Glandular Odontogenic Cyst Presenting as an Aggressive Multifocal Lesion: Case Report and Review of Literature
Atulkumar A Patil, Suresh R Barpande, Jyoti D Bhavthankar, Mandakini S Mandale

Abstract
Glandular odontogenic cyst is a rare developmental lesion considered as a distinct entity because of its uncommon histopathological characteristics. It was formerly denominated as “Sialo-odontogenic cyst” because of probable origin from the salivary gland tissues. But, World Health Organization includes glandular odontogenic cyst as a developmental odontogenic cyst to support an odontogenic origin. The low incidence of Glandular odontogenic cyst (0.2% of odontogenic cysts) is because of not only its rarity, but principally to the fact that its main characteristics are also found in other pathologic entities there by generating controversial diagnosis. Although it is relatively rare, correct diagnosis is of major clinical importance, since Glandular odontogenic cyst has an aggressive potential, a high incidence of cortical perforation and relatively high rate of recurrence. So, clear definition of histopathological criterion is necessary to make a final diagnosis of Glandular odontogenic cyst. Documentation of more and more cases will help in exploring the definite histopathologic criteria for this lesion. The present case report is a case of Glandular odontogenic cyst in a 51 year old male patient with multiple cystic lesions involving the entire left mandibular ramus area and also to highlight the clinical, radiological and histopathological findings of Glandular odontogenic cyst.

Keywords: Glandular Odontogenic Cyst; Immunohistochemical Markers; Sialo-Odontogenic Cyst; Mucoepidermoid Carcinoma; Odontogenic; Cysts.

Introduction
Glandular odontogenic cyst (GOC) is an uncommon jaw bone cyst of odontogenic origin, first described in 1988 by Gardner et al., as a distinct clinicopathologic entity. In 1987, Padayachee and Van Wyk reported two cases similar to botryoid odontogenic cyst (BOC) but with a glandular element and proposed the term ‘Sialo odontogenic cyst’. Until, then the cyst had an uncertain histogenesis but is recently listed by World Health Organization (WHO) as a developmental odontogenic cyst. It is characterised by an epithelial lining with cuboidal or columnar cells with mucous cell component, both at the surface and also lining the crypts or cyst like spaces within the thickness of the epithelium. The low incidence of GOC (0.2% of odontogenic cyst) is because of not only its rarity, but also to the fact that its main histopathological characteristics are also found in other entities like BOC and low grade Central Mucoepidermoid Carcinoma (MEC). Although rare, its correct diagnosis is of major clinical importance because it has aggressive potential and relatively high rate of recurrence. Treatment of GOC include curettage and enucleation, although some authors prefer marginal resection due to a tendency of the cyst to recur after curettage or enucleation. The aim of this report is to describe a case of GOC occurring as a multifocal lesion involving the mandibular ramus area and also to emphasize the histopathological criteria for diagnosis of GOC.

Case Report
A 51 year old male patient with multiple cystic lesions involving the entire left mandibular ramus area, extending from zygomatic arch to the inferior border of the mandible. Intraorally the swelling was firm in consistency extending from distal of tooth #38 over the anterior border of ramus with expansion of buccal and lingual cortices. The overlying mucosa was intact with normal colour and appearance. (Figure 1a) The presumptive clinical diagnosis included multicystic ameloblastomas and keratocystic...
odontogenic tumor. Panoramic radiograph of mandible showed two well defined, unilocular, expansile osteolytic lesions of size 3x3 cm each extending distal to tooth #37 region and involving most of the mandibular ramus area (Figure 1b).

Figure 1: Intraoral swelling extending from distal aspect of tooth #37 over the anterior border of ramus (a) and orthopantamograph demonstrating two well-defined expansile radiolucencies involving most of the left mandibular ramus area. The gross specimen of resected mandibular ramus (c) and radiograph (d) of the same showing with two independent cystic cavities of size 3x3 cm and 2x2 cm.

Aspiration yielded a straw coloured clear fluid, indicative of a cystic lesion. Incisional biopsy showed cystic cavity with a lining of non-keratinized stratified squamous epithelium surrounded by a connective tissue capsule. The epithelial lining was of variable thickness, exhibiting focal thickenings of epithelium. The connective tissue interface was flat (Figure 2a). Some areas showed separation of epithelium from connective tissue. The superficial layer of epithelial lining consisted of cuboidal and columnar cells showing eosinophilic mucinous material. Some vacuolated cells were present within the basal cell layer (Figure 2b). The epithelial thickenings exhibiting intra-epithelial crypts and duct like structures lined by mucus cells. Underlying connective tissue was densely fibrous with sparse chronic inflammatory infiltrate. Diagnosis of glandular odontogenic cyst was made. Periodic acid Schiff (PAS) staining revealed numerous positive mucous cells present throughout the epithelial lining (Figure 2c). Immunostaining for CK-19 revealed strong positivity within the epithelium of the lesion (Figure 2d). Final diagnosis of glandular odontogenic cyst was made by correlating the clinical, radiographic and histopathological features.

Considering multifocal areas and extensive involvement of ramus, resection of left mandibular ramus area was performed. Macroscopic examination of resected specimen showed two independent cystic cavities approximately of size 3x3 cm and 2x2 cm with cortical expansion and perforations at places (Figure 1c). The tissue lining the cavities was greyish in colour. Radiograph of resected specimen also revealed two independent, well defined, unilocular radiolucent lesions (Figure 1d). Microscopically the tissue from both cystic areas showed similar histological features and was consistent with the diagnosis of glandular odontogenic cyst as seen on incisional biopsy.

Discussion
Glandular odontogenic cyst is an uncommon jaw bone cyst of odontogenic origin with approximately 114 cases reported in the literature.² GOC has a frequency rate of only 0.012 - 1.3% of all the jaw cysts and its prevalence is 0.17%.¹ Most of the GOCs in the literature are reported with slight male predilection and mean age of occurrence 45.7 years.² GOCs usually present as painless, slow growing swelling that tends to affect anterior part of the mandible.¹ In the present case age, sex and clinical features were corroborating with what has been reported in the literature, but the site of the lesion was in the mandibular ramus area which is not common for GOC.

Radiographically, GOC is localized intraosseous and may appear as a unilocular or multilocular radiolucent lesion with well-defined borders. It may sometime present with peripheral osteo-sclerotic border, scalloping, root resorption and displacement of the teeth.¹ Radiographic findings of GOC do not display any specific or pathognomonic features.¹ In the present case two separate unilocular radiolucencies involving left mandibular ramus area were seen, indicating a multifocal nature. Krishnamurthy et al., 2009¹ reported that aspiration of clear, low-viscosity fluid can be a helpful clinical indication of GOC, and preoperative aspiration and fluid inspection may be advisable.¹ In the present case clear straw coloured aspirate was obtained.

Due to some of overlapping of histopathological features of GOC with other lesions such as botryoid cyst, radicular or dentigerous cysts with mucous metaplasia and low-grade Central Mucoepidermoid Carcinoma, a set of criteria for histological diagnosis of GOC has been proposed by Kaplan et al (2005).⁵ These criteria have been divided into major and minor. They suggested at least focal presence of each of the major ones necessary for diagnosis, while the minor criteria supported the diagnosis were not mandatory.

Major criteria:
1. Squamous epithelial lining with a flat epithelial - connective tissue interface, lacking basal cell palisading
2. Epithelium exhibiting variations in thickness with or without epithelial spheres' and focal luminal proliferation
3. Cuboidal eosinophilic cells or “hob-nail' cells
4. Mucous “goblet” cells with inter-epithelial mucous pools with or without crypts lined by mucous-producing cells
5. Intra epithelial glandular microcystic or duct like structures

Figure 2: The photomicrographs of hematoxylin and eosin stained tissue sections showing cystic lining of non-keratinised stratified squamous epithelium of variable thickness with flat connective tissue interface (a) and intraepithelial crypt lined by cuboidal to columnar mucous cells (b). The periodic acid schiff stained section showing PAS positive mucous cells and few microcystic areas within the epithelial lining (c). The Immuno histochemical staining with
CK-19 was noted in all layers of epithelial lining (d).

Minor criteria:
1. Papillary proliferation of the lining epithelium
2. Ciliated cells
3. Multiluminal or multicystic architecture
4. Vacuolated or clear cells in basal or spinous layers

Histopathologically present case showed cystic lining of non-keratinized stratified squamous epithelium of varying thickness with flat connective tissue interface. The superficial layer of epithelium consisted of cuboidal and columnar epithelial cells exhibiting eosinophilic mucinous material. Epithelial lining also demonstrated intra-epithelial crypts and duct like structures, at places. So, the present case showed all of the above mentioned major criteria and certain minor criteria for diagnosis of GOC. In addition, it also showed the histopathological features that have been described by other authors.6,8 The mucous cells in the present case were PAS positive and are considered to be metaplastic in origin. These mucous cells occur in many intraosseous odontogenic cysts; however, in GOC they are remarkably abundant as was seen in the present case.1

Epithelial plaques or whorls may also be seen in lateral periodontal cyst (LPC) and BOC, pointing towards the odontogenic nature of GOC. These areas of epithelial thickening may be comparable to the proliferative changes seen in dental lamina. Immunohistochemical studies using cytokeratin - 7, 13, 14 and 19 and their positivity support the odontogenic nature of GOC.1,2 The identification of osteodentin and negative reaction for epithelial membrane antigen (EMA) and maspin in the area of glandular structures suggest that these features are not of glandular origin and support the concept of odontogenic differentiation in GOC.1 The present case showed positive staining for CK-19 indicating odontogenic origin of GOC.

The GOC is well accepted as being of odontogenic origin, but also shows distinctly glandular features, such as mucus producing cells and ductal structures; presumably demonstrating the pluripotentiality of odontogenic epithelium to develop diverse differentiation.10 Histopathologically GOC should be differentiated from LPC, BOC, and Central Mucoepidermoid Carcinoma (MEC) as they exhibit considerable overlap of histological features. LPC is a developmental odontogenic cyst lined by thin non-keratinized epithelium and exhibits focal epithelial thickenings and glycogen rich epithelial cells, similar to those observed in GOC. BOC is a locally aggressive polycystic variant of LPC, shows similar histomorphological features as that of GOC. However, in the present case identification of intraepithelial duct like spaces lined with mucus cells specifically differentiate GOC from LPC and BOC and favours the diagnosis of GOC.1,3 The differentiation of low grade Central MEC from GOC especially its multicystic variant is more difficult as significant histological overlap exists between GOC and central MEC. However, superficial cuboidal cells, epithelial whorls, and intraepithelial microcysts or duct like structures are not typical for central MEC and their presence or absence can help in establishing a definitive diagnosis. Immunostaining with CK-18 and 19 and their positivity in GOC may help in differentiating GOC from central MEC.1

The GOC is relatively aggressive lesion with high tendency for erosion or perforation of the cortical plates as well as high recurrence rate. In the present case gross specimen showed cortical perforation at places and multiple cystic cavities indicating the aggressive behaviour. The aggressive biologic behaviour of GOC and its propensity for recurrence might be associated with cell kinetics in the lining epithelium. Other factors responsible for increased recurrence rate are thin cystic wall and presence of microcysts causing incomplete removal of cyst with conservative methods.1

Various treatment modalities have been recommended for the treatment of GOC ranging from curettage, enucleation to enblock or partial osteotomy. The present case underwent enblock resection due to its extensive ramus involvement at the time of presentation.1 Due to propensity of a GOC to recur and become large, it is important for patients diagnosed with this cyst to be followed carefully for minimum of three years post operatively.2

Conclusion
GOC is a relatively uncommon and aggressive lesion with a high rate of recurrence. Due to the varied clinical and radiological findings with overlapping
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histopathological features with other lesions, GOC often presents a diagnostic challenge to oral pathologist. So, a careful clinical, radiological and histopathological evaluation must be carried out along with advanced techniques such as immunohistochemistry to ensure correct diagnosis and treatment.

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