Pathological Findings for Mucous Retention Cyst in Maxillary Sinus

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Mucous retention cyst (MRC) is not uncommon in the pathology of maxillary sinus, which should be differentially diagnosed from chronic maxillary sinusitis. The main stream of diagnosis usually depends on the clinical symptoms and radiological findings. Thus it was sometimes puzzling to confirm the histological features of mucous retention phenomenon in the antral mucosa, when the specimen was from a limited portion or much degenerated by inflammatory reaction. This study aims to define the histopathological features of MRC through reevaluation of MRCs (n=19) and maxillary sinusitis (n=65) diagnosed previously. The present study classified three types of MRC, i.e., an extravasation type, a luminal retention type, and a mixed type of MRC. The extravasation type MRC showed clear pseudocyst cavity under sinus mucosa with infiltration of foamy macrophage, and the luminal retention type MRC showed mucous retention in the luminal cavity of maxillary sinus accompanied with inflammatory reaction, and the mixed type MRC showed the both features of extravasation and luminal retention type MRCs. Resultantly, among nineteen cases of MRC only three cases belonged to the extravasation type MRC, eleven cases belonged to luminal retention type MRC, and three cases belonged to mixed type MRC, while two cases were turned out to be postoperative residual cysts of maxillary sinus. The MRCs examined in this study showed different pathological features from ordinary maxillary sinusitis, exhibiting the typical mucin retention phenomenon of extravasation type or luminal retention type with relatively mild inflammatory reaction with infiltration of mucin–pooled macrophages. However, the luminal retention type MRC was predominant among the MRCs (11/17, 64.7%) and each of the extravasation and mixed type MRCs was only three cases out of 17 MRCs (17,0%). The extravasation type MRC characteristically produces a pseudocyst by the overexpressions of matrix metalloprotease–3 (MMP–3) and connective tissue growth factor (CTGF). Because not only the pathogenetic mechanism but also the prognosis of MRC is different from chronic maxillary sinusitis, we suggest that the MRC of maxillary sinus should be classified into extravasation, luminal retention, and mixed types in the histological observations in addition to the clinical and radiological informations.

Key words: CTGF, Extravasation type, Luminal retention type, Mixed type, MMP–3

I. INTRODUCTION

The mucous retention cyst (MRC) is not a rare phenomenon. It was reported that the incidence of MRC was about 2.6% in 1685 dental patients clinically reviewed radiologically1–5. Studies also have alluded to a relationship between the MRC and certain signs or symptoms of disease. The prevalence of MRC in a general clinic population had some important correlations with clinical signs and symptoms6,7. The dome–shaped radiopaque shadows frequently seen on the floor of the
maxillary sinus, and sometimes inaccurately referred to as antral mucoceles, appear to represent focal accumulation of inflammatory exudate that lifts the epithelial lining of the sinus and the periosteum away from the underlying bone to form the characteristically shaped structures. Their histologic appearance is therefore that of normal or inflamed maxillary sinus lining, and also there is no epithelium–lined cavity present beneath the sinus mucosa; consequently, the term pseudocyst of the maxillary sinus is advocated. Less commonly, epithelium–lined retention cysts, similar to those of the minor salivary glands, are found, but mucocele features found in the oral cavity apparently do not occur in the maxillary sinus.

There is a considerable confusion in the literature regarding the terminology and distribution of cysts and pseudocysts of the maxillary antrum, which are therefore often lumped together as dome-shaped shadows on the floor of the maxillary sinus. We report a case of MRC in maxillary antrum, occurred in a 25-year-old male, and review the clinical, radiographic and histological features of cysts and pseudocysts of the maxillary sinus including antral mucoceles, postoperative maxillary cysts, pseudocysts and retention cysts; and highlight some of the pertinent distinguishing features. Awareness of the appropriate nomenclature and correlation of clinical, radiographic and histological features of MRC will be helpful in the correct diagnosis and proper treatment for MRC.

**II. MATERIALS AND METHODS**

Total 19 cases of MRCs previously diagnosed were examined to define the pathological features of MRC in comparison with common maxillary sinusitis (n=65) filed in the Department of Oral Pathology, Kangnung National University Dental Hospital (KNUDH). Among 19 cases of MRCs two cases were turned out to be postoperative residual cysts from lesions of odontogenic maxillary cyst and chronic maxillary sinusitis. Thus, 17 cases of MRCs were analyzed and grouped into extravasation type, luminal retention type, and mixed type MRC. Especially, one case of extravasation type MRC (S2009–249) incidentally found during maxillofacial orthognathic surgery showed almost no inflammatory reaction, thereby, was selected and carried out for immunohistochemical examination using antibodies of connective tissue growth factor (CTGF), mucin–1, proline rich proteins, and matrix metalloprotease (MMP) 1 and 3. The biopsy specimens were fixed in 10% neutral formalin, embedded in paraffin, and sectioned in 4 μm thickness. The serial microsections were stained with hematoxylin and eosin, and followed by immunohistochemical (IHC) staining. The immunostaining was performed with indirect triple sandwich method, and the background cross reaction was minimized by the negative control staining using no primary antibody in the same immunohistochemical procedures. The histological and IHC images were captured by digital camera (DP–70, Olympus, Japan), and compared with each other using ImageQuant version 5.2 program (Molecular Dynamic, USA). The usage of the biopsy specimens filed in the Department of Oral Pathology, Kangnung National University Dental Hospital was approved by Life Ethic Committee (IRB2009–1–3).

**III. RESULTS**

Among 19 cases of MRCs diagnosed previously in the Department of Oral Pathology, KNUDH, 17 cases were confirmed to be true MRCs, but 2 cases were turned out to be residual cysts originated from an odontogenic maxillary cyst and a sequela after Caldwell Luc operation for chronic maxillary sinusitis. In the cases of residual cyst the clinical and radiological features were almost similar to the features of MRC, thus the pathological...
diagnosis was made with the comment of the cystic condition possibly recurred from the previous lesions. However, the remaining 17 cases of MRCs were analyzed in this paper, grouped into 3 types, i.e., an extravasation type, a luminal retention type, and a mixed type. Especially a case of MRC (S2009–249) incidentally found during maxillofacial orthognathic surgery showed almost intact sinus mucosa containing extravasation type MRC in the underlying mucosa. The clear pseudocyst cavity was found under the thin mucosa with an extensive hemorrhage occurred during operation. The pseudocyst cavity was lined by flattened fibroblasts instead of epithelial lining, and infiltrated with many macrophages. In the immunostain of CTGF the pseudocyst was well demarcated in the underlying connective tissue, strongly positive for the fibrous collagen bundle of the pseudocyst wall. The immunostains of mucin-1, PRPs, and MMP-1 were weakly positive in the pseudocyst wall, while the immunostain of MMP-3 was condensedly localized at the pseudocyst wall. With these histological features of extravasation type MRC the other type MRCs were classified depending on the pathogenetic processes of mucous retention phenomena.

The extravasation type MRC (n=3) usually showed a pseudocyst composed of thin fibrous connective tissue wall with the infiltration of many macrophages containing eosinophilic materials in their cytoplasm, The luminal surface of the pseudocyst showed no epithelial lining but mainly composed of loose connective tissue containing fine fibrous collagen bundles. The extravasation type MRC showed relatively mild inflammatory reaction throughout the pseudocyst lesion.

The luminal retention type MRC (n=11) usually showed a greatly dilated luminal retention phenomenon

### Table 1. The maxillary sinus retention cysts observed in this study

<table>
<thead>
<tr>
<th>No., type</th>
<th>findings</th>
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<tbody>
<tr>
<td>1(S2001–127)*</td>
<td>extravasation no symptom, found during sinus floor elevation for maxillary implant</td>
</tr>
<tr>
<td>2(S2008–182)</td>
<td>extravasation both nose stuffiness</td>
</tr>
<tr>
<td>3(S2009–249)</td>
<td>extravasation no symptom, found during maxillofacial orthognathic surgery</td>
</tr>
<tr>
<td></td>
<td>Total 3 cases</td>
</tr>
<tr>
<td>1(S2003–122)</td>
<td>luminal R, chronic maxillary sinusitis of dental origin</td>
</tr>
<tr>
<td>2(S2003–158)</td>
<td>luminal R, no symptom</td>
</tr>
<tr>
<td>3(S2003–185)</td>
<td>luminal R, chronic maxillary sinusitis of dental origin</td>
</tr>
<tr>
<td>4(S2003–249)</td>
<td>luminal R, no symptom</td>
</tr>
<tr>
<td>5(S2003–302)</td>
<td>luminal R, no symptom</td>
</tr>
<tr>
<td>6(S2004–009)</td>
<td>luminal R, no symptom</td>
</tr>
<tr>
<td>7(S2004–135)</td>
<td>luminal R, Rt, palatal area swelling and tenderness, Rt, Mx, sinus enlargement, Rt, stuffiness and discharge, epiphora</td>
</tr>
<tr>
<td>8(S2004–229)</td>
<td>luminal R, mild rhinitis</td>
</tr>
<tr>
<td>9(S2008–034)</td>
<td>luminal R, nose stuffiness, discharge and bleeding</td>
</tr>
<tr>
<td>10(S2008–221)</td>
<td>luminal R, no symptom</td>
</tr>
<tr>
<td>11(S2009–122)</td>
<td>luminal R, drug allergy (pyrine derivatives &amp; analgesic), nose stuffiness</td>
</tr>
<tr>
<td></td>
<td>Total 11 cases</td>
</tr>
<tr>
<td>1(S2004–129)</td>
<td>mixed, chronic maxillary sinusitis of dental origin</td>
</tr>
<tr>
<td>2(S2008–215)</td>
<td>mixed, allergic rhinitis</td>
</tr>
<tr>
<td>3(S2003–227)</td>
<td>mixed, allergic rhinitis</td>
</tr>
<tr>
<td></td>
<td>Total 3 cases</td>
</tr>
<tr>
<td>1(S2005–013)</td>
<td>residual cyst allergic rhinitis, #22 residual cyst, Rt, MRC</td>
</tr>
<tr>
<td>2(S2008–134)</td>
<td>residual cyst previous Caldwell Luc operation, chronic tonsillitis</td>
</tr>
<tr>
<td></td>
<td>Total 2 cases</td>
</tr>
</tbody>
</table>

*Biopsy number registered in Department of Oral Pathology, KNUDH
Fig. 1. Photomicrographs for a case of MRC (S2009–249) incidentally found during maxillofacial orthognathic surgery. This case showed almost intact sinus mucosa containing extravasation type MRC in the underlying mucosa. A: Hematoxylin and eosin stains. A1: The pseudocyst cavity (arrows) was found under the thin mucosa. Noted an extensive hemorrhage (H) occurred during operation. A2: Higher magnification of A1, the pseudocyst cavity had no epithelial lining. A3: The luminal surface of the pseudocyst (*) was lined by flattened fibroblasts (arrows), and several macrophages were infiltrated (arrow heads). B: Immunostain of CTGF. B1: The pseudocyst was demarcated in the underlying connective tissue (arrows), B2: Higher magnification of b1, noted positive reaction of CTGF in the fibrous luminal wall (arrows) of the pseudocyst (*), B3: Higher magnification of b2 showed positive reaction of CTGF in the fibrous collagen bundle of the pseudocyst wall (*). C: Immunostain of mucin–1, C1: The fibrous wall of pseudocyst (*) was weakly positive, C2: Higher magnification of C1 showed the weak reaction of mucin–1 in the pseudocyst wall (arrows), D: Immunostain of PRPs, D1: The fibrous wall of pseudocyst (*) was weakly positive, D2: High magnification of D1 showed the weak reaction of PRPs in the pseudocyst wall (arrows), E: Immunostain of MMP–1, E1: The fibrous wall of pseudocyst (*) was weakly positive, E2: High magnification of e1 showed the weak reaction of MMP–1 in the pseudocyst wall (arrows), F: Immunostain of MMP–3, F1: The fibrous wall of pseudocyst (*) was strongly positive, F2: High magnification of F1 showed the condense localization of MMP–3 at the pseudocyst wall (arrows).
filled with mucinous materials in the cavity of maxillary sinus, The accumulated mucinous material in the luminal cavity of maxillary sinus was almost coagulated forming a negative mold, likely mucin plug in the microsections, Many macrophages were diffusely infiltrated into the mucinous material, and the inflammatory reaction was variable depending on the secondary infection of the mucinous materials accumulated in the maxillary sinus.

The mixed type MRC (n=3) showed both features of luminal retention and extravasation type MRCs, The mucinous materials were diffusely retained in the luminal cavity and also multifocally extravasated into underlying connective tissue, A lot of macrophages were infiltrated into the pseudocysts filled with mucinous materials,

Total 17 cases of MRCs showed different histological features from 65 cases of maxillary sinusitis examined in this study, Compared to the common maxillary sinusitis which showed severe inflammatory reaction in the sinus mucosa with or without squamous metaplasia of sinus epithelium, the MRCs showed relatively mild inflammatory reaction and tissue degeneration, Most of sinus mucosa epithelium was well preserved in the tall columnar goblet cells, and the infiltration of macrophages was characteristically increased, However, among the three MRCs the luminal retention type was most frequent (11/17, 64.7%), and each of the extravasation type and mixed type was found in three cases (3/17, 17.6%).

IV. DISCUSSION

Information on histopathological changes of MRC within sinus mucosa is lacking, both in the general population, and in subjects with a specific entity of sinus disease, To provide baseline data of the histological features in the pathological changes of MRC, 19 cases of MRCs previously diagnosed in our hospital were selected, Unfortunately two cases out of 19 MRCs were misdiagnosed due to the obscure histological findings and clinical informations, The two cases were finally re–diagnosed as residual cysts from the previous sinus lesions of odontogenic cyst and
chronic maxillary sinusitis. However, because the symptoms of maxillary sinusitis were obscure and chronically accompanied with mucous retention phenomenon with oversecreted mucus fluid, it might be difficult to define the primary lesion of mucous retention cyst in maxillary sinus. In this study we aimed to reevaluate the MRC distinguishable from chronic maxillary sinusitis histologically. Although it was also agreeable that the secondary mucous retention cyst could be occurred by the obstructive swelling due to the chronic maxillary sinusitis, the primary MRC showed the characteristic pseudocyst cavity lined by thick collagenous tissue with the infiltration of foamy macrophages. Therefore, in this study we tried to define the whole histological features of primary and secondary mucous retention phenomenon contrast to the features of chronic maxillary sinusitis.

As the most of mucous retention cyst in oral mucosa is caused by extravasation of salivary mucus from minor/major salivary gland into the surrounding connective tissue, it is also considered that the primary mucous retention cyst in sinus mucosa is an extravasation type of mucous retention phenomenon, and that the secondary mucous retention cyst could be occurred by the oversecretion of mucinous materials from mucous secretory sinus mucosa due to the allergic or inflammatory stimulation of mucous secretion.

Actually specimens from the diseased sinuses in cases of long standing chronic maxillary sinusitis revealed hyperplasia of the epithelium which may invaginate forming pouches and subepithelial nests, and their secretory glands increase both in number and size indicating the chronicity of the disease. In mucociliary transport analysis by photoelectric method, the chronic sinusitis showed a disturbed mucociliary transport as the result of not only change in secretory function but also a decrease in the frequency of ciliary beating. And the morphological changes of the mucosal epithelium in chronic sinusitis were swelling of the ciliary membrane, formation of compound cilia, dropping of epithelial cells, and metaplasia of a squamous epithelium, eventually resulted in the mucous retention in maxillary sinus. Therefore, it is presumed that the chronic maxillary sinusitis itself may play a role for the pathogenesis of MRC in maxillary sinus.

The present study was also performed the immunohistochemical detection of causative proteins related to the development of MRCs by using the antibodies of CTGF, mucin-1, PRPs, MMP-1, and MMP-3, CTGF, a downstream target of the transforming growth factor-beta (TGF-beta)/Smad pathway, is highly expressed in numerous fibrotic disorders, in which it is believed to stimulate excessive collagen production. The present study showed the strong positive reaction of CTGF in the pseudocyst wall of extravasation type MRC, thus it is supposed that the pseudocyst wall was abnormally regulated for the collagen production by the increased expression of CTGF in the environment of extravasation type MRC. And more, although MMP-1 (tissue collagenase I) was weakly expressed in the pseudocyst wall, MMP-3 (stromelysin I) which is a up-stream affector gene of CTGF was strongly positive in the pseudocyst wall. Therefore, it is presumed that the MMP-3 and CTGF expressions are closely related to the formation of pseudocyst wall in the extravasation type MRCs. On the other hands, mucin-1 and PRPs, which are the major proteins for the protection of mucosal surface, were only weakly positive in the pseudocyst wall of extravasation type MRC. These findings may indicate that the protective functions of mucin-1 and PRPs are not helpful in the healing processes for the ruptured wound by mucinous extravasation into surrounding connective tissue.

In the present study we classified the MRCs into three groups, extravasation type, luminal retention type, and mixed type, similar to the salivary retention
cysts of oral cavity. And then, the mucous retention phenomena of sinus mucosa were most dominant as the luminal retention type (64.7%), and followed by extravasation type (17.6%) and mixed type (17.6%). As the chronic maxillary sinusitis also showed the increased mucous secretion and accumulation of purulent mucous exudates, it is suggested that the luminal retention type MRC should be differentially diagnosed from chronic maxillary sinusitis which is a most frequent inflammatory disease of maxillary sinus\textsuperscript{25–28}. In other words, the luminal retention type MRC can be frequently occurred in the environment of maxillary sinus, and consequently the thick mucinous secretion may play a role as a coagulated plug obstructing the orifice of mucous secretory gland\textsuperscript{29}. If this situation is persisted with the stimulation of mucous secretion, it is supposed that the mucinous secretion is extravasated into surround loose connective tissue secondarily. We also suppose that the mucous retention phenomenon in sinus mucosa is somehow different from that in oral mucosa in the facts that the former is usually caused by over-secretion of mucous materials with inflammatory reaction, while the latter is mostly caused by traumatic severance of salivary ducts. However, in the present study, we demonstrated three cases of extravasation type MRC which clearly disclosed pseudocysts composed of fibrous wall and minimum inflammatory reaction in the sinus mucosa. Therefore, it is necessary to classify the MRCs into the extravasation type MRC and luminal retention type MRC, and then if the features of extravasation type and luminal retention type MRC were simultaneously appeared, the mixed type MRC would be proper description in diagnosis. These classification was supported by the highest incidence of luminal retention type MRC (11/17, 64.7%) and relative rare incidence of extravasation type MRC (3/17, 17.6%), and by the presence of mixed type MRC (3/17, 17.6%) shown in the present study.

Conclusively, the MRC in maxillary sinus is not uncommon disease which should be differentiated from chronic maxillary sinusitis. The extravasation type MRC characteristically produces a pseudocyst by the over–expressions of MMP–3 and CTGF. Because not only the pathogenetic mechanism but also the prognosis of MRC is different for chronic maxillary sinusitis, it is suggested that the MRC of maxillary sinus be classified into extravasation, luminal retention, and mixed types by the histological observations in addition to the clinical and radiological informations.

V. REFERENCES


