Chondrosarcoma in Hereditary Multiple Exostosis

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SUMMARY

Chondrosarcoma is believed by Jaffe to occur in as many as 25% of patients with hereditary multiple exostosis. This subject is discussed in the light of the author's experience of 25 cases of suspected or proved malignancy in multiple exostosis. The cases are divided into three categories: those in which a chondrosarcoma was suspected on the basis of the size of the tumour or the degree of calcification of the cartilage cap; those which showed progressive enlargement of a tumour after the end of the growth period; and those with unequivocal radiological and histological signs of malignant change. A critical examination of the diagnostic criteria is presented and a rational approach to treatment is suggested.

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The occurrence of chondrosarcoma in multiple exostosis was recognised by the earliest writers on the subject. Indeed, the first case of hereditary multiple exostosis recorded in the medical literature[1] was that of a young mother of 30 years of age with numerous bony tubercles on the ribs, tibiae and femora, who later developed a chondrosarcoma at the distal end of the right femur. The exostosis, which had been present for many years, suddenly started to enlarge after her fifth pregnancy. As the swelling could not be reduced by conservative measures, the limb was amputated 2 months later. From Boyer's[1] description, it seems likely that this was a malignant tumour. We learn that it was large and lobulated, mainly cartilaginous, but bony at its base. The other bones in the amputated limb were studded with typical benign, cartilage-capped exostoses.

The difficulties of diagnosis and treatment are seldom resolved as speedily as in Boyer's case. The dividing line between active growth and neoplasia in a cartilage-capped exostosis is uncertain, while the histological diagnosis of a chondrosarcoma arising in the cartilage cap is notoriously difficult, and frequently impossible to establish. The surgeon, looking to the pathologist for help in the management of such a case, will more often than not be forced to rely on his own judgement.

The incidence of this complication has been estimated by Jaffe[2] to be about 25%. That 1 out of every 4 patients with multiple exostosis will develop a chondrosarcoma seems incredible to most clinicians. It also emphasises the need for a critical evaluation of present-day concepts of this condition.

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The present study was undertaken in an attempt to clarify the diagnostic criteria and formulate a rational approach to the management of malignant neoplasia in hereditary multiple exostosis.

PATIENTS AND METHODS

Twenty-five cases of suspected or proved malignancy in multiple exostosis were studied by the author. They were divided into three categories: firstly, those in whom a chondrosarcoma was suspected or diagnosed purely on the basis of the size of the tumour, or the degree of calcification of the cartilage cap on radiographic examination (15 patients); secondly, those in whom malignant change was suspected because an exostosis continued to enlarge after the end of the normal growth period (7 patients); and lastly those with unequivocal clinical, radiological and histological evidence of malignant change (3 patients).

In an attempt to estimate the incidence of malignant change, 76 consecutive cases of hereditary multiple exostosis were collected for follow-up from the records of the Royal National Orthopaedic Hospital and the Great Ormond Street Hospital for Sick Children, London. Thirteen patients could not be traced, and another 9 declined to attend the follow-up clinic. The remaining 54 patients, of whom 4 had died, were considered as index patients for the purpose of these calculations.

CASE REPORTS

Group I

In 15 patients a chondrosarcoma was suspected merely because a large and heavily calcified tumour was discovered on routine clinical or radiological examination.

Case 1: A 50-year-old housewife had been aware of multiple swellings around the joints and over the scapulae for as long as she could remember. On a routine visit to the hospital, a large, firm tumour over the left scapula attracted attention and she was referred for further investigation as a case of suspected malignant change. On examination she presented the characteristic features of hereditary multiple exostosis. Her son, her father and her two sisters were similarly affected. A large exostosis at the vertebral border of the left scapula extended almost to the opposite scapula. It was firm and coarsely lobulated but had not increased in size since the end of adolescence. The radiograph showed a large, heavily calcified mass obscuring the left scapula. The calcification was uniformly dense and well-demarcated peripherally. There was no bone destruction.

At operation, the lobulated tumour was removed with a segment of the vertebral border of the scapula. The bulk of it consisted of calcified cartilage and calcium detritus, extending throughout the exostosis. Histological examination of several different zones showed simple cartilage tissue with areas of degeneration and calcification (Fig. 1). Seven years later she was well and there was no recurrence.

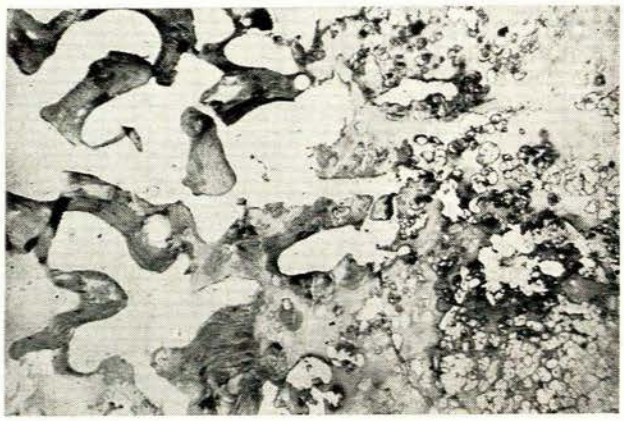

Fig. 1. Case 1. Photomicrograph of osteocartilaginous junction of the exostosis, showing cartilage degeneration and calcification (H. and E. × 200).

This tumour, and those of others in this category, were classified as benign. The common occurrence of this type of lesion among the index patients followed up over 10 years or more, suggests that a large tumour, with or without calcification of the cartilage cap, is not by itself indicative of malignant change. The criteria for inclusion in this category, however, should be strictly defined. The tumour should have remained painless and constant in size after the end of skeletal growth; the calcification should show as a uniform radiographic density with a well-demarcated outline; there should be no evidence of bone destruction and the histology should be that of benign cartilage.

Group II

The second group consisted of 7 patients in whom an exostosis continued to enlarge after the end of the normal growth period, but without any histological sign of malignancy on biopsy.

Case 2: A 19-year-old schoolboy with multiple exostosis complained of a large, painful swelling over the left scapula. Unlike the other lumps in various parts of his body, which had stopped enlarging some years before, the swelling over the scapula had continued to grow and had now reached an alarming size.

On examination the patient presented the features of diaphysial aclasis, with numerous juxta-epiphyseal exostoses and deformities of the forearms and knees. There was a paticularly large, lobulated tumour surrounding the left scapula and completely obscuring the anatomical contours of this bone. On radiographic examination only a small part of this lesion consisted of bone.

In view of the continued growth of the tumour and the recent onset of pain, it was regarded as an aggressive lesion, possibly an established chondrosarcoma. A total scapulectomy was carried out without exposing or incising any part of the cartilaginous tumour.

Macroscopically the tumour proved to be a large cartilage-capped exostosis arising from the vertebral border of the scapula and enveloping the bone anteriorly and posteriorly in lobules of firm cartilaginous tissue. A slab radiograph showed a comparatively small exostosis with the bulk of the lesion consisting of the cartilage cap. There was minimal calcification in this tissue (Fig. 2).

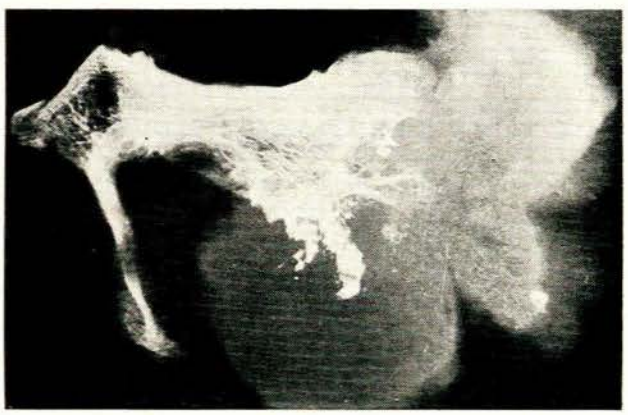

Fig. 2. Case 2. Radiography of a section of the scapular tumour. The bony element is small and most of the lesion consists of a large cartilaginous 'cap'.

Histological examination of numerous different segments failed to reveal any sign of malignancy.

Case 3: A student of 17 years of age presented with bony swellings around the knees and ankles. A diagnosis of multiple exostosis was confirmed radiologically. One exostosis in particular, arising from the iliac bone, attracted attention; the patient was advised to return at regular intervals for radiographic examination of this lesion.

Two years later the tumour had increased noticeably in size (Fig. 3). A specimen for biopsy taken at this stage showed only benign cartilage tissue. During the succeeding 8 years the exostosis continued to enlarge. He was repeatedly urged to have it removed, but he adamantly refused operation.

At the age of 29 years he was investigated at a distant hospital for an intractable cough. A diagnosis of a solitary pulmonary metastasis was made and a pneumonectomy was carried out. He became profoundly shocked after the operation and died. The presence of a chondrosarcoma of the ilium was established at necropsy.

Of the 7 patients in this group, 4 had a local resection of the tumour soon after it became clear that the exostosis was enlarging. There was 1 postoperative death (due to pulmonary embolism); the remaining 3 patients were alive, and showed no recurrence of the original lesion 8, 12 and 14 years after the operation. Case 2 is illustrative of this subgroup.

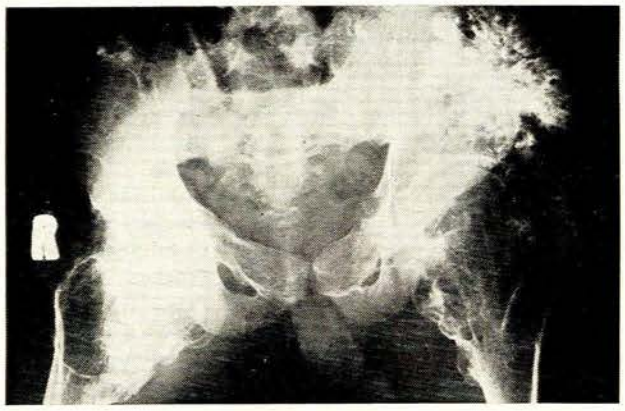

Fig. 3. Case 3. Radiographic appearance of a tumour which had increased noticeably in size over 2 years.

In 3 cases the enlarging tumour was not excised, either because the patient refused to submit to operation (case 3), or because the surgeon considered it unnecessary for a histologically benign lesion. All these patients eventually died with metastatic chondrosarcoma, 4, 10 and 12 years after the discovery of the enlarging tumour.

A chondrosarcoma arising in an exostosis may take many years to metastasise; during this period it is usual to find only benign-looking cartilage on biopsy. However, whether or not a histological diagnosis of a malignant lesion can be obtained, a cartilage-capped exostosis which enlarges progressively after the end of the skeletal growth period should be treated with grave suspicion. Inadequate resection at this stage invites a local recurrence; and the recurrent tumour is frequently much more cellular—and sometimes behaves much more like an established chondrosarcoma—than the original exostosis.[3]

Group III

In the third group of patients there was unequivocal malignant change in a cartilage-capped exostosis, with the development of a histologically proved chondrosarcoma. Three such cases were encountered; none, however, occurred in the original series of index patients.

Case 4: This case was discovered among the relatives of one of the index patients. As a boy the patient had been aware of multiple bony swellings around the joints. His paternal grandfather, his father and two sisters had similar lesions. At the age of 15 years he injured his right thigh in a bicycle accident; 6 months later a lump appeared at the site of the injury and increased considerably in size over the next 2 years.

Alarmed at the fact that this swelling continued to enlarge, unlike any of the other nodules, he consulted his doctor and was immediately referred for further investigation. The patient was then 18 years old. He presented the characteristic features of multiple exostosis. At the proximal end of the right femur, however, there was an unusually large mass, lobular in outline, soft in some parts and bony-hard in others. A radiograph showed this to be a cartilage-capped exostosis with diffuse calcification of the cartilaginous part of the tumour. A diagnosis of chondrosarcoma was made; amputation was advised but the patient refused this treatment. In spite of a course of radiation therapy the tumour continued to enlarge, and 4 years later there was radiological evidence of bone destruction and soft-tissue invasion.

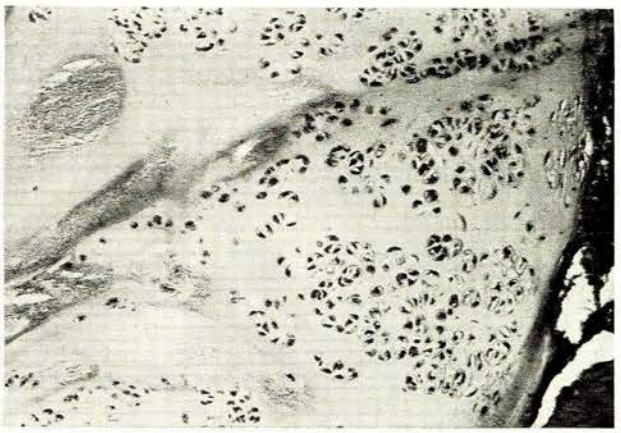

Fig. 4. Case 4. Photomicrograph showing the features of a chondrosarcoma. The tumour is very cellular and there are numerous cells with double nuclei, plump nuclei and hyperchromatism of the nuclei (H. and E. × 200).

At the age of 23 years he agreed to surgical treatment. There was still no evidence of metastases, but a biopsy specimen now showed the histological features of a chondrosarcoma (Fig. 4). Following a disarticulation of the hip, his general condition deteriorated rapidly and he died soon afterwards.

Two similar cases were subsequently seen; one was a 43-year-old male with a chondrosarcoma of the proximal end of the tibia, and the other a 37-year-old female with a chondrosarcoma of the proximal end of the humerus. In each of these patients the first biopsy established the diagnosis of malignancy and an appropriate ablative procedure was carried out.

DISCUSSION

Incidence

The incidence of malignant change in multiple exostosis is generally believed to be about 5%.[4] However, there are wide deviations from this figure, depending on the age distribution of the particular series, the criteria of malignancy and the degree of specialisation at the centre from which the report emanates. Dahlin,[5] on the basis of 272 cases of chondrosarcoma of all types studied at the Mayo Clinic, estimated the incidence of chondrosarcoma in patients with multiple exostosis at more than 10%. Jaffe,[6] in 1943, reported 3 cases of chondrosarcoma among 28 patients with hereditary multiple exostosis, an incidence of 11%. And this, he believed, was a conservative estimate,

because the follow-up was incomplete. In 1958 Jaffe[2] reported that a complicating chondrosarcoma can probably be expected, sooner or later, in about 25% of cases of multiple exostosis.

These figures are somewhat higher than the experience of most clinicians suggests. There was no case of a histologically proved chondrosarcoma among the index patients of the present series. Case 4 was a brother of the proband, and the other 2 proved cases were not in any way related to the index series. There were, however, 3 index patients with radiological evidence of tumour enlargement after the end of the growth period (group II, above); if they are regarded as cases of malignant change, this gives an incidence of 6% in the present series.

Clearly the age distribution of the patients studied is important. In a report of 212 cases of chondrosarcoma treated at the Mayo Clinic between 1905 and 1955, Dahlin and Henderson[7] found that 63% of the patients presented after the fourth decade. In the present series of patients only 19% had passed the fourth decade, and half of them were still under the age of 25 years at the time of examination. It is, in fact, impossible to give a valid figure for the incidence of malignant change until all these patients have died, and even then innumerable exostoses will have been excised that might otherwise have given rise to chondrosarcomas. Equally, though, the series of Jaffe and Dahlin may be weighted in the opposite direction, for the latter has been prompted, elsewhere, to comment that the high percentage of referred patients (at the Mayo Clinic) would tend to make the incidence of chondrosarcoma seen at the clinic relatively high.[7]

Familial Incidence

It is most unusual to find this complication described in more than one member of an affected family. Knight[8] reported its occurrence in 3 brothers known to have multiple exostosis, but in 2 of them the diagnosis was based entirely on verbal evidence.

Age and Sex

Malignant change in a cartilage-capped exostosis is rarely seen during the period of normal bone growth, though such cases have been reported.[9,10] The maximum incidence, however, occurs at a lower age than in the case of primary chondrosarcoma—the fourth and fifth decades as compared with the sixth decade in Dahlin and Henderson's[7] cases.

Site

The site of the exostosis developing a chondrosarcoma was recorded in 22 cases collected from the literature (Table I). To these may be added the 10 cases in groups II and III of the series studied here. In over half it was in the region around the hip or the shoulder. Other investigators[2,8] have also commented on the frequency with which these areas are affected. It is suggested that this is not so much an anatomical peculiarity as an indication that, wherever the lesions are inconspicuous, they tend to reach a size which, in any other situation, would have called for their early removal. In the present study it was remarkable how often the pelvis and the proximal end of the femur had harboured exostoses of considerable size without the patient being aware of them.

TABLE I. SITE OF CHONDROSARCOMA IN CARTILAGE-CAPPED EXOSTOSIS

Author	No. of cases	Site of sarcoma
Boyer[1]	1	Distal femur
Weber[11]	1	Pelvis
Barlow[12]	1	Distal femur
Phemister[13]	2	Proximal tibia (1) Distal femur (1)
Belot and Simchowitz[14]	1	Proximal humerus
Gardner[15]	2	Pelvis (1) Proximal femur (1)
Fennel[16]	1	Distal femur
Bennett and Berkheimer[9]	1	Distal femur
Drevon *et al.*[10]	1	Proximal humerus
Ellis and Taylor[17]	1	Proximal femur
Monro and Golding[18]	1	Pelvis
Flatt[19]	1	Proximal tibia
Gros *et al.*[20]	1	Pelvis
Knight[8]	3	Pelvis (2) Tibia (1)
Dotter[21]	4	Distal femur (1) Tibia (1) Metatarsal (1) Vertebra (1)
Solomon (1973)	10	Pelvis (3) Proximal femur (3) Distal femur (1) Proximal tibia (1) Proximal humerus (1) Scapula (1)
Total	32	Pelvis and proximal femur (14) Scapula and proximal humerus (4) Others (14)

Clinical Features

Trauma, and usually *severe* trauma, antedated the change in the character of the lesion in many of the recorded cases. Whether this really initiates the malignant change is still doubtful, but the relationship is real enough to make it obligatory to re-examine at frequent intervals every patient who reports an injury of more than minor degree.

In 3 of the reported cases the malignant change followed soon after a pregnancy.[1,15,19] However, the latter event

occurs sufficiently frequently to make a real causal relationship extremely doubtful.

The only clinical feature likely to emerge is a slow but definite increase in the size of one of the bony swellings after the end of the normal skeletal growth period. Often this is so gradual as to allay all suspicion, and it may be 8 or 10 years before the patient consults his doctor again. In the majority of cases the tumour is already of an alarming size by the time it is operated upon. There may be pain in the swelling or discomfort from pressure on adjacent organs.

Recurrence of the tumour after an adequate excision of a benign exostosis is highly suspicious of an aggressive lesion. This may occur repeatedly, with subsequent lesions showing a gradual change towards malignancy in histological pattern.

Radiological Features

Only rarely is the radiograph by itself conclusive; more often it has to be carefully weighed with all the other evidence available. Patchy or streaky calcification of the cartilaginous cap is generally more widespread, of more variable density and more indefinitely confined at the periphery of the tumour than that seen in a benign exostosis. Successive radiographs may show a gradual increase in the size of the tumour; this by itself is highly suspicious. When accompanied by signs of progressive invasion and destruction of bone, the diagnosis of malignancy is certain.

Pathology

By the time the patient presents for operation the chondrosarcoma is usually a large, lobulated, fleshy tumour, invading the soft tissues locally. A slab radiograph will show the extent of the cartilage mass compared with the bony exostosis. If the tumour has grown rapidly, central degeneration or haemorrhage may be found. Almost invariably there is some degree of calcification of the cartilage mass, although this finding is by no means restricted to malignant lesions.[22]

Jaffe and Lichtenstein's descriptions of the histological features of chondrosarcoma have become generally accepted as the most reliable criteria of malignancy in cartilaginous tumours.[2,5,23-25] Suspicious features are hypercellularity of the tissue, plump cell nuclei and more than an occasional cell with plump double nuclei. On these criteria alone several borderline lesions, and occasionally even a benign lesion, will inevitably be included in the net cast for signs of early malignant change. However, as Henderson and Dahlin[3] observed, the number of borderline tumours diagnosed is inversely proportionate to the experience of the pathologist. According to Jaffe[2] the diagnosis of chondrosarcoma is certain if in addition to the above features, there are pronounced irregularities in the size of the cells and their nuclei, marked hyperchromatism of the nuclei, many cells with multiple nuclei, and large or giant cartilage cells with single or multiple nuclei. Many of these features are shown in Fig. 4.

Diagnosis

When the clinical and radiological signs point to malignancy, and the histological features described above are present, the diagnosis of chondrosarcoma will be firm and confident. If either the clinical or the radiological signs suggest malignant change, but the histology is benign, one may be faced with one of the most taxing decisions in medicine. In these circumstances a needle biopsy cannot be relied upon; even after an incisional biopsy a negative report should not be accepted as final. The cellular appearance varies widely in different parts of the tumour and multiple blocks from different areas may have to be examined to discover some evidence of malignancy.

Jaffe[2] crystallised his own experience in these words: 'Altogether, in evaluating a cartilage tumour which is suspected of being a chondrosarcoma, whichever feature (pathological or clinical) is the more sinister should be regarded as the more important.' And Lichtenstein,[24] somewhat less circumspect, states: 'Any osteocartilaginous exostosis in an adult, and occasionally even in a younger patient, which takes on a spurt of growth, should be regarded as already a chondrosarcoma.'

It is my view that the problem of diagnosis is aggravated by attempts to establish a precise division between a benign lesion and a chondrosarcoma. By definition one should only apply the term sarcoma to a neoplasm which has the capacity to metastasise, and this is precisely what one hopes to avert by adequately treating the tumour before it manifests this characteristic! What is important, therefore, is to assess the probable behaviour of the tumour rather than its exact designation. Willis[26] stressed the viewpoint that 'innocence and malignancy are relative terms of value in the art of prognosis, but not denoting distinct species of tumours. The question is not, is it innocent or malignant? but, how innocent or malignant is the tumour?'

On the basis of the arguments presented here, a cartilage-capped exostosis which continues to enlarge after the end of the normal skeletal growth period, even in the absence of histological evidence of malignancy, should be regarded as an aggressive tumour. The danger here is not early metastatic spread, but the probability that an inadequate local excision will be followed by the recurrence of an even more aggressive lesion which will eventually behave like a true sarcoma.

Treatment and Prognosis

Although there are cases on record of secondary, peripheral chondrosarcoma proceeding to a fatal conclusion within months, the majority metastasise only after several years. This, however, is no justification for conservative treatment once a diagnosis of an aggressive cartilage tumour has been made. Considering chondrosarcomata of all types. Henderson and Dahlin[3] found that of 108 patients who had received no treatment or inadequate treatment 87 were dead within 10 years of diagnosis. Faced with these results, there is small consolation in the fact that they found that peripheral chondrosarcomata were less aggressive (or possibly more amenable to surgical

extirpation!) than central tumours.[7] By contrast, of 65 patients receiving adequate early treatment, 45 were alive and free from recurrence after 10 years.

Adequate treatment means total resection of the tumour and the segment of bone from which it arises, without exposing or incising the cartilaginous mass. If this is preceded by a biopsy, the biopsy wound should be so placed that it will be removed completely by the subsequent operation.

Henderson and Dahlin[3] found that an adequate excision offered as much to the patient as an amputation, and with this I agree, provided that every shred of cartilaginous tissue is removed, and that the location of the tumour is such that a recurrent lesion would still be operable. Where these factors cannot be assured, amputation is the correct treatment.

In the extremities local resection of large cartilaginous tumours, followed by bone grafting or replacement by bone implants or metal prostheses, has been carried out successfully.[27-30] A tumour of the scapula may be treated by total scapulectomy, and lesions of the ribs by rib resection. A pelvic tumour may be equally amenable to local resection, particularly if it arises from the pubic ramus, but where there is any doubt about the feasibility of total removal, a hindquarter amputation should be carried out.

Surgical removal of pulmonary metastases may be justified by the slow course of the disease, particularly if there is a solitary lesion or if the metastases are confined to one lung.

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