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Distraction of rhBMP-2-Generated Mandible: How Stable Is the Engineered Bone in Response to Subsequent Surgeries?

William K. Tom, DDS, MS, Martin Chin, DDS,† Theodore Ng, DDS,‡ Slim Bouchoucha, DDS,§ and Michael Carstens, MD‖*

Congenital craniofacial abnormalities and pediatric maxillofacial trauma present special management challenges for the reconstructive surgeon. The presenting structures of a child are naturally quite small. Many of the conditions require multiple staged surgeries throughout the lifetime of the patient to compensate for continued growth. If reconstruction of the pediatric patient is carried out, this will only provide a temporary solution, as children outgrow their correction through maturation and normal development. One alternative to carrying out multiple surgeries is to wait for skeletal maturity. However, the negative psychologic and social impact of the deformity must be taken into consideration when delaying surgery.

In current practice, a reconstructive surgeon replaces missing bone with harvested autogenous bone to help provide for structural support and strength. The problem with harvesting bone in a child is the limited amount of available bone, the creation of a second surgical site in the patient, the additional time for rehabilitation, and the increase in morbidity. Further, when future surgeries are necessary the available bone volume is compromised by the prior harvesting. Some patients simply run out of viable sites from which bone can be obtained. rhBMP-2 technology is a new and exciting clinical solution that may alleviate the need for harvesting the patient's own bone. Studies have shown that new bone can be grown predictability.[1]

In the studies where INFUSE Bone Graft (Medtronic, Memphis, TN) was used as a bone graft material before placement of dental implants, the bone formed by rhBMP-2/ACS was able to successfully accept and support implants.[2] It behaved like normal bone and continued to become more dense in response to loads, osseointegrated with the implants, and had equivalent functional loading rates to the autograft control group. Histologic samples provided further evidence of this normal bone formation. No studies have been undertaken, however, to specifically evaluate the response of this regenerated bone to subsequent surgery for distraction.

Although there has been concern about the potential for antibody formation, there has been little antibody response when measured in clinical trials (0.7% to 6%), and the antibody response was transitory and had no clinical effects. In a recent review assessing patients who received 2 separate exposures to rhBMP-2, no clinical complications or effects were reported although antibodies were not measured[3] (Dr Y.A. Cillo, personal communication, April 2007).

This article presents a case of mandibular bone that has been generated entirely with rhBMP-2. This mandible has subsequently been osteotomized and distracted again with consolidation and growth of this bone.

Report of a Case

The patient is a female born with a Tessier VII facial cleft and left mandibular hypoplasia (Figs 1, 2). There is no history of congenital abnormalities on either side of the family. At 2 years of age the patient underwent distraction of the rudimentary left mandible (Fig 3). Two months later, radiographs showed a 25-mm nonunion so the distracted chamber was re-entered (Fig 4). This distracted chamber was hypothesized to be an area with a fabricated functional matrix. The matrix

*Private Practice, Healdsburg, CA.

†Attending Surgeon, California Pacific Medical Center, San Francisco, CA.

‡Private Practice, Oakland, CA.

§Private Practice, Sonora, CA.

‖Associate Professor of Plastic Surgery, Director of Craniofacial Surgery, St Louis University, St Louis, MO.

Address correspondence and reprint requests to Dr Tom: Oral and Maxillofacial Surgery, 445 March Avenue, Suite B, Healdsburg, CA 95448; e-mail: wktomomfs@yahoo.com

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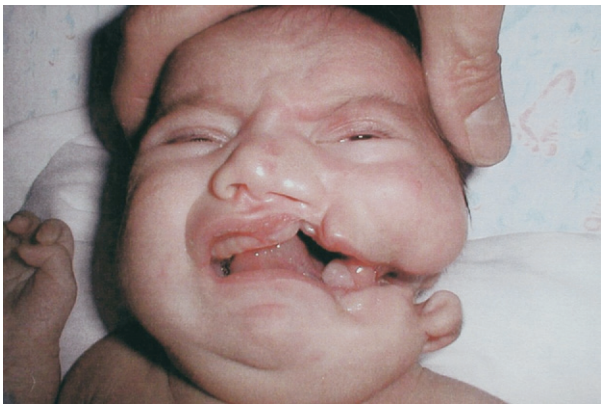

FIGURE 1. Anteroposterior view of facial cleft at birth. Note the incomplete left cleft lip and palate and lateral cleft (Tessier VII type). Reprinted with permission from Carstens et al.[4]

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unfortunately lacked the stimulus for bone formation, therefore an rhBMP-2/collagen sponge was inserted to initiate the in situ osteogenesis process (Fig 5). This resulted in complete consolidation of the 25-mm space.

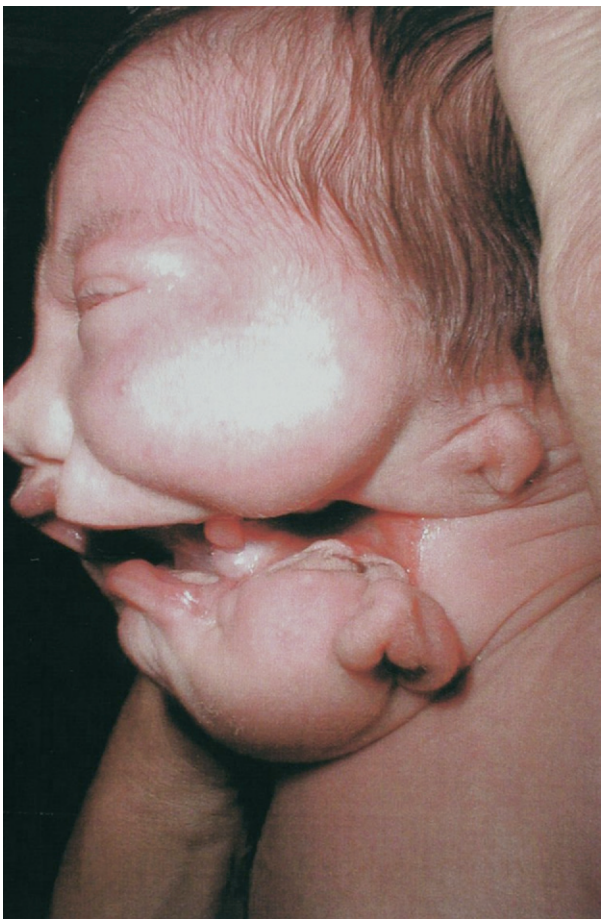

FIGURE 2. Lateral view of the patient at birth. Reprinted with permission from Carstens et al.[4]

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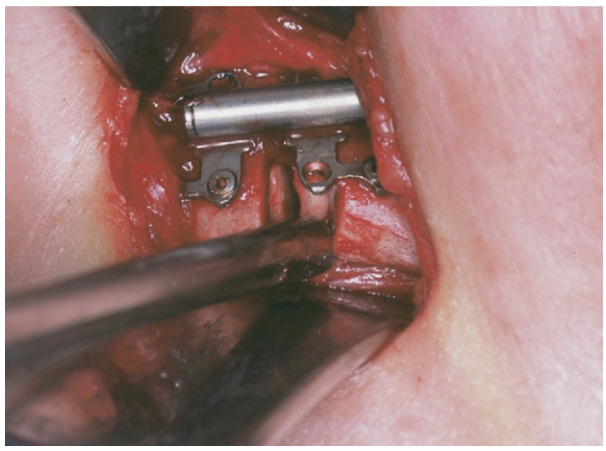

FIGURE 3. Intraoperative view of patient's mandible after the initial osteotomy and placement for the first distractor. Note the bone cut to the placement of the distractor.

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Twenty-five months later the site was re-entered for a second distraction. The patient had outgrown the previous 25-mm correction of the left lower jaw through normal development of the remaining face. The previous distractor was used as a guide to mark the most central portion of the regenerated bone (Fig 6). An osteotomy was placed through the center of the regenerate and a sample of the bone was taken (Fig 7). A new KLS-Martin Zurich mandibular distractor (KLS Martin, Jacksonville, FL) was mounted on the lateral side of the patient's jaw and an rhBMP-2 /collagen sponge was inserted (Fig 8). The right mandible also underwent an osteotomy and placement of a distractor to create bilateral distraction of the lower jaw. The distraction process was completed in a conventional manner. After 20 weeks of consolidation, the sites were re-entered to remove the distractors (Fig 9). At the time of removal, the regener-

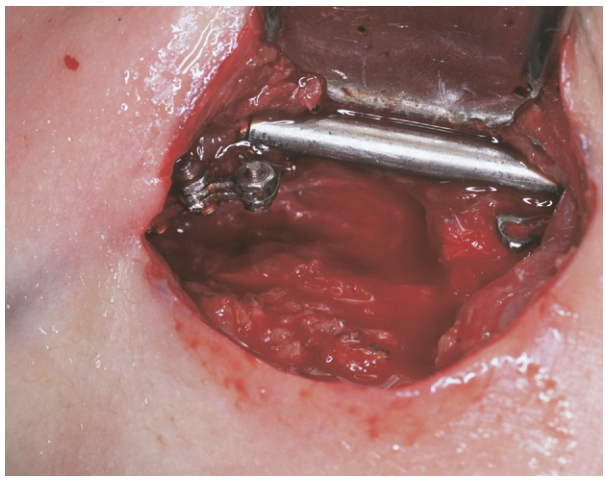

FIGURE 4. Intraoperative view of patient after distraction and reentry of the mandible but before placement of rhBMP-2. Note there is no bone in the distraction chamber. Reprinted with permission from Chin et al.[1]

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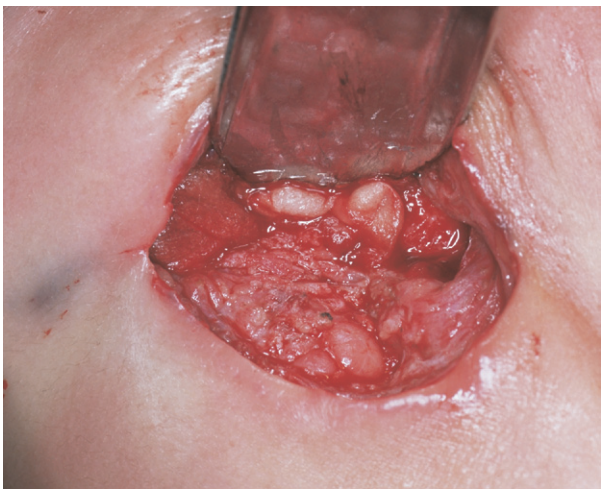

FIGURE 5. Intraoperative view of patient with placement of rhBMP-2 on collagen sponge. Reprinted with permission from Chin et al.[1]

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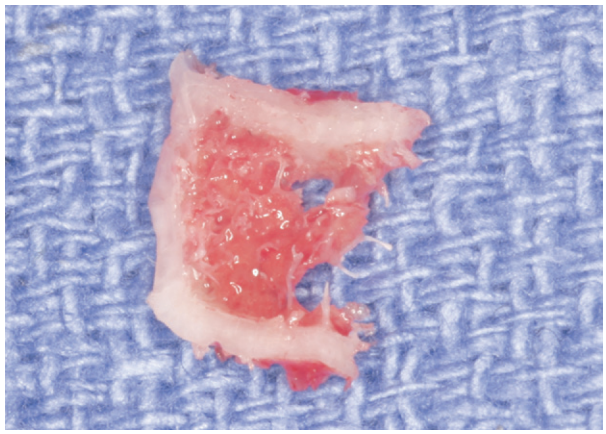

FIGURE 7. Section of bone obtained directly from the middle of the jawbone that was grown entirely from rhBMP-2. Note the distinct amount of cortical and cancellous bone. Reprinted with permission from Chin et al.[1]

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ate was verified to be mechanically stable and a trephine biopsy was obtained.

Results

The segment of left mandible constructed from rhBMP-2 was mechanically stable and showed normal histology (Figs 10-13). Figures 10 and 11 are histology of a section of a bone that was generated entirely from the use of rhBMP-2. Figures 12 and 13 represent bone sections that were cut after the rhBMP-2 generated this bone and it underwent a second distraction and application of rhBMP-2. The newly regenerated bone from the second distraction procedure was functionally stable and histologically similar to the original regenerate fabricated with rhBMP-2. The jaw bone that was generated and then redistracted has operated functionally for over 1 year (Figs 14, 15). There is no clinical evidence of any local or systemic effects seen in the patient.

Discussion

Congenital abnormalities present the craniofacial surgeon with many challenges. Similar abnormalities can be treated in different ways. Training philosophies will affect treatment approaches but the goal of the surgeon remains the same: the conversion of an abnormal defect, including soft and hard tissue, to

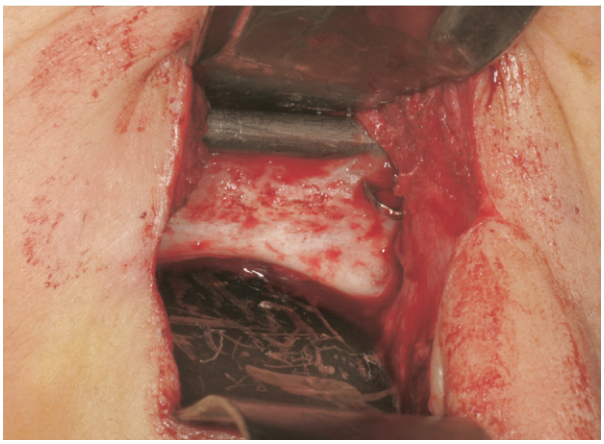

FIGURE 6. Intraoperative view of patient after the rhBMP-2 has stimulated the body to grow bone. Note that the distraction rod is still attached and the bone has formed up to the distractor. Reprinted with permission from Chin et al.[1]

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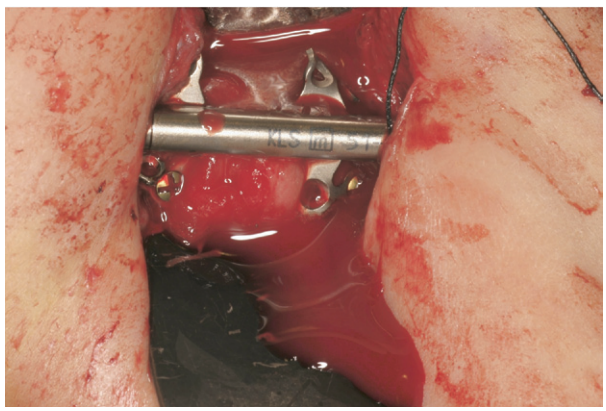

FIGURE 8. Intraoperative view of patient after distraction of the jaw; placement of rhBMP-2; removal of the previous distractor; placement of the new distractor after the second osteotomy; and second installation of rhBMP-2 on a collagen sponge.

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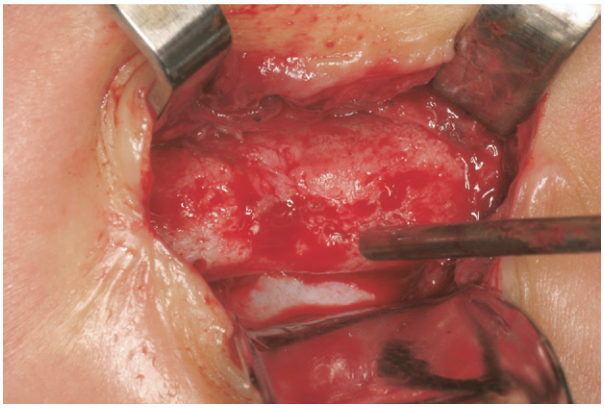

FIGURE 9. Intraoperative view of patient after removal of the second distractor. This is jawbone that was generated entirely by rhBMP-2 and then distracted again with rhBMP-2.

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normal appearance and function. In the past the approach to treating a lateral facial cleft would have been closure of the facial skin around 8 weeks of age and preparing the child for some type of bone grafting procedure in the future. The type of bone graft would involve a rib harvest as well as bone taken from the iliac crest to replace the temporomandibular joint and ascending ramus. However, there is high risk of scarring at the site of facial closure leading to insufficient soft tissue available to cover a large bone graft that is sufficient in replacing the amount of structure missing. Facial structures can undergo significant scarring or breakdown if too much tension or pressure is placed on the tissue from surgeries, leading to long term cosmetic defects. Further, there is a risk of ankylosis of the rib graft to the temporomandibular joint/maxilla region. When a costochondral graft grows, the magnitude and vector of enlargement is unpredictable. The underlying bony structure may not have the available blood supply to grow. As they continue to grow, patients will require additional surgeries in the same areas.

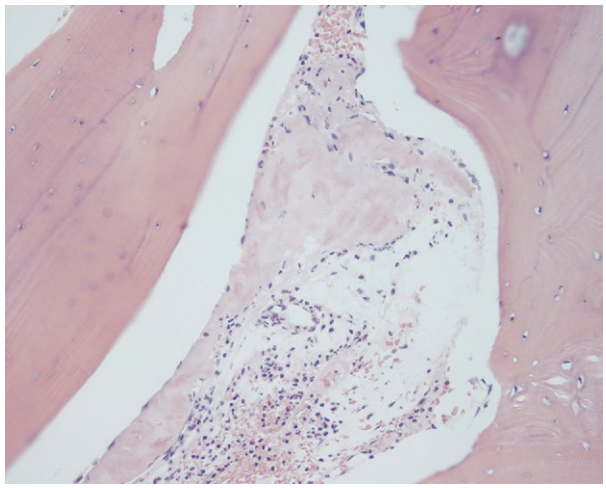

FIGURE 11. High-power view showing bone generated entirely by rhBMP-2. Reprinted with permission from Chin et al.[1]

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Distraction osteogenesis has the advantage of regenerating soft and hard tissues at the same time as enlarging the anatomic complex. Distraction does not generally require the harvesting of bone. This is a significant feature of this surgical technique, as many children do not have a large supply of harvestable bone. Therefore, distraction lessens patient morbidity and decreases hospitalization or postoperative care. Distraction can also provide some control of the mag-

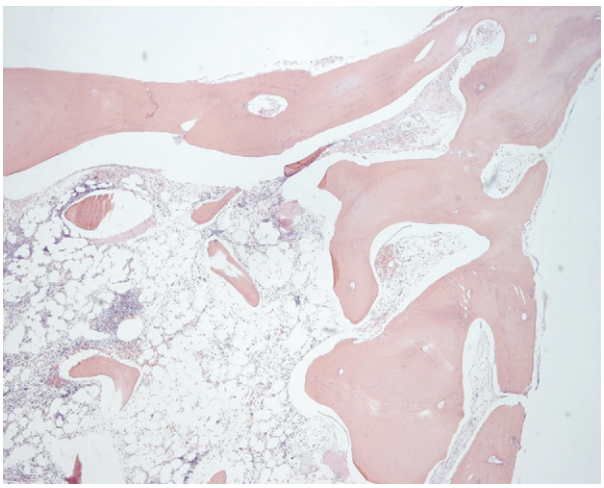

FIGURE 10. Low-power view showing bone generated entirely by rhBMP-2. Reprinted with permission from Chin et al.[1]

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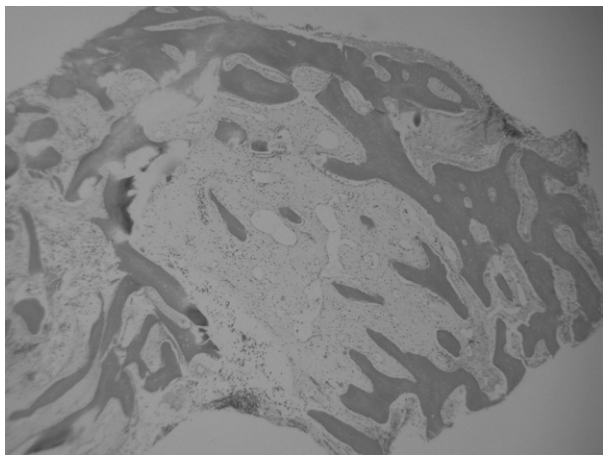

FIGURE 12. Low-power view of rhBMP-2 generated bone after second distraction and second insertion of rhBMP-2.

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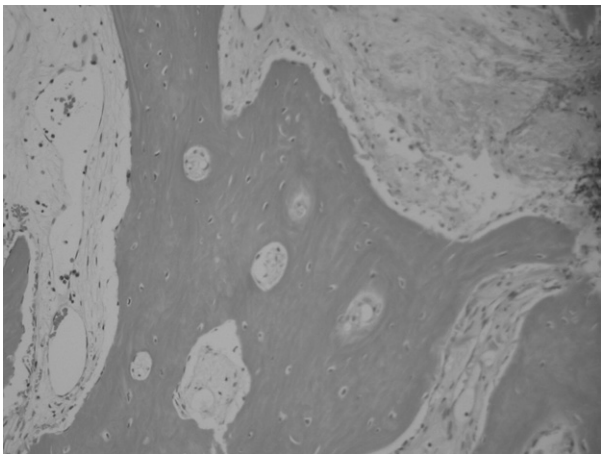

FIGURE 13. High-power view of rhBMP-2 generated bone after second distraction and second insertion of rhBMP-2.

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nitude and vector enlargement depending on the placement of the osteotomy as well as the placement position of the distraction device.

Unfortunately, there are clear limitations in the amount of bone that can be generated through maxillofacial distraction osteogenesis. The quality of the soft tissue at the distraction site may limit the ability of the regeneration chamber to consolidate. Prior surgeries can damage the site and may compromise response to conventional distraction osteogenesis. There are also cases where the deformity is so large that the potential for consolidation and union of the distracted bone is not expected because of the compromise in vasculature, available tissue, or cells.

The treatment approach we used for this unique case was to distract the mandible first. The regenerated mandible would then provide a stable base for the soft tissue of the facial cleft to rest on and be closed without tension. The mandible was initially distracted 25 mm. On entrance into the mandible 2 months later, we found that no bone had formed in the distracted chamber. There was some cartilage-like growth on the medial aspect with granulation tissue throughout the remaining chamber.

The use of recombinant technology allows the patient to form her own de novo bone. The advantage of this emerging molecular therapy is that it is truly osteoinductive. The rhBMP-2 promotes chemotaxis of the mesenchymal stem cells and directs the differentiation of the stem cells to become osteoblasts. The recombinant technology will allow for amplification of the cellular differentiation. The advantage to the patient is a faster consolidation of the bone growth in the deficient area. The mandible was allowed to consolidate and was followed with computed tomography scans and plain films. This newly generated bone proved to be as mechanically stable as the patient's regular bone.

As the patient continued to develop, she outgrew the 25 mm distraction, which had taken place 25 months prior. The patient was now retrognathic again. The patient was taken back to the operating room 25 months after the initial placement of the rhBMP-2. This second surgery consisted of bilateral mandibular osteotomies with placement of bilateral distractors.

On entrance of the first surgical site, the distraction rod was used as a guide to determine the most midportion of the engineered bone. By following the rod, this ensured that the area of bone osteotomy would be bone that was generated entirely from the rhBMP-2. From the lateral and inferior aspect of the mandible an osteotomy was carried out toward the medial and superior aspect of the jawbone. On cutting the cortex and entering the marrow portion of the bone, there was normal bleeding. Attention was paid to ensure that the medial and superior cuts remained within the cancellous portion of the jaw.

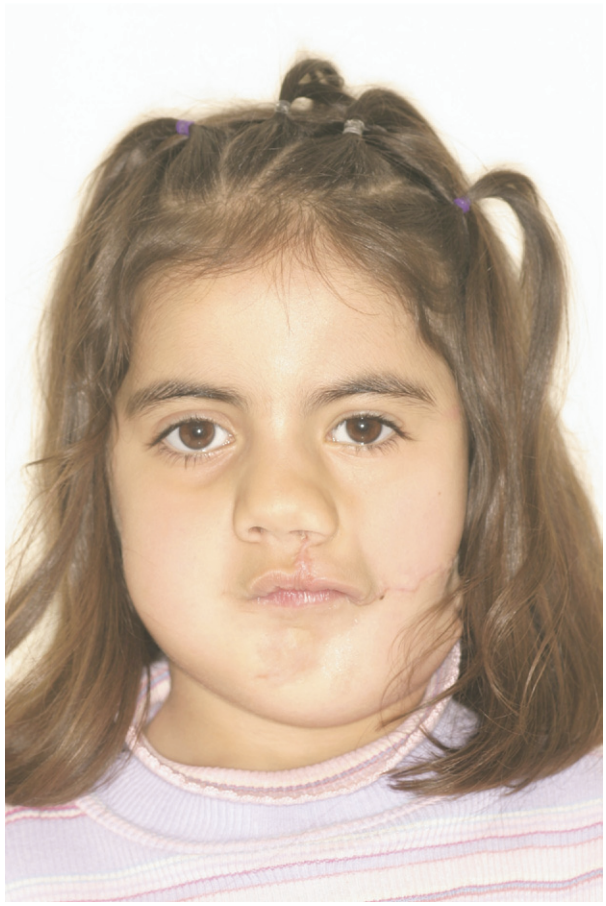

FIGURE 14. Clinical anteroposterior view of patient with mouth at rest. Reprinted with permission from Carstens et al.[4]

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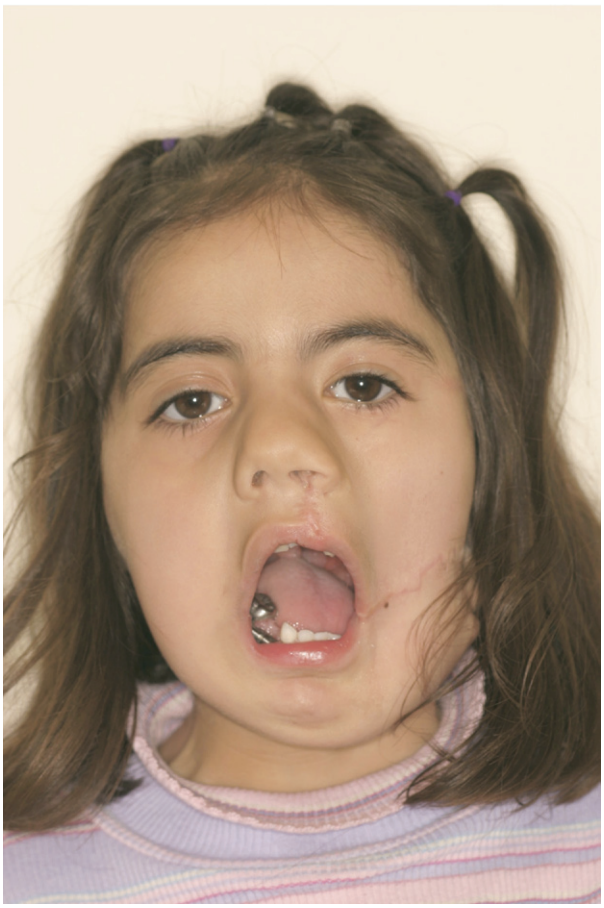

FIGURE 15. Clinical anteroposterior view of patient with her mouth in maximal opening. Note there is no ankylosis. Reprinted with permission from Carstens et al.[4]

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Preservation of the cortical bone on the medial and superior aspect would prevent any injury of the periosteum in these areas. The periosteum is critical in providing the necessary mesenchymal stem cells, which would be induced by the rhBMP-2 to form the newly generated bone. The final medial/superior bone was separated with hand instruments and chisels. Before completion of the osteotomy, a sample of bone was taken (Figs 10, 11).

The bone taken was examined grossly, showing good marrow component encased in cortical bone. The resulting mandibular bone bled on separation, as native bone would, with no significant decrease in density. A new KLS-Martin Zurich mandibular distractor with external activation arm was placed on the left side of the mandible as it had been previously. The distractor was opened to 4 mm. The space created allowed for placement of more rhBMP-2/collagen sponges to assist in early consolidation of the new bone regenerate. The area was then closed in multiple layers.

The native right body of the mandible was not treated previously. Due to the patient's retrognathia, bilateral distraction would be required to be consistent with the growth of her face and for continued symmetrical facial development. The right side was approached via an intraoral incision and a mandibular body osteotomy was carried out. Bony cuts were made similar to the left side except the bone was approached from a lateral/superior direction toward the medial/inferior aspect and a mandibular body osteotomy was carried out. The final cortical bones on the medial and inferior aspects were cut with hand instruments to preserve the periosteal tissue. A KLS-Martin Zurich mandibular distractor with an internal activation arm was placed and opened to 4 mm. An rhBMP-2/collagen sponge was inserted into the distracted space to assist with early consolidation and formation of bone.

The latency period for the distractors on the right and left sides was 5 days, allowing for rest and healing. The distraction rate was 1 mm per day (distracted 15 mm after 15 days). After 20 weeks, the left mandible was reentered and the distractor device removed via the previous extraoral incision. The middle of the distractor rod was again used to determine the most central portion of the regenerated mandible, the position was marked, and the distractor was removed. The regenerate (especially the central portion) was examined clinically and found to be mechanically stable. A trephine bur with copious irrigation was used to take a sample of bone for histological evaluation (Figs 12, 13). The surgical site was copiously irrigated and closed in multiple layers. The right side distractor was removed via an intraoral approach (no biopsy samples were taken). The use of in situ osteogenesis allowed the soft tissue to be enlarged while the bone was consolidating. The technique lowered the risk of wound breakdown and eliminated the need for bone harvesting. As the child continues to mature, more surgery will likely be necessary and we anticipate that the bone regenerate will respond as before to the surgical procedure.

Distraction of the bone segment constructed with rhBMP-2 resulted in rapid consolidation with viable bone. In contrast, prior distraction of the native bone in the same patient resulted in a nonunion. Once the original regenerate had matured, further distraction with the application of rhBMP-2 showed a similar response clinically and histologically. This suggests that segments formed in response to rhBMP-2 may perform more predictably than host bone. When rhBMP-2 was used in a patient that had been exposed previously to the material, osteogenesis resulted. There were no clinical signs that the prior exposure to rhBMP-2 compromised the effectiveness of the second application. Orthodontic movement, periodontal regeneration, and dental eruption have been shown to function well within the gen-

erous cellularity of the rhBMP-2-derived bone. Although further study is necessary, we must consider the possible advantages of resecting structurally intact, minimally cellular host bone segments and replacing them with constructed bone segments.

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Diagnosis and Treatment of Sinonasal Undifferentiated Carcinoma: Report of a Case and Review of the Literature

Eric R. Schmidt, DMD, and Ronald L. Berry, DMD†*

Sinonasal undifferentiated carcinoma (SNUC) is a rare and highly aggressive neoplasm that was first described by Frierson et al in 1986 and although the exact origin of SNUC is still not defined clearly, it is thought that it originates from within the epithelium of the Schneiderian membrane of the paranasal sinuses.[1,2] The clinical onset of SNUC is relatively subtle, and may initially be mistaken for a common cold, sinusitis, or even a tooth ache,[3,4] with such symptoms as chronic nasal obstruction and mild facial pain. However, because of the extremely rapid progression of the disease, these symptoms can quickly evolve into epistaxis, periorbital proptosis, and cranial nerve palsies and paresthesias.[5] Unfortunately, because of its innocuous presentation, many patients will present with advanced disease, often extending to the ethmoid, sphenoid, and maxillary sinuses, and even into the orbit or anterior cranial fossa.[3,6-9] For such cases, the prognosis has been dismal, with average reported survival rates of approximately 12 months.[1,2] However, with improved recognition, and multimodal treatment, to include craniofacial resection and chemoradiation therapy, outcomes have been improved marginally.[10]

Reports of SNUC have generally been confined to the pathology,[1,11-20] otolaryngology,[2,5,10,21-37] and oncology literature,[38-43] and to our knowledge, it has not been widely covered in the oral and maxillofacial surgery literature. Although SNUC may have a relatively benign presentation, and can easily be confused with more docile disease processes, it is important to realize that it is an extremely malignant, rapidly progressing, and highly invasive neoplasm with a poor prognosis. Therefore, suspected cases should be treated early and aggressively. We present a case of SNUC that originated in the left maxillary sinus, we discuss the diagnosis and treatment, and finally, we will review the bulk of literature that has been introduced on this rare, but interesting disease entity.

Received from David Grant Medical Center, Travis Air Force Base, CA.

*Major, USAF, DC, Former Chief Resident, Department of Oral and Maxillofacial Surgery.

†Colonel, USAF, DC, Former Chairman, Department of Oral and Maxillofacial Surgery.

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Address correspondence and reprint requests to Dr Schmidt: Ehrling Bergquist Clinic, Offutt Air Force Base, Oral and Maxillofacial Surgery, 2501 Capehart Rd, Offutt Air Force Base, NE 68113; e-mail: schmidteric71@gmail.com

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