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## Mandible reconstruction using rhBMP-2: Case report and literature review

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Recombinant human bone morphogenetic protein-type 2 (rhBMP-2) is used in oral and maxillofacial procedures due to its endochondral bone formation capacity, and this is also the reason for its use off-label in jaw reconstruction. This study reports a case of an extensive central giant cell lesion along the mandibular body and symphysis. Treatment consisted of enu-

cleation and curettage followed by off-label use of rhBMP-2 associated with bovine bone xenograft. The literature concerning mandibular reconstruction using rhBMP-2 was also reviewed. (*Quintessence Int* 2014;10:869–874; doi: 10.3290/j.qi.a32639)

**Key words:** bone graft, bone morphogenetic protein-type 2, mandibular reconstruction, xenograft

Mandibular resections caused by extensive and aggressive injuries can lead to large local defects that require reconstructive techniques, such as autograft bone graft, microvascularized graft, and off-label graft with recombinant human bone morphogenetic protein (rhBMP). The use of rhBMP is an option for reconstruction of large jaw bone defects because of its lower morbidity compared to other methods.<sup>1,2</sup>

Bone morphogenetic protein (BMP) is a member of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily. Approximately 20 members of the BMP supergroup have been identified, though osteoinduction is medi-

ated only by BMP-2 to BMP-7 and by BMP-9. BMP is naturally obtained by purification of demineralized bone matrix, although in small quantities. In contrast, molecular biology techniques and recombinant genetic technology can produce a large and uniform supply of BMP.

rhBMP-2 is the most studied BMP for oral and maxillofacial application. Its placement stimulates a series of events characteristic of endochondral bone formation: recruitment of endochondral cells, their differentiation into chondrocytes, chondrocyte hypertrophy, calcification of cartilage matrix, osteoblast differentiation, bone formation, and incidental remodeling of neoformed bone and creation of bone marrow.<sup>3-8</sup> The use of BMP-2 to repair human mandibular defects began in 2001 with Moghadam et al,<sup>9</sup> who obtained new formed bone in a 6-cm jaw defect, and several other off-label cases reported osteoinductive properties of rhBMP-2 for mandible reconstruction.<sup>2,8,10-20</sup>

The present study aimed to:

- report a case of large central giant cell lesion (CGCL) along the mandibular body and symphysis, treated

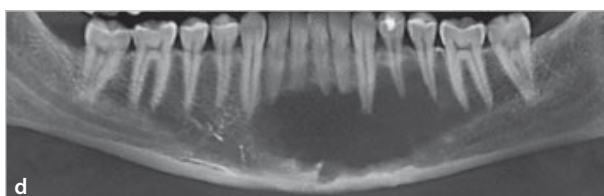
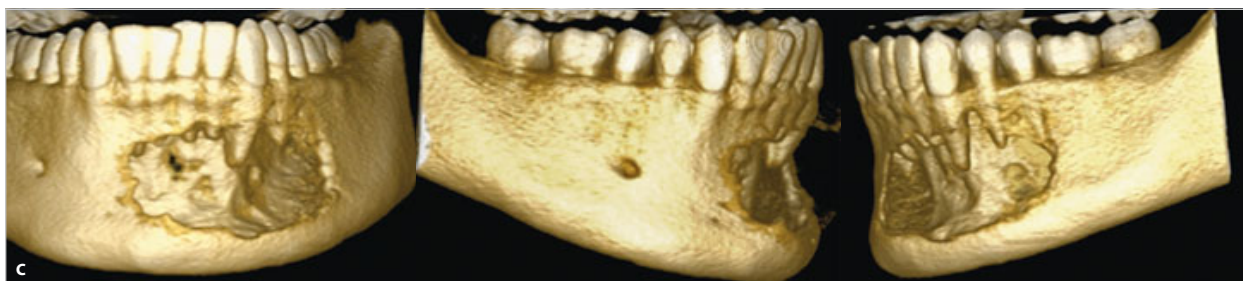
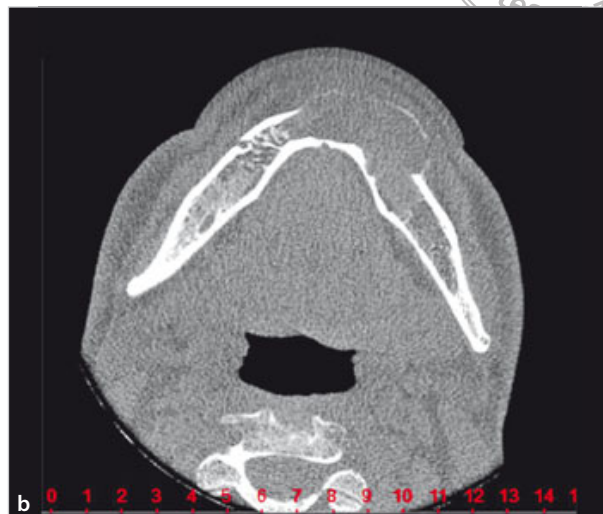
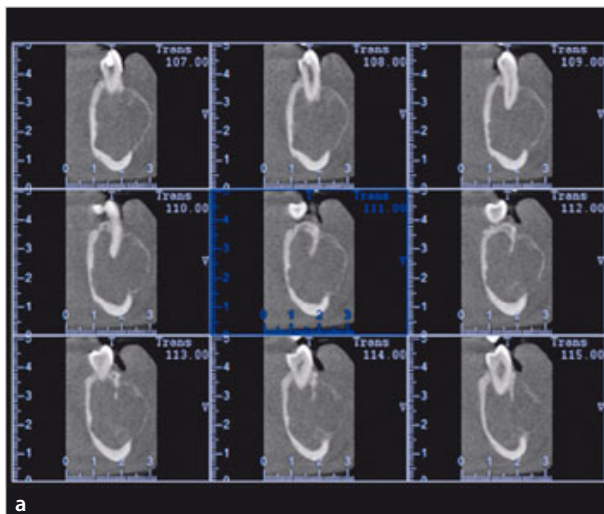
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**Figs 1a to 1d** CBCT-reformatted images of parasagittal (a) and axial (b) planes show expansion and thinning of the cortical bone in the left mandibular body and symphysis. (c) 3D reconstruction shows bone loss on vestibular bone wall. (d) Panoramic radiography shows unilocular hypodense area with scalloped limits from mandibular right first molar to left first molar.

with enucleation and curettage associated with off-label use of rhBMP-2 graft and bovine bone xenograft

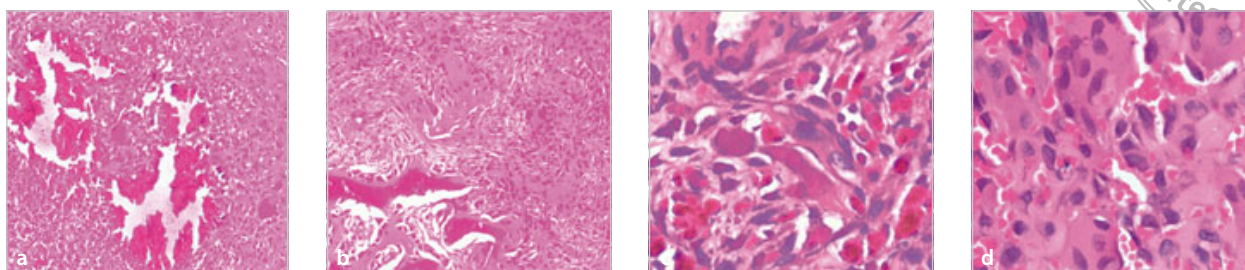
- review the literature concerning mandibular reconstruction using rhBMP-2 graft.

### CASE REPORT

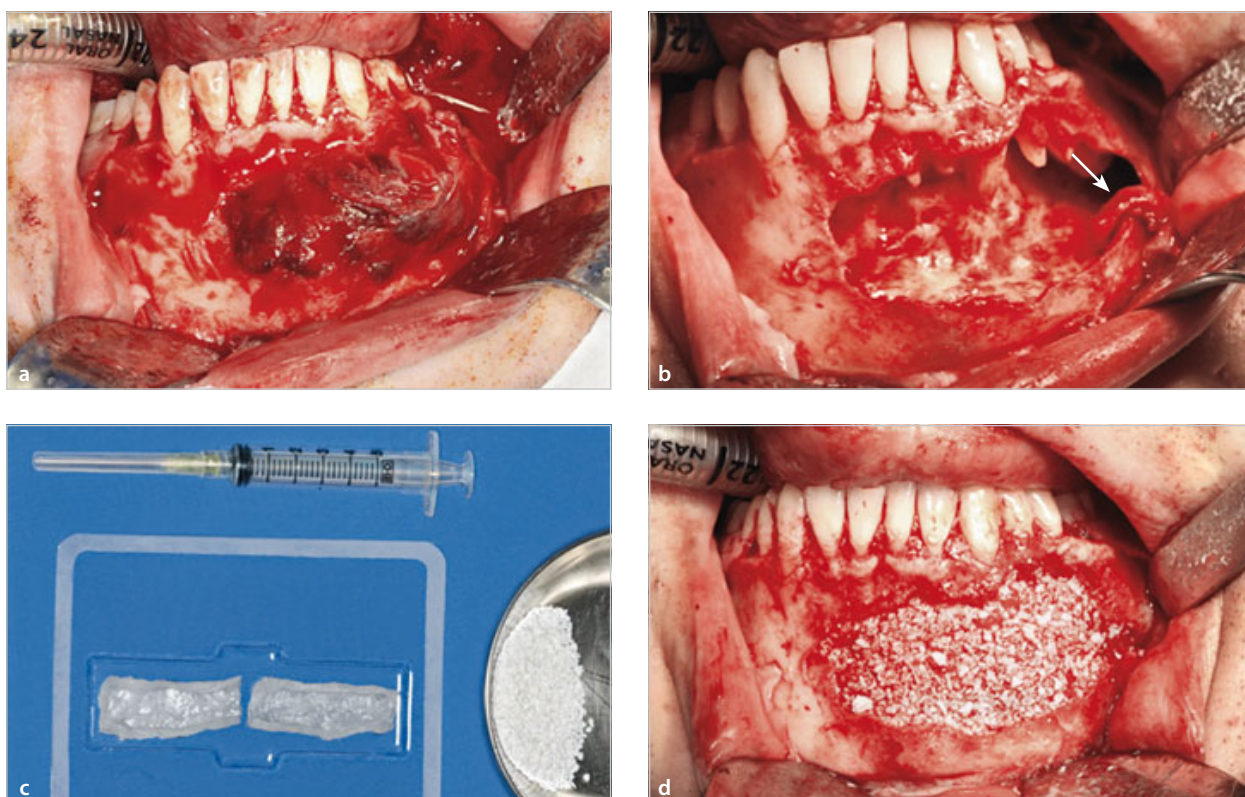
A 26-year old Caucasian male patient presented persistent swelling in the left mandibular body and symphysis region, with mild sensitivity and intact mucosa. Cone beam computed tomography (CBCT) revealed a unilocular hypodense lesion extending from distal of the mandibular right canine to distal of the mandibular

left second molar and to the lower edge of the jaw, measuring approximately 5 cm (Fig 1).

Biopsy followed by microscopic examination revealed osteoclastic giant cell proliferation associated with trabecular bone interspersed with hemosiderin-laden macrophages and spindle cells proliferation, consistent with CGCL (Fig 2). Blood test examining levels of triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), calcium, and phosphorus ruled out hyperparathyroidism. Treatment consisted of enucleation and curettage, as the bone plate at the lingual aspect of the defect was intact, associated with rhBMP-2 graft because of the large size of the defect. All teeth alongside the lesion



**Figs 2a to 2d** Microscopic examination confirmed diagnosis of CGCL. (a) Reactive bone and giant cells surrounded by dense connective stroma and hemorrhagic foci. (b) Osteoid and hemorrhagic foci in connective stroma. (c) Hemosiderin and giant cells in connective stroma. (d) Giant cells and hemorrhagic foci in connective stroma.



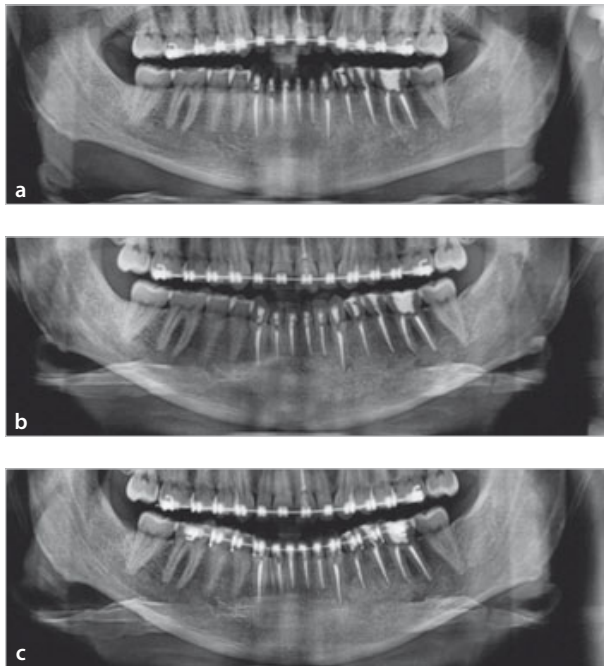
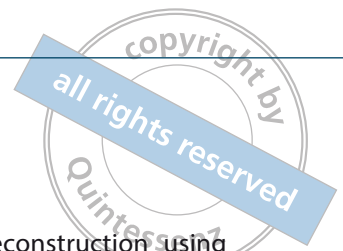
**Figs 3a to 3d** Surgical procedures. (a) Access to the lesion shows vestibular bone loss. (b) Enucleation and curettage followed by root scaling of the teeth involved by the lesion; the arrow shows preservation of mental nerve. (c) rhBMP-2 material (Infuse, Medtronic Sofamor Danek, 1.5 mg/mL). (d) Cavity is filled with 4.2 mg Infuse and 3.5 g Bio-Oss.

received endodontic treatment before surgery, as their neurovascular bundle was impaired.

Surgery was performed under general anesthesia. Intraoral access consisted of an incision made linearly in the gingival sulcus, from mesial of the mandibular right second premolar to mesial of the mandibular left first molar. At these end points, relaxing incisions were made for full mucoperiosteal detachment. Curettage

was followed by bone graft using 4.2 mg rhBMP-2 (Infuse, Medtronic Sofamor Danek) in absorbable collagen sponge (1.5 mg/mL), associated with 3.5 g bovine bone xenograft (Bio-Oss, Geistlich Biomaterials) (Fig 3).

Follow-up consisted of weekly appointments within the first postsurgical month, then at the end of the third and the sixth months and finally at the end of the first year. At the sixth month, neoformed bone and no



**Figs 4a to 4c** Postoperative panoramic radiographs at (a) 6 months, (b) 1 year, and (c) 2 years show endodontic treatment of the teeth involved by the lesion and satisfactory bone neoformation in the area.

signs of recurrence were observed, signs confirmed at the 2-year follow-up (Fig 4).

## LITERATURE REVIEW AND DISCUSSION

The first reported human application of native BMP-2 in mandible was reported by Moghadam et al<sup>9</sup> in 2001, who reconstructed a 6-cm defect and showed osteogenesis 9 months after the procedure. Since then, some studies on human mandibular reconstruction using rhBMP-2 have been carried out, the second object of investigation of the present study.

A review of the literature on mandibular reconstruction using rhBMP-2 used two inclusion criteria: studies in humans and articles published in English. The database sources were Medline and Lilacs and the searching terms were rhBMP-2 AND mandible AND reconstruction. Thirteen relevant articles were found, their methods and results are displayed in Table 1, along with those of the present study.

Of the total 45 cases of reconstruction using rhBMP-2 in the mandible, the most used surgical procedure was resection, and bone defect sizes ranged from 3.5 cm to 12 cm. Follow-up varied between 5 and 51 months, and newly formed bone was observed in 84.4% of the cases, whereas the remaining 15.6% showed insufficient bone formation or failure in bone regeneration. Concerning types of graft, in 18 cases rhBMP-2 was not associated with any other material; in 10 cases it was associated with allograft bone; in eight with autograft bone and/or autogenous bone marrow; in four with matrix of  $\beta$ -tricalcium phosphate; in two with hydroxyapatite-calcium triphosphate; in one case with platelet-rich plasma; and in one case with microfibrillar collagen.

Although the studies showed that resection was the most used procedure, the present case opted for enucleation and curettage, as the surgical team had previously been successful with the technique and the tumor showed no infiltration in the lingual bone plate. In addition, reconstruction plates were not needed, which helps to avoid infection or long-term replacement. Despite the use of a conservative procedure, the surgery caused a major bone defect. Given that iliac crest autograft and microvascularized graft can cause morbidity and pain, and that the resulting graft often lacks quality and height, the team considered the off-label use of rhBMP-2.<sup>2</sup> The patient was thoroughly informed about the treatment options and chose to have bovine bone xenograft associated with off-label use of rhBMP-2, making a fully informed decision based on the capacity of rhBMP-2 to regenerate bone defects that have three remaining walls.<sup>16</sup> Also, maintenance of space with increase in volume was required, and stability of the graft lay with the insertion of rhBMP-2 associated with bovine bone xenograft, which provides better regeneration of bone defect.<sup>21,22</sup> The patient was submitted to this procedure after receiving root canal treatment in all the teeth associated with the lesion due to loss of vitality.

The disadvantage of rhBMP-2 is its high cost. However, once using the material, there is no need to collect autogenous bone and, as a consequence, this



**Table 1** Review of literature of studies using rhBMP-2 to reconstruct human mandible

Study	No. of patients	Lesion	Type of surgery	Defect size (cm)	Associated graft	Results	Follow-up (months)
Present study	1	Central giant cell lesion	Enucleation and curettage	5	Bovine bone xenograft	Bone neoformation	24
Desai et al <sup>10</sup>	6	Infection due to nontreated mandibular fracture	Reconstruction	5	Allograft	Good healing	12
		Giant-cell reparative granuloma	Resection	3.5	Matrix of $\beta$ -tricalcium phosphate and platysma flap	Good healing	28
		Recurrent ameloblastoma	Resection	12	Allograft and matrix of $\beta$ -tricalcium phosphate	Poor healing	36
		Ameloblastoma	Resection	11	Allograft	Good healing	39
		Odontogenic keratocyst	Resection	10	Matrix of $\beta$ -tricalcium phosphate	Good healing	50
		Odontogenic keratocyst	Resection	6	Matrix of $\beta$ -tricalcium phosphate	Good healing	51
Cicciù et al <sup>11</sup>	1	Dentinogenic ghost cell tumor	Resection	NR	Allograft	Bone neoformation	9
Sweeny et al <sup>12</sup>	8	Osteoradionecrosis	Resection	Mean 5.9	No associations	Malunion in one patient	Mean > 12
Zétola et al <sup>13</sup>	1	Ameloblastoma	Resection	NR	Autograft and hydroxyapatite-calcium triphosphate	Bone neoformation	7
Herford & Cicciù <sup>2</sup>	1	Central giant cell lesion	Resection	NR	Autograft	Bone neoformation	6
Glied & Kraut <sup>8</sup>	3	Ameloblastoma	Resection	8	Allograft	Little bone neoformation	12
		Osteomyelitis		3.6			
		Ameloblastoma		4.5			
Balaji <sup>14</sup>	1	Aneurysmal bone cyst	Resection	6	Autograft	Bone neoformation	6
Schuckert et al <sup>15</sup>	1	Peri-implantitis	Implant removal	NR	Platelet-rich plasma	Bone neoformation	6
Carter et al <sup>16</sup>	5	Osteomyelitis	Resection	NR	Allograft and autogenous bone marrow	Insufficient bone formation	5
		Dentigerous cyst	Tooth extraction, enucleation, and curettage		Microfibrillar collagen	Bone neoformation	6
		Physical assault	Reduction and fixation of fracture		No associations	Insufficient bone formation	8
		Car crash	Mandibular reconstruction		Allograft and autogenous bone marrow	Bone neoformation	18
		Physical assault	Resection		Allograft and autogenous bone marrow	Bone neoformation	22
*Herford & Boyne <sup>17</sup>	14	Aggressive juvenile ossifying fibroma	Resection	Mean 6.1	No associations	Bone neoformation	6
		Osteonecrosis due to bisphosphonates	Removal of necrotic tissue			Complete bone healing	6
		Ameloblastoma	Resection			Bone neoformation	8
		Ameloblastoma	Resection			Bone neoformation	8
Herford et al <sup>18</sup>	2	Firearm related injury	Reconstruction	NR	Autograft; Cortical-medullary	Bone neoformation	NR
		Alveolar ridge atrophy	Reconstruction	NR	No associations	Bone neoformation	8
Chao et al <sup>19</sup>	1	Juvenile ossifying fibroma	Resection	12	Tricalcium phosphate and hydroxyapatite	Bone neoformation	9
Carstens et al <sup>20</sup>	1	Facial cleft	Reconstruction	NR	No associations	Bone neoformation	27

\*The authors mention 14 cases, although they discuss only four of them. NR, not reported.



reduces the risk of morbidity, of time spent in the operating room, and of hospitalization. As less time in hospital reduces the general cost of the procedure, the use of rhBMP-2 might be comparable to the cost of more traditional methods. Comparative studies between rhBMP-2 and autogenous graft are needed to determine whether both techniques have similar cost-benefit.<sup>16</sup>

In the present case, 2-year follow-up confirmed total remission of the lesion and bone formation, which had been first observed 6 months after surgery. Thus, treatment using rhBMP-2 was efficient and useful for mandibular bone reconstruction caused by CGCL, with no morbidity to the patient, and local rehabilitation in a considerably short time. Therefore, the present study reinforces the feasibility of a more conservative approach to certain types of aggressive tumors, given that enucleation and vigorous curettage were enough to resolve a case of CGCL. This procedure allowed the arrangement of a framework that favored bone formation, preservation of the teeth, no evidence of recurrence, and showed noticeable decrease of morbidity.

Though proved a valuable material in the present study, the use of rhBMP-2 for human mandible reconstruction is not extensively discussed in the literature, as demonstrated by the few studies found on the issue, only 13. In addition, out of these 13 studies, only eight used rhBMP-2 in the treatment of tumors. Moreover, to the best of our knowledge, the present study is the only one that associates rhBMP-2 with bovine bone xenograft for mandibular reconstruction in humans. We believe that the graft functioned as a space-maintainer, so that BMP was able to contribute to bone formation. It can also be supposed that if the bovine bone xenograft were used alone, the rehabilitation would be delayed and less predictable. It reinforces the role of the rhBMP-2 implant, which provides significant reduction of secondary interventions, accelerates wound healing by stimulating the production of bone, and reduces infection for the treatment of bony defects, delayed union, and nonunion.

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