Albright's Hereditary Osteodystrophy with Extensive Heterotopic Ossification of the Oral and Maxillofacial Region: How Fetuin Research May Help a Seemingly Impossible Condition

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ABSTRACT

Albright's hereditary osteodystrophy (AHO) is a complex genetic disorder characterized by brachydactyly, gonadotropin resistance, hypothyroidism, pseudohypoparathyroid syndrome and heterotopic ossification. Heterotopic ossification rarely occurs in the maxillofacial region. In this article, we present such a case, describe the etiology, characteristics and treatment of AHO and suggest a potential role of an inhibitor of bone formation such as fetuin in preventing recurrence of aberrant ossification.

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There are many causes of restricted mandibular movement, trismus and ankylosis of the temporomandibular joint (TMJ). Heterotopic ossification is the formation of highly organized mature ectopically located lamellar bone in soft tissue due to trauma, rare genetic conditions or idiopathic or pathologic processes.[1–5] A few cases have been reported where heterotopic ossification has affected the maxillofacial region, including tissues adjacent to the TMJ and the muscles used in mastication, resulting in varying degrees of restricted mandibular movement.[6–18] Only one case has been reported to be due to Albright's hereditary osteodystrophy (AHO).[2] We present a second.

Case Report

A 17-year-old male with the chief complaint of an inability to open his mouth was referred to a hospital dental clinic by his physician. Limited mouth opening had been present since early childhood with progressive reduction in mandibular range of motion. At the time of presentation, the lack of mandibular movement prevented normal mastication; however, the patient had adapted by passing food through spaces formed by a missing maxillary central incisor and a gap between the teeth at an open bite on the left buccal segment (**Fig. 1**). The patient was otherwise healthy. He could not recall any trauma to the right side of his face. His past medical history included

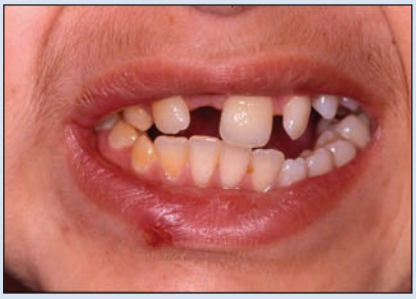

Figure 1: Patient with severe trismus straining to show maximum opening of his mouth limited by bony ankylosis of the temporomandibular joint.

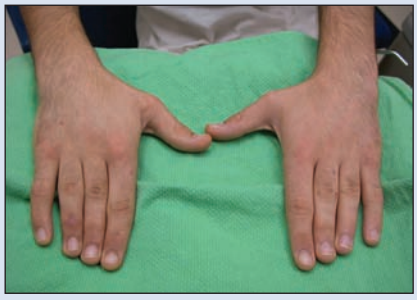

Figure 2a: Brachydactyly of both hands with bilateral shortened middle and ring fingers.

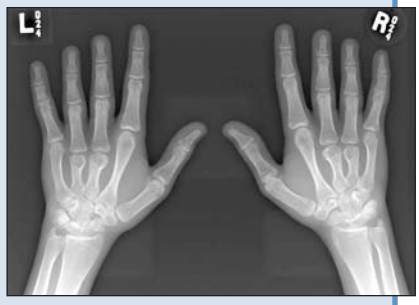

Figure 2b: Radiographs of both hands showing brachydactyly of the middle and ring fingers due to bilateral shortening of the third and fourth metacarpals.

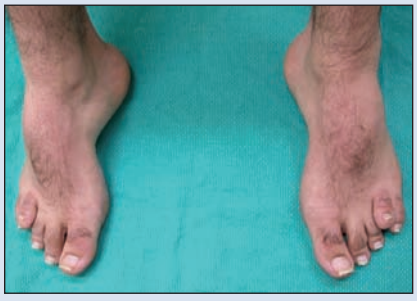

Figure 2c: Shortened fourth toes on both feet.

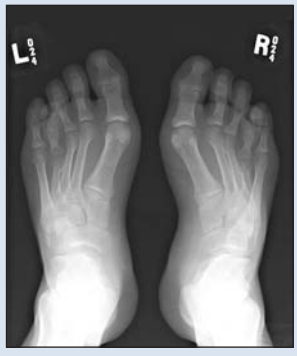

Figure 2d: Radiographs of both feet show bilateral shortening of the fourth metatarsals.

a forceps delivery and revealed below average growth and development. He had been admitted to hospital in Pakistan many times between 1989 and 1997, where he underwent surgical release of his mandible. The outcome was a short-lived improvement in opening.

General examination revealed that the patient was below average height and weight. The third and fourth knuckles on both hands were retruded. His third and fourth fingers and fourth toes were unusually short (**Figs. 2a–2d**). Aberrant hard tissue was noted beneath the skin in several areas of his body. Extraoral examination revealed an enlarged thyroid, facial asymmetry with a retrognathic mandible deviated to the right and weakness in the zygomatic and marginal mandibular branches of the right facial nerve. Hard subcutaneous masses were present in the right buccal region, on the inferior border of the mandible, bilaterally in the submental and submandibular regions and on the left dorsal aspect of the neck (**Fig. 3**).

Intraoral examination was limited because of the patient's lack of mandibular movement. A hard calcified mass within the buccal region prevented retraction of the right cheek. The patient was missing several teeth and had rampant dental caries.

A panoramic radiograph revealed a diffuse radiopacity overlying the patient's right mandible, rarefying osteitis, caries, several teeth with short, malformed roots, several unerupted teeth and ectopic eruption of the maxillary right first premolar. Plain films revealed extensive radiopacity within the patient's right buccal soft tissue (**Fig. 4**).

A computed tomography (CT) scan with 3-dimensional reconstruction revealed significant abnormality of the right hemimandible and right TMJ; a massive volume of hard tissue fused the right mandibular ramus and condylar to the skull base and the right mandibular coronoid process to the zygoma. The possibility of previous fracture of the right condyle and coronoid process was suspected based on their positions within the surrounding mass of bone. CT showed an extensive lace-like pattern of bone within the soft tissues overlying the right lateral face from the zygoma to the inferior border of the mandible and the inframandibular soft tissue bilaterally (**Figs. 5a–5c**). In addition, focal areas of fatty bone marrow could

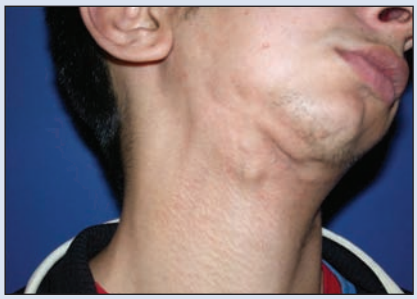

Figure 3: Extensive subcutaneous calcification in the right submandibular region and neck.

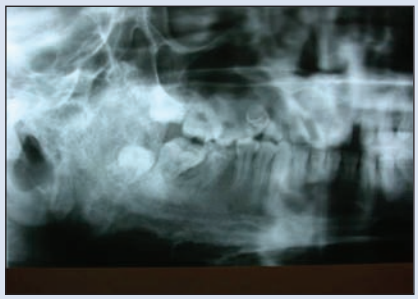

Figure 4: Panoramic radiograph with visible calcification of the right cheek.

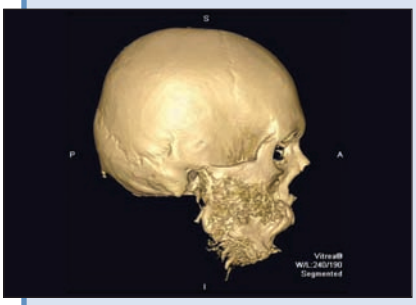

Figure 5a: Right lateral view of the skull, using 3-dimensional computed tomography (CT) scan reconstruction, showing extensive lattice-like calcification extending downward from the zygomatic arch to the submandibular region of the neck.

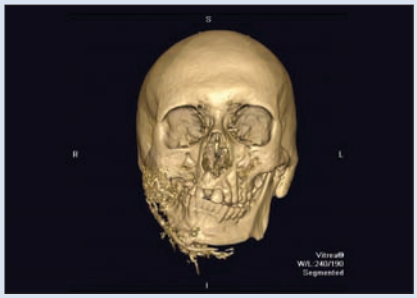

Figure 5b: Anterior 3-dimensional CT scan reconstruction of the skull showing fusion of the lattice-like calcification past the inferior border of the mandible.

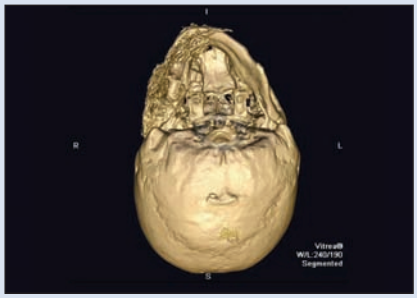

Figure 5c: Inferior 3-dimensional CT scan reconstruction of the skull showing a calcification lattice in the subcutaneous tissues immediately lateral to the mandible.

be seen within the heterotypic bone. Technetium-99 bone scintigraphy revealed mildly increased bony activity surrounding the right hemimandible, indicating a low rate of metabolic activity at the time of the scan.

Plain films of the hands and feet revealed bilateral short third and fourth metacarpals and short fourth metatarsals (**Figs. 2b** and **2d**). Blood tests, including biochemical and endocrine markers, were within normal limits except for parathyroid hormone (PTH), which was slightly elevated at 7.7 pmol/L (normal range 1.6–6.9 pmol/L).

Discussion

First reported by Fuller Albright in 1942,[1] AHO is an endocrine disorder of end-organ resistance to PTH. It can be described as pseudohypoparathyroidism (PHP) or pseudopseudohypoparathyroidism (PPHP).[1] In PPHP, calcium levels are normal, but urinary excretion of cAMP and phosphorus are high in response to PTH administration.[1,19] PHP is associated with hypocalcemia and hyperphosphatemia and does not respond to PTH administration with increased cAMP urinary excretion.[19] PHP can be further divided into several subtypes.

AHO is a very rare condition. A Japanese study reported the prevalence of PHP as 3.4 cases per million people.[20] There is no reported information on the oral manifestations of PPHP, but cases of PHP include reports of delayed tooth eruption, malocclusion and enamel aplasia and hypoplasia.[21,22]

AHO is caused by a mutation in the GNAS1 gene, located on the q13.11 region of chromosome 20.[23] This gene encodes for the alpha-subunit of the stimulatory G protein, which is found on the cell membrane and is involved in the activation of adenyl cyclase.[24,25] Mutations in the G protein interfere with the action of PTH, thyroid stimulating hormone and the gonadotropins.[25] Paternal transmission of the defective gene leads to PPHP whereas maternal transmission will result in a form of PHP.[26]

Reported physical characteristics of AHO include gonadotropin resistance, pseudohypoparathyroidism and hypothyroidism, round face, short stature and mental retardation.[1,27,28] The most significant clinical finding is brachydactyly, often including shortened fourth and fifth metacarpals and metatarsals.[25] This was evident in our patient. Other characteristics of AHO are cutaneous and

subcutaneous calcification, which were also found in our patient. Based on his normal biochemical levels, our patient's AHO was characterized as PPHP.

The pathophysiology of heterotopic ossification is largely unknown. Several theories have been proposed, including inflammatory factors resulting from denervated tissues, disrupted calcium homoeostasis, immobilization, prolonged pressure on periarticular structures, microtrauma, vascular stasis, hypoxia, hyperthermia and genetic factors.[4] Trauma is commonly an etiologic factor, although in many cases it may be minor, caused, for example by administration of an inferior alveolar nerve block.[11,15] It is common for the patient to be unable to recall a traumatic event. Heterotopic ossification often follows an inflammatory phase characterized by local swelling, pain, erythema and variable joint restriction that may include ankylosis, although it may also be asymptomatic. Palpable masses are present in the later stages.[4]

Treatment

Subcutaneous calcification is consistent with AHO. In most instances, it does not require treatment; however, in certain circumstances, surgical removal has been carried out even though there is a risk of recurrence. Only one case of AHO has been reported in which ankylosis of the TMJ was successfully treated by surgical removal of the ankylotic joint to allow for an acceptable range of movement.[21] In our patient, because of the extensive involvement of all muscles of mastication on the right side with further calcification of the soft tissues of the neck, back and abdomen, surgical intervention would be extremely complex and could leave the patient in a far worse state than his preoperative condition. Similar cases reported in the literature have resulted in short-lived improvement in range of motion,[4,8,10] required multiple surgeries[2,4] or were not followed up for more than a few years.[2,8,10]

Surgical treatment for this patient must address the likelihood of the recurrence of heterotopic ossification. Grafted or transplanted muscle, as in a free vascularized flap, could undergo heterotopic ossification intrinsically or in response to surgical trauma. Although the exact cause of heterotopic ossification is not completely understood, patients with genetic diseases affecting bone morphogenic proteins (BMPs) are at high risk of developing post-traumatic heterotopic ossification.[4] Thus, any surgical intervention might be accompanied by administration of an inhibitor of bone formation, such as fetuin, to suppress heterotopic ossification.

Most reports of treatment of heterotopic ossification are related to postoperative care following total hip arthroplasty and prosthetic reconstruction of the TMJ. Some have postulated that bone dust created during surgery seeds the surrounding tissue with BMP leading to heterotopic ossification. Generally accepted preventive measures include radiation and pharmacologic therapy. Radiation targets local osteoprogenitor cells. Pharmacologic agents, specifically the nonsteroidal anti-inflammatory drug indomethacin, have been used successfully to reduce heterotopic ossification by inhibiting the inflammatory mediator prostaglandin E2, which is involved in osteogenic cell proliferation and differentiation.[4]

Fetuin, a bovine cytokine binding protein, has attracted increasing interest as a unique treatment for ectopic ossification. Fetuin and its human homologue alpha-2 Heremans–Schmid glycoprotein (AHSG) bind to the transforming growth factor-beta (TGF-beta) superfamily of proteins including BMPs.[28–31] They are produced by hepatocytes and are found in serum and mineralized bone. Fetuin is more abundant in fetal blood, hence the name fetuin derived from the Latin word fetus.[30]

Multiple studies have shown that fetuin plays an important role in down-regulation of osteogenesis. AHSG was found to suppress dexamethasone-induced osteogenesis in rat bone marrow cells.[29–32] AHSG-deficient mice were shown to have increased cortical bone thickness and bone mineral density, greater trabecular bone remodeling and accelerated age-related cortical thickness and mineral density accumulations.[32] Furthermore, intramuscular injections of BMP in AHSG-deficient and wild-type (or naturally occurring) mice resulted in dose-dependent induction of ectopic bone formation.[32] The amount of ectopic bone formed was inversely proportional to the AHSG level in the mice, i.e., the AHSG-deficient mice were the most sensitive to BMP-induced bone formation.[32]

Fetuin is thought to have a local inhibitory effect on osteogenesis by competitively binding to osteogenic cytokines TGF-beta-1 and BMP-2, 4 and 6,[29,39,32] rendering them unavailable to induce early osteoblastic differentiation and proliferation.[32] Fetuin has been found to inhibit osteogenesis in dexamethasone-induced rat bone marrow cultures (dex-RBMC) when added during the first 6 days of culture when peak osteoblastic differentiation occurs.[28] Fetuin had no effect when added after 6 days of culture, which is well before the period (10–12 days) when osteoblastic mineralization is maximal. The addition of fetuin to these cultures suppressed the transcription of several genes involved in osteoblastic differentiation that are normally up-regulated in dex-RBMC.[28] This is consistent with findings that AHSG-deficient mice have increased alkaline phosphatase activity, a measure of osteoblast differentiation. Finally, many studies have noted that removal of fetuin also increases differentiation of adipocytes.[28,29,32] Researchers postulated that since adipocytes share the same precursor cells as osteoblasts, they also share a similar proliferation and differentiation pathway that is normally down-regulated by fetuin.[28,32]

Fetuins may also have a systemic role in the inhibition of osteogenesis, as they are not only found locally in bone but also systemically within the extracellular space.

Extracellular fluids are supersaturated with calcium and phosphate, which will precipitate in the absence of such inhibitors as fetuin.[31] At physiological concentrations, AHSG inhibits spontaneous calcium and phosphorus precipitation.[31] AHSG may bind with serum phosphate and calcium to form a transient insoluble colloidal sphere that prevents nucleation and formation of precipitate. These complexes are termed "calciprotein particles." It is important to note that as fetuin is found within the blood, further systemic administration could be an effective treatment in preventing heterotopic ossification.

Fetuin may be considered as a treatment to prevent postoperative heterotopic ossification in patients with AHO and those undergoing total hip arthroplasty or TMJ reconstruction. If heterotopic ossification is due to BMP seeding, fetuin could act locally and systemically to prevent osteoblast differentiation and proliferation. Fetuin could also act systemically by preventing calcium and phosphorus precipitation in the serum. With its diverse roles in local and systemic osteoinhibition, further study of the therapeutic role of fetuin is most certainly warranted.

More research is needed to understand the pathophysiology of heterotopic bone formation in patients with AHO and similar genetic diseases. With a better understanding of the deficiency responsible for heterotopic ossification and with more insight into osteogenic mediators and inhibitors in general, we may be able to circumvent heterotopic ossification in such predisposed patients.

Currently, no specific surgical interventions are planned for our patient. Surgery would likely cause more harm than benefit at this time because of the potential for further calcification of soft tissues traumatized by surgery. Morbidity at the donor site where reconstructive materials would be harvested would include further subcutaneous and soft tissue calcification, which could lead to further debilitating and mobility-limiting heterotopic ossification. Without the availability of adjuncts to reduce the potential for uncontrolled soft tissue calcification, the risks do not outweigh the anticipated benefit of a short-lived relief of this patient's TMJ ankylosis.

However, we are investigating the potential use of fetuin as well as other osteoblast-modulating factors. With further investigation and testing, we hope to develop adjuncts that may be offered to this patient to reduce the risk of postsurgical heterotopic ossification or aberrant bone formation.

Until such an adjunct is developed, we must address this patient's dental care as best we can. We plan to remove the caries using a buccal approach and restore the teeth in a way that maximizes self-cleansing. As the patient is not chewing or loading his teeth, we can undermine occlusal enamel to avoid the challenge of restoring the occlusal surfaces where possible. Clearly it is of utmost importance that the patient maintains meticulous oral hygiene and uses fortified fluoride dentifrice and rinses at home. Diet counselling will provide specific recommendations to further lower the patient's risk of caries. We plan to see him during frequent recalls to clean the buccal surfaces of his teeth and to apply fluoride.

Fortunately, the patient has fared remarkably well with practically no dental care, and we intend to maintain his dentition with conservative measures for as long as possible. Nonrestorable teeth will be evaluated for surgical extraction using a buccal approach. Situations not amenable to this approach would cause us to reconsider a surgical procedure to release his ankylosis. Likewise, pain or infection could be an indication for surgery. If surgical intervention becomes inevitable, we hope to be able to reduce the risk of recurrence and further soft tissue calcification with the use of fetuin or a related inhibitor of bone formation.

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