Case Report

Keratocystic Odontogenic Tumour Admixed With Giant Cells: Case Report and Review on the Role of RANK/RANKL in its Pathogenesis

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ABSTRACT

‘Odontogenic keratocyst’ (OKC) was the term coined by Philipsen in the year 1956, while Pindborg and Hansen in the year 1963 described the details of this cyst[1,2]. OKC is renamed as keratocystic odontogenic tumour (KCOT) by WHO[3] taking into view its aggressive and recurrent nature. OKC arises from the rests of dental lamina[1]. It can occur anywhere in the oral cavity wherever the osseous structures are present, but most commonly in the posterior regions of the mandible[2,4]. Since the clinical and radiological profile of OKC mimics other lesions it may affect the appropriate diagnosis. Here we report a case of aggressive OKC which affected an entire quadrant of the mandible along with the ramus.

KEYWORDS: Odontogenic keratocyst, Pathogenesis, Keratocystic odontogenic tumour

INTRODUCTION

Odontogenic keratocyst (OKC) was the term coined by Philipsen in year 1956, while Pindborg and Hansen in year 1963 described the essential features of the cyst. Odontogenic cysts arise from the rests of dental lamina[1]. Toller in the year 1967 suggested that this is better regarded as a benign neoplasm rather than a conventional cyst based on its clinical behaviour. WHO reclassified this cyst into a tumour based on numerous factors. Its clinical behaviour of high recurrence, budding of the cystic epithelium as satellite cysts into the connective tissue stroma and genetically, the association with the PTCH (patched) gene. This is a tumour suppressor gene involved in both syndroice and sporadic keratocystic odontogenic tumours (KCOTs) occurring on chromosomes 9q 22.3-q31[1,3]. Normally, PTCH is a receptor complex formed with the oncogene SMO (smoothened) for the SHH (Sonic Hedgehog) ligand[3]. Here we report the case of a 26-year-old female patient with an aggressive form of KCOT affecting the ramus and the body of the mandible.

CASE REPORT

A 26-year-old female patient came to our hospital with a chief complaint of difficulty and pain in opening the mouth since 1 month. Swelling was present on the right side of the cheek. It was firm and tender on palpation. There was no history of tobacco smoking or chewing. The teeth and periodontal status was normal. Submandibular lymph nodes were palpable on the right side. Radiographically a multilocular radiolucency was seen involving the entire ramus and condyle of the mandible on the right side extending up to the second molar region. Cone-beam computed tomography (CBCT) scan also revealed the cystic lesion involving the ramus and mandible of the jaw (Figure 1). An incisional biopsy was done in the right mandibular third molar region which did not give any

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diagnostic details of the lesion. Later a hemimandibulectomy was done (Figure 2). Histopathologically we observed cystic cavity with orthokeratinized odontogenic epithelium of four to five layer thickness and underlying connective tissue stroma. Epithelium showed palisading arrangement of cells in the basal layer, with parabasal cells arranged loosely and connected by their cytoplasmic projections resembling stellate reticulum cells. The entire cystic lumen is filled with keratin flecks. The underlying fibrous connective tissue stroma showed collagen bundles with moderate vascularity (Figure 3). A peculiar feature observed in the stroma is the occurrence of many giant cells. The giants are oval in shape with six to eight nuclei arranged irregularly (Figure 4).

DISCUSSION

OKCs are the odontogenic cysts of developmental origin arising from the rests of dental lamina. They can occur at any age with the second and third decades being the most common age group with a high incidence (Meera et al., 1996). Many workers have also suggested a bimodal age distribution with a second peak in the fifth decade of the life. The mandible is by far the most predominant site of occurrence for the OKC when compared to the maxilla. Almost half of all the OKCs occur in the angle extending into the ramus of the mandible[5].

Patients usually present with a painful swelling with infrequent paraesthesia of the lower lip or the teeth rarely resulting in pathologic fractures. A unilocular radiolucency with a sclerotic rim and peripheral scalloping borders is a usual presentation. The histologic features include an odontogenic epithelium of 6 to 10 layers in thickness with polarised basal cells arranged in a palisading fashion, described as the ‘tomb stone appearance’, a superficial para/orthokeratinised corrugated surface[6]. The lining epithelium is thus highly characteristic and resembles odontogenic epithelium describing its developmental origin. The connective tissue stroma often shows small islands of the epithelium described as the ‘daughter cysts’ or ‘satellite cyst.

The peculiar features of OK Careits aggressive course and high recurrence rate that have raised the question of classifying them under odontogenic cysts and have paved way to the concept of KCOT. Many concepts have been put forward to determine the reasons behinds its destructive nature and high recurrence: the occurrence of satellite cysts, the friable nature of the cystic lining, the remnants of dental lamina and genetic deviation in relation to the PTCH tumour suppressor gene. Also, other important features of bone resoring activity and the associated inflammatory cytokines are associated with it. Interleukins, tumour necrosis factor and matrix metalloproteinases (MMPs) were associated with the chronic bone lesions that resulted into aggressive bone resorption.

The present case also reported an aggressive destruction of the mandibular ramus and the body. The CT scan shows the three-dimensional view of the mandible, showing the aggressive destruction caused by the lesion which ultimately resulted in the hemimandibulectomy of the patient. The histopathology of the excised tissue showed an increased appearance of giant cells in the tissue. Though giant cells are common in areas of inflammation, we never encountered them in increased numbers in the cystic linings of OKCs as a regular finding. We then studied the course of giant cells in osteolytic lesions of the jaws and came across an interesting molecule RANK/RANKL which is associated with osteoclastogenesis.

Bone resorption is mainly caused by osteoclasts which originated from the haematopoietic cell lines from the monocyte–macrophage lineage. But the mesenchymal-derived osteoblasts play a pivotal role in the differentiation and activation of osteoclasts. The important molecule that has the significant part in the process is RANK (receptor activator of nuclear factor kappa B) and its ligand RANKL[6].

Human RANK is a 616-amino acid peptide, with a 28-amino acid signal peptide, an N-terminal extracellular domain, a short transmembrane domain of 21 amino acids and a large C-terminal cytoplasmic domain. It is
Keratocystic Odontogenic Tumour Admixed With Giant Cells: Case Report and Review

Figure 1: Intraoperative picture showing hemimandibulectomy on the right side

Figure 2: CBCT scan showing the three-dimensional view of the osteolytic lesion in the body and ramus of the mandible

Figure 3: 4× magnification view showing the thin parakeratinised odontogenic epithelium and an underlying connective tissue stroma. The stroma shows the presence of giant cells. The cystic cavity shows keratin flecks

Figure 4: 20× magnification. Connective tissue stroma shows giant cells with six to eight nuclei arranged haphazardly

expressed primarily on cells of the macrophage/monocytic lineage, including preosteoclastic cells, T and B cells, dendritic cells and fibroblasts. Human RANKL is a 317-amino acid peptide that has ~30% homology to the TNF-related apoptosis-inducing ligand and to CD40, and ~20% homology to Fasligand. RANKL mRNA is expressed at highest levels in bone and bone marrow, as well as in lymphoid tissues (lymph node, thymus, spleen, foetal liver and Peyer’s patches). Osteoprotegrin (OPG) forms an important part of this cascade which acts along with RANK/RANKL. OPG mRNA was expressed in variable tissues like lung, heart, kidney, liver, stomach, brain and spinal cord, thyroid gland and bone. The prime biologic action of OPG is
to inhibit osteoclast differentiation and activity. Thus, it acts as a road block in the function of RANK/ RANKL and forms an important part of the osteoclast differentiation process\[12,13\].

The prime cells taking part in the osteoclast giant cell formation are pre-osteoblast stromal cell and osteoclast precursor cell. Both these cells along with their receptors are required for the process. The pre-osteoblast cell expresses RANKL and M-CSF (Macrophage-colony stimulating factor) and also OPG on its surface. RANKL binds to RANK which is present on the surface of osteoclast precursor cell and M-CSF binds to its receptor c-Fms which is also present on the surface of the osteoclast precursor cell. The binding of M-CSF is a prime step in osteoclastogenesis which triggers the activation of all other receptors. The binding of RANK with its ligand on RANKL stimulates the differentiation and activation of the osteoclast precursor cell to finally form a multinucleate osteoclast giant cell\[14\]. OPG forms the decoy molecule of RANK/RANKL which can stop the entire process of osteoclastogenesis. Though RANK/RANKL are critical in the genesis of osteoclasts, various other molecules like TNF-α, IL-1, TGF-β, parathyroid hormone, oestrogen, glucocorticoids also play supporting roles in this entire cascade of events\[15\].

This RANK/RANKL-associated giant cell formation is also seen in many pathologies. It is reported mainly in the giant cell tumor of the bone, CGCG, PGCG, cherubism and ABC. It is also suggested that RANKL can replace the osteoblasts in the process of osteoclastogenesis and is considered to be the master cytokine sufficient for the induction of giant cells\[16\]. It was also seen in the neoplastic epithelium and stromal spindle cells of OKC, ameloblastoma, radicular cyst and dentigerous cyst. Its high expression was associated with an increase in its aggressive pattern\[17,18\]. Thus, in our case, the OKC expressed giant cells which are associated with a large osteolytic lesion of the bone.

Giant cells in OKC are a rare finding. Mitrou et al,.\[19\] linked VEGF to be involved in the chemotaxis, formation and survival of osteoclasts in OKC. Zakopoulos et al.,\[20\] also reported the expression of RANKL in OKCs. Thus, the bone resorption and aggressive nature of OKC could be linked to the action of RANK/RANKL cytokines which form the giant cells responsible for resorption.

**REFERENCES**


Keratocystic Odontogenic Tumour Admixed With Giant Cells: Case Report and Review


