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ORIGINAL PAPER

Significant reduction in the expression of interleukins-17A, 22 and 23A, forkhead box p3 and interferon gamma delineates lichen planus pigmentosus from lichen planus

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Abstract

Recent studies have noticed significant role of interleukin (IL)-17, 22, 23, Foxp3, interferon-gamma (IFN-γ) and Wnt5a in oral and cutaneous lichen planus (LP). This study was undertaken to assess whether similar expression exists in lichen planus pigmentosus (LPP). We recruited 30 patients of treatment-naïve 'LPP' (in absence of cutaneous/mucosal LP elsewhere, group 1), 10 patients having active treatment-naïve cutaneous 'LP' (group 2), 10 patients having 'post-LP' hyperpigmentation (in absence of active LP and off treatment for at least past 3 months, group 3), and 10 controls. Quantitative real-time polymerase chain reaction (qRT-PCR, peripheral blood mononuclear cells [PBMCs] and skin) and immunohistochemistry (IHC, skin) was performed. *mRNA expression* (*in PBMCs*) of IL-17A, IL-22, IL-23A, IFN-γ and Foxp3 was significantly decreased in *group* 1 *and* 3 as compared to *group* 2 ($p < 0.05$). Wnt5a expression was maximal in controls; and while there was no difference between group 1 and 2; whereas expression in group 3 was significantly lesser than group 1 and 2 ($p < 0.05$). *qRT-PCR* (*skin*) *and IHC* (*skin*) revealed similar results; and mRNA expression and mean fluorescence intensity of IL-17A, IL-22, IL-23A/R was significantly increased in *group* 2 *and* 3 compared to *group* 1 ($p < 0.05$). Mean fluorescence intensity and mRNA expression of IFN-γ, Foxp3 and Wnt5a were significantly increased in *group* 2 compared to *group* 1 ($p < 0.05$); whereas the difference between group 1 and 3 was not significant. Mean fluorescence intensity and mRNA expression of IL-17A, 1L-22 and IFN-γ showed no difference between group 2 and 3; whereas that of IL-23A/R, foxp3 and wnt5a were significantly higher in group 2 than group 3 ($p < 0.05$). Overall, maximal expression of IL-17A, IL-22, IL-23A, IFN-γ and Foxp3 (mRNA PBMCs) was observed in LP. Minimal expression of IL-17A, IL-22, IL-23A/R, IFN-γ and Foxp3 (mRNA skin and IHC skin) was seen in LPP patients. In contrast to LP, LPP lacks the expression of IFN-γ, Foxp3 and the cytokines representing Th17 pathway, and thus seems to have a distinct pathogenesis.

Keywords Lichen planus · Lichen planus pigmentosus · Interleukins 17, 22 and 23 · Interferon gamma

Introduction

Lichen planus pigmentosus (LPP) is an acquired dermal pigmentary disease with an unclear nosological status [1]. The term LPP was initially coined since it was considered to be a macular variant of lichen planus (LP), with some patients exhibiting evidence of classical LP elsewhere [2]. However, both dermatoses demonstrate stark clinical differences. Whereas LP manifests as recurrent itchy papules with a tendency for spontaneous resolution (exceptions are hypertrophic and ulcerative/erosive LP), LPP is macular to begin with, rarely symptomatic and runs a prolonged and protracted course, resistant to treatment. The post-inflammatory hyperpigmentation that occurs secondary to LP

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can potentially simulate LPP, especially in the absence of a definitive prior history of papules.

T-helper 17 (Th17) axis plays an important role in the pathogenesis of psoriasis and has been recently implicated in the causation of vitiligo [3], and oral and cutaneous LP [4]. Interleukin (IL)-23, 17A and 22 are the chief cytokines that orchestrate the Th17 pathway [5]. Interferon-gamma (IFN-γ) is the chief cytokine implicated in the mediation of interface dermatitis, hallmark of LP [6]. Expression of Wnt5a and Forkhead-box protein 3 (Foxp3) has been found to be elevated significantly in LP [7, 8]. With the objective to investigate if LPP does belong to the LP spectrum, we attempted to assess the expression of IL-17A, 22, 23A/R, IFN-γ, Wnt5a and Foxp3 in peripheral blood mononuclear cells (PBMCs) and skin of patients having LPP using quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC), and compared the same with patients having LP and post-LP hyperpigmentation.

Materials and methods

This was a prospective observational study, conducted in the pigmentary clinic of our tertiary care centre from January 2017 to January 2018. We recruited 30 patients having treatment-naïve LPP of disease duration < 3 months (in absence of cutaneous and mucosal LP elsewhere, group 1), ten patients having active treatment-naïve classical cutaneous ‘LP’ of disease duration < 3 months (group 2), 10 patients having ‘post-LP’ hyperpigmentation (absence of active LP, off treatment for at least past 3 months and following up with us since the histopathological diagnosis of LP was first made, group 3), and 10 controls. The patients recruited in group 2 were not subsequently recruited in group 3.

The inclusion criteria for LPP were

1. Clinical—hyperpigmented, non-scaly, macules and patches, either discrete or coalescing to from diffuse, blotchy, reticular or perifollicular patterns (Fig. 1a).
2. Histopathological—an ongoing interface dermatitis with prominent melanin incontinence (Fig. 1b).
3. An absent inflammatory phase prior to the appearance of the hyperpigmented patches.
4. Treatment naïve with a disease duration < 3 months.
5. Age > 18 years.

Exclusion criteria for LPP

1. Patients having LP elsewhere in body (mucosal, nails, scalp or cutaneous).
2. Patients on treatment.

Fig. 1 **a** Clinical morphology of lichen planus pigmentosus patient. Well-defined, hyperpigmented patches affecting face and neck are seen. **b** Lesional histopathology demonstrating slightly atrophic epidermis, basal cell vacuolization, mild lymphocytic infiltrate and dermal melanin incontinence (hematoxylin and eosin, 200 ×)

Approval of institute ethical committee was obtained prior to initiating this project (IEC-01/2016-320).

Two punch skin biopsies measuring 3 mm were procured from each patient in groups 1, 2 and 3. First biopsy was utilized to ascertain the clinical diagnosis by histopathology and perform IHC as per standard procedure [3]. The second biopsy was employed to perform qRT-PCR. Control skin samples were obtained from the healthy humans undergoing voluntary excision for benign skin lesions/cysts. Blood sample was obtained from all patients and controls under aseptic precautions (3 ml each, anticoagulant ethylenediamine tetra-acetic acid added). An informed written consent was obtained from the patients and controls before inclusion in the study.

RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR)

Total cellular messenger ribonucleic acid (mRNA) of PBMCs and tissue was isolated by trizol reagent using manufacturer's protocol. RNA quantification was done by multimode reader (Teccan) and 1 µg/µl (260/280 = 1.8–2.0) concentration of RNA was employed for complimentary deoxyribonucleic acid (cDNA) synthesis (using Revert aid first strand c-DNA synthesis kit). IFN-γ, IL-17A, IL-22, IL-23A, Wnt5a and Foxp3 were amplified by qRT-PCR using the USB VeriQuest SYBR Green qPCR Master Mix on Real-Time PCR System (Roche LC96) with a control β-actin. Table 1 depicts all the primers used in this study.

Reagents

First-Strand cDNA Synthesis kit was obtained from Verso. For qPCR, USB VeriQuest SYBR Green qPCR Master Mix was obtained from Affymetrix. The primary antibody for IL-17A (SC-7927) was obtained from Sigma; Foxp3 (Mab-8214), Wnt5a (Mab-645) and IL-22 (AF-782) were from R&D System; IL-23R (NB600-114SS) was from Novus Biologicals; and IFN-γ (H-145) was obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The FITC labelled secondary antibody was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All primers, Poly-L-Lysine (PB8920), Trizol reagent (T9424) and DAPI (D9542) used in the present study were of analytical grade and purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Statistical analyses

The data was analysed by SigmaStat V 3.5 software. The relative change in IL-17A, Foxp3, IL-22, IL-23A, Wnt5a and IFN-γ mRNA expression were calculated by Pfaffl analysis method and normalized by β-actin. Mean fluorescence intensity (MFI) was measured by ImageJ software. All pairwise multiple comparisons between groups were done by One Way ANOVA, Holm-Sidak method and Tukey Test. The results are shown as the means ± SD. $p < 0.05$ was considered significant.

Results

There were 30 patients in group 1 (LPP); 10 each in group 2 (LP) and 3 (post-LP hyperpigmentation); and 10 in the control arm. The mean age of patients in group 1, 2 and 3 was 34.3 ± 11.8, 29.3 ± 10.9 and 36.0 ± 19.7 years, respectively. There were 20 females and 10 males in group 1, 5 males and 5 females in group 2 and, 7 females and 3 males in group 3.

qRT-PCR in peripheral blood mononuclear cells

Expression of IL-17A, IL-22, IL-23A and Foxp3 mRNA was significantly decreased in both *group* 1 *and group* 3 as compared to *controls and group* 2 ($p < 0.001$, Table 2). Expression of IFN-γ mRNA in patients of group 2 was significantly higher than group 1 and 3 ($p < 0.0001$), and controls ($p < 0.001$). Wnt5a mRNA expression was maximal in controls and was significantly lower in group 1 and 2 ($p < 0.001$), and group 3 ($p < 0.0001$). No difference was observed between group 1 and 2 regarding Wnt5a expression. Overall, in PBMCs, maximal expression of IL-17A, IL-22, IL-23A, IFN-γ and Foxp3 was observed in group 2 (LP), whereas minimum expression of IL-17A, 22, 23A, Foxp3 was seen in group 1 and 3. Detailed values are mentioned in Fig. 2a and Table 2.

qRT-PCR in skin tissue

Expression of IL-17A, 22 and 23A mRNA was significantly higher in *group* 2 *and group* 3 compared to *group* 1 ($p < 0.05$), whereas the expression of these cytokines showed no difference between *controls and group* 1. IFN-γ and Foxp3 mRNA levels were significantly higher in group 2 as compared to group 1 and controls ($p < 0.001$). Expression of

Table 1 Primer sequences along with their annealing temperature for qPCR

Gene	Forward primer	Reverse primer	Annealing temperature (°C)
IL-17A	5′-CCAGGATGCCCAAATTC-3′	5′-TCTGCAAGGTGTCTGTCTGG-3′	54
Foxp3	5′-GGTTTCCACTGTCTTGCCTG-3′	5′-TTGTGAAGGCTCTGTTTGGC-3′	58
IL-22	5′-GTTCAGCACCTGCTTCATCA-3′	5′-ACCTTCATGCTGGCTAAGGA-3′	50
IL-23A	5′-ATGTTCCCCATATCCAGTGTG-3′	5′-GCTCCCCTGTGAAAATATCCG-3′	61
Wnt5a	5′-TCGCCCAGGTTGTAATTGAAG-3′	5′-TGAGAAAGTCCTGCCAGTTG-3′	61
IFN-γ	5′-TGACCAGAGCATCCAAA-3′	5′-GGACATTCAAGTCAGTTACC-3′	54
β-actin	5′-CATGTACGTTGCTATCCAGGC-3′	5′-CTCCTTAATGTCACGCACGAT-3′	58

Table 2 Group-wise comparison of the significance level of IL-17A, Foxp3, IL-22, IL-23, Wnt5a and IFN-γ in quantitative polymerase chain reaction (qPCR) and Immunohistochemistry (IHC)

Group	IL-17A			IL-22			IL-23A		IL-23R	Foxp3			IFN-γ			Wnt5a		
	qPCR PBMC	qPCR Tissue	IHC (MFI)	qPCR PBMC	qPCR Tissue	IHC (MFI)	qPCR PBMC	qPCR Tissue	IHC (MFI)	qPCR PBMC	qPCR Tissue	IHC (MFI)	qPCR PBMC	qPCR Tissue	IHC (MFI)	qPCR PBMC	qPCR Tissue	IHC (MFI)
Control	1	1	2.49 ± 0.05	1	1	1.04 ± 0.04	1	1	2.99 ± 0.008	1	1	1.70 ± 0.04	1	1	0.96 ± 0.004	1	–	–
LPP (Group 1)	0.01 fold	0.22 fold	1.56 ± 0.04	0.04 fold	0.35 fold	0.69 ± 0.02	0.16 fold	0.29 fold	1.66 ± 0.16	0.08 fold	0.32 fold	0.88 ± 0.03	0.73 fold	0.7 fold	0.93 ± 0.001	0.39 fold	1	0.95 ± 0.05
LP (Group 2)	1.60 fold	3.62 fold	4.16 ± 0.15	1.42 fold	15.75 fold	7.64 ± 0.15	1.85 fold	7.26 fold	6.64 ± 0.01	5.35 fold	9.93 fold	5.5 ± 0.01	1.82 fold	6.66 fold	3.53 ± 0.03	0.55 fold	11.10 fold	7.01 ± 0.03
Post-LP (Group 3)	0.07 fold	6.11 fold	5.54 ± 0.05	0.25 fold	11.53 fold	3.31 ± 0.12	0.22 fold	3.84 fold	4.83 ± 0.03	0.25 fold	2.68-fold	2.05 ± 0.05	0.27 fold	4.15-fold	1.35 ± 0.02	0.05 fold	2.66 fold	3.20 ± 0.07
Control vs LPP	***	ns	ns	***	ns	ns	**	ns	ns	***	ns	ns	ns	ns	ns	**	ns	ns
Controls vs LP	***	ns	ns	*	**	**	**	***	***	***	***	***	**	**	**	**	ns	ns
Controls vs Post-LP	***	**	*	***	**	**	**	*	*	***	ns	ns	**	ns	ns	***	ns	ns
LPP vs LP	***	*	*	***	***	**	***	***	***	***	***	***	***	**	**	ns	**	*
LPP vs Post-LP	ns	**	*	ns	**	**	ns	**	**	ns	ns	ns	ns	ns	ns	*	ns	ns
LP vs Post-LP	***	ns	ns	***	ns	ns	***	**	**	***	***	***	***	ns	ns	**	*	*

Statistical significance is shown by $*p < 0.05$, $**p < 0.001$, $***p < 0.0001$, non-significance is shown by *ns*

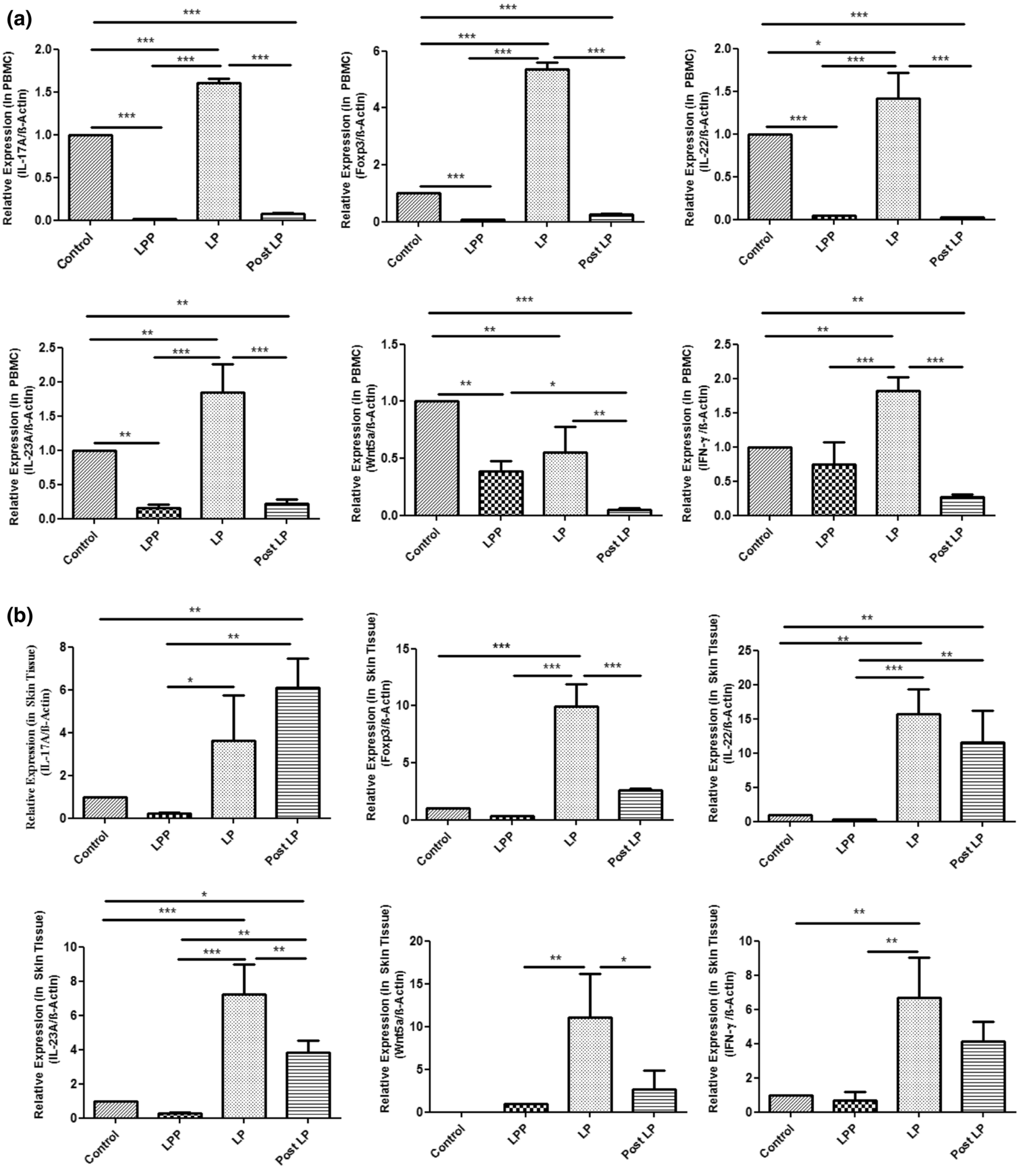

Fig. 2 **a** The relative mRNA expression of IL-17A, Foxp3, IL-22, IL-23A, Wnt5a and IFN-γ in peripheral blood mononuclear cells (PBMCs) of control, LPP patients, LP patients, and Post-LP patients. Statistical significance is shown by $*p < 0.05$, $**p < 0.001$, $***p < 0.0001$. **b** The relative mRNA expression of IL-17A, Foxp3, IL-22, IL-23A, Wnt5a and IFN-γ in skin tissue of controls, LPP patients, LP patients, and Post-LP patients. Statistical significance is shown by $*p < 0.05$, $**p < 0.001$, $***p < 0.0001$

Wnt5a was absent in the control skin, whereas its expression in group 2 was significantly increased compared to group 1 ($p < 0.001$) and group 3 ($p < 0.05$). Overall, in skin tissue, minimal expression of all cytokines was observed in group 1 (LPP) except Wnt5a, whereas maximal expression was observed in group 2 (LP) for all, except IL-17A. Detailed values are summarized in Fig. 2b and Table 2.

Immunohistochemistry

Mean fluorescence intensity (MFI) of IL-17A, IL-22 and IL-23R was significantly increased in *group* 2 *and group* 3 compared to *group* 1 ($p < 0.05$), whereas the MFI showed no difference between *controls and group* 1. MFI of IFN-γ and Foxp3 in group 2 was significantly increased when compared to group 1 and controls ($p < 0.001$). Expression of Wnt5a was absent in control skin. MFI of Wnt5a was significantly increased in group 2 as compared to group 1 ($p < 0.05$) and group 3 ($p < 0.05$). Overall, MFI of all cytokines was minimum in LPP except Wnt5a which showed no expression in control skin, and MFI for all cytokines was maximum in LP, except IL-17A, whose expression was maximum in post-LP pigmentation. Detailed values are summarized in Fig. 3a, b and Table 2.

In summary, expression of IL-17A, IL-22, IL-23A, IFN-γ and Foxp3 (mRNA PBMCs) was maximal in LP, whereas their minimal expression (mRNA skin and IHC skin) was observed in LPP patients. Moreover, in majority of the studied cytokines, expression matched in the *PBMCs* of post-LP hyperpigmentation and LPP, and *tissue* of post-LP hyperpigmentation and LP.

Discussion

LPP is traditionally considered to be a variant of LP, even though they are morphologically different. Dermatology literature debates much regarding this terminology as LPP shows frequent clinicopathological overlap with disorders such as erythema dyschromicum perstans, ashy dermatosis, pigmented contact dermatitis and idiopathic macular eruptive pigmentation [9, 10]; and a global consensus statement was recently published to summarize the existing scientific information regarding these disorders [11]. Few recent studies assessing the pathogenetic role of IL-17, 22, 23, Foxp3, IFN-γ and Wnt5a in oral and cutaneous LP found their expression to be significantly elevated, with some concluding a greater expression in oral (vs cutaneous) and erosive (vs reticular) variants [7, 12–16]. Herein, we attempted to assess the expression of these cytokines at the level of both mRNA (in the peripheral blood mononuclear cells and skin) and protein (skin) in LPP patients and compared their expression with that of patients having classical cutaneous LP, post-LP hyperpigmentation and healthy controls.

Prominent finding of the present study was that the expression of IL-17A, 22, 23 and IFN-γ (in both blood and skin) was almost negligible in LPP; and was reduced compared to LP and even healthy controls (reduction significant for most of the cytokines); suggesting a noteworthy down-regulation of Th17 and Th1 pathway in LPP. LP is a classical papulosquamous disorder that demonstrates both acanthosis (similar to psoriasis) and interface dermatitis on histopathology [17]. Usually, the intensive hydropic basal call degeneration in LP is accompanied by acanthosis, which probably hides the melanin incontinence till the papules disappear revealing post-inflammatory hyperpigmentation. In contrast, LPP lacks the compensatory acanthosis shown by LP and, therefore, manifests as macules and patches, where prominent hyperpigmentation manifests from the beginning [18, 19].

IFN-γ plays a significant role in the mediation of interface dermatitis [6, 13], whereas, IL-22 is designated as the chief cytokine that mediates acanthosis [20, 21], and the major amount of IL-22 stems from the IL-23 mediated Th17 pathway [12]. Therefore, the significantly reduced expression of cytokines representing Th17 pathway observed by us aptly correlates with the clinical morphology of LPP. Concomitant reduction in the expression of IFN-γ explains the pauci-inflammatory interface dermatitis that is usually observed in LPP.

Regarding the studied cytokines, the expression in PBMCs (blood) is almost similar in LPP and post-LP hyperpigmentation. However, the expression in skin (by qRT-PCR and IHC) was almost similar in LP and post-LP hyperpigmentation. This signifies that though the expression of inflammatory cytokines in post-LP state decreases in blood, the expression is still maintained locally in the skin. This persistent local inflammatory milieu might be responsible for the frequent relapses that are observed in cutaneous LP, and the frequent affliction of similar sites repeatedly.

Wnt5a increases the activity of nuclear factor kB and subsequently escalates inflammation. But its presence is also essential for maintaining the homeostasis [22]. Its expression has been previously found to be significantly enhanced in psoriasis and cutaneous LP [8]. The expression of Wnt5a mRNA was found to be maximum in control PBMCs (blood), whereas its expression was minimal when assessed in control skin (both RT-PCR and IHC), a transition that needs to be studied further. The expression of Wnt5a in PBMCs was not found to be significantly different between LPP and LP, whereas expression in skin tissue was significantly higher in LP compared to LPP.

Foxp3 is considered a specific marker of T-regulatory cells. In corollary to the pauci-inflammatory status of LPP (as demonstrated by the reduced Th17 and probably Th1

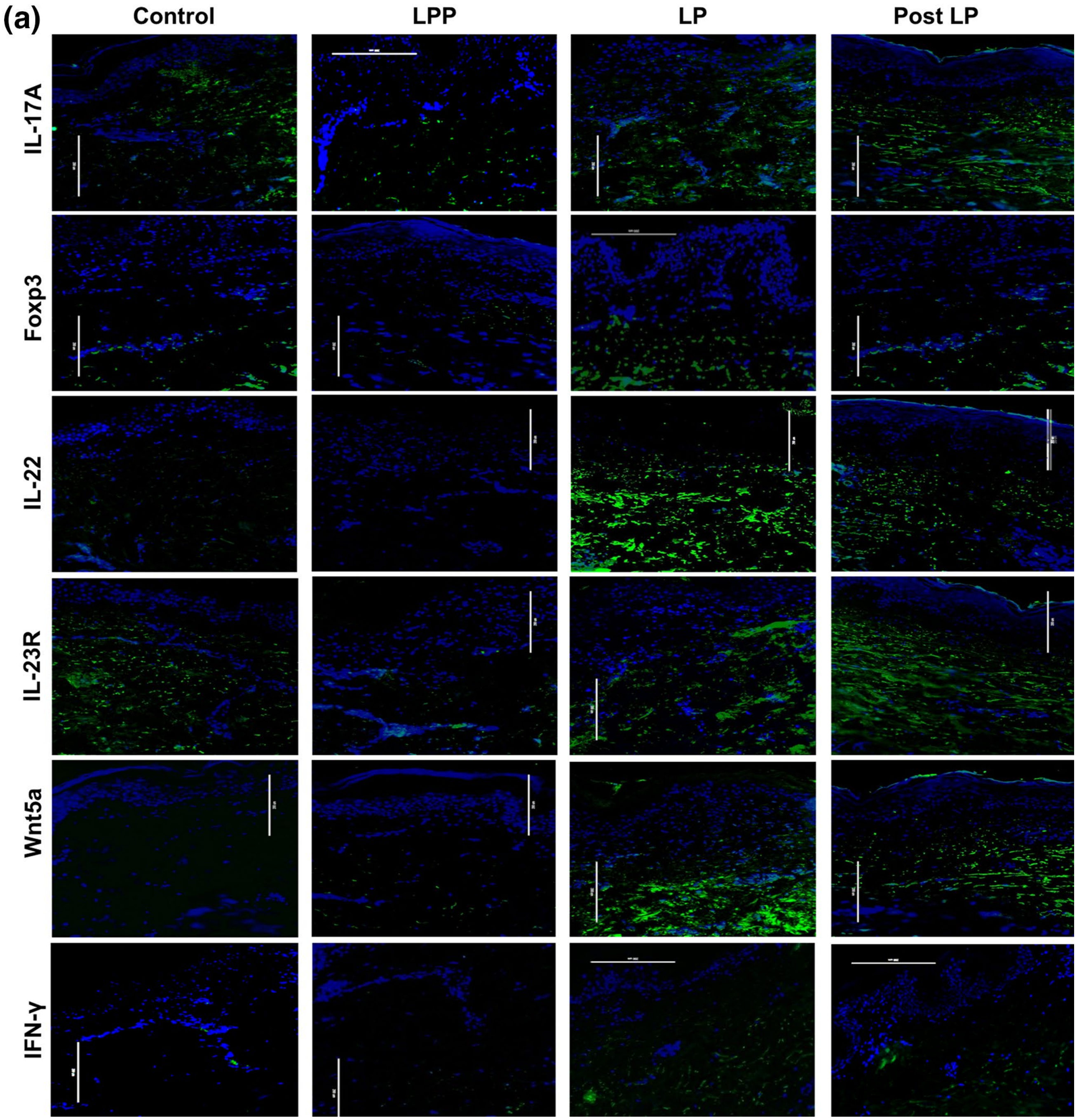

Fig. 3 **a** Immunohistochemical staining for IL-17A, Foxp3, IL-22, IL-23R, Wnt5a and IFN-γ from top to bottom panel, respectively, in skin tissue sections of controls, LPP patients, LP patients and Post-LP patients. From left to right: first panel shows control group, second panel shows LPP patients, third panel shows LP patients, and fourth panel shows Post-LP patients. **b** Mean Fluorescence intensity measurement of IL-17A, Foxp3, IL-22, IL-23R, Wnt5a and IFN-γ. Staining in skin tissue sections of control, LPP patients, LP patients and Post-LP patients was done using ImageJ software. Statistical significance is shown by $*p<0.05$, $**p<0.001$, $***p<0.0001$

axis in this study), the finding that Foxp3 is significantly reduced in LPP as compared to LP appears to be contradictory. However, this could be explained by the phenotype of T-regulatory cells. Though usually considered as regulatory, these cells actually demonstrate 2 phenotypes, actively suppressing and non-suppressive. In prior studies conducted in oral LP, it was noticed that although, the number of Foxp3 cells was elevated in oral LP, a significant proportion comprised of cells having a non-suppressive phenotype that actually stimulated IFN-γ production [23, 24]. We have not

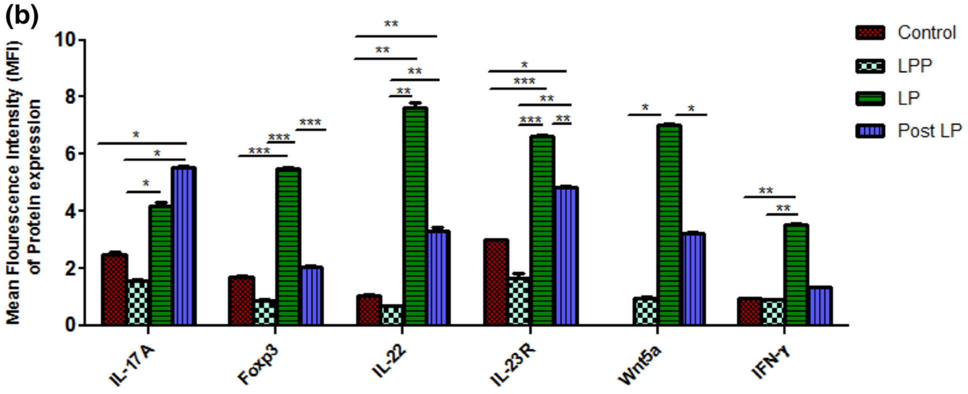

Fig. 3 (continued)

phenotypically segregated the Foxp3 positive cells in the present study, but it shall be interesting to see in future studies, whether LPP and LP express different phenotypes of Foxp3 cells. Similar to what has been suggested for different variants of mucosal LP (the reticular variant differentially expressed more of the Th2 pathway), the expression of Th2 pathway should also be studied in LPP [25].

Limitations

Number of patients in LP, post LP-hyperpigmentation and control group were lesser than those in LPP group. It would be better if the rate of progression and disease severity of LPP could be correlated prospectively with the expression of these cytokines. The serum levels of cytokines and specific lymphocyte-types (Th17, Th1, Th2) could not be measured using ELISA and flow cytometry, respectively, due to resource constraints. Also, in future, the expression of these cytokines should be studied sequentially in disorders characterized by an initial inflammatory phase and subsequent dermal pigmentation, such as fixed drug eruptions.

Conclusion

Our study exemplifies the fact that LPP is a pauci-inflammatory state that lacks the expression of Th17 pathway, which might be the primary pathogenic pathway mediating LP in conjunction with IFN-γ. Further studies are required to study the expression of these cytokines in overlapping dermatoses such as erythema dyschromicum perstans. A similar expression would add further credence to the acceptance of an uniform terminology to represent this unique group of dermal pigmentation disorders characterized by non-inflammatory, acquired, macular dermal hyperpigmentation [26].

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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