SARCOMA COMPLICATING PAGET'S DISEASE OF BONE
A CLINICOPATHOLOGICAL STUDY OF 62 CASES

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Out of 21 900 cases filed at the Latin-American Registry of Bone Pathology between April 1940 and July 1981, there were 987 with Paget's disease (4.51 per cent); 62 of these (6.28 per cent) were complicated by sarcoma and two were associated with giant-cell tumours of bone (osteoclastoma) without signs of malignancy.

There was a slight predominance of men and the ages ranged from 45 to 87 years, with an average of 66 years. The most frequent sites were the femur (23 cases), the humerus (nine), the pelvis (10), and the tibia (nine). The low incidence of vertebral involvement (five cases) is noteworthy and is in sharp contrast to uncomplicated Paget's disease. The most common tumour type was osteosarcoma (39 cases), followed by fibrosarcoma (15 cases); other varieties (chondrosarcoma, malignant fibrous histiocytoma and reticulum-cell sarcoma) were much rarer.

Most of the sarcomata occurred when the Paget's disease was polyostotic. Tumours often developed simultaneously, or at short time intervals, in the same or different bones; these bones had, in all cases, been affected by Paget's disease. The histological features of the osteosarcomata were characteristic, with large numbers of osteoclast giant cells, alternating with atypical osteoblasts, thus exaggerating the anarchic remodelling process of Paget's disease. The neighbouring areas of the pagetic bone showed an increased number of osteoclasts. These facts suggest a possible pathogenetic relationship between sarcoma and Paget's disease; the possibility of both processes having a viral aetiology is discussed.

The development of sarcoma is the most serious complication of Paget's disease. In fact, Paget's original case (1877) developed a fibrosarcoma in the radius after 22 years, and five of his 23 cases died of sarcoma. Although well recognised as a possible complication of Paget's disease, the exact incidence of malignancy is difficult to establish because there is no reliable statistical information on the frequency of uncomplicated disease; in the world literature the reported incidence of malignancy ranges from 0.15 to 20 per cent.

In view of the conflicting reports we decided to review the clinical and pathological features of our 62 cases of sarcomatous change in Paget's disease, together with the 987 cases of uncomplicated disease. This material had been collected over a period of 41 years.

MATERIAL AND METHODS

At the Center of Osteo-articular Pathology of the Latin-American Registry of Bone Pathology 21 900 cases of bone disorder were registered between April 1940 and the end of July 1981. These included 987 cases of Paget's disease; 62 of these had developed sarcoma (6.28 per cent) and two patients had giant-cell tumours (osteoclastoma) without histological signs of malignancy. Only cases with complete clinical, radiological and pathological documentation were included. In many cases we had received the amputation specimens; but in others, the material had been obtained by open or by puncture (aspiration) biopsy.

In addition to routine stains with haematoxylin and eosin, periodic acid-Schiff and reticulin stains were used for the histological studies.

CLINICAL AND PATHOLOGICAL FEATURES

Incidence. As already stated, the frequency of malignant change is difficult to establish, since the exact incidence of the uncomplicated disease is not known. The incidence of Paget's disease is high in some countries (United Kingdom and Australia), average in some (North America, Germany and France), and low in others (Sweden, Africa and Asia). In Argentina and Brazil the incidence is similar to that in the United States.
The only reliable data on frequency come from the necropsy studies of Schmorl in Germany (1932). He found 138 cases of Paget's disease out of 4614 necropsies on unselected people over 40 years of age, an incidence of three per cent. Similar figures were reported by Collins (1956): 3.7 per cent of 650 necropsies in patients aged over 40 had Paget's disease. At present we (with collaborators) are undertaking similar demographic studies in Argentina, Brazil and Uruguay.

Until the incidence of the disease itself is known, the frequency of malignant change cannot be established. The published data vary widely. In those series which consider only patients with advanced and clinically obvious disease the percentage with sarcoma is high—between 5 and 20 per cent (Schajowicz 1942; Jaffe 1958; Goldenberg 1961; Lichtenstein 1977); when the large number of asymptomatic patients with mild Paget's disease is considered, the complication rate is obviously much less, ranging from 0.15 per cent (Price 1962; Sisson 1965; Price and Goldie 1969) to 0.9 per cent and even two per cent (Porretta, Dahlin and Janes 1957; McKenna et al. 1964; Barry 1969). In a recent paper from the Mayo Clinic (Wick et al. 1981), out of 3964 patients with Paget's disease seen between 1927 and 1977, 38 had primary malignant bone tumours; this represents an incidence of sarcomatous change of 0.95 per cent.

Sex and age. Most series report that Paget's sarcoma is more common in men. In their review of the literature McKenna et al. (1964) reported 117 men and 52 women. Barry (1969), in his review of teaching hospitals in Australia, found that sarcoma occurred in 78 men and 38 women, though histological proof was sometimes lacking. The largest series, collected from registries in Bristol, London and Leeds, was reported by Ross, Middleton and Fitton (1973); there were 145 cases of histologically proven sarcoma arising in Paget's disease, with a sex ratio of 1.9 males to 1 female. In our 62 cases, however, there was only slight male predominance (1.6:1).

The age distribution is shown in Table I. Only one case was observed before the age of 50; the tumour occurring most often between the ages of 50 and 70, the average age being 66 years. This agrees with the figures reported by Ross et al. (1973) whose average was 67.4 years and with those of Wick et al. (1981), whose average was 64 years.

Localisation. The site of involvement (Fig. 1) and the type of sarcoma are shown in Table II. The most frequent sites, in descending order, were the femur (37 per cent; Figs 2, 3, and 4), the pelvis (16 per cent), the humerus (14.5 per cent) and the tibia (14.5 per cent). Unlike other series (Barry 1961; McKenna et al. 1964), in which the skull and facial bones were frequently involved, we had only four such cases; this is evidently due to the fact that we receive most of our material purely from orthopaedic departments. That the humerus (Figs 5 and 6) is commonly affected has been pointed out by most authors (Lake 1951; Porretta et al. 1957; Barry 1969; Wick et al.}

### Table I. The age and sex distribution of sarcoma in Paget's disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Per cent</td>
<td>Number</td>
</tr>
<tr>
<td>Unspecified</td>
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<td>15</td>
<td>6</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>60-69</td>
<td>25</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>70-79</td>
<td>12</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>80-89</td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>62</td>
<td>38</td>
<td>61</td>
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</table>
### Table II. The varieties of sarcoma and their anatomical distribution

<table>
<thead>
<tr>
<th>Site</th>
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<th>Fibrosarcoma</th>
<th>Chondrosarcoma</th>
<th>Malignant fibrohistiocytoma</th>
<th>Malignant lymphoma</th>
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<tr>
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<td>6</td>
<td>2</td>
<td>1</td>
<td></td>
<td>23</td>
</tr>
<tr>
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<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Innominate bone</td>
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<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>10</td>
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<tr>
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<td>2</td>
<td>1</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Vertebra</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
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<tr>
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<td>1</td>
<td></td>
<td></td>
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<td></td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>39</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>62</td>
</tr>
</tbody>
</table>

Fig. 5

A man aged 50 years. Polystotic Paget's disease with multicentric osteosarcoma. Figure 5—Radiograph showing Paget's disease of the humerus with, at its upper end, an osteolytic ill-defined lesion which has destroyed the inner aspect of the cortex. Figure 6—Photograph of a thin section of the amputation specimen, showing the fleshy and haemorrhagic nature of the tumour, the cortical destruction and the evident hyperaemia of the pagetic bone. Other osteolytic foci of sarcoma were found in the lower end of the humerus. (Reproduced, with permission, from Schajowicz F. Tumors and tumor-like lesions of bone and joints. New York: Springer Verlag, 1981.)

1981). Ross *et al.* (1973) in their series of 145 cases, found that sarcoma arose most frequently in the femur (39 per cent), followed by the humerus (14.5 per cent); our own findings were similar. On the other hand, Wick *et al.* (1981) found that the bone most commonly affected was the pelvis, followed by the femur and humerus. The low incidence of vertebral sarcoma (Figs 7 and 8) is evident in our series (only five cases) and in other large series—four of the 116 sarcomata in the Australian series (Barry 1969), three of the 145 reported by Ross *et al.* (1973), and one per cent in Wilner's (1982) review of 192 cases. This

Fig. 6

A man aged 83 years. Osteosarcoma of the third lumbar vertebra in pre-existing Paget's disease. Anteroposterior (Fig. 7) and lateral (Fig. 8) radiographs showing a destructive lesion of the posterior part of the vertebral body and increase of its diameter characteristic of the vertebral lesions of Paget's disease. Spinal cord compression occurred.

Fig. 7

Fig. 8

A man aged 66 years. This patient had had polystotic Paget's disease for 20 years. An osteosarcoma arising in the left ischium, is growing rapidly and destroying the bone. He died three months after the onset of symptoms.
A woman aged 68 years with polyostotic Paget's disease for 30 years. Multiple foci of osteosarcoma arose in the frontal bone of the cranium which shows very advanced pagetic lesions (Figs 10 and 11). An osteolytic sarcoma appeared at the same time in the left ischium (Fig. 12) which also was affected by Paget's disease.

is in sharp contrast with uncomplicated Paget's disease which, according to Schmorl's necropsy studies, occurred most commonly in the sacrum (56 per cent) and the spine (50 per cent), followed by the right femur (31 per cent) and the cranium (25 per cent). We had no examples of sarcoma involving the distal parts of the upper and lower extremities.

Most cases of sarcoma developed in patients with polyostotic disease (Fig. 9); it was rare in monostotic Paget's disease. An interesting feature is the occurrence of multiple sarcomatous foci which often developed simultaneously (or with short intervals) in different bones, or in different areas of the same bone (Figs 10 to 16). The incidence in our series, as in others, was between 20 and 30 per cent and the tumours occurred most frequently in the femur and skull. We wish to emphasize that whenever single or multifocal sarcoma developed in our series, it always occurred in a bone showing the characteristic changes of Paget's disease. This accords with the findings of Coley and Sharp (1931) and seems to favour a multicentric origin of the sarcomatous lesions rather than a metastatic spread, at least in the majority of cases.

**Symptoms.** The most constant symptoms are swelling, which is generally visible early, and an increase of the existing pain which is so characteristic of Paget's disease.

The effect of local injury, especially of fracture, on the development of sarcoma, is not convincing; it occurred in only one of our cases, in which a neoplasm arose at the site of a healed fracture (Fig. 15). Pathological fracture through the sarcomatous area on the other hand (Fig. 15) was a frequent finding (20 per cent; Schajowicz 1981).

The alkaline phosphatase level usually rises abruptly above the already high values in uncomplicated Paget's disease. But, because of the marked variation in alkaline phosphatase levels, this finding has no definite diagnostic value. The same considerations hold for the levels of urinary hydroxyproline excretion.

**Radiographic features.** The radiographic appearances
depend largely on the histological type of the tumour, which, in 63 per cent of our series and in 60 per cent of Ross’ series, was an osteosarcoma. In most instances the radiographs showed an ill-defined osteolytic lesion of the medulla with more or less destruction of the cortex and penetration into the surrounding soft tissues. In Ross’ series, soft-tissue tumours occurred in 78 cases (57 per cent) and destruction, either cortical or medullary, in nearly 90 per cent. Only rarely was the tumour predominantly osteoblastic with intra-osseous and extra-osseous sclerosis. More often it was osteolytic with occasional irregular areas of reactive bone formation. With fibrosarcomata and with the other uncommon varieties of malignancy, the lesion was usually purely osteolytic (Fig. 17) though two of the chondrosarcomata showed spots of calcification. The predominantly destructive nature of the lesions explains the frequency of pathological fractures, which occurred in 20 per cent of our cases and in 36 per cent of Ross’ series.

Pathological findings. The most common histological type of tumour was an osteosarcoma; there were 39 cases (63 per cent) in our series, 60 per cent in Ross’ series (1973) and in the Mayo Clinic series there were 32 osteosarcomata out of the 38 sarcomata (Wick et al. 1981). The next most common tumour type was a fibrosarcoma, with 15 cases (24 per cent) in our series and 19 per cent in Ross’ series. The distribution of the other rarer tumour types (chondrosarcoma five cases, malignant fibrohistiocytoma two cases, and reticulosarcoma one case), together with their location is shown in Table II. We would emphasise that among these rare tumour types the diagnosis was definite in only two cases of chondrosarcoma, in which the complete amputation specimens were available; in the other cases only open or aspiration biopsies had been performed, so that the presence of bone-forming tissue in

![Fig. 17](image1)

A man aged 56 years. Chondrosarcoma showing an ill-defined osteolytic lesion in the trochanteric region of the right femur.

![Fig. 18](image2)

![Fig. 19](image3)

A man aged 52 years. Radiographs of the entire clavicle (Fig. 18), and of a longitudinal section of the resected bone (Fig. 19) showing the characteristic structure of Paget’s disease, together with a central osteolytic lesion, thinning the cortex. Histologically this osteolytic lesion proved to be an ordinary giant-cell tumour without signs of malignancy, which had arisen in pagetic bone.
other areas of the tumour (that is, an osteosarcoma) cannot be definitely excluded. Only four instances of histologically verified malignant fibrohistiocytoma at the site of Paget’s disease have been previously reported, one by Spanier, Enneking and Enriquez (1975) and three by Dahlin (1978).

The histological features are similar to those of the same type of sarcoma arising in normal bone, but frequently there is more anaplasia. However, in a large number of osteosarcomata complicating Paget’s disease, a particular histological pattern was observed; it was characterised by a great number of osteoclast giant cells, alternating with numerous, often atypical, osteoblasts on the surface of the newly formed bone trabeculae. Thus the process of anarchic remodelling with alternation of osteoclastic bone resorption and osteoblastic bone apposition (the characteristic feature of Paget’s disease) is reproduced or even exaggerated. The fact that a fairly large number of giant cells of osteoclastic type can often be seen in sarcomata arising in Paget’s disease (Schajowicz and Oleaga Alarcon 1945; Schajowicz 1981), means that great care is needed when making the differential diagnosis from an ordinary giant-cell tumour. Although extremely rare, giant-cell tumours with no histological signs of malignancy may be associated with Paget’s disease; but, in contrast to osteosarcomata rich in giant cells, they have a relatively good prognosis; they are in fact less aggressive than giant-cell tumours originating in normal bones. To the small number of such cases (12) found in the English literature by McKenna et al. (1964), we added another situated in the diaphysis of the tibia (a monostotic lesion) in a 45-year-old patient who was followed up for more than four years (Schajowicz and Slullitel 1966); and in this present paper we also include a second case, affecting the clavicle, a rare site for Paget’s sarcoma; this tumour (Figs 18 and 19) was resected, and had not recurred after three years. The few cases reported as malignant giant-cell tumours are in our opinion examples of osteosarcomata rich in giant cells or malignant fibrous histiocytoma; a positive histochemical finding of alkaline phosphatase could help to establish the diagnosis of osteosarcoma in those cases in which tumour osteoid tissue is rare or apparently non-existent (Schajowicz and Cabrini 1954; Sanerkin and Jeffree 1980). Another conspicuous finding was the increased number of osteoclasts in the areas of pagetic bone adjacent to the tumour. All these histological findings in osteosarcoma associated with Paget’s disease are responsible for the most common osteolytic pattern and seem to support a close histogenetic relationship between the two.

On the other hand, in some of our cases we observed in the neighbouring pagetic bone the existence of a fibrous marrow, more cellular and more anaplastic than commonly found in this area; this could possibly correspond to an incipient atypical proliferation, that is a presarcomatous stage of the bone marrow, a hypothesis...
put forward by von Albertini (1928). Typical histological findings are shown in Figures 20 to 29.

TREATMENT AND PROGNOSIS

The prognosis of Paget's sarcoma is poor. It is particularly bad in tumours not amenable to operation, in patients with pathological fractures, in multicentric lesions and in those with histologically anaplastic and pleomorphic tumours. In the Australian series of 116 patients (Barry 1969), none survived more than five years; most cases were rapidly fatal, death occurring within 12 months of the onset of the sarcoma.

Only a few cases have been reported with a survival of more than five years. All were treated by amputation or disarticulation, with or without radiotherapy: one by Russell (1949), two cases of Platt's (1947) followed up and reported by Stevens and Lennox (1958), one case by Cowie, Barr and Dudley (1958), two by Schatzki and Dudley (1961), two by Price and Goldie (1969) and three cases by Dahlin (1978). Russell reported a malignant osteoclastoma arising in Paget's disease: this patient, a women of 59, had a tumour of the tibia treated by mid-thigh amputation and was alive and well after more than 10 years; this tumour was probably a giant-cell rich osteosarcoma. In our series we had only one patient who survived more than five years; the tumour was a fibrosarcoma in the upper tibia (which was the only bone affected by Paget's disease) and was treated by mid-thigh amputation.

DISCUSSION

The reported incidence of sarcoma in Paget's disease varies widely from 0.15 to 10 per cent or even to 20 per cent, according to whether asymptomatic cases of Paget's disease are included or not. The fairly high incidence in our series (6.28 per cent) is not typical and is due to the large number of advanced, often polyostotic and symptomatic cases of Paget's disease which are sent to us. The real incidence seems to be closer to one per cent; a figure of 0.95 per cent was found in the recent Mayo Clinic series (Wick et al. 1981).

It seems clear, however, that a close histopathogenetic relationship exists between Paget's disease and the associated sarcoma. This supposition is based on three separate observations.

Firstly, osteosarcoma complicating Paget's disease occurs at an age when osteosarcoma is otherwise rare. Coley and Sharp (1931) first emphasised that 28 per cent of osteosarcomata occurring in patients of more than 50 years of age had Paget's disease. Sissons (1965) found that 26 per cent of all primary malignant bone tumours occurring in patients over 40 years of age were associated with Paget's disease and that this percentage rose progressively with increasing age. In our series Paget's sarcoma was most common after 55 years of age.
Secondly, in our series, whenever sarcoma (whether single or multiple) developed, this always occurred in bones which were already affected by Paget's disease; this agrees with the findings of Coley and Sharp (1931). When sarcomata were multiple, they were frequently more or less synchronous, and they affected different areas of one single already pagetic bone or several already pagetic bones. This also suggests that, in most instances at least, there is a multicentric origin of the sarcomatous change rather than a metastatic spread.

The third feature was that, in the pagetic bone near the sarcoma, there was a conspicuous increase in the cellular activity involved in the remodelling process, especially in the number of osteoclast giant cells. Frequently the osteosarcoma developing in pagetic bone showed a great number of giant cells of osteoclastic type, accompanied by active and atypical osteoblasts, thus imitating in an exaggerated manner the process of anarchic remodelling characteristic of Paget's disease. These observations constitute in our opinion important findings favouring the close pathogenetic relationship between Paget's disease and its sarcomatous transformation.

In a few cases, we found in the fibrous marrow in the vicinity of the sarcoma (especially with fibrosarcoma) an increase in the number and activity of the fibroblasts; this finding has been reported previously by von Albertini (1928). We also agree with him that the cellular features suggest that Paget's disease may possibly be considered a presarcomatous lesion.

We would emphasise that not all tumours associated with Paget's disease are highly malignant. Although extremely rare, a giant-cell tumour with no histological signs of malignancy may arise in a pagetic bone; such a tumour should not be confused with an osteosarcoma rich in giant cells of osteoclastic type, which is highly malignant and nearly always fatal. Our two patients with giant-cell tumours did well. One has a tumour in the tibial shaft, the other in the clavicle; in both the lesion was resected and both were satisfactory when followed up after fours years.

In the last decade viral-like intranuclear inclusions have been reported in the osteoclasts of Paget's disease (Rebel, Malkani and Basle 1974; Mills and Singer 1976; Gherardi, Lo Cascio and Bonucci 1980; Schajowicz et al. 1980). If we accept a viral aetiology for Paget's disease, and this has been supported recently by Mills et al. (1981), then the same mechanism might cause the sarcoma which supervene. Mills and Singer (1976) have, in fact, reported identical inclusions in a sarcoma with giant cells arising in a case of Paget's disease of the maxilla and Mirra, Henrik Bauer and Grant (1981) described similar inclusions in a giant-cell tumour associated with Paget's disease; similar findings have previously been reported in isolated cases of giant-cell tumour (osteoclastoma) without Paget's disease (Welsh and Meyer 1970; Le Charpentier et al. 1977; Schajowicz et al. 1980). However, in the only case of osteosarcoma arising in Paget's disease studied ultrastructurally by Reddick et al. (1980), no such inclusions were found in the giant-cell osteoclasts. Future studies investigating the presence of similar inclusions in osteoclast giant cells in Paget's sarcoma are needed; if they are found, this would support a viral aetiology.

Finally, it should be pointed out that although sarcomata arising in Paget's disease are relatively rare, the absolute number of patients with this complication is significant, because Paget's disease is so common.

REFERENCES


