Mandibular cystic defect: A composite approach with rhBMP-2 and rib graft

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Received: 12 November 2008 / Accepted: 28 February 2009
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Abstract

Objective To report treatment of severe mandibular defect caused by Aneurysmal Bone Cyst (ABC) in a 6-year-old child, with off-label use of Recombinant Bone Morphogenetic Protein-2 (rhBMP-2)

Study Design Clinical Study.

Method After corrective segmental mandibulectomy, mandible was stabilized by pre-contoured titanium reconstruction plates spanning the entire defect. After confirming final diagnosis and a wait and watch approach, rhBMP-2 was inserted into mandibular defect along with conventional split rib graft.

Result New bone formation was identified at 3 months and was evident at radiographic examinations upto 5 months.

Conclusion Reconstruction of a large mandibular defect was facilitated by use of an osteoinductive factor (rhBMP-2) as a graft additive.

Clinical Relevance One-step salvage and reconstruction could be facilitated by use of an osteoinductive factor, as a graft additive, may be an alternative strategy for repair of large mandibular defects.

Keywords rhBMP-2 • Rib graft • Segmental reconstructions

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Introduction

Aneurysmal Bone Cyst (ABC) can be described as an expansile osteolytic, cystic lesion often appearing multilocular in radiographs and histologically appearing with blood filled spaces separated by fibrous septa containing osteoclast type giant cells and reactive bone formation. ABC has an incidence of 0.014 per 100 patients commonly occurring in the patients aged below 30 years with a peak in the second decade [1]. ABC in the jaws is rare encompassing only 1–3% [1] of all ABC, certain reports site a range of 2–12% with only 60–70 cases have been described in the head and neck region [2]. The existing Spanish literature reports that about 90% of head and neck ABCs affect the mandible. The median age at diagnosis is 13-years-old and 80 % of the patients are under 20 years old. There is a slight greater incidence in women (62%) [2]. ABC may arise primarily or as a secondary event in other lytic bone lesion like giant cell lesion or

fibrous dysplasia. Although there are several theories about its etiology, mostly referring to alterations of the homeostatic-vascular equilibrium of the bone [2], most lesions are believed to be reactive, however, an association with trauma is unlikely, especially for maxillary ABCs. Cytogenetic data provide evidence that atleast some ABCs are neoplastic [1].

The development of Bone Morphogenetic Proteins (BMP) has offered an alternative to traditional bone grafting or substitution techniques, which has been the gold standard for oral and maxillofacial reconstruction. A recombinant, genetically modified BMP2 product rhBMP-2, has been used successfully in subhuman primates to restore hemisected mandibles and large critical-sized defects. rhBMP-2 has also been used successfully in simulated alveolar clefts and large defect left behind after tumor surgery. The development of effective reconstruction procedures using this osteoinductive factors without the need for bone grafting have

tremendous impact on head and neck reconstruction surgery [3].

This article aims to present a case of a large ABC occurring in a 6-year-old boy who had underwent a segmental resection of mandible. Reconstruction was done in 2 steps-first involving plating done during the resection. After 3 months, a split rib graft and rhBMP-2 was placed inside the defect. Follow up for this case for a year is being presented.

Case report

A 6-year-old child reported to my hospital for pain in the left angle of the mandible. The physical examination showed pain and an expansion of the outer cortex at the left posterior part of mandible. In the orthopantomogram a unilocular radiolucent lesion 6 cm in diameter at its maximum extension was observed. The CT scan report revealed a cystic lesion at the left body of the mandible of 6×1.8 cm extending till the

Fig. 1 CT scan axial view showing the anteroposterior and bucco-lingual extent of the unilocular radiolucent lesion

Fig. 3 Second stage of reconstruction showing the rhBMP-2 being packed into the defect

Fig. 5 Orthopantomogram showing split rib graft in position - 5th month postoperative showing vertical height of regenerate

symphysis. Bone erosion was observed in the buccal aspect (Fig. 1).

Incisional biopsy from the buccal aspect was performed. The histopathological report was suggestive of an ABC. Segmental resection of the mandible was planned under general anaesthesia after adequate preparation. Complete excision of the lesion was performed through a submandibular approach. Thread lock titanium reconstruction with thread lock screws were used to reconstruct the defect (Fig. 2). After achieving hemostasis, the flap was repositioned and sutured. Prophylactic antibiotic was administered as well as NSAIDS and corticosteroids on the following days.

Histopathological analysis of excisional specimen confirmed the diagnosis of ABC. After 3 months wait and watch period, surgical defect closure was performed. A regular split rib graft, harvested from the 6th rib, was placed. 8.4mg of 1.5 mg/cubic cms of freeze dried rhBMP-2 was reconstituted to 5.6 cubic cms and bound to 2.54 cmsx5.08 cms of Absorbable

Fig. 2 Orthopantomogram showing reconstruction plate bridging the defect

Fig. 4 Orthopantomogram showing split rib graft in position - immediate postoperative

Fig. 6 3D CT scan view of the mandible - coronal view showing the closure of the mandibular defect and the width of the regenerate

Collagen Sponge (ACS) as bioactive carrier and prepared as per manufacturer's instruction and packed into the defect along with the graft. The defect was closed as per regular protocol and no drains were placed (Figs. 3 and 4).

Postoperatively, patient developed more significant swelling and edema than is usually observed with an autogenous free bone graft. Patient was discharged on the 7th postoperative day after the swelling subsided. Patient was kept on observation and radiographs repeated once in a month.

Follow up

Subsequent visit radiographs revealed gradual resorption of the rib bone graft placed in the defect and gradual increase in height of the mandible at the site of defect was observed (Figs. 5 and 6). At the end of the 6th month, a 3D CT scan was taken to check the length, breadth and continuity of the bone formation in defect (Fig. 7). It revealed that the defect was bridged and the thickness and breadth of the

reconstructed segment of the mandible approximately resembled that of the normal, contralateral side, the height at the center being 13.4mm, and breadth being 9.3 mm. Coronal, axial and sagittal sections revealed homogenous bone formation.

Discussion

Mandibular reconstruction after resection of tumour has yet to find a universally endorsed procedure. There are many procedures described in literature that are used to fill the defect including the simple bone graft with or without a myocutaneous flap, Pedicled osteo(-myo)-cutaneous flap and the complex vascularised free flap [4]. The type of graft chosen is guided by the age of patient, site, size and shape of the defect. Reconstruction of mandibular defects requires grafts of sufficient length to achieve symmetry and correct shape [5]. Autogenous bone grafting for reconstruction of craniofacial defects is limited by resorption of grafted bone, potential donor site morbidity, and, at times, insufficient quantities of donor bone that matches the structural and functional qualities of the defect. Age of the patient becomes a single most determinant factor, as the donor site and recipient site growth is dependent on the outcome of the surgery. In a young age individual, surgical defect at the donor site could significantly alter the growth pattern. Homologous and heterologous bone grafts carry the risks of disease transmission, variable resorption, and potential activation of the host immune system. Although vascularized bone grafts carry less risk of resorption than free bone grafts and enable the transfer of larger quantities of tissue, they require increased technical expertise and additional surgical time and cannot be routinely employed for patients in younger age groups [5].

Reports of successful reconstruction of major mandibular defects have been earlier achieved using a BMP bioimplant consisting of recombinant BMP-7. The outcome of this surgery was comparable with conventional bone grafting in terms of function and esthetics. In addition, this procedure saved costs as a result of decreased operating room time and length of hospital stay [6]. This study was conducted on patients belonging to age group of 18 - 61 years and not on children. The procedure has also employed demineralised bone matrix in a reverse phase medium that is analogous to the split rib graft. Moreover the split rib graft contains a

lot of progenitor cells, which will initiate the bone formation at a short span of time, as early as 6 months whereas it has took up to a year to manifest with BMP7 as in a study by Clokie CML et al., 2008 [6]. It is also to be noted that BMP7 plays a role in conversion of osteoprogenitor cells to osteoblasts whereas BMP2 facilitates stem cell differentiation as well as Osteoblast progenitor differentiation [7].

Though rhBMP-2 are produced successfully since 1988, the Food and Drug Administration, USA has approved this material 'as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge defects associated with extraction sockets' only in 2007, its use in the present case constituted an off-label use [8]. Similar reports of safe off-label use have been reported in Maxillofacial Surgery literature. Similarly, safe off-label use of rhBMP-2 in 6 to 18 years old is also found in literature [8,9]. The diffuse soft tissue swelling in the postoperative period at the surgical site is not unusual with rhBMP-2 use and the cause of this phenomenon is unknown [10]. However it is believed that an exaggerated inflammatory reaction is likely responsible for both the success in promoting bone formation as well as the adverse effect of soft-tissue swelling. This may very well be a dose-dependent phenomenon that still needs to be investigated for future use of rhBMP-2 [10].

Combination of bone graft and rhBMP-2 have been reported in recent surgical literature for cranio-vertebral fusion as a treatment modality in craniovertebral instability in a case of Down's syndrome, a first of its kind in a 4 month old boy [11]. Earlier animal spine models have proved the efficacy of rhBMP-2, and resulting in a significantly increased prevalence and quality of the spinal fusion after thoracoscopically assisted anterior arthrodesis and instrumentation in an animal model compared with that in the other treatment groups (animals treated with autologous rib graft or autologous iliac crest graft composite sponge carrier alone) and in the controls (received no graft material) [12]. Recent literature on BMPs reveals that reconstructive surgery has been successfully performed for large jaw defects arising as a result of tumor resection. The jaws were stabilized with bone plates or titanium mesh and treated with rhBMP-2 combined with freeze dried demineralized or mineralized particulate bone [13]. Veterinary literature reports of cases where large mandibular defect has been

Picture 1 Flow chart depicting the probable course of events from surgery to healing

reconstructed using rhBMP-2 with plates holding mandible in position [14].

In the present case, rib graft was favored as the donor site morbidity is less as the bone recovers by creeping substitution in a young individual and lacks the pain and decreased postoperative mobility associated with iliac crest harvesting [4,15]. When the superficial periosteum of such a graft is preserved, osteogenesis can begin early, aided by the differentiation into osteoblasts and osteoclasts of cells in the surrounding mandible and soft tissues [16]. When signal inductors such as BMP4 are adjacent, the deposition of bone begins earlier than anticipated.

Carter TG et al. [8] reported 5 cases of mandibular bone defects treated with tissue engineered bone grafts using rhBMP-2 with or without bone grafts. Of these 5 cases, 2 cases were reported as failure. Of these failures, one case was treated using only rhBMP-2 and the other was a case of long standing refractory osteomyelitis treated using autogenous bone marrow aspirate and allogenic cancellous bone with rhBMP-2. The subsequent corticocancellous graft was also reported as slow to heal. Of the three successful cases, 2 cases were treated with autogenous bone marrow aspirate and allogenic cancellous bone with rhBMP-2 and 1 case of bilateral dentigerous cyst; enucleation were performed and bony cavities were treated with rhBMP-2 and microfibrillar collagen. All these cases were aged between 41–81 years of age. However our present case is a 6 year old male child in whom use of rhBMP-2 and split rib graft was employed together, 3 months after

initial surgery, with successful growth of bone in the mandible.

Although spontaneous mandibular bone regeneration is uncommon, rare occurrence, commonly reported among children in English literature. The intact periosteum could serve as a source of osteogenic tissue and mandibular stabilisation as cited by Pramono DC, 2004 [16]. However in our present case, the resection was performed with the attached periosteum. Also a gap of little more than 3 month existed between resection and reconstruction. There were no evidence of any regeneration phenomenon taking place, neither in imaging studies nor during surgical exploration during reconstruction and hence this phenomenon could be ruled out.

Reports of large mandibular cystic defects healing to near perfection using rhBMP-2 are found in literature [3,15]. This present case is unique because it has combined conventional split rib graft with the newer rhBMP-2 material. In the present case, probably, the ACS served as a scaffold upon which split rib graft supplied the undifferentiated mesenchymal cells (progenitor cells) and osteoinductive rhBMP-2 brings in the necessary signals for deposition of newer bone. The patient has tolerated and accepted the rhBMP-2 without complications. The formation of new osteoid areas is confirmed as evidenced by successive radiographs. The application of the rib graft with marrow and rhBMP-2 has accelerated the deposition of new bone leading to a complete healing of the defect with rapid growth leading to

establishment of lost anatomical continuity of the mandible. Reports of superior performance of rhBMP-2 combined with bone marrow in comparison with each component alone strongly support a biologic synergism between both these entities [17]. This logic when applied to clinical situation fetches quicker result as observed in present case. This case shows the clinical importance of establishing operative site proximity for the osteoinductive factors (rhBMP-2) and responding progenitor cells (Rib graft). The probable events that has followed the surgery has been depicted in the flow-chart.

The therapeutic outcome of rhBMP-2 depends on quantity, concentration, and time of application of rhBMP-2 [8]. ACS acts as an appropriate carrier for the delivery, retention, and release of BMPs at the site of defect. Furthermore, maintenance of space for bone in-growth is essential as compression of this may impede the normal bone formation [8]. In the present case, 8.4mg of rhBMP-2 reconstituted to 5.6 cubic cms, provided the osteoinduction, the 2.54 cms X 5.08 cms of ACS provided the essential space maintenance with an autogenic split rib graft acting as an osteoconductive bone scaffold may have produced the successful outcome.

Future treatment plan includes removal of the reconstruction plate and provisional restoration using conventional removable partial dentures, till the maximum growth spurt. Once the growth is completed, implant supported prosthesis may be provided. Long term follow up will only indicate the normal growth pattern and the functional ability of the new bone that is been formed.

Conclusion

Bony reconstruction for oral and maxillofacial rehabilitation has significantly advanced over the past decade with improved understanding of bone healing and the discovery of growth-inducing factors, such as BMPs. Tissue engineered grafts are probably the future, aiming to amend imperfections of previous methods. As technologies that facilitate the delivery of these agents, becomes refined

and defined, making these techniques more clinically manageable, cost effective with accelerated healing and defect shrinkage, it is expected to have a significant impact on the future of reconstructive surgery. Combination of traditional surgical methods with newer materials such as rhBMP-2 will enhance the rate of success as well as the post – surgical quality of life of the patient at a much subsided cost. Probably such tissue engineered osteoinductive grafts when added as an additive to the conventional grafts that are osteoconductive scaffolds, will likely be needed to achieve predictable reconstruction of many orofacial bony defects in future.

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Source of Support: Nil, **Conflict of interest:** None declared.