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Case Report

Topical 5-Fluorouracil as an Adjunct to Enucleation in the Management of Odontogenic Keratocyst

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Abstract: The odontogenic keratocyst (OKC) accounts for approximately 3% to 11% of all odontogenic cysts and is characterized by aggressive behavior, significant growth potential, and a high recurrence rate, prompting the exploration of more effective and conservative adjuvant therapies. This report describes the clinical management of a case treated with surgical enucleation and topical application of 5-fluorouracil (5-FU), an antimetabolite widely used in oncology and dermatology, whose application has been extrapolated to the treatment of OKCs due to molecular similarities in their pathophysiology. A 66-year-old female patient with an odontogenic keratocyst in the right mandibular ramus was treated by enucleation and placement of a gauze dressing impregnated with 5% 5-FU. After 15 months of clinical and radiographic follow-up, a favorable outcome was observed, with adequate bone regeneration and no evidence of recurrence. This case adds to the growing body of evidence supporting the use of 5-FU as an effective, minimally invasive therapeutic alternative for odontogenic keratocysts.

Keywords: Odontogenic Keratocyst, Enucleation, Coadjuvant Therapy, 5-Fluorouracil, Oral Pathology, Odontogenic Cyst.

INTRODUCTION

The odontogenic keratocyst (OKC) is a lesion of odontogenic origin that has attracted considerable interest due to its unpredictable clinical behavior, local expansion potential, and high recurrence rate. It was first described as a distinct clinical entity by Philipsen and Reichart in 1956, and since then, its classification and management have been the subject of extensive debate (Borghesi *et al*., 2018). In 2005, the World Health Organization (WHO) reclassified it as a benign keratocystic odontogenic tumor (KCOT), based on its infiltrative growth pattern, the presence of satellite cysts, and its association with genetic syndromes such as Gorlin–Goltz syndrome. However, this classification was reversed in the 2017 edition, as available evidence did not fully support its neoplastic nature; thus, the term "odontogenic keratocyst" was again widely accepted (Vered & Wright, 2022; Grover *et al*., 2024).

OKCs arise from remnants of odontogenic epithelium, specifically from the dental lamina, and occur most frequently in the mandible, particularly in the posterior region and ascending ramus. Clinically, they are often asymptomatic until they reach a considerable size, which may delay diagnosis. Radiographically, they appear as well-defined radiolucent lesions, either unilocular or multilocular, and may be confused with other entities such as ameloblastomas or dentigerous cysts (Vered & Wright, 2022). Histologically, they are classified into parakeratinized and orthokeratinized subtypes; the former is more common and associated with a higher recurrence potential, with important diagnostic, therapeutic, and prognostic implications (Jeyaraman, Anbinselvam, & Akintoye, 2024).

The choice of treatment for OKC remains controversial. Therapeutic options range from conservative approaches such as marsupialization or decompression to more invasive procedures, including enucleation with or without adjuvant therapies (Carnoy's solution, cryotherapy, peripheral ostectomy), and even segmental surgical resection (Al-Moraissi *et al*., 2017).

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Enucleation combined with adjuvant techniques has been one of the most commonly employed approaches to reduce recurrence; however, the effectiveness of these adjuvants varies. For example, the use of Carnoy's solution, a chemical fixative, initially showed promising results, but its reformulation after the FDA banned chloroform in 1992 led to a significant reduction in its effectiveness. This limitation necessitated exploring new therapeutic alternatives with comparable efficacy but improved safety profiles (Lal *et al*., 2021).

In this context, increasing attention has been directed toward the use of 5-fluorouracil (5-FU) as a topical adjuvant agent in the treatment of OKC. This antimetabolite, introduced into clinical oncology in the 1950s, primarily inhibits thymidylate synthase (TS), an enzyme essential for thymidine synthesis and, consequently, DNA replication. This mechanism makes it particularly effective against highly proliferative cells, as observed in basal cell carcinoma, actinic keratosis, and, more recently, in proliferative odontogenic lesions such as OKC. Its topical efficacy and favorable safety profile have positioned it as a viable, accessible, and less aggressive option for patients in whom extensive resection is undesirable (Berberi *et al*., 2023).

At the molecular level, recent studies have demonstrated that OKCs exhibit alterations in the Sonic Hedgehog (SHH) signaling pathway, particularly mutations in the PTCH1 gene (also implicated in basal cell carcinoma), leading to uncontrolled activation of the smoothened (SMO) protein and subsequent increased epithelial proliferation. This molecular similarity between both entities supports the rationale for extrapolating the use of 5-FU to the management of OKC. Unlike agents such as liquid nitrogen or modified Carnoy's solution, which induce nonspecific chemical necrosis, 5-FU exerts a more targeted effect on residual epithelial remnants and satellite cysts, thereby reducing the risk of recurrence and surgical morbidity (Jeyaraman *et al*., 2024; Grover *et al*., 2024).

Several clinical studies have shown that the topical application of 5% 5-FU, using dressings placed directly within the residual cavity after enucleation, can achieve outcomes comparable to or even superior to those obtained with traditional adjuvant therapies, with recurrence rates approaching 0% in controlled series and without significant adverse effects such as permanent paresthesia or extensive necrosis. Furthermore, this approach does not require specialized containment measures, facilitating its use in conventional surgical settings (Al-Moraissi *et al*., 2017; Wanve *et al*., 2023; Barua *et al*., 2023).

This clinical report details a 66-year-old woman with an odontogenic keratocyst in the right mandibular ramus, treated by surgical enucleation and topical 5% 5-fluorouracil. Postoperatively, she showed consistent bone regeneration and no recurrence at 15 months. These results strengthen evidence for 5-FU as a safe, accessible, and effective conservative treatment for OKC.

CASE REPORT

A 66-year-old female patient presented to the Admission Clinic of the School of Dentistry at the Autonomous University of Baja California for evaluation of her periodontal health. During the initial examination, chronic periodontal disease characterized by generalized moderate gingival and bone recession was detected. She was referred to the undergraduate Periodontics Department for complementary evaluation.

As part of the preoperative assessment, a panoramic radiograph was obtained, in which an incidental finding was identified: a well-circumscribed, unilocular radiolucent lesion with clearly defined radiopaque margins, with no apparent relationship to adjacent dental structures, located in the region of the right mandibular ramus (Figure 1). Given the absence of associated clinical signs or symptoms, the patient was referred to the Oral Pathology Service for further evaluation.

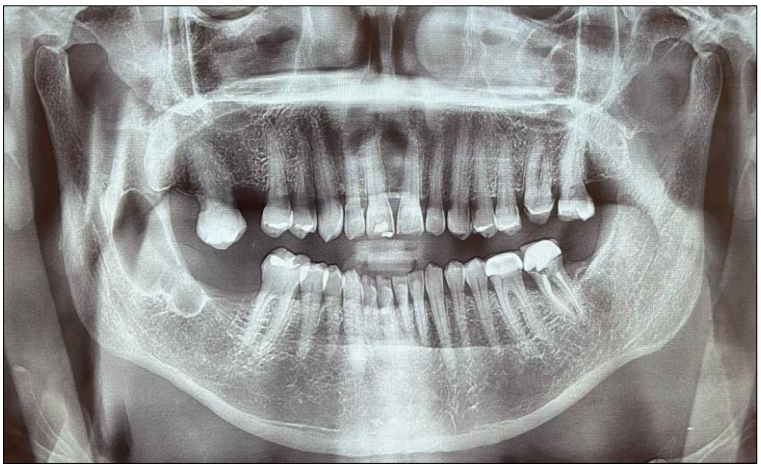

Figure 1: Panoramic radiograph showing an oval-shaped radiolucent lesion with well-defined radiopaque cortical borders, located in the mandibular ramus with extension toward the ascending border

During the intraoral and extraoral clinical examination, no relevant alterations were observed. However, upon directed questioning, the patient reported having undergone surgical intervention in the same mandibular region 12 years earlier for the presence of a "cyst," although she did not recall the definitive histopathological diagnosis. She also mentioned a history of persistent whitish discharge. Based on the radiographic findings, surgical history, and anatomical location, a presumptive clinical diagnosis of odontogenic keratocyst was established.

Subsequently, she was referred to the Department of Oral Surgery, where an excisional biopsy under local anesthesia was planned, given the accessibility, size, and location of the lesion. In accordance with the presumptive diagnosis, topical adjuvant therapy with 5-FU was selected as a preventive measure to reduce the risk of recurrence, following recent protocols described in the literature (Figure 2).

Figure 2: Efudix® (5% 5-fluorouracil). An antimetabolite that is commonly used in the treatment of premalignant and superficial malignant dermatologic lesions. In this case, it was used as an adjuvant agent applied to sterile dressings placed within the postsurgical bone cavity to prevent recurrence of the odontogenic keratocyst

The surgical procedure was performed under standard aseptic and antiseptic conditions. Local anesthesia (2% lidocaine with 1:100,000 epinephrine) was administered, and a mucoperiosteal flap was reflected to expose the surgical site. Using rotary instruments, the cortical bone was removed until the cystic capsule was identified (Figure 3A). Complete enucleation of the lesion was performed, followed by surgical curettage of the residual bone cavity (Figure 3B). As adjuvant treatment, interwoven sterile gauze strips impregnated with topical 5-FU (Efudex® 5%) were placed directly into the cavity (Figure 3C). The gauze was secured in place with sutures, leaving approximately 1 cm of the gauze exposed to facilitate removal. After 24 hours, the patient returned for removal of the medicated dressing. Mild intraoral and extraoral swelling was observed, with no signs of infection or significant pain (Figure 3D). At the seven-day follow-up, during suture removal, the patient reported no paresthesia, bleeding, pain, or other postoperative complications.

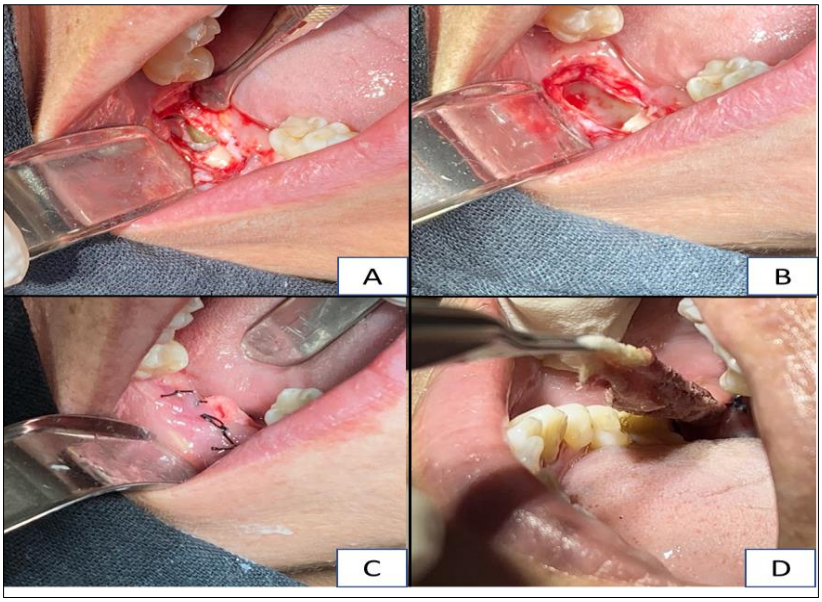

Figure 3: (A) Intraoperative view showing the epithelial capsule during enucleation. (B) Surgical curettage and peripheral osteotomy. (C) Topical 5-fluorouracil is applied using sterile gauze. (D) Clinical appearance 24 hours later during gauze removal

At the histological level, the lesion was characterized by a cystic capsule lined by parakeratinized stratified squamous epithelium, with a well-defined basal layer of hyperchromatic nuclei arranged in a palisaded pattern (Figure 4A). The epithelial lining exhibited a corrugated surface, which is typical of odontogenic keratocysts, with no evidence of epithelial projections or invaginations into the underlying connective tissue. The basement membrane appeared intact and showed no signs of invasion.

At lower magnification (Figure 4B), the general architecture of the cyst was observed, with a well-defined central lumen and a cystic capsule surrounded by fibrous connective tissue. No signs of acute or chronic inflammation were identified, nor were satellite cysts or residual islands of odontogenic epithelium observed. These findings are consistent with a parakeratinized-type odontogenic keratocyst, without features of malignant transformation or aggressive behavior at the time of analysis.

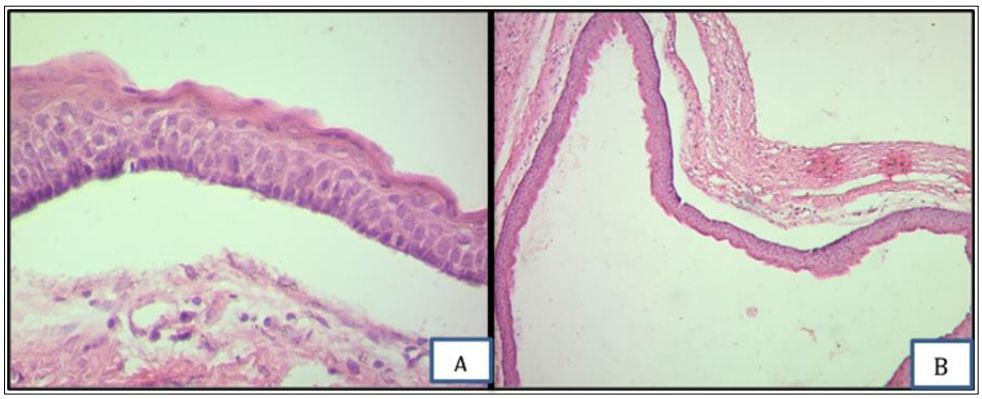

Figure 4: (A) Parakeratinized epithelium with palisaded basal layer (10×). (B) Panoramic view of the cystic capsule without inflammatory infiltrate (4×)

At 15 months postoperatively, a follow-up panoramic radiograph demonstrated adequate bone regeneration, with no evidence of recurrence or bone sequestration (Figure 5). The patient remained asymptomatic. Figure 5. Follow-up panoramic radiograph 15 months after surgery showing appropriate bone apposition.

Figure 5: Follow-up panoramic radiograph 15 months after surgery showing appropriate bone apposition

DISCUSSION

The management of odontogenic keratocysts remains a clinical challenge due to their locally aggressive behavior and high recurrence rate. Al-Moraissi *et al*., (2017) reported higher recurrence rates with conservative procedures such as marsupialization and simple enucleation, while the use of adjuvant methods significantly reduced recurrence. Surgical resection showed the lowest recurrence, but at the cost of greater morbidity.

Topical 5-fluorouracil has emerged as a promising alternative due to its antiproliferative effects and its effectiveness in basal cell carcinoma, a tumor that shares molecular pathways with OKC, particularly mutations in the PTCH1 gene that activate the Sonic Hedgehog pathway (Ledderhof *et al*., 2017).

Wanve *et al*., (2023) demonstrated no recurrences in patients treated with 5-FU compared with those treated with modified Carnoy's solution. In addition, fewer neurosensory complications and absence of bone necrosis were observed in the 5-FU group.

The present case supports these findings. After enucleation, curettage, and 5-FU application, the patient

showed no signs of recurrence or complications after 15 months of follow-up. Histopathology revealed a typical parakeratinized OKC without satellite cysts or inflammatory activity.

Despite these favorable results, long-term follow-up remains mandatory, as late recurrences have been reported even beyond 5 years after treatment (Fidele *et al*., 2019). Additionally, enzymatic expression profiles in the cyst lining may influence the biological response to 5-FU and require further investigation.

CONCLUSION

This case demonstrates the successful use of 5-fluorouracil as a conservative adjuvant treatment in a patient with recurrent odontogenic keratocyst treated by enucleation and topical drug application. No recurrence or postoperative complications were detected after 15 months of follow-up, supporting its safety and effectiveness.

The use of 5-FU was based on its antiproliferative mechanism and its molecular rationale, which are shared with basal cell carcinoma. Compared with modified Carnoy's solution, 5-FU showed simpler application, lower morbidity, and excellent tissue tolerance.

Long-term follow-up and multicenter studies are recommended to validate 5-FU as a standard conservative adjuvant therapy for odontogenic keratocysts.

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