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Clinicopathologic and immunophenotypic characterization of lichen planopilaris and central centrifugal cicatricial alopecia: A comparative study of 51 cases

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Abstract

Background: The purpose of the study was to compare the histopathologic and immunophenotypic features of central centrifugal cicatricial alopecia (CCCA) and lichen planopilaris (LPP) to better characterize and differentiate these two clinical entities. CCCA remains an ill-defined and still-unsettled histologic entity and many hair loss experts regard CCCA to be histologically indistinguishable from LPP. Given the overlapping histologic features of these two lymphocyte-predominant cicatricial alopecias, and the lack of consensus regarding the significance of proposed distinctions, dermatopathologists face difficulty in providing clinicians and patients certainty with a definitive diagnosis of CCCA vs LPP.

Methods: We performed a retrospective review of 51 scalp biopsies of patients with either the clinical diagnosis of CCCA (27 cases) or LPP (24 cases). Clinical information, histologic features of hematoxylin-eosin-stained sections, and a panel of immunohistochemical markers were evaluated on scalp biopsies. Tested parameters were quantified, and statistical analysis was performed.

Results: Our study found no differences on either histologic assessment or immunophenotypic characterization between cases of classic LPP and CCCA.

Conclusion: The conclusion of this study is that the inflammatory infiltrates in CCCA and LPP are not only histologically similar but also immunophenotypically indistinguishable.

KEYWORDS

biopsy, central centrifugal alopecia, cicatricial, cicatricial alopecia, diagnosis, hair, immunohistochemistry, lichen planopilaris, scarring

1 | INTRODUCTION

Primary scarring alopecia, also referred to as cicatricial or permanent alopecia, has traditionally been categorized based upon the character of the inflammatory cell infiltrate (ie, lymphocytic, neutrophilic, mixed, and nonspecific).[1] Lichen planopilaris (LPP) presents with permanent hair loss in highly variable patterns that can be pruritic, tender, or asymptomatic, most frequently in females in young adulthood. It commonly results in scattered foci of hair loss associated with perifollicular erythema, follicular hyperkeratosis, and scarring. Most experts recognize three distinct clinical patterns, namely, classic LPP, Graham-Little-Piccardi Syndrome, and frontal fibrosing alopecia (FFA).[2-4] Central centrifugal cicatricial alopecia (CCCA) most often affects middle-aged females of African descent and presents with a

gradually expanding patch of permanent hair loss centered on the crown or vertex of the scalp. Similar to LPP, lesions of CCCA may be pruritic, tender, or asymptomatic.[2]

Since the pattern of hair loss seen in LPP, CCCA, and other permanent alopecias may have significant clinical overlap, the diagnosis of these entities cannot be reliably made on clinical features alone.[5,6] Diagnostic limitations remain, clinically and histologically, both for making definitive diagnoses of primary cicatricial alopecias and understanding the biologic natures of the different alopecic processes.

Lymphocyte-predominant primary cicatricial alopecias, including LPP and CCCA, share the following histopathologic features: blue/gray-staining perifollicular fibrosis at the infundibulo-isthmic portion of the hair follicle, a perifollicular lymphocytic infiltrate associated with the fibrosis, compound follicles, "eccentric epithelial atrophy,"[7,8] eccrine duct dilation,[9] premature desquamation of the inner root sheath (PDIRS) of inflamed follicles, and loss of sebaceous glands.

There is no study that has fully evaluated the immunohistochemistry (IHC) of LPP and CCCA to help better define these diagnoses. IHC markers have been used to characterize other alopecic conditions such as alopecia areata, pattern hair loss (androgenetic alopecia), DLE, and LPP. A recent immunohistochemical analysis of the three primary scarring lymphocytic alopecias (LPP, DLE, and CCCA) found that LPP and CCCA share identical $CD123^{+}$ plasmacytoid cell (PDC) features (PDCs arranged as single, interstitial cells,) whereas DLE has markedly distinct PDC characteristics (PDCs comprising a greater percentage of the infiltrate and arranged in clusters).[10] These molecular findings suggest a common pathophysiology for LPP and CCCA, distinct from that of DLE.

The present study is the most comprehensive immunohistochemical profile published of LPP and CCCA, with the aim of differentiating LPP from CCCA with IHC staining. This will help in understanding etiology, diagnosis, and management of these two distinct clinical entities with identical histopathologic features.

2 | METHODS

2.1 | Inclusion criteria

This study was approved by the institutional review board of the Saint-Pierre University Hospital. Archived biopsy samples between January 2014 and December 2016 were obtained from CTA Labs, Portland, OR and Saint-Pierre University Hospital in Brussels, Belgium. All involved patients had a diagnosis of either LPP or CCCA by a clinical dermatologist with expertise in alopecia using characteristic clinical presentations along with histologic confirmation by two dermatopathologists with expertise in hair pathology.

Cases included in this study met the following criteria: (a) a characteristic clinical presentation of either CCCA or LPP as determined by a clinical dermatologist with expertise in alopecia along with (b) confirmed histopathologic diagnosis by two dermatopathologists with expertise in hair pathology and (c) histopathologic findings including all three of the following conditions: (a) perifollicular scarring at the level of the infundibulum or superficial isthmus with a perifollicular lymphocytic infiltrate at the same level; (b) absence of interfollicular epidermal interface dermatitis; and (c) absence of any infiltrate in the deep dermis, subcutis, and around eccrine coils.

2.2 | Processing of specimens

Tissues samples from 4-mm punch biopsies were fixed in 10% formaldehyde, embedded in paraffin, and stained with hematoxylin-eosin (H&E). All specimens were processed using the HoVert technique[11] followed by immunohistochemical staining of both vertical and horizontal sections. All processing was performed in the Department of Pathology in Jules Bordet Institute in Brussels and CTA Labs. Two dermatopathologists (C.T.T. and A.K.) reviewed the H&E-stained sections using a checklist of histologic features. The following features on each biopsy H&E were documented: perifollicular fibrosis at the level of the isthmus-infundibulum, depth/location and magnitude of lymphocytic infiltrate, loss of sebaceous lobules, the presence of compound follicles, squamatization of the follicular basal layer, and catagen/telogen shift.

2.3 | Examination of specimens

CD3, CD4, CD8, CD20, CD68, CD123, myeloperoxidase, and CK15 IHC staining was performed on all samples. All immunohistochemical studies were performed on formalin-fixed tissues samples, using the avidin-biotin complex immunoperoxidase technique with diaminobenzidine as

TABLE 1 Demographic and clinical data on 51 adults with CCCA and LPP

	CCCA (n = 27), n	LPP (n = 24), n	P value
Sex			.717
Male	2	2	
Female	26	22	
Age distribution			.978
21-30	5	5	
31-40	5	5	
41-50	4	4	
51-60	4	4	
61-70	7	7	
71-80	2	2	
81+	0	0	
Race			<.001
African/Black	27	7	
Caucasian	0	16	
Other	0	1	
Clinical			<.001
Central alopecia	27	0	
Patchy alopecia	0	11	
Diffuse alopecia	0	11	
Frontal alopecia	0	2	

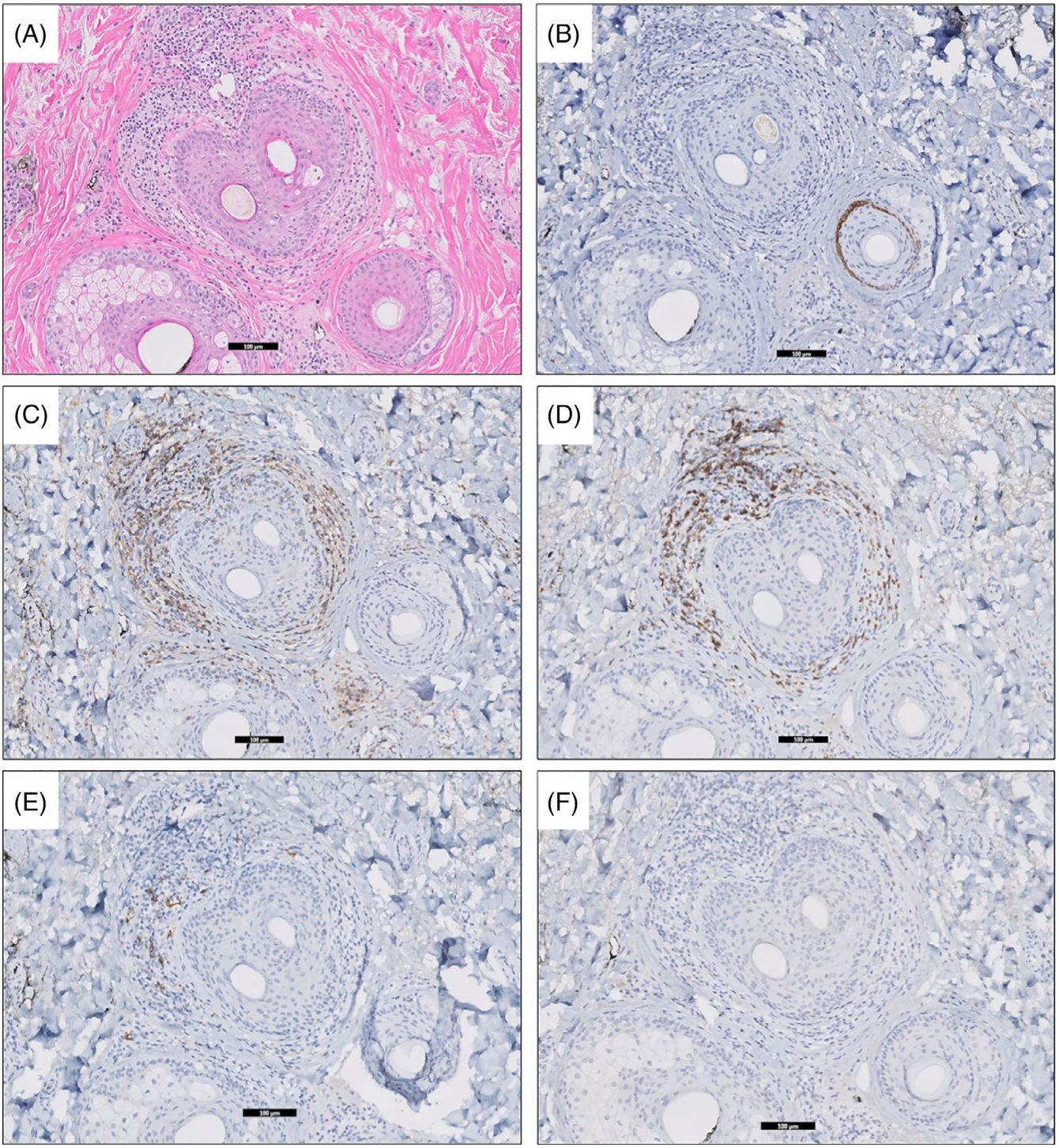

FIGURE 1 Histopathology and immunophenotype of central centrifugal cicatricial alopecia (CCCA). Horizontal histopathologic sections from a punch biopsy demonstrating, A, hematoxylin-eosin (H&E) staining of an affected follicle (center) with typical features of CCCA (perifollicular lymphocytic infiltrate and perifollicular fibrosis,) and a smaller unaffected follicle (bottom right) for comparison (H&E, 40×). B-F, Horizontal sections of the same follicles demonstrating representative immunohistochemical staining patterns for (B) CK15, (C) CD4, (D) CD8, (E) CD20, and (F) CD123

chromogen, on unstained 4-μm sections placed on charged slides. The automated staining involves 74 steps beginning with deparaffinization at 72°C and ending with a final slide rinse and cover slipping. Histologic and immunophenotypic features were compared between LPP and CCCA by χ^2 test using Yates's correction to calculate *P* values. A *P* value of less than .05 was considered statistically significant.

All samples were evaluated by two hair-expert dermatopathologists. Densities of CD3-, CD4-, CD8-, CD20-, CD68-, and myeloperoxidase-

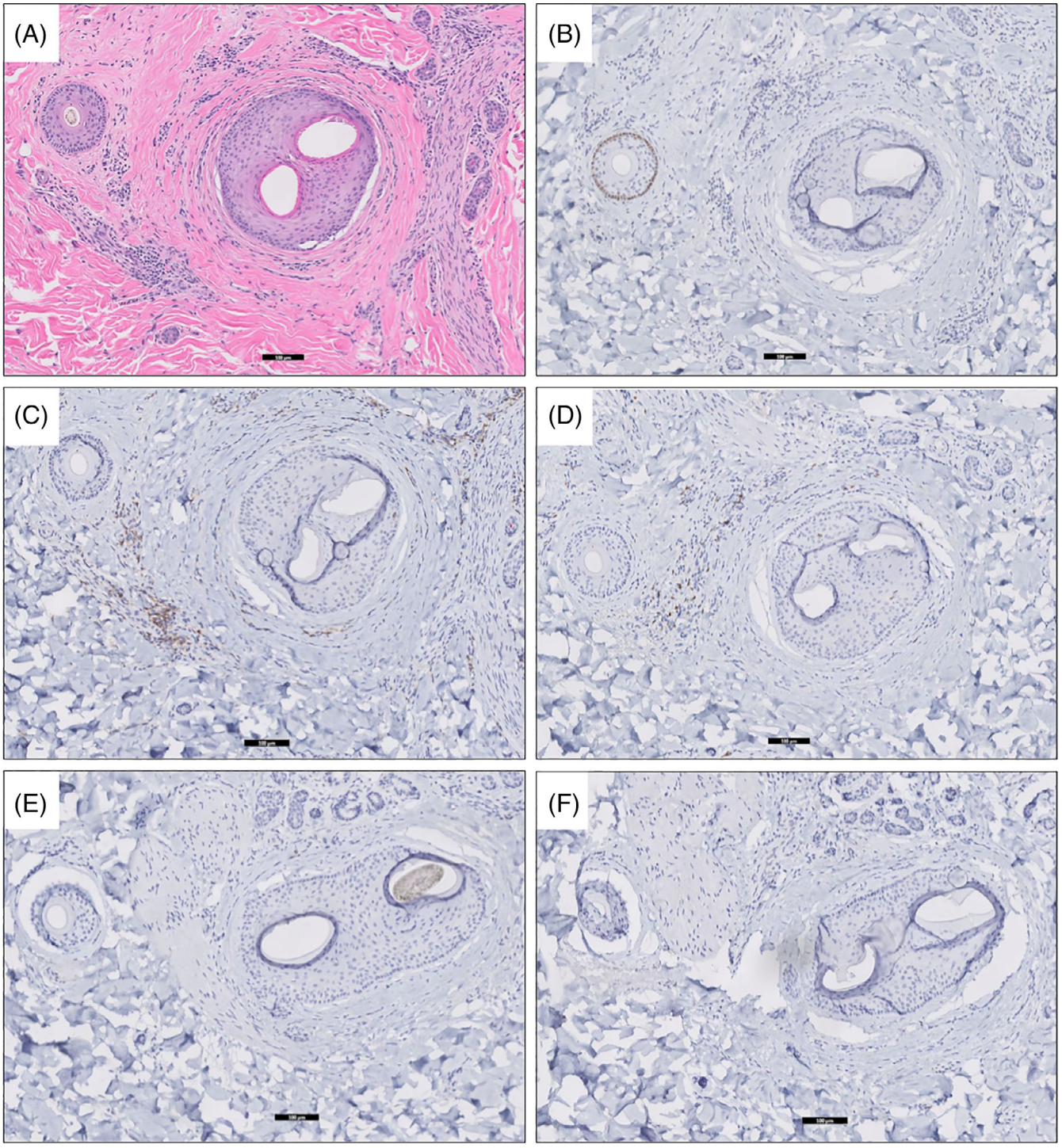

FIGURE 2 Histopathology and immunophenotype of lichen planopilaris (LPP). Horizontal histopathologic sections from a punch biopsy demonstrating, A, hematoxylin-eosin (H&E) staining of an affected follicle (center) with typical features of LPP (perifollicular lymphocytic infiltrate and perifollicular fibrosis,) and a smaller unaffected follicle (left) for comparison (H&E, 40×). B-F, Horizontal sections of the same follicles demonstrating representative immunohistochemical staining patterns for (B) CK15, (C) CD4, (D) CD8, (E) CD20, and (F) CD123

positive immune cells within the infiltrates were assessed using a five-point ordinal grading system (0, trace, 1+, 2+, 3+) within the epidermis, papillary dermis, reticular dermis, subcutis, peri-infundibular dermis, peribulbar dermis and empty follicular fibrous tracts (stela). Percentage of $CD123^{+}$ PDCs of the entire infiltrate was estimated in a semiquantitative manner from 0% to 100% in 25% increments as follows: sparse when 0% to 25% PDCs present; 1+ when 25% to 50% PDCs are present; 2+ when 50% to 75% PDCs are present; and 3+ when 75% to 100% PDCs are present. CK expression was read as positive or negative.

3 | RESULTS

3.1 | Patient demographics and clinical presentations

Fifty-one patients were included in this study, 27 with a clinical diagnosis of CCCA and 24 with LPP. All patients diagnosed with CCCA were African Americans with central scalp alopecia, while the majority of patients with LPP were Caucasian with either patchy or diffuse alopecia. The sex and age distributions were nearly identical in both groups (Table 1).

TABLE 2 Histologic features of samples of CCCA and LPP

	CCCA (*n* = 27), *n* (%)	LPP (*n* = 24), *n* (%)	*P* value
Perifollicular fibrosis			.437
Negative	5 (19)	0 (0)	
Trace	4 (15)	2 (8)	
+	2 (7)	3 (13)	
++	7 (26)	11 (46)	
+++	9 (33)	8 (33)	
Lymphocytic infiltrate density			.483
Negative	2 (7)	0 (0)	
Trace	0 (0)	1 (4)	
+	11 (41)	4 (17)	
++	8 (30)	13 (54)	
+++	6 (22)	6 (25)	
Squamatization of the basal layer of follicle			.201
Present	20 (74)	22 (92)	
Absent	7 (26)	2 (8)	
T:V ratio			.941
4:1	8 (30)	4 (17)	
3:1	1 (4)	0 (0)	
2.5:1	0 (0)	1 (4)	
2:1	3 (11)	2 (8)	
1.5:1	0 (0)	1 (4)	
1:1	8 (30)	4 (17)	
1:2	6 (22)	6 (25)	
1:3	1 (4)	3 (13)	
1:4	0 (0)	3 (13)	
Catagen-telogen shift (%)			.671
0	16 (59)	10 (42)	
1–5	1 (4)	6 (25)	
6-10	7 (26)	7 (29)	
11-15	2 (7)	0 (0)	
16-20	0 (0)	0 (0)	
21-25	1 (4)	1 (4)	
>25	0 (0)	0 (0)	

3.2 | Histopathologic and immunophenotypic analysis

The histopathologic and immunophenotypic features are represented in Figures 1 and 2 and summarized in Tables 2 and 3. Consistent with published data, there was no difference in any of the histopathologic

TABLE 3 Immunohistochemical features of samples of CCCA and LPP

	CCCA (*n* = 27), *n*	LPP (*n* = 24), *n*	*P* value
CD4			.340
Negative	0	0	
Trace	6	1	
+	7	5	
++	7	14	
+++	7	4	
CD8			.254
Negative	1	1	
Trace	14	5	
+	11	15	
++	1	3	
+++	0	0	
CD20			.802
Negative	9	4	
Trace	8	11	
+	5	3	
++	3	5	
+++	2	1	
CD123			.969
Negative	18	15	
Trace	7	8	
+	2	1	
++	0	0	
+++	0	0	
MPO			.781
Negative	22	16	
Trace	4	6	
+	0	2	
++	1	0	
+++	0	0	
CD68			.490
Negative	5	1	
Trace	18	17	
+	4	6	
++	0	0	
+++	0	0	
CD15			.277
Absent	24	24	
Present	3	0	

features examined and compared between the two groups, including the presence and degree of perifollicular fibrosis, the presence and degree of lymphocytic infiltrate, squamatization of the basal layer of the hair follicle, terminal-to-vellus hair ratio, and percent of catagen/telogen follicles; these results are summarized in Table 2. No differences between the two groups were noted with regard to additional histologic features including basal vacuolization, exocytosis of lymphocytes, dyskeratosis, or the number of follicular units affected. In line with these findings, the immunophenotypic analyses, which included CD4, CD8, CD20, CD123, MPO, CD68, and CK15, did not demonstrate any statistically significant differences between the two groups. Cases of both LPP and CCCA demonstrated significant enrichment of $CD4^+$ T-lymphocytes, and to a lesser degree $CD8^+$ T-lymphocytes and $CD20^+$ B-lymphocytes, in their inflammatory infiltrates. No differences were observed in lymphocyte subtypes present at the follicular epithelium between the two groups. There was no involvement of MPO-positive neutrophils, CD68-positive macrophages, or CD123-positive PDCs. Both LPP and CCCA were mostly or completely devoid of CK15-positive cells.

4 | DISCUSSION

A prospective, blinded study comparing the scarring alopecias published in 2005 illustrates the diagnostic limitations among lymphocyte-predominant primary cicatricial alopecias (excluding alopecic lupus erythematosus), demonstrating that histopathologic features of lymphocytic-associated scarring alopecias do not correlate with the clinical variants. In this study, a group of dermatopathologists assessed six clinically distinct primary cicatricial alopecias: four lymphocyte-predominant (classic LPP, FFA, pseudopelade of Brocq, and CCCA) and two neutrophil-predominant (folliculitis decalvans and tufted folliculitis). The experts were able to distinguish between lymphocyte- and neutrophil-predominant alopecias, but "within the two groups, the clinically distinct entities could not be distinguished on their histopathology."[12]

The present study adds to the existing data evaluating the histologic and immunohistochemical features of CCCA and LPP in order to aid in the immunohistopathologic distinction between these two lymphocyte-predominant primary cicatricial alopecias. Several markers, including PDIRS of noninflamed follicles and patterns of follicular fibrosis[13,14] have been proposed as differentiating criteria. PDIRS in LPP is limited to inflamed follicles[15] sparing noninflamed follicles,[8] in distinction to CCCA, which has PDIRS in both inflamed and noninflamed follicles.[16,17] However, the precise histologic uniqueness of CCCA remains a dynamic and actively evolving area of interest.[2,17] The present study represents the largest and only study to date examining both the histologic and immunophenotypic characteristics of CCCA and LPP.

This study establishes that among the immunophenotypic markers tested (CD4, CD8, CD20, CD123, MPO, CD68, and CK15,) there are no differences that distinguish LPP from CCCA. In addition, consistent with prior reports, among histologic parameters assessed (presence and degree of perifollicular fibrosis, presence and degree of lymphocytic infiltrate, squamatization of the basal layer of the hair follicle, terminal-to-vellus hair ratio, and percent of catagen/telogen follicles) there were no differences between the two groups. The feature of PDIRS, which in the opinion of these authors represent squamatization of the follicular basal layer, likely secondary to inflammation and degenerative changes produced by the lymphocytic infiltrate, was not specific to either CCCA or LPP, consistent with prior studies.[7] The pattern of perifollicular fibrosis was not assessed in this study.

It is our experience and that of others[12] that the histologic findings of nonlupus lymphocyte predominant primary cicatricial alopecias do not correlate with or help define the clinical variants. Our study demonstrates for the first time that CCCA and LPP are immunophenotypically indistinguishable. These findings support to view that these two forms of lymphocyte-predominant primary cicatricial alopecias, which can only be differentiated by clinicopathologic correlation, have more similarities than differences, with similar therapeutic approaches, histologic features, and, as demonstrated by this study, indistinguishable immune cell immunophenotypes.

This study was limited by its small study size, retrospective design, limited clinical information (such as disease duration or activity at time of biopsy,) and the possibility of clinical or histologic misclassification bias.

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