An Insight into the Histopathology and Biologic Behavior of an Inflamed Odontogenic Keratocyst: A Case Report.

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Abstract

Introduction: Odontogenic Keratocyst (OKC) is a benign locally aggressive developmental cyst of the jaw characterized by high proliferative potential with significant recurrence rate. The presence of inflammation induces significant alterations in the histopathological presentation of this cyst. Although aggressive behavior is primarily attributed to factors such as a weak epithelial–connective tissue interface and the presence of satellite cysts, inflammation also modulates the behavior of the lesion through responses to various inflammatory cytokines.

Case report: This article reports an inflamed OKC in the mandibular left posterior region, confirmed by histopathological examination in a 27-year-old male patient and emphasizes the significant secondary changes induced by inflammation.

Management and prognosis: The treatment protocol consisted of enucleation with peripheral osteotomy, supplemented by the adjunctive application of Carnoy's solution to minimize recurrence risk.

Conclusion: The aggressive nature of OKC is exemplified in this case, with inflammation being a prominent feature. Notably, the high recurrence encompassing OKC is a critical concern which necessitated a meticulous approach in the management, ensuring that optimal care and follow-up has been offered simultaneously. This paper provides insight into the modification of the cyst's biological behavior, with the aim of potentially identifying patients at risk of developing recurrent lesions over their lifetime.

Keywords: Odontogenic keratocyst, Inflammation, Recurrence, Enucleation

Introduction

The term "odontogenic keratocyst" (OKC) was first introduced by Philipsen in 1956. In 1963, Pindborg and Hansen described the key characteristics of this cyst. It is called a keratocyst since its epithelial lining produces an extensive amount of keratin, which nearly fills the cyst lumen. In 1967, Toller proposed that OKC should be considered a benign neoplasm rather than a conventional cyst due to its biological behaviour.[1] In 1976, Brannon proposed three mechanisms for the recurrence of OKC which includes the following:[2]

- Incomplete removal of the cyst lining.
- Development of new cyst from satellite cysts or residual odontogenic epithelial islands in the primary cyst site.
- Formation of a new OKC in an adjacent area.

In 2005, the World Health Organization (WHO) reclassified OKC as a keratocystic odontogenic tumour (KCOT), recognizing it as a cystic neoplasm due to its aggressive clinical behavior, high recurrence rate, and emerging evidence at the time suggesting genetic mutations in its pathogenesis. However, in 2017, the WHO reverted KCOT to the cyst category, citing insufficient evidence to confirm its genetic etiology. Additionally, more recent studies indicated that KCOT responds well to conservative treatments like marsupialization which is not typically associated with neoplastic conditions.[3]

The cyst originates from the remnants of the dental lamina in the mandible and maxilla before odontogenesis is complete and may also develop from the basal cells of the overlying epithelium.[4]

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OKC accounts for approximately 7.8% of all jaw cysts, with an incidence ranging from 4% to 16.5%. It can occur at any age but is most commonly seen during the second and fourth decades of life. It occurs in the mandible approximately twice as frequently as in the maxilla, with mandibular involvement accounting for about 66.9% of cases.[5]

This article offers a comprehensive understanding of the histopathology and biological behavior of an inflamed OKC, emphasizing the crucial role of histopathological diagnosis in guiding effective treatment strategies.

Case report

A 27-year-old male patient presented with pain and swelling in the left posterior mandibular region for the past few months. The patient reported a history of pericoronitis, followed by the surgical removal of a vertically impacted tooth 38, performed four months ago. On clinical examination, a non-tender, smooth, diffuse extra-oral swelling was observed, with normal overlying skin color and no evidence of a sinus tract or local temperature rise. Orthopantomogram imaging revealed a well-defined, multilocular radiolucent lesion with a sclerotic border, extending from the mandibular left third molar region to the ascending ramus. (Figure 1A). The preliminary diagnosis, based on clinical and radiographic assessment, suggested an OKC. However, due to its radiographic similarity, unicystic ameloblastoma and lateral variant of a dentigerous cyst were considered in the differential diagnosis.

Incisional biopsy was performed prior to enucleation. Histopathological examination of the incisional biopsy specimen exhibited intensely inflamed connective tissue stroma. The specimen was devoid of cystic lining. Correlating with radiographic findings it was diagnosed as inflamed odontogenic cyst and excisional biopsy was advised for confirmatory diagnosis.

Complete enucleation of the cystic lesion with peripheral osteotomy was performed along with the application of Carnoy's solution for two to three minutes. The enucleated soft tissue specimen was submitted for histopathological analysis.

Two soft tissue specimens brownish in color, soft to firm in consistency were obtained for histopathological examination (Figure 1B). Microscopic analysis revealed parakeratinized stratified squamous epithelium with focal corrugation (Figure 2A), associated with intense inflammation in the underlying connective tissue (Figure 2B). Odontogenic epithelial islands of varying sizes were observed exhibiting focal cystic degeneration (Figure 2C) Strikingly, focal areas exhibited loss of para keratinization. The lining epithelium displayed cellular atypia, epithelial budding, and mitotic activity, particularly in the basal and para basal layers. (Figure 2D) The epithelial-connective tissue interface appeared obscured due to intense chronic inflammation. Inflammatory infiltrate was composed predominantly of lymphocytes and plasma cells along with Russel bodies. The connective tissue wall was moderately collagenous with proliferating fibroblasts. The histopathological features were consistent with an inflamed OKC. Immunohistochemical analysis of P53 and Ki-67 was performed to assess the biological behavior of the lesion. Ki67 staining was significantly present in the lower half of the epithelium ranging from patchy staining in few areas to moderately intense staining in many other areas (Figure 2E). Mild to moderate intensity staining in the suprabasal layers of cystic epithelium was exhibited by p53 (Figure 2F).

Considering the recurrence potential, a long-term follow up was recommended. The patient recovery was closely monitored to ensure optimal outcomes.

Discussion

OKC is a distinct type of odontogenic cyst characterized by aggressive biological behavior. The reported case represents an inflamed OKC involving the mandibular ramus and presenting as a multilocular radiolucency.

While bone expansion may be absent in some cases of OKC, a significant number, especially those involving the angle or ramus, exhibit varying degrees of expansion.[4] In the present case, a multilocular radiolucency distal to the third molar was observed, necessitating differentiation from odontogenic tumors such as ameloblastoma. Accurate diagnosis of OKC is essential because of their locally aggressive behavior and high recurrence potential. Recent advances in understanding the molecular pathways involved in the pathogenesis of OKC have

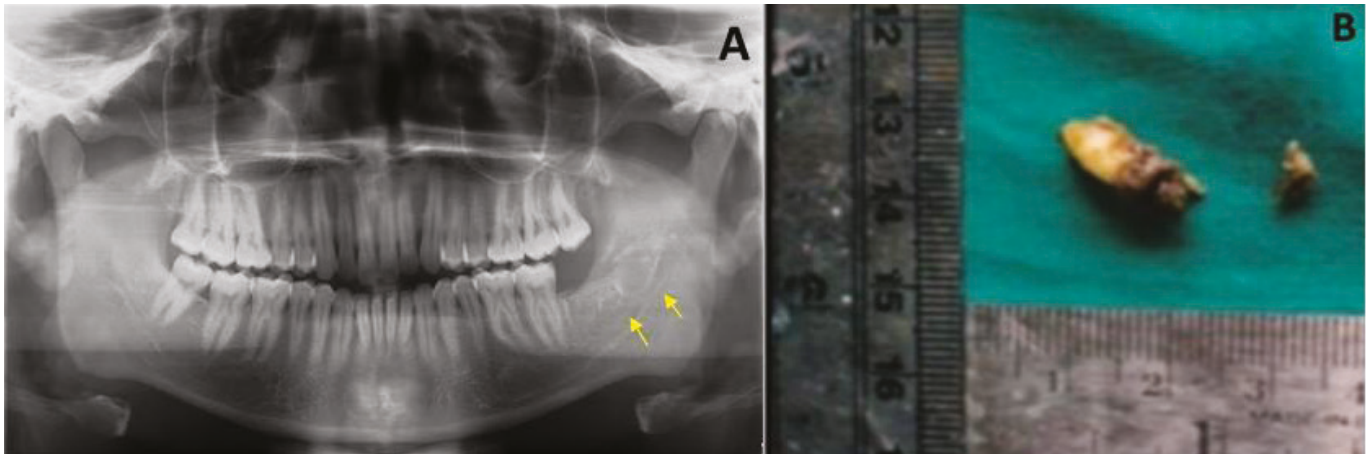

Fig. 1: A) OPG revealing a well-defined multilocular radiolucency with sclerotic margin extending from 38 region to ascending ramus. **B)** Two soft tissue specimens obtained after enucleation.

provided valuable insights into their growth, progression, and biologic behavior. These findings also contribute to improved diagnostic and therapeutic approaches. Surgical intervention remains the cornerstone of OKC management, with enucleation and curettage being the standard treatment modalities.6 Enucleation followed by application of Carnoy's solution and peripheral osteotomy was performed in this case.

The aggressive behavior and high recurrence rate of OKC's may be attributed to the following factors:[4]

- A higher mitotic index of the cystic lining and its intrinsic growth potential.
- PTCH gene mutation, more common with syndromic cases.
- Possible origin from basal cell hamartias.
- Fragile cystic lining.
- Satellite cysts and islands of proliferating odontogenic epithelium in the cyst wall.

The factors determining the growth of OKC are: [6,7,8]

- Intrinsic proliferation of epithelium.
- Osmolality of cyst fluid.
- Bone resorption and collagenolytic activity.
- Myofibroblast proliferation in the connective tissue wall. Tumour derived cytokines, such as TGF-β, promote the emergence of myofibroblasts, which produce growth factors and proteases that aid tumour growth and invasion. Considering that the myofibroblasts contribute to lesion behavior, and targeting them with anti-myofibroblast drugs may help reduce lesion severity prior to surgery.
- Secondary changes induced by inflammation. A cyst may become inflamed due to communication with the oral mucosa through cortical perforations or via periodontal ligament of adjacent infected teeth. In the present case, a history of pericoronitis in the adjacent third molar indicates a potential source of inflammation.

Role of inflammation in the growth of cyst:

During inflammation, the cystic epithelium exhibits altered cytokeratin expression, accompanied by increased lysosomal activity. Additionally, there is a loss of parakeratinization and altered permeability of the cystic lining.[6] Similar inflammation

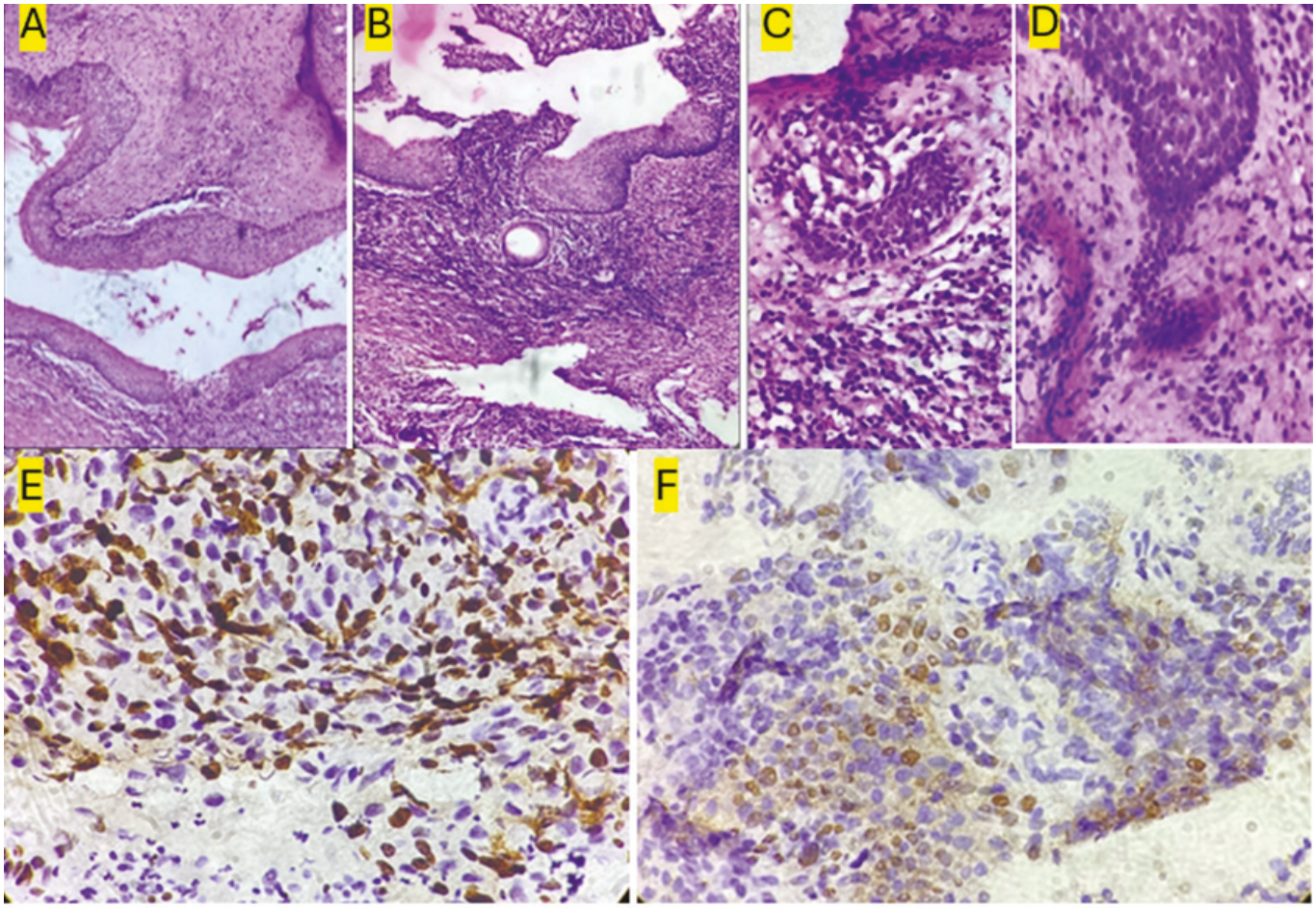

Fig. 2: A) H and E stained section exhibiting focally corrugated para keratinized stratified squamous cystic epithelium. **B)** Focally ulcerated epithelium with underlying intensely inflamed connective tissue wall. **C)** Evidence of odontogenic epithelial islands undergoing cystic degeneration. **D)** Epithelial budding. **E)** Immunohistochemical staining with Ki67 exhibiting moderately intense staining. **F)** P53 labelling showing mild to moderate intensity staining in the suprabasal layers of cystic epithelium.

induced changes were evident in the present case, along with inflammatory atypia exhibited in the cystic epithelium. The chronic inflammatory cell infiltration in the connective tissue wall was predominantly comprising of lymphocytes and plasma cells. Russell bodies, which are characteristic inclusions formed by plasma cells, were also noted within the inflammatory infiltrate.

The cyst is characterized by numerous capillaries, endothelial cell proliferation, and elevated VEGF levels. These factors contribute to the degradation of the extracellular matrix and subsequent bone resorption, thereby facilitating cyst enlargement.[6]

The growth of OKC involve a complex interplay of immune cells and molecular mediators. Mast cells release eosinophil chemoattractant factors and histamine, recruiting eosinophils to the lesion site. Together, these cells stimulate prostaglandin production, contributing to bone resorption and cyst enlargement. Furthermore, OKC exhibits elevated levels of osteolytic cytokines, including interleukin-1 and interleukin-6. Notably, the concentration of these interleukins in OKC fluids is higher than those observed in other types of cysts, such as dentigerous and radicular cysts. [6,7] Inflammation in OKCs leads to increased vascular permeability, allowing glycosaminoglycans (GAGs) to diffuse through the cystic epithelium and accumulate in the cyst fluid. This accumulation of GAGs elevates osmotic pressure, attracting more fluid into the cyst and promoting its growth.

Additionally, the progressive fluid accumulation increases the hydrostatic pressure within the cyst contributing to cyst expansion.[6]

Molecular aspects and advanced treatment modalities:

P53, a tumour suppressor gene, may play a role in the aggressive behavior of OKCs. Altered p53 expression may influence the mitotic activity, particularly within the suprabasal layer of the cystic epithelium of OKC.[9] PCNA and Ki-67, are also expressed in actively proliferating cells, particularly in neoplasms. Their expression is higher in OKC compared to other odontogenic cysts.[10] The present case exhibited p53 expression, predominantly within the suprabasal layer along with increased ki67 expression.

Mutations in the tumour suppressor gene Patched (PTCH) leads to activation of Hedgehog signaling pathway. Therefore, Shh pathway inhibitors may represent a potential therapeutic approach in the management of OKC.[11]

A study by Pogrel, Voorsmit, and Stoelinga have demonstrated promising outcomes, reporting negligible recurrence after marsupialization and enucleation, with a recurrence rate of 2.7% with enucleation using Carnoy's solution, and a significant reduction in recurrence when combined with removal of the overlying alveolar mucosa.[12] In this case the peripheral osteotomy was performed to ensure complete removal of odontogenic islands and satellite cysts in the connective tissue wall along with application of Carnoy's solution to promote necrosis of any residual tissue.

Conclusion

This case highlights the aggressive nature of inflamed OKC. Inflammation induces significant alterations in the histopathological and molecular features of OKC. The characteristics of the lining epithelium and the connective tissue wall play a critical role in determining cyst's aggressiveness and propensity for recurrence. Understanding the influence of inflammation on histopathological and molecular aspects is critical as it may impact cyst expansion and overall biologic behavior.

Contrary to conventional belief, inflamed OKC may require more aggressive management to reduce recurrence and progression, since inflammation can induce structural alterations that affect surgical management.

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