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CASE REPORT

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Primary epithelioid leiomyosarcoma of bone

Case report and literature review

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Abstract We describe an epithelioid leiomyosarcoma of bone located in the right knee of a 51-year-old woman. Plain radiograph and CT scan revealed a poorly defined lytic and destructive mass in the upper metaepiphyseal right tibia which involved surrounding soft tissues. The lesion was composed of proliferating monotonous round cells with a high mitotic activity with scanty intersecting spindle cell fascicles. Immunohistochemistry of both areas demonstrated a strong positivity for actin (HHF-35 and α-SMA) and vimentin, and negative reactions for desmin, keratin (AE_1 AE_3), epithelial membrane antigen, S-100 protein, factor VIII-related antigen, CD 31 and CD 34. Ultrastructural study confirmed a diagnosis of leiomyosarcoma. This is the first detailed description of the microscopic and radiological features of primary epithelioid leiomyosarcoma of bone.

Key words Epithelioid leiomyosarcoma · Bone tumours

Introduction

Leiomyosarcoma is one of the more frequent malignant mesenchymal tumours arising in soft tissues, the skin, the gastrointestinal tract and the uterus [5, 10, 35, 36]. It is characterized by proliferating fascicles of atypical spindle cells with smooth muscle differentiation, which intersect at different angles. Several histopathological variants, including epithelioid, granular cell, clear cell and myxoid leiomyosarcoma [10], have been defined in the literature. Epithelioid leiomyosarcoma has been reported only recently in bone [3, 26]. Epithelioid changes indicate that the lesion might be metastatic rather than primary [8].

We report an unusual case of primary epithelioid leiomyosarcoma of bone in the proximal meta-epiphysis of the tibia in a 51-year-old woman.

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Case report

A 51-year-old woman was admitted to hospital because of a 5-month history of pain in her right knee. She was treated with analgesics and antirheumatic drugs but the symptoms persisted. Physical examination revealed partial limitation of motion of the right knee attributable to the pain. On palpation, a tender, ill-defined swelling on the anterior upper third of the patient's right leg, just proximal to the knee, was noted. The only abnormal laboratory finding was a sedimentation rate of 94 mm in the first hour. The serum alkaline phosphatase, phosphorus, calcium, and uric acids levels were within normal limits.

X-rays of the right leg revealed a poorly defined lytic mass with destruction of bone in the upper third of the tibia. The tumour had a mainly metaphyseal location extending into epiphysis. This neoplasm occupied the medullary channel, breaking through the cortex and extending to surrounding soft tissue with slight periosteal laminated new bone formation (Fig. 1A, B). Scintigraphy using technetium-99 polyphosphonate demonstrated a markedly increased uptake at the tumour site.

Computed tomography (CT) scan confirmed the presence of an osteolytic upper tibial mass, which was expanding the medullar channel, destroying the antero-external cortex and involving the surrounding soft tissue (Fig. 2). A periosteal bone reaction was clearly seen. A later thoracic TAC excluded pulmonary metastases. The histological diagnosis of leiomyosarcoma was made on the basis of an open incisional biopsy.

Gynaecological investigation revealed that the patient had a normal menstrual history with painless periods every 28 days. She denied any abdominal or pelvic pain. Abdominal and pelvic ultrasound and gastrointestinal barium radiograph revealed no evidence of a tumour in the uterus or gastrointestinal tract. Fibreoptic endoscopy demonstrated a completely normal oesophagogastric and doudenal mucosa. Since no primary tumour could be demonstrated at anyother localization, an en bloc resection of the upper meta-

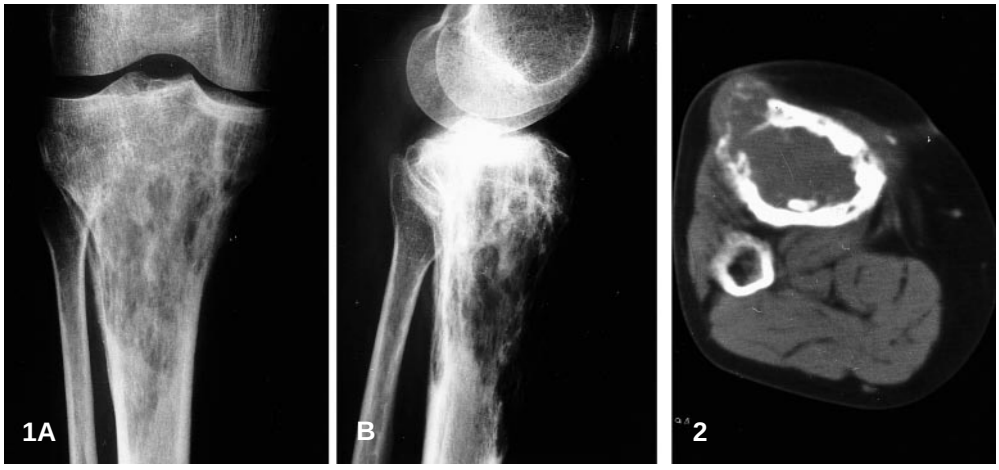


Fig. 1 **A** Anteroposterior and **B** lateral radiographs of the right knee reveal a metaepiphyseal tibial lesion with lytic and permeative destruction of trabecular and cortical bone

Fig. 2 CT scan of the lesion shows an anterointernal lytic mass with destruction of cortical bone and extension to surrounding soft tissues

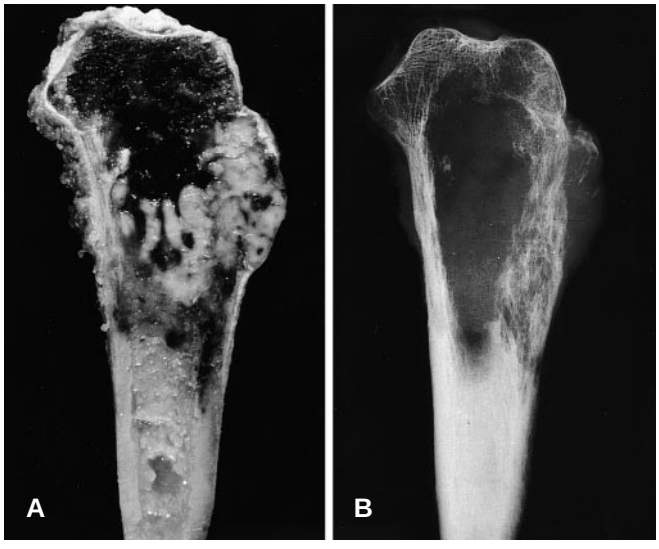


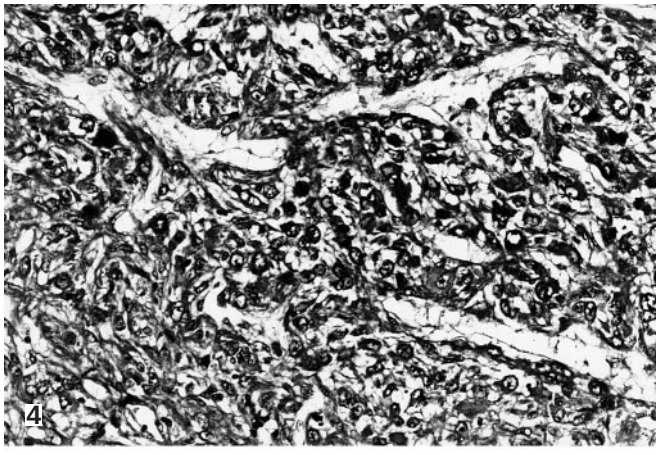
Fig. 3 **A** Macroscopic cross section of the tibial epithelioid leiomyosarcoma; a meatepiphyseal lesion with large areas of necrosis and hemorrhage is seen. **B** Radiographic appearance of the surgical specimen

epiphyseal right tibia was performed. The area was stabilized with a cemented GBS tibial prothesis. The patient received postsurgical radiotherapy treatment (60 Gy). At 36 months after surgery she is well, has good leg mobility, and has presented no recurrence or signs of other tumours.

Pathological findings

The en bloc tibial resection yielded of a 15-cm segment with a greyish, ill-defined 8×4×5-cm metaepiphyseal mass, predominantely confined to the bone, disrupting the anterior cortex and involving soft tissue (Fig. 3A, B). The tumour had large haemorrhagic and myxoid areas.

The tumour was composed mainly of a proliferation of monotonous round cells (Fig. 4) with well-defined borders and largely eosinophilic or clear cytoplasm, large nuclei with dense chromatic patterns and small nu-



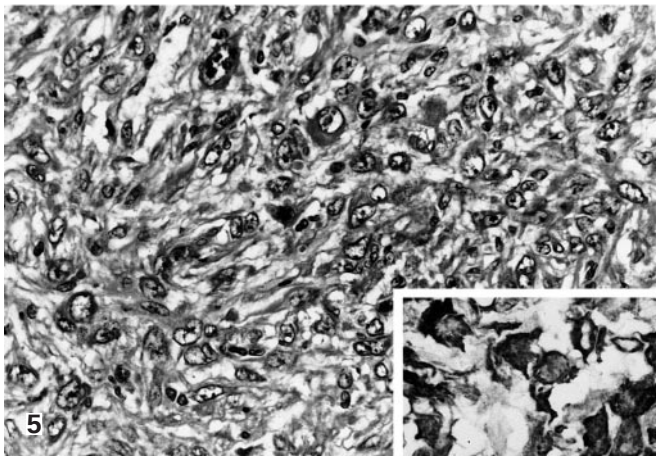


Fig. 4 Microscopic view of the lesion showing an epithelioid cell proliferation with a haemangiopericytoid pattern. H&E, ×250

Fig. 5 High-power view of epithelioid cells exhibing abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli. H&E, ×400 *Inset* Intracytoplasmic homogeneous strong positive reaction for actin antibody. Actin, ×500

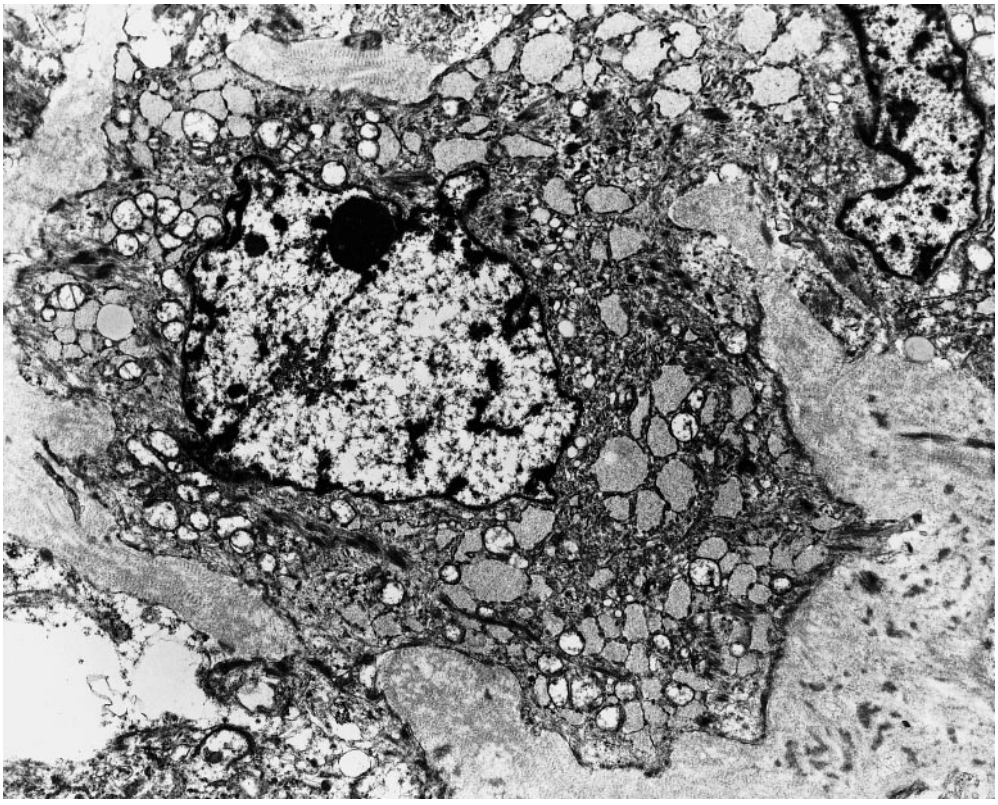


Fig. 6 Ultrastructural appearance of an epithelioid cell showing large cytoplasm, dilated rough endoplasmic reticulum, abundant mitochondria and intermediate filaments with dense bodies and atachment plaques. ×2,750

cleoli (Fig. 5). Profuse vascularization of these epithelioid areas produced a haemangiopericytomatous pattern (Fig. 4). Discrete areas of the tumour had a fascicular appearance owing to intersecting bundles of short spindle cells with elongated nuclei and a finely fibrillar cytoplasm. Mitotic activity was high: 5–15 mitoses per 10 high-power fields. There were atypical forms. A few areas of necrosis were observed. Isolated pleomorphic cells with abundant acidophilic cytoplasm and large uninucleated and multinucleated cells were also present. The epithelioid cells were surrounded by a delicate network of reticulin fibres, while spindle cells had long and straight fibres running parallel to the long axis.

In immunohistochemical studies performed on paraffin-embedded tissue sections after protein predigestion (except for vimentin, desmin and EMA), the cytoplasm of all epithelioid and spindle cells showed strong and homogeneous positive reactivity for actin (HHF-35, α-SMA) and vimentin antibodies but was negative for desmin, keratin (AE_1 AE_3), epithelial membrane antigen (EMA), S-100 protein, factor VIII-related antigen (FVIII), CD 31 and CD 34 antibodies.

Electron microscopy revealed large, polygonal epithelioid cells scattered in the collagenous interstitial matrix. These cells, with abundant cytoplasm, contained scattered ribosomes, rough endoplasmic reticulum and numerous mitochondria. Bundles of fine filament aggregates with frequent fusiform dense bodies were usually located beneath the plasma membrane. Other ultrastructural features included remmants of basal lamina, plasmalemmal attachment plaques, and pinocytotic surface vesicles. The nuclei were often round and large with a smooth membrane, irregular clumping of chromatin and centrally placed nucleoli (Fig. 6). The spindle cells showed fusiform and often indented nuclei with cytoplasms that contained fewer organelles but more intermediate filaments with dense bodies than did the epithelioid cells.

Discussion

Primary leiomyosarcoma of bone is an extremely uncommon malignant condition first described by Evans and Sanerkin [11]; since their report only about 97 cases have been reported [1–4, 6, 7, 9, 11, 12 ,15–18, 20, 22, 24–28, 30, 34, 39–41]. Epithelioid leiomyosarcoma is a variety of malignant smooth muscle tumour that has been well documented in the gastrointestinal and female genital tracts. The term was coined by Martin et al. [23] in 1960 to characterize a stomach tumour of smooth muscle origin and prominently epithelioid appearance. Since the original description, similar cases have been reported under a variety of designations, including “bizarre” leiomyoma, clear cell leiomyoma, leiomyoblastoma, epithelioid leiomyoma or the generic term of “gastrointestinal stromal tumour” [13, 21, 29]. Epithelioid leiomyosarcomata have also been described in the omentum, mesentery, retroperitoneum [10], skin and soft tissues [35]. However, this tumour had never been re-

ported in bone before the cases recently four described briefly by Antonescu et al. [3] in their revision of 33 primary leiomyosarcomas of bone.

Seventy-three of the 97 primary leiomyosarcomas of bone reported in the literature were located in the long bones of the extremities and involved mainly the metaepiphyseal area. The remaining 23 were located in the jaw bones and axial skeleton, and 1 case was in the phalanx. The femur is the long bone most frequently involved (42%), followed by the tibia (38%) and the humerus (15%). The present case was located in the metaepiphyseal region of the right tibia. Radiologically, this tumour and most of the reported primary leiomyosarcoma of long bones show similar findings: they are usually osteolytic and may exhibit aggressive characteristics, such as permeation of the cortical bone and extension to surrounding soft tissue. Leiomyosarcoma of bone does not have a typical radiographic appearance and can mimic any other primary or secondary malignant tumour [3].

The diagnosis of epithelioid leiomyosarcoma of bone was established by its characteristic microscopic appearance and supported by the positive immunohistochemical staining for actin antibodies (α-SMA & HHF-35) and typical electron microscopic features. So far, all the leiomyosarcomas described in bone have shown the same features, consisting of a sheet-like proliferation of spindle cells arranged in intersecting fascicles with focal malignant fibrous histiocytoma-like storiform or haemangiopericytoid areas [31]. Morphological variants include tumours with pleomorphic and bizarre nuclei, and osteoclast-like giant cells have also been described in bone [3, 26].

The epithelioid variant of primary leiomyosarcoma of bone has only recently been described [3]. Antonescu et al. [3] report 33 primary leiomyosarcomnas of bone, 4 of which had an epithelioid appearance. Previously, Myers et al. [26], in their review of 5 leiomyosarcomas of bone, mentioned a case predominantly composed of rounded epithelioid cells with abundant, pale to clear cytoplasm. These five previously reported cases and this case share an appearance of large, round cells with clear or acidophilic cytoplasm and atypical nuclei arranged in a diffuse growth pattern. Moreover, in our case there were also a large number of thin-walled vessels with a staghorn configuration and pleomorphic areas with isolated bizarre uni- or multinucleated giant cells, phenomena well described in regular leiomyosarcomas [33]. Immunohistochemically, all cases display strong positivity for actin (SMA and HHF35) and vimentin and, in two cases [3], weak and focal reactivity for low-molecular-weight keratin (CAM5.2). Ultrastructurally, the epithelioid cells show unequivocal smooth muscle differentiation.

The pathogenesis of bone leiomyosarcoma is unclear. Most authors [1, 11, 12, 27] consider that it arises from the smooth muscle cells of blood vessels, although an origin in perivascular myofibroblasts or mesenchymal fibroblasts capable of synthesizing myofilaments in reactive and neoplastic states cannot be ruled out [4, 30, 41]. In our opinion, the immunohistochemical positivity for actin (α-SMA and HHF-35) and vimentin and the negativity for desmin support an origin in the wall of blood vessels [32].

In any case of leiomyosarcoma involving bone, a metastatic lesion must be ruled out before the lesion can be designated a primary tumour. In the present case the differential diagnosis included malignant haemangiopericytoma, epithelioid angiosarcoma and epithelioid haemangioendothelioma [19, 38]. Malignant haemangiopericytoma of bone, although rare [37], may be difficult to differentiate from leiomyosarcomas that contain large foci of haemangiopericytoid pattern. Hemangiopericytoma does not show immunoreactivity for actin antibodies [10, 32] and does not display a complete ultrastructural smooth muscle differentiation. Nevertheless, these two tumours may be related; recent ultrastructural and immunohistochemical studies suggest that haemangiopericytoma may be a peculiar smooth muscle tumour with vascular differentiation [32]. The two vascular tumours, epithelioid angiosarcoma and haemangioendothelioma show small lumina with atypically prominent endothelium and a epithelioid morphology peculiar to them and thus different from that in the present case. Moreover, epithelioid angiosarcoma displays abundant areas of necrosis. Both show immunoreactivity for endothelial antibodies. Our case is negative for CD 34, CD 31 and factor VIII and demonstrates reactivity for smooth muscle antibodies (α-SMA and HHF-35). Furthermore, electron microscopy has identified myofilaments and pinocytotic structures that confirm the diagnosis of leiomyosarcoma and exclude an endothelial nature for the tumour.

Recently, Hasegawa et al. [14] have described an epithelioid fibrous histiocytoma of bone in the left calcaneus of a 45-year-old man. This tumour [14] contained abundant epithelioid cells but there was no cytological atypia, haemangiopericytoid pattern or pleomorphism; in addition, the presence of a low mitotic rate without atypical mitosis distinguishes it from our case. Furthermore, Hasegawa's case [14] displayed weak, focal reactivity for α-SMA and HHF-35 and also scarce microfilaments with focal densities on ultrastructural studies, which is suggestive of a fibro-/myofibroblastic differentiation.

Malignant fibrous histiocytoma (MFH) or fibrosarcoma of bone must be differentiated from malignant spindle cell leiomyosarcoma [8]. Epithelioid leiomyosarcoma shows a characteristic haemangiopericytoid pattern and epithelioid cells not seen in MFH or fibrosarcoma.

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