Conservative Treatment Protocol of Keratocystic Odontogenic Tumor: Report of a Case with Nevoid Basal Cell Carcinoma Syndrome and Literature Review

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Abstract Keratocystic odontogenic tumor (KOT) is one of the major components of nevoid basal cell carcinoma syndrome (NBCCS), which usually occurs in young ages and includes significant structures of jaws. According to high recurrence rate of KOT, there are many controversies in treatment of the lesion, especially in syndromic cases with younger ages. In current report, authors suggest a conservative protocol in the treatment of KOT in a patient with NBCCS.

Keywords KOT · OKC · NBCC · Gorlin's syndrome

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin's syndrome, is an inherited autosomal dominant disorder with high penetrance and variable expression of abnormalities including neoplastic and developmental disorders [1]. The prevalence of NBCCS is about 1 in 60,000 [2]. According to investigations, mutation of patched (PTCH), a tumor suppressor gene located on chromosome 9, is the main cause of Gorlin's syndrome [3]. Major characteristics of Gorlin's syndrome which have been observed in 50 % or more of patients are multiple basal cell carcinomas (BCC), keratocystic odontogenic tumors (KOT), calcified falx cerebri, palmar and plantar pits, hypertelorism, skeletal disorders such as rib (bifid, split, fused) and vertebral disorders.

Odontogenic keratocyst (OKC) first seen in 1956 was identified as an odontogenic cyst of jaws [4], and later was classified as KOT. In fact KOT behaves similar to tumors in many dimensions; frequent recurrences, high extension in jaw bone and disruptive nature of this lesion are usual in many odontogenic tumors [5]. KOT is one of the most common complications of Gorlin's syndrome that is found at least in 75 % of patients [6]. Nevoid basal cell carcinoma syndrome associated KOTs in comparison with non-syndromic KOTs are usually more extensive and more numerous and recognized in younger ages [7]. Considering the extension of syndromic lesions, emotional status of children, growth of jaws and involvement of permanent tooth buds, choosing the most appropriate treatment is so challenging.

The recurrence rate of KOT is relatively high, that returns to intransient nature of epithelium and connective tissue of the lesion. Satellite or daughter cysts which remain after surgical treatments could result in the recurrence of KOT. Regarding the size, location and type of treatment, the recurrence rates are different. Different treatments have been used in management of KOT including marsupialization and decompression, enucleation with or without adjunctive procedures and resection as the most aggressive treatment modality.

Marsupialization is a conservative treatment method to open out a cyst by removing the external wall of the lesion and decompression of internal contents leading to reduction in the size of the lesion [8]. Therefore marsupialization has the lowest morbidity rate and destruction among other treatment methods and could meet treatment goals of syndromic KOTs in children with growing jaws and unerupted teeth.

In this article, authors report a patient with some characteristic indications of nevoid basal cell carcinoma syndrome

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and the treatment intervention for KOTs of his jaws with regard to age of the patient and extension of lesions.

Case Report

A 9-year old white boy with recognized nevoid basal cell carcinoma syndrome and a chief complaint of bilateral painless swelling of mandibular body recourse came to Department of Oral and Maxillofacial Surgery, Alzahra Hospital, Isfahan University of Medical Sciences. He was born after an uncomplicated pregnancy and with a natural parturition. No evidence of familial history of Nevoid basal cell carcinoma syndrome was observed in parental dynasty. A ventricular shunt was applied for treatment of hydrocephaly. Facial and skeletal malformations such as increased head circumference, hypertelorism and kyphoscoliosis were apparent on physical examination (Fig. 1). Calcification of falx cerebri was seen in head and brain MRI (Fig. 2). Multiple BCC were seen before patient referral and were removed by dermatologist. Palmar and plantar pits were not observed in the patient.

Intra oral examination revealed large expansion in buccal and lingual cortical plates of mandible in parasymphysis and body regions on both right and left sides. In panoramic view, five large and well-defined radiolucent lesions were visible in the mandible and maxilla (Fig. 3a). Radiolucencies include: (1) A well-defined radiolucent lesion in the right ramus, angle and body of mandible around third molar bud. (2) A well-defined scalloped radiolucency in the right body of mandible from first molar to midline. The lesion displaced unerupted right permanent canine close to the inferior border of mandible and displaced erupted right permanent incisors and premolars. (3) A well-defined radiolucent lesion in left parasymphysis which displaced unerupted left permanent canine to inferior border of mandible. (4) A large well-defined radiolucent lesion including left ramus of mandible from coronoid process to left mandibular angle and body. First mandibular molar and unerupted third molar were involved in the lesion. (5) A well-defined radiolucent lesion around the right canine of maxilla widened to midline.

All of the patient's teeth were vital in electrical pulp test. Aspiration of lesions under local anesthesia was done and showed creamy or cheesy liquid. Finally, marsupialization of lesions was accomplished under general anesthesia; after incision and reflecting of soft tissue, additional bone of buccal cortex of the lesions was removed to create five bony windows out to the oral cavity; in addition the third molar buds were extracted. Removal of lining tissue of lesions placed in the windows was done and the tissue was sutured to the oral mucosa. The excised soft and hard tissues were fixed in formalin and sent for histopathologic

Fig. 1 Facial appearance of patient including hypertelorism, inflated mandible and relative macrocephaly

examination. Tetracycline gauzes were placed into the cystic lumens and were substituted once a week. After 3 weeks the gauzes were removed and five acrylic valve caps were made for protecting of the windows and preventing of entry of dross to the cavities.

Microscopic assessments of specimens confirmed diagnosis of KOT (Fig. 4). Palisaded basal cells, thin epithelial lining layer with 6–8 cells in thickness and parakeratinization in luminal surface were apparent in histopathologic features. Daughter or satellite cysts were observed in fibrous connective tissue. In addition, separation of epithelial lining from capsular wall was seen in some parts of the removed wall.

The patient's parents were trained for home care and drenching the cyst cavities three times a day with normal saline. The patient was meted in 1 and 2 weeks appointments after operation and then followed in 3, 6, 9, 12 and 18 months follow-up meets with panoramic view as radiographic examination (Fig. 3b–f).

After 18 months the size of lesions were reduced significantly (Fig. 3f). The right mandibular canine was in the normal eruption path, but the left one was stopped. The residual lesions in left canine area and bilateral ramus of mandible, also the right maxillary lesion were enucleated under general anesthesia and carnoy's solution was applied in remained cavities. The right maxillary and left mandibular canines were removed simultaneously. The patient was followed-up 6, 12 and 30 months after second surgical procedure with panoramic radiographs. There was no evidence of recurrence in clinical and radiographic examination after 30 months (Fig. 3h); although a radiolucent defect in

Fig. 2 Brain MRI showing calcification of cerebral falx and tentorium

left mandibular ramus remained after the treatment, but according to densitometric assessment of radiographic images with no changes in size of the defect in long follow up period, the defect seems to be post-surgical bony scar.

Discussion

Nevoid basal cell carcinoma syndrome is characterized with some major and minor specifications. Major features include multiple BCC or familial history of BCC, KOT of jaws, intra cranial calcification (falx and tentorium), and palmar and plantar pits. Skeletal anomalies (kyphoscoliosis, spina bifida, bifid or fused ribs), hypertelorism, ovarian and cardiac fibromas, macrocephaly, medulloblastoma, lip and palate cleft, mental retardation are some of minor criteria of the syndrome. Two major criteria or one major accompanied by two minor criteria are sufficient for definitive diagnosis. The patient reported in present study indicated three major criteria including KOTs (Fig. 3), intra cranial calcification of falx and tentorium (Fig. 2) and BCCs in scalp (were removed before patient referral). Also minor features such as hypertelorism (Fig. 1), macrocephaly and slight kyphoscoliosis were apparent.

Keratocystic odontogenic tumor also known as OKC includes about 11 % of all cysts of jaws [9] and occurs in more than 75 % of Gorlin's syndrome patients [6, 10, 11]. The prevalent age is second and third decades and it has a slight male tendency. Mandible is involved 3 or 4 times more than maxilla, especially in ramus, angle and posterior body [6, 12]. Unlike other odontogenic cysts, the recurrence rate of KOT is relatively high. The high recurrence rate is mainly concerned to incomplete removal of lesion

due to the thin and fragile lining wall of the cyst and residual penetrating daughter cysts in connective tissue [6, 13]. In fact the recurrence rate of KOT in different studies varies in a wide range from 0 to 100 % that is related to the number of evaluated cases, various follow-up periods and different treatment techniques [14–16]. KOT associated with the nevoid basal cell carcinoma syndrome compared to non-syndromic lesions are usually more extensive in size and numbers and occur in younger ages [7]. Also recurrence rate in KOTs associated with the nevoid basal cell carcinoma syndrome is much higher than non-related syndrome lesions, in which the reported recurrence rate is about 82 % [17].

Based on systematic reviews, the recurrence rate of KOT varies according to treatment methods. Blanas et al. [14] in a systematic review included investigations from 1970 to 1998 which showed that resection has the lowest recurrence rate (0 %), but other treatments have a wide range of relapses. A systematic review stand on Blanas's criteria was done by Johnson et al. [15] in that the recurrence rate of KOT was evaluated on studies from 1999 to 2010. Combined data from Blanas et al. and Johnson et al. reviews show that resection has the lowest recurrence rate (1.85 %). On the other hand, resection is associated with the most morbidity rate among the treatment methods that leaves great tissue destruction and is not suitable for large or multiple lesions. The recurrence rate of other treatment methods include: enucleation (27.8 %), enucleation with carnoy's solution (4.8 %) and marsupialization (18.2 %).

In young patients with large and numerous cystic lesions that involved mixed dentition and growing jaw structures, conservative treatment methods with lower invalidism are preferred. Preservation of jaw integrity, neuromuscular

Fig. 3 Panoramic view of jaws in regular examination appointments. **a** first meet; five radiolucent lesions in maxillae and mandible (arrows). **b** three months after marsupialization. **c** six months after marsupialization. **d** nine months after marsupialization. **e** twelve months after marsupialization. **f** eighteen months after

marsupialization; the size of lesions were reduced. The right mandibular canine was in the normal eruption path, but the left one was stopped **g** six months after enucleation of lesions with Carnoy's solution. **h** final examination, 30 months after enucleation with Carnoy's solution

function and dental structures are significant as functional and psychiatric aspects.

Marsupialization was first introduced by Partsch [8, 18] and is based on osmotic pressure principles. Exteriorization of cystic cavity and opening out to oral space leads to contraction of cyst and gradual shrinkage of lesion. Low morbidity rate of marsupialization compared to other treatment methods such as resection or enucleation is the main advantage of this technique that is particularly significant in cases with large or multiple cystic lesions including major anatomical structures like inferior alveolar

nerve. In children with mixed dentition, marsupialization is a good choice to avoid damage to evolving teeth and other growing structures. However in this process the pathologic lesion could not completely be removed and the cystic cavity remains in the jaw for a long period that may increase worries about spreading of the lesion or even neoplastic transformations. Many investigations have been done regarding histopathologic changes of KOT subsequent to marsupialization or decompression. Most of the histopathologic changes result in lower invasion behavior and decreased recurrence potential of lesion. Forssell and

Fig. 4 Histopathologic findings of lesions

Sainio [19] demonstrated that the parakeratinized epithelium of lesions changed to orthokeratotic or even normal epithelium during marsupialization. Again in a study by Marker et al. [20] alteration of epithelium to non-keratotic form is seen in 83 % of lesions after decompression.

August et al. [21] used cytokeratin-10 antibody staining to determine changes in epithelium layer of KOT lesions in decompression period. The expression of cytokeratin-10 as an immunohistochemical marker is positive in keratinized epithelium of KOT and is used to distinguish between KOT and non-keratinized cysts like dentigerous cyst. After 9 months of decompression, epithelial dedifferentiation and loss of cytokeratin-10 occurred in 64 % of cystic lesions. As said by the authors the marker helps to determine the timing of cystectomy. Complete dedifferentiation of epithelial layer results in decreased recurrence rate of lesion similar to other odontogenic cysts like dentigerous. As researchers suggested, the minimum time required for complete dedifferentiation is 9 months.

The possibility of neoplastic or malignant transformation of odontogenic cysts is very low. Despite this some reports represent malignant lesions arising from odontogenic cysts [22–25], but there is no evidence that shows marsupialization or decompression would increase risk of malignancy. Clark et al. [26] measured the expression of p53, Ki-67 and growth factor genes in KOT cells before and after decompression. None of measured factors have changed significantly after decompression. It can be interpreted that risk of malignancy does not increase following decompression treatment. However many surgeons prefer to apply marsupialization as an adjunctive technique with other treatment methods such as enucleation. The treatment duration of marsupialization is relatively long and patient cooperation is important during this period [9, 27, 28].

The case reported in the current article diagnosed with multiple large cystic lesions included huge structures of mandible. Large parts of mandible, dentition and neuromuscular functions could be destroyed subsequent to aggressive treatments. Hence in such cases conservative protocols like marsupialization with or without later enucleation are more appropriate to preserve anatomical and physiological figures.

Maurette et al. [9] in 2006 evaluated the effectiveness of treatment and the recurrence rate of KOT after marsupialization in 28 patients with 30 KOTs. The mean time for marsupialization was 9.27 months and the average duration of follow-up was 24.89 months. As reported in this investigation, the recurrence rate of marsupialization (14.3 %) is close to other treatment methods such as enucleation.

Considering the 3–4 times prevalence of KOT in mandible compared to maxillae, most studies report the treatment of mandibular lesions. Thus some concerns remain about marsupialization or decompression in maxillary KOTs. In a retrospective study, Guler et al. [29] examined 43 KOT lesions (33 in mandible and 10 in maxillae). One lesion in maxillae and 14 lesions in mandible were treated with marsupialization. After a mean of 40 months follow up, no recurrence was observed among the lesions. According to authors' views, enucleation with carnoy's solution is the best treatment for small lesions and marsupialization is the treatment of choice for large KOTs.

Pogrel and Jordan [27] also reported ten patients with KOTs, including eight lesions in mandible and two lesions in maxillae. Based on histologic examination and immunohistologic determination of bcl-2, complete elimination of all lesions was observed following marsupialization. Thorough resolution of epithelial layer and sub-connective tissue including daughter cysts occurred and expression of

bcl-2 was stopped after treatment. Of course there are not sufficient evidences concerning marsupialization and decompression in maxillary lesions, but it appears that marsupialization is a useful adjunctive treatment, especially in large lesions. More investigations with systematic methods are required in this field.

With lower morbidity and rational recurrence rate, marsupialization is a conservative option in extensive KOTs which might prevent large wasting of jaw structures and preserve mandibular integration, neurologic functions and muscular activities.

Based on investigations, relapse of KOTs are more probable in first 5 years after treatment [30–32].

Thus regular follow-ups in long term is recommended in patients with KOTs who received conservative treatment methods, especially in multiple and extensive lesions such as syndromic cases. In current report, the patient was followed-up for 2 years after the last surgical procedure with no evidence of relapse. Regarding underlying syndromic disease, longer follow-up periods with more regular meetings are required for cystic lesions of NBCC patients.

As a conclusion, marsupialization with or without adjunctive treatments is a conservative and effective protocol with low cost and morbidity, especially in multiple and extensive cystic lesions such as KOT in NBCC patients.

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