MALIGNANT GIANT-CELL SYNOMIOMA OF PHALANX

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(RECEIVED FOR PUBLICATION MARCH 4, 1954)

Primary sarcoma of a phalanx is uncommon. Osteogenic sarcoma, fibrosarcoma, and chondrosarcoma have been infrequently reported, but a search of the literature has not revealed any previous record of a primary malignant synovial tumour arising endosteally, although benign synoviomata are fairly common in the digital soft tissues.

The unusual site of origin of the tumour described here is suggested both by the clinical and radiological findings. Invasion of bone by synovial tumours of digits and other sites has been reported by Wright (1952), Fletcher and Horn (1951), and by others, but in such examples the involvement generally appears to be either the result of pressure atrophy or due to direct extension of a parosteal growth. Certain primary expansive tumours of phalanges and metacarpals have been described (vide infra), which characteristically produce a rich osteoid matrix. These are usually classified with osteogenic fibroma of bone and present a histological picture which in some ways resembles the less cellular parts of the tumour reported here.

Case History

Mrs. N. F., aged 35, a housewife (BTR/511), in March, 1952, fell from a chair while hanging out washing. She fell on to the outstretched right hand, injuring the fifth finger. Before this there was no evidence of any bony or arthritic changes. Following the accident, the finger became painful and swollen but no medical advice was sought. As the symptoms were progressive, the patient consulted her doctor in July, 1952, who referred her for surgical advice. On examination at that time there was a deformity of the fifth right finger, with a tender swelling of the middle phalanx region.

X-ray examination on July 19, 1952, showed an extensive cystic swelling of the intermediate phalanx, with expansion and marked thinning of the cortex (Figs. 1, 2a). There may have been a former fracture of the phalangeal shaft in the antero-medial region. Apart from a very slight periosteal reaction, there was no sign of any new bone formation. There appeared to be perforation of the thinned cortex antero-externally. The other two phalanges were normal, as also were radio-

graphs of the skull and other bones. The finger was amputated at the metacarpo-phalangeal joint in September, 1952.

Amputation Specimen.—The finger when received had already been partly cut sagitally. It showed an irregular spheroidal mass of solid pale yellow-white tissue approximately 1.5 × 1 cm. occupying the middle segment of the finger in place of the intermediate phalanx (Fig. 2b). This solid tissue cut easily with the knife and was of a uniform rubbery consistency. It was fairly well circumscribed, more especially upon the volar aspect, and consisted of a main mass formed of a number of
ill-defined, rounded nodules fused together (A, Fig. 2b). There was also an adjacent distal part (B, Fig. 2b) of rather deeper hue, attached to, but separated from, the main mass by a transverse band of dense collagen. The flexor profundus tendon could be identified, but appears to have been invaded deeply by the tumour at C (Fig. 2b). The distal phalanx was decalcified in vivo and offered but little resistance to the knife. No naked-eye abnormality was noted in the proximal phalanx.

A radiograph of the specimen (Fig. 2c) showed almost entire destruction of the intermediate phalanx, and that the proximal two-thirds of the distal phalanx was markedly radiolucent, although a dim "ghost" of this bone could still be discerned. The proximal phalanx was normal except for some loss in density indicating decalcification.

**Histological Examination**

The entire finger was sectioned sagittally in three blocks; but section No. 2 (middle) was at a somewhat lateral plane to Nos. 1 and 3 (Fig. 2b). Both paraffin and frozen sections were cut. These were stained by haematoxylin and eosin, haematoxylin, phloxin and tartrazine, Gomori's silver impregnation, periodic-acid-Schiff, sudan III, sudan IV, alkaline methylene blue (pH 9.0), and Perls' method for iron. Both stained and unstained sections were examined by polarized light.

**Section 1: Proximal.**—There were early degenerative changes in the bone of the phalanx shaft. Both articular cartilages and their related synovia showed evidence of early degenerative arthritis. There was no neoplastic invasion of the phalanx, but dorsally a few tumour cells were tracking along the peritendinous tissue.

**Section 2: Middle.**—Both flexor and extensor tendons were distorted and invaded by tumour cells, the tendon sheaths showing early proliferative changes. The distal articular cartilage was fairly well preserved together with a thin sliver of subchondral bone and a short fragment of ventral shaft cortex. The major part of this section consisted of a mass of fibro-cellular tumour tissue which had an ill-defined nodularity, and a few small fragments of incompletely absorbed mature bone were found lying between the tumour cells. Ventrally, the tumour was bounded by a layer of dense collagen fibres, probably representative of the displaced periosteum. This limiting layer was less well defined dorsally where it had been invaded by the tumour. Distally, there was also a well-defined transverse band of collagen fibres which enclosed the main mass of the growth, and which itself was probably the residue of the bony transverse septum seen in Fig. 2a. The main tumour consisted of irregular spheroidal and fusiform cells lying in a rich stroma of dense collagen fibres (Figs. 3 and 4). There were also numerous bizarre giant cells mainly around the peripheral areas of the ill-defined nodules. Many of these giant cells were heavily laden with small globules of sudanophil material (Fig. 5). In unstained frozen sections, the globular material showed birefringence of a low order. No steroid crystals or spherulites were found. It was generally
observed that the sudanophil material was minimal or absent from those giant cells showing mitosis or cytoplasmic vacuolation. The dense stromal collagen showed typical birefringence and its form mainly suggested new fibre formation by the tumour cells rather than residual collagen matrix from destroyed bone, cartilage, or tendon. In certain areas there was a suggestion of a trabecular arrangement.

Lying between the collagen fibres were numerous round or oval "clefts," in some instances forming larger spaces by confluence. It had originally been thought that many of these were fat cells, but in frozen sections these spaces were again empty and
devoid of sudanophil material. Neither in paraffin nor frozen sections stained with methylene blue and by the periodic-acid-Schiff method was any evidence found of a mucinous content in these clefts, and one can only conclude that they must have contained a water-miscible fluid which had been lost into the formal fixative.

It was possible to observe the manner in which these small clefts were formed. The earliest evidence was to be found in the foamy cytoplasm of the larger multinucleated giant cells. Small vacuoles appear to form which grow, and a number of clefts of moderate size were noted in which there was still a thin rim of granular cell cytoplasm, with the deeply stained pyknotic nuclei compressed and aggregated to one side (Figs. 4 and 6). Occasionally, such clefts or vacuolated giant cells were surrounded by a thin phloxinophil rim of material which showed feeble birefringence. This latter feature is probably due to protein crystallization at a gel/fluid interface, and is essentially similar to the early radial zone of osteoid which may be seen around the periphery of the mature cartilage cells of an orderly column of epiphyseal chondrocytes, and may represent the earliest sign of endochondral ossification. It was generally noted that the giant cells which showed this cytoplasmic vacuolation stained metachromatically a pale mahogany colour with the phloxin-tartrazine staining, whereas those giant cells in which there were no vacuoles were typically phloxinophil. (These tissue clefts are generally typical of synovioma, and may be numerous and large even in the absence of any giant cells. Obviously, the manner of cleft formation indicated here may not be the only one; on the contrary, the modified cell structure seen in the central fibrous areas of this tumour suggests that maturation of the giant cells, with concomitant morphological changes, is associated with a well-marked collagen stroma and numerous clefts. Hence, in certain synoviomata these latter features may be the more prominent.)

There were also quite a number of larger spaces lined with flattened cells whose appearance suggested dilated lymphatics. There was little or no sudanophil material lying between the stromal collagen fibres, nor yet between the fibres of the limiting collagen bundles and the adjacent tendons. This latter feature is usually well marked in giant-cell tumours of tendon sheaths.

In the cells of the main tumour mass, mitoses were numerous and often abnormal. The mitotic ratio (Price, 1952) was 97 to 1, and in many high-power fields 3% or more of the cell nuclei were in mitosis. No necrosis was seen, and no evidence found of any new bone formation in the collagen matrix, even in the denser areas where it resembled osteoid. Many of the giant cells were multinucleated, and transitional forms were noted to be fairly typical osteoclasts (Figs. 6 and 7).
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Fig. 9.—Scanty reticulin network of distal outlying nodule of tumour. This appearance was also characteristic of the peripheral parts of the main tumour mass which were predominantly giant celled. Gomori silver method, × 190.

Fig. 10.—Area of degeneration of cartilage matrix at the edge of residual fragment of proximal articular cartilage of intermediate phalanx. Haematoxylin and eosin, × 46.

Fig. 11.—Area of tumour near residue base of intermediate phalanx. There are a number of large complex spaces lined by flattened cells suggesting a synovial structure. Haematoxylin and eosin, × 180.

The distal part of the tumour (Fig. 2b) lay in the concavity formed by the residue of the head of the phalanx. It consisted almost entirely of atypical multi-nucleated giant cells similar to those of the peri-nodular areas described above (Fig. 8). These cells mainly showed marked cytoplasmic phloxino-philia, with five to 10 irregular pyknotic or vesicular nuclei. In many cells the deeply staining irregular nuclei were indistinct and conjoined, an appearance suggesting either incomplete separation, atypical nuclear lobation, or fusion of an aggregated mass of the smaller nuclei observed in other cells. Nucleoli were, in general, indistinct. Many of the cells resembled atypical osteoclasts and showed coarsely granular cytoplasm, a few having small vacuoles. Mingled with these cells were smaller numbers of spheroidal and fusiform cells mostly related to the small blood capillaries. The intercellular stroma was scanty, consisting of a few reticulin and collagen fibres, together with a small amount of amorphous collagen (Fig. 9). Occasional mitoses were seen but were far fewer than in the main tumour mass.

Three main residual fragments represented the proximal articular cartilage of the intermediate phalanx. These showed a thinned shell of old sub-chondral bone. The cartilage was degenerate, and there were areas of amorphous granular material apparently derived from the disintegrated juxta-osseous zone of the articular cartilage (Fig. 10). The granular debris was isotropic, strongly phloxino-phil, did not stain metachromatically with methylene blue, but showed a strongly positive reaction with
the periodic-acid-Schiff method. Surrounding this material was reactive tissue, including a few cells of osteoclastic type. No neoplastic cartilage was found anywhere in the tumour. The synovium of the proximal interphalangeal joint showed early villonodular changes but no iron-containing or other pigment was found. In the vicinity of these cartilaginous fragments were a number of large branched tissue spaces lined with a layer of cells simulating normal synovium (Fig. 11). Deep to this surface cell layer were numerous tumour giant cells. It is difficult to be certain whether this represented invasion of displaced joint synovium by the tumour, or whether the structure was proper to the new growth. A close examination of the branched spaces suggested a relationship to the larger ones mentioned above, which had been regarded as dilated lymph spaces.

Section 3: Distal.—The bone and cartilage of the distal phalanx showed degenerative changes but were not invaded by tumour cells.

Comment

The tumour described here appears to have a double morphology: (1) areas, mainly giant celled, with very scanty stroma (Figs. 6 and 8); (2) other parts, usually central, showing fewer giant cells but with fairly numerous smaller spheroidal and fusiform cells associated with numerous small tissue clefts and much tumour collagen or osteoid (Figs. 3 and 4).

The cell pleomorphism, the degree of mitotic activity, and the invasiveness indicate malignancy, and although apparently of osteoelastic origin, the tumour should be regarded as a synovial sarcoma of giant-cell type.

The osteoid-forming expansive tumour of a metacarpal bone reported by Jaffe and Mayer (1932) may have had a similar origin and be closely related to the one reported here. The former, however, consisted mainly of spindle and spheroidal cells producing much trabecular osteoid ("coarse, irregular decussating, fibres which stained like collagen"). This osteoid was partly calcified, partly ossified. These authors mention the complete absence of tumour giant cells and relate their tumour to the "osteoid chondroma" of Virchow (1863) also reported by others, mainly in the German literature. By virtue of the ability of such a tumour to form osteoid and/or bone the malignant counterpart would naturally fall within the broad class of osteogenic sarcoma. Jaffe and Mayer express the opinion, moreover, that had surgical removal of this growth and the metacarpal bone been long delayed it would have undergone malignant changes and have developed into true osteogenic sarcoma. Such a view is conjecture based upon experience and judgment, but nevertheless it implies that the osteoid-producing tumour was to be regarded as a presarcomatous lesion. Lichtenstein (1952), who mentions this particular tumour in his chapter on "Osteogenic Fibroma of Bone," comments further upon the rarity of this type, and relates such neoplasms to the bones of the hand and foot in particular. He also points out their slow rate of growth and characteristic bone expansion.

Irrespective of its malignancy, the present tumour appears to be able both to produce and destroy osteoid, the change in function being accompanied by modified cell morphology as seen in the two forms noted above. It is of interest to note that the intracellular sudanophil material appears in the collagen-destroying giant cell areas, while, on the contrary, it is generally absent in the more central areas of dense collagen stroma, smaller cell size, cytoplasmic metachromasia, and tissue cleft formation. It seems probable that with further maturation of the stromal collagen of these central areas some degree of ossification would have taken place.

The nodular appearance of the tumour (Fig. 2b) while not well defined, is very similar to that depicted in synovioma by Wright (1951); in fact, this author's low-power photomicrograph (Fig. 376, Wright, 1951) is a very close image. In Wright's series of 57 benign giant-cell synoviomas of fingers and toes there is no mention, however, of invasion and expansion of the adjacent bones. His paper does illustrate the typical pressure atrophy of adjacent bone which may be caused by a benign giant cell synovioma especially when occurring in the foot, but is unusual in the finger growths. This latter point is also made by Coley (1949), and others. Nevertheless, malignant synovioma, of which about one half occur around the knee, not infrequently erode and destroy adjacent bone but do not usually cause cortical expansion.

The recurrent synovioma of the finger described by Wright (1949) shows some histological features in common with the present tumour, but in its recurrent malignant form seems to have been a more cellular growth, predominantly of spheroidal cells with relatively scanty stroma. This latter form has been seen in two other cases in the Bristol Bone Tumour Register collection (BTR/7 and BTR/426). The latter recurred eight months after surgical excision.

The case reported by Berger (1938) is of great interest, since it was essentially a fibrosarcoma with
areas suggesting typical synovioma. The reverse of these conditions has also recently been seen in a tumour from the knee region by one of us in a man aged 31 (BTR/597). The tumours reported by De Santo, Tennant, and Rosahn (1941) are described as of mixed cellular structure, showing polyhedral and spindle cells with foci of numerous giant cells. Their patient (No. 11) died with terminal pulmonary metastases.

Fletcher and Horn, in describing the features of bone involvement by giant cell synovioma, mention destruction of bone by erosion with subsequent tumour growth within the marrow cavity. The radiographs illustrated by these authors certainly show well marked focal osteolysis with cortical perforation, but only very questionable evidence of cortical expansion (Case No. 1). In their reported cases there was an extra-osseous soft tissue tumour in three instances (Nos. 1, 7, and 8), the radiological appearances clearly suggesting invasion of bone from without. Erosion of adjacent bone ends is well shown in the radiograph of their Case 2 described in this series.

Vermooten (1925) has reported a benign central osteolytic phalangeal tumour under the term "xanthosarcoma." This was described as having been of a bright yellow cast, and contained numbers of "foamy" cells together with a few giant cells intermingled with the fibrous stroma. In addition to the central area of marked bone destruction there were a number of small cortical erosions, and a soft tissue tumour. These findings, in the light of the relevant case history, suggest bone invasion from without, the tumour being probably a giant cell synovioma with an unusually large "foamy" cell component.

Clark (1952) reported an osteogenic sarcoma of phalanx, which appears to have been primarily a fibrosarcoma with evidence of both osteolytic and osteoblastic activity. It appears to have invaded the distal and intermediate phalanges from without, and the history and published skagrams suggest a parosteal origin.

Histogenesis.—King (1952) rightly draws attention to the insecure basis of the presumed origin of synovioma. Tumours showing the structure of synovioma but unrelated to anatomical synovium have also been reported by Fisher (1942), Briggs (1942), and by Haagensen and Stout (1944). The histogenesis of these atypical growths can be open to only two explanations: (1) origin from heterotopic synovium, or (2) origin from pluripotential mesenchymal cells.

Appearances suggest that the giant cells of the present tumour are associated with destruction of collagen, being related functionally and morphologically to osteoclasts. In a paper on the Strangeways Collection, Lawford Knaggs (1932) briefly described the formation of osteoclasts from cells of degenerate bone and cartilage, changes which have also been seen by one of us. Furthermore, in the articular cartilage of a rat, which was invaded by a methylcholanthrene-induced fibrosarcoma, the chondrocytes were greatly enlarged and granular, closely simulating many of the giant cells seen in this phalangeal tumour. Moreover, in view of the mutations of cell form which may be seen in active callus, it is not surprising that wide variation may occur in cell differentiation in mesenchymal tumours of a similar origin. From these considerations, the second alternative of an origin in pluripotential cells would seem preferable. There were no features in the present tumour to support the assertion of Foster (1947), who suggested a vascular origin for giant-cell synovioma.

As a corollary to King’s morphological classification of synovioma, one may perhaps borrow by analogy the classification applied by Meyerding and Jackson (1950) to giant-cell tumours of bone, with reference to the whole group of synovial tumours (the term "synovial" is here used in a descriptive rather than a histogenetic sense), namely benign, malignant (a) malignant ab initio and (b) showing delayed malignancy, which may possibly be associated with such factors as trauma, sepsis, surgical intervention, and/or irradiation.

Subdivision in this manner overlaps the classification suggested by Stevenson (1950), who separated giant-cell synovial tumours into two groups on the basis of presence or absence of concomitant general metabolic changes.

The more slowly growing benign synoviomata not infrequently show some atypical mesenchymal differentiation, often in the form of dense collagen (simulating osteoid), myxoid tissue, or occasionally islets of cartilage. The in vitro tissue culture methods applied to three synovial sarcomas by Murray, Stout, and Poggeff (1944) yielded results interpreted as representing two main tissue forms, synovial and fibroblastic, but it was uncertain whether the latter may not have arisen from reactive, vascular, or other mesenchyme included in the tumour tissue taken for culture. Whatever may be the true explanation, the fibroblast element may at least be considered as having a potential ability to differentiate in many ways under a suitable stimulus.

With the disordered metabolism of more aggressive growth, as in malignancy, a wider stromal differentiation may be expected and appears as sarcoma, which morphologically may take any of the forms of...
synovial sarcoma of the more usual classic pattern, reticulo-sarcoma, fibrosarcoma, osteogenic sarcoma, chondrosarcoma, malignant giant-cell tumour, or mixed tumours in which the various cell and stromal types are intermingled.

One may from this assertion then perhaps pose the question, If sarcoma is related to the existence of a preceding benign tumour, why the very marked disproportion of the malignant and benign forms of neoplasia in the digits where the former are very rare and the latter relatively common? One obvious feature with tumours of the hand and foot is the urgency of symptoms, which lead to early treatment. In other anatomical sites, the proportion of malignant forms of synovia would be much higher, and more closely follow the group incidence of malignant forms of other mesenchymal tumours, e.g., giant-cell tumours of bone or chondroid growths of major bones.

Considered in this light, it becomes apparent that the histological picture of giant-cell synovia may be shown by a mesenchymal growth potentially capable of further tissue differentiation in several directions. This parallels in most respects the behaviour of giant-cell bone tumours. The literature relating to the latter growths records acceptable examples of supervening or associated malignancy taking the form of fibrosarcoma, osteogenic sarcoma, and malignant giant-cell tumours of mainly osteolytic form. There are also reported cases of giant-cell bone tumours which have been malignant from the time of initial examination, although, in such cases (e.g., that reported by Cameron and Marsden, 1952), the history may be atypical in symptom sequence or timing, either for benign giant-cell tumour or primary sarcoma.

The most tenable view is surely that giant-cell tumours, whether of bone or otherwise, grade from the so-called "benign" to the obviously malignant; and that the features, both clinical and histological, which typify the latter may appear either at an early or late stage, and may possibly be provoked by the factors mentioned above.

While any attempted sub-division of a tumour type may add unwanted fuel to the conflagration which burns around the differentiation of benign and malignant forms, it yet may be of some practical value. The useful application of this would seem to be the rational basis for treatment and prognosis, founded upon careful consideration of at least five major features in each instance, viz., the tumour type, histological grading, site, stage, and potential ability for further aggressive development.

Summary

A detailed description is given of a malignant giant-cell synovia of the phalanx apparently of intraosseous origin.

The structure of this tumour has been interpreted in the light of other closely related growths, and a histogenesis from pluripotential mesenchymal cells is suggested.

The relationship and similarity of behaviour of this tumour to other giant-cell mesenchymal growths is discussed.

The authors wish to record their thanks to Mr. G. S. Storrs for permission to publish this case. The personal examination of this tumour made by one of us forms part of a wider programme of investigation into the causation of giant-cell tumours and their relationship to osteogenic sarcoma. This more extensive research is generously supported by the British Empire Cancer Campaign. The reproductions of the radiographs and photomicrographs are the work of Mr. J. E. Hancox of the Medical Research Laboratory, Department of Pathology, University of Bristol.

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