Oral Diseases (2005) 11, 46–49

http://www.blackwellmunksgaard.com

CASE REPORT

Osteopetrosis – a review and report of two cases

AM Filho[1], A de Castro Domingos[1], DQ de Freitas[1], EJ Whaites[2]

[1]*Dental Radiology Department, Piracicaba Dentistry School, University of Campinas, Piracicaba, Brazil;* [2]*Dental Radiology Department, Guy's King's and St Thomas' Dental Institute, King's College, London, UK*

We present a brief review of the rare condition of osteopetrosis together with two case reports of this disease in the same family affecting the jaws. The first in a 41-year-old woman, and the second in her 39-year-old brother. Plain films and computed tomography showed marked sclerosis of the affected bones with obliteration of the medullary cavities and thickening of the cortices as well as multiple absent and unerupted teeth. In addition radiographs showed discrete mixed radiopaque/radiolucent areas consistent with the appearance of fibro-cemento-osseous dysplasia, but which may also represent part of the overall spectrum of bone changes in osteopetrosis.
Oral Diseases (2005) **11**, 46–49

Keywords: Osteopetrosis; bone diseases; computed tomography; X-ray film

Introduction

Several names have been used to describe the rare hereditary bone disorder of osteopetrosis. These include *Albers-Schönberg disease*, (named after the German radiologist who in 1904 described a 26-year-old man with generalized sclerosis of the skeleton with multiple fractures) *marble bone disease* and *osteopetrosis*, introduced because of the dense rock-like appearance of the bone (Worth, 1963).

The precise nature of the disease is not known, although three genes have been associated with osteopetrosis in humans (Van Hul *et al*, 2002). It is thought that bone formation is normal and that bone resorption is reduced, resulting in the presence of excessive calcified tissue. The abnormal resorption results in the normal structural pattern of the bone being grossly altered – the cortices are thickened, individual bony trabeculae are increased, the marrow spaces are encroached upon leading to a paucity of haemopoetic tissue with consequent secondary anaemia (White and Pharoah, 2000; Van Hul *et al*, 2001). One unexpected feature of this hypercalcification is an increased bone fragility so that fractures are common (Worth, 1963).

Four types of osteopetrosis have been described (Bollerslev and Andersen, 1988; Frattini *et al*, 2000; Kornak *et al*, 2001; Van Hul *et al*, 2002):

- Severe infantile or malignant type which is associated with mutations in the TCIRG and C1CN7 genes.
- Osteopetrosis with renal tubular acidosis and cerebral calcifications which is associated with a deficiency of carbonic anhydrase II (CA II) and mutations in the gene encoding the CA II protein.
- Benign type whose causative gene still needs to be identified in the chromosome 11q12–13 region that has been shown to be genetically linked to this type.
- Intermediate type.

Severe infantile or malignant osteopetrosis is present at birth or develops within the first months of infancy. Neurological and haematological manifestations include hepatomegaly, splenomegaly (both resulting from compensatory extramedullary haemopoesis), lymphadenopathy, blindness (caused by optical nerve atrophy), fractures, osteomyelitis and severe anaemia. As a result, patients do not usually live beyond the age of 20 years. Radiographically, a generalized increased bone density is seen together with modelling defects at the metaphyseal ends of long bones, resulting in typically widened and blunted diaphyses and metaphyses (Worth, 1963; Shapiro, 1993).

Osteopetrosis with renal tubular acidosis and cerebral calcifications is an autosomal recessive type of the disease that manifests in early childhood with pathological fractures, short stature and in most cases mental retardation. The radiological findings are very similar to those seen in other types of osteopetrosis but there seems to be a spontaneous regression of the osteosclerosis in later childhood (Bollerslev and Andersen, 1988).

Correspondence: AM Filho, Avenida Limeira, 901 Areião Caixa Postal 52 CEP: 13414-018 Piracicaba – SP Brazil. Tel: 55 19 3412 5327 or 55 19 3412 5329, Fax: 55 19 3412 5218, E-mail: montebel@fop.unicamp.br
Received 19 December 2003; revised 22 March 2004; accepted 31 March 2004

Benign osteopetrosis usually affects adults but it has also been detected in very young people, progressing until the end of bone growth (Worth, 1963). Although cases of benign osteopetrosis have been reported affecting children at an early age (Rosenthal, 1990; el-Tawil and Stoker, 1993). The patients do not usually present with any symptoms, and in some instances the disease is only detected when radiographs are taken for some other purpose. Fractures and osteomyelitis of the jaws are common complications of this form of the disease (Shaff and Mathis, 1982). Despite this increased susceptibility to fractures, healing appears to proceed normally. The serum levels of calcium, phosphorus and alkaline phosphatase are usually normal. Gross examination of affected long bones shows them to be shorter than normal, heavy, thick, deformed with their ends splayed out and in some cases there is fibrosis of the marrow spaces (Van Hul *et al*, 2001). Radiologically, autosomal dominant osteopetrosis is characterized by a generalized, uniform osteosclerosis mainly of the skull, the spine and the long bones (Van Hul *et al*, 2002).

Intermediate type osteopetrosis, may affect children or adults and may present with either the clinical features of the infantile manifestation or be asymptomatic (Beighton *et al*, 1979; Colônia *et al*, 1993). It consists of an autosomal recessive mode of inheritance and is shown on radiological survey as diffuse osteosclerosis.

Case report 1

A 41-year-old Brazillian woman was referred to the dental hospital by her general dental practitioner for possible implant placement and subsequent prosthesis to restore her dentition as she was experiencing difficulty when eating. Extra-oral physical examination revealed nothing abnormal and there was no apparent facial asymmetry. Panoramic and lateral skull radiographs (Figures 1 and 2) showed an abnormal appearance of the bone, characterized primarily by an increased overall density. The medullar cavities were obliterated and the cortices were thickened. Several teeth were absent and others were impacted. Several mixed radiolucent/radiopaque areas were observed on the panoramic radiograph in the region of the lower molars, above the mandibular canal, resembling florid fibro-cemento-osseous dysplasia. Intra-oral radiography of the lower incisor region (Figure 3) showed multiple radiolucent/radiopaque lesions in the apical regions resembling periapical fibro-cemento-osseous dysplasia, but these may also represent part of the overall spectrum of bone changes seen in osteopetrosis.

Computed tomography (CT, Figure 4) showed the intense bony sclerosis in both jaws. The normal blood picture showed serum levels of calcium 10.2 mg%,

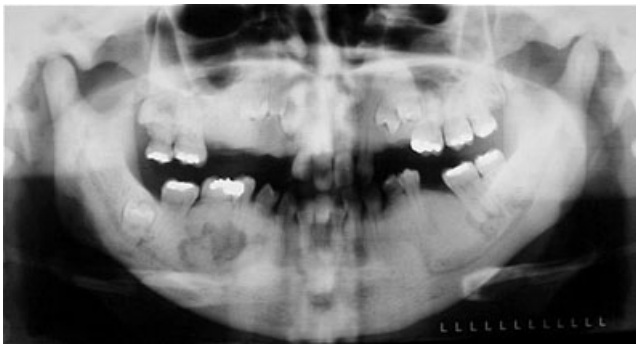

Figure 1 Panoramic radiograph of patient (1) showing an increased overall bone density, several unerupted impacted teeth and the presence of mixed radiolucent/radiopaque areas particularly in the lower molar regions

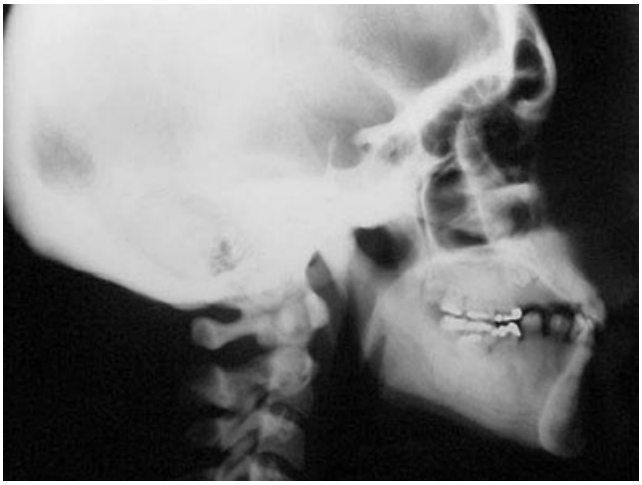

Figure 2 Lateral skull radiograph of patient (1) showing the increased overall bone density in both jaws

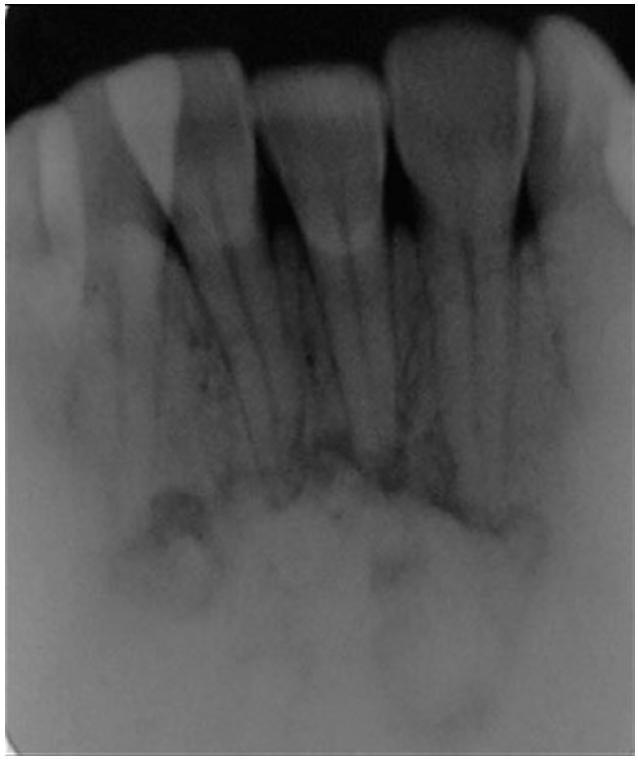

Figure 3 Periapical radiograph of the lower incisor region of patient (1) showing multiple mixed radiolucent/radiopaque areas

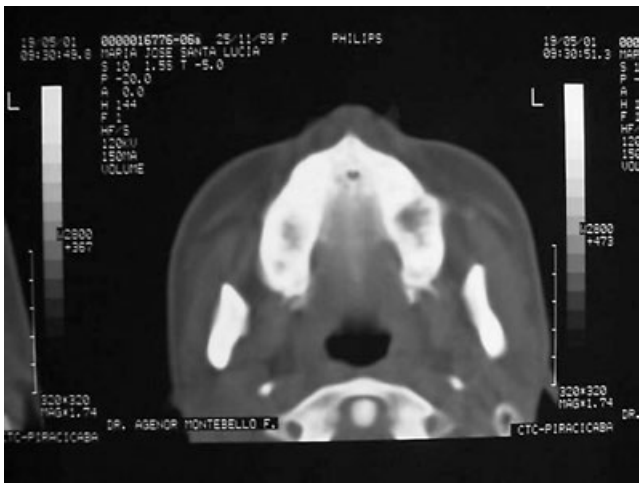

Figure 4 Axial computed tomography image of patient (1) showing intense bony sclerosis in the maxilla

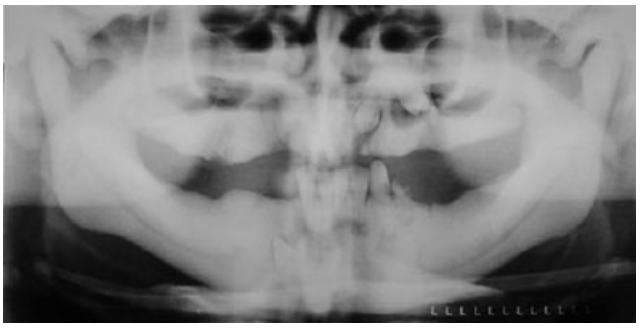

Figure 5 Panoramic radiograph of patient (2) revealing the similar typical sclerotic bone of osteopetrosis with three unerupted impacted teeth – the two in the maxilla appear to have dentigerous cysts associated with their crowns

phosphorus 3.5 mg% and alkaline phosphatase 180 U I^{-1}. A biopsy was not performed because of the risk of development of osteomyelitis and a diagnosis of osteopetrosis was made based on the radiographic and clinical findings. Further skeletal radiographs of her arms, vertebrae and clavicles were carried out to assess other bony involvement, but only the right arm showed evidence of osteopetrosis.

As the patient was asymptomatic the oral and maxillofacial surgeons decided not to treat the patient surgically either to insert implants or to remove the unerupted teeth because of the risk of osteomyelitis. The patient was referred to the Prosthetics Department and a simple removable prosthesis was constructed to improve function. The patient has been followed up subsequently and remains symptom-free.

Other close members of her family were asked to attend for examination and investigation. These included her mother, father, brother and her son. Her mother, father and son showed no clinical or radiographic evidence of osteopetrosis in their jaws, however her brother did and is described below.

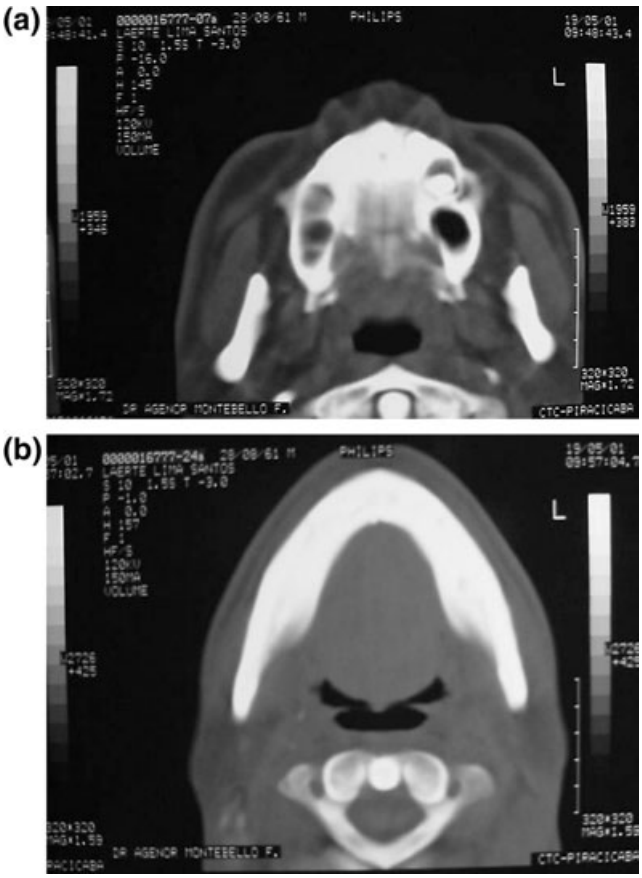

Figure 6 Two axial computed tomography images of patient (2) displaying the similar intense increased bone density in both jaws that was evident in his sister

Case report 2

The 39-year-old brother was also missing several teeth, although, like his sister, examination showed no apparent abnormality extra-orally. Panoramic and CT examination however showed the same dense sclerotic bone of osteopetrosis (Figures 5 and 6). Although several of his teeth were missing, presumably extracted, several teeth were still unerupted, with the two retained in the maxilla apparently associated with dentigerous cysts. Intraoral radiography of the lower incisor teeth (Figure 7) again showed several mixed radiolucent/radiopaque areas resembling periapical fibro-cemento-osseous dysplasia. The patient did not want any form of restorative treatment, and as the upper right central incisor and lower left first premolar were causing him pain, these were extracted and prophylactic antibiotics prescribed because of the risk of osteomyelitis. He has subsequently been followed up and is symptom-free.

Discussion

As osteopetrosis is rare, it is very unusual to diagnose it in two members of the same family as illustrated here. In both cases the diagnosis was based on the clinical and radiographic appearances – an approach frequently defended (Beighton *et al*, 1979; Demirci and Sze, 1991;

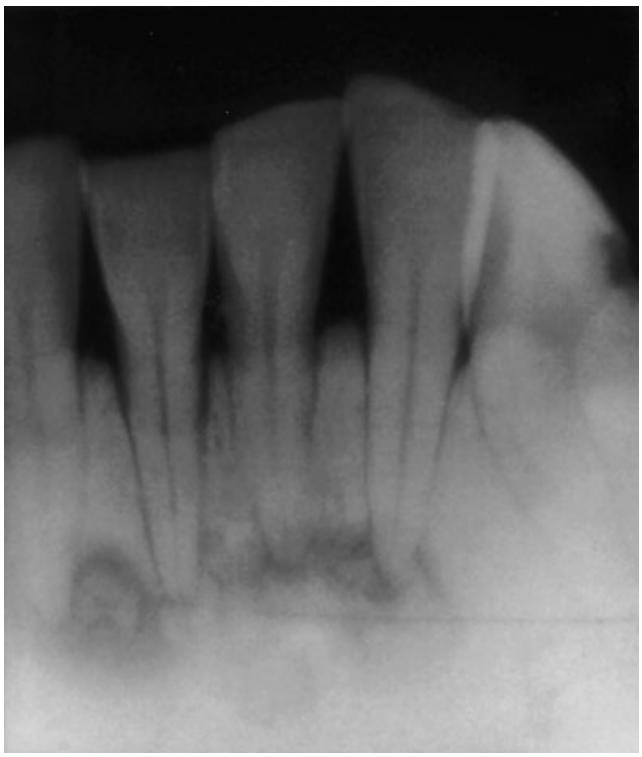

Figure 7 Periapical radiograph of the lower incisor region of patient (2) showing similar multiple mixed radiolucent/radiopaque areas

Shapiro, 1993). Biopsy was not performed in either case because of the risk of development of osteomyelitis (Shaff and Mathis, 1982).

The radiographic findings are compatible with those described in the literature which include: an overall sclerotic appearance and obliteration of the medullary cavities, thickened cortices in the calvaria with loss of the normal skull markings, gross thickening and increased opacity of the cranial base with narrowing of the foramina, increased bone density in the jaws, more commonly in the maxilla, initially presenting as thickening of the lamina dura, but which can eventually obscure the roots, and unerupted, impacted or missing teeth.

Although it has been reported that the mandible is less frequently involved than other bones, it was affected in both these cases. The dental findings of absent and impacted teeth correspond with those reported by several authors (Regezi and Sciubba, 1989; White and Pharoah, 2000). Neither of the cases presented with any clinical signs or symptoms – a characteristic of not only the benign, but also the intermediate type of osteopetrosis, and both were diagnosed radiographically. The patients were subjected to CT examinations to analyse their bone density. This diagnostic method has been previously used and advocated (Kaplan *et al*, 1993).

The familial nature of these two cases would suggest that this condition was transmitted as an autosomal recessive trait, which is a feature of both the malignant and intermediate forms of osteopetrosis. The autosomal dominant type, on the other hand, may present either as a fully penetrant disease (type I) or a may have a penetrance estimated between 60 or 80% (type II) (Van Hul *et al*, 2002). These two cases may therefore more accurately represent examples of either the intermediate or the benign forms of osteopetrosis. A genetic evaluation would be fundamental to determine the type of osteopetrosis these cases belong to.

References

Beighton P, Hamersma H, Cremin BJ (1979). Osteopetrosis in South Africa. The benign, lethal and intermediate forms. *S Afr Med J* **55:** 659–665.

Bollerslev J, Andersen PE Jr (1988). Radiological, biochemical and hereditary evidence of two types of autosomal dominant osteopetrosis. *Bone* **9:** 7–13.

Colônia AMN, Schaimberg CG, Yoshinari NH, Santos M, Jorgetti V, Cossermelli W (1993). Osteopetrose: Relato de dois casos e revisão da literatura. *Rev Hosp Clin Fac Med S Paulo* **48:** 242–247.

Demirci A, Sze G (1991). Cranial osteopetrosis: MR findings. *Am J Neuroradiol* **12:** 781–782.

Frattini A, Orchard PJ, Sobacchi C, Giliani S, Abinum M, Mattsson *et al* (2000). Defects in TCIRG1 subunit of the vacuolar proton pump are responsible subset of human autosomal recessive osteopetrosis. *Nat Genet* **25:** 343–346.

Kaplan FS, August CS, Dalinka MK, Karp J, Fallon MD, Haddad JG (1993). Bone densitometry observations of osteopetrosis in response to bone marrow transplantation. *Clin Orthop* **294:** 79–84.

Kornak U, Kasper D, Bosl MR, Kaiser E, Schweizer M, Schulz A *et al* (2001). Loss of the CIC-7 chloride channel leads to osteopetrosis in mice and man. *Cell* **104:** 205–215.

Regezi JA, Sciubba JJ (1989). *Oral pathology: clinical-pathologic correlations. Genetic and metabolic diseases of the jaws*. WB Saunders: Philadelphia, pp. 326–327.

Rosenthal L (1990). Benign osteopetrosis. *Clin Nucl Med* **15:** 412–414.

Shaff MI, Mathis JM (1982). Osteomyelitis of the mandible. An initial feature in late-onset osteopetrosis. *Arch Otolaryngol* **108:** 120–121.

Shapiro F (1993). Osteopetrosis. Current clinical considerations. *Clin Orthop* **294:** 34–44.

el-Tawil T, Stoker DJ (1993). Benign osteopetrosis: a review of 42 cases showing two different patterns. *Skeletal Radiol* **22:** 587–593.

Van Hul W, Vanhoenacker F, Balemans W, Janssens, De Schepper AM (2001). Molecular and radiological diagnosis of sclerosing bone dysplasias. *Eur J Radiol* **40:** 198–207.

Van Hul E, Gram J, Bollerslev J *et al* (2002). Localization of the gene causing autosomal dominant osteopetrosis type I chromosome 11q12–13. *J Bone Miner Res* **17:** 1111–1117.

White SC, Pharoah MJ (2000). *Oral radiology: principles and interpretation. 4th edn. Systemic diseases manifested in the jaws*. Mosby: St Louis, pp. 472–492.

Worth HM (1963). *Principles and practice of oral radiologic interpretation*. Year Book Publishers: Chicago, USA, pp. 128–131.