MALIGNANT OSTEOCLASTOMA

And the Association of Malignant Osteoclastoma with Paget's Osteitis Deformans

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It is generally conceded that solitary osteoclastomata of long bones may occasionally prove malignant, but there is no agreement as to the frequency of this occurrence or as to the diagnostic criteria of the histological appearances of malignancy in primary growths. Clinical evidence of pulmonary metastasis has been recorded in a number of cases published during the last thirty-five years after curettage of the primary tumour, irradiation, and amputation of the limb; but unfortunately autopsy has seldom been performed. The well documented case of Finch and Gleave (1926) was the first metastasizing osteoclastoma to be verified histologically (the case reported in 1922 by Augé and Roux being in all probability an osteogenic sarcoma). Dyke (1931), and Orr (1931), reported single cases which should also be accepted, though each was incomplete in certain respects. In other relevant papers of this period, pathological observations were confined to the primary tumour. It is generally agreed that the character of the cellular matrix, or the so-called "stroma cells" as distinct from osteoclastic giant cells, demands careful scrutiny in the assessment of malignancy. In certain examples, such as those reported by Stone and Ewing (1923), Coley (1924, Case 3), and Stewart et al. (1938, Case 3), these stroma cells may at first be indistinguishable from those of a benign growth; but subsequent biopsies show malignant characters such as marked polymorphism of the cells and their nuclei, increasing numbers of mitotic figures, and the formation of a distinctive and malignant type of giant cell to which attention was drawn by Mallory (1911) and, more specifically, by Stewart (1914). In other examples, the stroma cells displayed malignant features at the first biopsy (Kleinberg 1939) or there were appearances that proved controversial and at a later date declared themselves as frankly malignant (King 1932, Stewart et al. 1938, Cases 1, 2, 5, 7). Jaffe et al. (1940) went so far as to attempt grading the primary tumour on the basis of these changes in stroma cells, a procedure that appears valueless in the light of personal experiences to be related in this paper.

A survey of the material preserved in the Bernhard Baron Institute of the London Hospital since 1907 shows that, excluding osteitis fibrosa, the surgical specimens include forty-six solitary osteoclastomata in bones other than the jaw. Only one example of osteoclastoma came to necropsy, namely Case 4—osteoclastoma complicating Paget's osteitis deformans. The subsequent history of many of these patients is unknown, but two are alive and well thirty-three and thirty-four years after amputation. The second of these cases is of interest because the tumour, which was situated in the lower end of the humerus, showed a cellular stroma with many mitoses in the growing edge, and the adjacent muscle was infiltrated by the growth. Such infiltration is not, however, uncommon in osteoclastomas and it has not the same sinister significance as infiltration in other types of tumour.

Five cases have been selected for detailed consideration—two osteoclastomas of the upper end of the tibia, treated along parallel lines by curettage, irradiation, and amputation, in which metastasis supervened; and three osteoclastomas of histologically malignant character complicating osteitis deformans (Paget's disease).

TWO CASES OF MALIGNANT OSTEOCLASTOMA

Case 1. S. K., female, aged 29 years—The clinical particulars of this case are recorded by Ellis (1949) in a separate communication in this issue of the Journal. Pathological examination—The available material consisted of two drill biopsies, taken at an interval of eight months, and the amputation specimen
The first drill biopsy was composed of small fragments of a cellular tumour containing osteoclastic giant cells of variable size, most being rather small and containing from six to twelve nuclei. These cells were distributed throughout the tissue, more numerous in some areas than others. They were separated by polygonal stroma cells which varied in size and exhibited a few mitoses. Their nuclei were even in form and chromatin content, and there were no features suggestive of malignancy (Fig. 1). The specimen was reported as "osteoclastoma." The second drill biopsy, received eight months later, presented similar appearances with many osteoclasts of large size throughout the tissue. But the stroma cells, though similar, exhibited many more mitoses including abnormal forms. Moreover the chromatin content of the nuclei was variable. Some cells appeared to be multinucleate but close crowding made it difficult to assess the number (Fig. 2). This specimen was suspected of malignancy and it was reported as "probably malignant osteoclastoma." Amputation specimen—Amputation was performed six months later through the upper thigh. There was an ill-defined swelling below the knee due to a growth that had almost completely destroyed the upper end of the tibia and extended widely into the soft tissues and muscles of the calf, capsule of the knee joint, soft tissues between the tibia and fibula, and bone of the inner aspect of the tibial head. Much of the tumour was soft, opaque, pink and necrotic; a few areas were rubbery, pale yellow and slightly bony. The more peripheral parts were soft and white, including a distinct area of tumour, 8 centimetres in diameter, occupying the lower third of the tibia and projecting through the inner cortex and periosteum. There was normal adipose marrow in the shaft immediately above and below this area. Microscopic examination—Six blocks, taken from representative parts of the tumour, showed extensive destruction of tissue with haemorrhage and necrosis. Osteoclastic giant cells were abundant in many areas and sparse in others. They were separated by plump, polygonal stroma cells which varied greatly in size and shape, and in the size and chromatin-content of their nuclei (Fig. 3). In some fields they were angular, with a deeply basophil cytoplasm. There were many multinucleate giant cells, obviously derived from these stroma cells; but the relationship between these giant cells and the osteoclastic giant cells was by no means clear; and the more close the study the more difficult was it to avoid the

received fourteen months after the first biopsy. Later, there was radiographic evidence of pulmonary metastases but when the patient died there was no necropsy. The first drill biopsy was composed of small fragments of a cellular tumour containing osteoclastic giant cells of variable size, most being rather small and containing from six to twelve nuclei. These cells were distributed throughout the tissue, more numerous in some areas than others. They were separated by polygonal stroma cells which varied in size and exhibited a few mitoses. Their nuclei were even in form and chromatin content, and there were no features suggestive of malignancy (Fig. 1). The specimen was reported as "osteoclastoma." The second drill biopsy, received eight months later, presented similar appearances with many osteoclasts of large size throughout the tissue. But the stroma cells, though similar, exhibited many more mitoses including abnormal forms. Moreover the chromatin content of the nuclei was variable. Some cells appeared to be multinucleate but close crowding made it difficult to assess the number (Fig. 2). This specimen was suspected of malignancy and it was reported as "probably malignant osteoclastoma." Amputation specimen—Amputation was performed six months later through the upper thigh. There was an ill-defined swelling below the knee due to a growth that had almost completely destroyed the upper end of the tibia and extended widely into the soft tissues and muscles of the calf, capsule of the knee joint, soft tissues between the tibia and fibula, and bone of the inner aspect of the tibial head. Much of the tumour was soft, opaque, pink and necrotic; a few areas were rubbery, pale yellow and slightly bony. The more peripheral parts were soft and white, including a distinct area of tumour, 8 centimetres in diameter, occupying the lower third of the tibia and projecting through the inner cortex and periosteum. There was normal adipose marrow in the shaft immediately above and below this area. Microscopic examination—Six blocks, taken from representative parts of the tumour, showed extensive destruction of tissue with haemorrhage and necrosis. Osteoclastic giant cells were abundant in many areas and sparse in others. They were separated by plump, polygonal stroma cells which varied greatly in size and shape, and in the size and chromatin-content of their nuclei (Fig. 3). In some fields they were angular, with a deeply basophil cytoplasm. There were many multinucleate giant cells, obviously derived from these stroma cells; but the relationship between these giant cells and the osteoclastic giant cells was by no means clear; and the more close the study the more difficult was it to avoid the

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Conclusion that there were transitions between the two (Fig. 4). Osteoid tissue was present in many areas, forming a coarse net between the plump stroma cells. In a few places calcium had been deposited and there was early coarse-fibred bone. No cartilage or myxomatous tissue was identified.

Comment—The three specimens from this case showed steady progression from an apparently benign to an obviously malignant tumour. It is true, of course, that drill biopsy provides no more than scanty material for diagnostic purposes; but the appearances in both drill specimens were sufficiently dissimilar from each other, and from any field examined in the six sections taken after amputation from the main tumour, to justify the conclusion that they were representative preparations. The histological appearances in the terminal stage were suggestive of osteogenic sarcoma; but osteoclastic giant cells were more numerous, and of wider distribution, than would have been expected in such a tumour. Nevertheless if the tumour had first been examined at this stage, the differential diagnosis would surely have been controversial.

Case 2. J. L., girl, aged 19 years—Patient was never admitted to this hospital and full clinical notes have not been traced. The primary tumour was first observed in November 1939, after there had been pain over the inner aspect of the upper right tibia with no history of injury. There was a tender “fluctuating” swelling. A small biopsy specimen described as “cortex and scrapings from bone cyst” was received by my colleague, Dr W. W. Woods, at the Emergency Medical Service Laboratory, Southend. The serum-calcium was estimated and found to be 9.4 mgm. per cent., thus excluding generalised osteitis fibrosa. In April 1940 the cyst was curetted and filled with iodic bone chips. In January 1941 it was noted that she was walking well; but in April 1941 two small sequestra separated. A course of radiation treatment was given. In July 1941 the limb was amputated through the middle third of the thigh. The fate of this specimen cannot be traced and no histological report is available. In May 1942 she was admitted to the Connaught Hospital, under Mr W. Welph, with haemophyisis, radiographic evidence of three “golf-ball” secondary deposits in one lung, and a subcutaneous metastasis in front of the left ear which was excised for histological examination. She died in August 1943, four years after the primary tumour was first observed. Necropsy was not performed.

Pathological examination—Pathological material was limited to biopsy of the primary tumour in 1939 and of the precarticular metastasis excised in 1942. The first biopsy specimen consisted of fragments of bone the
trabeculae being separated by many osteoclastic giant cells in a spindle-celled matrix (Fig. 5). Other areas were composed of dense fibrous tissue and bone trabeculae separated by spindle cells. There were many pigment-macrophages. No mitoses were present and there were no giant cells other than osteoclasts. Macroscopically the second specimen consisted of a dome-shaped swelling.

Fig. 5
Case 2. Biopsy from the primary tumour of the tibia—osteoclastic giant cells in a spindle-celled matrix (haematoxylin and cosin; × 280).

Fig. 6
Case 2. Subcutaneous metastasis of the tumour showing, on the left, the border of a blood space; and on the right, osteoid tissue with a trabecula of coarse-fibred bone (haematoxylin and cosin; × 110).

1.3 centimetres in diameter, projecting into the skin. On section there was a well-defined mass, 2 centimetres in diameter, consisting of haemorrhagic and grey tissue containing gritty particles. Microscopically the tumour expanded the dermis and was well-defined above and below by circumferential collagenous tissue. The lateral borders were less sharp and were occupied by fine trabeculae of coarse.
fibred bone embedded in collagenous tissue containing spindle cells. Similar foci of bone lay nearer the centre, much of which was composed of large irregular blood spaces lined by cellular tumour tissue (Fig. 6). In this, large osteoclastic giant cells were conspicuous, associated with closely packed round, ovoid and polygonal mononuclear stroma cells containing nuclei of even shape, size and chromatin-content, except where they had become pyknotic and angular (Fig. 7). Occasional mitotic figures were present but there were no giant forms. More remote from the blood spaces, the cellularity of the tumour tissue was reduced; the cells were more frequently spindle-shaped and osteoclasts were less abundant. Mitotic figures were rare. Such areas merged into the still less cellular areas which were rich in collagen and associated with bone formation. Reticulin fibrils were abundant throughout the tumour, separating the smaller cells and enclosing the osteoclasts.

![Image](image.png)

**Fig. 7**

Case 2. Another field of the subcutaneous metastasis showing the character of the cells of the more cellular central areas (haematoxylin and eosin; × 620).

**Comment**—It is unfortunate that the amputation specimen could not be traced, particularly since the early biopsy specimen provided no more than meagre material for histological assessment. It is clear, however, that the cellular character of the tumour showed no departure from that of the type generally accepted as benign. Indeed, for a time, the diagnosis of osteitis fibrosa was considered. The metastasis itself showed no obvious cytological evidence of malignancy and there is little doubt that if it had been presented to a pathologist as a primary growth it would have been labelled "benign." The case is therefore important, both in showing the difficulty of assessing malignancy in microscopic examination of the primary tumour, and in demonstrating that such benign features may be perpetuated in metastases. Incidentally the metastasis shows clearly the osteogenic capacity of osteoclastoma.
THREE CASES OF MALIGNANT OSTEOCLASTOMA IN PAGET'S OSTEITIS DEFORMANS

The association of malignant osteoclastoma with osteitis deformans (Paget's disease) does not appear to be recognised generally but, quite evidently, it accounts for a proportion of the malignant tumours that complicate this disease and it was represented in the records of this Department by three cases.

Case 3. W. H. W., male, aged 70 years—The left lower limb was amputated through the hip joint at another hospital in 1931 for a tumour of the left upper femur. Six months later a pulsating swelling appeared at the lower end of the right femur necessitating amputation through the right thigh. A tumour was also observed in the lumbar muscles. The patient died a few months later. There was no necropsy.

Pathological examination—The material available consisted of the left lower limb. This showed antero-posterior bowing of the femur and tibia. On section, a polycystic tumour, measuring 13 centimetres by 5 centimetres, occupied the anterior aspect of the neck, greater trochanter and upper part of the shaft of the femur (Fig. 8). It had invaded adjacent muscles and completely destroyed the cortex for a distance of 6.5 centimetres. Cystic spaces measured up to 3 centimetres by 1.7 centimetres and contained blood. Their walls consisted of thin grey-yellow tissue of fibrous consistency. The rest of the medullary cavity was occupied by gelatinous brown-red marrow. The femur, tibia and fibula showed the characteristic changes of Paget's osteitis deformans. Microscopic examination—The growth included large spaces filled with fresh blood, lined for the most part with large osteoclastic giant cells interspersed with spindle and polymorphic stroma cells. Elsewhere the lining was composed of flattened cells of endothelial appearance. The more solid parts of the growth contained similar osteoclastic giant cells in large numbers, separated by plump polymorphic and spindle cells which varied greatly in size and shape (Fig. 9). The nuclei of these cells also varied in size, shape, and chromatin-content. Mitotic figures were numerous and there were multinucleate giant cells of malignant type. In some areas, between the cysts, there were conspicuous...
masses of pigment macrophages. The tumour had invaded adjacent soft tissues and in many places, outside the confines of the bone, osteoid tissue was laid down as a net between the polymorphic tumour cells. Other parts of the bone showed stages of osteitis deformans.

Comment—The cytology of this tumour is clearly indicative of its malignancy. The many osteoclastic giant cells, and the situation of these cells in the walls of large blood spaces throughout the tumour, are characteristic of osteoclastoma. The tumours that subsequently arose in the other femur, and in the lumbar muscles, were presumably metastases although it might be possible to interpret the second femoral tumour as being of independent origin.

Case 4. W. M., male, aged 49 years. Clinical history—For eight years this patient had noticed thickening and bowing of the lower limbs below the knees. Recently there had been headaches without vomiting and, during the week before admission, numbness and loss of power in the right lower limb, weakness of the right upper limb, and the appearance of a lump on the left side of the skull which was said to have grown larger. Two days before admission there had been Jacksonian attacks starting with twitching movements in the right great toe, extending up the right lower limb, and then involving the right upper limb. On examination—There was a tense, pulsating, painless swelling, one inch in diameter, over the postero-superior angle of the left parietal bone. The edge of the bone could be palpated about its margins. The circumference of the head was 22.6 inches. Both tibiae were thickened and bowed. Operation—After reflection of the scalp, a highly vascular growth was disclosed, replacing the bone and invading the pericranium and parasagittal dura. The tumour was partly removed. Five days later, motor power was regained in the right upper and lower limbs. Two weeks later, paresis returned with increasing involuntary movements. Aphasia and incontinence developed and the patient died two months after admission to hospital. Necropsy—Bronchopneumonia. Haemorrhagic tumour of the left parietal bone invading the subjacent cerebrum. Osteitis deformans of the skull, femora, tibiae and sternum. The vault of the skull, which has been preserved as a museum specimen, was diffusely thickened up to 1.3 centimetres, but there was no additional expansion in the region of the tumour. The margins of the bone showed a sharp transition to the tumour which formed a mass measuring 2.5 centimetres by 2 centimetres. Half the tumour projected into the pericranium but did not penetrate beyond it. The cut surfaces were homogeneous and grey. The outer aspect of the dura showed a layer of similar tumour, several millimetres thick, forming a fringe along the left border of the superior longitudinal sinus which was slightly deflected to the right. The inner aspect of the dura showed a small mass of tumour, 2 centimetres in diameter, projecting into the angle between the sinus and the falc. The tumour also extended through the cerebral cortex to reach the central white matter. No metastases or other bone tumours
were observed. *Microscopic examination*—Sections showed a highly vascular and cellular growth occupying the whole thickness of the bone and protruding into the pericranium. Finger-like extensions occupied the adjacent diploe but, on the whole, the margins were well defined. The cytological characters of this part of the tumour, and of the extensions towards the brain, were similar. Large osteoclastic giant cells were numerous and widely distributed. They were separated by closely packed spindle, ovoid and angular stroma cells, which varied greatly in size. Their nuclei varied in size and in chromatin-content. Many mitoses and multinucleate giant cells of malignant aspect were present (Fig. 10). There was much destruction of the tumour by haemorrhage and necrosis. No bone, cartilage or osteoid tissue was detected. There were foci of dense collagen; elsewhere a fine network of reticulin fibrils separated the tumour cells. The bone of the skull showed advanced osteitis deformans.

*Comment*—The rapid deterioration of the patient after appearance of the growth and its surgical exploration accord with macroscopic and microscopic appearances, both of which are indicative of a malignant neoplasm.

Case 4. Paget's disease with malignant osteoclastoma of the skull causing cerebral symptoms. Two osteoclastic giant cells and polymorphic stroma cells of malignant appearance (haematoxylin and eosin; ×380).

**Fig. 10**

Case 5. E. P., female, aged 59 years—Admitted to the London Hospital under the care of Mr Osmond-Clarke with Paget's osteitis deformans and a tumour of the left tibia. *Clinical features*—For many years the left tibia, left humerus, skull and proximal phalanx of the right index finger had been affected by osteitis deformans. For three months before admission, after a blow on the upper end of the left tibia, there had been continuous pain with gradual development of a pulsating swelling. On admission the swelling measured 3 inches by 1·5 inches. *Operation*—The limb was amputated through the middle of the thigh. She made a good recovery and to-day, nearly two years later, she is alive and well. *Pathological examination*—*Macroscopic*—There was marked bowing of the leg. Section showed a tumour in the medullary cavity of the tibia, 9 centimetres in diameter, composed of grey-white tissue with a yellow centre, and containing patches of haemorrhage and one well-defined cyst near the upper end. The anterior cortex was eroded over an area measuring 7·5 centimetres. The posterior cortex was bayed by growth in several places. No calcification was detected in the growth. The rest of the bone showed the changes of osteitis deformans. *Microscopic examination* showed a cellular tumour which had eroded the bone of the tibia and extended into the periosteum but not beyond it. Large osteoclastic giant cells were distributed throughout the tissue (Fig. 11). They were separated by polymorphic, angular, mononucleated cells which varied greatly in size as well as shape. Among these were many large multinucleate giant cells with relatively large vesicular, often lobed, nuclei of malignant type. Some of these giant cells were as large as the osteoclastic giant cells. Mitotic figures were abundant. There was extensive necrosis of the tumour in many areas. No cartilage or osteoid tissue appeared to have been formed in the tumour. In
one section there was a large irregular area of closely packed foam cells, apparently corresponding to the yellow patch seen with the naked eye. A few polymorphic tumour cells were scattered among these foam cells.

Comment—By all the usual criteria this was a highly malignant tumour, and the diagnosis lay between osteogenic sarcoma and malignant osteoclastoma. The diagnosis of malignant osteoclastoma is favoured by the many characteristic osteoclastic giant cells, and the xanthomatous area within the tumour. This interpretation is perhaps supported by the fact that the patient is in good health nineteen months after amputation.

DISCUSSION

If the first two cases reported in this contribution are acceptable as authentic examples of metastasizing osteoclastoma, it follows that metastasis in this tumour is associated with two different types of evolution in the growth. A frankly malignant change may take place in the stroma cells of the primary tumour with the production of cytological appearances that are difficult to distinguish from those of osteogenic sarcoma (Case 1); alternatively the tumour may proceed to metastasis without appreciable morphological changes in its cells (Case 2). Confirmation of the first is to be found in many published reports, and it is exemplified in the case reported by Finch and Gleave in which the metastases had malignant appearances. In Dyke's case there was no detailed description of the stroma cells and the photomicrographs are at too low a magnification to rectify this omission. Orr's case, in which the pulmonary metastases alone are described and illustrated, shows some resemblance to Case 2 of this paper in the character of the stroma cells which were for the most part spindle-shaped—"perhaps larger than the corresponding cells of the benign osteoclastoma"—and a few showed mitoses.

Further experience alone can decide whether these two types of metastasizing osteoclastoma are to be distinguished. If such a distinction is confirmed it follows that no accurate prognosis can be based upon the histological appearances of a solitary osteoclastoma even although, by ordinary criteria, it may appear benign.
Absence of bone formation has been regarded as an important diagnostic feature of osteoclastomata in general (Stewart 1922, Stewart et al. 1938). However, osteoid tissue was present in the metastases in Finch and Gleave’s case; and bone was reported in the metastases by Dyke. The conspicuous amount of coarse-fibred bone in the subcutaneous metastasis in Case 2 of this series appears to establish the osteogenic capacity of the tumour cells. This point is of fundamental importance in that it links osteoclastoma and osteogenic sarcoma more closely than has been conceded, and explains many of the difficulties of interpretation of malignant varieties of osteoclastoma.

Finally the association of malignant osteoclastoma with osteitis deformans, as reported in Cases 3, 4 and 5 of this series, casts an interesting side-light on the disputed question as to whether or not a distinction should be drawn between the osteoclastomata that may be associated with generalised osteitis fibrosa and the solitary osteoclastoma that occurs without general bone disease. Turnbull (1931), from study of many examples, was unable to distinguish the tumours of these two groups on a purely histological basis. In Paget’s osteitis deformans, a disease which in its early stages closely resembles osteitis fibrosa, he found that both osteoclastomata and cysts occurred, even although they were rare (Turnbull 1931–32). Malignant tumours of bone complicate osteitis deformans in a small percentage of cases, estimated by Geschickter and Copeland (1931) at 5 to 7 per cent. These tumours are usually said to be osteogenic sarcomata. Such a diagnosis may possibly be correct for Case 5 in this series; but it is believed on histological grounds, that malignant osteoclastoma is the true interpretation of Cases 3 and 4.

I am indebted to Mr W. R. Welply for information about Case 2, and to Mr Osmond-Clarke for notes on Case 5. The photographs were prepared by Mr A. J. King.

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