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# Histological Grouping of Branchial Cleft Anomaly - With Retrospective Pathologic Review of Branchial Cleft Anomaly for 10 Years

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## Abstract

**Background**: The characteristic histological feature of branchial cleft anomaly is aberrant space lined by squamous orrespiratory epithelium with variable amount of lymphoid aggregates, occasionally with lymphoid follicle formation. Sometimes these findings require the differential diagnosis from other lymphoepithelial lesion. The aim of this study is to find the other, helpful histological findings.

**Method**: All patients with a pathologically-confirmed post-operative diagnosis of a branchial cleft anomaly were retrospectively collected from pathology file of Gospel hospital, Kosin university from January 2000 to June 2010. The cases wereclassified into 4 groups by the combination of clinical manifestation and pattern of lymphoid component: Group A. Cases in the form of fistula or sinus; Group B. Cases in the form of well-defined cyst with remarkable lymphoid aggregates resembling lymph nodes; Group C. Cases in the form of cyst but short of group B for the margin, and extent and amount of lymphocytes; Group D. Unclassified cases resulted from marked inflammation. Original Haematoxylin-Eosin slides were reexamined to check for the features of overall lesion, lumen, wall, lining epithelium, lymphoid cells and accompanied other components.

**Results**: Of the collected 60 cases, the common form of branchial cleft anomaly was Group A and Group B. The mostbranchial cleft anomalies were located in neck and ear, but they were also found in pharynx, epiglottis, and vocal cord. The purpose to operate was removal of itself in 50 cases and incidental removal during operation for thyroid mass in 10 cases. Distinctively, all latter cases belongedto Group C. The size of overall lesion and lumen, and the thickness of the wall were significantly higher in cases of Group B and Group D. The number of aberrant space was one in almost groups, except Group C with multiple spaces. The undulation of cystic wall was significantly often found among cystic groups. Branchial cleft anomaly were commonly lined by squamous epithelium, and the cases lined by respiratory epithelium belonged to Group C. Cartilage and skin adnexa were identified in only Group A. Although the fibroadipose tissue deposits were not significant, their patterns were variable.

**Conclusions**: Groups by the combination of clinical manifestation and pattern of lymphoid component have several distinct histological features. The recognition of the other histological findings of branchial cleft anomaly will be helpful for pathologic diagnosis and differential diagnosis.

**Key words** : Branchial cleft anomaly, clinical manifestation, size, lumen, histological feature

## INTRODUCTION

Branchial cleft anomaly is development disorder formed by incomplete involution of the branchial apparatus.[1] It manifests as cysts, fistulas or sinuses in head and neck.[2-4]They are classified into first to fourth branchial anomaly by the location of branchial cleft-derived organ from ear, parotid area to mediastinum.[1]

Basically, the characteristic histological feature is aberrant space lined by squamous or respiratory epithelium with variable amount of lymphoid aggregates, occasionally with lymphoid follicle formation. Exceptionally,first branchial cleft anomaly may be accompanied with skin adnexa or cartilage.[5]

Although there are many reports about branchial cleft anomaly, almost of them have focused on clinical and radiologic findings.[5-8]In this study, we analyzed the

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histological findings of branchial cleft anomaly for 10 years and tried to find the other, helpful histological findings.

## MATERIAL AND METHOD

### Case collection and Grouping

All 62 patients with a pathologically-confirmed post-operative diagnosis of a branchial cleft anomaly were included in a retrospective pathology file review of Gospel Hospital, Kosin University from January 2000 to June 2010. The 2 patients of parathyroid cyst and thyroid cyst without prompt lining epithelium were excluded. Therefore, the study consisted of 60 patients who were evaluated and operated for the diagnosis of branchial cleft anomaly at Gospel hospital, Kosin university, Busan, Korea, during 10 years. The cases wereclassified into 4 groups by the combination of clinical manifestation and pattern of lymphoid component: Group A, Cases in the form of fistula or sinus; Group B, Cases in the form of well-defined cyst with remarkable lymphoid aggregates resembling lymph nodes; Group C, Cases in the form of cyst, but short of group B for the margin, and extent and amount of lymphocytes; Group D, Unclassified cases resulted from remarkable inflammation. (Fig. 1)

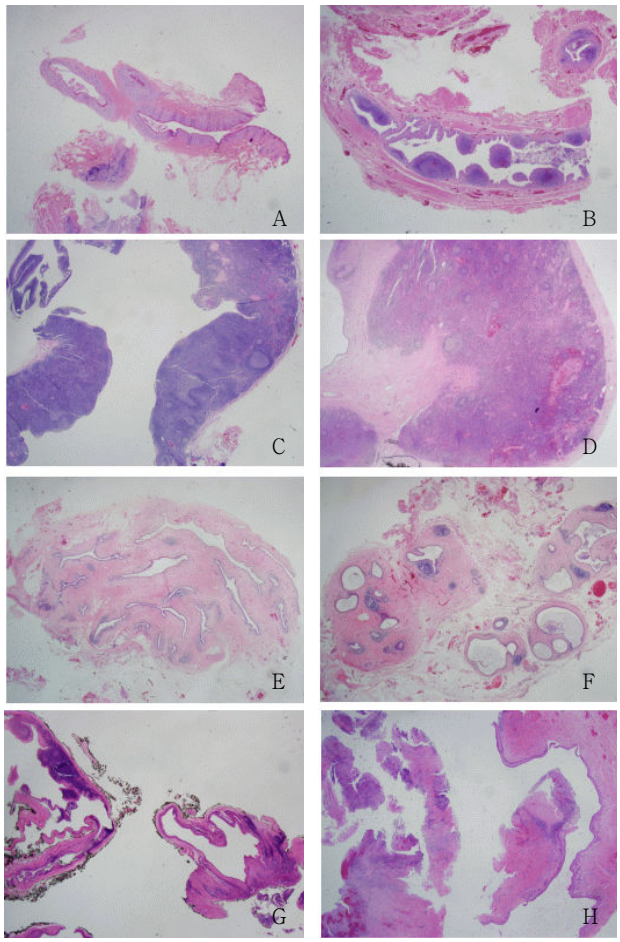


Fig. 1. Groups of branchial cleft anomaly.
(A): Group A, Sinus with sparse lymphoid component. (B): Group A,Fistula/sinus with focal lymphoid component and undulation. (C): Group B, Cyst with well-defined margin, prominent but uneven lymphoid component and undulation. (D): Group B, Cyst with well defined margin and prominent lymphoid component. (E-G): Group C, Cyst with irregular and multiple lumen with sparse lymphoid component. (H): Group D, Cases with remarkable inflammatory reaction.

### Histological and Clinical Review

Original Haematoxylin-Eosin slides were reexamined to check for the features of overall lesion, lumen, wall, lining epithelium, lymphoid cells and accompanied other components. In detail, they were evaluated for the location, size of the overall lesion; for size and number of lumen, shape of the luminal surface; for thickness of the wall in most thick area for type of the lining epithelium (squamous epithelium, ciliated pseudostratified columnar epithelium, mixed typeof squamous and respiratory epithelium), denudation of lining epithelium, presence of goblet cell metaplasia, oncocytic change; for degree of the lymphoid cells, degree of thegerminal center; for presence of cartilage, skin adnexa or thyroid gland. Also the fibroadipose tissue deposits in the wall were identified. The degree of the lymphoid cells were graded, 1. Nil or sparse lymphoid cells; 2. Discontinuous lymphoid aggregates along the circumference; 3. Continuous lymphoid aggregates along the entire circumference, less than 1mm in thickness; 4. Continuous lymphoid aggregates along the entire circumference, more than 1mm in thickness in less 1/2 of the circumference; 5. Continuous lymphoid aggregates along the entire circumference, more

than 1mm in thickness in more 1/2 of the circumference. The degree of germinal center in lymphoid aggregates were graded, 1. Nil germinal center2. Germinal center in less than 1/4 of the lymphoid aggregates 3. Germinal center from 1/4 to 1/2 of the lymphoid aggregates4. Germinal center in more than 1/2 of the lymphoid aggregates, but not complete 5. Germinal center in almost lymphoid aggregates. When the information from the slide review was insufficient, the operation and medical records were reviewed for reference. The medical records were also reviewed to determine the age, gender and the purpose to operate.

### Statistics

The clinicopathologic features between groups of branchial cleft anomaly were compared using analysis of variance (ANOVA). Statistical significance was determined if the $p$ value of a test was less than 0.01. Computation was performed using the IBM−SPSS (PASW statistics 18.0, Somers, NY).

## RESULTS

Of the 60 patients, Group A (n=21) and Group B (n=21) were the mostcommon form of branchial cleft anomaly. Group C and Group D followed with 15 cases and 3 cases, respectively. The most cases were located in neck and ear, but they were also found in pharynx, epiglottis, and vocal cord. Some of them were removed in surgery for itself in 50 cases and others were incidentally removed during operation for thyroid mass in 10 cases. Distinctively, all latter cases belonged to Group C. (Table 1)

The size of overall lesion and lumen, and the thickness of the wall were significantly higher in cases of Group B and Group D than other groups. The number of aberrant space was one in almost groups, except Group C with multiple spaces ($p$=0.006). The undulation of cystic wall was significantly often found among cystic groups, although also seen in fistula or sinus. (Fig. 2) (Table 2)

Table 1. Clinical features in each groups of branchial cleft anomaly

| Group | Age (Average years) | Gender (Male: Female) | Location (Neck:Ear: Other) | Purpose to operate* |
|---|---|---|---|---|
| A (n=21) | 18.9 | 12:9 | 2:18:1 (Pharynx) | Surgery for itself (n=21) |
| B (n=21) | 27.8 | 8:13 | 20:0:1 (Vocal cord) | Surgery for itself (n=21) |
| C (n=15) | 42.86 | 4:11 | 13:1:1 (Epiglottis) | Surgery for itself (n=5) Incidental removal (n=10) |
| D (n=3) | 27.6 | 2:1 | 1:2:0 | Surgery for itself (n=3) |
| Total (n=60) | 31.1 | 26:34 | Neck (n=36) Ear (n=21) Pharynx (n=1) Epiglottis (n=1) Vocal cord (n=1) | Surgery for itself (n=50) Incidental removal (n=10) |

*, $p < 0.01$

Table 2. Pathologic features ( I ) in each groups of branchial cleft anomaly

| Group | Size of overall lesion (mm)* | Size of lumen (mm)* | Thickness of wall (mm)* | Number of lumen* | Shape of surface (Flat:Undulated)* |
|---|---|---|---|---|---|
| A (n=21) | 4.54±3.26 (11) | 3.78±3.19 (15) | 1.30±0.83 (21) | 1.06±0.25 (15) | 13:8 |
| B (n=21) | 22.00±10.03 (10) | 14.54±7.01 (12) | 4.83±3.62 (21) | 1.09±0.09 (11) | 2:19 |
| C (n=15) | 7.42±3.48 (11) | 4.50±3.27 (14) | 2.04±1.81 (15) | 3.07±2.39 (13) | 2:13 |
| D (n=3) | 38.50±12.02 (2) | 27.00±24.04 (2) | 3.33±1.15 (3) | 1.00±0 (2) | 2:1 |
| Total (n=60) | 12.60 ± 11.69 (34) | 8.10±8.55 (43) | 2.82±2.81 (60) | 1.70±1.63 (41) | 19:41 |

( ), number of studied cases; *, $p < 0.01$

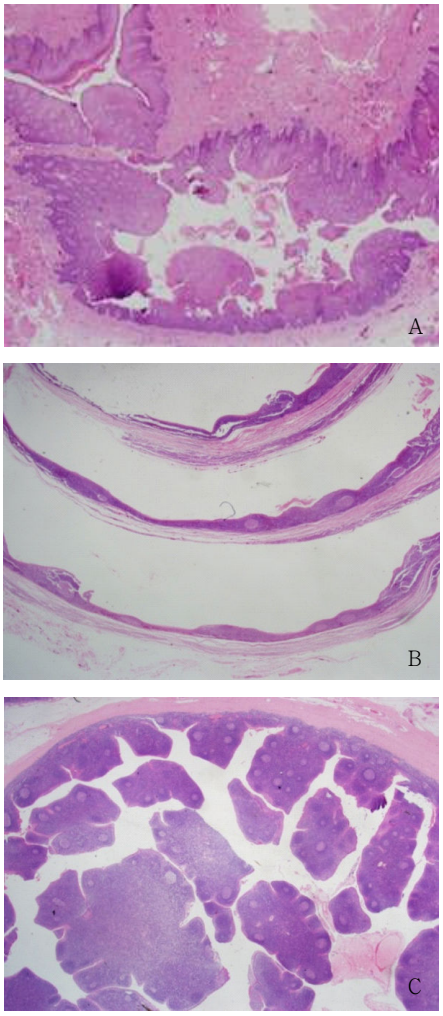


Fig. 2. Shape of luminal surface.
(A): Undulating surface with protruded enlarged lymphoid follicles. (B): Flat surface with focal undulation with few enlarged lymphoid follicles. (C): Pleated surface with epithelial folding.

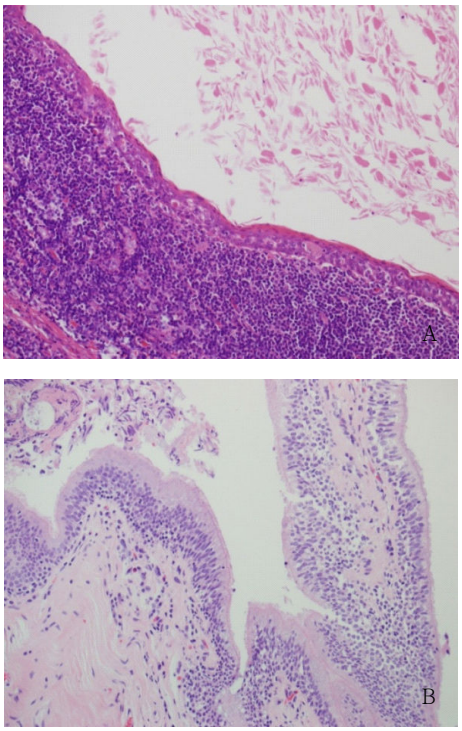


Fig. 3. Lining epithelium of branchial cleft anomaly.
(A): Squamous epithelial lining with luminal debris. (B): Respiratory (Pseudostratified ciliated columnar cells) epithelial lining.

The degree of extent and amount of lymphoid aggregates of branchial cleft anomaly was significantly related with extent of lymphoid follicle ($p$=0.000) and wall thickness ($p$=0.003). Branchial cleft anomaly was commonly lined by squamous epithelium (75% of all cases). Except 4 cases with mixed type epithelium, remaining cases (18% of all cases) were lined by respiratory epithelium. Almost of the latter (10 cases / 11cases) belonged to Group C. (Fig. 3) When Group C wasanalyzed separately, epithelial type was significantly correlated with purpose to operate among the clinicopathologic features. Epithelial denudation or goblet cell metaplasia was sometimes found,but they had no association between groups. The oncocytic change of epithelial cells or accompanied thyroid tissue was not found. Other components of cartilage and skin adnexa

Table 3. Pathologic features ( II ) in each groups of branchial cleft anomaly

| Group | Epithelial lining* (Re:Sq:M) | Denudation | Goblet cell metaplasia | Oncocytic change | Cartilage * | Skin adnexa * | Thyroid gland | Fibro-adipose tissue |
|---|---|---|---|---|---|---|---|---|
| A (n=21) | 1:18:2 | 2 (9%) | 1 (4%) | 0 (0%) | 13 (6%) | 10 (47%) | 0 (0%) | 1 (4%) |
| B (n=21) | 0:21:0 | 5 (23%) | 1 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 8 (38%) |
| C (n=15) | 10:3:2 | 1(6%) | 1 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (13%) |
| D (n=3) | 0:3:0 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Total (n=60) | 11:45:4 | 8 (13%) | 3 (5%) | 0 (0%) | 13 (21%) | 10 (16%) | 0 (0%) | 11 (18%) |

Re, respiratory epithelium ; Sq, squamous epithelium ; M, Mixed squamous and respiratory epithelium; *, $p < 0.01$

were identified in only Group A. Although the fibroadipose tissue deposits was not significant, they had variable patterns as irregularly nodular fibrosis, fibrosis/fibroadipose tissue splitting the lymphoid component into inner and outer layer and subepithelial fibrosis with peripheral lymphocytic cuffing. (Fig. 4)

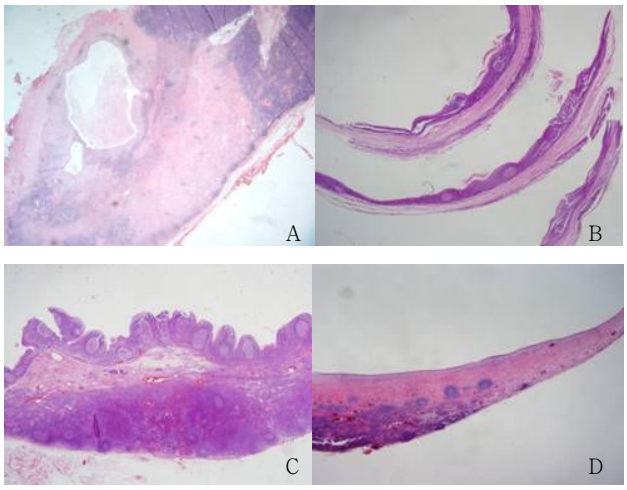


Fig. 4. Patterns of fibrosis and fibroadipose tissue deposits. (A): Irregularly nodular fibrosis. (B): Fibrosis splitting the lymphoid component into inner and outer layer. (C): Fibroadipose tissue splitting lymphoid component into inner and outer layer. (D): Subepithelial fibrosis with peripheral lymphocytic cuffing.

## DISCUSSION

Branchial apparatus is embryonic structure developed into variable organ, such as ear, pharynx, larynx, thymus, parathyroid glands. So, branchial cleft anomaly may be found in these variable site, and are classified into first to fourth branchial anomaly by the location along branchial cleft−derived organ from ear, parotid area to mediastinum.[1,9] Sukgi et al. reported that the frequency of first, second, third, fourth and undetermined branchial cleft anomaly is 25%, 40%, 8%, 2% and 25%, respectively. That result shows higher incidence of first branchial cleft anomaly than other reports.[10] In our study, the cases presented in ear including the periauricular or parotid area was 35% of all cases (21 cases/60 all cases), more frequently.

The clinical manifestation of branchial cleft anomaly is aberrant spaces, in form of cyst, sinus or fistula according to the status of luminal opening. Among the three major forms, cyst or sinus is more frequent than fistula.[10−12] In this study, Group A composed with both fistula and sinus was 35% of all cases. The relative low incidence of sinus may be interpretive as true low incidence like reports of the McPhail N et al. or as misclassification due to lack of clinical information.[12] The uncommon clinical manifestation as ectopic glands and malformations of head and neck structure has been reported.[13−15]

The general pathologic finding of branchial cleft anomaly is space with squamous or respiratory epithelial lining and subepithelial lymphoid aggregates with variable lymphoid follicles. In this study, the degree of extent and amount of lymphoid aggregates of branchial cleft anomaly were significantly related with extent of lymphoid follicles and wall thickness. In cases with florid lymphoid components of Group B, they resembled lymph node in view of the remarkable volume of lymphoid cells. But these components were not fully circumferential, so a part of them showed minimal lymphoid aggregates. (Fig. 1C) Among the squamous and respiratory epithelial lining, columnar epithelium (respiratory type) is observed in a second branchial pouch cyst and a second branchial fistula.[5] In this study, the majority of pure respiratory epithelial lining was found in Group C, all of them were incidentally removed during surgery for thyroid mass($p$=0.005). (Fig. 5) All of them were located in level 5 or 6 of neck. The other one case in earshowed respiratory epithelial lining, although almost cases in ear showed squamous epithelial lining. The lumen of Group C were more multiple and irregular than other groups. (Fig. 1 E and F) The age of Group C was higher than other groups, but age was not significant.

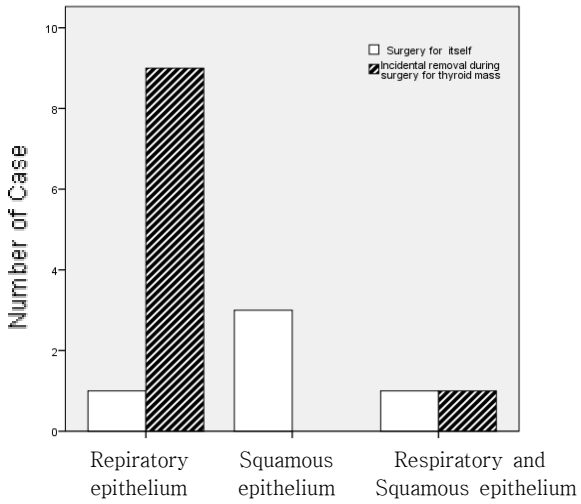


Fig. 5. Correlation of type of lining epithelium and purpose to operate in Group C.

The undulation of cystic surface was identified in 61% (41 cases/ 60 all cases). Although thisundulated surface was found in all groups, it wasmost frequently identified in cystic groups, Group B and Group C. The undulation was often made by protruded and enlarged germinal center, but in part, by epithelial folding or protruded stroma. (Fig. 2)

Skin adnexa and cartilage wereobserved in first branchial cleft sinuses (Work's classification Type II).[5] In this study, because cartilaginous component can't be decided as either accompanied component of the branchial cleft cyst or normal component removed during ear surgery,the interpretation of cartilage are limited. But all cartilaginous components in reviewed slide were identified in specimen from ear.

The pathologic findings of squamous or respiratory epithelial lining space with the accompanied lymphoid cells mimics the several lymphoepithelial lesions of head and neck, even mediastinum, for example, thyroglossal duct cyst, multiple cysts in Hashimoto's thyroiditis, lymphoepithelial cyst of salivary gland in HIV infection, thymic cyst, Warthin's tumor, benign epithelial inclusion of lymph node and metastatic carcinoma of lymph node.[16-18] Among them, multiple cysts in Hashimoto's thyroiditis and thymic cyst belong to disease arising from true branchial derivatives, such as ultimobranchial bodies. For the differential diagnosis with above disease, the comprehension for tendency between clinical manifestation, degree of lymphoid cell, type of epithelial lining, size and number of lumen as well as lack of epithelial oncocytic change and accompanied thyroid tissue may be helpful.

The deposits of fibroadipose tissue was identified in 18% (11 cases / 60 all cases) and majority of them, 8 cases, belonged to Group B, but they had no significant correlation between each groups ($p$=0.023). Although the correlation of deposits of fibroadipose tissue and size were not evaluated due to frequent lack of information for size in Group B, the overall diameter of them were larger than 2.8cm, based in minimal measurement with slide as a part of whole. So the correlation of deposits of fibroadipose tissue and size may be presumable. The fibrosis was like irregular or regular band orfibrotic nodule. Also these changes were presented in subepithelial lesion with peripheral lymphoid cuffing or split the lymphoid aggregation into inner and outer lymphoid layer. Inflammation was not accompanied in this fibrosis. In one other case, fibroadipose tissue split the lymphoid aggregation into inner and outer lymphoid layer. This deposit was linear along the considerable circumference, in contrast of eccentric and non-linear hilum of lymph nodes. (Fig. 4)

Distinct inflammatory changes were identified in three cases. One of them was present in neck, and other two cases were present in ear. In contrast to this study of few cases with inflammatory reaction, James et al. reported more frequent inflammatory reaction in branchial cleft anomaly. In their reports of 97 pediatric branchial anomaly, 32% of branchial anomalies were previously infected, and 71% of them have more than one preoperative infection, and first, second and third arch derivatives are 18%, 69% and 7%, respectively.[19] They didn't describe how to define the previous inflammation, and this study had limited information for previous history

of inflammation. The inflammatory reaction shows ulceration, congestion and irregular fibrosis making adhered appearance with adjacent soft tissue, enough to make a need to extended surgical removal according to adjacent structure.[20] If the cases with fibrosis were considered as the case with history of inflammatory reaction, the frequency of inflammatory reaction may be 23%.

In practice, some other disease are considerable with preoperative finding, such as dermoid cyst, vascular malformation, vascular tumor, parathyroid cyst, cervical cyst, tuberculous lymphadenopathy, purulent lymphadenitis, cystically necrotic schwannoma and metastatic lymph node with cystic degeneration.[7]While the majority of cystic lesions in young adults represent branchial cleft anomaly, it has been reported that 80% of cystic lesions in patients over 40 years of age are malignant.[21] In relation to the malignant potential of branchial cleft anomaly, branchiogenic carcinoma had been proposed in 19th century.[22] However, they are extremely rare, and the considerable patients with preoperative diagnosis of branchial anomaly have been known cystic neck metastasis.[23−25] In these cases with cystic neck mass as first clinical presentation, the most common locations of tumor origin are Waldeyer's ring, where Human papillomavirus (HPV) have important role in pathogenesis.[26] In addition, about one−half of HPV positive oropharyngeal carcinomas result in cystic nodal metastases.[27] In 2008, Goldenberg D et al. used the terminology of "HPV−associated phenomenon"that expresses the close relation of HPV infection and cystic lymph node metastasis in head and neck cancer. If pathologists and surgeons meet the cases ofmalignant cystic neck mass resembling branchial anomaly, diagnosis should be made by strict criteria.[28]

Branchial cleft anomaly is permanently cured with complete resection. But delayed and inadequate management may lead to recurrent infection and secondary development of fistulous tracts. And iatrogenic injuries of the facial nerve have been reported.[8] Repeated incision and drainage and incomplete excisions are frequently seen with first, third, and fourth anomalies due to misdiagnosis.[10,20]

Fine needle aspiration cytology is a useful tool and the current standard of care when applied to solid masses of head and neck, with a high positive predictive value (100%) and high sensitivity (94%).[29] However, fine needle aspiration cytology is a less reliable technique for assessing the cystic lesions, because of a high false−negative rate (38−63%).[30] Moreover, the detecting malignancy within a cyst is more difficult. For differential diagnosis of branchial cleft cyst from malignancy within a cyst, repeated aspirations from different sites of the lesion and some preoperative ancillary tests may be helpful, for example, HPV test, immunohistochemistry for GLUT−1, TTF−1, thyroglobulin and image cytometry DNA analysis for aneuploidy with fine needle aspiration cytology specimen.[27,31−33]

## CONCLUSION

By the combination of clinical manifestation and patterns of lymphoid component, branchial cleft anomaly may be classified into several groups with distinct

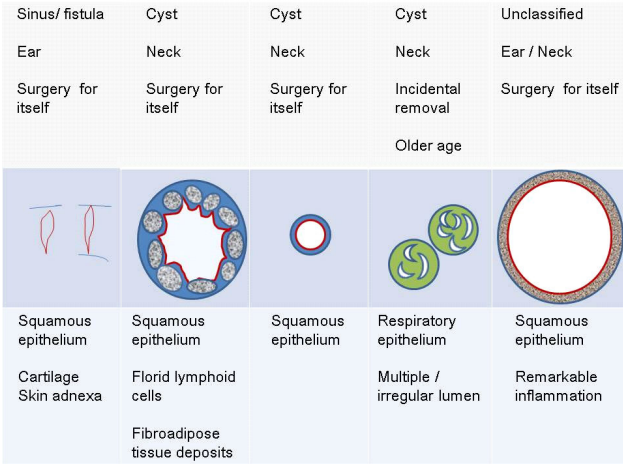


Fig. 6. Summary of histological grouping of branchial cleft anomaly.

histological feature. (Fig. 6) In brief, the cases of sinus or fistula are lined by squamous epithelium with cartilage and skin adnexa, and commonly located in ear. The cystic cases lined by squamous epithelium may be large with florid lymphoid aggregation and prominent lymphoid follicles or small with less lymphoid aggregation. Another cystic cases lined by respiratory epithelium are small with multiple and irregular lumen. They are frequently removed during other surgery in older patients. The most cystic cases are located in neck. Cases with remarkable inflammation are largeand lined by squamous epithelium. The undulated surface is often found in cystic lesion, but they are made by variable components, lymphoid, epithelial and stromal components. Although the fibroadipose tissue deposits are not significant, histological patterns are variable. Oncocytic epithelial change or thyroid tissue is not found in any cases. The branchial cleft anomaly may mimic other lymphoepithelial lesions, so the recognition of these additional histological findings will be helpful forpathologic diagnosis and differential diagnosis.

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