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CASE REPORT

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Type II autosomal dominant osteopetrosis

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Abstract Two principal types of osteopetrosis have been distinguished. One is the dominantly inherited, relatively benign condition which is often detected radiologically in asymptomatic adults. A second type is the recessive, lethal, malignant form. Autosomal dominant osteopetrosis (ADO) has two distinct radiological subtypes known as types I and II. We report here a 23-year-old patient with ADO type II. Radiographic investigations of a skeletal survey showed generalised osteosclerosis with thickened cortex. Magnetic resonance imaging (MRI) scan disclosed osteosclerosis in superior and inferior portions of the vertebral bodies which produced a 'sandwich' appearance. The 'bone-within-bone' appearance was seen in the ileum of the patient. The vertebral bone density was found markedly elevated. The carbonic anhydrase II level was found to be normal. We discuss here the genetic etiology of this disorder.

Keywords Autosomal dominant osteopetrosis · Bone resorption · Genetic etiology

Introduction

Osteopetrosis is an inherited metabolic bone disease in which a generalised accumulation of bone mass prevents normal development of marrow cavities and the enlargement of osseous foramena. It has been called 'marble bone disease' because the bones are very dense radiographically, although they typically have increased susceptibility to fracture [1].

Two principal types of this disease have been described. The autosomal recessive form is clinically severe and has onset in infancy, produces anaemia, leukopoenia, hepatomegaly, failure to thrive, and cranial nerve symptoms, and it leads to early death [2].

The second, autosomal dominant type of osteopetrosis is also designated Albers-Schönberg disease [3]. Affected persons may be relatively asymptomatic, or the disease may be detected because of pathologic fractures, mild anaemia, or cranial nerve palsies. The bones are diffusely osteosclerotic with defective tubulation and thickened cortices. The disorder is compatible with a normal life span and is referred to as the adult or benign form of osteopetrosis [4].

Here we describe a patient with type II ADO and discuss the clinical, laboratory, and radiographic features and the genetic aetiology of this disorder in light of the literature.

Case report

Patient YK was a 23-year-old man first seen in April 1996. He had an 8-year history of low back pain. He had been treated with various anti-inflammatory drugs in previous years. Father, mother, and other sibships were normal, and there was no parental consanguinity.

The patient's height was 170 cm, and he weighed 66 kg. Dorsal and lumbar vertebrae motions were painful and limited. The other joints were normal. Lumbar Schober, chest expansion, and fingertip-to-floor were found to be 3, 4, and 35 cm, respectively. Neurological and otolaryngological examinations revealed no abnormalities. Psychomotor development was normal.

Biochemical studies revealed a haemoglobin level of 10 g/dL and an elevated Westergren sedimentation rate at 35 mm/h. Serum blood urea nitrogen (BUN) was 30 mg/dL, serum creatinine 0.6 mg/dL, serum calcium 8.5 mg/dL, serum phosphorus 1.3 mg/dL, and alkaline and acid phosphatase levels were 250 U/L and 12 U/L, respectively. Urine analyses showed urinary BUN 2000 mg/dL, urinary creatinine 65 mg/dL, and creatinine clearance 125 ml/min. Carbonic anhydrase II (CA II) level was measured in erythrocyte haemolysates according to routine technique and was found to be normal (CA-II

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CO_2 hydratase activity was 12.5 U/mg haemoglobin) [5]. The CA II levels and radiographic and laboratory examinations in the patient and other members of family were found to be normal.

Radiographic investigations of the skeletal survey showed generalised osteosclerosis with thickened cortex, but intracranial calcifications were not seen on skull films. The MRI scan disclosed osteosclerosis in superior and inferior portions of the vertebral bodies which produced a sandwich appearance. The bone-within-bone appearance was seen in the ileum of the patient (Fig. 1). The vertebral bone density was assessed by quantitative computerised tomography (QCT) and found to be markedly elevated (Fig. 2). Ultrasonography of the abdominal organs was normal.

Cytogenetical analyses were performed from skin fibroblast and peripheral lymphocytes of all members in family. All karyotypes were found to be of normal constitution. Pedigree analysis of the family was performed and showed no inheritance pattern.

Discussion

Based on standard radiographs, it is possible to describe two different subtypes with different clinical, biochemical, and histologic manifestations. Type I is radiographically characterised by pronounced osteosclerosis of the cranial vault, whereas type II has end-plate thickening of the vertebrae (Rugger-Jersey spine) and endobones in the pelvis. Patients with ADO are often asymptomatic, and the diagnosis may be reached by chance. However, by systematic investigations, nearly all patients have manifestations related to the disorder. Symptoms are progressive with age and correlate with osteosclerosis [6].

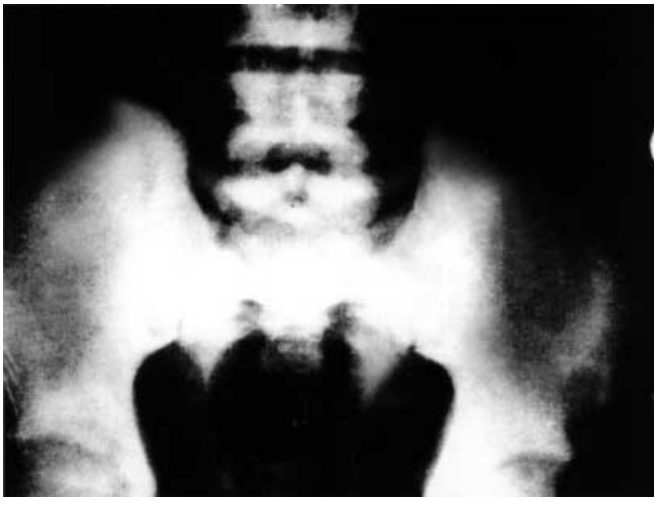

Fig. 1. Bone-within-bone appearance in the ileum

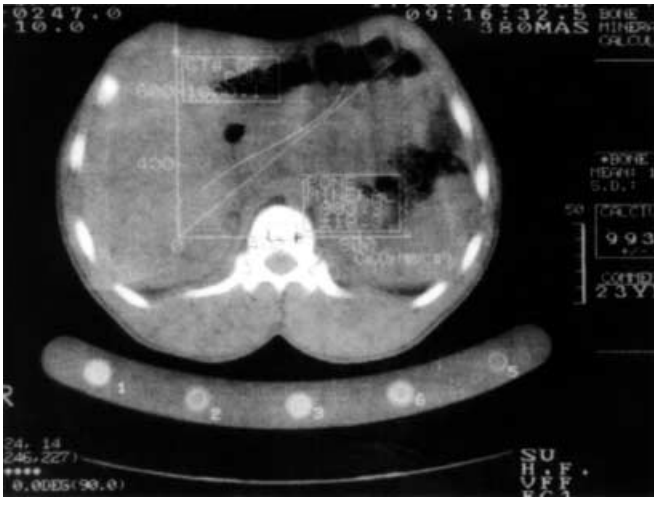

Fig. 2. Increased bone mineral density in quantitative computerised tomography

All forms of osteopetrosis are associated with failure to resorb bone [7]. An impaired hypercalamic response to infuse parathyroid hormone (PTH) has been demonstrated in osteopetrosis. The cause for this impairment might differ in the different forms of osteopetrosis. Studies showing inhibition of PTH-induced release of calcium from bone by CA inhibitors have suggested a role for CA in bone resorption. On the basis of these and other observations, it has been suggested that PTH activates CA in certain bone cells and promotes bone resorption by facilitating the secretion of hydrogen ions [8]. Carbonic anhydrase II deficiency is the primary defect in the syndrome of autosomal recessive osteopetrosis [9]. However, it has been demonstrated that CA II does not seem to play any pathogenetic role in the two forms of ADO [10].

There is some variability in the severity of different clinical manifestations in different families. In some families, the symptoms related to the osteopetrosis dominated the clinical picture. Previous studies suggested that clinical heterogeneity is due to genetic heterogeneity.

Multiple genetic defects produce osteopetrosis, but the mechanism common to all the known forms of osteopetrosis is the failure of bone resorption.

In the present case, the CA II level was found to be normal. However, except for radiological findings and anaemia, the case did not show the other findings such as metabolic acidosis, growth failure, mental retardation, bone fracture, severe dental malocclusion, cerebral calcification, and visual and hearing handicaps. Considering the normal CA II levels and the absence other findings mentioned above, the present case could not be evaluated as autosomal recessive osteopetrosis.

Interestingly, in some patients, symptoms are few, and the phenotypic spectrum varied from an asymptomatic condition to severe findings such as anaemia, hepatosplenomegaly, hydrocephalus, and blindness. In such cases, relatively benign and asymptomatic conditions are often diagnosed as osteopetrosis by radiography and other biochemical findings. The clinical picture of the present case was evaluated as being compatible with these observations, because he was first seen when 23 years old and had only the complaint of low back pain. Biochemically, normal CA II levels, mild anaemia, increased acid and alkaline phosphatase levels, low plasma phosphate level, radiologically increased bone mineral density, the sandwich appearance in MRI scan of the spine and the bone-within-bone appearance in the

ileum were detected. Further, the bones were diffusely osteosclerotic with thickened cortex. According these data, the case was evaluated as the autosomal dominant type.

Andersen and Bollerslev suggested that ADO may be a heterogeneous group. In type I, the most striking finding was pronounced sclerosis of the cranial vault, while the spine was almost unaffected. In type II, the sclerosis of the skull was most pronounced at the base, the vertebrae always had end-plate thickening, and in the pelvis the iliac wings contained convex arcs of sclerotic bone [11]. Biochemically, serum phosphate was found to be lower in type I than in type II, and serum acid phosphatase was markedly increased in type II [12]. In light of these data, the present case may be evaluated as type II ADO. Recently, the osteoclasts were found markedly reduced in number and size in type I, but in type II, the osteoclasts were large and highly multinucleated, with increased number [13]. Additionally, serum carboxy-terminal propeptide of type I collagen (S-PICP) was found significantly lower in type II ADO. Serum osteocalcin values in the two types of ADO were insignificantly lower than in controls [14]. Unfortunately, in the present case, osteoclast morphologies and S-PICP values could not be examined.

In genetic assessment, pedigree analysis revealed that the condition is not inherited, because the probands had no relative showing similar findings. Therefore, the case may interpreted as type II ADO resulting from a de novo mutation. There is no satisfactory information about the genetic aetiology of ADO in the literature. However, it can be speculated that collagen and/or osteocalcin gene mutations may contribute to the aetiopathogenesis of ADO.

In conclusion, we wish to stress that ADO is a rare condition and may be characterised by an asymptomatic clinical picture. Because of this, some patients with only low back pain of undetermined aetiology must be suspected of having ADO. Finally, the present case can provide new insights into the inheritance of ADO.

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