Familial ectopic ossification

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SUMMARY We report a family with dominantly inherited ectopic ossification. It is characterised by childhood onset of multifocal subcutaneous ossifications (primary osteoma cutis), which are of trivial clinical significance. One family member had extensive ectopic ossification involving one limb. We speculate that this may reflect somatic mutation having caused conversion to homozygosity.

The formation of true bone in the skin, as opposed to calcification, is rare. It may be primary (idiopathic) or secondary to many conditions including surgical scars, chronic venous insufficiency, pseudohypoparathyroidism, scleroderma, dermatomyositis, and a wide variety of skin tumours and naevi.¹ By far the majority are secondary and only a small number of cases of primary osteoma cutis are on record.^{2,3} Inherited forms are very rare.

We report here a family with a dominantly inherited primary osteoma cutis. One of the family had severe and florid involvement localised to one limb. We speculate that this may reflect conversion of the abnormal gene to the homozygous state in the severely involved region.

Case reports

The pedigree is shown in fig 1. The proband (II.7) was first noted at the age of three weeks to have a small subcutaneous area of thickening in the right groin during a hospital admission for respiratory infection in 1962. Over the next few months this

area of induration extended within the inner aspect of the thigh. At three months her knee was noted to be fixed in moderate flexion and an x ray of the right thigh revealed quite extensive true ossification (cortex and trabeculae being discernible) in the periarticular soft tissue around the hip, knee, and ankle joints. There was no evidence of any radiological abnormality elsewhere. A biopsy of skin and subcutaneous tissue was taken at this time (see below). A series of serum calcium measurements done then and on several later occasions all gave normal results. Over the years the ectopic ossification within the soft tissue of the limb progressed, extending from pelvis to mid-foot, and apparently acting as an internal impediment to growth of the limb (fig 2). Serial x rays showed increasing strands and sheets of bone extending along muscle planes out into the soft tissues from the pelvic and limb bones on the right side. By the age of eight small spicules of bony tissue erupting through the skin began to appear and this continues to be present. By the time adult height was reached, the right lower limb was very short, curving inwards, with no movement at the hip, knee or ankle. Distal foot joints remained uninvolved; the big toe is biphalangeal. X ray at the age of 24 (figs 3 and 4) shows the exuberant nature of the abnormal growth in the region of the hip joint. There does not appear to have been any progression since adulthood. Elsewhere, the only ectopic growth detected was a small 3 to 4 mm subcutaneous mobile lump above her right elbow.

Three of her five sibs had evidence of ectopic bony masses. II.2 noticed a lump in her right lower anterior abdominal wall at the age of nine, which increased to become the size and shape of an egg by the age of 11, since which time it had not changed. An x ray at the time was reported as showing soft

FIG 1 Pedigree of the family. Black symbol indicates severe localised disease. Cross hatched symbols indicate minor involvement. N indicates apparently or reportedly no detectable involvement.

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FIG 2 Lower limbs of the proband aged eight years.

tissue calcifications in subcutaneous tissue from symphysis to umbilicus. In addition, a small fleck of calcification on the medial aspect of the medial tibial condyle in the vicinity of the attachment of the medial ligament of the knee joint was noted. Measurements of serum calcium phosphorus and alkaline phosphatase, and of urinary calcium and phosphorus secretion, gave normal results. No other ectopic growth has been detected.

II.5 had a lump over the left shin which appeared in childhood. This, and a similar one on her right forearm, were removed at the age of 24 and examined histologically (see below). She had many tiny hard subcutaneous specks palpable over the anterior abdomen. At the age of 21, two plaques appeared on her forehead, one over each temple. X ray survey showed a number of opacities: a 1 cm³ area just lateral to the lateral border of the lateral sesamoid of the right hallux; a tiny area about 2 mm across between the distal heads of the fourth and fifth metatarsals on the right foot; an irregular area, somewhat larger than this, in a similar position on the left; on the left foot, what looked to be a tubular area of ossification about 10 × 1 mm having origin

from the medial aspect of the calcaneus; scattered tiny areas in forearm, wrists, and hands bilaterally, and a single small area adjacent to the right ischium.

II.6 is the fraternal twin of the proband. She had only one 2 cm diameter plaque and three tiny specks, palpable over the lower back. No radiological survey was done.

In the next generation, three boys were affected. III.3 had an appearance of subcutaneous lumps in infancy on the right lower limb. On examination at the age of six, two 'islets' of two or three lumps were palpable in the region of the right popliteal fossa; the lumps felt flat and polygonal. Two other lumps over the right leg were palpable only with difficulty, and there was one small lump in the left lumbar region. X rays showed, as well as foci of radio-opacity corresponding to the palpable lumps in the popliteal fossa, a 30 × 3 mm cylindrical structure apparently attached to the medial border of the femoral condyle, and a few foci of irregular islands of radio-opacity in the subcutaneous tissues of the leg, the largest being 10 × 4 mm. The latter appeared to comprise an ovoid mass out of which sprouted two mushroom shaped excrescences.

In III.6 at four months of age, two small lumps were noted on the left thigh and three over the mid lower back. They were indicated by an overlying red spot, below which the hard lump was palpable. He died suddenly and unexpectedly at the age of five months.

His younger brother (III.7) was first noted to have palpable subcutaneous specks at six weeks, firstly on his left buttock and behind the left knee and thereafter appearing over the abdomen, back, arms and wrists. Other than one on the right forearm they did not appear to be increasing in size, but new ones continued to appear and some seemed to be coalescing. Serum calcium, phosphorus, and magnesium measurements at 14 months were within normal limits, except for a single calcium measurement at 2.6 mmol/l, marginally above the upper limit of normal (2.58). X ray of the limbs showed subcutaneous plaques at each wrist and at the left elbow.

No other family member is known to have any such lumps. Generally, we did not attempt to palpate the skin of other members of the family; the lumps are either obvious, or so subtle that they require to be pointed out by the person to the investigator. We suspected that if the person (or their spouse or parent) was unaware of the 'family lumps', we ourselves would not be able to find any by palpation. We did undertake x ray studies of the limbs of I.2, III.2, III.4, and III.5. No opacities were seen. In none of those x rayed were any phalangeal abnormalities shown.

FIG 3 *X ray of pelvis and upper femora of proband aged 24 years.*

FIG 4 *Fine quality x ray of proximal right lower limb of proband aged 24, showing the pattern of ossification within the limb.*

HISTOLOGICAL FINDINGS

Fresh slides were prepared from the original thigh biopsy taken from the proband in 1962 (fig 5a). Ectopic ossification was present within the dermis. The lesion comprised irregular nodules of osteoid of varying degrees of calcification, frequently associated with hair follicles and eccrine glands. There was extensive fibrosis of overlying dermis, with a de-

creased number of skin appendages. The striated muscle generally showed fibres of normal size and shape, although in some areas there was considerable fibrosis, interpreted as being consistent with atrophy due to immobility. One of the spicules erupting through the skin at the age of 23 was studied (fig 5b). This fragment comprised well organised lamellar bone containing adipose marrow

FIG 5 (a) Histological appearance of tissue taken from right thigh of proband aged three months showing immature ectopic ossification. (b) Erupted spicule from proband as an adult showing mature ossification. (c) Biopsy from II.5 showing subcutaneous islet of mature ectopic ossification. Bar scale: a and b = 0.25 mm, c = 0.5 mm.

tissue. The piece removed from II.5 also comprised mature bone surrounding adipose marrow tissue (fig 5c). Ultrastructural examination showed an appearance of normal ossification.

Discussion

It is apparent that this entity of ectopic ossification is genetically determined and inherited as a dominant trait. We did not detect any lesions in I.2, and she reported no palpable lumps in her husband I.1. Either the gene has been non-penetrant in which-ever of these is the heterozygote, or its expression

has been so subtle that its effects cannot be palpated or (in I.2) seen on limited radiology. There was no suggestive history elsewhere in the families of I.1 or I.2. Among their offspring, 60% (excluding the proband) are detectably affected, and of their grandchildren born to affected children, 37.5% are affected.

In all but the proband, the condition has bordered upon being a 'non-disease'. Only when a plaque of ectopic bone has caused discomfort due to inflammation of overlying skin, or interfered with comfortable movement of skin over a joint, has there been cause for physical complaint. The major concern of the family has been whether any others might expect to have disease of the severity seen in the proband.

There have been three previous reports of familial primary osteoma cutis. Peterson and Mandel¹ described a mother and son with multifocal skin ossification. The mother also had multiple deeply pigmented naevi and the son died at 15 months of age with an alveolar sarcoma of the cerebellum. Maclean *et al*² reported a mother and daughter with primary osteoma cutis. The daughter was mildly mentally retarded. She also had deeper linear radiodense lesions appearing similar to those we saw in III.3. More recently, Fawcett and Marsden³ described a three generation family with grandfather, father, and two grand-daughters affected with primary osteoma cutis. While the lesions reported in these three families resemble those we describe in the relatives of our proband (perhaps, therefore, reflecting genetic homogeneity), none had localised extensive disease of the sort the proband herself had. Her disease stands in striking contrast. The question is, why?

No convincing case could be made for variable expressivity. A possibility we considered more plausible is that the proband's local severe disease might reflect, as a sporadic event, somatic conversion to homozygosity of the postulated abnormal gene (analogous to the genesis of Wilms' tumour and retinoblastoma). A somatic crossing over followed by segregation at a mitotic division, such that both homologues carried the abnormal allele, would result in that cell and its progeny thereafter being homozygous. Homozygosity could reasonably be expected to cause a more abnormal phenotype. We may speculate that this process happened during embryogenesis in an early mesenchymal cell destined to contribute to the formation of the right lower limb bud. We plan to address this question by using molecular genetic techniques to analyse skin tissue cultured from each limb (considering that skin fibroblasts and internal structures of the limb both derive embryonically from limb bud mesenchyme).

A genetic difference between the good and the bad limb would strongly support our speculation. Besides being of academic interest, such a demonstration would allow us to offer with more confidence our tentative advice to the effect that it is unlikely that future family members would suffer severe deformity due to ectopic ossification.

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