Progressive osseous heteroplasia

REPORT OF A FAMILY

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We report a case of progressive osseous heteroplasia in a female infant who had progressive ossification of the skin and deep connective tissues. Isolated dermal ossification is present in her father and younger sister suggesting an autosomal dominant mode of inheritance with variable expressivity or possible somatic mosaicism. This report of a family with progressive osseous heteroplasia contributes to the understanding of this uncommon genetic disorder, which must be distinguished from fibrodysplasia ossificans progressiva and Albright’s hereditary osteodystrophy. The paucity of familial cases of progressive osseous heteroplasia currently limits the use of a genome-wide linkage analysis, but linkage exclusion analysis with promising candidate genes is a possibility.

Progressive osseous heteroplasia (POH) is a recently defined developmental disorder of mesenchymal differentiation. It is characterised by dermal ossification in infancy, and by progressive ossification of the skin and deep connective tissues. Most cases are sporadic and in only two instances has a familial transmission been documented, suggesting an autosomal dominant mode of inheritance with possible somatic mosaicism.

Case report

A female infant was born after an uncomplicated vaginal delivery at 32 weeks of gestation to non-consanguineous parents living on Réunion Island, a French territory in the Indian Ocean. The father is Indian and the mother is Creole (her ancestors came from France four generations ago). Her father and a paternal aunt had scattered subcutaneous ‘nodules’ on the hands and feet.

At birth, the infant weighed 1.8 kg, was 41 cm in length and had a head circumference of 31.5 cm. Apgar scores were normal. Clinical examination at birth showed no abnormalities. At the age of one month, her mother detected hardened cutaneous lesions in the right leg. These coalesced into plaques and extended rapidly to the trunk and to both lower limbs, with subsequent ulcerations through the epidermis by the age of eight months. A skin biopsy revealed primary cutaneous osteomas.

The child was sent to the Hôpital Trousseau in Paris for further investigation. On examination, ossified plaques were found on the right half of the trunk and although present on both lower limbs the right side was predominantly affected (Fig. 1). The affected skin was rough and tender. A series of diagnostic skin and muscle biopsies was performed. Extensive areas of ossification were found in the subcutaneous tissue and dermis, but the muscle appeared normal (Fig. 2). An atypical scleroderma-like inflammation was seen in the elastic fibres of the dermis. By the age of 20 months, all the joints of the lower limbs were ankylosed and the child was unable to walk. Radiological examination showed diffuse and extensive ossification in the deep connective tissues, osteoporosis of the normotopic skeleton, and mild thoracic scoliosis (Fig. 3). Whole-body CT ruled out any visceral involvement but clearly showed encasing dermal ossification extending into skeletal muscle in the involved areas. Serum and urine levels of calcium and phosphorus were normal as were those of parathyroid hormone and vitamin-D metabolites. Liver function tests and creatine kinase and aldolase levels were also within the normal range. The scoliosis progressed...
Fig. 1a
Photographs of the child at the age of four years, when the ossified lesions were clearly hemimelic (a) and after subsequent generalisation at the age of 14 years when there was marked ankylosis of both lower limbs and skin ulceration (b).

Fig. 1b

Fig. 2
Photomicrograph showing cornified (*) cutaneous epithelium. Numerous trabeculae of mature, lamellar bone (arrows) are present within subcutaneous fat and reticular dermis, intermixed with epithelial skin appendages (Masson’s Trichrome stain ×20).

Fig. 3a
Radiographs showing extensive ossification of the trunk, predominantly in the right side (a) and in both lower limbs (b).
and it was feared that it would have a deleterious effect on ventilatory function. The ossified lesions of the trunk were removed and skin grafting performed when the child was three years old, but this gave no benefit since the graft became ossified within a few months. The upper limbs, neck and head remained uninvolved.

At a recent follow-up examination at 14 years of age, the condition had stabilised. Severe growth retardation and scoliosis were present but no new ossified plaques had formed. The joints of the lower limbs were ankylosed with flexion deformities. The forced vital capacity was reduced to 60% of the predicted value, and the child suffered numerous pulmonary infections and attacks of asthma. Neurological examination revealed no abnormalities. There was no facial dysmorphism or digital malformation. She was mentally normal and attended normal school.

Her father, aged 43 years, was also examined. At 15 years of age, he had noticed several centimetre-long ossified plaques in his right thigh, left leg, back and inguinal region. Ossified nodules were found on the dorsum of both feet and hands. They seemed to extend slowly with time but were not painful and did not appear to involve deep connective tissue or skeletal muscle. The remainder of the examination was normal.

A younger sister, aged six years, was said to be free from symptoms, but careful examination showed hardened maculopapular lesions in both feet and ankles. Dermal ossification was confirmed by radiography. The great toes appeared normal on clinical and radiological examination. It has not been possible to trace and examine the patient’s paternal aunt who is said to have similar skin lesions.

Discussion

The term ‘progressive osseous heteroplasia’ was coined in 1994 by Kaplan et al1 to describe children with progressive heterotopic ossification of the skin, subcutaneous fat and deep connective tissue. Since then, only 14 cases have been reported, mostly in females.2-5 The recent recognition of severe POH by Rosenfeld and Kaplan6 in two boys has broadened the distribution of the disorder. In only two instances has a familial transmission been documented.7,8 In both cases, a few relatives of the proband had signs of minimal ossification, such as isolated ossified maculopapules, mainly in the limbs. These findings suggested an autosomal dominant mode of inheritance with variable expressivity and possible somatic mosaicism, as in tumour suppressor gene expression.

The first symptoms of POH are usually noted during infancy, and consist of maculopapular rashes at sites of future ossification. Triggering factors such as trauma, infection or needle punctures do not seem to occur as they do in fibrodysplasia ossificans progressiva. Dermal lesions coalesce rapidly to form extensive ossified plaques. Hemimelic distribution has been described in three other cases and was present in our patient in the trunk.

The severity and morbidity of POH depend largely on the location and extent of the heterotopic ossification. In this respect, our patient was particularly severely affected. The combination of thoracic rigidity and scoliosis poses a risk of life-threatening pulmonary complications. The results of laboratory studies are usually normal, and help to exclude other diagnoses such as Albright’s hereditary osteodystrophy. Unlike fibrodysplasia ossificans progressiva, the mechanism of bone formation is predominantly intramembranous affecting the dermis before involving deeper tissues such as skeletal muscle.9

The distinction between POH and other conditions of heterotopic ossification in young children is straightforward, provided that clinical, pathological and radiological signs are properly ascertained. Fibrodysplasia ossificans progressiva is genetically determined, but often sporadic. The diagnostic features are the presence of malformations of the great toes and heterotopic endochondral ossification in characteristic anatomical patterns. Albright’s hereditary osteodystrophy is an autosomal dominant disorder, typically associated with a dysmorphic ‘moon’ facies, obesity, short stature, brachydactyly and end-organ resistance to parathyroid hormone. The recent discovery of mutations in the gene encoding the alpha subunit of the stimulatory G-protein of adenylcyclase can facilitate the diagnosis of Albright’s hereditary osteodystrophy in atypical cases.10

The treatment of POH is very disappointing. The removal of involved tissue has led to recurrence in most patients. From our experience, skin grafting should be avoided. Physiotherapy to preserve movement and the prevention of skin breakdown is the only currently acceptable, but limited, treatment available. Patients and relatives should be given adequate counselling particularly with regard to education as the patients are not mentally impaired and because the disease does not seem to progress rapidly in the adult. Genetic counselling is extremely difficult in this disorder as the genetic defect is unknown and the prognosis is difficult to establish.

Very little is known about the pathogenesis of POH.11 In the absence of markers or biological clues, the genetic approach remains the most likely way to progress. An entire genome search is hampered by the rarity of large pedigrees. Recent findings indicate that the bone morphogenetic proteins, the G-proteins and the recently described Osf-2/Cbfa1 obligatory osteoblast transcription factor12 could lead to potentially interesting candidate genes.

As with many new and extremely rare conditions, POH is probably underdiagnosed. Careful consideration of clinical and radiological signs is usually enough to recognise the disorder and to differentiate it from fibrodyplasia ossificans progressiva and Albright’s hereditary osteodystrophy. The absence of large multigenerational families impedes gene identification by linkage analysis and positional cloning, but linkage exclusion analysis with promising candidate genes is a possibility. It is important for geneticists, dermatologists, paediatricians, pathologists and
orthopaedic surgeons to be aware of POH so that unnecessary treatments can be avoided, and proper counselling offered.

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References


