OSTEOSARCOMA ARISING IN RELATION TO AN ENCHONDROMA

A REPORT OF THREE CASES

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Three cases are reported in which an osteosarcoma developed in relation to an enchondroma in a long bone. Two of the cases were in the proximal femur whilst one occurred in the proximal humerus, both recognised sites for old calcified enchondromas or "cartilage rests". The ages of the patients at presentation were 55, 63 and 84 years and all were women. Two patients died with pulmonary metastases within six months of the onset of clinical symptoms.

Despite their intimate relationship to the enchondromas, none of the osteosarcomas could be shown histologically to have arisen from tumour cartilage. It appears probable that these are cases in which independently arising tumours have merged to form a so-called "collision" tumour, but the possibility that they could have been derived by dedifferentiation of a previously benign neoplasm cannot be discounted.

The development of a highly anaplastic sarcoma in relation to a histologically low-grade chondrosarcoma is well recognised (Dahlin and Beabout 1971; Mirra and Marcove 1974; McFarland, McKinley and Reed 1977). In a series of 370 chondrosarcomas reported by Dahlin and Beabout (1971), such "dedifferentiation" occurred in 33, with osteosarcoma as the highly malignant component in 11 of these.

However, the development of an osteosarcoma adjacent to an enchondroma, independent of chondrosarcomatous change, is a much rarer event; a review of the literature yielded one case of osteosarcoma arising in relation to a solitary pre-existing enchondroma of the tibia (Rockwell and Enneking 1971) and two cases of osteosarcoma developing in patients with multiple enchondromatosis (Braddock and Hadlow 1966; Dahlin 1978).

In this paper we present three cases of osteosarcoma, each intimately associated with an enchondroma, and discuss the implications.

CASE REPORTS

Case 1. A 55-year-old woman developed a left hemiplegia in January 1983 after a subarachnoid haemorrhage from an aneurysm of the right middle cerebral artery. After operation she regained some power in her

leg, but her arm remained functionless. In July 1983 she was knocked down by a car, sustaining a minimally displaced fracture of the left olecranon. Radiographs also revealed a pathological fracture through a partly calcified lesion within the neck of the left humerus. The appearances were in keeping with a chondroma or low-grade chondrosarcoma and the presence of callus suggested that the fracture had been present for a considerable time. There was no clinical swelling. A biopsy taken from the anterolateral aspect of the neck of the humerus yielded white, rubbery, focally haemorrhagic tissue consisting histologically of a high-grade sarcoma producing ribbons of malignant osteoid. A left fore-quarter amputation was performed.

Gross examination and slab radiographs of the specimen revealed the fracture plane running almost transversely through the neck of the humerus (Fig. 1). Immediately inferior to the fracture, there was a pale grey sclerotic intramedullary tumour (3 × 2 × 2 cm) destroying the bony cortex anteriorly with extra-osseous extension (Fig. 2). Superiorly, the humeral head contained numerous small nodules of calcified cartilage for a distance of 2 cm; two clusters of similar nodules were also present within the substance of the sclerotic tumour (Figs 1 and 2). The posterior limit of the fracture was defined by a well-circumscribed oval plug of fleshy fawn tissue (3.5 × 2 × 1.5 cm) adherent to the bony cortex (Fig. 2).

Histologically, the cartilaginous nodules were entirely benign, being formed of poorly cellular or necrotic hyaline cartilage with many nodules showing ossified margins, often blending into surrounding bony trabeculae. Within the fracture plane, several cartilaginous nodules were enmeshed in a reparative fibrous stroma, rich in thin-walled ectatic blood vessels (Fig. 3). From this fibrous tissue and from the oedematous

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Fig. 1

Fig. 2

Case 1

Figure 1—Slab radiograph showing a pathological fracture through the neck of the humerus and a poorly defined intramedullary sclerotic lesion extending distally. Flocculent or "pop-corn" foci of calcification are present above and within the fracture plane, and at the lower border of the sclerotic lesion. Calcified callus is continuous with the anterior end of the fracture, uncalcified soft-tissue is present posteriorly.

Figure 2—Histological section of the proximal left humerus, corresponding to the slab radiograph of Figure 1. NC, nodules of benign cartilage; M, malignant fibrous histiocytoma-like zone; O, osteosarcoma; ET, extra-osseous deposits of osteosarcoma; BC, bony callus; OC, oedematous connective tissue (H & E, same size).

Fig. 3

Histology from the fracture plane showing several nodules of benign cartilage, demonstrating focal necrosis and chondroclasia, embedded in a fibrovascular stroma (H & E, × 35).

Fig. 4

Gradual transition from sparsely cellular connective tissue posterior to the fracture (bottom left) to a highly cellular sarcoma with a focally storiform pattern (right). Part of a cartilaginous nodule is included (bottom right) (H & E, × 25).

Fig. 5

The intramedullary portion of the sarcoma with abundant osteoid production by the neoplastic cells (H & E, × 230).

Fig. 6

A necrotic portion of the enchondroma caught up in the osteosarcoma: deposition of malignant osteoid on the cartilaginous framework (H & E, × 115).

Fig. 7

Fig. 8

Case 2. Figure 7—Radiograph showing flocculent calcification within the upper shaft of the right femur. The periosteum is elevated medially. Figure 8—The junction between the degenerate enchondroma and the cellular osteosarcoma (H & E, $\times 55$).

sparsely cellular connective tissue constituting the fleshy fawn tissue posterior to the fracture, there was a relatively gradual transition inferiorly to frankly sarcomatous tissue. This consisted of a mixture of large spindle cells and collagen arranged in a whorled and focally storiform pattern (Fig. 4), a small number of large polygonal cells with foamy cytoplasm, and a prominent round-cell infiltrate, reminiscent of malignant fibrous histiocytoma. This portion of the sarcoma, having surrounded and eroded several cartilaginous nodules and bony trabeculae, blended anteriorly with the remainder of the intramedullary sclerotic tumour which was an osteosarcoma showing, in most areas, abundant formation of osteoid matrix (Fig. 5), focally organised in a plexiform pattern of broad trabeculae. Neoplastic bone matrix had also been deposited on the eroded surfaces of a few cartilaginous nodules entrapped by the osteosarcoma (Fig. 6). Anterior to the fracture plane, the intertrabecular spaces of maturing osseous callus were invaded by osteosarcoma, two nodules of which were present in the extracortical fascia.

One and a half years later, the patient was doing well with no evidence of metastases. The lesion was diagnosed as osteosarcoma arising in relation to a solitary enchondroma.

Case 2. A woman aged 63 presented in June 1969 with a two-month history of pain in the anteromedial aspect of the right thigh, with radiation to the groin. Radiographs of the right femur (Fig. 7) showed an irregular calcified mass in the upper shaft with surrounding porosis, and periosteal reaction and elevation medially. Two weeks later she suffered a pathological fracture through the lesion. A biopsy was performed and showed an osteosarcoma containing several nodules of degenerating acellular cartilage consistent with an old benign enchondroma (Fig. 8). Disarticulation of the right hip was subsequently carried out.

Gross examination of the specimen revealed a pathological fracture through the tumour mass ($10 \times 8 \times 7$ cm) which extended from a point 7 cm distal to the head of the femur. There was a good deal of haemorrhage into the surrounding musculature which was infiltrated by fleshy tumour tissue.

Histological sections confirmed the original diagnosis of osteosarcoma with plugging of adjacent extra-osseous veins by tumour. Further nodules of hypocellular cartilage were encountered within the medullary cavity proximal to the fracture site. The osteosarcoma was purely osteoblastic without either fibrous or chondroid zones. There was no evidence of Paget's disease.

Multiple pulmonary metastases appeared in August 1969; the patient deteriorated rapidly and died six weeks after disarticulation of the right hip.

Case 3. A woman aged 84 was admitted to hospital in November 1969 in a senile confusional state. She complained of pain in the right femur and radiographs revealed irregular sclerosis and rarefaction of the medulla in the subtrochanteric region, with localised cortical destruction and irregular calcification in adjacent soft tissues (Fig. 9). Because of her advanced age and severe ischaemic heart disease, major surgery was considered to be inappropriate; she was treated with narcotic analgesics and succumbed from bronchopneumonia six weeks after admission.

At necropsy the right thigh was swollen due to the presence of a large firm white tumour arising from and encircling the upper end of the femur, with extension deep to the inguinal ligament into the right side of the pelvis. The tumour had a variegated appearance on sectioning, with some areas glistening and cartilaginous in appearance. A few small round grey-pink nodules of metastatic tumour, the largest 0.5 cm in diameter, were scattered throughout both lungs.

Histologically, the femoral neoplasm was an osteo-

Fig. 9

Fig. 10

Case 3. Figure 9 Radiograph of the right femur showing a large sclerotic lesion in the subtrochanteric region with extension into the adjacent soft tissue. Figure 10—Necrotic chondromatous tissue invaded by sclerotic osteosarcoma.

sarcoma forming a mass of sclerotic bone within the medullary cavity. Less matrix production was evident within the extra-osseous component of the tumour. Neither fibrous nor chondroid differentiation was present. Within the osteosarcoma, there were several irregular nodules of hypocellular and rather degenerate cartilage indicative of an old medullary enchondroma (Fig. 10). There was no evidence of Paget's disease.

DISCUSSION

The main features common to these three cases of osteosarcoma are:

1. The osteosarcoma was associated with and had invaded an entirely benign calcifying enchondroma.
2. The relationship of the enchondroma to the sarcoma was of contact only, with no features indicative of malignancy in the cartilage.
3. Occurrence was in the proximal shaft of the affected femur or humerus.
4. The patients were at least 50 years old.

The case reported by Rockwell and Enneking (1971) of an osteosarcoma developing in a solitary enchondroma of the tibia is essentially similar in terms of the patient's age, the site of the lesion and the relationship of the benign to the malignant tumour.

Multiple enchondromatosis is frequently associated with the development of a sarcoma in one or occasionally more than one bone; whilst the malignancy usually takes the form of a chondrosarcoma, osteosarcomatous transformation is not unknown (Braddock and Hadlow 1966; Dahlin 1978). By contrast, malignant change in a proven benign enchondroma is considered to be extremely rare, not a single example being present in either the Mayo Clinic series of 59 cases of secondary chondrosarcoma (Dahlin 1978) or amongst the 89 cases of secondary chondrosarcoma seen at the International

Reference Centre of Bone Tumours of the World Health Organisation (Schajowicz 1981). Although in some cases there may be presumptive clinical evidence of such an event, histological documentation of malignant transformation of a benign enchondroma is almost impossible to achieve, not least because of the scarcity of microscopic fields satisfying the histological criteria of malignancy (Lichtenstein and Jaffe 1943) in some low-grade chondrosarcomas. In those cases of chondrosarcoma occurring at the site of a previous "enchondroma", review of the original histological sections has revealed that those tumours were in reality low-grade chondrosarcomas from the beginning (Schajowicz 1981). Barnes and Catto (1966) to some extent avoid the argument by concluding that cartilaginous tumours present an unbroken spectrum in their clinical behaviour and histological appearances from the entirely benign to the frankly malignant whilst emphasising that those arising in the trunk, upper femur and upper humerus are particularly liable to behave in a malignant fashion.

The concept of "dedifferentiation" of a histologically low-grade and clinically indolent cartilaginous tumour was emphasised by Dahlin and Beabout (1971) and is now widely accepted. In their series of 33 dedifferentiated chondrosarcomas, 11 tumours were osteosarcomas, 10 of which expressed fibroblastic zones. The dedifferentiated neoplasm generally abutted sharply against the distinctly different low-grade chondrosarcoma. By merging the conclusions of Barnes and Catto (1966) with the concept of "dedifferentiation", our three cases may be regarded as lying at the extreme end of the spectrum of dedifferentiated cartilaginous tumours. In this context it is relevant to note that four of the cartilaginous tumours of the Mayo Clinic series (Dahlin and Beabout 1971) were not frankly sarcomatous but rather were considered to be of "borderline" malignancy, and that three of the five cases of dedifferentiated chondro-

sarcoma reported by Mirra and Marcove (1974) appeared to be related to a pre-existing solitary enchondroma. Furthermore, our cases all occurred in either the femur or humerus in patients over the age of 50 years, common findings in dedifferentiated chondrosarcoma. Indeed, all of the cases reported by Mirra and Marcove (1974) occurred in these two sites with a mean age of presentation of 57 years.

Sanerkin and Woods (1979) presented six cases of fibrosarcoma or malignant fibrous histiocytoma developing in relation to an enchondroma in a long bone. These sarcomas did not appear to have arisen directly from the tumour cartilage but rather from dense fibrous tissue surrounding necrotic areas in the enchondroma; the authors postulated that some so-called dedifferentiated chondrosarcomas were in fact "collision" tumours—two independently arising tumours, originally separate but subsequently one growing into the substance of the other. Our first case is similar in that malignant fibrous histiocytoma-like areas appeared to develop from reparative fibrous tissue surrounding enchondromatous nodules adjacent to the plane of the fracture. In this case, the pathological fracture of the humeral neck had evidently been present for some time, but could not have antedated the onset of anaesthesia in the arm.

It is interesting to speculate on the role of chronic soft-tissue trauma (induced by the non-immobilised bone ends) in the genesis of the sarcoma. Ewing (1935) put forward five criteria to be met before a cancer could be even remotely considered to have been induced by trauma: (1) previous integrity of the wounded part, (2) authenticity and adequacy of trauma, (3) origin of tumour at the exact point of injury, (4) reasonable time limit between injury and time of appearance of the tumour and (5) positive diagnosis of the presence and nature of the tumour. Whilst criteria (2) to (5) are possibly satisfied in this case, there is no documented proof that the fracture antedated the development of the osteosarcoma; the hypothesis that this case represents a traumatically induced malignancy therefore remains unproven.

In cases 2 and 3, the osteosarcomas were large tumours and it was not possible to identify their sites of origin, fibrous or otherwise. They differed from the first case by being purely osteoblastic and unassociated with a

long-standing pathological fracture. Their biological behaviour was more aggressive, with rapid appearance of pulmonary metastases, whereas the first patient remains free of disease one and a half years after fore-quarter amputation.

Although it is not possible to prove that these three cases of osteosarcoma, developing in close proximity to an enchondroma, are dedifferentiated cartilage tumours rather than simply collision tumours, their occurrence late in life, in common with osteosarcomas associated with Paget's disease and bone infarcts (Mirra *et al.* 1974), suggests that the enchondromas were not merely innocent bystanders. Such cartilaginous lesions may in fact have initiated more of the osteosarcomas occurring in middle-aged and elderly patients than has heretofore been recognised.

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