A Histopathological Study of Mucous Cyst of the Maxillary Sinus

Miyuki Morikawa-Saito, and Kayo Kuyama

Department of Oral Pathology, Nihon University School of Dentistry at Matsudo, Matsudo, Chiba, 271-8587, Japan

Abstract

Mucous cysts of the maxillary sinus are a pathological entity caused by dilatation and disturbance of ducts within the sinus mucosa resulting from damage or blockage of the ducts of seromucous nasal glands. There has been little histopathological and immunohistochemical research about the characteristics and onset mechanism of these cysts, until now. The present study was to investigate the mucous cysts of the maxillary sinus in order to understand their nature and genesis.

Mucous cysts of the maxillary sinus were rare, occurring in seven cases (4.1%) among the 171 cases with cysts in the maxillary sinus. Four of the cases had cysts corresponding to primary cysts, and three cases corresponding to secondary cysts due to some treatments. Histologically, the extravasation type cysts of six cases showed a lot of mucoid material in connective tissue with mucinophagocyte, lymphocyte, plasmacyte, and eosinophilic inflammatory cell infiltration and then mucous granuloma formation, and bleeding. In the retention type cyst of one case, the inner surface of the cyst was covered with ciliated columnar, cuboidal epithelium and sometimes apocrine metaplasia including mucoid material in it.

Immunohistochemically, IgG and IgA positive plasmacytes were seen most often, and these cells were thought to contribute to the humoral immunity. There were also some IgE-positive cells (3 cases) only associated with mast cells, which had the relationship of type I allergy. Anti-GCDFP-15 antibody was observed not only in apocrine metaplasia cells, but also in existing dilated and hyperplastic ductal epithelial cells in the extravasation type. Anti-GCDFP-15 was thought to have a cross relationship to dilatation and hyperplasia of the cyst.

Introduction

Cystic lesions of the maxillary sinus are a disease encountered comparatively often in clinical dental practice. Postoperative maxillary cyst, seen as a late complication following surgery for maxillary sinusitis, occurs with a high incidence(1), while in rare cases, the mucous cyst of the maxillary sinus is also encountered. Mucous cyst of the maxillary sinus is a pathological entity caused by dilatation and disturbance of ducts within the paranasal sinus mucosa resulting from damage or blockage of the ducts of seromucous nasal glands. Of all the mucous cysts that occur in the paranasal sinuses, those that occur in the maxillary sinus account for no more than 10%. They occur most often in the frontal sinus, followed by the ethmoidal sinus(2, 3). Histopathologically, they are classified into non-secretory cyst (extravasation type) and secretory cyst (retention type). The extravasation type is defined as having cavities with no epithelial lining and mucous retention, surrounded by edematous connective tissue with inflammatory cell infiltration, while the retention type is defined as having an epithelial lining derived from ductal epithelium in the cyst wall and retention of mucoid material within the cavity(1, 4).

Mucous cyst of the maxillary sinus is also classified from the onset mechanism as primary cyst, in which outflow obstruction and cystic expansion of ducts occur due to inflammation, and secondary cyst due to cystic growth of remaining mucous following treatment or surgery for primary lesions(5). These classifications are based on past
treatment or surgery, and an association with treatment or surgery of the maxillary sinus or maxillary bone has often been discussed. Other reported causes of mucous cyst of the maxillary sinus include chronic infection, chronic maxillary sinusitis, trauma, allergy, and ectopic teeth (6–9). However, there are also reports denying an association between these cysts and a history of surgery, and the cause has not been firmly established (2, 10), as yet. From general pathological points of view, these are the morphological classifications of the pseudocyst or true cyst. Despite this, however, there has been little histopathological and immunological research based on these classifications, and much remains unknown about the characteristics and onset mechanism of the cyst, until now.

Therefore, in this study, clinicohistopathological, histochemical, and immunohistochemical examinations were conducted with the aim of investigating the characteristics and onset mechanisms of mucous cyst of the maxillary sinus.

Materials and Methods

Materials

The materials used were pathologically diagnosed mucous cyst of the maxillary sinus that was surgically removed from seven cases between 1999 and 2011 at Nihon University Hospital at Matsudo. A breakdown of the seven cases is shown in Table 1. This study was conducted with the patients’ informed consent, with full consideration of privacy, diagnostic results, and their management (Ethics Committee approval No. EC 12-001).

Methods

Extracted specimens were immersion-fixed in 10% neutral formalin solution for 1–2 days at room temperature, and paraffin-embedded blocks prepared according to usual procedures were used. Thin sections, approximately 4 μm thick, were cut, after which hematoxylin and eosin stain (HE stain) was used as a general stain, and toluidine blue (pH 2.5) stain (TB stain) and PAS-alcian blue (pH 2.5) stain (PAS-AB stain) were also done as histochemical analysis.

The primary antibodies used for immunohistochemical staining were immunoglobulin markers anti-human IgG rabbit polyclonal antibody (IgG, DAKO A423, dilution 1 : 500, Dako Glostrup, Denmark), anti-human IgA rabbit polyclonal antibody (IgA, DAKO A262, dilution 1 : 200, Dako Glostrup, Denmark), anti-human IgM rabbit monoclonal antibody (IgM, DAKO A425, dilution 1 : 300, Dako Glostrup, Denmark), anti-human IgE rabbit polyclonal antibody (IgE, DAKO A0094, dilution 1 : 750, Dako Glostrup, Denmark), and anti-human gross cystic disease fluid protein-15 mouse monoclonal antibody (GCDFP-15, diluted antibody, Signet Pathology Systems, Ma, USA), with an EnVision TM System (EnVision TM/HRP kit, Dako Glostrup, Denmark). The staining procedure was as follows: after deparaffinization, microwave processing in 0.01 mL/L citrate buffer (pH 6.0) was done for antigen activation against each of the immunoglobulin markers. Then, 1% hydrogen peroxide in methanol was applied for 30 min to block endogenous peroxidase reaction, and the sections were washed with PBS. In the anti-GCDFP-15 antibody, only elimination of endogenous peroxidase was done without pretreatment. Reaction with primary antibodies was then done for 60 min at room temperature, followed by washing with PBS. After this, reaction with EnVision TM System/HRP universal polymer reagent was done for 30 min, followed by washing with PBS.

As negative controls, normal rabbit control immunoglobulin and normal mouse serum were used instead of primary antibodies. As positive controls, sections of normal lymph node tissue were used for IgA, IgG, and IgM antibodies, pathological tissue diagnosed as nasal polyp was used for IgE antibodies, and normal salivary gland tissue was used for GCDFP-15 antibodies. Color production was done with 3.3-diamino-benzidine E4HCl (DAB), and counterstaining was done with Mayer’s hematoxylin.

Immunoglobulin expression was judged to be positive if the cytoplasm stained with each antibody was colored brownish-red. The percentage of cells positive for each immunoglobulin was calculated with respect to the total number of positive cells in five visual fields of specimens. The number of mast cells showing metachromasia in five visual fields (×600) of TB-stained specimens was calculated, and the mean number of cells per visual field was obtained.

Results

Clinicopathological findings

A list of the materials used in this study is presented in Table 1. Of all cysts in the maxillary sinus of 171 cases treated during the years 1999–2011, mucous cyst of the maxillary sinus was present in seven cases (4.1%): four men (57%) and three women (43%), with a mean age of 38.1 years (range, 21–52 years). Only focal cystic lesions of
the maxillary sinus were dealt with in the present study, with the whole maxillary cyst lesion caused by the closed ostiums of maxillary sinus were not included. The site of occurrence was the left side in three cases and the right side (Fig. 1) in four. The chief complaint in six cases was cheek pain or pressure. One case was presented to the hospital with drainage from the nasal cavity. In addition, one case had a history of surgery for maxillary sinusitis, one case a history of root canal treatment of the maxilla, one case a tooth extraction on the same side as the lesion, and one case an impacted wisdom tooth in the maxillary sinus in this study.

**Histopathological findings**

Histopathological and immunohistochemical results are shown in Table 2. Histopathologically, six cases were extravasation type (Figs. 2–3) and one was retention type (Figs. 4–6). Extravasation type showed retention of mucoid material in connective tissue of covering with ciliated columnar epithelium (Fig. 2), and mucous granuloma formation consisting of mucinophage, lymphocytes, plasma-cytes, eosinophils, fibroblast, blood capillary dilatation and proliferation, and bleeding were also observed (Fig. 3). With PAS-AB stain, the mucous matrix of the mucous granuloma was stained from purplish red to pale-blue and their mixed color (Fig. 7), and mucinophages were stained purplish red. On the periphery of the cyst, dilated ducts with mucoid material were seen in the nasal glands, and this was diagnosed as an extravasation type mucous cyst of the maxillary sinus. In the extravasation type cyst, especially those with conspicuous eosinophils, and mast cells showing metachromasia with TB stain were also seen in three cases (Fig. 8). The mean number of mast cells in one visual field was 4.1 cells (Tables 3, 4).

In retention type, the inner surface of the cyst wall was covered irregularly with mainly ciliated columnar and cuboidal epithelium (Figs. 4, 5). As for PAS-AB staining, a substance turning from purplish-red to blue and mixed color was contained within the cystic cavity, and goblet cells stained purplish-red were present in the epithelium. Squamous metaplasia and apocrine metaplasia were also seen in part of the epithelium (Fig. 6). Lining epithelium was missing in some places. In subepithelial fibrous connective tissue, fibroblasts, myxoid degeneration, edema, dilatation and proliferation of blood capillaries, mild inflammatory cell infiltration mainly of lymphocytes, and hyalinization were also observed. Existing nasal glands with a tendency for slight to moderate dilatation were also found around the cyst, and the case was diagnosed as retention type mucous cyst of the maxillary sinus.

### Table 1 Clinical data of the cases

<table>
<thead>
<tr>
<th>CaseNo.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Past history</th>
<th>Cheek Pain/Pressure</th>
<th>Nasal Drainage</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>N</td>
<td>+</td>
<td>-</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>Root canal treatment</td>
<td>+</td>
<td>-</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>M</td>
<td>N</td>
<td>-</td>
<td>+</td>
<td>L</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>F</td>
<td>Odontogenic maxillary sinusitis (23y past)</td>
<td>+</td>
<td>-</td>
<td>L</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>F</td>
<td>N</td>
<td>+</td>
<td>-</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>Tooth extraction</td>
<td>+</td>
<td>-</td>
<td>L</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>F</td>
<td>Impacted tooth</td>
<td>+</td>
<td>-</td>
<td>R</td>
</tr>
</tbody>
</table>

Av. = 38.1  M:F = 4:3  R.L=4:3  
M: male, F: female, R: right maxillary sinus, L: left maxillary sinus. Av.:average, N: no important notice

Fig. 1 Orthopantomograph shows a radiopaque mass in the right maxillary sinus.
Immunohistochemical findings

In the six cases with the extravasation type, cells (plasmacytes) positive for anti-IgA antibody and anti-IgG antibody were seen within connective tissue (Figs. 9, 10). Cells positive for anti-IgE antibody (Fig. 11) were also seen in three cases, which corresponded to those in which only mast cells appeared. The proportion of IgA, IgG and IgE were 42.5, 46.7 and 10.8%, respectively (Table 3). In these three cases, the mean number of mast cells seen per visual field was 4.1 as described before. In three IgE-negative cases, the proportion of IgA and IgG were 34.4 and 65.6% (Table 4), and no mast cells were seen. All cases were negative for anti-IgM antibody (Table 2). Anti-GCDFP-15 antibody was not only seen in the apocrine cells, but also in existing cystic ductal epithelial cells that showed a tendency for hyperplasia and dilatation in the extravasation type, and in the retention type (Fig. 12).

Discussion

Mucous cyst of the maxillary sinus is a pathological entity caused by dilatation and disturbance by ducts within the paranasal sinus mucosa resulting from damage or blockage of the ducts of seromucous nasal glands (11). They are rare lesions that account for 10% of all paranasal sinus mucous cysts (2, 3). Mucous cyst of the maxillary sinus was rare in the present study as well, occurring in 7 cases (4.1%) of the all 171 cases with cysts in the maxillary sinus over 13 years.

Some reports described that this condition tends to occur in people in their teens to 30s, with the majority seen in people in their 30s (10, 12–15). This was concordant with the present findings. It is reported that either there is no sex difference (10, 14, 16), or that there is male predominance.
The present seven cases included four males (57%) and three females (43%), with a mean age of 38.1 years (range, 21–52 years).

The site of occurrence is often in the maxillary sinus floor (12, 16, 18, 20), with bilaterality being rare (14, 21). In the present study, the cyst was on the left side in three cases and on the right side in four cases, appearing with focal cystic lesion.

In general, mucous cyst of the maxillary sinus is mentioned to be asymptomatic (12, 18, 22). However, symptoms including gingival swelling, buccal pain, and nasal congestion were reported (19, 21, 23). The patients in the present study had symptoms, with chief complaints of maxillary sinus pain and swelling in six patients and drainage from the nasal cavity in one patient.

Clinically, mucous cyst of the maxillary sinus is categorized as primary cyst, in which impaired outflow and cystic dilatation of ducts occur due to inflammation or other conditions resulting from the mechanism responsible for their occurrence, and secondary cyst that grows based on long-term retention of remaining mucous and tissue fluid from surgery for primary cysts or treatment (5). Secondary
Fig. 8 Mucous cyst (extravasation type) of the maxillary sinus
Mast cells showing metachromasia to TB are presented (TB × 600).

Fig. 9 Mucous cyst (extravasation type) of the maxillary sinus
Diffuse plasmacytes showing a positive response are observed (Anti-IgA × 600).

Fig. 10 Mucous cyst (extravasation type) of the maxillary sinus
Diffuse plasmacytes showing a positive response are seen (Anti-IgG × 600).

Fig. 11 Mucous cyst (extravasation type) of the maxillary sinus
A positive response is found in some cells (Anti-IgE × 600).

Table 3 Total immunoglobulin-positive cells number and mast cell number in patients with IgE-positive cells

<table>
<thead>
<tr>
<th></th>
<th>IgA</th>
<th>IgG</th>
<th>IgE</th>
<th>IgM</th>
<th>Total</th>
<th>Mast cell</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive cells</td>
<td>338</td>
<td>371</td>
<td>86</td>
<td>0</td>
<td>795</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The ratio of the number (%)</td>
<td>42.5</td>
<td>46.7</td>
<td>10.8</td>
<td>0.0</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TB Stain,
Number of Metachromatic cells

Number of field
Number per field

62
15

4.1
cyst is defined as cyst that appears as a complication 10 to 30 years after maxillary sinus surgery or treatments (3). Secondary cysts occur with a frequency of two (24) or five times (5) greater than primary cysts, with a high incidence in the maxillary sinus (24). Moreover, many cases with secondary cyst in the maxillary sinus previously underwent the Caldwell-Luc procedure as a surgical method for a primary cyst, suggesting a relationship between the mucous cyst of the maxillary sinus and this procedure (24). However, at this time, differential diagnosis from a postoperative maxillary cyst, which is also a secondary cyst, remains problematic.

When diagnosing mucous cyst of the maxillary sinus in the present study, cysts seen to have mucous granuloma histopathologically were taken as extravasation type mucous cysts, and those that had a lining epithelium and contained mucoid material were taken to be retention type mucous cysts. Based on the definition above, six cases had extravasation type and one case had retention type cyst. A review of the head and cervical region history of these seven cases revealed that one case had a history of surgery for maxillary sinusitis, one case a history of root canal treatment of the maxilla, one case a tooth extraction on the same side of the cyst, and one case an impacted wisdom tooth in the maxillary sinus. Thus, three of the cases in this study had cysts corresponding to secondary cysts.

In mucous cyst of the paranasal sinuses, the cause of primary cyst against a background of inflammation is described to be blockage of ventilation of the sinus orifice, such as the anatomical position relationship, mucous membrane hyperplasia, tumor, or other functional impairments (2, 5). Chronic inflammation and allergy are widely accepted as causative factors for mucous cyst of the maxillary sinus (18, 22, 23). Other factors that are suggested include chronic infection and trauma (6, 7), foreign body reaction (26), and ectopic teeth (8, 9). Whereas causes of infection of the maxillary sinus are thought to originate in the roots of teeth and periodontal tissue (26), bacteria are reported in 45.5% of cases in bacteriological tests during surgery for mucous cysts of the maxillary sinus (6). Thus, not all cases have infection. In the present study, two cases were suspected of having infections originating in the teeth, and in one case, infection was thought to be related to an impacted tooth within the maxillary sinus.

As mentioned above, histopathologically, six of the cases in the present study had extravasation type, which was a pseudocyst, and one had retention type, which was a true cyst. In the extravasation type, a mucous granuloma was formed from mucoid material and mucinophage, lymphocyte, plasmacyte, and eosinophilic inflammatory cell infiltration. Mucoid materials seen in the cystic cavity and within connective tissue showed positivity to both alcian blue and/or PAS, and their mixture, and they were thought to have acid and neutral mucopolysaccharides or glycogenic aspects. Nasal glands are seromucous glands consisting essentially of mucous glands and serous glands, but the mucous glands are reported to be dominant (27).
vasiated mucous was phagocytosed and disposed of in macrophages as foreign material, but mucous that could not be completely excreted might accumulate in tissue and then form mucous granuloma.

Infiltrating inflammatory cells were mainly lymphocytes and plasmacytes, but in the six cases with extravasation type, there was accompanying eosinophilic infiltration. In three of these cases, mast cells showing metachromasia also appeared.

Concerning about immunohistochemical result of extravasation type cyst in the present study, it was suggested that the mucous granuloma might be the chronic inflammatory reaction accompanied by infiltration of plasmacytes with IgG predominance and IgA positivity, and IgM negatively, humoral immunity. There were also some cells showing an IgE-positive response. IgE-positive cases corresponded to cases only with mast cells showing metachromasia with TB staining, and might be related to involvement type I allergy.

The role of immunoglobulins (IgG, IgA, IgE) in eosinophilic activation is to promote degranulation of eosinophils. The result is thought to be a release of cytotoxic proteins like eosinophil peroxidase (28). In addition, IgA regulates eosinophil degranulation and promotes expression of eosinophil IgA receptors at the time of allergic reactions (29). Nasal polyps, which are reported to be related to allergic rhinitis, are inflammatory mucosal masses with cystic dilatation of ducts in some parts. Histopathologically, they present a finding similar to mucous cysts of the maxillary sinus. As for retention type cyst, the inflammatory reaction was histopathologically and immunohistochemically scarce. The anomaly of the duct was considered to be one of a factor of cystic dilatation.

GCDFP-15 is a secretory type of monomeric glycoprotein with a molecular weight of about 15 kDa (gene: 7q34). It is also called prolactin-inducible protein (PIP) and secretory actin binding protein (SABP). It is a glycoprotein that exists in the serum of healthy women and is localized in salivary glands, lacrimal glands, and bronchial glands (30). GCDFP-15 is a marker of apocrine differentiation that is more sensitive than apocrine cell markers or morphology (31), since it is also present in apocrine-derived salivary gland tumors (32). In the present study of GCDFP-15, positive findings were not only seen in the apocrine metaplasia but also in hyperplastic or dilated ducts around the mucous cyst in the extravasation type and in ducts showing cystic dilatation in the retention type. Thus, the GCDFP-15 might be related to the hyperplasia and dilatation of the cyst.

**Conclusion**

The present study was to investigate the clinicohistopathological, histochemical and immunohistochemical analyses of mucous cyst of the maxillary sinus in order to understand the nature and genesis, and the following results were obtained:

1. Mucous cyst of the maxillary sinus was rare, occurring in seven cases (4.1%) among the 171 cases with cysts in the maxillary sinus. Four of the cases had cysts corresponding to primary cyst, and three cases corresponding to secondary cyst due to some treatments.

2. Histologically, the extravasation type cyst of six cases showed a lot of mucoid material in connective tissue with mucinophage, lymphocyte, plasmacyte, and eosinophilic inflammatory cell infiltration and mucous granuloma formation with fibroblast, blood capillary dilatation and proliferation, and bleeding. In the retention type cyst of one case, the inner surface of the cyst was covered with ciliated columnar, cuboidal epithelium and sometimes apocrine metaplasia including mucoid material in it.

3. Mucoid materials seen in the cystic cavity and within connective tissue were so revealed positivity to both alcian blue and PAS or mixture that they were thought to have acid mucopolysaccharide and neutral mucopolysaccharide or glycogenic aspects.

4. Immunohistochemically, IgG and IgA positive plasmacytes were most seen, and these cells were thought to contribute the humoral immunity. There were also some IgE-positive cells only associated with mast cells, which had the relationship of type I allergy.

5. Anti-GCDFP-15 antibody was observed not only in apocrine metaplasia cells, but also in existing dilated and hyperplastic ductal epithelial cells in the extravasation type. Anti-GCDFP-15 might be a role of the formation of this cyst.

**Acknowledgments**

We would like to show my deepest gratitude to Professor H. Yamamoto (Department of Oral Pathology, Nihon University School of Dentistry at Matsudo) for his direction and helpful advice, and appreciate Professors M. Fukumoto and Y. Makiyama (Department of Laboratory Medicine for Dentistry and Department of Head and Neck Surgery, Nihon University School of Dentistry at Matsudo) for reviewing the manuscript. We thank Mr. T. Matsumoto and...
References


