Osteosarcoma complicating familial Paget's disease

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Summary

A most unusual family with aggressive Paget's disease is reported. Three brothers out of 10 siblings developed the disease at a relatively early age. Two of these brothers developed an osteosarcoma and died. It is emphasized that very little information is available concerning the predisposition to severe polyostotic disease and even sarcomatous change when Paget's disease begins at a young age or is familial. Possibly the risk of these serious complications is then greater than when the disease is sporadic and begins later in life.

Introduction

Although Paget himself was unable to find a familial form of the bone disease he described, numerous reports have subsequently appeared (e.g. McKusick, 1972; Jones and Reed, 1967). The mode of inheritance in these cases has been discussed. Ashley-Montague (1949) suggested an X-linked intermediate inheritance. More recently both McKusick (1972) and Carter and Fairbank (1974) have reviewed the role of genetic factors in the disease. They favoured the view that the trait for Paget's disease is controlled by an autosomal Mendelian dominant gene.

A family of 10 siblings is now described, 3 of whom have had Paget's disease. Two of these 3 siblings subsequently developed osteosarcoma and died. There have been very few similar cases described. Barry (1961) reported a family in which 2 brothers with Paget's disease developed osteosarcomas, one in the humerus and one in the sacrum. Subsequently he briefly reported 2 other families (Barry, 1969) in which osteosarcomas had developed in parent and offspring when both generations were affected by Paget's disease.

Case histories

The pedigree of the family is illustrated in Fig. 1.

The parents of the 10 siblings are both dead and it is not known if they had Paget's disease. It is however of interest that the father was described as having bowed legs. Apart from the 3 siblings described below no other members of the family have presented with the condition or have been investigated to exclude it.

* (Age in years)

FIG. 1. Family tree.

Patient A.C. (II₄ in Fig. 1.).

In November 1971 this man, then aged 53 years, was first referred to the Royal Naval Hospital, Stonehouse, Plymouth, complaining of pain in both knees intermittently present for 8 years.

Radiographs revealed osteoarthritis in both knees and Paget's disease involving the pelvis and both femora. The plasma alkaline phosphatase concentration in early 1972 was 103 KAu. (normal 3-13 KAu.). He was successfully treated with mild analgesics.

He attended the Royal Naval Hospital in February 1974 having fallen and fractured his right patella, which was affected by Paget's disease. Patellectomy was subsequently undertaken. He was eventually discharged in July 1974.

He was referred in December 1975 to one of the

authors (J.B.), with pains in the back, left thigh and the left knee. He had active Paget's disease. The alkaline phosphatase level was 2095 i.u./l (normal upper limit 140 i.u./l). Calcitonin 50 u. thrice/day was commenced in April 1976. His alkaline phosphatase fell to 696 i.u./l in April and May 1976 although there was little clinical improvement.

In July 1976 he complained of greatly increased pain and massive swelling in his left leg. Radiographs now showed (Fig. 2) an osteosarcoma of the left acetabulum, confirmed by bone biopsy (Fig. 3). Despite intensive radiotherapy and chemotherapy his clinical features persisted and he died in November 1976.

Patient W.C. (II₃ in Fig. 1).

Unfortunately this man's case notes have been destroyed. It is known that he developed Paget's disease in his late 40s. He subsequently came under the care of Mr F. T. Wheeldon at Mount Gould Hospital, Plymouth. He developed an osteosarcoma of the right femur (Fig. 4). This was confirmed by bone biopsy (Fig. 5). He died aged 55 years.

Patient D.C. (II₉ in Fig. 1).

This patient is currently under the care of one of

the authors (D.P.B.). In 1961, aged 38 years he developed osteoarthritis in the left hip treated by left cup arthroplasty in 1964. No pelvic X-ray is available from that time but Paget's disease may already have been present.

Radiography in 1971 revealed Paget's disease in the lumbar spine, left ankle, left shoulder and pelvis. He had increasing pain and was referred to University College Hospital, London, in April 1975. He had already been treated with a 5-month course of porcine calcitonin 80 u./day. No baseline biochemical data were established. After this treatment his plasma alkaline phosphatase and 24-hr urinary hydroxyproline remained elevated at 66 KAu./100 ml and 270 mg/day (upper limit normal 50 mg/day) respectively; and there was little symptomatic benefit.

In June 1975 he was treated with i.v. glucagon (Condon, 1971). This helped symptomatically and reduced his plasma alkaline phosphatase and 24-hr urinary hydroxyproline to 37 KAu./100 ml and 193 mg/day respectively. He continued on intramuscular glucagon 5 mg/day but stopped after a few weeks because of nausea.

In December 1975 he was started on salmon calcitonin initially 50 u./day, increasing to 80 u./day in

FIG. 2. Radiograph of the pelvis of case II₄ showing osteosarcoma of the left acetabulum.

FIG. 3. Bone biopsy from the left acetabulum of case II₄ showing osteoid and malignant osteoblasts ($\times 320$).

FIG. 4. Radiograph of the right femur of case II₅ showing osteosarcoma at the distal end.

FIG. 5. Bone biopsy from the right femur of case II₃ showing osteosarcoma. Tumour cells are seen invading from above ($\times 320$).

FIG. 6. Tomogram of the lower thoracic and upper lumbar spine (left lateral view) showing collapse of the L3 vertebra. Case II₃.

December 1976. In December 1977 after 2 years' continuous treatment his alkaline phosphatase had slowly risen to 140 KA.U. and his 24-hr urinary hydroxyproline to 443 mg/day.

Because of the destructive appearance of the lumbar bone disease (Fig. 6), a bone biopsy of the L3 vertebra was performed in October 1976. This, however, was compatible with Paget's disease (Fig. 7), there being no evidence of osteosarcoma.

FIG. 7. Bone biopsy from the third lumbar vertebra of case II₉ showing Paget's disease with cement lines ($\times 70$).

Discussion

Sir James Paget reported the disease which bears his name in 1877. Over the next 25 years few additional cases were reported; perhaps not more than 6 (Watson, 1898). The advent of radiology in the early years of this century provided a reliable diagnostic tool. Despite this some very basic questions about the disease remain unanswered. Several of these questions are relevant to the patients presented here. For example, is the predisposition to sarcoma greater in patients with a positive family history of the disease or an early age of onset?

The overall incidence of Paget's disease in the community appears to be 3–4% based on both post-mortem studies (Schmorl, 1932; Collins, 1956) and radiological studies (Pygott, 1957). The lower incidence among hospital admission studies (e.g.

one in 673, Barry, 1969) probably indicates that severe symptoms from the disease are relatively uncommon. Incidence of the disease is a function of age. Thus Schmorl (1932) noted a 10% incidence in persons aged > 90 years. The incidence of the disease under 40 years of age is not certain, but Galbraith, Evans and Lacey (1977) had only 3 such patients in their series of 285 with Paget's disease and only 12 under the age of 50 years.

The surviving patient described here was probably suffering from Paget's disease of the pelvis when he developed osteoarthritis of the left hip aged 38 years. His 2 affected brothers must have developed Paget's disease in their 40s and quite possibly earlier. Three siblings out of 10 developing Paget's disease relatively early in life strongly suggests a genetic predisposition. The mode of inheritance is uncertain in this family since there is no information about the parents other than that the father was bow-legged.

From 1% to 7% of patients with Paget's disease have been reported in different series to have similarly affected relatives. Galbraith, Evans and Lacey (1977) suggested that a positive family history is more likely to be associated with severe polyostotic disease. A very early age of onset of Paget's disease in a familial situation was noted by Irvine (1959) in 2 affected daughters of an affected male patient who subsequently developed an osteoclastoma. Severe polyostotic Paget's is an extremely disabling condition. The factors pre-disposing to early onset and rapid progression of the disease are not known. It is relevant to ask whether a positive family history is one of them.

Sarcoma is clearly the most disastrous of the complications of Paget's disease. The 5-year survival is almost nil (Dahlin and Coventry, 1967; Price and Goldie, 1969). The mean survival is about 7 months. The incidence of Paget's disease in published series of patients with osteosarcoma has varied from 6% (McKenna *et al.*, 1964) to 26% (Sissons 1966). However, it is unlikely that sarcomatous change occurs more than once in 500 cases of Paget's disease (Price and Goldie 1969). The chances of 2 brothers with Paget's disease developing osteosarcoma as a result of random chance are therefore extremely small. It seems more likely that some predisposition to sarcoma formation must have existed. Again no information appears to exist indicating whether early age of onset, family history of Paget's or even a strong family history of other types of cancer (as in this family) predisposes to sarcoma formation. The patients with Paget's disease complicated by osteosarcoma in 2 of the families reported by Barry (1969) had relatives with uncomplicated Paget's disease. This would support the suggestion that a familial tendency to the

disorder increases the risk of sarcomatous change. Series of patients with Paget's disease published in the future might provide answers to some of the questions raised in this report of a very unusual family.

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