Myoepithelial Tumors of Bone

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ABSTRACT

Myoepithelial tumors (METs) of bone (BMETs) are a rare but distinct tumor entity. METs that are cytologically benign are termed myoepitheliomas; METs with malignant histologic features are called myoepithelial carcinomas. BMETs have a wide age range, may involve any part of the skeleton, and have a variable spindle cell and epithelioid morphology. Bone tumors to be considered in the differential diagnosis are discussed. Additional techniques are indispensable to correctly diagnose BMETs. By immunohistochemistry, BMETs often express cytokeratins and/or EMA together with S100, GFAP, or calponin. Half of BMETs harbor EWSR1 (or rare FUS) gene rearrangements with different gene partners.

OVERVIEW, HISTORICAL PERSPECTIVE

To the novice in musculoskeletal pathology who was taught in medical school that the most common bone tumors differentiate along mesenchymal or neuroectodermal lines, it may come as a surprise that some bone tumors show myoepithelial differentiation.

Myoepithelial tumors (METs) of bone (BMETs) are rare. To date, up to 30 cases have been described in the literature.1–12 BMETs were recognized as a distinct clinicopathological entity only after their initial description in soft tissue.

In 1997, Kilpatrick and colleagues13 first proposed the unifying concept that METs morphologically resembling myoepithelial counterparts presenting as skin adnexal or salivary gland tumors, may also occur in soft tissue. Hornick and Fletcher14 described a series of 101 soft tissue METs in 2003, after which Gleason and Fletcher15 reported a series of 29 soft tissue METs presenting in childhood in 2007. Soft tissue METs represent a wide histologic spectrum with cases showing benign and malignant histomorphology and clinical behavior. In the 2013 World Health Organization (WHO) classification of tumors of soft tissue and bone,16 the terms myoepithelioma and mixed tumor are used for the benign variants and myoepithelial carcinoma is the proper name for the malignant phenotypes. Myoepithelioma is mainly composed of myoepithelial cells, whereas mixed tumor also shows clear-cut ductal differentiation. The older term parachordoma, which was still used as a synonym for myoepithelioma in the 2002 WHO classification,16 reflects the morphologic resemblance of some METs to chordoma, but clearly chordoma is a completely different tumor entity, as shown by nuclear immunostaining for the T-box transcription factor brachyury.17

Only in the past decade have molecular pathologic studies revealed that the molecular genetic pathogenesis of METs of soft tissue and bone is different from those occurring in skin and salivary glands.

EPIDEMIOLOGY, SITES OF INVOLVEMENT, AND GROSS FEATURES

BMETs have a wide age distribution and show an almost equal sex distribution. Most patients are adults and adolescents, but BMETs also arise in teenagers. The elderly are seldom affected.
By location, BMETs have a variable distribution. The tumors most often present in long tubular bones (femur, tibia, fibula, humerus), but also occur in small tubular bones (phalanges), and axial skeleton (iliac bone, sacrum, vertebra, ribs, skull, and maxilla).

Although BMETs are usually intraosseous tumors, juxtacortical lesions also have been reported.8 By imaging studies (radiographs, computed tomography [CT], MRI) BMETs are well-demarcated, lytic tumors that may have aggressive features and show invasion of surrounding soft tissue (Fig. 1). By gross examination of surgical specimens, BMETs are solid, nodular tumors. Cortical destruction and extension in surrounding soft tissue may be present (see Fig. 1, Fig. 2).

Grossly, BMETs are well-demarcated, nodular, lobulated masses. On cut surface, color and consistency are proportionate to cellularity, collagenization, and myxoid change or hemorrhage. Commonly, BMETs are solid and gray-white, whereas myxochondroid areas are gelatinous and glistening.

MICROSCOPIC FEATURES AND DIAGNOSIS

The histology of benign BMETs (myoepitheliomas) is variable and resembles their salivary gland counterparts (Fig. 3). Microscopically, myoepithelial tumor cells can have different features,18 with areas consisting of bland eosinophilic spindle cells, epithelioid cells, clear cells, squamous cells, or plasmacytoid cells (Figs. 4–7). Some tumors are predominantly composed of spindle cells arranged in bundles (Fig. 8), whereas other BMETs show foci with epithelioid cells and clear or vacuolated tumor cells that form cohesive cell nests and cords (Figs. 9 and 10). Myxoid areas with spindle or epithelioid cells can show a reticular architectural pattern (Fig. 11). These neoplastic myoepithelial cells are embedded in a variable amount of fibrous, hyaline fibrous, myxoid, or myxohyaline stroma (see Figs. 9–11, Fig. 12). Frank cartilaginous or osseous differentiation is rather rare.

Fig. 1. Myoepithelioma of the proximal tibia. (A) The plain radiograph and (B) MRI both show an intramedullary lytic lesion that is well demarcated, but destroys the cortical bone (arrows). (C) Gross examination of the cut surface of the resection specimen reveals a well-demarcated, solid, gray-white tumor that is located intramedullary but destroys cortical bone.
Malignant BMETs (myoepithelial carcinomas) show cytonuclear atypia, prominent nucleoli, increased mitotic activity, and areas of necrosis. Morphologic features that distinguish benign myoepitheliomas of bone from malignant variants are not well established. In soft tissue locations, nuclear atypia and prominent nucleoli are currently considered to be the sole histologic features of (potential) malignant behavior. A subset of myoepithelial carcinomas is composed of solid sheets of round tumor cells with nuclear atypia with prominent nucleoli (Fig. 13).

The myoepithelial phenotype of BMETs can be demonstrated by immunohistochemistry (IHC) using an appropriate panel of antibodies (Fig. 14). The large majority of METs show combined expression of cytokeratins and/or epithelial membrane antigen (EMA) together with S100 and/or...
glial fibrillary acidic protein (GFAP), an immunophenotype required to make a confirmatory diagnosis (Fig. 15). Sox-10 is another useful marker for myoepithelial tumors. Smooth muscle markers that have proven to be useful are calponin, smooth muscle actin (SMA), or smooth muscle myosin heavy chain (SMMS-1). A small percentage of myoepithelial carcinomas show loss of SMARCB1/INI1 in tumor cell nuclei. Nearly half of the BMETs harbor recurrent EWSR1 (and rare FUS) gene fusions, that can be demonstrated using a break-apart fluorescence in situ hybridization (FISH) assay or, more specifically, by reverse-transcriptase polymerase chain reaction (RT-PCR) or next-generation sequencing (NGS). Several different fusion partners have been found in METs (Fig. 16). In BMETs, EWSR1 (or FUS) fusion partners described to date are

Fig. 4. Myoepithelioma of bone. H&E microphotograph showing an area of spindled tumor cells with monomorphic oval nuclei with fine chromatin and inconspicuous nucleoli. The tumor cells are surrounded by a small amount of fibrillary collagen (H&E, original magnification, ×200).

Fig. 5. Myoepithelioma of bone. H&E microphotograph showing an area in which the tumor is composed of epithelioid cells with monomorphic round nuclei with fine chromatin and inconspicuous nucleoli (H&E, original magnification, ×200).
POU5F1, PBX1, PBX3, and KLF17. Additional fusion partners detected in soft tissue tumors are ZNF444 and ATF1.

The molecular pathology of METs of bone and soft tissue is different from METs in salivary glands that lack EWSR1 fusion genes and often show PLAG1 rearrangements. Hence, despite morphologic overlap between these counterparts, METs in bone or soft tissue and salivary gland METs appear to be separate clinicopathological entities.

**DIFFERENTIAL DIAGNOSIS**

Given their rarity, occurrence in almost any bone, and variable histologic features, it is not surprising that the differential diagnosis of BMETs can be difficult and troubling. Moreover, in daily practice, needle bone biopsies taken for diagnostic histopathology of bone tumors may contain only a limited amount of tumor tissue. Therefore, IHC and molecular pathology are indispensable for an accurate diagnosis.
Herein, we focus on the differential diagnosis of METs presenting as bone tumors.

In the differential diagnosis, we consider the variable histologic appearance of BMETs and discuss bone tumors with relatively bland spindle cells and/or epithelioid cells that are embedded in a variable amount of fibrous, myxoid, or myxohyaline stroma.

Spindle cell bone tumors that enter the differential diagnosis of myoepithelioma are fibrous dysplasia, fibro-osseous dysplasia, desmoplastic fibroma, chondromyxoid fibroma, smooth muscle tumors, and myxoma of jawbones.

Fibrous dysplasia (FD) can present as a solitary nonaggressive and expansile bone lesion. FD often has a typical ground glass appearance on radiographs or CT images, whereas BMETs are lytic and radiolucent. Histologically, FD is easily discriminated from BMETs when areas of metaplastic woven bone are seen. However, needle

**Fig. 8.** Myoepithelioma of bone. H&E microphotograph illustrating that myoepithelioma may be predominantly composed of bundles of eosinophilic spindle cells, by which the tumor may be confused with a smooth muscle tumor (H&E, original magnification, ×200).

**Fig. 9.** Myoepithelioma of bone. H&E microphotograph showing an area in which the tumor is composed of hyaline stroma with radiating cords of cohesive tumor cells with eosinophilic and clear cytoplasm, by which the tumor may be confused with chordoma or extraskeletal myxoid chondrosarcoma (H&E, original magnification, ×200).
biopsies may contain only the cellular component, woven bone being absent. The bland fibroblastic spindle cells in FD may be arranged in short storiform bundles, a growth pattern that is uncommon in BMETs. IHC expression of keratins and EMA does not occur in FD. Most FD lesions harbor GNAS1 gene mutations that may be detected by PCR, which is a very useful tool when confronted with diagnostically difficult cases.

Osteofibrous dysplasia (OFD) and the closely related OFD-like adamantinoma are bone tumors that predominantly occur in children. The typical location is the diaphysis of the tibia, with few cases presenting in the fibula. OFD and OFD-like

Fig. 10. Myoepithelioma of bone. H&E microphotograph showing an area in which the tumor invades bone marrow and is composed of tumor cells with eosinophilic and strongly vacuolated cytoplasm that is arranged in nests, by which the tumor may be confused with metastatic adenocarcinoma (H&E, original magnification, ×200).

Fig. 11. Myoepithelioma of bone. H&E microphotograph, showing a myxoid area in which the tumor has a reticular architecture, reminiscent of extraskeletal myxoid chondrosarcoma (H&E, original magnification, ×100).
adamantinoma are intracortical lesions, clearly different from the intramedullary location of BMETs. Confusion may arise, however, because OFD and OFD-like adamantinoma contain single or grouped spindle cells that are positive for (basal type) cytokeratins and EMA. Importantly, IHC for S100, GFAP, and calponin is negative.

The clinical and radiologic presentation of desmoplastic fibroma (DF) and BMETs show much overlap, as both lesions may present as expansile, lytic lesions with cortical breakthrough. DF is most common in the mandible, but also may occur in other bones. Microscopically, DF is usually composed of bundles of fibroblastic spindle cells with tapering cytoplasm arranged in a collagenous stroma, by which the tumor resembles desmoid-type fibromatosis of soft tissue. Approximately half of DF cases show cytoplasmic staining for Myoepithelioma of bone. H&E microphotograph showing an area in which the tumor has abundant fibrous stroma with spindle cells, by which the tumor may be confused with FD, fibro-osseous dysplasia, or DF (H&E, original magnification, ×50).

![Fig. 12. Myoepithelioma of bone. H&E microphotograph showing an area in which the tumor has abundant fibrous stroma with spindle cells, by which the tumor may be confused with FD, fibro-osseous dysplasia, or DF (H&E, original magnification, ×50).](image1)

Myoepithelial carcinoma. H&E microphotograph showing sheets of round tumor cells with hyperchromatic nuclei, prominent nucleoli, and mitotic activity (H&E, original magnification, ×200).

![Fig. 13. Myoepithelial carcinoma. H&E microphotograph showing sheets of round tumor cells with hyperchromatic nuclei, prominent nucleoli, and mitotic activity (H&E, original magnification, ×200).](image2)
beta-catenin, whereas nuclear staining is seldom found. DF has no beta-catenin gene mutations. Moreover, DF lacks expression of the IHC markers and gene fusions typical of BMETs.

The clinical and radiologic presentation of chondromyxoid fibroma (CMF) and BMETs may mimic each other. Microscopically distinctive features of CMF are lobules of which central zones contain eosinophilic spindle and stellate cells in a myxoid background, whereas peripheral zones tend to be more cellular and harbor osteoclasts. CMF is often S100 positive, but lacks expression of cytokeratins, EMA, or GFAP.

The preferential sites of leiomyoma of bone are mandible and tibia. Well-differentiated leiomyosarcoma may present in the long tubular bones of the lower extremity but also in craniofacial bones. With imaging, leiomyoma and well-differentiated leiomyosarcoma are lytic lesions that may show cortical expansion. Microscopically, smooth...
Muscle tumors typically have interlacing bundles of eosinophilic spindle cells with elongated, hyperchromatic, cigar-shaped nuclei and well-defined eosinophilic cytoplasm. By IHC, smooth muscle tumors may express keratin, EMA, and calponin, but lack positivity for S100 or GFAP. Caldesmon and desmin are discriminatory markers of smooth muscle tumors. Given that primary smooth muscle tumors of bone are exceptionally rare, metastatic smooth muscle tumors should also be considered in the differential diagnosis. Metastatic gynecologic smooth muscle tumors show nuclear staining for hormone receptors.

Myxomas presenting in the mandible and maxilla, thought to be of odontogenic origin, are well-circumscribed lytic lesions and show a high T2-weighted signal by MRI. Histologically, myxomas of jawbones have abundant myxoid stroma containing bland stellate and spindle cells. BMETs may contain areas resembling myxoma, but
BMETs usually have a more variable histology and will stain for the IHC markers mentioned previously. Myxoma of jawbones does not have specific gene mutations or fusions (See Daniel Baumhoer’s article, “Bone Related Lesions of the Jaws,” in this issue).

Epithelioid tumors considered in the differential diagnosis of BMETs are chordoma, extraskeletal myxoid chondrosarcoma, sclerosing epithelioid fibrosarcoma, and epithelioid hemangioendothelioma.

Chordomas characteristically arise in the vertebral column, although rare extra-axial lesions also have been diagnosed.\textsuperscript{17} Epithelioid areas in BMETs may show a striking resemblance to those seen in chordoma, hence the older term parachordoma for METs. However, usually, the tumor cells in chordomas are larger and more vacuolated than
in BMETs. Both chordomas and BMETs express cytokeratins, EMA, and S100. Therefore, immunostaining for brachyury is required to diagnose chordoma (Fig. 17).17

Extraskeletal myxoid chondrosarcoma (EMC) is a distinct soft tissue sarcoma that may also show a striking resemblance to myoepithelioma. Although few cases have been described,22 it is well appreciated that EMC also may present in bone. By IHC, EMC is often positive for S100 and EMA, but lacks cytokeratin expression. EMC often contains an NR4A3 fusion gene that allows a specific diagnosis. Importantly, EWSR1 is the most common fusion partner of NR4A3. Therefore, when using FISH, NR4A3 probes must be used instead of EWSR1 probes to distinguish between EMC and BMET.23

Fig. 14. (continued).

Fig. 15. IHC markers for myoepithelial tumors. (Data from Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 2003;27:1183–96.)

Fig. 16. Gene fusions in myoepithelial tumors.
Sclerosing epithelioid fibrosarcoma (SEF) is a distinct soft tissue tumor that is related to low-grade fibromyxoid sarcoma (LGFMS). Rare cases of SEF have been described as primary bone tumors. A case of SEF occurring in the distal femur is illustrated in Fig. 18. MUC4 immunostaining is very sensitive and specific for SEF and LGFMS. BMETs are negative for MUC4. SEF and LGFMS often have a gene fusion of either FUS or EWSR1 with CREBL1 or CREBL2. Thus, FISH for EWSR1 and FUS cannot be used to differentiate SEF from BMETs. RT-PCR or NGS can be applied for further confirmation of SEF by molecular pathology.

Epithelioid hemangioendothelioma (EHE) is an endothelial neoplasm composed of cords, nests, and strands of epithelioid endothelial cells arranged in myxohyaline stroma, by which it may...
Fig. 17. (continued). (C) H and E microphotograph showing cords and nests with cohesive epithelioid tumor cells with strongly vacuolated (so-called physaliferous) cytoplasm. The tumor cells are embedded in myxohyaline stroma (H&E, original magnification, ×200). (D) IHC for brachyury showing nuclear staining of tumor cells (H&E, original magnification, ×200).
strongly resemble BMET. Bone locations of EHE include long and small tubular bones, vertebra, and jawbones. The tumor cells of EHE often have vacuolated cytoplasm and may contain engulfed erythrocytes. EHE may express cytokeratins and EMA. However, IHC for endothelial markers (ERG, CD31, and CD34) will render a correct diagnosis. EHE has a consistent WWTR1-CAMTA1 fusion gene. An alternate YAP1-TFE3 fusion is present in a small subset of cases. For further details, see David G.P. van IJzendoorn and Judith V.M.G. Bovée’s article, “Vascular Tumors of Bone: The Evolvement of a Classification Based on Molecular Developments,” in this issue.

Understandably, myoepitheliomas with an epithelioid phenotype and cytoplasmic vacuolization or myoepithelial carcinomas showing clear-cut cytonuclear malignant features are easily confused with metastatic carcinoma. Hence, clinical evaluation and a panel of appropriate IHC markers for carcinomas that often metastasize to bone must be applied. Approximately 10% of myoepithelial carcinomas show loss of SMARCB1/INI1 in tumor cell nuclei by IHC.

Helpful distinguishing clinicopathological features of bone tumors mimicking BMETs are summarized in Boxes 1 and 2.

**PROGNOSIS**

Because of the rarity of METs in bone and limited follow-up of few published case series, it is as yet impossible to establish the prognostic value of cytologic features. It seems reasonable to adapt the criteria used for METs arising in soft tissue locations. Nuclear atypia and prominent nucleoli are currently considered to be the sole histologic features of (potential) malignant behavior. METs arising in soft tissue that show bland cytonuclear features usually have a good outcome, whereas METs with nuclear atypia and prominent nucleoli have metastatic potential.

![Fig. 18. SEF of the distal femur. (A) Plain radiograph showing a lytic and destructive tumor of the distal femur that invades surrounding soft tissue. (B) Gross specimen showing a well-demarcated gray-white tumor that invades surrounding soft tissue. (C) H&E microphotograph showing cords of epithelioid tumor cells with clear cytoplasm surrounded by strands of hyalinized collagen (H&E, original magnification, ×100).](image)
### Box 1

**Differential diagnosis of myoepithelioma**

Helpful distinguishing features of spindle cell bone tumors resembling myoepithelioma

**Fibrous dysplasia**
- Imaging: nonaggressive, but often expansile lesion with ground glass appearance
- Histology: deposition of woven bone by spindle cells arranged in storiform pattern
- Immunohistochemistry (IHC): negative for keratins, epithelial membrane antigen (EMA), S100, glial fibrillary acidic protein (GFAP), and calponin
- Molecular pathology: 90% have GNAS1 mutations

**Osteofibrous dysplasia (OFD) and OFD-like adamantinoma**
- Epidemiology: predominantly presenting in children
- Imaging: cortical lesion in the diaphysis of the tibia
- Histology: deposition of woven bone by osteoblasts
- IHC: keratin/EMA-positive spindle cells are negative for S100, GFAP, and calponin

**Desmoplastic fibroma**
- Histology: collagen-rich bundles with fibroblasts, resembling desmoid fibromatosis
- IHC: negative for keratins, EMA, S100, and GFAP

**Chondromyxoid fibroma**
- Histology: lobular architecture with spindle and stellate cells in myxoid background
- IHC: S100 often positive, whereas keratins, EMA, and GFAP are negative

**Leiomyoma and well-differentiated leiomyosarcoma**
- Histology: interlacing bundles of smooth muscle cells with elongated nuclei
- IHC: caldesmon and desmin are positive in smooth muscle tumors, negative in bone myoepithelial tumors (BMETs)

**Myxoma of jawbones**
- Imaging: high T2-weighted signal on MRI
- Histology: abundant myxoid stroma with stellate tumor cells
- IHC: negative for keratins, EMA, S100, and GFAP

(Continued)
Differential diagnosis of myoepithelioma (continued)

Helpful distinguishing features of epithelioid bone tumors resembling myoepithelioma

**Chordoma**
- Imaging: high T2-weighted signal on MRI
- Histology: large vacuolated (physaliferous) tumor cells
- IHC: chordoma is positive for the transcription factor brachyury

**Extraskeletal myxoid chondrosarcoma**
- IHC: EMC is keratin negative
- Molecular pathology: NR4A3 gene fusions (fluorescence in situ hybridization for EWSR1 does not help)

**Sclerosing epithelioid fibrosarcoma**
- IHC: MUC4 is a sensitive and specific marker
- Molecular pathology: FUS or EWSR1 gene fusions with CREBL1 or CREBL2

**Epithelioid hemangioendothelioma**
- Histology: few vacuolated tumor cells have engulfed erythrocytes
- IHC: tumor cells are positive for endothelial markers: ERG, CD31, and CD34
- Molecular pathology: WWTR1-CAMTA1 fusion gene. A YAP1-TFE3 fusion is found in a small subset of epithelioid hemangioendothelioma cases

Pathologic Key Features

**Myoepithelioma of bone**
- May arise in many different bones, including long and small tubular bones, the axial skeleton, and craniofacial bones
- Has a wide age range, but is rare in the elderly
- Has a variable histology, often with spindled and/or epithelioid cells in a variable amount of fibrous and myxohyaline stroma
- In addition to morphology, expression of cytokeratin/EMA with either S100 or GFAP, or calponin is required for an appropriate diagnosis
- Nearly half of the tumors harbor EWSR1 (or rare FUS) gene fusion with different partners
- Myoepithelial carcinoma shows cytonuclear atypia and prominent nucleoli and sometimes consists of sheets of undifferentiated round epithelioid cells

Key Features

- Myoepithelial tumors (METs) of bone (BMETs) are a rare but distinct tumor entity.
- METs that are cytologically benign are termed myoepitheliomas, whereas METs with malignant histologic features are called myoepithelial carcinomas.
- BMETs have a wide age range, may involve any part of the skeleton, and have a variable spindle cell and epithelioid morphology.
REFERENCES