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ORIGINAL ARTICLE

Oral lichen planus and chronic junctional stomatitis: differences in lymphocyte subpopulations

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Abstract

Objective. Oral lichen planus (OLP) is an oral counterpart or oral manifestation of the common skin disease lichen planus. Chronic junctional stomatitis (CJS) is a relatively unknown condition characterized by a stromal lymphocyte infiltrate, which is also a diagnostic feature of OLP. The differential diagnosis of OLP and CJS is unclear and they have been suggested to represent variants of the same disease. ***Material and methods.*** To investigate possible differences in lymphocyte (sub)populations between these two conditions, we immunostained 10 OLP and 10 CJS specimens for CD1-a, and the lymphocyte markers, CD3, CD4, CD5, CD8, and CD20. We scored the staining results by a four-step grading system and used the Fisher exact test to analyze them statistically. ***Results.*** The proportional amount of (CD20 positive) B lymphocytes was higher in CJS than in OLP and the predominance of CD4 positive T lymphocytes over CD8 positive T lymphocytes was stronger in OLP than in CJS. The differences were statistically significant. ***Conclusion.*** The results reflect differences in the lymphatic infiltrate between OLP and CJS. Their significance needs further investigation.

Key Words: *CJS, immunohistochemistry, lymphocytes, OLP*

Introduction

Lichen planus (LP) is a common skin disease that can also be manifested in the oral mucosa. Oral lichen planus (OLP) occurs most often in middle-aged women, but is not sex privileged. OLP is extremely rare among children [1]. The prevalence of OLP among the general population is approximately 2% [2]. The etiology of OLP is unclear, but an immunological background is widely accepted [3]. OLP closely resembles a non-specific, sometimes hypersensitivity-based, reaction of the oral mucosa, known as lichenoid reaction. It can be difficult to distinguish between these conditions both clinically and histopathologically. However, clinically, OLP usually appears symmetrically, but this is not necessarily the case for lichenoid reaction [4]. Histopathologically, the mucosal epithelium in OLP is keratinized and epithelial atrophy and acanthosis may be seen. Definitive diagnostic criteria of OLP are degenerative changes in the basal cell layer, which are usually not seen in lichenoid reaction, and a subepithelial, stripe-like, chronic inflammatory cell infiltration mainly composed of lymphocytes but not plasma cells [1,4]. The majority of lymphocytes in OLP represent T cell subpopulations that express CD8 and CD4 antigens [5]. CD4-positive T lymphocytes are mostly found in deep lamina propria [6]. CD1-a positive dendritic cells are numerous in the basal cell layer of the epithelium [7].

Chronic junctional stomatitis (CJS), which was first introduced by Eversole and Eversole [8], has been suggested to be an immunity-related condition. Like OLP, CJS exhibits a superficial chronic inflammatory cell infiltrate, but, in addition, deep lymphatic follicles with or without germinal centers (GCs) are seen. In both types of CJS, CD45 and, in part, CD20-positive lymphocytes infiltrate submucosa and dendrocytes occur in the epithelium and submucosa.

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While lymphocytes in GCs mainly represent B cells, as indicated by their CD20 positivity, lymphatic follicle-like structures without GCs also contain CD20-positive lymphocytes [8]. Lymphatic follicle-like structures have also been reported in lichenoid reactions elicited by contact with amalgam restorations [9]. Currently, there is little information available about CJS. To further clarify the nature of this condition, we studied immunohistochemically possible differences in the expression of selected lymphocyte markers in the lymphoid infiltrate between OLP and CJS.

Material and methods

Tissue sample collection

We analysed a total of 20 oral mucosal biopsy specimens from the archives of the Central Laboratory of Pathology, HUSLAB, Helsinki University Central Hospital, Helsinki, Finland. The tissue specimens, which had been sent for diagnostic purposes, had been fixed in formalin and embedded in paraffin. Representative sections were cut and stained with hematoxylin and eosin. Of the 20 specimens, 10 had been diagnosed as OLP and 10 as CJS. Cases selected from the archives as representing OLP or CJS had been signed out in the histopathological laboratory. The diagnoses were based on histopathological appearance and relevant clinical information accompanying submission of the specimens. The slides were revisited by an authorized oral pathologist (J.H.) and were included in the study only when re-evaluation was in full agreement with the original diagnosis. Histological criteria for OLP were keratinization of the epithelium and a stripe-like chronic inflammatory cell infiltrate in the subepithelial connective tissue with lymphocytes predominating. A further requirement was that the lesions were clinically symmetric. The prerequisite for the diagnosis of CJS was the presence of deep submucosal lymphatic follicle-like structures. Attention was paid to the exclusion of other conditions/lesions that can mimic OLP, but can show deep lymphatic infiltrates [10]. Age and sex of the patients were unknown. No patient records were handled. Ten 3 μm thick sections were cut of each tissue specimen for immunohistochemical analysis. The study was performed anonymously with the permission of the chief physician of the Central Laboratory of Pathology, HUSLAB and, therefore, no permission from the Ethics Committee was needed.

Immunohistochemistry

Immunohistochemical staining was carried out in the Immunohistochemical Laboratory, Central Laboratory of Pathology, HUSLAB, using a routine staining procedure. Staining was performed with a Labvision staining machine (Lab Vision, Fremont, Calif., USA). The polymer-based Envision+method was applied. Monoclonal mouse antibodies to human CD1-a (MTB1; Novocastra, Newcastle upon Tyne, UK), CD3 (UK, PS1; Novocastra), CD4 (4B12; Novocastra), CD5 (4C7; Novocastra), CD8 (4B11; Novocastra), and CD20 (L26; Dako, Glostrup, Denmark) were used. Working dilutions for the antibodies had been previously determined for routine diagnostic purposes. Sections were deparaffinized, placed in tris-EDTA, immunostained, counterstained with hematoxylin and covered with Mountex glycine (Histolab Products AB, Stockholm, Sweden) in a mounting machine.

Analysis of immunohistochemical stainings

CJS specimens with and without GCs were analysed collectively. Quantitative analysis of the expression levels of the different antigens was performed by two different methods. First, the immunopositivity of each antigen was quantified by a four-step grading system: none, mild, moderate, and strong. Estimated percentages of reactive cells were 0%, 0–10%, 10–50%, and 50–100%, respectively. B lymphocytes were identified by their positive staining for CD20 and T lymphocytes by their staining for CD3. The proportional amounts of T lymphocytes staining for CD4 and CD8 were compared by determining the ratio of CD4-positive cells to CD8-positive cells with a method modified from the study of Timár et al. [11]. The antigen with a more widely distributed reactivity (higher proportional amount of cells) was given the value 3 (strong). The antigen showing a more limited reactivity (lower proportional amount of cells) was given the value 1 (weak) or 2 (moderate), depending on the difference in the reactivities between the antigens. The ratio of CD4 reactivity to CD8 reactivity was considered strong CD8 (1/3), moderate CD8 (2/3), no difference (3/3), moderate CD4 (3/2), and strong CD4 (3/1).

Statistical analysis

Statistical analysis was done using the Fisher exact test and a p-value <0.05 was considered significant.

Results

We found differences in the distribution pattern and expression level of CD20 reactivity and in the ratio of CD4 to CD8 reactivities between OLP and CJS. Positive immunostaining for CD20 was present in the subepithelial stromal infiltrate in CJS and in most lymphatic follicles with and without GCs (Figure 1). Cells staining for CD20 were about three times more abundant in CJS than in OLP, mainly due to the existence of lymphatic follicles in CJS (Figure 1). The difference in the expression

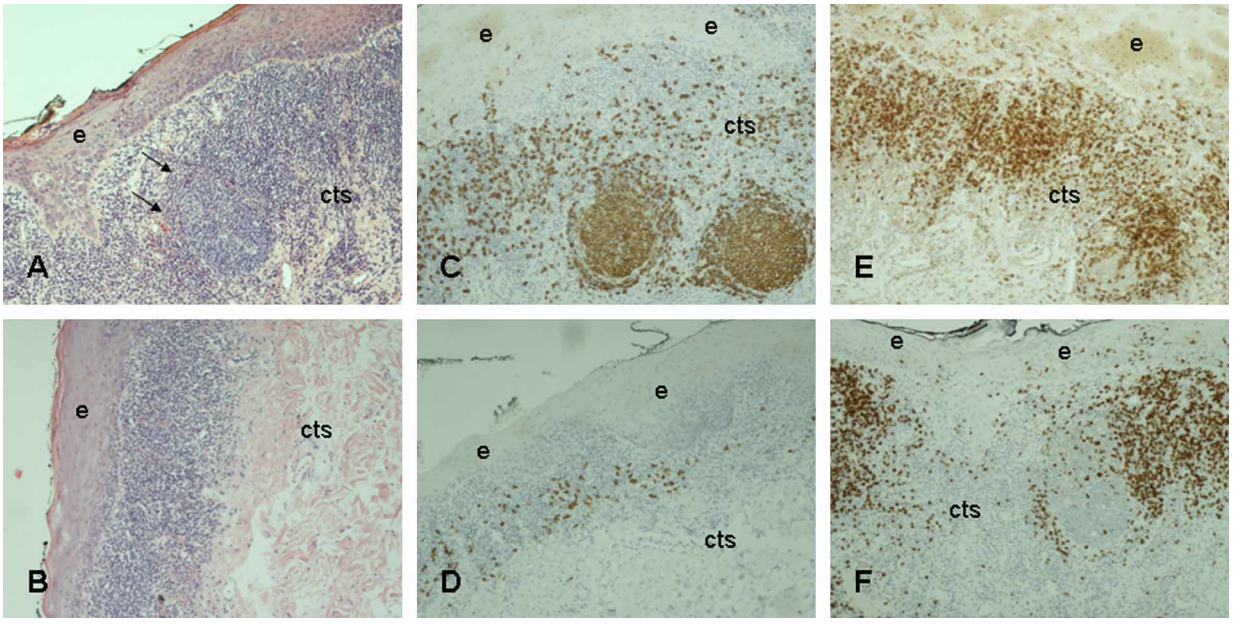

Figure 1. Histological appearance of chronic junctional stomatitis with follicular structures (A) (arrows) and of oral lichen planus (B). He-stained paraffin sections (A and B). Immunohistochemical staining for CD20 in chronic junctional stomatitis is more widely distributed (C) than in oral lichen planus (D). Immunostaining for CD4 (E) and CD8 (F) in chronic junctional stomatitis shows an equal expression level. (A, B, E, and F magnification $\times 100$, C and D $\times 200$). e = epithelium, cts = connective tissue stroma.

level of CD20 in the stromal lymphatic infiltrate between OLP and CJS was statistically significant ($p = 0.016$). Differences in the reactivities of the remaining antigens, CD1-a, CD3, CD4, CD5, and CD8, between OLP and CJS showed no statistical significance (Figure 2). In OLP CD4-positive T-cells were dominant in the stromal lymphatic infiltrate and the proportional amount of CD4-positive T cells was higher in OLP than in CJS (Figure 3). Differences in the ratio of CD4-positive T cells to CD8-positive T cells between OLP and CJS showed statistical significance ($p = 0.041$).

Discussion

To our knowledge, the only previous study of CJS is that of Eversole & Eversole [8]. Neither did we find any study concerning differences between OLP and CJS sharing in common the stromal lymphocyte infiltrate. While OLP is a T-cell-mediated inflammatory/autoimmune reaction, CJS shows a marked B cell component. B cells are especially abundant in the deep lymphatic follicles in CJS. Consistently with the previous study by Eversole & Eversole [8], we found that the proportional amount of B cells is

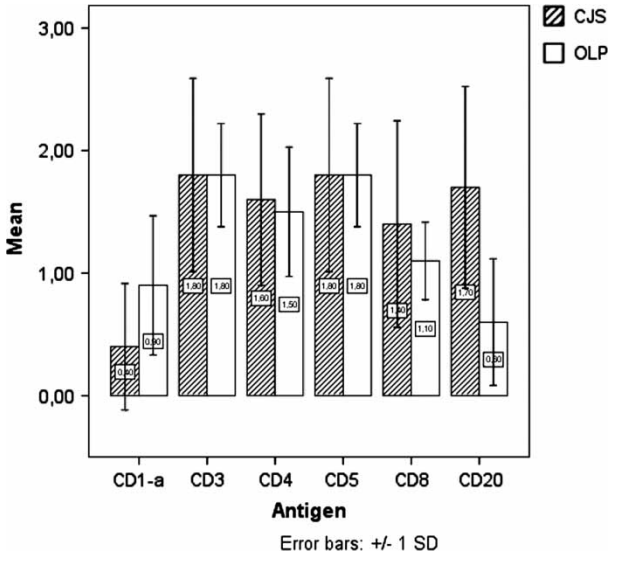

Figure 2. Antigen expression levels in mucosal stromal tissue of OLP and CJS.

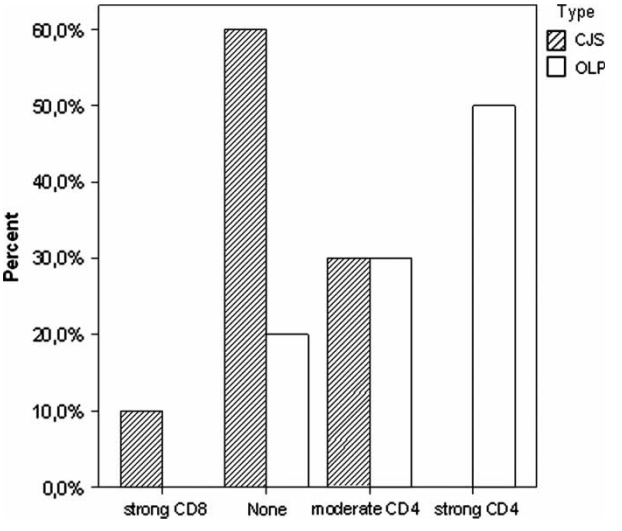

Figure 3. Ratio of CD4 to CD8 in stromal tissue of OLP and CJS.

higher in CJS than in OLP and is for the most part attributable to the presence of lymphatic follicles in CJS.

The expression of various antigens helps divide T lymphocytes into different subgroups. For example, whereas CD4 is expressed by a helper/inducer T cell subpopulation, CD8 is a marker for suppressor/cytotoxic T cells. The ratio of T cells expressing CD4 and T cells expressing CD8 has been used to describe the status of the immune system and in earlier studies this ratio has shown a greater amount of helper/inducer cells in OLP [5,12]. Our study showed that OLP and CJS differ not only in terms of the proportional amount of B cells, but also of T cells expressing CD4 and CD8 antigens. The CD4+/CD8+value was quite high (2.15) in OLP and lower (1.08) in CJS. Thus, whereas CD4 positive helper/inducer T cells predominate over CD8-positive suppressor/cytotoxic T cells in OLP, the proportional amount of these T cell subpopulations is almost equal in CJS.

Stromal lymphatic infiltrate is a histological key feature of OLP and CJS. Based on the differences found here in the composition and distribution pattern of the lymphatic infiltrate, we suggest that OLP and CJS could be distinct entities. However, there are other conditions that can mimic OLP and/or CJS; for example, oral manifestations of lupus erythematosus, lichenoid and granulomatous stomatitis [13], lichenoid reaction with candidiasis [10], and chronic ulcerative stomatitis [14]. Comparative immunohistochemical studies on lymphocyte populations between CJS and these conditions would help reveal the true nature of CJS.

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