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ORIGINAL ARTICLE

Significant association of inflammation grade with the number of Langerhans cells in odontogenic keratocysts

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Langerhans cell;
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Aggressive clinical behavior;
High recurrence rate;
Immunosurveillance

Background/Purpose: Langerhans cells (LCs) are antigen-presenting cells. This study assessed the LC counts in odontogenic keratocysts (OKCs).
Methods: The LC numbers in the lining epithelia and subepithelial connective tissues were counted at 60 OKC sites without inflammation, 39 OKC sites with mild/moderate inflammation, and 13 OKC sites with severe inflammation from 60 OKC specimens immunostained with anti-S100 antibodies.
Results: The mean LC counts in the lining epithelia and subepithelial connective tissues increased significantly from no inflammation (0.5 ± 0.4 and 0.7 ± 0.6 cell/high-power field or HPF, respectively) through mild/moderate inflammation (5.9 ± 2.7 and 5.0 ± 3.5 cells/HPF, respectively) to severe inflammation OKC sites (14.7 ± 5.3 and 13.3 ± 6.8 cells/HPF, respectively; all P-values < 0.001). OKC sites with inflammation had thicker lining epithelia than those without inflammation. Moreover, the mean LC counts in the lining epithelia and subepithelial connective tissues of OKCs were significantly higher in the thicker lining epithelium (>100 μm) group (7.7 ± 5.6 and 6.5 ± 5.8 cells/HPF, respectively) than in the thinner lining epithelium (≦ 100 μm) group (1.0 ± 2.0 and 1.4 ± 2.6 cells/HPF, respectively; both P-values < 0.001).
Conclusion: A significant association of inflammation grade with the number of LCs in OKCs is found. The paucity of finding LCs in the lining epithelia of OKCs without inflammation indicates

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the loss of immunosurveillance ability against the OKC lining epithelial cells; this can explain why OKCs have aggressive clinical behavior, a great growth potential, and a high recurrence rate.

Introduction

Odontogenic keratocyst (OKC) has been called as keratocystic odontogenic tumor in the third edition of World Health Organization (WHO) Classification of Head and Neck Tumours published in 2005 because it shows aggressive clinical behavior, a great growth potential, and a high recurrence rate.[1] However, the old name of OKC was reused recently in the fourth edition of the same book published in 2017 probably due to lack of sufficient evidence to support a neoplastic origin of OKC.[2] Multiple OKCs in the jaw bones may be one of the major clinical features of nevoid basal cell carcinoma syndrome (NBCCS).[1–4] Pathogenetic mechanisms that favor growth and expansions of OKCs include a high proliferation rate, overexpression of antiapoptotic protein Bcl-2, and expression of matrix metalloproteinases 2 and 9.[4] Mutations of PTCH1 tumor suppressor gene have been discovered in 85% of NBCCS-associated OKCs and in 30% of sporadic OKCs.[3] If the *PTCH* gene is mutated and nonfunctional, there is no *PTCH* gene product that in turn leads to overexpression of sonic hedgehog and/or smoothened proteins, resulting in increased lining epithelial cell proliferation in OKCs.[4]

Langerhans cells (LC) are bone marrow-derived dendritic cells that reside within the stratified squamous epithelium of skin and the mucosa of the upper gastrointestinal and female genital tracts. LCs are usually located at the suprabasal and spinous cell layers of the epithelium and constitute 2–8% of the intra-epithelial cell content. In the oral mucosa, LCs work as antigen-presenting cells that phagocytose the antigens in the oral epithelia, migrate from the oral epithelia to the lamina propria and further to the paracortical area of the draining lymph node where they process the antigenic proteins into antigenic peptides and then present the antigenic peptides to T cells. Consequently, T-cell-mediated effector mechanisms are activated by the secondary stimulation of the specific antigens.[5]

Previous studies have demonstrated the presence of LCs in the parakeratinized lining epithelia and subepithelial connective tissues of small series of OKCs.[6–11] LCs are more frequently detected in the lining epithelia of orthokeratinized odontogenic cysts than in those of OKCs.[6,7] Furthermore, there are more LCs discovered in the thick hyperplastic lining epithelia overlying the inflamed fibrous cystic walls of OKCs than in the thin atrophic lining epithelia overlying the uninflamed fibrous cystic walls of OKCs.[9,10] However, it was still unclear whether the LC counts in the lining epithelia and subepithelial connective tissues of OKCs were associated with the grade of inflammation in the subepithelial connective tissue, the thickness of the lining epithelium, and clinical parameters of OKC.

In this study, we used the anti-S100 protein immunostaining to study the LCs in a relatively large series of 60 OKCs. The LC numbers in the lining epithelia and subepithelial connective tissues of OKC samples were separately counted at many OKC sites with or without inflammation. The main purposes of this study were to explore whether the LC counts in the lining epithelia and subepithelial connective tissues of OKC samples were associated with the grade of inflammation in the subepithelial connective tissue, the thickness of the lining epithelium, and the clinical parameters including the patient age and gender as well as the location, size and recurrence of OKC.

Materials and methods

Patients and specimens

In this study, formalin-fixed, paraffin-embedded specimens were retrospectively collected from 60 OKC patients (33 men and 27 women, mean age 34 ± 18 years, range 6–75 years). Two of the 60 OKC specimens were enucleated from the two NBCCS patients. Diagnosis of OKC was based on histological examination of hematoxylin and eosin-stained tissue sections. Histologically, the OKC was usually lined by parakeratinized stratified squamous epithelium of 5 to 8 cells in thickness overlying a thin layer of fibrous connective tissue wall without inflammation. The surface parakeratin usually presented a wavy or corrugated appearance and the lining basal epithelial cells were cuboidal or columnar and arranged in a palisaded pattern. However, in some OKC cases, there might be a concomitant mild, moderate or severe chronic inflammatory cell infiltrate in focal fibrous walls of OKCs. All patients received total surgical enucleation of their OKC lesions at the Department of Oral and Maxillofacial Surgery, National Taiwan University Hospital (NTUH), Taipei, Taiwan during the period from 2005 to 2011. Specimens were obtained from total surgical excision of the lesions. Of the 60 OKC lesions, 23 (38%) were found in the maxilla (3 in the anterior and 20 in the posterior region) and 37 (62%) in the mandible (5 in the anterior and 32 in the posterior region). The mean greatest dimension of the OKC measured from the panoramic radiographs was 3.4 ± 1.4 (range 1.0–7.1) cm. Of the 60 OKCs, 54 were primary and 6 were recurrent OKCs. This study has been reviewed and approved by the Institutional Review Board of NTUH.

Immunohistochemical staining for Langerhans cells

The immunohistochemical staining for the detection of LCs in different lesional tissues has been described

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