]. A study conducted on oral lichen planus revealed elevated mast cell levels in tissue [11]. Similarly, the development of perifollicular fibrosis in patients with LPP supports the role of mast cells and T lymphocytes in the etiopathogenesis of the disease. In our study, patients' blood periostin levels were not evaluated, precluding a comparison between tissue and blood periostin levels. The lack of evaluation of mast cells can be considered another limitation of our study.

The staining of fibroblasts, perifollicular areas, keratinocytes, and inflammatory cells with periostin indicates that periostin has a significant effect on patients with LPP. However, due to the small number of severe cases in our study, the relationship between periostin and disease severity did not show statistical significance. The observation of periostin staining in all areas histopathologically affected by LPP suggests that periostin could serve as a promising marker in patients with this disease. Further comprehensive studies on this subject may shed light on the relationship between periostin, hair follicles, and the severity of LPP.

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