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ORIGINAL PAPER

Accumulation of CD1a-positive Langerhans cells and mast cells in actinic cheilitis

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Abstract LCs and MCs are known to be directly influenced by UV radiation. This study investigated the presence of Langerhans cells (LCs) and mast cells (MCs) in actinic cheilitis (AC) exhibiting epithelial dysplasia (ED). Using immunohistochemistry for CD1a and mast cell tryptase, LCs and MCs density was assessed in 35 cases of AC with different degrees of ED. LCs were found in 32 cases of AC whereas MCs were found in all cases. There was an increase in LCs density irrespective of degree of ED when the cases were compared to normal lip mucosa ($P = 0.04343$). No statistical difference in LCs density was observed regarding the different degrees of dysplasia ($P > 0.05$). Significant difference in MCs density between mild and moderate dysplasia and normal lip mucosa was found ($P < 0.05$). No significant correlation between LCs and MCs was seen ($P = 0.1258$). Although no correlation could be established between LCs and MCs and the different degrees of ED; it is possible that the accumulation of LCs plays an immunostimulatory and protective role in the defense against progression of dysplasia. Further studies are necessary to determine the role of MCs in the development of AC.

Keywords Actinic chelitis · Langerhans cells · Mast cells · Epithelial dysplasia

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Introduction

Actinic cheilitis (AC) is a premalignant lesion that manifests as a diffuse lesion of the lower lip vermilion resulting from excessive exposure to sunlight. The condition is more frequent in light-skinned individuals. AC is analogous to solar keratosis, exhibiting variable degrees of ED, and may even undergo malignant transformation to squamous cell carcinoma (Cataldo and Doku 1981; Cavalcante et al. 2008; Markopoulos et al. 2004; Rojas et al. 2004; Santos et al. 2003). Histopathologically, AC is characterized by atrophy or acanthosis of the stratified squamous epithelium. The latter can be hyperkeratinized or parakeratinized (Cavalcante et al. 2008; Kaugars et al. 1999; Markopoulos et al. 2004; Santos 2000; Santos et al. 2003). In general, a mild to moderate inflammatory infiltrate mainly consisting of lymphocytes and occasional plasma cells is present in the lamina propria (Cataldo and Doku, 1981; Kaugars et al.

1999; Santos 2000; Santos et al. 2003), amidst amorphous basophilic degeneration of collagen fibers in superficial connective tissue (Cavalcante et al. 2008; Kaugars et al. 1999; Markopoulos et al. 2004; Rojas et al. 2004; Santos 2000; Santos et al. 2003).

Ultraviolet (UV) radiation, especially UVB (280–315 nm), exerts diverse effects on the immune system of human skin (Facy et al. 2005; Kolgen et al. 2002; Meunier et al. 1995; Norval et al. 2008) and also contributes to the development of AC and lip cancer (Cavalcante et al. 2008; Picascia and Robinson 1987). These effects include the suppression of cellular immunity, such as the disappearance of antigen-presenting cells of the epidermis, called LC (Facy et al. 2005; Kolgen et al. 2002; Meunier et al. 1995). These cells are the main antigen-presenting cells of the epidermis and actively participate in Th1 and Th2 responses, presenting antigens to B or T lymphocytes (Cutler and Jotwani 2004; Holiková et al. 2001).

MCs are bone marrow-derived cells (Chen et al. 2005; Rodewald et al. 1996) widely found in human tissues (Fukushima et al. 2006). Depending on their location and stage of maturation, these cells express different quantities of surface antigens that are involved in cell activation and recognition (Valent et al. 2001). MCs are classified according to the secretion of proteins, called endopeptidases, and they are divided into tryptases and chymases (Caughey 2007). The secretion of these enzymes promotes inflammation, matrix destruction, tissue remodeling, and angiogenesis (Caughey 2007; Huttunen and Harvina 2005). According to Rojas et al. 2005, actinic damage on the epithelial cells activates MCs, and this contributes to the degeneration of connective tissue observed in AC and also stimulate angiogenesis and inflammation; therefore, these cells are important for skin remodeling after actinic damage and mediate the immunosuppression induced by UV rays (Grimbaldeston et al. 2006).

We previously demonstrated an altered pattern of keratin differentiation in AC (Santos et al. 2003). In addition, it is known that cell proliferation associated with an altered differentiation program may cause the development of tumor cells (Hahn and Weinberg 2002). Furthermore, the inflammatory microenvironment modulates cell migration and invasion, facilitating the proliferation of altered cells and contributing to the formation and progression of cancer (Le Bitoux and Stamenkovic 2008; Lin and Karin 2007).

Therefore, as cellular components such as LCs and MCs are known to be directly influenced by UV radiation, the aim of the present study was to investigate by immunohistochemistry the presence of LCs and MCs in AC lesions with different degrees of ED since these lesions, frequently found in the lower lip, show a potential to become malignant.

Materials and methods

The study was approved by the Ethics Committee of School of Denstistry of the Federal University of Bahia. Thirty-five cases of AC diagnosed at the Laboratory of Surgical Pathology, School of Dentistry, Federal University of Bahia, were studied. Clinical data obtained from the request forms of the anatomopathological exams indicated that 21 (60%) patients were males and 14 (40%) were females, with a mean age of 54.8 years (range 20–75).

For morphological analysis, 4-μm thick sections were obtained from material fixed in formalin and embedded in paraffin. The slides obtained for each case were stained with hematoxylin and eosin and analyzed by light microscopy.

Each case ($n = 35$) was reassessed based on the histological criteria for the diagnosis and histological grading of ED defined by the World Health Organization for precursor epithelial lesions: mild dysplasia, moderate dysplasia, and severe dysplasia (Gale et al. 2005).

For immunohistochemical analysis, 3-μm thick sections were cut from each tissue specimen. Immunostaining was performed with the streptavidin–biotin complex (LSAB, Dako Cytomation, Glostrup, Denmark) using anti-CD1a antibody (clone MTB1, Novocastra, Newcastle, United Kingdom; dilution 1:30) for the detection of LCs and anti-mast cell tryptase (clone AA1, Dako Cytomation; dilution 1:50, Glostrup, Denmark) for the detection of MCs. The sections were deparaffinized, rehydrated and washed in distilled water. Next, antigen retrieval was performed with Tris/EDTA buffer, pH 9.0, heated to 96°C for 30 min for CD1a, and by enzymatic digestion with 1% trypsin at 37°C for 20 min, for mast cells. Endogenous peroxidase was blocked by incubation in 3% hydrogen peroxide for 10 min. The slides were then incubated with the primary antibody for 60 min in a humid chamber, at room temperature (RT). Then, the slides were washed with 1% PBS/BSA and incubated with the biotinylated secondary antibodies (link reagent, Dako Cytomation, Glostrup, Denmark) for 60 min, at RT, followed by washing and incubation with the streptavidin–biotin-peroxidase complex. Diaminobenzidine (Dako Cytomation, Glostrup, Denmark) was used as chromogen and the slides were counterstained with Harris hematoxylin for 15 s. As positive control, a fragment of LCs histiocytosis was used for the anti-CD1a antibody and a fragment of pyogenic granuloma presenting marked granulation tissue for MCs. The negative control consisted of replacement of the primary antibody with an antibody of the same isotype as the primary antibody. Three fragments of normal lip mucosa without solar elastosis were also studied for the purpose of comparison.

LCs and MCs were analyzed by a previously trained observer by light microscopy, taking into accounting the

same areas as those used for histological grading of ED. For the analysis of LCs, the density of CD1a-positive cells was obtained by the observation of immunostained epithelial strata. CD1a-positive cells were counted in up to 10 microscopic fields at final magnification of 200×. For evaluation of the distribution of MCs, all cells present in the superficial and deep lamina propria, including the area of basophilic degeneration, were counted in up to 20 fields at final magnification of 100×. The shape of the cells and the presence of degranulated mast cells were also described.

The descriptive results were expressed as the mean ± standard deviation (SD) of positive cells per field. Differences between groups (LCs, MCs, degree of ED) were evaluated using the Kruskal–Wallis test, followed by Dunn's test. The correlation between CD1a- and tryptase-positive cells was analyzed using Spearman's correlation coefficient. All statistical calculations were performed using the GraphPad Prism 4.0 program. The level of significance was set at 5%.

Results

According to the histological parameters defined by the WHO for the diagnosis of epithelial dysplasia, 17 (48.7%) of the 35 cases were classified as mild dysplasia, 13 (37.14%) as moderate dysplasia, and 5 (14.29%) as severe dysplasia.

CD1a-positive LCs were observed in 32 (91.43%) cases irrespective of presence of inflammation. Most stained cells presented a dendritic aspect and long and irregular cytoplasmic prolongations and were detected in the basal to intermediate layers. No positive cells were found in the stratum corneum in any case. Interstitial dendritic cells were also observed in the superficial lamina propria (Fig. 1). The mean density of positive cells ranged from 0 to 40.1, and the variations in number of CD1a-positive LCs are presented in Table 1. In addition, an increase in LC density irrespective of the degree of ED was observed when the cases were compared to normal lip mucosa ($P = 0.04343$, Kruskal–Wallis test). However, Dunn's post-test revealed no significant difference in LC density when the different degrees of ED were compared separately ($P > 0.05$).

MCs were found throughout the superficial and deep lamina propria, including especially the area corresponding to basophilic degeneration; in this area degranulated mast cells were found. The cells presented a round, angular or elongated shape, and were observed in all cases studied irrespective of presence of inflammation (Fig. 2). Submucosa was not observed in all cases, but when present mast cells were also detected around medium-caliber blood vessels in the presence or absence of basophilic degeneration. The mean density of MCs ranged from 7.0 to 65.5, and the variations in number of MCs are presented in Table 1.

Comparison of mast cell density between the different degrees of ED and normal mucosa showed a higher density of these cells in cases of mild and moderate dysplasia ($P < 0.05$, Kruskal–Wallis test and Dunn's post-test) (Fig. 3). Spearman's correlation coefficient revealed no significant correlation between the CD1a and mast cell tryptase markers in the sample studied ($P = 0.1258$, rs = 0.2637).

Discussion

LCs play a role in the initiation and regulation of immune responses, especially in the stimulation of lymphocyte proliferation (Hubert et al. 2005; Schroder et al. 2006). These cells detect antigens on the epidermis, migrate to lymph nodes that drain the region and present these antigens to T lymphocytes, thus acting as sentinels of actinic damage to the skin (Cutler and Jotwani 2004; Kaugars et al. 1999; Schroder et al. 2006; Timares et al. 2008). The mobilization and migration of LCs are induced and regulated by cytokines, mainly tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β) (Antonopoulos et al. 2008; Facy et al. 2005; Cumberbatch et al. 2002). It is important to state that Kolgen et al. 2002 report that this migratory capacity of LCs is impaired after actinic damage, with consequent accumulation of these cells in the dermis.

Chronic exposure to sunlight has been indicated as the main etiological agent of both AC and squamous cell carcinoma of lip (Cavalcante et al. 2008; Cataldo and Doku 1981; Markopoulos et al. 2004; Santos et al. 2003). UV radiation exerts various biological effects on the human skin, including the suppression of immune reactions and a reduction in the number of LCs (Facy et al. 2005; Kolgen et al. 2002; Meunier et al. 1995). This reduction in the number of epidermal LCs and functional disturbances after UVB radiation can be explained by two still controversial mechanisms: migration of structurally and functionally altered LCs to the lymph nodes (Kolgen et al. 2002) or induction of apoptosis of these cells (Takashima 2005; Rattis et al. 1998). Kolgen et al. 2002 raised blisters on the skin of healthy individuals overexposed to UVB and showed a considerable number of Langerhans cells in the blister fluid, concluding that these cells came from the epidermis and thus the reduction of Langerhans cells is attributed not only to apoptosis, but the migration of cells to the lymph nodes. Experiments on mice showed that LCs apoptosis is induced by UVB radiation through the production of reactive oxygen species by keratinocytes, among

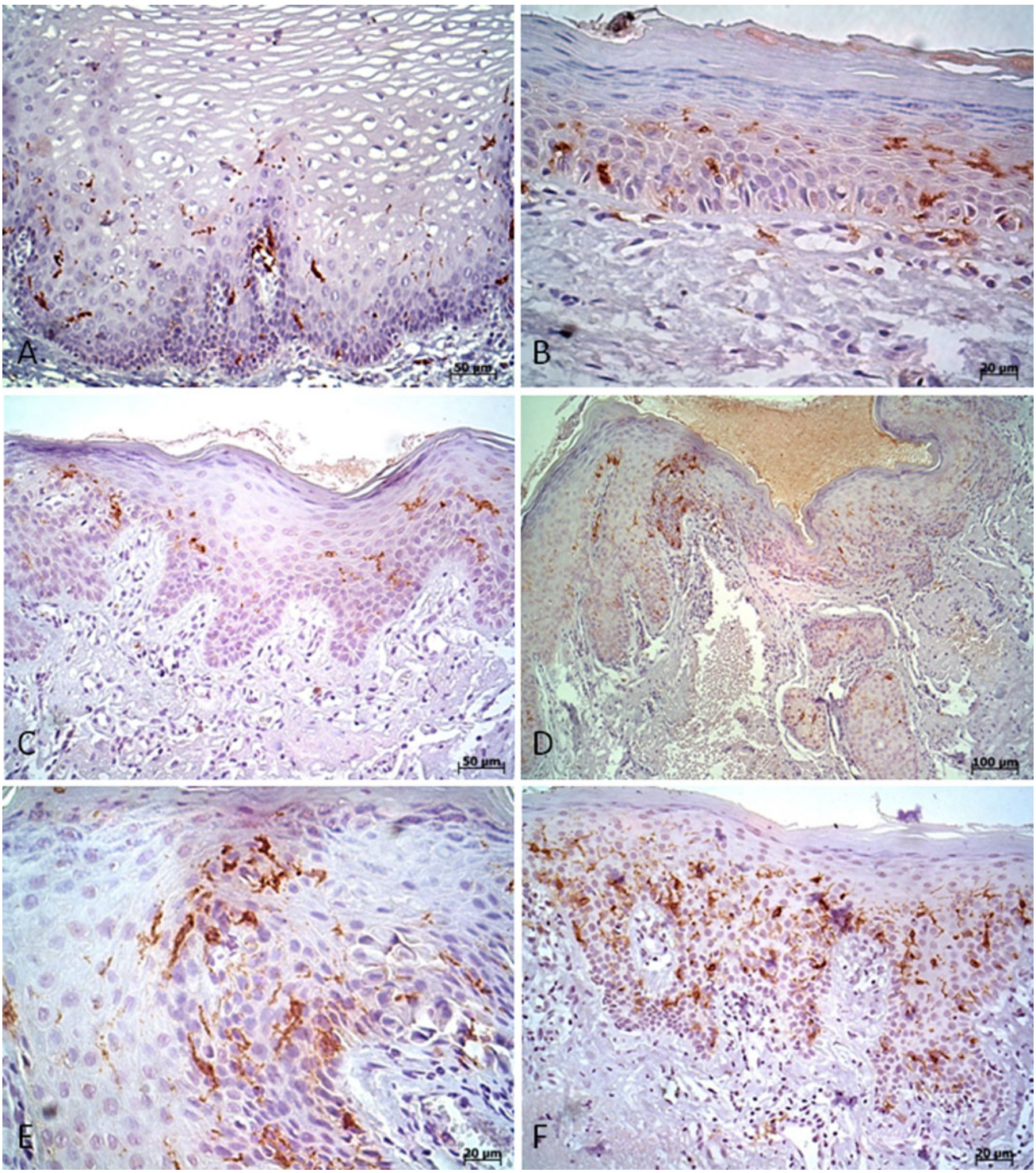

Fig. 1 Langerhans cells in normal oral mucosa and actinic cheilitis with different degrees of dysplasia. **a** Normal oral mucosa exhibiting CD1a-positive Langerhans cells reaching stratum basal and upper layers. **b** Actinic cheilitis with mild dysplasia exhibiting CD1a-positive Langerhans cells reaching basal and intermediate layers; note dendritic cells in the subepithelial region. **c** Actinic cheilitis with mild dysplasia displaying CD1a-positive Langerhans cells located mainly in the basal and parabasal layers. **d** Actinic cheilitis with moderate dysplasia displaying CD1a-positive Langerhans cells located along the epithelium lining. **e** Detail of previous figure displaying marked distribution of CD1a-positive Langerhans cells; note the dendritic extensions presented by the cells. **f** Actinic cheilitis with severe dysplasia showing marked distribution of dendritic cells; note that these cells are not found in the stratum corneum

Table 1 Variations in number of CD1a-positive LCs and MCs in AC lesions with different degrees of ED and normal mucosa

	Mild Dysplasia Mean (SD)	Moderate Dysplasia Mean (SD)	Severe Dysplasia Mean (SD)	Normal Lip Mucosa Mean (SD)
Cd1a positive cells	53.00 (48.65)	32.91 (29.54)	85.25 (82.70)	29.33 (13.01)
Mast cell tryptase positive cells	213.20 (108.4)	202.60 (80.39)	136.00 (71.07)	36.00 (10.48)

SD standard deviation

other mechanisms (Takashima 2005). Schwartz et al. 1998 also demonstrated a possible induction of dendritic cell apoptosis through the stimulation of suppressor T cells via the FAS pathway. Probably, other immunological aspects especially those related to the host should be further investigated.

Despite reports of the influence of UV radiation on the behavior of LCs and on the development of AC lesions, to our knowledge, there are no studies in the English literature investigating the relationship between these cells and AC lesions. In the present study, CD1a-positive Langerhans cells was observed in almost 92% of AC lesions, and although this research could not demonstrate the direct involvement of UV on the disappearance of these cells in AC as observed in basal cell carcinomas (De Melo et al. 2006), it shows the importance of dendritic cells as effector cells of the oral mucosal immune response (Cutler and Jotwani 2006; Mowat 2005).

With respect to the degree of ED shown by AC lesions, in the present study the number of LCs did not differ significantly between the different degrees of ED, although an increase in cell counts was observed when compared to control. The present results permit to attribute the increase in the density of LCs in AC lesions to an immunostimulatory and protective signal of the lip or organism, after the lesion has become chronic, possibly from adjacent healthy tissue. It is possible that an elevated number of these cells may indicate a possible limit between AC and the development of squamous cell carcinoma of the lip. However, further studies are necessary to clarify this aspect. Furthermore, some patients may have developed AC many years ago and protected their lips from direct exposure to sunlight during recent years whereas others may presently have been exposed to excessive UV radiation on a daily basis, and this might explain the variation in cell count.

Some authors have shown a high density of LCs in oral squamous cell carcinoma, but this increase was attributed to the presence of an inflammatory infiltrate in the tumor Albuquerque et al. (2003). In the present study, the increase in the density of LCs in AC lesions was found in the presence or absence of inflammatory cells. The presence of a large number of LCs in different types of tumors predicts a better prognosis, a fact demonstrating the efficiency of these cells in the tumor immune response. Despite these aspects, La Rocca et al. 2000 observed that the higher the infiltration of CD1a positive dendritic cells in primary invasive ductal breast carcinoma, the lower the possibility of lymph nodes metastases, suggesting that CD1a positive cells might be a favorable prognostic marker in these tumors. Miyagi et al. 2001 also associated the presence of a large number of these cells in HPV-infected lung cancer with a better prognosis. Taken together, these data thus support the capacity of these cells in monitoring cancerigenic lesions.

We studied the distribution of MCs in AC lesions because of the role of these cells in the immunosuppression provoked by UV radiation (Grimbaldeston et al. 2006), matrix degradation, induction of angiogenesis, and degeneration of connective tissue in solar elastosis (Caughey 2007; Huttunen and Harvina 2005; Rojas et al. 2005). An increase in the number of these cells was observed in cases of discrete and moderate dysplasias when compared to control (Erbagci and Erkiliç 2002; Hart et al. 2000; Hart et al. 2001). In this study, MCs were found to be concentrated in the region of the lamina propria, whereas Rojas et al. 2004 observed a higher accumulation of these cells at the epithelial/connective tissue junction and in connective tissue itself. According to many authors, the number of MCs is significantly increased in skin exposed to radiation as well as in different types of cancer (Bosset et al. 2003; Gomes et al. 2008; Grimbaldeston et al. 2006; Hart et al. 2000; Hart et al. 2001; Humphreys et al. 2000; Iamaroon et al. 2003; Rojas et al. 2005).

Although no significant association between MCs and the degree of epithelial dysplasia was observed in the present study, the number of these cells was increased when compared to normal lip mucosa (Costa et al. 2009; Gomes et al. 2008). The presence of MCs and their distribution in premalignant and malignant lesions indicate an association of these cells with the severity of these lesions, as well as an increase in the immunosuppression provoked by UV radiation. In this respect, some investigators showed a larger mean number of MCs (40.1) in lip cancer when compared to different degrees of ED (moderate: 30.5, severe: 28.6) in AC and normal oral mucosa (Gomes et al. 2008). Costa et al. 2009 studying 37 cases of squamous cell carcinoma of the lip and 15 cases of AC, observed a similar number of MCs in the two lesions; however, the number of

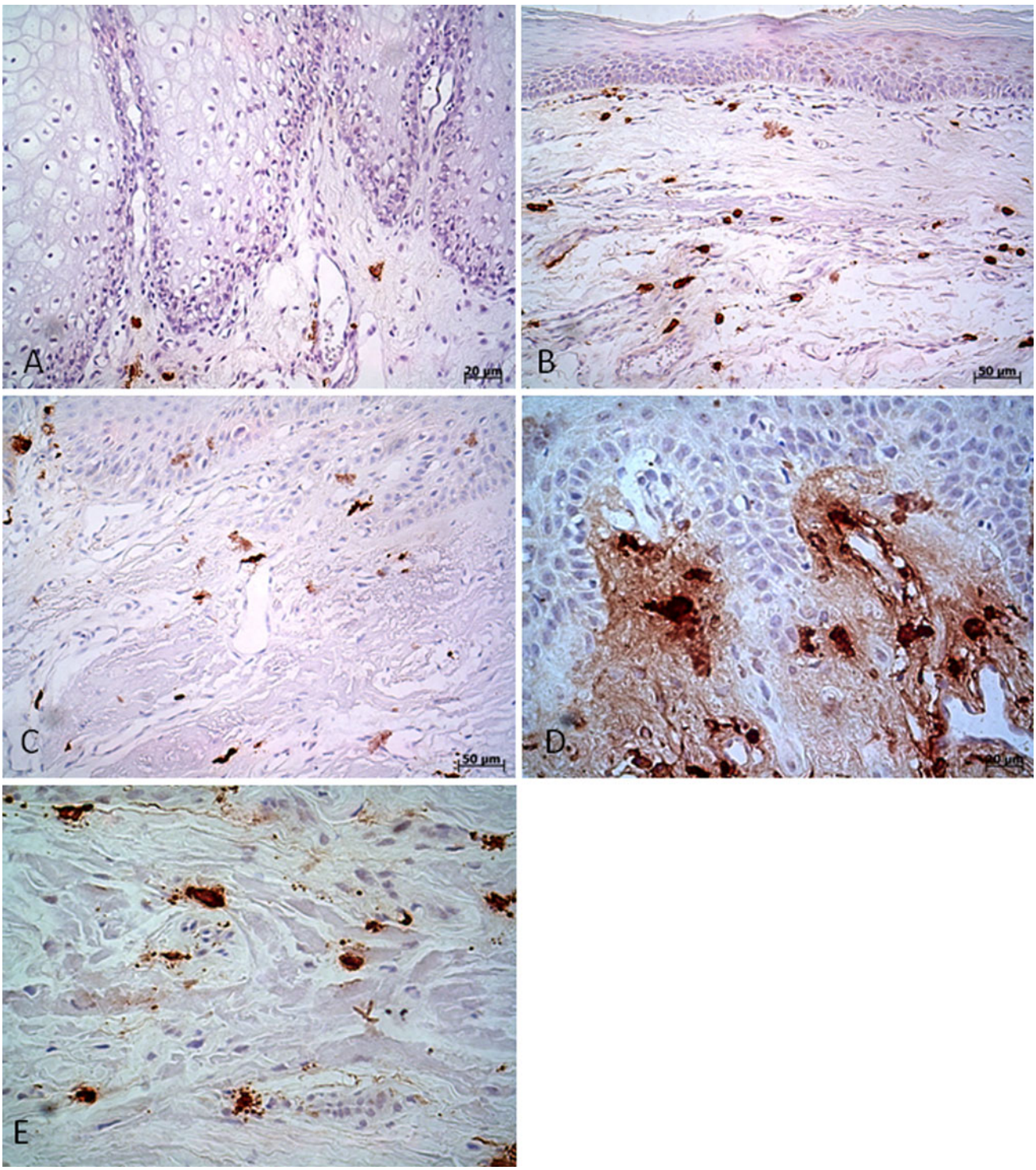

Fig. 2 Mast cells in normal oral mucosa and actinic cheilitis with different degrees of dysplasia. **a** Normal oral mucosa showing few mast cells in the superficial lamina propria and close to vessels. **b** Actinic cheilitis with mild dysplasia showing several mast cells located mainly around the areas corresponding to the solar elastosis. **c** Actinic cheilitis with moderate dysplasia displaying mast cells with elongated shape. **d** Actinic cheilitis with severe dysplasia showing several angular mast cells close to vessels. **e** Actinic cheilitis with severe dysplasia showing degranulated mast cells around the area corresponding to the solar elastosis; these cells are close to vessels

these cells was significantly higher when compared to normal lip mucosa. Michailidou et al. 2008 also found an elevated number of MCs when comparing normal oral mucosa and cases of leukoplakia with discrete, moderate and severe dysplasia and squamous cell carcinoma. Despite their role in tumor development and progression, MCs are

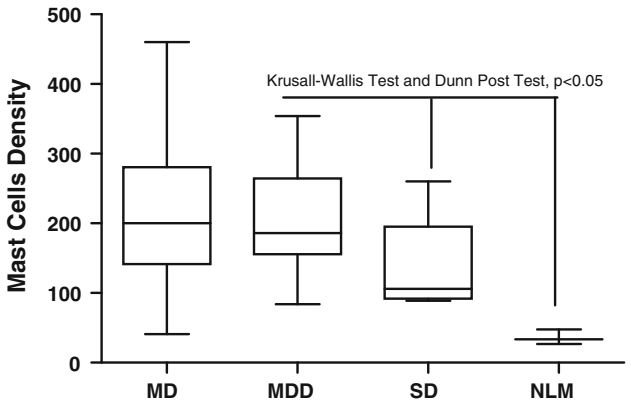

Fig. 3 Distribution of MCs in AC with different degrees of ED and normal mucosa (*MD* mild dysplasia, *MDD* moderate dysplasia, *SD* severe dysplasia, *NLM* normal lip mucosa)

directly affected by UV radiation which alters their potential to release mediators (Guhl et al. 2005; Hart et al. 1998). Furthermore, MCs are important for the structural maintenance of skin through the production of growth factors and fibroblasts (Erbagci and Erkiliç 2002; Maurer et al. 2003). It is important to state that the participation of mast cells in epithelial remodeling and tissue repair after actinic damage has also been reported (Grimbaldeston et al. 2006; Humphreys et al. 2000; Huttunen and Harvina 2005; Nagata et al. 2003; Wang et al. 2005).

One of the function of mast cells includes their involvement in the release of mediators such as histamine, IL-8 and TNF-α and in the accumulation of neutrophils at sites of inflammation (Clydesdale et al. 2001; Endoh et al. 2007; Henz 2008; Grimbaldeston et al. 2006; Guhl et al. 2005). In the present study, these cells were seen in areas of inflammation. However, they were also observed in the absence of inflammation and located close to tortuous blood vessels of the AC lesions, irrespective of their shape. According to Costa et al. 2009, angiogenesis is significantly increased in lip carcinoma when compared to AC. Some investigators suggest that in different cancers resulting from exposure to UV radiation or not, the increase in the number of MCs is associated with inflammation and angiogenesis, favoring the occurrence of cancer and its proliferation (Fisher et al. 1989; Grimbaldeston et al. 2002; Kankkunen et al. 1997; Ribatti et al. 2007; Rojas et al. 2005). In contrast, an association between the presence of MCs and a more favorable prognosis has been reported by others (Aaltomaa et al. 1993; Chan et al. 2005; Fleischmann et al. 2009; Grimbaldeston et al. 2006; Welsh et al. 2005), either increasing survival as observed in patients with lung and ovarian carcinomas (Chan et al. 2005; Welsh et al. 2005) or inducing tumor fibrosis and thus limiting the growth and metastasis of malignant cells (Ruoss et al. 1991). Taken together, the role of MCs in tumor progression does not seem to be well defined. Nevertheless, it is likely that accumulation of MCs influences the development of AC. In addition, as AC becomes malignant, MCs may induce an immunosuppressive state, reducing the host response against tumor antigens and thus permitting the occurrence of squamous cell carcinoma (Grimbaldeston et al. 2006). Further studies are necessary to better understand the role of mast cells in lesions caused by UV radiation.

In conclusion, although no correlation could be established between the density of LCs and mast cells in AC lesions and the different degrees of ED, the present study suggests that the accumulation of CD1a-positive LCs is an important immunostimulatory and protector agent in the defense against progression of ED. Further studies are necessary to determine the role of MCs in the development of AC.

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