Adamantinoma of long bones: clinical, pathological and ultrastructural features

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SUMMARY The clinical, pathological and ultrastructural features of two cases of tibial adamantinoma are described. Both lesions showed identical features with a mixed histological picture exhibiting basaloid, tubular and squamous differentiation and a prominent stromal (mesenchymal) component. By light microscopy there appeared to be an intimate relation between the epithelial and mesenchymal components. By electronmicroscopy the cellular constituents of these components could be readily distinguished. In the former the cells contained tonofilaments and desmosomes which were associated with basement membrane material. In the latter (mesenchymal component) none of these features were noted, instead the cells appeared similar to fibroblasts and occasional myofibroblasts.

Extragnathic adamantinomas are rare and distinctive primary tumours of long bones with somewhat primary more than 100 cases having been reported. The origin and pathogenesis of these peculiar tumours are controversial and there are three basic theories (i) that they are epithelial in origin; (ii) that they are derived from angioblasts; and (iii) that they are synovial tumours arising in ectopic sites. Four of the recorded cases in English reports contain results of electronmicroscopical studies and the evidence from these would suggest that the constituent tumour cells are epithelial in type.

We have had the opportunity of studying two tibial adamantinomas and details of the clinical and pathological findings with special emphasis on the ultrastructural features are presented here.

Case reports

CASE 1
A 40-year-old male presented with a seven-year history of a slowly enlarging lump on the anterior aspect of the left tibia. There was also a history of having received a blow to the left tibia. In the last two years, the patient had experienced increasing pain and discomfort exacerbated by twisting movements. The lesion was 30 mm in diameter and situated on the anterior aspect of the left tibia at the junction of the middle and upper third. It was slightly tender to pressure.

The x-ray examination showed a lytic lesion within the left tibia at the approximate junction of the upper and middle third. It was eccentrically placed and caused some expansion of the overlying cortex. The margins were a little irregular but there was some condensation of the surrounding bone. In places, the lesion had a "soap bubble" appearance.

The patient was treated with a local block excision and 22 months later there was no evidence of recurrence or metastasis.

CASE 2
This was a 41-year-old male who presented with a painless lump on the left tibia which had been present for two to three years and which had been gradually increasing in size. There was a history of having been struck on the tibia by a cricket ball. The lump was situated at the junction of the middle and lower third of the tibia on the medical aspect. It was 40 mm long on the vertical axis and 40 mm wide. An x-ray examination showed an eccentric lytic lesion with a "soap bubble" appearance. Open biopsy showed the presence of an adamantinoma and a below knee amputation was performed.

Material and methods

The resection specimen from case 1 was fixed in 10% buffered formalin for 24 h and sectioned with a band saw. Decalcification by EDTA with x-ray con-
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trol was performed, thin sections (5 μm) were cut and stained with haematoxylin and eosin (HE).

Later material for ultrastructural study was obtained from the paraffin-embedded blocks, post-fixed in osmium tetroxide and processed into Spurr's resin.

Dissection of the specimen obtained in case 2 was performed immediately after amputation. Tissue was fixed in glutaraldehyde, post-fixed in osmium tetroxide and processed into Spurr's resin. After fixation and decalcification conventional paraffin sections were prepared and stained by the HE, Miller's elastin and Gordon and Sweet's reticulin methods.

PATHOLOGY

In both cases, the tumours were confined to the tibia. They were eccentrically located and caused fusiform swelling of the bone. In case 1, the tumour measured 50 × 20 mm and in case 2, 60 × 20 mm. The tumour margins were ill-defined. The cut surfaces showed a fibrotic tumour infiltrating cortex with areas of haemorrhage and cavitation with foci of new bone formation.

Both tumours showed a striking biphasic pattern by light microscopy (Fig. 1). The stroma was composed of loosely packed spindle cells with elongated slender nuclei which was very similar in appearance to that seen in fibrous dysplasia. The density of the stroma varied from area to area and in case 2, it had a slightly mucoid appearance in places although mucin stains failed to reveal the presence of extracellular mucin.

Embedded in the stroma were small basophilic cells with hyperchromatic but regular nuclei with very little slightly basophilic cytoplasm. These cells were arranged in trabeculae, tubules and nests. In many areas, peripheral palisading of cells was seen (Fig. 2). This was the predominant cell pattern in both cases. Also present were collections of squamous cells with intracellular bridges and keratin formation. In many foci these grouped cells blended into adjacent fibro dysplastic-looking stroma in an intimate fashion so that there seemed, at the light microscopical level, to be a transition in cell type from those of the compacted cellular zone to those lying free in the stromal areas (Fig. 3). No mitotic figures were observed. Small thin and thick-walled blood vessels were relatively evenly scattered throughout the tumour. The endothelial cells in both cases were inconspicuous. Small focal aggregates of foamy macrophages were present.

Special stains revealed stromal collagen (in high concentration) and reticulin fibres but failed to demonstrate elastic fibres. In the stromal zones reticulin fibres were seen surrounding individual cells.

Ultrastructurally the tumour cells occurred in islands scattered throughout a collagenous stroma. A discontinuous basal lamina separated these cells from the collagen (Fig. 4). The cell nuclei were large, mildly irregular and nucleoli were common.

The large cytoplasm contained minimal to moderate amounts of rough endoplasmic reticulum, small to moderate numbers of mitochondria and

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Fig. 1  *The biphasic pattern of adamantinoma is illustrated with islands of epithelial-type cells embedded in a spindle-cell stroma. Haematoxylin and eosin, original magnification ×200.*

Fig. 2  *Islands of epithelial-type cells show focal peripheral palisading of nuclei (arrowed). Haematoxylin and eosin ×400.*
interdigitated in a loose manner. Small amounts of actin-like myofilaments were also frequently seen just beneath the plasma membrane and most commonly in that part of the cell facing the basal lamina (Fig. 6). The stromal cells were spindle and stellate in shape and contained mildly convoluted nuclei in which nucleoli were observed infrequently. The dominant cytoplasmic organelle was rough endoplasmic reticulum which occurred in large amounts and was often dilated. Small to moderate numbers of mitochondria, free ribosomes and lipid droplets were also present (Fig. 7). Small amounts of smooth muscle-like myofilaments were seen just beneath the plasma membrane of the occasional cell but this feature was very rare. No basal lamina or cell surface specialisation—that is, cellular junctions or processes, was observed in association with these cells.

Although the material of case 1 was obtained from formalin-fixed paraffin-processed tissue, there was good preservation of structures and the tumours were essentially identical at the ultrastructural level except that the myofilaments were less readily identified.

**Discussion**

The so-called adamantinoma of long bone is a rare distinctive primary tumour of bone which forms only 0·33% of the Mayo Clinic collection of bone tumours. The tumour was labelled as adamantinoma by Fischer in 1913 because it resembled...
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Fig. 5 A higher power view of an epithelial-type cell showing part of a nucleus (N), tonofila\ms (T) and a desmosome (D) with an intermediate line (single arrow) and prominent dense plaques (double arrows). \( \times 62 \) 100.

Fig. 6 The edge of an island of epithelial-type cells showing discontinuous basal lamina (single arrow), mildly irregular nuclei (N), tonofila\ms (double arrows) and a band of actin-like myofilaments with characteristic periodic densities (triple arrows). \( \times 6600. \)

Adamantinoma of the jaw bone. Schulenberg12 points out that there are no less than 18 different names for this tumour. These tumours occur over a very wide age ranging from 8–74 yr13 with a peak incidence in the third and fourth decades. There is a male preponderance.14 The majority of tumours occur in the tibia but cases occurring in the fibula,4 ulna,15 femur,16 humerus,7 ischium,17 capitate bone,18 carpal lunate,13 metatarsal bone19 and extra-osseous sites20 have been reported. Simultaneous involvement of the tibia and fibula on the same side without direct continuity has been reported.3

Clinical symptoms are non-specific and the most frequent symptom is pain. Symptoms occurring for up to 50 yr have been reported and there appears to be no relation between duration of symptoms and prognosis.5 There is often a history of previous injury as in our cases.21 Fibrous dysplasia occurring adjacent to the tumour was reported by Cohen et al22 and in association with congenital pseudoarthrosis by Johnson.23

The radiological appearance is not specific, but is frequently described as a multicystic osteolytic lesion with surrounding sclerosis. Relatively late in the course of the tumour, the tumour is multiloculated and has a "soap bubble" appearance.5 7 13 The tumour is frequently eccentrically situated but can be predominantly intramedullary.5 The tumour size is quite variable and our two cases are of average size compared with the recorded cases. They are generally ill-defined grey-white lesions with focal haemorrhage and cystic change.6 Baker et al4 emphasise the point that these tumours have quite a variable histological appearance. Typical and probably essential for the diagnosis is the biphasic pattern of mesodermal stroma and epithelial-like cells.5 3 The stroma resembles that seen in fibrous dysplasia7 and is intimately associated with the epithelial-like components. Weiss and Dorfman3 found the most frequent cell type was that of small basophilic cells and this was also our experience. Squamous cells with keratin formation were also seen in our cases (albeit infrequently) and this is a
thought that they were epithelial in type and this was supported by Ryrie\(^2\) and later by Baker et al.\(^4\) Changus et al.\(^8\) on the basis of the sometimes prominent vascular pattern and the results of histochemical studies, postulated that tumours were derived from the primitive angioblast and proposed the term angioblastoma. Dahlin and Huvos supported the angioblastic theory. The third theory is that the tumour is an ectopic synovial sarcoma.\(^10\) \(^11\)

Four reports of ultrastructural studies on adamantinomas have been reported.\(^5\) \(^19\) \(^26\) \(^27\) These studies have been generally performed on formalin-fixed material as was our first case. This showed good preservation of ultrastructure and showed identical features to the second case except that actin-like myofilaments were more readily seen in the second case. Therefore both tumours showed the presence of a basal lamina, cell processes, desmosomes, tonofilaments and actin-like myofilaments. Although desmosomes and a basal lamina are suggestive of an epithelial cell origin, they are not conclusive. However, tonofilaments are generally accepted as being characteristic of squamous cells.\(^28\) Our studies show that the major cellular constituents exhibit epithelial characteristics and this is in agreement with the other published ultrastructural studies.

The presence of actin-like myofilaments was of particular interest. That they have not been previously described in adamantinoma of long bones may be accounted for by the detrimental effects of formalin fixation. Malech and Lentz\(^24\) noted such filaments in chemically-induced squamous cell carcinoma of mouse skin. Toh and Muller\(^23\) found more smooth-muscle associated antigen in experimental squamous cell carcinomas than in squamous papillomas. Gabbiani et al.\(^16\) have shown increased actin and myosin antigen as well as increased myofilaments in invasive squamous and basal cell carcinomas of skin and adenocarcinoma of the breast. In addition prominent myofilaments have been found in basal keratinocytes during epidermal wound healing.\(^37\) McNutt\(^28\) reported a decrease in numbers of hemidesmosomes and an increase in actin-like microfilaments of marginal cells of basal cell carcinoma in comparison to seborrhoeic and actinic keratoses and non-tumour control skin. McNutt considered that these features correlated with the invasive capacity of the tumour cells with increased microfilaments being related to enhanced motility and decreased hemidesmosomes related to loss of cell to substratum or "anchorage" dependence of growth in malignant cells.

Weiss and Dorfman\(^3\) envisaged adamantinoma of long bones as a distinctive neoplasm capable of differentiating along both epithelial and mesenchymal lines. In our cases the light microscopical findings

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feature which has also been noted by Weiss and Dorfman\(^3\) and by Donner and Dik.\(^24\)

Although vascularity was not a striking feature of our cases, these tumours can be very vascular and it is this vascularity which is responsible for the fact that some authors regard these tumours as angioblastomas.\(^6\)\(^-)\(^9\) Foci of calcification,\(^24\) giant cells,\(^4\) xanthoma and spindle cells\(^5\) have all been recorded in adamantinomas. Mitotic figures are usually sparse and a low mitotic count is not indicative of a less aggressive behaviour.\(^3\)

Originally, adamantinomas were regarded as slowly growing locally invasive tumours and conservative treatment was regarded as adequate.\(^4\) \(^30\) Several cases have since been reported with more aggressive behaviour, some with metastasis and death.\(^3\) \(^4\) \(^13\) \(^31\) Of 101 cases, Moon\(^16\) found 16 deaths due to tumour. Metastases have been discovered as long as 20 yr after amputation.\(^14\) \(^16\)

Since curettage usually results in recurrence\(^32\) and radiotherapy is ineffective\(^33\) amputation appears to be the treatment of choice\(^14\) \(^19\) \(^7\) although it is also suggested\(^4\) that local resection when technically feasible should be performed.

There are, therefore, three schools of thought in regard to the origin of these tumours. Fischer\(^2\)
suggested an intimate relation between the epithelial and mesenchymal components but ultrastructurally the grouped or epithelial cells could be readily distinguished from the mesenchymal cells and the epithelial cells were of an identical appearance irrespective of the light microscopical pattern (tubular, basolaid, squamous) of their sites of origin. On the other hand the stromal cells lacked the stigmata of epithelial-type differentiation and instead exhibited features identical to those of fibroblasts and an occasional myofibroblast. These findings suggest that the stromal component is reactive and not an intrinsic part of the tumour.

There has been speculation about the origin of the constituent cells of adamantinomas. Fischer2 has suggested congenital implantation of epithelial cells whilst Ryrie25 favoured traumatic implantation. Both suggestions have been criticised by Hicks11 who suggested a synovial origin. Ectodermally derived entities may exhibit mesodermal differentiation—for example, the intrinsic muscles of the eye are of ectodermal derivation. Neural crest cells apparently have the ability to form peripheral ganglia, subcutaneous tissues in the cranial region and to differentiate into various cell types such as the Schwann cell, branchial cartilage, arachnoidal, pial and mesenchymal cells.29 The converse of this may be that mesodermally derived cells have the capacity to elaborate structures usually associated with ectodermal derivatives. On a more fundamental level all cells retain the full genetic code and as part of the neoplastic process desuppression of the appropriate part of the genetic code may allow the manufacture of cell organelles not normally present in the cells of a particular location.

However, the presence of actin-like microfilaments with other characteristics of epithelial cells indicate a resemblance of adamantinoma cells to neoplastic keratinocytes and basal keratinocytes in invasive basal cell carcinomas and in epidermal wound healing.38 Perhaps in the light of this the implantation theory of aetiopathogenesis requires re-evaluation. In both our cases there was a clear history of trauma of the overlying skin but without a breach of the epidermis. It may be that damage to the epidermal basement membrane allows the ingress of basal keratinocytes which because of the number and activity of microfilaments are motile to a degree that allows translocation to the underlying bone. Such a mechanism is of course speculative but it is intriguing that adamantinoma cells contain a motility apparatus which could allow translocation from an ectopic site without the application of a substantial amount of force.

We wish to thank Mrs L Murray and Miss R Noble for cutting EM sections and Miss X Kleut for typing the manuscript.

References


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