CASE REPORT

Regeneration of a Compromized Masticatory Unit in a Large Mandibular Defect Caused by a Huge Solitary Bone Cyst: A Case Report and Review of the Regenerative Literature

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Abstract The reconstructive options for large expansive cystic lesion affecting the jaws are many. The first stage of treatment may involve enucleation or marsupialization of the cyst. Attempted reconstruction of large osseous defects arising from the destruction of local tissue can present formidable challenges. The literature reports the use of bone grafts, free tissue transfer, bone morphogenic protein and reconstruction plates to assist in the healing and rehabilitation process. The management of huge mandibular cysts needs to take into account the preservation of existing intact structures, removal of the pathology and the reconstructive objectives which focus both on aesthetic and functional rehabilitation. The planning and execution of such treatment requires not only the compliance of the patient and family but also their assent as customers with a voice in determining their surgical destiny. The authors would like to report a unique case of a

huge solitary bone cyst that had reduced the ramus, angle and part of the body of one side of the mandible to a pencil-thin-like strut of bone. A combination of decompression through marsupialization, serial packing, and the fabrication of a custom made obturator facilitated the regeneration of the myo-osseous components of the masticatory unit of this patient. Serial CT scans showed evidence of concurrent periosteal and endosteal bone formation and, quite elegantly, the regeneration of the first branchial arch components of the right myo-osseous masticatory complex. The microenvironmental factors that may have favored regeneration of these complex structures are discussed.

Keywords Guided tissue regeneration · Myo-osseous masticatory unit · Solitary bone cyst · Marsupialization · First branchial arch components

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Introduction

Simple or solitary mandibular bone cysts are quite rare and are reported to account for about 1 % of jaw cysts [1]. Often they have a thin wall and contain no epithelial lining [2]. A study by Howe [3] showed that no visible lining was seen in 58 % of cases. Solitary bone cysts usually present as asymptomatic radiolucent lesions in the mandible [4, 5] that have irregular or scalloped borders with some cortication [1, 4]. Teeth involved by the cyst are usually vital [5]. Although such cysts are considered benign, they may be a cause of pain [6] and temporary hypoesthesia in the distribution of the inferior alveolar nerve [6]. Benign is a relative term as the cyst we present caused a huge amount of bone resorption and displacement of the masticatory

musculature in the region of the right mandibular ramus and angle.

Expansion of a cyst into the soft tissues may cause facial deformity. A large mandibular cyst can also weaken the mandible and affect mastication on the affected side. If infected, cysts may be a cause of pain and localised sepsis. Surgical treatment of a large mandibular cyst if associated with the removal of a deeply impacted tooth may result in iatrogenic fracture of the mandible.

The management of huge mandibular cysts needs to take into account the preservation of existing intact structures, removal of the pathology, and the reconstructive objectives, which focus both on aesthetic and functional rehabilitation. The planning and execution of such treatment requires not only the compliance of the patient and family but also their assent. It is the current trend that patients no longer see themselves as passive participants in the healthcare process but customers with a voice in determining their surgical outcome.

We report a unique case of a young woman for whom expansion of a large mandibular solitary bone cyst had reduced the ramus, angle and part of the body of one side of the mandible to a pencil-thin-like strut of bone. She opted for treatment by decompression, marsupialization and serial packing of the cyst rather than a major reconstructive procedure. The outcome of this conservative approach was the successful regeneration of the missing osseous and skeletal muscle components of her right masticatory unit. The regenerative principles including microenvironmental factors that may have underpinned this process are discussed.

Case Report

A 22 year old female was referred to the maxillofacial service with a 4 month history of swelling on the right side of the lower face, which later became painful. Previous treatment abroad had included a single episode of drainage of the lesion with a canula attached to a hypodermic syringe. The purpose of that procedure was to reduce the trismus that had accompanied the swelling so that the patient could eat without pain. Once this objective had been obtained the patient was advised to see a maxillofacial surgeon. Microbiology of the pus had yielded no growth.

Examination

On presentation, the patient looked well and was not in distress. However, there was a very obvious large swelling over the right mandibular angle region (Fig. 1). The swelling could easily be compressed with a finger and was

Fig. 1 Soft tissue expansion in the right angle region causing facial asymmetry. Photograph taken at time of operation

soft to palpation. There was no facial nerve weakness or sensory disturbance in the region of the second and third divisions of the right trigeminal nerve. The patient had right submandibular lymphadenopathy. Intraorally, there appeared to be an open wound in the right retromolar region. On closer inspection it was found to be a depression in the mucosa at the site of previous drainage. The mucosa was thick in this area. No fluid could be expressed from this site as it was sealed at its base. The teeth on the right side of the mandible showed no evidence of non-vitality. They were neither mobile nor tender to percussion and had no dental decay.

Investigations

Plain radiographs showed a large unilocular expansile lesion extending from the distal surface of the lower 2nd molar to the right condylar neck. The complete destruction of mandibular buccal and lingual alveolar bone by the cyst and its expansion into the adjacent soft tissue in our patient gave the appearance on three dimensional reformatted CT scans of a bubble sitting on the right mandibular basal bone. All that remained of the region previously occupied by the right angle, ramus and condylar neck of the mandible was a “pencil-like-strut of bone” (Fig. 2). Coronal CT scan, (Fig. 3a) showed that the masseter muscle was barely attached at the right mandibular lower border. Only the tip remained of the right mandibular coronoid process, which had still retained some of the right temporalis muscle insertion. The right masticatory unit was indeed compromised.

Despite the considerable loss of bone from the mandible, there was no resorption of teeth. The inferior alveolar nerve was exposed at the base of the lesion (Fig. 3b). The cyst-like lesion appeared to have enveloped the right mandibular unerupted 3rd molar (Figs. 2, 3a, b) which

Fig. 2 Reformatted 3D CT scan lateral view

(a) Tip of coronoid process with temporalis muscle attachment preserved

Fig. 3 **a** Coronal CT scan image showing the extent of buccal lingual cystic expansion with resorption of a considerable amount of mandibular buccal plate. There is no lingual or buccal cortical plate in this region of the mandible. Only the tip of the coronoid process remains. **b** Sagittal CT scan. Note the cystic envelope around the crown of the impacted right 3rd molar and the inferior alveolar nerve canal which appears exposed in the distal mandible

suggested it could be a dentigerous cyst. There was no periapical pathology associated with the teeth in the lower right quadrant. Included in the differential diagnosis were ameloblastoma and odontogenic keratocyst. A diagnosis of solitary bone cyst was not initially considered. Serological

tests showed that the hemoglobin, white blood cell count, and parathyroid hormone were within normal limits.

Operative Procedure

The patient had opted for a conservative approach to the management of her lesion. She was quite specific about not wanting either a donor site to harvest tissue for reconstructive purposes or an external facial scar. A cyst of this magnitude put the patient at risk of pathological fracture. The patient was informed of this risk and told that an external approach may be required to access a fracture should it occur. Consent for the possibility of harvesting tissue for reconstructive purposes and the use of osteosynthesis in the right mandibular region was also obtained.

Under general anesthesia the cyst-like lesion was drained through an opening made at the site where previous drainage had been performed. The impacted lower 3rd molar was removed. Intubation and extubation focused on applying minimum pressure to the mandible. After the cyst fluid was drained, inspection of the cyst revealed that the inner lining appeared to be periosteum. Apart from periosteum there was no distinct cyst lining to biopsy. Part of the inferior alveolar nerve was exposed at the base of the cyst. The wound was kept open with a corrugated drain and the residual cavity packed with ribbon gauze. The aim of the packing was to prevent the cyst cavity from collapsing and to stop the reaccumulation of fluid. The drain kept the wound open to facilitate marsupialization. There was no need to suture the periosteum of the cyst cavity to the adjacent oral mucosa as these tissues were in continuity. Three days later, at a relook operation, the cavity was irrigated with normal saline and the pack replaced with a new one. For the following weeks the patient was advised to have a soft diet and avoid trauma to the right side of the face.

Histopathology

At operation it was noted that nothing remained of the mandibular buccal and lingual cortical plates in the angle and ramus region apart from periosteum. There was no distinct lining to biopsy. This is not surprising as many solitary bone cysts have no visible lining [3].

An initial biopsy was therefore not taken of the periosteum to preserve its integrity both as a scaffold for future bone regeneration and as a barrier against the ingrowth of soft tissue. A breach in the periosteum could disturb the regenerative process. At a follow-up appointment, a biopsy was taken of the healing cyst cavity. It showed non-specific chronic inflammation.

Follow Up

The patient attended the outpatient service over a period of several months to have the cyst cavity irrigated and the pack replaced (Fig. 4). Throughout this period, the patient assumed responsibility for regularly changing the packs and irrigating the healing cavity. At the initial stages of treatment the healing cavity gave off an unpleasant odour. We found that the periodic use of oral metronidazole 400 mg three times a day eliminated this problem. After several weeks of this regimen, it was noticed that the soft lining of the cavity began to harden and form an outer shell. To prevent premature closure of the opening to the cavity (Fig. 5a) and promote self-care, an obturator was made (Fig. 5b). The technique for construction of the obturator has been described [7]. It was trimmed periodically to ensure a close fit to prevent the accumulation of food debris in the cavity. Patient progress was monitored through regular clinical examination, serial panoramic radiographs (Fig. 6), and CT scans.

Radiological Follow Up

Follow up CT scans taken 15 weeks post decompression and marsupialization showed the beginnings of the re-establishment of the right mandibular masticatory unit. Interestingly, the masseter muscle became reattached to the new bone that had formed in the right mandibular ramus and angle region (Fig. 7a). The reattachments of the temporalis to the regenerated but not completely ossified part of the coronoid process was also evident (Fig. 7b).

CT scans also confirmed the clinical impression that bone deposition was occurring from all sides of the cavity (Figs. 7b and 8), confirming that bone deposition was both periosteal and endosteal. The shape of the regenerated neck of condyle and deposition of new bone could clearly be observed (Fig. 8).

Fig. 4 Entrance to cyst cavity in the right retromolar region

Fig. 5 **a** Cyst cavity packed with ribbon gauze. **b** Cavity occluded with customized obturator

Fig. 6 Post surgery panoramic radiograph showing the cyst cavity volume being maintained with ribbon gauze. It was initially overpacked in the region distal to the mandibular right second molar. Compare this radiograph with the one taken at 15 months post treatment (Fig. 11)

3D reformatted CT scans (Fig. 9a, b) clearly showed the difference in the amount and distribution of bone in the right angle, ramus and neck of the condyle region before intervention and afterwards. Although the contour and thickness of the regenerated part of the mandible on the

Fig. 7 **a** Coronal CT scan at 15 weeks post intervention. Intramembranous bone formation can be seen arising from the previous cyst envelope. Note also the endosteal bone formation arising from the basal mandibular bone. **b** Axial CT scan showing bone regeneration occurring circumferentially (see *yellow arrows*) at a high level on the ascending ramus, with the insertion of the lateral pterygoid muscle (*red arrow*). *Blue arrow* indicates lateral pterygoid plate at 15 weeks post intervention

Fig. 8 Coronal CT scan showing the regeneration of a new condylar neck (*red arrow*) at 15 weeks post intervention

right side at 15 weeks post-intervention was larger than that of the left, it still resembled that of the left side (Fig. 10).

Fig. 9 **a** The 3 Dimensional reformatted CT scan of the patient's facial skeleton before intervention and **b** The scan taken at 15 weeks post decompression, marsupialization and serial packing

Fig. 10 The patient at 15 weeks post surgery. The contour and thickness on the right side resembles that of the left side of the mandible

The latest panoramic radiograph, taken 15 months after the commencement of treatment, showed very good distal bone support for the mandibular right second molar (Fig. 11). It also showed re-establishment of the right mandibular antegonial notch, an anatomical feature determined by functional masseter activity

Fig. 11 Panoramic radiograph 15 months post surgery shows the excellent relation of the regenerated bone distal surface to the lower 2nd right mandibular molar. The elliptical area of radiolucency (*red arrow*) at the anterior border of the regenerated right mandibular ramus represents the entrance to the almost healed cavity

Discussion

Reconstructive Philosophy *Functional and Aesthetic End Points*

Although Rushton's [2] definition of a solitary bone cyst describes a bony cavity devoid of an epithelial lining, it is clear that in our patient, cystic resorption of the mandibular lingual and buccal cortical plates had resulted in a cyst cavity that had neither bony walls nor an epithelial lining. Instead, all that remained after this resorption was a strut of basal bone in the right mandibular ramus and angle region, the tip of the right coronoid process, and an intact right inferior alveolar nerve. Interestingly, rudimentary attachments of the right masseter and temporalis muscles could be seen on the coronal CT scan (Fig. 3a) at the base of the right angle and tip of the right coronoid process respectively.

Such large osseous defects in the facial skeleton present considerable reconstructive and functional challenges. The loss of the myo-osseous masticatory unit on the right side of the mandible restricted the patient to eating only on the left side of the jaw. An absence of bone in the right mandibular angle and ramus region had led to less hard tissue support for the facial soft tissues which was a major aesthetic concern. Restoration of function and facial drape are the key reconstructive objectives.

Treatment Options

Drainage

Treatment options of large cysts include drainage, marsupialization and enucleation. Drainage of a large cyst can be achieved via a drain or a wide bore tube [1]. It is worth

noting that periodic drainage of a cyst is not a long term solution and should only be considered as a temporary measure until the patient obtains definitive treatment. Irrigation and drainage also does not prevent the risks of infection and pathological fracture occurring in large cysts that occupy the mandible. A review by Suei et al. [8], focusing on the treatment outcomes of 132 simple bone cysts, found that fenestration or packing the cyst cavity gave less recurrence rates than exploration or bone curettage. The latter option was not feasible in our patient as the cyst envelope had lost its bone.

Marsupialization Versus Enucleation

Marsupialization was preferred for our patient because the cyst had expanded beyond the normal boundary of the bone into the soft tissue of the cheek. Enucleation was not possible as there appeared to be no distinct cyst lining to remove and no specimen for pathological study. Attempted enucleation could have also injured the exposed inferior alveolar nerve at the base of the cavity (Fig. 3b). Marsupialization does however require strong patient compliance in terms of self-care [9] which involves regular irrigation and packing of the cavity and attendance at outpatient follow-up appointments. An obturator, if used, would need to be adjusted as the cyst defect changed in size and shape with ongoing healing. A recent study [10] that focused solely on enucleation to treat jaw cysts found that at 6 month follow-up, subjects had between 50.4 and 100 % regeneration of bone. Interestingly, those patients with least evidence of bone regeneration had one or both cortical plates eroded by the cyst.

Regenerating the Compromized Myo Osseous Masticatory unit

Criteria for Deposition of Bone in a Cavity

Murray et al. [11] had laid down important requisites for the unhindered deposition of bone in a cavity. These conditions included: the presence of a blood clot, a source of osteoblasts, and contact with living tissue [11, 12]. They also observed that moulding of the blood clot by external forces appeared to influence the final shape of the new bone. Prevention of soft tissue invasion of the cavity was also considered essential for bone regeneration [11].

Unhindered bone remodelling of grafted autogenous bone in an osseous defect can benefit from coverage with a membrane which prevents ingress of soft tissue into the cavity [13]. The membrane should also maintain the volume of the cavity so that bone deposition can take place [14].

The Role of Periosteum as an Endogenous Scaffold

In addition to acting as a barrier and a space maintainer, a membrane should also be biocompatible, safe and offer the opportunity for tissue integration [15]. Mandibular periosteum not only meets these criteria but has the potential to act as a living construct for bone tissue engineering [16]. Cells derived from human periosteum can differentiate into cells capable of forming bone and skeletal muscle [17].

Since the periosteum of our cyst was both intact and in continuity with the mandibular basal bone, it acted both as a membrane and, through support from the gauze pack, as a scaffold which helped maintain the volume of the space until an outer shell of bone was formed. The shape this periosteal sleeve took was determined by how much it was pushed out by the gauze. Indeed, the periosteal envelope was the template for future bone deposition at all sides of the cavity apart from the basal bone. It had an important influence on the final shape of the regenerated part of mandible. It was therefore important initially not to overpack the cavity buccally with gauze, which would have displaced the cheek outwards and caused facial asymmetry. Artificial bio-inert membranes such as polytetrafluoroethylene (PTFE) which do not integrate with the host tissue have the disadvantage of requiring a second operation for their removal.

At the base of the osseous defect, where periosteum was absent and the inferior alveolar nerve was exposed, endosteal bone formation could be observed (Fig. 7a). Around the inferior alveolar nerve canal, a new canal was forming (Fig. 7b). The contribution of endosteal bone formation to bone regeneration in an osseous cavity has been demonstrated in animal studies [18]. It appears that in our patient both periosteal and endosteal bone deposition was occurring simultaneously. Direct intramembranous bone formation can arise from both endosteal and periosteal surfaces if there is a good blood supply and the tensile stresses acting in these regions are low [19]. Facial soft tissues have excellent vascularity and the mandibular basal bone in our patient was initially covered by blood clot following extraction of the impacted 3rd molar.

The Contribution of the Residual Masticatory Muscle Attachments to On-Site Neovascularization

In a recent review of bone tissue engineering for craniofacial defect repair [20], the importance of both vasculogenesis and angiogenesis as prelude to osteogenesis in the regeneration of the craniofacial skeleton was highlighted. Preservation of the muscle attachments to the remaining strut of mandibular bone in our patient may have ensured that a vital source of cells and cytokines required for the initial neovascularization and later myogenesis was available. One should not also discount the potential

contribution of the intact inferior alveolar nerve at the base of the defect to influence regeneration of the mandible through the release of trophic factors. Indeed, it has been shown experimentally that human nerve growth factor β (hNGF β) can significantly improve the density, quality and apposition of regenerated bone [21].

Extraction of the 3rd Molar

The microenvironment at a cellular level has an important role in tissue regeneration. Adult mesenchymal stem cells (MSCs) are present in most craniofacial tissues. Removal of the unerupted lower right 3rd molar may have initiated the regenerative process through the release of growth factors, cytokines, the activation of neighbourhood MSCs, and the recruitment of bone marrow MSCs to the region. The MSCs may have contributed not only to the formation of a microenvironment conducive to regeneration [22], but also to the differentiation of cells capable of osteogenesis and muscle regeneration [23].

Satellite cells (SC) present in skeletal muscle are believed to influence muscle regeneration [24]. They can be activated by insulin growth-like factor which when released from skeletal muscle can lead to recruitment of non-muscle stem cells from the bone marrow [24, 25], which could assist in tissue regeneration. MSC can also arise from human gingiva. These gingiva-derived mesenchymal stem cells (GMSCs) have an important immunomodulatory role [26]. Through the immunosuppression of the inflammatory response that follows injury, GMSCs can promote an environment which favours tissue regeneration rather than repair with scar tissue.

Site-Specific Pluripotent Adult Stem Cells

Although there is a view which supports a role for bone marrow derived MSCs in the initiation and regeneration of tissue at different sites in the body, there is also evidence to suggest that location-specific pluripotent stem cells have an important role to play in the regeneration of complex tissue peculiar to a particular site.

Embryologically, the muscles of mastication, the trigeminal nerve and the mandible (through intramembranous ossification of the mesenchymal tissue surrounding Meckels cartilage) are derived from the first branchial arch [27]. The regenerated masticatory unit in our patient embryologically belongs to that first arch. In the embryo, at between 3 and 5 weeks gestation, the neural crest cells are selectively forming discrete populations through encoding genes that orchestrate the regulatory blueprint for making specific parts of the face [28]. Avian studies have shown that these neural crest cells are important for determining facial characteristics and morphology [29].

Mesenchymal cells that originate from the neural crest can differentiate into cartilage, bone and the musculature of the craniofacial skeleton. They can undergo asymmetric cell division leading to one cell with the potential of a stem cell, and the other committed to being a differentiated cell [30]. The former reside in facial structures and are called mesenchymal stem cells. Postnatally they retain their ability as stem cells to regenerate facial tissue [30]. Their behaviour appears to be site specific [31].

The possibility that site-specific adult mesenchymal stem cells derived from the neural crest could be directed like their neural crest predecessors to form complex craniofacial tissue would represent an important breakthrough in regenerative medicine. Although our discourse has focused on guided tissue regeneration of a craniofacial structure and the possible impact of the microenvironment on healing and renewal, the genetic factors responsible for diverse variations in facial features are largely unknown [32].

The age of the patient may have an influence on bone healing. A study by Ihan Hren and Miljavec [33] has shown that spontaneous bone regeneration in mandibular defects diminished as patients got older, especially after 33 years of age. Our patient was 22 years of age. Although Rubio and Mombru [10] report in their retrospective study of bone healing following cyst enucleation, that age had no effect on bone regeneration, 60 % of their patients who had incomplete bone regeneration at 6 months follow up, were 36 years or older.

Cyst Decompression Through Marsupialization *Potential Mechanisms to Trigger the Switch from Cyst Expansion to Tissue Regeneration*

According to Merriam Webster Dictionary, decompression may be regarded as an operation or technique to relieve pressure in a hollow organ. Decompression of a fluid containing cyst can only be achieved if the fluid is not allowed to reaccumulate within it. Through effective cyst decompression, a significant change in the hydrostatic pressure occurs. This procedure produces not only an alteration in the tensile forces acting per unit area at the periphery of the cyst but also changes the extracellular environment within the cyst [9]. We used a combination of marsupialization and packing of the cyst with gauze to decompress it, prevent reaccumulation of fluid, and change the internal environment of the cyst. It was also important to fully pack the cyst cavity to prevent collapse of the periosteal capsule as the latter will provide the shell or template of the regenerated mandible. A drain was placed to ensure that the lumen to the cyst remained patent. This intervention meant that there was continuity of the cyst lining with the oral cavity thus allowing marsupialization to progress. The possible mechanisms of bone regeneration

following decompression of the cyst through marsupialization will be outlined.

Cellular Mechanotransduction

Cellular mechanotransduction has been defined as the process by which a cell is able to sense a mechanical or physical force and convert it into an intracellular biochemical signal, thus allowing cellular metabolism to regulate extracellular matrix (ECM) homeostasis [34]. The fluid within a cyst can exercise hydrostatic pressure on its surrounding envelope. This force acting per unit area outwards is known as tensile stress [35]. Removal of cyst fluid that follows effective decompression through marsupialization could alter the balance of forces acting on both the cells and the ECM at the periphery of the cyst envelope. These changes in tensional forces could lead to mechanical, chemical and structural changes that have an impact both on the surrounding ECM and cell biology. Lower tensile hydrostatic stresses and strains acting at the periphery of the cyst capsule may favour bone deposition [19].

Epithelial cells lining odontogenic cyst are capable of synthesizing interleukin-1 (IL1). IL1 is a pro-inflammatory cytokine which has a strategic role in both normal bone metabolism and disease [36]. It indirectly stimulates bone resorption through the release of prostaglandin E2 (PGE2) from osteoblasts which stimulates osteoclast formation [37]. Decompression of odontogenic keratocysts through marsupialization has been followed by reduced synthesis of interleukin-1 [38] producing a situation which may favour osteogenesis rather than osteolysis.

Solitary bone cysts by definition have no epithelial lining [2]. However, the synthesis of interleukin 33, a member of the IL 1 family can be affected by the mechanical stimuli acting on mechanoreceptor cells [39]. Indeed, a hypothesis has been put forward that bone formation after cyst marsupialization is due to negative pressure induced osteogenesis [40].

Shear Forces and Changes in the Properties of the 3D Extracellular Scaffold

Alteration in the ECM as a result of mechanical stress can result in changes to its permeability, affecting the movement of soluble factors that are important for cell growth and differentiation [41]. Very importantly the stiffness of the tissues in the vicinity of a cell may also act as cue for differentiation along a particular cell line [42]. Indeed, with respect to our case, the hardness of the newly formed bone in the regenerating mandible may have acted as a prompt to initiate the differentiation of adult skeletal muscle stem cells and the subsequent reattachment of muscles of mastication to the regenerated parts of the mandible.

Although it is known that shear stress can stimulate osteoblast activity, *in vitro* studies suggest it may also influence osteogenic differentiation [43]. The gradual loading of the mandible on the right side as healing progressed, could have stimulated muscle in the region to activate satellite cells which later become muscle precursor cells [44]. Satellite cells can be activated by diverse stimuli such as injury and stretching [45]. Ingber [46] mentions the importance of having a basic scaffold in place before specialized 3D tissue can be raised or remodelled, and cites the importance of mechanical cues in the microenvironment to regulate the differentiation of cells according to the demands of the situation. Although, his findings are related to the development of the embryonic structures, these same observations may apply to the regeneration of complex craniofacial structures in adults, a process that would involve cell proliferation and the differentiation of adult stem cells into specialized cells capable of regenerating craniofacial tissue.

Prior to our intervention, the soft tissue cyst envelope of our patient was essentially spherical in shape, but after decompression, marsupialization and serial packing, the regenerated right side of the mandible resembled the normal contralateral side. It would be erroneous, however, to expect the right mandible to be an exact replica of the left side, as external factors such as function [47] and pathology affect morphology of the mandible. It would be a tall claim to credit the regeneration of this complex facial structure solely to the skill of the team involved in her care. It would be more appropriate to say that both environmental and genetic factors harnessed through a mechanism still not fully understood led to the regeneration of a complex facial subunit in a young adult without the need for complex craniomaxillofacial surgery.

Engineered Scaffolds

Research into the use of synthetic scaffolds to deliver bioactive molecules and stem cells for the regeneration of complex facial tissue is an ongoing process fraught with many challenges. It has been driven in part by a desire to avoid the donor site morbidity associated with harvesting of the patient's own tissue for reconstructive purposes.

An ideal tissue-engineered-scaffold should be able to deliver or promote the recruitment of specialized cells for the regeneration of a particular anatomical craniofacial subunit. It should mimic the function of the extracellular matrix in providing an environment receptive to vasculogenesis, angiogenesis, osteoinduction, osteoconduction osteogenesis and myogenesis. If such a scaffold could also provide structural support, maintain volume, and interact with the extracellular matrix as the periosteal sleeve did in our patient, the shape and form of the regenerated structure could be addressed.

Polymer Scaffolds

Central to tissue engineering constructs is the polymer scaffold, which is formulated to mimic the role of the extracellular matrices [48]. Polymer scaffolds can either be natural or synthetic. Natural polymer scaffolds include those made from collagen, chitosan, keratin and hyaluronic acid. Collagen and fibrin scaffolds have been known to suffer from consistency in quality [49] and therefore predictability. Synthetic polymers may include those based on poly(L-lactic acid), poly(amino acids), poly(orthoesters) and poly(glutamic acid) [50]. Modifications to the synthesis of 3D polymer scaffolds and alterations to their compositions can also affect their flow [51], degradation rate and capacity to expand.

The response of recipient tissue to polymer scaffolds depends on the biomolecules they contain [49]. Growth factors and amino acids added to a polymer hydrogel can have a huge impact on the chemical and physical properties of the scaffold. Such changes can lead to changes in signal transmission mechanisms at the cellular level [50]. Electrospun nanofibre scaffolds can be made from poly lactide co glycolide (PGLA) [52, 53], type 1 collagen [53, 54] and poly ε caprolactone [53, 55]. Their topography can promote stem cell mediated osteogenesis [53]. Indeed, improved bone regeneration has been reported with a nanofibre scaffold of poly(L-lactic acid) impregnated with demineralized bone powder.

Interestingly, Moghadam et al. [56] used a bone morphogenic protein (BMP) bioimplant to reconstruct a mandibular defect following tumour surgery. The bioimplant was made up of human native BMP with the vehicle for delivery being demineralized bone matrix in a poloxamer gel [56]. The authors reported clinically excellent bone height and width, and histologically viable bone at follow-up. Gels incorporating bone morphogenic protein-2 (BMP-2) have also been successfully deployed to regenerate bone in rat calvarial defects [57].

3D Printer Technology in Combination with Regenerative Science

Using a combination of regenerative medicine science and 3D printing technology, Anthony Atala and his team produced human kidneys in the laboratory. Ingeniously, they used a 3D kidney shaped collagen scaffold as a template onto which human cells were deposited layer by layer to form a living kidney [58]. Furthermore, Atala and his team are investigating the use of 3D printers to engineer muscle and bone for reconstruction purposes [59]. The challenge in regenerative medicine is not just about acquiring the experience and scientific knowledge in engineering organs but also to ensure that regulatory and ethical concerns are also addressed.

Conclusion

Although there has been a focus on the discontinuity, location and size of critical defects in experimental studies on bone remodelling after fractures, our understanding of the pattern and mechanism of tissue regeneration after cyst marsupialization is still evolving. Regeneration of complex tissue after marsupialization of cysts may serve as an excellent in vivo model to study tissue regeneration.

As we move into an era of personalized medicine, the emphasis will be on surgical teams to work not only with the patient to deliver individualized solutions to reconstructive challenges but to harness and leverage the scientific advances made by colleagues working in the life sciences. Through an established technique of decompression, marsupialization and serial packing, a complex facial subunit was restored. Although the method described is simple, the mechanical and molecular signals underpinning the process are complex, ordered, and coordinated. The challenge for those working in regenerative medicine is to unlock these secrets so that they can be used in a predictable and cost-effective way for our patients.

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