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Cystic Fluid And Its Diagnostic Applications In Head And Neck Pathology: A Review

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Abstract:
The majority of cystic lesions in the oral and maxillofacial region are odontogenic in origin. It is formed by odontogenic cell rests entangled inside jaw tissue, such as cell rests of malassez, cell rests of serre, and the enamel organ. The permeability of the cyst wall, the protein content of the cyst fluid, and the intracystic fluid pressure on the jaw bone are all factors that contribute to the enlargement of these jaw cysts. The colour, consistency, presence of cholesterol crystals, keratin flecks, and different protein fractions such as albumin, alpha and beta globulin, total protein content, and inorganic phosphates can all be examined in the odontogenic cyst fluid. The contents of cystic fluids can be analysed to help with an accurate diagnosis whenever a cyst is detected before surgical excision or conservative therapy. This review attempts to give a general overview of odontogenic cyst and discuss about albumin, globulin, total protein content of different odontogenic cysts.

Key Word: *maxillofacial; odontogenic; cell rests of malassez; cell rests of serre; intracystic.*

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I. Introduction

Killey and Kay (1966) gave the definition of cyst as an epithelium lined sac filled with fluid or semi fluid material.[1] Kramer in 1974 has defined cyst as a pathological cavity having fluid, semisolid or gaseous material, which is not created by accumulation of pus. It is frequently but not always lined by epithelium.[2] Shafer defined cyst as a pathologic epithelium lined cavity usually containing fluid or semisolid material.[3]

Classification [1]

Robinson (1945)	- From odontogenic tissues - From non-dental tissues
Gorlin (1964)	- Odontogenic cysts - Non odontogenic and fissural cysts Cysts of neck and oral floor and salivary glands - Pseudo cysts
WHO (1992)	- Developmental cysts • Odontogenic • Non- odontogenic - Inflammatory cysts
Shear (2007)	- Cysts of oral and facial region - Epithelial • Odontogenic- • Non -odontogenic - Non-epithelial - Cysts associated with maxillary sinus - Cysts of soft tissue of mouth, face and neck

Epithelial cysts- Odontogenic cysts

DEVELOPMENTAL	INFLAMMATORY
• Gingival cysts of infants • Odontogenic keratocyst • Dentigerous cyst • Eruption cyst • Lateral periodontal cyst • Botryoid odontogenic cyst • Gingival cyst of adults • Glandular odontogenic cyst • Calcifying odontogenic cyst	• Radicular cyst • Residual cyst • Paradental cyst • Inflammatory collateral cyst

Epithelial cysts - non-odontogenic

- Nasopalatine duct cyst
- Median palatine, median alveolar, median mandibular cyst
- Globulomaxillary cyst
- Nasolabial cyst

Non epithelial cysts

- Simple bone cyst
- Aneurysmal bone cyst

Cysts associated with maxillary antrum

- Benign mucosal cyst of maxillary antrum
- Surgical ciliated cyst of maxillary antrum

Cysts of soft tissues of mouth, face and neck

- Dermoid and Epidermoid cyst
- Lymphoepithelial cyst/Branchial cyst
- Thyroglossal Duct cyst
- Anterior median lingual cysts
- Cystic hygroma
- Nasopharyngeal cyst
- -Thymic cyst

Cysts of salivary glands

- Mucous extravasation phenomenon
- Mucous retention cyst-Ranula

Para cystic cysts

- Hydatid cyst
- Cysticercus cellulose

The pathogenesis of odontogenic cysts heavily relies on the proliferation of odontogenic epithelial remnants, such as the epithelial cells of Malassez and the cell rests of Serres, within the jawbones. [15]

Non neoplastic lesions can occur due to infections, inflammations, congenital or developmental disorders. These cysts vary in the age and site of presentation. Due to the extensive array of clinically analogous and similar lesions that betide in the head and neck region, diagnostic conundrums frequently arise thereby confounding the clinical picture and management protocol. [14]

The investigations for cystic lesion can be through clinical examination, radiological examination, cystic fluid examination, gross examination and immunohistochemistry. One of the most significant elements of the cyst is the cyst fluid (Browne 1976).[4]

Cyst enlargement has been associated to hydrostatic pressure exerted by its luminal fluid. The nature of cyst fluid helps in understanding pathogenesis and act as an adjunct in preoperative diagnosis of the cyst. It has been shown that the consistency of this fluid varies from a clear yellow fluid to a solid cheesy lump (Toller 1970).[5]

Some proteins are present in the cyst fluid which are formed via blood or are synthesized in the cyst wall. Investigations of the type and concentration of soluble proteins in cyst fluid has been discovered to be one of the constructive techniques to diagnose cyst prior to surgery which may influence the treatment plan (Shear 1983).[1]

The presence of cholesterol crystals suspended in the fluid has been considered a characteristic of odontogenic cysts. Cholesterol crystals are less prevalent in odontogenic keratocysts than in other forms of odontogenic cyst. The cystic lesion that affects the oral cavity are predominantly odontogenic in origin. Odontogenic cysts arise from the odontogenic epithelium. Epithelial lining of odontogenic cyst is derived from the basal cells of oral mucosa, dental lamina, enamel organ, reduced enamel epithelium, cell rests of malassez, cell rests of Serres.[6]

There are three parts in a cyst-lining, connective tissue, and lumen (Neville et al 2004). Keratin filled or cell debris is commonly found in the lumen of the cyst. All true cysts have three phases in their formation

1. Phase of initiation
2. Phase of cyst formation
3. Phase of Cyst enlargement.

Phase of initiation is associated with genetic factors, immunosuppression, by inflammatory mediators and local factors like decrease in oxygen tension and increase in carbon-dioxide tension.

In the phase of cyst formation, cystic degeneration of central cells occurs due to lack of vascularity. Epithelial cell rests start proliferating and the central cell break down, and cysts expands because of osmotic gradient. The cyst matures with flattened surface cells, a basement membrane and connective tissue wall. Osmotic gradient continues, cyst lining proliferates and cyst expands. There is increase in intercellular edema, acid phosphatase activity accompanied by formation of microcysts and smaller microcysts coalesce to form larger cysts.

On the phase of cyst enlargement, there is attraction of fluid into the cystic cavity, retention of the fluid and raised hydrostatic pressure, bone resorption and epithelial proliferation. Cysts are believed to enlarge by increased permeability of cyst wall, increased protein content of cyst fluid and increased intracystic fluid pressure on the jaw bone.

On the other hand. cysts are thought to expand when prostaglandin like chemical produced in the wall is released. Cysts in the jaw bone have an active transporting mechanism for Na^+ and K^+ ion, a secreting and selection mechanism. They have a permeability mechanism that allows electrolytes, proteins and lipids to pass through.

The contents of odontogenic cysts vary from clear yellow fluid to semisolid cheese like mass. It comprises of serum proteins, immunoglobulins, proteases and inhibitors, keratin and possible keratocyst antigen, glycosaminoglycans, proteoglycans, glycoproteins and lipids. The color, consistency, presence of cholesterol crystals, keratin flecks and other characteristics of odontogenic cyst fluid like albumin, alpha and beta globulin, total protein content and inorganic phosphates can all be investigated.

Cysts expand due to the collection of cystic fluid. Almost all odontogenic cysts can be detected with a syringe aspiration. All odontogenic cysts require pre operative diagnosis in order to achieve favorable results. The technique of fine needle aspiration cytology is routinely utilized for preoperative diagnosis. Aspirates collected from cystic lesion have a low cellular content.

Cyst fluid can be investigated by physical examination, smear and investigation of cystic proteins. In physical examination, the color varies from straw or yellow color to brown color in absence of contamination by blood. Color is dark brown or reddish when blood is mixed in the aspirate.[7]

The presence of cholesterol crystals imparts shimmering yellow color to the fluid. The presence of keratin imparts yellow color resembling cheese and pseudocyst and pseudocyst like aneurysmal bone cyst and infected cyst are usually blood colored/reddish brown in color. The consistency of cystic fluid varies from a watery fluid to an almost semisolid cheese like mass. Odontogenic keratocyst have a cheesy consistency, radicular cyst is serosanguinous and dentigerous cyst is often watery. The odontogenic cyst fluid can be studied for their color, consistency, presence of cholesterol crystals, keratin flecks and different protein fractions such as albumin and alpha and beta globulin, total protein content and inorganic phosphates.[6]

II. Discussion

The protein level in cystic fluids helps to understand the pathogenesis and act as an adjunct in preoperative diagnosis. The electrophoretic mobilities of serum and cyst fluid proteins are comparable, cystic proteins are derived from serum. In a study by R.M Browne 1976, he investigated the fluids of 44 dental cysts,19 dentigerous cyst and 36 odontogenic keratocysts and 12 ameloblastomas. Smears were examined for epithelial cells, inflammatory cells, cholesterol crystals and bacteria. Epithelial cells were found in abundance in odontogenic keratocysts but not in other lesions. Cholesterol crystals had similar occurrence in all lesions. Cellulose acetate electrophoresis was used to evaluate the proportion of soluble proteins and total protein content. Dental cysts contained an average of 51.19% albumin,17.52% β globulin,22.04% γ globulin and 6.30g/100 ml protein.

Dentigerous cyst contained an average of 61.35% albumin,13.98 % β globulin,12.70% γ globulin and 5.40g/100 ml protein.

Odontogenic keratocysts contained an average of 78.03% albumin,7.51% β globulin,7.91%γglobulin and 2.09g/100 ml protein [4]

Proteins

Name of the protein	Ascending levels in cystic fluids in mg/100ml			
Albumin	Radicular cyst 51.9	Dentigerous cyst 61.35	Ameloblastoma 67.38	Odontogenic keratocyst 78.03
Alpha 1 Globulin	Ameloblastoma 0.91	Radicular cyst 1.54	Dentigerous cyst 1.84	Odontogenic keratocyst 2.25
Alpha 2 Globulin	Odontogenic keratocyst	Ameloblastoma	Dentigerous cyst	Radicular cyst

	3.56	5.46	5.83	6.57
Beta Globulin	Odontogenic keratocyst 7.51	Ameloblastoma 12.83	Dentigerous cyst 13.98	Radicular cyst 17.52
Gamma Globulin	Odontogenic keratocyst 7.91	Ameloblastoma 12.60	Dentigerous cyst 12.70	Radicular cyst 22.04
Soluble protein	Odontogenic keratocyst 2.09	Ameloblastoma 4.86	Dentigerous cyst 5.4	Radicular cyst 6.3

Browne RM. Some observations on the fluids of odontogenic cysts. Journal of Oral Pathology & Medicine. 1976;5(2):74-87.

Immunoglobulins

Immunoglobulin	**Quantity in Cystic Fluids in mg/100ml**		
IgA	Odontogenic keratocyst 135.6	Dentigerous cyst 308.4	Radicular cyst 488.9
IgG	Odontogenic keratocyst 491.9	Dentigerous cyst 1618.2	Radicular cyst 2535.4
IgM	Odontogenic keratocyst 54.1	Dentigerous cyst 135.6	Radicular cyst 155.6

Ameloblastomas contained 67.38% albumin,12.83% β globul1in, G and 12.60% γ globulin and 4.86g/100 ml protein. Dental cysts contained an average of 488.9 mg/100 ml IgA, 2535.4mg/100 ml Ig G and 135.6 mg/100ml IgM. Dentigerous cysts contained an average of 308.4 mg/100 ml IgA 1618.2 mg/100ml IgG and 155.6mg/100 ml IgM. Odontogenic keratocyst contain 135.6 mg/100 ml IgA,491.9 mg/100 ml IgG and 54.1 mg/100 ml IgM. Other authors have reported significant differences between concentration of soluble protein in fluids from odontogenic keratocyst and other forms of odontogenic cyst.

Toller (1970) found a mean level of 7.1g/100ml in non-keratinizing cysts and 2.2g/100 ml in odontogenic keratocysts whereas Skaug (1975) reported mean level of 7.84g/100 ml in dental cysts and 6.75g/100 ml in dentigerous cysts. Although soluble proteins in non- keratinizing cysts are electrophoretically comparable to those in serum, implying that they are mostly sourced from the blood, at least some of the proteins is produced in the cyst wall. Immunoglobulins may be generated locally in the capsule of non-keratinizing odontogenic cysts according to data (Toller and Holborlow 1969, Skaug et al.1974) and passed in the cyst cavity so that concentration in the cyst fluid are greater than serum. However, small amounts of immunoglobulins are present in the fluids of OKCs.[5]

In a study by Madhvika Patidervet al.2015, they evaluated the levels of albumin, prealbumin, total protein, inorganic phosphate and presence of keratinocytes in the cystic fluid to diagnose and plan treatment of keratinizing odontogenic tumor and non-keratinizing odontogenic cyst. Fifteen cases of keratocystic odontogenic tumor and 15 controls of Non keratinizing odontogenic cysts were studied. A comparison of total protein between cases and control showed highly significant difference. The total protein content in the cases ranged from 2.11 to 6.85gm/dl with a mean value of 3.984gm/dl. The total protein content in controls ranged from 6.1 to 11.2gm/dl with a mean volume of 8.54gm/dl. A comparison of total protein between cases with inflammation and cases without inflammation showed significant difference. Total protein content in 6 cases with inflammation showed a range of 4.6-6.85gm/dl with a mean of 5.542gm/dl and 9 cases without inflammation showed arrange of 2.1-4.2gm/dl with a mean of 2.946gm/dl.[8]

In a study by Muaz Abdelmajeed Saleh et al.2017, they observed that the lowest concentration in the fluid of Keratocystic odontogenic tumor (mean level was 2.9g/dl±1.5). Their results also showed that infected samples of Keratocystic odontogenic tumor are associated with higher concentration of total protein. The highest total protein concentration was found in radicular cyst, the mean being 8.5gm/dl±2.0. The study proved that the protein level of dentigerous cyst is similar to serum, the mean level was 5.4g/dl±0.9. The mean of toral protein for cystic ameloblastoma was 5.3g/dl±1.2, similar to the study of Browne. The mean of total protein concentration

of Keratocystic odontogenic tumor fluid was significantly lower than those in radicular, dentigerous cyst similar to results of Browne, Smith and Douglas et al. [9,10]

According to the results obtained in the study by Hamidreza et al, the concentration of the proteins in radicular cyst fluid is higher than all other cysts, this could be due to the inflammatory nature of the cyst and the presence of bacteria. In addition, the soluble protein content in keratinized cysts like odontocystsgenic keratocyst is lower than non- keratinized cysts.[11]

In a study by Nils Skaug, contents of IgG, IgA and IgM in the fluids from 45 non-keratinizing jaw cysts, and of albumin aphai1acid glycoprotein, alpha1-antrypsin, as-macroglobulin, Ceruloplasmin, and transferrin in 15 of these cyst fluids have been determined by single radial immunodiffusion. Cystic "fibrinogen" was measured in 37 cyst fluids. The mean ratios of lgG:IgA:IgM were for cyst fluid 20.1:4.8:1 and for the autologous serum 14.6:2.5:1. On the average, cyst fluid contained IgG, IgA and IgM, in concentrations 1.2, 1.7 and 0.9 times, respectively, that of autologous serum. These ratios as well as data obtained from other calculations indicate partly local synthesis of cyst fluid immunoglobulins, mainly IgA and IgG. Remarkably high IgA levels were found in some cyst fluids.[12]

Prakash et al in his review stated that the analysis of contents of cystic fluids may aid in an accurate diagnosis whenever a cyst is detected before surgical excision or conservative management. He provided an overview of various odontogenic cysts and evaluate the quantity of albumin, globulin and protein content among various odontogenic cysts like dentigerous cyst, radicular cyst and benign tumors such as keratocystic odontogenic tumor, He stated the fluid in radicular cyst is usually brown and cholesterol crystal give the substance a gleaming gold or straw color. Total protein content is usually 5 and 11g/100 ml. The cystic fluid of dentigerous cyst is 4-8g/100ml. Dirty cheese like whitish material was found on aspiration in all cases of OKC. Keratin squames are usually found in the aspirated cystic fluid. Electrophoretic analysis revealed that the ratio of soluble protein to total protein content was lower than that in serum. Total protein content is less than 5g/100ml. [6]

Electrophoresis separates proteins based on their physical properties. The movement of charged particles through an electrolyte subjected to an electric field is called electrophoresis. Different plasma proteins have different surface charges. They migrate at varying speeds from the place where the protein combination is applied to the cellulose acetate membrane (CAM) strips. The protein content and its different fractions can be quantified by scanning the CAM strips in a densitometer at 590nm (green filter) and the relative percentage, and absolute value of different protein fractions such as albumin, globulin content along with different globulin fractions can be calculated.[6]

Toller et al. suggested that these proteins are transported to the cystic fluid by immunoglobulins (Ig) producing cells IgA, IgG, IgM level in cystic fluid and can be assessed quantitatively. He hypothesized that clinically uninfected cyst walls of various types may produce immunoglobulins that may enter the cyst cavities by an active cellular transport mechanism. Smaller amounts of secretory IgA found in cystic fluids on the other hand, suggested that a small proportion of cystic fluid immunoglobulin came through simple diffusion through the epithelial cyst wall.[5]

Smith et al. in their investigation discovered that most cysts had greater molecular weight Proteins Lactoferrin entry into the cystic lumen is facilitated by enhanced epithelial permeability as discontinuity in the epithelial lining and intraepithelial channels.[13]

III. Conclusion

Cystic fluid accumulation caused the expansion of cysts. Almost all odontogenic cysts can be detected with a syringe aspiration. The technique of fine needle aspiration cytology is routinely utilized for preoperative diagnosis of cyst. All odontogenic cysts require preoperative diagnosis in order to achieve favorable results. From the above studies, the composition and components of various odontogenic cyst fluids such as Odontogenic keratocyst, dentigerous cyst and radicular cyst have been examined and came to the conclusion that fluid is an integral part of the cyst. Cyst enlargement is attributed to hydrostatic pressure exerted by its luminal fluid. The nature of cyst fluid can help in understanding the pathogenesis of the cyst. The cystic fluid could aid in non-surgical diagnosis of cyst. Different biochemical findings can be used for diagnosing cysts before surgery and thereby formulating the surgical procedure. Thus, we conclude that the cystic fluid and its constituents can be utilized as a diagnostic adjunct in the preoperative diagnosis of odontogenic cysts in a minimally invasive and accurate fashion.

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