CASE REPORT

Osteopetrosis of the mandible masquerading as tubercular osteomyelitis

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SUMMARY

Osteopetrosis is a rare congenital (autosomal type) disorder of the skeletal system. Several variants have been described in the literature with grossly variant prognosis and clinical behaviour. Several reports of intractable osteomyelitis of the jaw bones secondary to osteopetrosis, particularly the mandible, have been published widely. However, there is no published report of the complete mandible sequestering de novo, in the literature. An overview of this spectrum of sclerotic bone disease, its presentation in the oro-facial region, the diagnostic challenge it poses and the management dilemma it offers to the maxillofacial surgeon is discussed and a protocol for managing this disease effectively is presented. A clinical illustration of the complexities of management of osteopetrosis-induced osteomyelitis of jaw bones is demonstrated with a very rare case in which the entire mandible had sequestered.

BACKGROUND

Osteopetrosis is a causative factor often ignored while dealing with chronic inflammatory diseases of the mandible. These lesions are wrongly identified to arise from microbial infections (tuberculosis) rather than a deficiency in the underlying tissues (metabolic disease of bone). This case especially illustrates the prolonged treatments provided, assuming the infections to be of tuberculosis in origin while the underlying osteopetrosis of the skeleton was ignored. This eventually led to overall slowdown of growth, and total exfoliation of the mandible due to several surgeries over 12 years. Now, though the mandible is lost, yet the soft tissue structures attached to the mandible are quite intact leading to patency of the oropharyngeal tract and a reasonable quality of life for the patient in spite of prolonged hospitalisation and medications.

INTRODUCTION

Osteopetrosis or 'marble bone disease' is a congenital autosomal disorder with defective osteoclastic function. It was initially described by Albers-Schonberg in 1904.¹ The disorder manifests with a marked increase of bone density due to defective remodelling caused by failure of osteoclastic function. The reported rate of incidence varies from 1:100 000 to 1:500 000.¹⁻² Different clinical types of osteopetrosis have been described.³ An autosomal dominant variety (ADO-OMIM no.166 600) which has minimal clinical expression may be discovered during routine radiological examinations. A much severe autosomal recessive type infantile (malignant)

osteopetrosis (ARO-OMIM no.259 700), if untreated, could be fatal in infancy or early childhood. A rare intermediate type, autosomal recessive type (OMIM no.259 710) could be present in infancy with some signs and symptoms of malignant osteopetrosis.¹⁻⁵

Jaw bones, particularly the mandible, are prone to osteomyelitis in these conditions. The simple physiological process of tooth eruption, or extraction of a tooth, can initiate the process of protracted osteomyelitis.¹⁻¹² Large areas of exposed necrotic bone with accompanying oro-cutaneous fistula are common complications. The underlying altered bone physiology and morphology, haematopoietic dysfunction and perioperative anaesthetic complications throw significant challenges in management of these patients.

CASE PRESENTATION

A 15-year-old boy dwarfed for his age, having been treated as suspected tuberculous osteomyelitis of the mandible for the past 10 years, presented with an exophytic mass on right angle of mandible region with a chronic orocutaneous fistula discharging pus (figure 1). He was still on antituberculous (HRZ - isoniazid (H), rifampicin (R) and pyrazinamide (Z)) regime on presentation.

Figure 1 Preoperative clinical view of face.

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Figure 2 x-Ray of skull lateral view—preoperative.

INVESTIGATIONS

Blood investigation

Blood investigations revealed microcytic anaemia with haemoglobin 6.2 g%. His white blood cell count was 11 600 with mild thrombocytosis of 600 000. Peripheral smear showed a moderate number of reticulocytes. His biochemical parameters were within normal clinical limits. Packed cell transfusions were given at weekly intervals for 3 weeks, and at the end of 1 month, the haemoglobin recorded was 11.2g%. The patient was monitored diligently by paediatricians and physicians to restore systemic equilibrium through dietary supplements, etc.

Radiological investigations

Radiological survey in the form of full body skeletal digital radiographs was performed (figure 2). Evidence of old healed fractures in the ribs and right humerus was evident. All the classical radiographical signs of osteopetrosis are demonstrated (club-shaped proximal ends of long bones and transverse banding) (figure 3). CT scan confirmed the presence of two

Figure 3 Club-shaped widening of proximal ends and transverse banding in limbs.

large sequestrae of the mandible which were the only remnants of the entire mandible (figure 4). The maxilla showed evidence of multiple unerupted teeth.

Microbiological investigation

Microbiological investigation of pus culture from orocutaneous fistula revealed growth of *Pseudomonas* which was sensitive to ciprofloxacin. However, both the pus sample and sputum failed to show any mycobacterial acid-fast bacillus (AFB). Samples were sent to the Regional Tuberculous Research Centre. A rapid analyser 'BACTEC' test was performed which reported negative growth for mycobacterial AFB (after 4 weeks). His antituberculous drugs were stopped and the patient was started on intravenous ciprofloxacin based on current body weight (180 mg daily in two divided doses for a total duration of 2 weeks).

After thorough preoperative anaesthetic work-up, the child was taken up for general anaesthesia. Although there was a history of multiple surgeries in the past, all necessary precautions including fibreoptic intubation kit and emergency tracheostomy set were kept on standby. Under general anaesthesia, total mandibulectomy was performed with excision of the fistula and primary closure being achieved.

Biopsy and culture sensitivity tests

Bone biopsy from the Tibia confirmed the diagnosis of osteopetrosis (figures 5 and 6). However, the remnants of the mandible showed non-specific inflammatory infiltrates and necrosis (figures 7 and 8). Further, tissue samples for chromosomal analysis were sent to a reputed genetic centre. The chromosomal study revealed no specific abnormality. Based on all relevant data, this patient was diagnosed to suffer from *osteopetrosis (autosomal dominant type) type II*. However, the patient does not suffer from nerve palsies and hearing impairment.

DIFFERENTIAL DIAGNOSIS

- ▶ Metabolic diseases of the bone (eg, Gaucher's disease)
- ▶ Osteomyelitis of bone due to microbial infections (tuberculosis, fungal, etc)
- ▶ Bisphosphonates-induced osteonecrosis

TREATMENT

Under general anaesthesia, total mandibulectomy was performed with excision of the fistula and primary closure being achieved.

OUTCOME AND FOLLOW-UP

Fortunately and possibly due to multiple surgeries in the past and the presence of fibrosis, the tongue maintained its support even after complete mandibulectomy (figures 9 and 10).

The patient is currently on long-term follow-up both at our maxillofacial department and paediatric department. His haemoglobin level is stable at around 10 g%. As the haematological parameters are largely stable, no further active interventions in the form of calcitriol or interferon have been started. The patient is maintaining adequate nutritional intake orally.

DISCUSSION

The Nosology group of the International Skeletal Dysplasia Society has classified osteopetrosis as follows:¹³

- ▶ ARO Classic, Neuropathic and ARO with renal tubular acidosis.
- ▶ X linked osteopetrosis.
- ▶ Intermediate recessive osteopetrosis.
- ▶ Autosomal dominant osteopetrosis (ADO)-types I & II.

Figure 4 CT scan of mandible—preoperative two-dimensional.

Osteopetrosis being an autosomal disorder with varying degrees of severity has been widely reported in the literature. No race predilection has been reported. However, consanguinity seems to be a contributory factor.

The aetiology of osteopetrosis is purely due to defects in the osteoclasts which can be of two types—osteoclast-rich and osteoclast-poor forms. In the former, the osteoclasts are either normal or increased in number but are unable to form the ruffle border which is indispensable for resorbing bone. In the osteoclast-poor form, there is a reduction in the number of osteoclasts which could be due to reduced number or absence of osteoclast progenitor/precursor cells. The defect is with osteoclastogenesis signalling, hence the progenitor cells do not progress into mature osteoclasts. The ability of mature osteoclasts to resorb bone is also reduced due to mutations in RANKL genes. Lack of bone resorption explains

the pathogenesis of haematological and neural failure and of bone fragility.¹²

Incidence of osteomyelitis of the jaws, particularly the mandible has been reported widely. However, there is no report where the entire mandible had been sequestered.^{1–10 14–16}

Clinically, ARO presents at birth to early infancy with diffuse generalised sclerotic skeleton.^{11–14} Marrow spaces are obliterated resulting in severe anaemia. Hepatosplenomegaly is present due to extramedullary haematopoiesis. There is increased susceptibility to infections due to defective granulocytes. Progressive narrowing of the foramina in the base of the skull may lead to blindness and other cranial nerve palsies. The disease, if untreated, is fatal in the first decade of life.^{3 13–15} Penetrated x-rays of long bones reveal transverse bands in the metaphyseal region and longitudinal striation along the shaft.

Figure 5 Histopathology image of medulla high power cartilage in bony trabeculae.

Figure 6 Histopathology image of cortex of tibia—irregular thickened trabeculae with cartilage.

Figure 7 Sequesterum of right mandible.

Eventually, the long bones assume a 'flask shape' or club shape, particularly in the proximal end of the humerus and distal end of femur.^{16–20} Skull bones show progressive sclerosis with the base of the skull affected more. However, in type I ADO, the skull vault is affected more than the skull base. Narrowing of the foramina may be demonstrable on CT scans. The vertebral spine shows thickening of the end plates causing a transverse band termed as 'Rugger jersey' appearance. In ADO, the appearance can vary between Rugger jersey type and that of uniform density, or it may be uninvolved.^{15 18} 'Endobones' or bone in bone appearance is evident in the pelvis, spine and distal long bones.¹⁸ These signs are usually considered pathognomic of osteopetrosis. Chest radiograph shows sclerotic ribs with no medullary differentiation.¹⁶

In the maxillofacial region, both maxilla and mandible show diffuse sclerosis with no cortico-medullary differentiation. The maxillary sinus is generally sclerotic and may be completely obliterated in some cases. Multiple teeth may be unerupted or impacted. The teeth may be malformed and prone to caries.^{1 4 11 16} Ribs and long bones may show sign of old fractures. These patients are prone to fractures even with trivial injury.

The intermediate variety presents with varying degree of skeletal sclerosis, anaemia and pathological fractures.

Figure 8 Sequesterum of body of mandible (intraoral sequesterum).

Figure 9 x-Ray of skull lateral view — postoperative.

Manifestations in X linked osteopetrosis include generalised skeletal sclerosis, tooth eruption defects, lymphoedema, anhidrotic ectodermal dysplasia and immunodeficiency.³

The molecular basis of these conditions still remains unclear. Diagnosis of this condition is based on clinical signs and symptoms and is largely aided by radiographical signs.^{15–17} The gene for the adult type of osteopetrosis has been mapped to 1p21.^{14 15 21 22} Genetic mapping for this condition is still not available in many parts of the world.¹¹ We encountered a similar problem in our patient as well. Genetic study was unable to fix the causative genetic mutation. Our diagnosis was based on the clinical and radiological features which were confirmed by histopathology of the bone sample from tibia.

Figure 10 Postoperative clinical view of patient without mandible.

Treatment of severe infantile malignant osteopetrosis is either bone marrow transplant or haematopoietic stem cell transplant.^{15 23–26} Treatment with calcitriol to stimulate dormant osteoclast has been tried with mixed success. Other therapies including interferon and corticosteroids have been reported.^{1 2 11 15} Differential diagnoses of conditions which may resemble osteopetrosis, particularly of the jaw bones include Bisphosphonate-induced osteonecrosis as described by Whyte *et al*²⁷ in a 12-year-old boy who was on pamdronate.

Management of this condition depends on the type and clinical severity of the disease. The aggressive infantile malignant ARO still carries a significant mortality rate. Late onset osteopetrosis of ADO type II may not be fatal but still leaves a significant morbidity for the patient.

Anaesthetic complications

The literature is abundant on the potential anaesthetic complications in this group of children.^{23 28} Burt *et al*, in their study, have detailed the general morbidity and mortality associated with general anaesthesia for patients with osteopetrosis.²⁷ ARO is characterised by altered neurological, respiratory and haematological functions. These patients are likely to have a high-arched palate and narrowed nasal passage due to the sclerotic turbinates, hypertelorism, frontal bossing and broad facies. They also may have limitations in their temporomandibular joint function. Airway management via a mask or laryngeal mask may be desirable for short procedures like bone biopsy. However, complex surgeries including craniofacial procedures necessitates definitive airway which requires tracheal intubation. Extreme precaution is necessary to maintain the patient on spontaneous ventilation till the vocal cords can be clearly visualised and the airway secured. In spite of the anaesthetic advances, the morbidity and mortality rates are still high in patients with osteopetrosis. The most common problem is difficult intubation with inability to intubate the trachea in a significant percentage.^{23 28}

Dental extractions may become necessary due to defective enamel and poor oral hygiene. However, performing extractions are difficult and are usually followed by large exposed necrotic bone leading to a protracted osteomyelitis and draining orocutaneous fistulae. Even erupting teeth may lead to severe infection such as orbital cellulitis.^{1–11}

Surgical options in such cases necessitated judicious removal of hopeless teeth and saucerisation of the bone to achieve adequate soft tissue cover for the exposed bone. The surgeon often faces an intraoperative dilemma of how much to remove as there is poor delineation between necrotic bone and sclerotic bone. Prudent judgment is warranted in striking a balance between leaving gross facial disfigurement to that of risking persistent infection.

In the oral cavity, particular attention should be given to accurate and early diagnosis of the disease and initiating prophylactic treatment in the form of restorations and periodontal care to prevent onset of infection. Any oral surgical procedures including extractions, if needed, should be meticulously planned and better be performed at specialised centres.

Learning points

In summary, the following sequence is suggested for the management of intractable osteomyelitis of the jaws with doubtful aetiology.

- ▶ Awareness about metabolic disorders/diseases of the bone as the predisposing factor for intractable osteomyelitis to set in and have an insidious course, rather than presume all long-standing osteomyelitis cases to be of microbial origin and treat it as a pure case of bone infection. The commonly implicated microbes in intractable osteomyelitis may be opportunistic pathogens in a defective bone environment.
- ▶ Generalised full body skeletal radiographical survey. Routine use will help differentiate between localised disease and general skeletal disease.
- ▶ Thorough haematological and biochemical investigations (including: serum levels of alkaline phosphatase, and immunoglobins and ACE) help in understanding the general status of the patient and provide a basis for formulating the medical treatment plan prior to aggressive surgery. This step also eliminates rare conditions such as metabolic disorders (Gaucher's disease) and other collagen disorders.
- ▶ Microbiological sampling of tissue gives both a diagnostic and therapeutic guideline to initiate an appropriate treatment regime and aids in continuing the same line of treatment.
- ▶ Histopathology usually is confirmatory in nature; however, it needs correlation with other facts to arrive at a definitive diagnosis.
- ▶ Genetic studies may provide the missing piece of the complex jigsaw puzzle in the most challenging of cases.
- ▶ As a thumb rule, systemic antimicrobial therapy (therapeutic) based on specificity of response to repeated culture and sensitivity testing, coupled with extended therapeutic doses of more than 3–6 weeks with appropriate monitoring of general condition of the patients helps to control super added infections.
- ▶ Subsequently, aggressive but judicious surgical curettage/tissue removal to eliminate dead/dying tissue and encourage healing will arrest the spread of disease. Caution should be exercised when large areas are removed as they may impair function. In such cases, prudence is required to limit the size of the excision such that most of the disease is removed.
- ▶ System status of the patient and management of comorbid conditions needs to be monitored meticulously.
- ▶ Practice of evidence-based medicine, with a multidisciplinary approach in diagnosis, treatment planning and management, is the key to successful management of these challenging clinical scenarios.
- ▶ Last, genetic counselling and antenatal diagnosis allow the affected families to make reproductive decisions. In families with severe autosomal recessive type infantile osteopetrosis, haematopoietic stem cell transplant within 3 months can be planned to improve haematological and neural outcomes.

Competing interests None.

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REFERENCES

- Lam DK, Sándor GK, Holmes HI, *et al.* Marble bone disease: a review of Osteopetrosis and its oral health implications for dentists. *J Can Dent Assoc* 2007;73:839–43.
- Roopashri RK, Gopakumar R, Subhas BG. Osteomyelitis in infantile osteopetrosis: a case report with review of literature. *J Indian Soc Pedod Prev Dent* 2008;26 (Suppl 3):S125–8.
- Stark Z, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis* 2009;4:5.
- Krithika C, Neelakandan RS, Sivapathasundaram B, *et al.* Osteopetrosis-associated osteomyelitis of the jaws: a report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:e56–65.
- Yamada T, Mishima K, Imura H, *et al.* Osteomyelitis of the mandible secondary to infantile osteopetrosis: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:e25–9.
- Satomura K, Kon M, Tokuyama R, *et al.* Osteopetrosis complicated by osteomyelitis of the mandible: a case report including characterization of the osteopetrotic bone. *Int J Oral Maxillofac Surg* 2007;36:86–93.
- Vázquez E, López-Arcas JM, Navarro I, *et al.* Maxillomandibular osteomyelitis in osteopetrosis. Report of a case and review of the literature. *Oral Maxillofac Surg* 2009;13:105–8.
- Oğütçen-Toller M, Tek M, Sener I, *et al.* Intractable bimaxillary osteomyelitis in osteopetrosis: review of the literature and current therapy. *J Oral Maxillofac Surg* 2010;68:167–75.
- Rajathi M, Austin RD, Mathew P, *et al.* Autosomal-dominant Osteopetrosis: an incidental finding. *Indian J Dent Res* 2010;21:611–14.
- Albuquerque MA, Melo ES, Jorge WA, *et al.* Osteomyelitis of the mandible associated with autosomal dominant osteopetrosis: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:94–8.
- Chattopadhyay P, Kundu AK, Saha A K, *et al.* Mandibular osteomyelitis and multiple skeletal complications in Albers-Schönberg disease. *Singapore Med J* 2008;49:e229.
- Del Fattore A, Capriello A, Teti A. Genetics, pathogenesis and complications of osteopetrosis. *Bone* 2008;42:19–29.
- Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders; 2006 Revision. *Am J Med Genet Part A* 2007;143A:1–18.
- Beighton P, Horan F, Hamersma H. A review of the osteopetroses. *Postgrad Med J* 1977;53:507–16.
- Wilson CJ, Vellodi A. Autosomal recessive osteopetrosis: diagnosis, management, and outcome. *Arch Dis Child* 2000;83:449–52.
- Bénichou OD, Laredo JD, de Vernejoul MC. Type II autosomal dominant osteopetrosis (Albers-Schönberg disease): clinical and radiological manifestations in 42 patients. *Bone* 2000;26:87–93.
- Bollerslev J, Andersen PE Jr. Radiological, biochemical and hereditary evidence of two types of autosomal dominant Osteopetrosis. *Bone* 1988;9:17–13.
- Van den Broek T, Bulk S, Pruijs JE, *et al.* Radiological “bone within a bone” appearance with atraumatic fractures. *Postgrad Med J* 2009;85:514.
- Ihde LL, Forrester DM, Gottsegen CJ, *et al.* Sclerosing bone dysplasia's: review and differentiation from other causes of osteosclerosis. *Radiographics* 2011;31:1865–82.
- Anderson PE, Bollerslev J. Heterogeneity of autosomal dominant Osteopetrosis. *Radiology* 1987;164:223–5.
- Van Hul W, Bollerslev J, Gram J, *et al.* Localization of a gene for autosomal dominant Osteopetrosis (Albers-Schönberg disease) to chromosome 1p21. *Am J Hum Genet* 1997;61:363–9.
- Van Hul E, Mathysen D, Bollerslev J, *et al.* Autosomal dominant Osteopetrosis type I is genetically linked to the same region on human chromosome 11 as the high bone mass phenotype. *J Bone Miner Res* 2000;15(Suppl 11):S260.
- Burgoyne LL, Kaur A, Billups CA, *et al.* Complications of anesthesia for children with malignant infantile Osteopetrosis before and after hematopoietic stem cell transplantation. *Paediatr Anaesth* 2010;20:1046–51.
- Jälevik B, Fasth A, Dahllöf G. Dental development after successful treatment of infantile Osteopetrosis with bone marrow transplantation. *Bone Marrow Transplant* 2002;29:537–40.
- Steward CG. Hematopoietic stem cell transplantation for Osteopetrosis. *Pediatr Clin North Am* 2010;57:171–80.
- Cheow HK, Steward CG, Grier DJ. Imaging of malignant infantile Osteopetrosis before and after bone marrow transplantation. *Pediatr Radiol* 2001;31:869–75.
- Whyte MP, Wenkert D, Clements KL, *et al.* Bisphosphonate-induced Osteopetrosis. *N Engl J Med* 2003;349:457–63.
- Burt N, Haynes GR, Bailey MK. Patients with malignant Osteopetrosis are at high risk of anesthetic morbidity and mortality. *Anesth Analg* 1999;88:1292–7.

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