OSTEOSARCOMA OCCURRING IN OSTEGENESIS IMPERFECTA

Report of Two Cases

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The formation of hyperplastic callus is a frequent and well recognised complication of osteogenesis imperfecta (Baker 1946, Fairbank and Baker 1948, Vandemark and Page 1948, Apley 1951) and the clinical picture may be indistinguishable from that of osteosarcoma (Baker 1946, Strach 1953). Osteosarcoma occurring in a patient with osteogenesis imperfecta is, however, extremely rare and has only been recorded indisputably once (Jewell and Lofstrom 1940) in the pelvis of a forty-nine-year-old man with familial osteogenesis imperfecta. Another bone tumour was reported by Brailsford (1943) in a paper on osteogenesis imperfecta: there was radiological evidence of a cancellous involucrum on both femora and tibiae and malignant destruction of the lower end of the right tibia. Fairbank and Baker (1948) recorded the death of this patient with metastases, but there is no record that the tumour was examined histologically and although obviously malignant it cannot be accepted as an osteosarcoma.

Two further examples of the association of osteosarcoma and osteogenesis imperfecta are presented here. In one of them differentiation from hyperplastic callus was difficult.

CASE REPORTS

Case 1—This girl was a sixth child and was born in September 1954 after a normal pregnancy and labour and weighed six pounds. There was no family history of osteogenesis imperfecta. At birth she was noted to have left talipes equinovarus. A fracture of the tibia occurred when an attempt was made to manipulate the foot and soon after this she sustained a fracture of the humerus and the left fourth rib without any antecedent injury. At fifteen months of age she was first seen at the Hospital for Sick Children, London, and was described as a pale child with blue sclerae, marked cranio-tubes and thin limbs in comparison with the rest of her body. Because of repeated fractures of the right femur she was late in walking. In order to correct the severe outward bowing of the right femur, which had been fractured on three occasions, in March 1958 an intramedullary nail was inserted after corrective osteotomies. In January 1960 this procedure was repeated on the left side.

Two years later she complained of pain in the right upper thigh. On examination the right hip was found to have a full range of movement and there was no local tenderness. Radiographs showed no additional pathological lesions (Fig. 1): those of the skull showed the typical appearances of osteogenesis imperfecta with multiple Wormian bones (Fig. 4). The pain persisted for four months, and in May 1962 examination revealed an "irritable" hip. Radiographs showed a fracture through the neck of the femur with fluffy opacity thought to be avascular necrosis of the head and neck (Fig. 2). The pelvis, upper right tibia and fibula, and left femur showed no other changes. She was immobilised in a hip spica for relief of pain.

By September 1962 radiographs revealed massive new bone formation around the upper part of the shaft of the femur (Fig. 3). This was thought to be hyperplastic callus, but because of the large size of the mass biopsy was done. Sections of the fragments of tissue showed
areas of irregular cartilage with some calcification and osteoid formation. Although this was not typical of hyperplastic callus a diagnosis of an osteosarcoma was not made on these sections (Fig. 5). Three months later the diagnosis of a malignant tumour was clear because chest radiographs showed obvious metastases in both lungs. The child's general condition gradually deteriorated and she died in February 1963 at the age of eight years and five months.

Necropsy revealed a very emaciated and deformed girl weighing only thirty-six pounds and measuring forty-two inches in length (Fig. 6). The skull was symmetrical but square because of bulging of the temporo-parietal regions. The sclerae were a pale translucent blue. There was gross precordial bulging of the chest wall, and nodules of hard callus could be seen and felt along the right and left sixth and seventh ribs in the axillary lines. The limbs were all very slender. The left tibia showed some lateral bowing and the right anterior bowing. The right thigh was laterally rotated and had a hard fusiform enlargement extending from the ilium to the knee; it was twice the size of the left thigh. The overlying skin was mauve and shiny but not ulcerated, and numerous dilated veins were visible. Internal examination revealed that all the bones were fragile with egg-shell thin compact bone. The skull vault consisted of a thin layer of compact bone with no visible diploë; the base showed much reduction in depth of the posterior and middle fossae from invagination of the foramen magnum and surrounding bone. Hard masses of callus around old fractures were present along many of the ribs. The upper two-thirds of the right femur were completely replaced by a huge lobulated bony and cartilaginous tumour measuring fourteen by twenty by twenty centimetres, large areas of which showed necrosis or mucoid degeneration (Fig. 7). The tumour had infiltrated the overlying thigh muscles and subcutaneous tissues and had extended through the ilium into the pelvic connective tissues. Tumours of similar appearance and of varying size were present in the head of the left humerus, the upper shaft of the right tibia, the head of the right fibula and in the right frontal bone. Pathological fractures had occurred through
the humeral and tibial lesions. The pulmonary hilar lymph nodes were all enlarged and replaced by tumour. The lungs contained numerous huge metastases, some of which were smooth, white and easily cut whereas others were obviously bony and had to be sawn in half.

(Fig. 8). One vast metastasis, involving the left upper lobe and lingula, had infiltrated the adjacent pleura and parietal pericardium and projected into the pericardial sac. A further soft metastasis was present in the cortex of the right kidney.

_Histological examination_ of the bones showed the severe disturbance of enchondral and intramembranous bone formation characteristic of osteogenesis imperfecta. Numerous blocks
Case 1. Figure 6—The generalised skeletal deformation and gross enlargement of the right femur. Figure 7—The cut surface of the right femur showing complete replacement of the upper two thirds by bony and cartilaginous necrotic tumour. Figure 8—Cut surface of the lungs showing the large bony and cartilaginous metastases.

Case 1. Figure 9—Photomicrograph of part of the right femoral tumour showing plump polyhedral cells, multinucleate cells and mitoses. (Haematoxylin and eosin, × 540.) Figure 10—Another part, as in Figure 9, showing bone formation. (Haematoxylin and eosin, × 160.)
of the main tumour in the right thigh showed that no residual femur could be identified, except at its lower end. The upper two-thirds were completely destroyed and replaced by a pleomorphic tumour which infiltrated the surrounding muscles and soft tissues and which had undergone extensive central necrosis. The tumour showed a very variable pattern, being composed of interlacing elongated spindle-shaped cells with ovoid palely staining nuclei in some areas; in others the cells were plump, polygonal or rounded with large round nuclei with a delicate chromatin network and many multinucleate giant cells; mitoses were present (Fig. 9). Elsewhere the matrix was more pleomorphic and osteoid production marked. Large areas consisted entirely of sheets of irregular cartilage whilst chondroid and bone formation was seen elsewhere (Fig. 10). The histological picture was that of an osteosarcoma with considerable cartilage production, that is, an osteochondrosarcoma. Sections of the lesion in the left humerus showed that the bone of the epiphysis and upper shaft was destroyed and replaced by osteogenic sarcoma which was predominantly producing cartilage. The articular cartilage and that of the epiphysial plate were relatively unaffected. Sections of the right tibial tumour revealed that the upper shaft was expanded by predominantly osteoid-producing sarcomatous tissue which was just beginning to penetrate the upper epiphysial plate. Similar variability of histological pattern was seen in sections of the visceral metastases. A right hilar lymph node was replaced by completely undifferentiated pleomorphic tumour containing numerous multinucleated giant cells and mitoses, whereas the right renal cortical metastasis, although pleomorphic, showed osteoid production. The pulmonary metastases were, in the main, fairly pleomorphic but were all actively producing cartilage, osteoid and bone.

Sections from the rest of the lungs showed gross atelectasis and acute purulent bronchitis and bronchiolitis. The left pleura was covered by a thick organising fibrinous exudate. Sections of skin, liver, spleen, left kidney, intestines, endocrine and exocrine glands, and central nervous system showed no abnormality.

**Case 2**—This girl was born in July 1944 by breech delivery and weighed five and a half pounds. There was no family history of osteogenesis imperfecta. Five days after birth bowing of the thighs was noticed, and at one month swelling of the left thigh with some shortening of the leg. She was referred to the Princess Elizabeth Orthopaedic Hospital and found to have a recent fracture of the left femur and a healed fracture of the right femur. Both tibiae showed marked bowing of their lower ends. The sclerae were blue.

The recent fracture united well in a double hip spica and improvement of the tibial bowing was subsequently obtained by serial plaster. By the age of three years she had learned to walk despite continuing to have many fractures. One of the radiographs taken during this period showed an area of rarefaction at the lower end of one femur which later disappeared. No further fractures occurred after the age of five (except for a slight infraction of the right tibial condyle after amputation of the left leg in 1958).

She developed severe coxa vara (Fig. 11) and marked structural scoliosis. The femoral shafts showed ununited fractures until 1953. In August 1957 she was forty-five inches tall and walked surprisingly well considering the extreme femoral deformities.

In January 1958, when she was thirteen, she developed a painful swelling of her left thigh: there was no history of recent injury. Radiographs showed a destructive lesion in the lower third of the femur suggestive of an osteosarcoma (Fig. 12). This was explored; an obviously malignant haemorrhagic tumour was found and a biopsy was done. Histological examination showed a poorly differentiated malignant connective tissue tumour. Most of the cells were polyhedral with round medium-sized nuclei. In some areas there was differentiation to bone and in others multinucleate giant cells were seen (Figs. 13 and 14). A diagnosis of an osteosarcoma was made by Dr Stewart Smith and Dr H. A. Sissons. Other investigations, including blood counts, serum proteins and electrophoresis, bone marrow biopsy and chest radiographs were all normal. The urine contained no abnormal proteins.
Case 2. Figure 11—A radiograph taken in 1957 showing abnormalities of the bones, multiple old fractures and varus deformities of both hips. Figure 12—A radiograph of the left knee taken in January 1958 showing the destructive lesion in the lower third of the femur.

Case 2. Figure 13—Photomicrograph of material from the biopsy of the left femur showing poorly differentiated tumour with multinucleate giant cells. (Haematoxylin and eosin, ×240.) Figure 14—The same as Figure 13, but showing polyhedral tumour cells and bone formation. (Haematoxylin and eosin, ×240.) Figure 15—The left leg in June 1958 showing the enlargement and the ulceration of the knee.
Radiotherapy was begun. Almost immediately the femur fractured through the tumour, but the full course was given. Despite this the tumour ulcerated at the biopsy incision (Fig. 15). For four months the girl remained extremely ill with an infected and ulcerated thigh and repeated transfusions were given to keep her haemoglobin above 50 per cent. Ultimately, in June 1958, a disarticulation of the hip was done by Mr Norman Capener. Histological examination of the specimen showed a small amount of residual tumour.

She made a rapid recovery and was on crutches within six weeks. She remained well for two and a half years and was able to walk using a Canadian hip prosthesis. In February 1961 she had a haemoptysis and radiographs showed lung secondaries. Later she developed signs of cerebral metastases and died, aged seventeen, in November 1961. Permission for necropsy was refused.

DISCUSSION

It is probable that the incidence of osteosarcomata in osteogenesis imperfecta is no greater than in the general population. But, because both are relatively rare disorders, this cannot be confirmed; however, before the premise is accepted, the pathology of osteosarcoma in osteogenesis imperfecta must be seen to be similar to that of spontaneously occurring tumours and etiological factors of significance must be dismissed. Jewell and Lofstrom (1940) reported an osteosarcoma in the ilium in a man of forty-nine. Spontaneously occurring osteosarcomata in patients over fifty almost always arise in flat bones and most frequently in the ilium (Aegerter and Kirkpatrick 1963). Most primary osteosarcomata arising under thirty are in cylindrical bones. Almost half involve the femur and the distal metaphysis, usually very near the epiphysial line (Aegerter and Kirkpatrick 1963). Our Case 2 was fourteen years old when the tumour occurred and involved the lower third of the femur.

Histologically both tumours were typical osteosarcomata, being more poorly differentiated in Case 2. The radiological appearances were also compatible with an intracortical origin in both cases. Thus, both Jewell and Lofstrom's case and our Case 2 are entirely compatible with spontaneously occurring osteosarcomata.

Our Case 1 is rather different because the tumour arose at the upper end of the femur, which is an unusual site for a primary osteosarcoma; Coley (1960) recorded seventy-six at this site out of a total of 985, an incidence of 8 per cent. The possibility that intramedullary nailing or irradiation influenced the sarcomatous change must be considered.

Despite the vast numbers of metallic implants used in patients remarkably few cases of neoplasm have been reported (Scales 1958), none of which were osteosarcomata. The tumours recorded all developed in relation to corroded metallic implants or metallic foreign bodies which had been present for a very long time (Siddons and MacArthur 1952, Penn and Epstein 1953, McDougall 1956). All were carcinomata with the exception of one which, although not histologically classifiable, did not resemble an osteosarcoma (McDougall 1956) and was in a man who died aged forty-two from a tumour which arose around a corroded plate and screws inserted thirty years earlier. In our Case 1 the intramedullary nail was in excellent condition and had been present for less than five years. It is therefore most improbable that it played any part in the etiology of the tumour.

The radiation given during the numerous diagnostic radiographs before the onset of the tumour has been calculated to have been about about five roentgen. Twenty roentgen per year is the upper limit recommended by the Medical Research Council for diagnostic purposes. Case 1 had received far less. Most reported cases of sarcomata of bone after irradiation had received large doses of low energy radiation and the interval between treatment and occurrence averaged about eleven years (Hatcher 1945). Five out of the twelve cases reported by Steiner (1965) had between 3,600 and 6,300 roentgen to the tumour field and also most showed radiographic evidence of radiation in the form of sclerosis or radiation osteitis years before the onset of the tumour. Because Case 1 had had such a relatively minute radiation dose
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before the onset of the tumour, and because there was no radiographic evidence of radiation changes it seems extremely unlikely that radiation played any part in the etiology.

Histologically the femoral tumour in Case 1 showed the wide variation in differentiation so typical of osteosarcoma (Jaffe 1958, Willis 1960, 1962) and its intracortical origin was well demonstrated radiologically. Therefore despite its uncommon site it was compatible with spontaneously occurring osteosarcomata. This patient showed another unusual feature; at necropsy numerous bone tumours were found which had not been suspected clinically. Osteosarcomata seldom metastasise to bone (Willis 1952, Lichtenstein 1959) and when they do it is secondary to pulmonary involvement. Ross (1946) reported bone metastases in 15 per cent of cases which was a much higher incidence than previously suspected. Osteosarcomata of multicentric origin often occur in Paget's disease (Porretta, Dahlin and Janes 1957). In the absence of osteitis deformans the development of multiple bone tumours without evidence of previous or simultaneous pulmonary metastases have been reported by Busso and Schajowicz (1945-46), Moseley and Bass (1956), Coley (1960), Singleton, Rosenberg, Dodd and Dolan (1962), and Davidson, Chacha and James (1965); it may be that they were of multicentric origin. The simultaneous development of multiple bone tumours with pulmonary involvement, in which it is questionable whether the lesions were multicentric or metastatic, has been described by Halpert, Russo and Hackney (1949), Lichtenstein (1959) and Singh and Scudder (1965).

In our Case 1 it is unlikely that the multiple tumours were of multicentric origin. Radiographs taken when the clinical symptoms were confined to her right hip included the upper right tibia and fibula which showed neither opacity nor destruction of the bones although both contained malignant growth at necropsy. Furthermore, when the radiographs showing pulmonary secondaries were reviewed the upper left humerus did not show any evidence of malignant destruction although this was also the site of a tumour at necropsy. It is, therefore, evident that the bone lesions did not occur simultaneously and that one at least developed after the pulmonary metastasis had occurred. Because of this and of the haematogenous metastasis in the right kidney this case must be regarded as having had a primary tumour in the right upper femur and haematogenous metastases in lungs, humerus, tibia and fibula, skull and kidney.

Previous fractures as an exciting factor in the later development of osteosarcoma have often been suggested and disproved; the associated fracture was usually pathological. Coley (1960) does cite two cases "in which after thorough examination it was impossible to deny the fact that the bone was normal at the site of fracture and later became involved by osteogenic sarcoma." Jaffe (1958), however, wrote that he had never seen an unequivocal case in which an osteogenic sarcoma developed at the site of fracture in an otherwise normal bone.

Of the three cases under discussion, the patient described by Jewell and Lofstrom (1940) had a sarcoma of the ilium in which there was no suggestion of any previous fracture. In our Case 1 there had been repeated fractures of the upper shaft of the femur, necessitating nailing. The tumour arose in the head and neck through which a pathological fracture occurred. This fracture of the femoral neck was not present four months previously and although we cannot be sure that it did not antedate the development of the osteosarcoma it seems more probable that it was caused by it. In our second case there was no history of a fracture in the lower third of the femur, but it is of interest to note that ten years before the clinical onset of the lesion radiographs showed an area of rarefaction—which might have been from an old fracture—in the medial femoral cortex where the sarcoma later occurred. In both these cases, therefore, there is a remote possibility that the two may be connected. However, if fractures are a definite precipitating factor in the causation of osteosarcomata a greatly increased incidence in osteogenesis imperfecta would be expected, and this is not so.

There is no correlation with sex, age or severity and genetic type of the osteogenesis imperfecta. Jewell and Lofstrom's patient had a relatively mild osteogenesis imperfecta which first manifested itself by recurrent fractures when he was aged eight years. His sclerae were
blue and there was an extensive family history. Our two girls were more severely affected and were first diagnosed in early infancy because of repeated fractures. They were found to have blue sclerae but they had no family history of the disease.

The basic feature of osteogenesis imperfecta is inadequate osteoid production and it is paradoxical that in this disorder there is the ability to form hyperplastic callus. The tumours which developed in both of our cases certainly showed bone formation, as did Jewell and Lofstrom’s case. In Case 1 differentiation to osteoid was marked, especially in some metastases. However, there was a preponderance of chondroid and cartilage formation and it is interesting to speculate if this is related to the underlying congenital developmental disturbance.

Finally, we wish to stress the fact that an osteosarcoma occurring as a complication of osteogenesis imperfecta is exceedingly rare whereas hyperplastic callus formation is a frequent and well recognised entity. That the clinical picture of hyperplastic callus formation may be indistinguishable from that of an osteosarcoma is well known and it has been emphasised by Baker (1946) and Strach (1953). It is not necessarily associated with a previous fracture and it may be six months before resolution begins. Biopsy is a worthwhile procedure but if inadequate it may be misleading as in Case 1. However, if a wedge of tissue extending from the overlying muscles down to the underlying bone is removed and examined systematically it should be possible to arrive at the correct diagnosis (Baker 1946, Strach 1953).

SUMMARY
1. Two girls with non-familial osteogenesis imperfecta who subsequently developed osteosarcoma of the femur are described. One is of special interest in that there were multiple bone metastases.
2. It is suggested that the tumours arose spontaneously and were not related to the underlying bone disorder.
3. Because of the relative frequency of hyperplastic callus formation in osteogenesis imperfecta it is most important that adequate biopsy material of any suspicious lesion is examined because the early clinical picture may be indistinguishable from a tumour.

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REFERENCES


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