Original Article

Horoscopic role of CD105 (Endoglin) in progression of oral lichen planus: An immunohistochemical study

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Abstract

Context: Role of CD105(Endoglin) in Pathogenesis and progression of OLP.

Aim: To assess the role of neoangiogenesis in the progression of OLP by determining the expression of CD105 in OLP and normal mucosa.

Settings and Design: The present study includes a total of 70 formalin-fixed paraffin-embedded blocks of which the study group comprises 50 tissue sections histopathologically confirmed as OLP. They were subdivided into two groups - Group I (Reticular OLP) and Group II (Erosive OLP) - 25 each. The control group (designated as Group III) included 20 sections of normal mucosa.

Materials and Methods: All the sections were 4 μm thick and stained with CD105 antibodies. After identifying areas of highest vascularity (hot spots) in low power (×10) magnification, individual microvessels were counted manually at high power (×40) magnification.

Statistical Analysis Used: Analysis of variance test was used to determine the difference of microvessel density (MVD) between variants of OLP and normal mucosa and Cohen's kappa statistic was used to check interobserver variability.

Results: CD105 staining showed a mean MVD of 1.31 ± 1.8 in the normal mucosa compared to 1.68 ± 1.4 and 4.14 ± 2.7 in the reticular and erosive variants, respectively, with a $P = 0.000^{*}$, which is statistically significant ($^{*}P < 0.05$ is statistically significant).

Conclusion: Based on our observations, it is evident that compared to normal mucosa, MVD is greater in lichen planus. Within the two variants of OLP, MVD is higher in Erosive variant compared with Reticular variant, foreshadowing the role of neoangiogenesis in the progression of OLP and its possible malignant transformation.

Keywords: CD105, microvessel density, neoangiogenesis, oral lichen planus

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INTRODUCTION

Sir William Osler, father of modern medicine, quoted that "*Failure to examine the throat is a glaring sin of omission*" which bespeaks that mouth is the mirror of health and disease.[1] Oral lichen planus (OLP) is a chronic mucocutaneous

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disorder with unknown etiology. The term lichen planus has taken its origin from two Greek words: "*Lichen"* means *"tree moss"* and *"Planus"* means *"flat"*[2,3] It was first described by an English physician, Erasmus Wilson in 1869 and the first clinical variant was reported by Kaposi in 1892.[4]

According to Axell and Rundqvist, OLP affects 1%–2% of the general population worldwide.[5] The Indian subcontinent has particularly higher incidence of disease with a prevalence of 2.6%.[6] It usually affects adults over 40 years of age with a female predominance showing female: male ratio of 1.4: 1.[6,7]

OLP may present anywhere in the oral cavity. It usually manifests as a mixture of white and red lesions that usually exhibit multiple foci and almost always a bilaterally symmetric pattern. It most commonly involves buccal mucosa followed by tongue, gingiva and lower lip, whereas palatal lesions are uncommon.[8,9] Andreasen divided OLP into six types: reticular, papular, plaque-like, erosive, atrophic and bullous forms.[10-12]

Although the exact cause is unknown, literature supports that it is an immunological process triggered by an antigen which might be extrinsic such as dental restorations and drugs or intrinsic such as heat shock proteins. The other etiological agents include viruses such as hepatitis-C virus and human papilloma virus and psychological disorders such as depression, anxiety and stress also act as etiological factors.[13]

There are many controversies about the pathogenesis of OLP, but a large body of evidence supports the role of immune dysregulation.[14] OLP is a T-cell–mediated autoimmune disease in which apoptosis of basal cells of the oral epithelium occurs due to autocytotoxic CD8+ T-cells.[15]

As OLP is an autoimmune disease with an inflammatory origin and chronic progression, it satisfies all the prerequisites of hypoxia which is responsible for angiogenesis.[16] Angiogenesis represents neoformation of anomalous blood vessels in preexisting vascular channels. It may be both physiological or pathological.[16,17] Hypoxia induces expression of vascular endothelial growth factor (VEGF) that provokes degradation, proliferation and migration of endothelial cells and also regulates vascular permeability which is important for start of angiogenesis. Further, inflammatory mediators facilitate the activated cells in the stroma to promote angiogenesis.[16,18] Few past studies have proven that angiogenesis plays a role in etiopathogenesis and progression and may act as an underlying marker of disease activity of OLP. A hallmark of pathologic angiogenesis is sustained neoangiogenesis.[16,18,19]

Malignant transformation of OLP remains a controversial issue. Although the WHO has categorized OLP as a potentially malignant disorder, its malignant potential remains a subject of debate in the literature.[9] According to previous immunohistochemical studies done, Scardina *et al.* suggested that there is an intervention of angiogenesis in malignant transformation of many premalignant conditions including OLP.[16] The first crucial evaluation of the literature was presented by Krutchkoff in 1978 who proposed an inclusion diagnostic criterion, which was further reviewed by Van der Meij in 1999, and emphasized the need for a standard criteria. Mattson *et al.* and Gonzalez–Moles *et al.* determined malignant transformation rate of 0.5%–2% and 0%–12.5% respectively.[20-24]

Various immunohistochemical markers used for quantifying angiogenesis are pan-endothelial markers such as CD34, CD31 and Von Willebrand factor (Factor VIII); CD106 (VCAM-1) and CD54 (ICAM-1). These markers cannot differentiate newly formed vessels from parental vessels.[16,23] An ideal marker for angiogenesis should detect the newly formed vessel quality as well as quantity.[24] It has been recently demonstrated that CD105 (Endoglin) is a proliferation-associated and hypoxia-inducible protein which is preferentially expressed over the endothelial cells participating in neoangiogenesis.[23]

Human CD105 (Endoglin) is a homodimeric transmembrane glycoprotein composed of 633 amino acids weighing about 180 kDa, composed of two disulfide-linked subunits of 95 kDa.[25,26] It is an accessory protein of transforming growth factor-beta (TGF-β) receptor system and is expressed on activated vascular endothelial cells.[26,27]

Wang *et al*., 1994 observed that stronger intensity of staining for CD105 was detected on the vascular endothelial cells in tissues undergoing active angiogenesis, such as regenerating and inflamed tissues or tumors when compared to normal mucosa. They observed CD105-positive expression in various benign and malignant tissues such as intradermal nevi, melanocytic melanomas, breast carcinomas, ovarian carcinomas, hematopoietic tumors and oral squamous cell carcinoma.[28] Nassiri *et al*., 2011 observed intratumoral microvessel density (IMVD) quantified by anti-Endoglin mAb (Monoclonal Antibody) has been inversely correlated with tumor prognosis in patients with astrocytomas and glioblastomas, whereas IMVD measured by the pan-endothelial marker CD31 did not show any prognostic value.[27]

In the present study, we aim to study the quantitative expression of CD105 (Endoglin) in OLP and its role in progression and malignant transformation of OLP.

MATERIALS AND METHODS

The present study was designed to quantitatively assess the neoangiogenesis through expression of CD105 in OLP by measuring MVD, using immunohistochemistry in paraffin-embedded tissues.

Study setting

The study was conducted at the Department of Oral Pathology and Microbiology, Panineeya Mahavidyalaya Institute of dental Sciences and Research Centre, Hyderabad. Tissue specimens of clinically and histologically diagnosed cases of reticular variant of OLP, erosive variant of OLP and normal mucosa were retrospectively retrieved from the archives of the department after ethical approval (Ethical No. PMVIDS/OP/0021/2014)

Case selection

Sample size was determined after discussing with a statistician to avoid bias and type of sampling was random sampling. The study group comprised a total of 50 tissue sections from formalin-fixed paraffin-embedded archival blocks after histopathological confirmation as OLP among which 25 cases were reticular variant of OLP – Group I and 25 cases were erosive variant of OLP – Group II. The control group comprised 20 normal oral mucosa specimens (which were obtained during prophylactic extraction for orthodontic treatment and the gingival tissue obtained while crown lengthening) – Group III.

We performed immunostaining on all the sections using Rabbit monoclonal primary antibody CD105 (Clone EP 274), (1 : 50 dilution). Observed under Olympus CX21i Binocular microscope, the presence of brown-cultured precipitate on target antigens – newly proliferating endothelial vessels indicates positive immunoreactivity. Tonsil specimens were used as external positive control as the mesenchymal stem cells in the tonsillar tissue show positive expression of CD105 (Antun Bacic *et al*., 2018) – the formalin-fixed paraffin-embedded tonsil sections were retrieved from archives of Private Pathology Laboratory and normal mucosa was used as external negative control.

Observations

Tissue sections were evaluated under light microscope; special attention was given to the microvessels in the subepithelial connective tissue of OLP and normal mucosa. We evaluated CD105 expression in tissue sections, and quantitative assessment of MVD in both the study and control groups was done.

Selection of field for measuring microvessel density

Sections were screened according to Weidner *et al*.[29] in which the first step was identification of areas with highest vessel density in the connective tissue by scanning whole section at low power (×10) magnification, which were termed as "hot spots." Four hot spots which were not continuum with each other were taken into consideration. Later, the individual microvessels were counted at high power (×40) magnification in each of the hotspots. Any stained endothelial cell or clusters separate from adjacent vessels were counted as a single microvessel, even in the absence of vessel lumen, and each count was expressed as the highest number of microvessels identified within ×40 field. All the four counts were performed twice manually by the same observer and once manually by a qualified oral pathologist to check the reliability of counting method using Olympus CX21i Binocular microscope, and the arithmetical mean in each area were used to calculate the mean MVD for each section.

Statistical analysis

All the analysis was done using SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. A $P < 0.05$ was considered statistically significant. We used one-way analysis of variance (ANOVA) test to analyze the difference between group means and their mean MVD.

RESULTS

Our study endeavored to assess the role of neoangiogenesis in the pathogenesis of reticular and erosive variants of OLP in comparison with normal mucosa. We selected 50 formalin-fixed paraffin-embedded tissue sections which were histopathologically confirmed as reticular and erosive OLP 25 each. They were designated as Group I and Group II, respectively. The control group (designated as Group III) included tissue sections from 20 formalin-fixed paraffin-embedded blocks of the normal mucosa. All the sections were stained with CD105.

- The age distribution of subjects in all the three groups was as follows: 18 (25.71%) out of total 70 were <30 years (with 4, 5 and 9 subjects in Group I, II and III, respectively), 42 (60%) out of 70 were between 30 and 50 years (with 16, 15 and 11 subjects in Group I, II and III, respectively) and 10 (14.29%) were >50 years (with 5, 5 and 0 subjects in Group I, II and III, respectively) [Table 1 and Graph 1]
- The age distribution of subjects in two groups

of OLP was as follows: 9 (18%) out of total 50 were <30 years (with 4 and 5 subjects in Group I and II, respectively); 31 (62%) out of 50 were between 30 and 50 years (with 16 and 15 subjects in Group I and II, respectively) and 10 (20%) were >50 years (with 5 and 5 subjects in Group I and II, respectively) [Table 2 and Graph 2]

- The distribution of gender among all the three groups was as follows: In a total of 70, 25 (35.7%) were males and 45 (64.3%) were females participated in the study [Table 3 and Graph 3]
  - Group I comprised 8 (32%) males and 17 (68%) females
  - Group II comprised 10 (40%) males and 15 (60%) females and
  - Group III comprised 7 (35%) males and 13 (65%) females
- The distribution of gender among two groups of OLP: In a total of 50, 18 (36%) were males and 32 (64%) were females [Table 4 and Graph 4]
- The mean MVD was compared in all the three groups by using one-way ANOVA test in which the mean MVD we obtained in Group I (reticular OLP) was 1.68 ± 1.4, Group II (erosive OLP) was 4.14 ± 2.7 and Group III (normal mucosa) was 1.31 ± 1.8
- We obtained a $P = 0.000$* between two parameters which is statistically significant.*$P < 0.05$ is statistically significant. It was found that Group II had highest mean MVD, followed by Group I and Group III, respectively [Table 5 and Graph 5]

- Histological images of H & E stained and CD105 Stained slides of Reticular OLP (Figure 1- H&E at low power (x10) magnification, Figure 2 –IHC with CD105 at low power (x10) magnification & Figure 3 - IHC with CD105 at high power (x40) magnification), Erosive OLP (Figure 4 - H&E at low power (x10) magnification, Figure 5 - IHC with CD105 at low power (x10) magnification & Figure 6 - IHC with CD105 at high power (x40) agnification) and Normal mucosa (Figure 7- H&E at low power (x10) magnification, Figure 8 - IHC with CD105 at low power (x10) magnification & Figure 9 - IHC with CD105 at high power x40) magnification) were included.

Table 1: Age distribution of subjects in all the three groups

Age (years)	Group 1	Group 2	Group 3	Total (%)
<30	4	5	9	18 (25.71)
30-50	16	15	11	42 (60.00)
>50	5	5	0	10 (14.29)
Grand total	25	25	20	70

Table 2: Age distribution of subjects among two groups of oral lichen planus

Age (years)	Group 1	Group 2	*n*
<30	4	5	9
30-50	16	15	31
>50	5	5	10
Total	25	25	50

Table 3: Sex distribution of subjects in all the three group

Gender	Group 1	Group 2	Group 3	Total (%)
Male	8	10	7	25 (35.71)
Female	17	15	13	45 (64.29)
Grand total	25	25	20	70

Table 4: Sex distribution of subjects among two groups of oral lichen planus

	Group 1	Group 2	*n*
Male	8	10	18
Female	17	15	32
Total	25	25	50

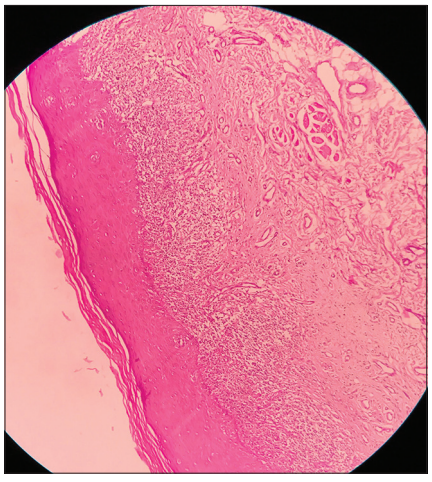


Figure 1: Image of reticular oral lichen planus showing blood vessels in the subepithelial connective tissue. H & E, ×10

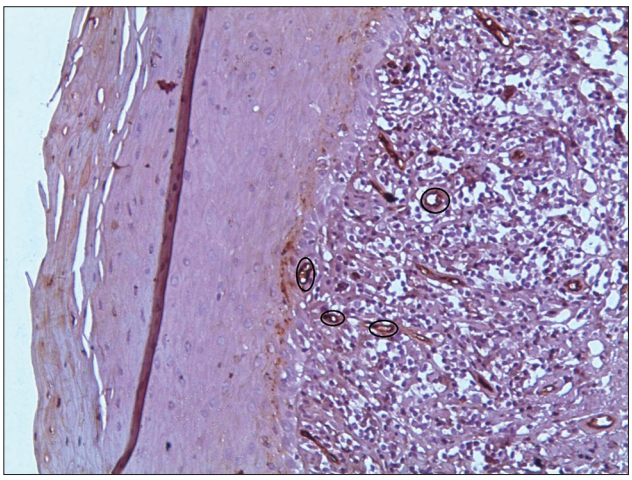


Figure 2: Image of reticular oral lichen planus showing expression of CD105 by blood vessels in the subepithelial connective tissue. Immunohistochemistry, ×10

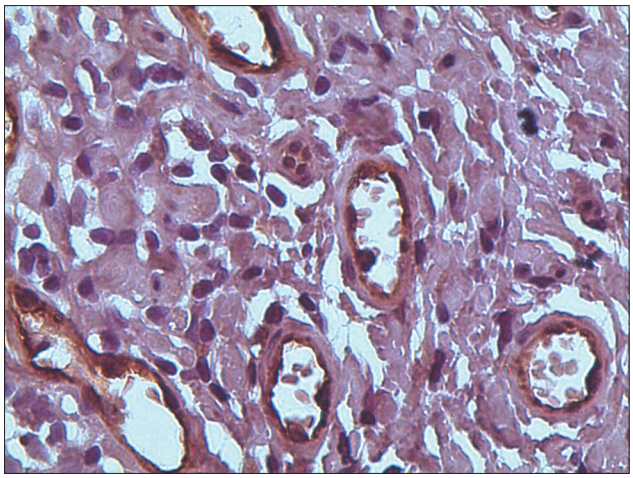


Figure 3: Image of reticular oral lichen planus showing expression of CD105 by blood vessels in the subepithelial connective tissue. Immunohistochemistry, ×40

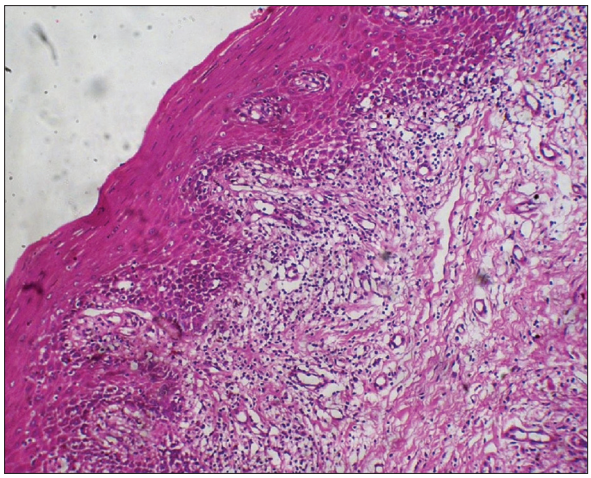


Figure 4: Image of erosive oral lichen planus showing numerous blood vessels in the subepithelial connective tissue. H and E, ×10

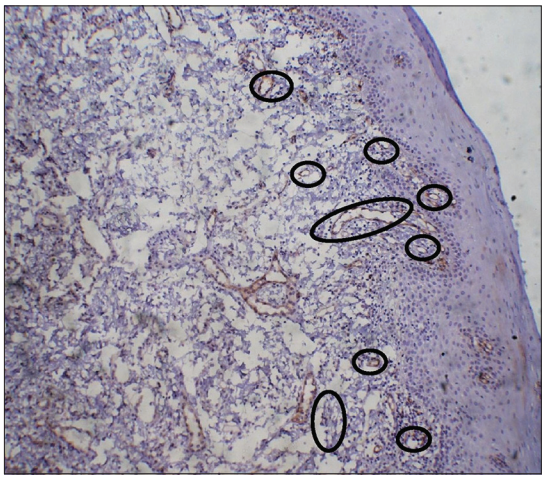


Figure 5: Image of erosive oral lichen planus showing expression of CD105 by numerous blood vessels in the subepithelial connective tissue. Immunohistochemistry, ×10

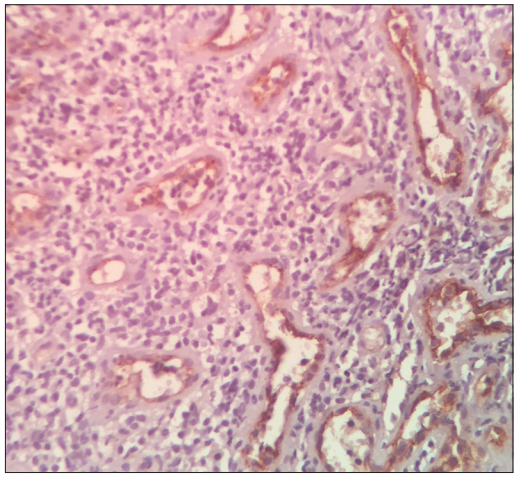


Figure 6: Image of erosive oral lichen planus showing expression of CD105 by numerousblood vessels in the subepithelial connective tissue. Immunohistochemistry, ×40

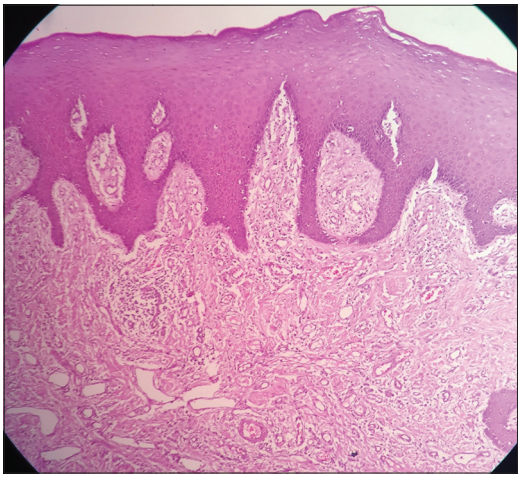


Figure 7: Image of normal mucosa showing blood vessels in the subepithelial connective tissue. H and E, ×10

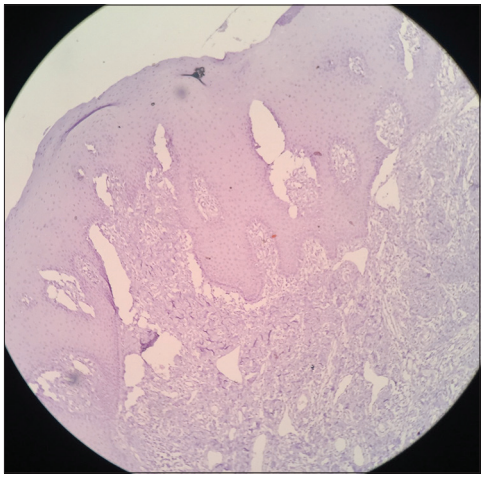
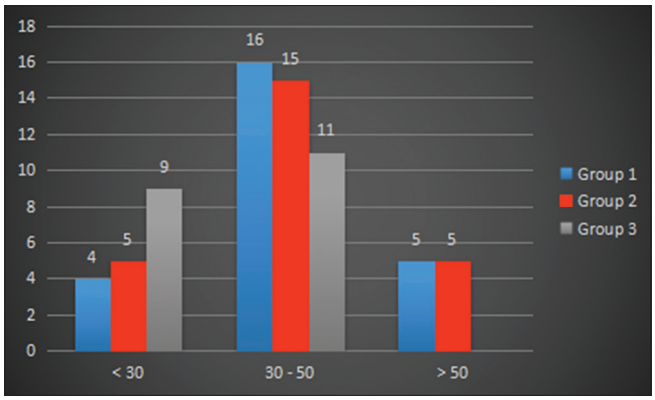
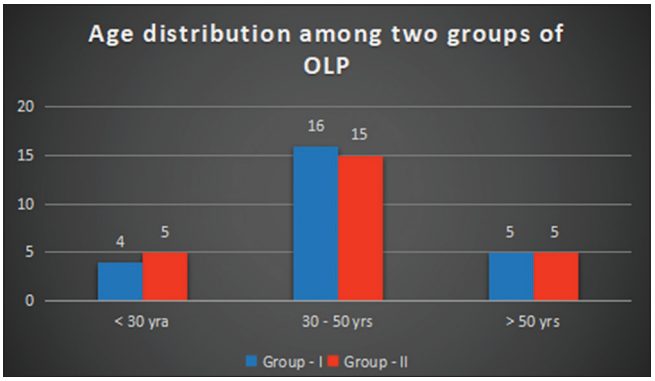


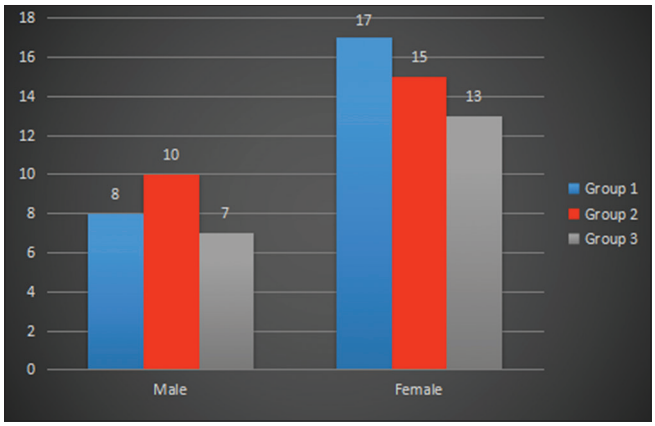
Figure 8: Image of Normal mucosa showing lack of expression of CD105 by blood vessels in the subepithelial connective tissue. Immunohistochemistry, ×10



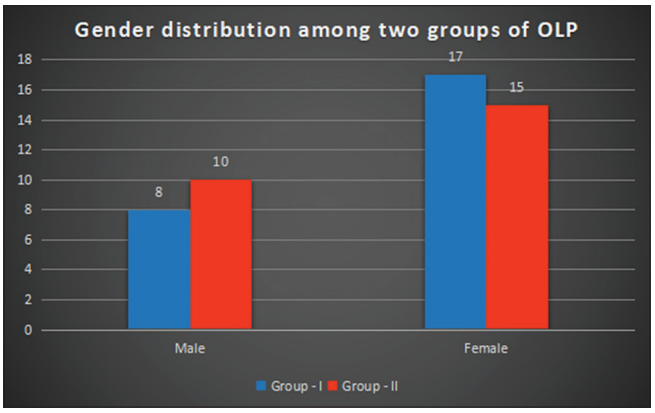
Graph 1: Age distribution of subjects in all the three groups



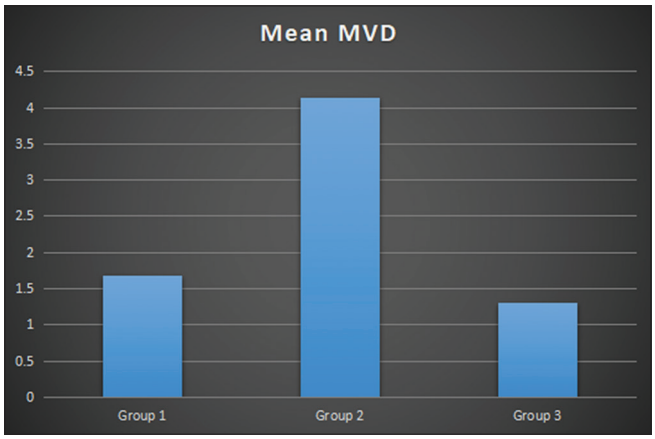
Graph 2: Age distribution of subjects among two groups of oral lichen planus



Graph 3: Sex distribution of subjects in all the three groups



Graph 4: Sex distribution of subjects among two groups of oral lichen planus



Graph 5: Mean microvessel density distribution of subjects in all three groups

Table 5: Mean microvessel density distribution of subjects in all three groups

Groups	*n*	Mean±SD	95% CI		*P*
			Lower bound	Upper bound	
Group-I (reticular OLP)	25	1.68±1.4	1.07	2.29	0.000*
Group-II (erosive OLP)	25	4.14±2.7	3.01	5.28	
Group-III (normal mucosa)	20	1.31±1.8	0.46	2.16	

ANOVA test. OLP: Oral lichen planus, SD: Standard deviation, CI: Confidence interval

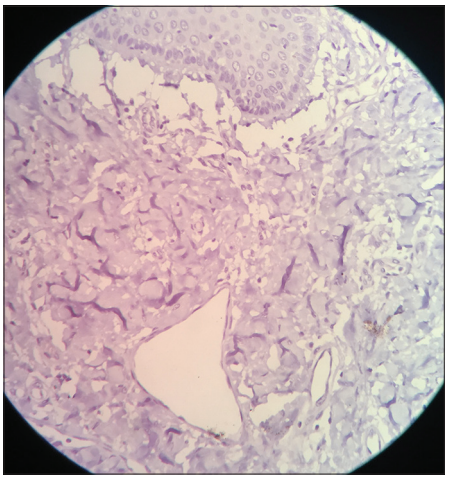


Figure 9: Image of normal mucosa showing lack of expression of CD105 by blood vessels in the subepithelial connective tissue. Immunohistochemistry, ×40

DISCUSSION

OLP is a T-cell–mediated chronic inflammatory mucocutaneous disease of unknown etiology.[2] The classic microscopic features of OLP include parakeratosis, acanthosis and "saw-tooth" retepegs, a dense band of

subepithelial lymphohistiocytic infiltrate, intraepithelial lymphocytic infiltration and degeneration of basal keratinocytes, leading to the formation of colloid and disruption of the basement membrane.[2,3] This disruption leads to the formation of histological cleft formation termed as Max–Joseph spaces.[2]

As an autoimmune disease with an inflammatory origin and chronic progression, OLP satisfies all the prerequisites of hypoxia which induces angiogenesis. According to Scardina *et al*., the term neoangiogenesis is preferable for pathological angiogenesis in chronic inflammatory diseases such as OLP.[16] Hence, the terms angiogenesis and neoangiogenesis can be used interchangeably in OLP.

CD105 (Endoglin) can be used as a marker for neoangiogenesis in inflamed and neoplastic tissues.[28] Although there are some pan-endothelial markers available, these markers cannot differentiate quiescent endothelium from actively proliferating endothelium and an ideal marker should detect quality and quantity of newly formed vessels. The antibodies which can stain proliferating endothelial cells include E-9, CD105 and LM-609 to integrin $\alpha v\beta_3$. Nico B *et al*., 2008 stated that careful estimation of neoangiogenesis using CD105 is crucial in accurate determination of prognosis and particular identification of subset of high-risk patients who could benefit from antiangiogenic therapies.[26,29]

The present study aimed to explore the role of angiogenesis in the pathogenesis of OLP by evaluating the mean MVD through the immunohistochemical expression of CD105 and we have compared it with that of normal mucosa.

In the present study, the prevalence of OLP was compared among all the three groups and within the study group. The prevalence was 60% and 62% in the age group of 30–50 years, respectively. This was in accordance with the studies carried over by Sugerman and Savage,[2] Roopashree *et al*.,[14] Shirasuna,[10] and Gupta and Jawanda,[12] who also stated that it is more common in fourth and fifth decades. This was in contrast with Haqiqi *et al*.,[4] who stated that it is more common around 60 years of age.

The present study revealed female predominance in the study group, i.e., 64% with a female: male ratio of 1.78: 1 which correlated with the studies carried out by Ingafou *et al*.,[30] who stated that it was 1.75: 1. This was in contrast to studies by Sugerman and Savage,[2] who mentioned the ratio as 1.4:1; Roopashree *et al*.,[14] who observed that it was 1.4:1 and Sousa *et al*.[31] who mentioned that it was 4:1.

The current study showed that angiogenesis, as estimated by MVD using the endothelial marker CD105 was significantly increased in Study group (Group– I and II) compared to control group (Group– III). Furthermore, in this study, we accomplished highest mean MVD of 4.14 ± 2.7 for erosive OLP, followed by 1.68 ± 1.4 and 1.31 ± 1.8 for reticular OLP and normal mucosa respectively. We obtained a *P* value of 0.000* which is statistically significant and implies connotation between angiogenesis and various groups. A similar distribution of mean MVD was corroborated by previous investigations done by Mittal *et al*.,[17] Tao *et al*.[21] Scardina *et al*.[16] and Hazzaa *et al*.[32] These observations suggested that angiogenesis is one of the key contributing factors in the progression of OLP.

Hypoxia in OLP induces expression of VEGF that provokes degradation, proliferation and migration of endothelial cells and also regulates vascular permeability which is important for the start of angiogenesis. According to Scardina *et al*., (2009)[16] angiogenesis not only causes new blood vessel formation but also provides better oxygenation facilitating turnover of inflammatory cells.[16] Inflammatory cells along with their secreted cytokines release pro-angiogenic and angiogenic factors such as histamine, heparin, chymase, bFGF, VEGF and TGF-beta which in turn potentiate angiogenic mechanism in OLP.[17]

According to Li *et al*.,[33] hypoxia is a prime stimulus of neovascularization which activates CD105 gene promoter responsible for expression of CD105. An adequate level of CD105 in the endothelial cells is required for neoangiogenesis and CD105 is strongly expressed in activated cells than quiescent cells, which suggested that it is a proliferation associated gene.[33] CD105 is an accessory receptor of TGF-β cytokine which is a regulator of proliferation, migration and survival of endothelial, cells and it can both stimulate proliferation and migration of the endothelial cells.[33-36]

Otero-Rey *et al*.[37] explained the role of various cells such as macrophages capable of producing TGF-β1 and cytokines such as interleukin (IL)-1, IL-6–promoting tumor growth, invasion and metastasis through stimulating angiogenic factors such as VEGF.[37] Secreted TGF-β1 will promote the expression of CD105 which is responsible for neoangiogenesis as Endoglin is an accessory receptor of TGF-β which is a regulator of proliferation, migration and survival of the endothelial cells and it can both stimulate proliferation and migration of endothelial cells.[35]

In 1910, Hallopeau reported a case of OLP with malignant transformation after which several studies were carried out to elucidate possible mechanisms behind its malignant transformation. Many studies revealed various malignant transformation rates of OLP as 0.9% by Bermejo-Fenoll *et al*.,[38] 0.8% by Eisen[39] and 1.9% by Ingafou *et al*.[30] Varghese *et al*.[40] specified that it was 0.5%–2% in Indian population. Studies also demonstrated that malignant transformation rate is more in erosive variant than reticular variant, which also connotes that there may be an association between angiogenesis and malignant transformation as the present study demonstrated higher mean MVD for erosive form compared to reticular form.[30,38-40]

Chen *et al*.[41] hypothesized that TGF-β1 might be responsible for the malignant transformation of OLP as TGF-β1 induces expression of CD105 which is amarker of neoangiogenesis which notifies its role in malignant transformation of OLP.

Payeras *et al*.[13] described the role of immune cells and their cytokines in malignant transformation of OLP through angiogenesis which includes pro-inflammatory cytokines such as TNF-α, IL-1 β, IL-6, IL-12, IL-23 which are released by CD4+ T-cells; RANTES and cyclooxygenase-2 were associated with neoangiogenesis and malignant transformation.[13,17]

As there were very few studies that have demonstrated a direct relationship between angiogenesis and OLP, we have made an attempt to explore the role of neoangiogenesis in the pathogenesis of OLP. This study is first of its kind. The present study showcased the role of neoangiogenesis in the pathogenesis of OLP and its possible role in malignant transformation.

CONCLUSION

The present study highlights the possible role of neoangiogenesis in malignant transformation of OLP. The present study offers a valuable idea for future studies which can be scheduled on foreshadowing the role of neoangiogenesis in malignant transformation with larger sample and long-term follow-up. Pointing neoangiogenesis might act as a promising target for treatment of OLP, which is beneficial in reducing the dependency on corticosteroid drugs and averting its malignant transformation.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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