Salivary Oncocytic Cystadenoma with Intraluminal Crystalloids: a Case Report with Review of the Literature

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Abstract Oncocytic cystadenoma is a rare benign tumor of major salivary glands that in rare occasions may present histologically with intraluminal crystalloids. We report a case of 53-year-old man with a progressively enlarging lump in the left submandibular region. Ultrasound examination revealed a cystic mass with an intraluminal fluid collection. The tumor was surgically removed. Histologic examination yielded a diagnosis of oncocytic cystadenoma with a high concentration of intraluminal crystalloids. The microscopic features of the crystalloids were compatible with nontyrosine (alpha-amylase) crystalloids. When compared with previously published cases in the literature, this is the first report of oncocytic cystadenoma with intraluminal crystalloids arising in the submandibular gland, and the second reported case of the nontyrosine type of crystalloids occurring in association with this tumor. The nontyrosine crystalloids may be highly characteristic to salivary gland tumors with oncocytic differentiation.

Keywords Salivary glands · Oncocytic cystadenoma · Intraluminal crystalloids · Nontyrosin crystalloids · Tyrosin-rich crystalloids

Introduction

Oncocytic cystadenoma is a rare benign lesion of salivary glands histologically characterized by multicystic growth and an oncocytic epithelial lining. It usually presents as a

slowly enlarging painless mass of major and minor salivary glands. The course of the disease is benign with conservative but complete surgical removal as the treatment of choice [1, 2]. Rarely, crystalloids are described within the luminal spaces of these tumors [3–6].

Several types of crystalline structures have been documented in association with salivary gland lesions: tyrosine-rich, nontyrosine (alpha-amylase), collagenous, oxalate, intraductal birefringent, and intraluminal crystalloids [7–12]. They can occur in association with neoplastic and nonneoplastic conditions, and can be localized both in the stroma and in the secretory material, intraluminally.

We report a case of submandibular oncocytic cystadenoma with a high concentration of nontyrosine intraluminal crystalloids with a review of the literature.

Case Report

A 53-year-old man presented with a progressively enlarging mass of the left submandibular region. The tumor was soft on palpation with intact overlaying skin. Ultrasound examination revealed a cystic mass, 2.6 cm in greatest dimension, with an intraluminal fluid collection. By physical examination and ultrasound, the cervical lymph nodes were without any changes. A fine-needle aspiration biopsy was not performed and the tumor was surgically removed.

On gross examination, the tumor was a soft, fluid-filled mass, measuring 3×1.8 cm, with a grayish smooth external surface. On sectioning, the cut surface revealed a multiloculated cyst filled with white-colored fluid and smooth inner walls.

The tissue was fixed in neutral buffered formalin and embedded in paraffin for routine histologic examination. The slides were stained with haematoxylin and eosin.

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Low-power microscopic examination showed a multiloculated cystic lesion with epithelial lining and a small focus of salivary gland tissue on the periphery (Fig. 1). The epithelial lining was composed of cuboidal to columnar cells arranged in a single or double layer. The epithelial cells had a single round nucleus with visible central nucleolus and abundant eosinophilic granular cytoplasm consistent with oncocytic cells (Fig. 2). Papillary infoldings of oncocytic epithelium were observed in some cystic spaces. These spaces were filled with amorphous debris and numerous glassy pink crystalloids (Figs. 2, 3). The crystalloids varied in shape, including rectangular, polyhedral, ovoid, rhomboid, and rod-like forms (Fig. 3). Their size varied from 5 to 350 μm in length. The crystalloids were not birefringent on polarized light. The microscopic features of the crystalloids were compatible with nontyrosine crystalloids.

Fig. 1 Multiloculated cystic tumor with a small focus of salivary gland tissue on the periphery (H&E, original magnification $\times 40$)

Fig. 2 Oncocytic epithelial lining of cystic spaces and intraluminal crystalloids (H&E, original magnification $\times 400$)

Fig. 3 Intraluminal crystalloids of various sizes and shapes (H&E, original magnification $\times 400$)

Discussion

Cystadenoma is a rare benign tumor of salivary glands composed of cystic spaces lined by cuboidal to columnar cells and separated by fibrous stroma. Cystadenomas may show a mixture of cell types in the epithelial lining, including oncocytic, mucinous, signet ring cell, apocrine, and squamous [1, 2]. The oncocytic variant of cystadenoma is characterized by a single or double layer of oncocytes which line the cyst walls, resembling Warthin's tumor without the lymphoid stroma. The lumina usually contain eosinophilic material with scattered epithelial, foamy, and inflammatory cells. Rarely, crystalloids may be found [3–6].

Table 1 summarizes select clinicopathologic features of oncocytic cystadenomas with intraluminal crystalloids reported to date in the English-language literature.

The case presented here represents the fifth case of oncocytic cystadenoma with intraluminal crystalloids, and the first one described in the submandibular gland. An additional possible case was reported as a parotid gland cyst with oncocytic metaplasia and nontyrosine crystalloids, as seen by FNA biopsy [13]. However, this case failed to confirm histologically that the lesion was an oncocytic cystadenoma.

Several types of crystalline structures may be found in cytologic or histologic specimens of salivary glands. Tyrosine-rich crystalloids, nontyrosine (alpha-amylase) crystalloids, and collagenous crystalloids are the most commonly encountered forms. By light microscopy, the large (5–500 μm), geometrically shaped nontyrosine crystalloids may be easily distinguished from the much smaller (30–60 μm), floret-shaped tyrosine-rich crystalloids, and the radially arranged, needle-shaped clusters of collagenous crystalloids [6, 9, 14]. Tyrosine-rich crystalloids are occasionally found in the stroma of benign (e.g., pleomorphic

Table 1 Oncocytic cystadenomas with intraluminal crystalloids—review of the literature

Reference no.	Site	Type of crystalloids
Gilcrease et al. [3]	Parotid gland	Tyrosine-rich
Chaushu et al. [4]	Parotid gland	Tyrosine-rich
Skálová et al. [5]	Parotid gland	Tyrosine-rich
Nasuti et al. [6]	Parotid gland	Nontyrosine
Present case	Submandibular gland	Nontyrosine

adenoma) and malignant (e.g., polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma) salivary gland neoplasms, as well as in the lumen of nonneoplastic parotid gland cysts [6, 14, 15]. On the other hand, nontyrosine crystalloids have been observed only in benign and reactive salivary gland lesions, such as sialadenitis with sialolithiasis, lymphoepithelial cyst, pleomorphic adenoma, oncocytic cystadenoma, Warthin's tumor, and benign parotid gland cysts [6, 16–18]. Collagenous crystalloids have been described in association with both benign and malignant neoplasms, including pleomorphic adenomas, myoepitheliomas, and myoepithelial carcinoma, respectively [9, 19].

Nontyrosine crystalloids are chemically composed of protein consistent with crystallized alpha-amylase produced by salivary gland cells in supersaturated saliva [17]. As in our case, Nasuti et al. [6] noticed the relationship between nontyrosine (alpha-amylase) crystalloids and cells with oncocytic features. Among the four cases in their series showing crystalloids occurring in association with salivary gland tumors, oncocytic cells were present in three of these cases: one oncocytic papillary cystadenoma and two Warthin's tumors. They speculated that nontyrosine crystalloids might represent a secretory product of salivary gland oncocytes.

However, our literature review, which focused on crystalloids arising in association with oncocytic cystadenomas, specifically (Table 1), revealed that the crystalloids in the majority of cases were of the tyrosine-rich type. One possible explanation for this discrepancy, as Granter et al. pointed out, is that some examples of nontyrosine (alpha-amylase) crystalloids may have been erroneously reported as tyrosine-rich because they showed histochemical positivity for Millon's reagent, used to detect the presence of tyrosine. However, as Granter et al. [20] clearly stated, a complex protein such as alpha-amylase contains some tyrosine and may therefore exhibit histochemical positivity for Millon's reagent. In addition, the authors pointed out that the crystalloids associated with salivary oncocytic neoplasms, as reported by Gilcrease et al. (five Warthin's tumors, one oncocytoma, and one oncocytic cystadenoma) were morphologically similar to alpha-amylase crystalloids reported in their and others' works [3, 18, 20]. Similarly,

Chaushu et al. [4] in their case of multiple oncocytic cysts with crystalloids (also included in Table 1) clearly stated that microscopic and ultrastructural features of the crystalloids were compatible with alpha-amylase crystalloids; however, the crystalloids were histochemically positive for tyrosine and nonimmunoreactive for human salivary alpha-amylase.

If the suggestion that intraluminal crystalloids in some reported cases of oncocytic cystadenomas are actually of the nontyrosine type (instead of the tyrosine-rich type) were proven to be true, this could help confirm the possible relationship between nontyrosine crystalloids and cells with oncocytic differentiation.

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