

## ORIGINAL ARTICLES

# Oral lichen Planus and Dermal Dendrocytes

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**Resumen.** *Introducción.* El liquen plano oral (LPO) es una enfermedad inflamatoria relativamente frecuente que se presenta con un amplio abanico de formas clínicas. Todavía no se ha determinado completamente su patogenia, aunque se sabe que los linfocitos actúan de mediadores con la participación de citoquinas y otras células inflamatorias, entre ellas los dendrocitos dérmicos (DD) tipo I y tipo II (DD positivos para el factor XIIIa y CD34, respectivamente).

*Objetivos.* Describir la presencia y distribución de estas células en el tejido, mediante técnicas inmunohistoquímicas, en 23 muestras procedentes de pacientes que reunían los criterios clínicos e histopatológicos de LPO.

*Resultados.* Los DD factor XIIIa+ estaban localizados principalmente en la dermis superficial ( $p < 0,0001$ ) y no en la submucosa profunda. Dichas células se encontraban en abundancia en toda la unión dermoepidérmica y se relacionaban estrechamente con la infiltración linfocitaria. Los DD factor XIIIa+ se encontraban además en el epitelio y la dermis profunda. En cambio, los DD CD34+ se distribuyeron principalmente en la dermis profunda, directamente por debajo del infiltrado linfocitario, con pocas células en la zona subepitelial.

*Conclusiones.* Los DD estaban presentes en el LPO, con diferentes distribuciones en los tejidos. Así, los DD factor XIIIa+ predominaban en la dermis superficial, mientras que los DD CD34+ se encontraban principalmente en la dermis profunda. Esto apunta a que los DD, y sobre todo los DD factor XIIIa+ debido a su capacidad para expresar moléculas de adhesión intercelulares-1 (ICAM-1) y el factor de necrosis tumoral alfa (TNF- $\alpha$ ), pueden desempeñar una función destacada en la patogénesis del LPO.

**Palabras clave:** liquen plano, célula dendrítica dérmica, dendrocitos, oral.

## ORAL LICHEN PLANUS AND DERMAL DENDROCYTES

**Abstract.** *Introduction.* Oral lichen planus (OLP) is a relatively common inflammatory disease with a wide range of clinical forms. Its pathogenesis has not been fully elucidated although it is known to be mediated by lymphocytes with the participation of cytokines and other inflammatory cells, including type I and type II dermal dendrocytes (DD) (factor XIIIa+ DD and CD34+ DD, respectively).

*Objectives.* To describe the presence and tissue distribution of these cells, through immunohistochemistry, in 23 specimens from patients with clinical and histopathological criteria of OLP.

*Results.* Factor XIIIa+ DD were mainly located in the superficial dermis ( $p < 0.0001$ ) as opposed to the deep submucosa. These cells were abundant throughout the dermal-epidermal junction and closely related to lymphocyte infiltration. Moreover, factor XIIIa+ DD were also found in the epithelium and deep dermis. CD34+ DD were distributed mostly to the deep dermis directly below the lymphocyte infiltrate with few cells in the subepithelial region.

*Conclusions.* DD were present in OLP, with distinct tissue distributions. Factor XIIIa+ DD were predominant in the superficial dermis while CD34+ DD could be found mostly in the deep dermis. These findings suggest that DD, and those positive for factor XIIIa+ in particular in view of their ability to express intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), may play an important role in pathogenesis of OLP.

**Key words:** lichen planus, dermal dendritic cell, dendrocytes, mouth.

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## Introduction

Oral lichen planus (OLP) is a chronic and relatively common inflammatory disease. Unlike cutaneous lichen planus, which is generally self-limiting and accompanied only by itching, OLP follows a chronic course with rare spontaneous remission and is often accompanied by discomfort and pain, with a potential for malignant transformation.<sup>1,2</sup> Its etiology remains unclear although recent studies suggest that immunological mechanisms play a fundamental role in the onset and perpetuation of the clinical picture.

Dermal dendrocytes (DD) are bone-marrow-derived cells that differ from Langerhans cells and that present characteristics similar to mononuclear phagocytes (monocyte/macrophage). Two basic types of DD have been identified by immunohistochemical study: factor XIIIa+, also called DD type I, and CD34+, or DD type II.<sup>3,4</sup>

Factor XIIIa is a plasma trans-glutaminase that is important in the coagulation sequence and for the production of collagen by fibroblasts and connections between fibrin, fibronectin, and collagen. These factor XIIIa+ cells were first observed around the portal space,<sup>5</sup> and, because of their spindle cell morphology, were thought to be fibroblasts. In 1986, Headington<sup>6</sup> described dendritic cells in the normal dermis with histoenzymatic, immunohistochemical, and ultrastructural characteristics that differ from fibroblasts and Langerhans cells. He named those cells dermal DD. Cerio et al<sup>3</sup> subsequently detected factor XIIIa that correlated with the DD described by Headington and so factor XIIIa was considered the immunohistochemical marker for DD.

Other authors observed that most of these cells, besides being present in the papillar and upper reticular dermis, were strongly associated with the blood vessels and had a similar morphology to phagocytic mononuclear cells (macrophage/monocyte).<sup>7</sup> Those cells are supposedly derived from bone marrow (HLE-1+) and co-express markers for cells presenting antigens, macrophages or monocytes (human leukocyte antigen [HLA]-DR+, lymphocyte function antigen [LFA]-1+, HLA-DQ+, OKM5, Mo1+, Mono-1+, Leu M3+).<sup>8</sup> Some authors suggested that DD are immature precursors of Langerhans cells<sup>9</sup>; however, like macrophages, Birbeck granules are not apparent in electron microscopy study (ultrastructural aspect), thereby contradicting that hypothesis.<sup>10</sup> The characteristics of factor XIIIa+ DD are described in Table 1.

In normal skin and oral mucosa factor XIIIa+ DD are located in the upper dermis and dermis in association with collagen, and especially around blood vessels.<sup>11</sup> In inflamed skin, they are also found in dermal and epidermal inflammatory infiltrate, and in the epidermis in association with lymphocytes.<sup>8,10</sup>

**Table 1.** Characteristics of the dermal dendrocytes' factor XIIIa+

HLA-DR +
Distribution predominantly in the papillary dermis around vessels
Origin from bone marrow
Monocyte and macrophage marker

HLA-DR: human leukocyte antigen DR.

**Table 2.** Possible immunological functions of DD

Antigen presentation
Differentiation to Langerhans cells?
Increase of the ICAM-1 expression
Stimulus for LT migration
Stimulus for TNF $\alpha$ expression?
Phagocytic capacity?

DD: dendrocytes; ICAM-1: intercellular adhesion molecule-1; LT: T-lymphocytes; TNF $\alpha$ : tumor necrosis factor  $\alpha$ .

Many authors have studied the immunological function of dermal DD. In 1989, Cerio et al<sup>8</sup> suggested that dermal DD comprise a multipotent population able to act as macrophages and antigen-presenting, with the possibility of differentiating into Langerhans cells on migrating to the epidermis. These authors also observed that DD expressed intercellular adhesion molecule-1 (ICAM-1) after stimulation by interferon- $\gamma$  (IFN- $\gamma$ ) in inflamed skin. Their phagocytic capacity was demonstrated by Headington,<sup>6</sup> and confirmed by Cerio et al,<sup>11</sup> who also observed proliferation of these cells in inflammatory processes. Although not confirmed, DD may be capable of phagocytosis of antigen-antibody complexes<sup>12</sup> and *in vitro* these cells are as potent as Langerhans cells for antigen presentation.<sup>13</sup> It has also been suggested that DD can stimulate T-cell migration through the production of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ).<sup>14</sup> DD seem to be closely related to mastocytes, both in terms of being located near to those cells in the dermis and their possible activation and proliferation after degranulation of the mastocytes and release of TNF $\alpha$ .<sup>15,16</sup> DD also have an *in vitro* capacity to alter their shape to rounded cells similar to monocytes; and again mastocytes seem to be involved in this process.<sup>17</sup> The main immunological functions of DD are listed in Table 2.

In 1992, Regezi et al<sup>4</sup> observed another dendritic cell, similar to factor XIIIa+ DD in the normal deep dermis. This cell presented the antigen for CD34, a glycoprotein

found in hematopoietic progenitor cells. In the dermis, CD34 is expressed by endothelial cells, cells of fusiform aspect around adnexal structures and deeply located dendritic cells.<sup>4,18</sup> The function of these cells still remains unclear and there is no solid evidence that these cells contribute to the inflammatory process. For some authors, the CD34+ cells may represent a reservoir of multipotential stromal cells able to migrate to tissues during inflammation and repair.<sup>19</sup>

Other antigenic markers for DD, besides factor XIIIa+, such as HLA-DR, HLA-DQ, Leu M3 (CD14), CD36 (OKM5), Mono1, Mo1 have also been described but they are less specific.<sup>8</sup>

Recently, using immunohistochemistry, Monteiro et al<sup>17</sup> identified the GPIIb/IIIa receptor of the von Willebrand factor (vWF), which, according to the authors, would be a more specific and sensitive marker for DD factor XIIIa+. Those same authors demonstrated greater expression of the GPIIb/IIIa receptor in DD after mastocyte degranulation possibly by a mechanism independent of TNF $\alpha$ .

Recent studies have searched for associations of these cells with inflammatory processes of immunological origin, among them OLP, in the hope of elucidating some unclear points about the pathophysiology of the disease.

Given the participation of DD in the pathophysiology of T-cell mediated inflammatory processes, we believe that DD play an important role in OLP.

## Material and Methods

### Patients

A retrospective study of 23 biopsies from patients with a clinical and histopathological diagnosis of OLP was conducted.

### Selection of Material

The biopsy samples were taken from the library of the Sector of Pathology of the School of Medicine and HUCFF/UFRJ, of the Federal University of Rio de Janeiro, Brazil. The presence of at least 3 of the 5 following histopathological abnormalities were used as criteria for the histopathological diagnosis of OLP: a) dyskeratosis (hypergranulosis and/or parakeratosis); b) keratinocyte necrosis (Civatte bodies); c) lichenoid infiltrate; d) vacuolation of the basal layer, and e) pigmentary incontinence.

The histologic sections with little dermis (conjunctive stroma underlying the epithelium of the mucosa) were discarded because the immunohistochemical technique for the DD would be impaired.

### Primary Antibodies

The primary antibodies were a polyclonal antibody produced in rabbit (Calbiochem-Novabiochem Co; La Jolla, CA) at a dilution of 1:200 for factor XIIIa, and a monoclonal antibody produced in mouse (HPCA-1, Becton-Dickinson, San Jose, CA) at a dilution of 1:50 for CD34.

### Immunohistochemical Method

Immunohistochemical staining was carried out according to the manufacturer's instructions.

### Immunohistochemical Analysis

Cases in which at least four histological fields with a 40x magnification could be analyzed were considered. For the purpose of an approximate quantification of the infiltrate we adopted the following classifications:

1. Scattered - less than 20 cells in the 4 fields.
2. Concentrated -  $\geq 21$  cells in the 4 fields.

### Statistical Analysis

Statistical analysis was performed applying the Fisher exact test to investigate the association between qualitative variables and the McNemar test to determine whether differences in the factor XIIIa (or CD34) count from one position to the another were significant. Significance was set at 5%. The statistical analysis was performed using SAS System statistical software.

## Results

Factor XIIIa+ and CD34+ DD were recognized by presence of brown and red coloration, respectively, in the cytoplasm of the cells with dendritic morphology. Semiquantification of the infiltrate is presented in Tables 3 and 4.

Factor XIIIa+ DD were concentrated in the superficial dermis (Figures 1 and 2), mainly in the subepithelium, in some cases paving this area (Figure 3). Some cells were also observed in the lower dermis (Figure 4) and in the epithelium (Figure 5). Of the 19 cases studied for factor XIIIa+ DD, in the superficial dermis, 18 were considered as concentrated (94.7 %) and 1 case was described as scattered. A significant decrease was observed ( $P=.0001$ ) in factor XIIIa+ DD count in the deep dermis (26.3 %) compared to the superficial dermis (94.7 %).

**Table 3.** Numeric and percentage distribution of factor XIIIa+ DD in 19 analyzed samples

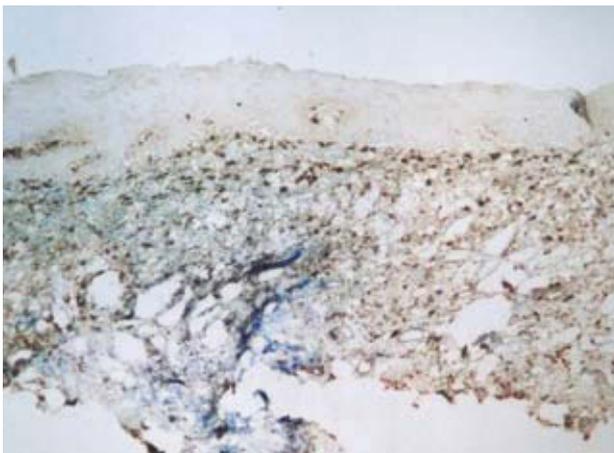
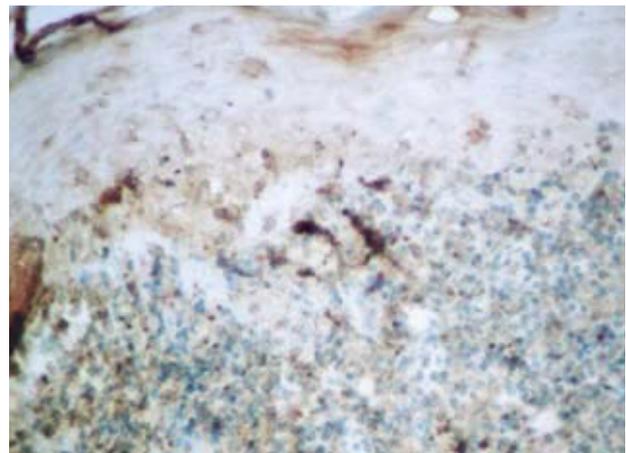
FXIIIa+ DD Semiquantification of the infiltrate	Superficial corion		Deep corion	
	Frequency	Percentage	Frequency	Percentage
Concentrated	18	94.7	5	26.3
Scattered	1	5.3%	14	74.7

Frequency missing = 4. DD: dermal dendrocytes.

**Table 4.** Numeric and percentage distribution of CD34+ DD in 23 analyzed samples

CD34+ DD Semiquantification of the infiltrate	Superficial corion		Deep corion	
	Frequency	Percentage	Frequency	Percentage
Concentrated	1	4.4	5	22.7
Scattered	22	95.6	17	77.3

Frequency missing = 1. DD: dermal dendrocytes.

**Figure 1.** Factor XIIIa+ DD mainly in the upper corion.**Figure 2.** Detail of factor XIIIa+ DD in superficial corion.

CD34+ DD were most often observed in the lower dermis, just below the inflammatory infiltrate (Figures 6 and 7). These cells were absent or were scattered in the superficial dermis and around vessels (4.4 %) (Figure 8). A significant increase was observed ( $P=.020$ ) in the CD34+ DD count in the deep dermis (22.7 %) compared to the superficial dermis (6.3 %).

For the purpose of statistical analysis, the clinical forms were grouped into erosive and nonerosive forms, including reticular and plaque forms.

The statistical analysis of the association of factor XIIIa and CD34 proved impossible for the upper dermis since there was an absolute frequency of the number of increased cells (94.7%).

In relation to the lower dermis, as observed below (Table 5), the group with erosive disease and concentrated

infiltrate in the lower dermis does not differ statistically from the group without erosive disease, related both to factor XIIIa+ and CD34+ DD ( $P=.39$  and  $.41$ , respectively).

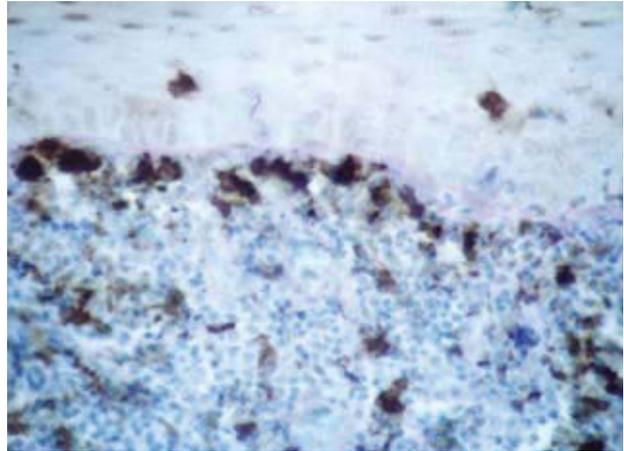
## Discussion

OLP is a relatively common disease, with different clinical presentations. Although the pathophysiology is not entirely known, recent studies point to cell damage by lymphocytes, with the participation of cytokines and adhesion molecules.

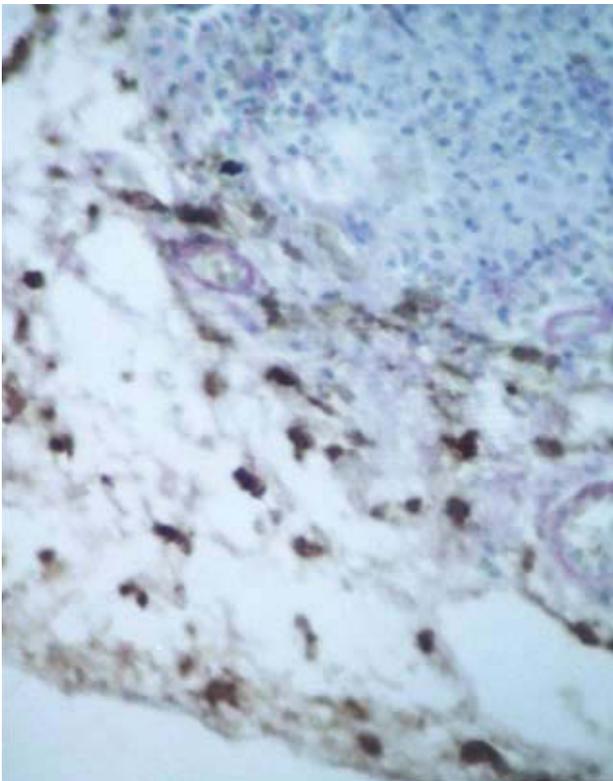
For many years, researchers have been questioning the importance of DD cells in the natural immune response and, consequently, in the pathophysiology of certain diseases. The importance of the Langerhans cells for antigen presentation is well known and they are crucial for



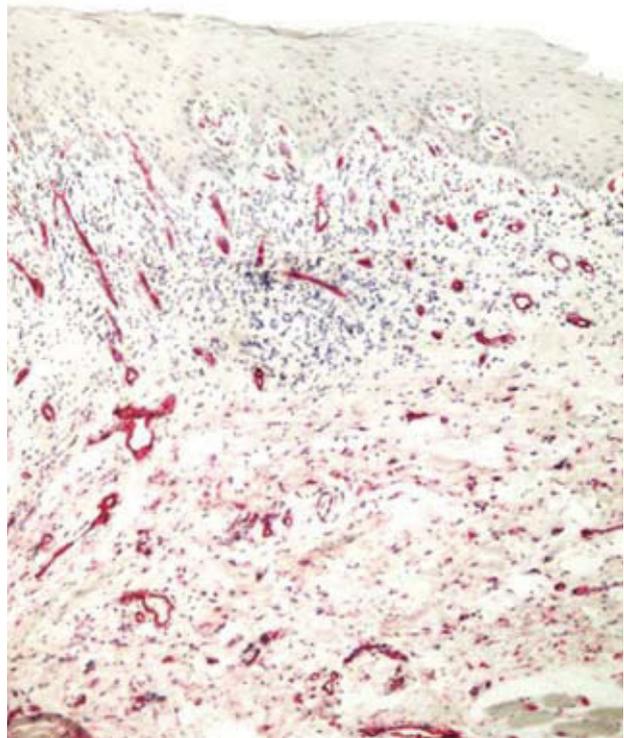
**Figure 3.** Factor XIIIa+ DD in a sub-epithelial position.



**Figure 5.** Factor XIIIa+ DD in the epithelium.



**Figure 4.** Few factor XIIIa+ DD in the inferior corion.



**Figure 6.** CD34+ DD mainly in the lower corion.

the activation of lymphocytes in the process of sensitization of allergic contact dermatitis.<sup>20</sup> However, little is known about the function of DD in the cutaneous immune process.<sup>21</sup> Identification of those cells in the inflamed skin<sup>8</sup> points to their possible participation in the immunological processes.

We know that factor XIIIa+ DD are cells present in the dermis and normal dermis and are increased in some

diseases where a disturbance of the immune system and tissue repair processes occur.<sup>10,11,16,22</sup>

In 1994, Regezi et al<sup>23</sup> observed a statistically significant increase in numbers and size of factor XIIIa+ DD in the submucosa of 16 patients with OLP. Like us, most of the factor XIIIa+ DD were in the upper dermis. Those authors used adjacent healthy tissue as control for the histopathological aspects observed in OLP, and found an average of 10 cells in

the upper and 8 in the lower dermis, in both cases characterized as scattered according to the definition of the present study, which showed that the biopsies did not present lesion-free areas, with all samples compromised by inflammatory infiltrate or by other characteristics that were adopted as criteria for histopathological inclusion. We prefer not to use the area adjacent to the lesion as control, even if histopathological abnormalities were not observed, since we cannot be sure that that area, theoretically free from lesions, was also free from cytokine action, other mediators, and adhesion molecules.

Recently, Deguchi et al<sup>21</sup> described a similar pattern of factor XIIIa+ cells in the dermis of cutaneous lichen planus (CLP). Those researchers, however, like Regezi et al,<sup>23</sup> used the area adjacent to benign tumors such as seborrheic keratosis and melanocytic nevus for control.

A significant increase in factor XIIIa+ DD ( $P < .0001$ ) in the upper dermis was observed. However, it was not possible to correlate this with the clinical form or histopathological aspects of OLP. In the present study, factor XIIIa+ DD were closely related to the inflammatory infiltrate and seemed to be part of it, in contrast to that reported by other authors, who reported most cells around the lymphocyte infiltrate without direct contact with it in studies of factor XIIIa+ DD in lesions of CLP and in inflamed skin.<sup>10,22</sup> It was observed that regardless of whether the inflammatory infiltrate was bundled or irregular, factor XIIIa+ DD were present in large numbers.

Like us, both Deguchi et al<sup>21</sup> and Regezi et al<sup>4</sup> described factor XIIIa+ DD in the epithelium in CLP and OLP. One hypothesis is that factor XIIIa+ DD are indirectly connected to apoptosis, possibly through either stimulation of TNF- $\alpha$ ,<sup>14</sup> or influence on antigen presentation and differentiation by Langerhans cells.<sup>8</sup>

In comparison with what was considered normal in the aforementioned study by Regezi et al,<sup>23</sup> it could be stated that factor XIIIa+ DD were more numerous in the 19 biopsies analyzed, both in the upper and lower dermis. However, as mentioned earlier, the area adjacent to the lesion may be compromised and, in view of this, we chose to only describe factor XIIIa+ and CD34+ DD in the patients' submucosa with OLP.

Although double staining for CD34 and factor XIIIa was not performed, the tissue distribution of DD confirms the hypothesis that they are different subsets of dendritic cells.<sup>4,23</sup>

In normal submucosa, CD34+ DD are present in the lower dermis. In diseased mucosa, CD34+ DD distribution is similar to the normal mucosa.<sup>4,18,24,25</sup> The present study is the first to describe CD34+ DD distribution in the biopsies of OLP.

CD34+ DD are numerous immediately below the inflammatory infiltrate ( $P < .020$ ). This suggests that these cells might be involved in sustaining or triggering the inflammatory process. However, the possible immunological

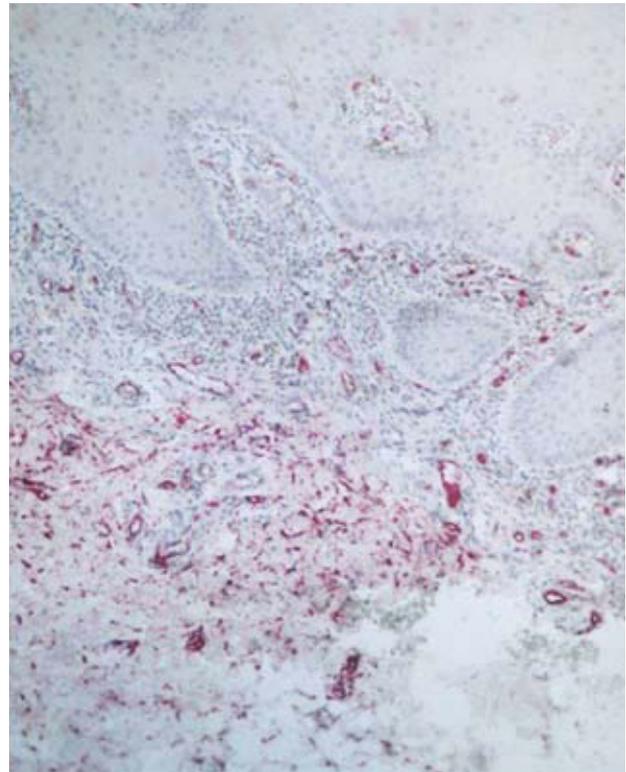


Figure 7. CD34+ DD right below the inflammatory infiltrate.

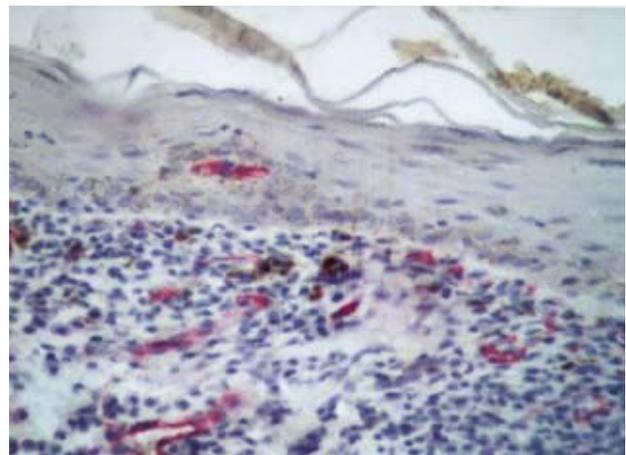


Figure 8. Few CD34+ cells in the upper corion.

Table 5. Distribution of the infiltrate in the lower corion, related to the clinical forms

	Factor XIIIa+		CD34+	
	Erosive OLP	Non-erosive OLP	Erosive OLP	Non-erosive OLP
Concentrated	40.0	21.43	33.3	18.75
Scattered	60.0	78.57	66.7	81.25

OLP: oral lichen planus.

functions attributed to factor XIIIa+ DD, such as antigen presentation,<sup>13</sup> T-cell migration,<sup>14</sup> and expression of ICAM-1 and TNF- $\alpha$ ,<sup>15,16</sup> were not described for CD34+ DD.

## Conclusions

1. Factor XIIIa+ and CD34+ DD are present in OLP lesions and those cells have a distinct tissue distribution in OLP.
2. Factor XIIIa+ DD predominated in the upper portions of the dermis, amongst the inflammatory infiltrate, while CD34+ cells were predominant in deeper locations, below the inflammatory infiltrate. Factor XIIIa+ cells were also detected amongst keratinocytes and in the lower dermis. CD34+ cells were observed, in smaller numbers, in the upper dermis.
3. Factor XIIIa+ and CD34+ DD distribution is not associated with the clinical forms nor with histopathological aspects of OLP.

## Conflict of Interest

We declare that we have no conflict of interests.

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