Matrix-Producing Tumors

Case 1: Soft tissue chondroma with calcium pyrophosphate crystal deposition.

Soft tissue chondromas are relatively uncommon tumors that usually present in middle aged adults as painless masses involving the distal extremities. Most are composed of mature chondrocytes arranged in a clustered pattern embedded within well-formed hyaline cartilage. The lesional cells may demonstrate mild nuclear irregularity and visible nucleoli but mitotic figures are only rarely encountered. The overall cellularity of these tumors is greater than normal hyaline articular cartilage and may resemble or exceed that of low-grade osseous chondrosarcoma. The tumors are lobulated and although well demarcated from the adjacent soft tissues they are non-encapsulated. Microscopic stromal calcification, with or without enchondral ossification is commonly found. Occasionally, Soft tissue chondromas may exhibit near-total calcification, inciting a foreign body giant cell reaction. Some may show greater cellularity, resembling chondroblastoma of bone. Rarely they may contain calcium pyrophosphate crystals, simulating pseudogout. Unlike synovial chondromatosis, Soft tissue chondromas do not occur in association with a joint space, and tend to lack the distinctly lobular growth pattern seen in the former entity.

Case 2: Extra-axial chordoma

Extra-axial chordomas are exceedingly rare, with fewer than 20 reported cases. Morphologically, they are identical to axial chordomas, consisting of a lobular proliferation of relatively uniform, eosinophilic, epithelioid cells growing in cords and chains within a mucoid background. Multivacuolated cells (“physaliphorous cells”) are typically present. In the soft tissues, extra-axial chordomas tend to grown in a relatively circumscribed pattern, without the diffuse infiltration into the surrounding soft tissues often seen in sacral lesions. Chordomas in any location express keratins of low and
high molecular weights, are variably positive for S100 protein, and express brachyury in a nuclear pattern. S100 protein may be only focally expressed or even absent in all chordomas. Brachyury is a chordoma-specific marker of notochordal lineage. The prognosis for extra-axial chordomas is usually excellent, owing to their resectability. Metastasis from an occult axial chordoma or a previously resected chordoma should always be excluded. The differential diagnosis of these tumors includes carcinoma (brachyury-negative), extraskeletal myxoid chondrosarcoma (keratin and brachyury-negative) and myoepithelial tumors of soft parts (brachyury-negative, frequently positive for EWSR1 rearrangements by FISH).

Case 3: Ossifying fibromyxoid tumor

OFMT is an extremely rare mesenchymal tumor that may occur in essentially any location, usually in adults. OFMT present as relatively small, painless masses, often with a radiographically apparent shell of bone. Typical OFMT are characterized by a peripheral shell of bone in 70% of cases, lobulated growth, and small, bland cells arranged in cords and nests within a fibromyxoid stroma. A very characteristic feature of OFMT is its even and regular cell-cell spacing. Mitotic activity is usually very low. Malignant OFMT maintain the overall cytoarchitectural features of benign OFMT, but show accentuated lobularity, greatly increased cellularity with nuclear overlapping, coarse chromatin and prominent nucleoli, necrosis, vascular invasion and mitotic activity of > 2/50 HPF. Bone production may either be absent or may be increased, sometimes within the center of the lesion. S100 protein is expressed by over 70% of typical OFMT and by a smaller percentage of atypical and/or malignant OFMT. Desmin, neurofilament protein and CD56 are expressed in 30-50% of cases. Some OFMT’s are S100-negative and desmin-positive. At the genetic level, OFMT’s frequently show rearrangements of the PHF1 gene, with a variety of fusion partners. PHF1 rearrangement may be detected by FISH. “Typical” OFMT (those with low nuclear grade, low cellularity and a mitotic rate < 2/50 HPF) have a local recurrence and metastatic risk of approximately 12% and 4%, as compared with 60% and 60% in “malignant” OFMT (those showing high nuclear grade or a combination of high cellularity and mitotic activity > 2/50 HPF). “Atypical”
OFMT, defined as those tumors deviating from “typical” OFMT but not meeting criteria for “malignant” OFMT show similar outcome to “typical” OFMT.

The differential diagnosis of OFMT includes epithelioid schwannoma, epithelioid MPNST, mixed tumor/myoepithelioma, extraskeletal myxoid chondrosarcoma, and most importantly, osteosarcoma. Epithelioid schwannomas lack the bone shell and extremely uniform cell-cell spacing seen in OFMT, and often arise adjacent to a nerve. Epithelioid malignant peripheral nerve sheath tumors show much greater cytologic atypia than do OFMT, resembling melanoma. Mixed tumors/ myoepitheliomas do not produce a bone shell, usually show epithelial differentiation, and express epithelial markers, such as cytokeratins much more often than do OFMT. Extraskeletal myxoid chondrosarcomas contain distinctly eosinophilic cells that grow in nests, cords and chains, often with abundant associated hemorrhage and hemosiderin deposition. Osteosarcomas lack a lobular growth pattern, show much greater cytologic atypia and pleomorphism than do even malignant OFMT, and often produce abundant lace-like osteoid, as well as malignant-appearing chondroid matrix. It should be emphasized that malignant OFMT, which may produce an osteosarcoma-like calcified matrix, maintain the overall cytoarchitectural features of typical OFMT and often arise within pre-existing typical OFMT.

Case 4: Extraskeletal myxoid chondrosarcoma

Extraskeletal myxoid chondrosarcoma typically presents as a painless mass occurring in the deep soft tissues of adults in the fourth through seventh decades. Males are more commonly affected than females. The original descriptions of EMCs suggested that they were low-grade tumors however, as greater numbers of patients with this tumor have been identified, treated and followed up for longer periods of time it has become apparent that distant metastases and aggressive clinical behavior is more common than originally thought. EMCs demonstrate a lobular growth pattern at low-power examination. Typically, these are composed of cords, chains, clusters and nests of uniform oval to spindled cells embedded within a “dense appearing” basophilic matrix. Blood vessels are indistinct and individual lobules of tumor are separated by fibrous bands. Intratumoral hemorrhage is frequent, and these tumors may present clinically as
a hematoma. The tumor cells have distinctly eosinophilic cytoplasm and uniform dark staining nuclei with indistinct nucleoli and frequent nuclear folds or clefts. In recent years the existence of cellular matrix poor regions of EMC has been recognized. In these areas there is often a sheet-like growth of tumor cells with relatively little intervening extracellular matrix. The tumor cells in these areas are larger, have higher nuclear/cytoplasmic ratios and demonstrate increased nuclear atypia with hyperchromatism and visible eosinophilic nucleoli. Mitotic figures are readily found in these areas but are usually infrequent in the conventional matrix-rich areas.

Immunohistochemistry is of relatively little value in the diagnosis of EMC, as S100 protein is positive in fewer than 20% of cases. Synaptophysin, CD117 and EMA expression may be present. At the genetic level, EMC show rearrangements of the NR4A3 gene with a variety of partners, most often EWSR1. FISH for NR4A3 may be very valuable in making this diagnosis. Treatment of EMC is principally by wide surgical excision. Five year survivals are high (>80%) however 10 and 15 year disease free survivals are considerably lower, primarily due to a high metastatic rate. Histologic grading, including the presence of highly cellular areas, does not appear to predict outcome. However, clinical factors, such as older patient age, larger tumor size and more proximal location have been associated with adverse outcome.

The differential diagnosis includes soft tissue chondroma, soft tissue osteosarcoma, osseous chondrosarcoma with soft tissue extension, and other myxoid soft tissue sarcoma, such as myxofibrosarcoma and myxoid liposarcoma. In both soft tissue chondroma and soft tissue osteosarcoma bone fide hyaline cartilage matrix occurs, whereas EMC does not produce true hyaline cartilage. Osseous chondrosarcoma with soft tissue extension, particularly when myxoid might be confused with EMC however appropriate clinical and radiologic information should readily clarify the issue. EMC lack the thick-walled, arborizing blood vessels and pleomorphic spindled cells seen in myxofibrosarcoma and lack the delicately arborizing capillary network and the small lipoblasts that typify myxoid liposarcoma. Myoepithelioma/mixed tumor of soft tissue and ossifying fibromyxoid tumor are discussed elsewhere in this handout.

Case 5: Mesenchymal chondrosarcoma
Mesenchymal chondrosarcomas are uncommon tumors accounting for less than 1% of soft tissue sarcomas. Males and females are affected equally. The tumors may occur at any age although most cases are diagnosed in adults within the second through fourth decades. The tumors may occur at diverse locations although they most commonly arise in the soft tissues adjacent to the cranio-spinal axis including the paraspinal musculature. The meninges are one of the commonest extra-skeletal sites for these tumors. Typically the majority of the tumor consists of the undifferentiated "small blue cell" component. These cells are usually arranged as sheets and/or vague nests. A characteristic feature is the presence of a supporting capillary network that has acute angle branching resulting in a “hemangiopericytoma-like” growth pattern. The blue cells often are associated with bands of hyalinized eosinophilic collagen that may resemble the “rope-like” collagen of solitary fibrous tumor. The defining light microscopic feature is the presence of islands of hyaline cartilage. These typically form only a minority of the tumor and show an abrupt separation from the blue cell regions. Focal coarse purple deposits of calcification may occur on the hyaline matrix. Mitotic activity is variable but often high within the blue cell regions. Similarly necrosis usually involved this component of the tumor. Immunohistochemistry is of very little value in the diagnosis of MCS. At the genetic level, these tumors are characterized by the HEY1-NCOA2 fusion gene, detectable by RT-PCR. Despite early reports to the contrary, they are not related to Ewing sarcoma and do not show EWSR1 rearrangements. MCS are high-grade clinically aggressive tumors that are treated by a combination of surgery and systemic chemotherapy. Up to 50% of patients have died of disease at 5 year follow up.

The differential diagnosis of MCS includes other primitive sarcomas such as Ewing sarcoma/PNET and small cell osteosarcoma. Since the island of cartilage, that allow distinction of MCS from Ewing sarcoma/PNET are often few in number, this differential may be extremely difficult on small biopsy samples. Molecular genetic examination for the translocation associated with Ewings/PNET (t(11;22)) is extremely helpful in resolving this differential, as MCS do not contain this translocation. Small cell osteosarcoma may demonstrate sheets and nests of blue cells similar to MCS, however, lace-like osteoid outlining individual cells or clusters of cells is present in the former tumor and not found in the latter. Solitary fibrous tumor and synovial sarcoma are two
tumors that may exhibit sheets of small rather undifferentiated appearing cells often associated with a hemangiopericytoma-like vascular pattern. These tumors do not show islands of hyaline cartilage however.

**Case 6: Crystal-storing histiocytosis**

Crystal-storing histiocytosis is a rare process that may present in soft tissue, skin, lung and other locations. Microscopically, it consists of a sheet-like to vaguely fascicular proliferation of distinctly eosinophilic histiocytes, often mimicking some type of myoid tumor, such as rhabdomyosarcoma. Closer examination, however, shows these eosinophilic cells to be filled with refractile crystalline material, usually representing kappa light chain. These histiocytes are typically accompanied by atypical lymphoid cells and plasma cells, and essentially all patients with CSH ultimately prove to have some sort of hematolymphoid disorder (myeloma, lymphoplasmacytic lymphoma, monoclonal gammapathy of undetermined significance). By immunohistochemistry, the cells of CSH mark as histiocytes (CD68, CD163, CD11c etc.) and are negative for muscle markers. Kappa and lambda light chain immunostains sometimes show plasma cell clonality.

**Case 7: Tenosynovitis with psammomatous calcifications**

Tenosynovitis with psammomatous calcification (TPC), described in 1983 by Gravanis and Gaffney, is a distinctive clinicopathologic variant of “idiopathic calcifying tenosynovitis” or “calcific tendinitis”. TPC usually involves the tendons and adjacent synovium of the distal extremities of women; a history of occupational or sports-related repetitive motion and/or persistent mild trauma is almost always present. Histologically, TPC is centered in the tendon and composed of a mixed (myo) fibroblastic and histiocytic proliferation in association with dystrophic calcification, including distinctive psammoma body-like spheroidal bodies. The clinical and morphological characteristics of tenosynovitis with psammomatous calcification (distal location, absent hyperphosphatemia, psammomatous calcifications) differ from those of typical idiopathic calcifying tenosynovitis/calcific tendinitis (proximal location, dystrophic tendinous calcification) and tumoral calcinosis (hyperphosphatemia, amorphous soft tissue calcification). Local excision and conservative management are curative.
**Case 8: Tumoral calcinosis**

Tumoral calcinosis is a rare condition in which patients present with large painless calcified masses in the periarticular soft tissues, including the elbows and hips, and less often the knees. TC has been divided into primary and secondary varieties. Two subtypes of the primary variety exist; a hyper-phosphatemic type with familial basis caused by mutations in the GALNT3, KLOTHO or FGF23 genes, and a normo-phosphatemic type, possibly related to mutation in the SAMD9 gene. The secondary variety is mainly associated with chronic renal failure and the resulting secondary or tertiary hyperparathyroidism.

Microscopically, all forms of TC are characterized by deposition of deeply basophilic, amorphous debris with a variable degree of calcification, with the soft tissues. A foreign body giant cell reaction is often present. Unlike heavily calcified soft tissue chondromas, areas of cartilaginous differentiation are absent. TC is distinguished from phosphaturic mesenchymal tumors by a combination of clinical features (hyperphosphatemia versus hypophosphatemia) and morphological features (TC lacks the spindle cell proliferation and elaborate vasculature of PMT).

**Case 9: Myxochondroid metaplasia of the plantar foot**

Myxochondroid metaplasia of the plantar foot is a very rare, distinctive pseudotumor that almost always involves the foot (although I have recently seen two similar cases in the hands). Patients of any age may be affected. This process involves the subcutis without involvement of the underlying bone. Histologically, it is characterized by a partially circumscribed, variably cellular proliferation of bland fibroblastic cells in a fibromyxoid background, in areas showing distinct stromal basophilia and a chondroid appearance. Small foci of true cartilaginous metaplasia (positive for S100 and ERG proteins) with lacuna formation are occasionally seen. Intralesional cystic change and a variety of other reactive-appearing changes in the surrounding connective tissue are often present. These lesions are entirely benign, and do not seem to recur locally. Myxochondroid metaplasia of the plantar foot appears to represent a reactive, metaplastic process, presumably secondary to chronic mechanical stress. The morphological features of myxochondroid metaplasia of the plantar foot are very similar.
to those of nuchal fibrocartilaginous pseudotumor, however, this only occurs in the neck. Interestingly, it also very closely resembles the equine digital cushion, an acquired structure seen only in well-exercised horses, suggesting that it may similarly represent an attempt by the body to prevent further tissue injury to the foot.

**Case 10: Myositis ossificans**

Myositis ossificans, along with nodular fasciitis, represents one of the classic “pseudosarcomas” in Pathology. Patients with MO typically present with a rapidly growing mass of the extremities, worrisome for sarcoma. A history of trauma is usually but not always present. The radiographic presence of a peripheral shell of calcification may suggest this diagnosis in well-developed examples. The morphological appearance of MO depends on the age of the lesion, with very early examples chiefly consisting of a highly cellular, nodular fasciitis-like proliferation of mitotically active, bland myofibroblastic cells, with focal osteocartilaginous differentiation. As the lesion matures, a larger amount of woven bone is present, sometimes forming a shell around the lesion. MO typically displays a “zonated” appearance, with more primitive, spindled, central areas and maturation to the periphery. However, many cases of MO have a “jumbled” architecture, and this zonation may not always be immediately obvious. The most important differential diagnosis is with extraskeletal osteosarcoma, a tumor that usually occurs in older patients, and one that lacks the shell of bone and zonation of MO, and displays in almost all instances flagrant cytologic atypia.

**Case 11: Phosphaturic mesenchymal tumor**

PMT are extremely rare tumors, which most often occur in middle-aged adults, in soft tissue, bone and sinonasal locations. Most PMT present as small, inapparent lesions that may require very careful clinical examination and radionuclide scans (e.g., octreotide scans, FDG-PET) for localization in some cases. A long history of osteomalacia is typically, but not always present. “Non-phosphaturic” PMT in most instances are superficial soft tissue tumors which have been identified before patients became clinically symptomatic, although I have seen occasional cases in which patients were only realized to be suffering from osteomalacia after identification of their tumor. The overwhelming majority of PMT are histologically and clinically benign, with
complete excision resulting in dramatic improvement of phosphate wasting and osteomalacia. Histologically benign PMT behave in a clinically benign fashion, although they frequently recur locally if incompletely excised. Histologically malignant PMT have significant potential for aggressive local recurrence, distant metastasis, and adverse patient outcome.

Most PMT present as non-specific soft tissue or bone masses. Some tumors may be highly calcified. Histologically, they are characterized by a highly vascular proliferation of bland, spindled to stellate cells, which produce an unusual “smudgy” matrix. The vasculature of PMTMCT may be hemangiopericytoma-like, or may consist simply of numerous arborizing capillaries. The matrix of PMTMCT calcifies in a distinctive “grungy” or flocculent fashion, and may resemble primitive cartilage or osteoid. This calcification in turn appears to serve as a stimulus for the recruitment of osteoclasts, occasionally provokes a fibrohistiocytic reaction and/or aneurysmal bone cyst-like changes, and may undergo osseous metaplasia. A variable component of mature adipose tissue is also frequently present. Malignant PMT show frankly sarcomatous features, such as high nuclear grade, high cellularity, necrosis and elevated mitotic activity, resembling undifferentiated pleomorphic sarcoma in most instances.

By immunohistochemistry, the cells of PMTMCT typically express FGF-23 and vimentin, in the absence of other markers (11). Currently available FGF-23 antibodies are, however, neither perfectly specific nor sensitive. Chromogenic in situ hybridization for FGF-23 mRNA expression is a much better test, applicable to routinely fixed and processed tissues. At the genetic level 60-70% of PMT show fusions involving the FN1-FGFR1 and FN1-FGF1 genes, detectable by FISH or other molecular methods.

In most cases, a clinical history of osteomalacia will be available, and the tumor will have been resected specifically for treatment of tumor-induced osteomalacia, greatly simplifying the diagnosis of PMT. Unsuspected PMT may be confused with hemangiopericytomas/ solitary fibrous tumors, hemangiomas, giant cell tumors, spindle cell lipomas, and various cartilaginous tumors, among others. Recognition of the unique constellation of histologic features shown by PMTMCT, in particular the distinctive “grungy”-appearing calcified matrix, is the best way to distinguish it from other tumors.
Case 12: Extraskeletal osteosarcoma

Extraskeletal osteosarcoma occurs in adults with a peak incidence in the fifth and sixth decades. This is in contrast with skeletal osteosarcoma that most commonly occurs in younger patients. The tumors typically arise in the deep soft tissues of the proximal extremities where they present as a painless mass. Rarely patients may have a history of prior therapeutic irradiation at the site of the tumor. Males are affected approximately twice as frequently as females. Radiographic studies may occasional demonstrate osteoid matrix production.

The morphological features of ESOS are identical to those of conventional high-grade skeletal osteosarcomas, typically showing a highly cellular proliferation of obviously malignant spindled to epithelioid cells with multifocal osteoid and chondroid production. Mitotic activity is usually high and necrosis often present. Immunohistochemistry plays essentially no role in the diagnosis of ESOS. The differential diagnosis of ESOS is chiefly with other pleomorphic soft tissue sarcomas; identification of osteo/chondroid matrix is the key distinguishing feature. The prognosis for ESOS is poor.

Case 13: Malignant myoepithelioma of soft tissue

Parachordoma, described initially by Laskowski as “chordoma periphericum” and more fully by Maria Dabska as an entity distinct from extra-axial chordoma and extraskeletal myxoid chondrosarcoma, is a rare and controversial entity. With the recognition in the mid-1990’s of soft tissue myoepithelial tumors, it has become increasingly apparent that parachordoma and soft tissue myoepithelioma are manifestations of a single entity. The WHO currently considers parachordoma and myoepithelioma to represent the same entity. Soft tissue mixed tumors showing epithelial differentiation, as in salivary gland pleomorphic adenomas, are also considered to fall within this histopathological spectrum.

Myoepitheliomas occur in middle aged adults, with a median age of approximately 35 years. These tumors occur equally in men and women and most often present as painless soft tissue masses. Common locations for myoepithelioma include the extremities, trunk, and less often head/neck. Most lesions occur in deep soft tissue,
although subcutaneous tumors may be seen as well. Microscopically, most tumors consist of cords, chain and nests of epithelioid to spindled cells set in a myxochondroid to hyalinized matrix. The neoplastic cells may show glomoid, hepatoid, plasmacytoid or clear cell features. Some lesions contain vacuolated tumor cells, resembling the physaliphorous cells of axial chordoma. As in their salivary gland counterparts, fat, cartilage and bone may occasionally be present. Tumors showing true epithelial differentiation should be diagnosed as “mixed tumors” of soft tissue. It is unclear whether the distinction of mixed tumor and myoepithelioma is clinically significant in soft tissue. Pleomorphism and mitotic activity are absent in most tumors. Although these tumors are generally well-circumscribed, they are not encapsulated, and often contain small nests of tumor cells outside of the main mass, likely accounting for their tendency to recur locally. Rare myoepitheliomas show histological features suggestive of malignancy, including high nuclear grade, elevated mitotic activity (>2/10HPF), necrosis and vascular invasion. The great majority of myoepitheliomas are histologically and clinically benign. However, rare histologically benign tumors have been reported to metastasize, and all soft tissue myoepithelial tumors should be regarded as having uncertain malignant potential. Tumors showing histologic features of malignancy, as noted above, have a greater risk of aggressive local recurrence and metastasis. Metastases may be to lymph nodes, bone, lung or rarely other locations. All soft tissue myoepithelial tumors should be entirely resected with histologically negative margins. There is no known role for adjuvant therapies. At the genetic level, roughly 40% of soft tissue myoepitheliomas show rearrangements of the EWSR1 gene, with a variety of different partners. Soft tissue mixed tumors showed PLAG1 gene rearrangements, as seen in pleomorphic adenomas of the salivary glands. SMARCB1 (INI1) expression is lost in a subset of soft tissue myoepithelial tumors, usually malignant-appearing ones.

The most difficult distinction on purely histological grounds is with extraskelatal myxoid chondrosarcoma (EMC). In general, EMC occurs in older patients, and is frequently larger at the time of diagnosis. Many EMC present with hemorrhage and may be mistaken clinically for a hematoma. Microscopically, EMC consist of cords and chains of small, uniform, eosinophilic cells with grooved nuclei, embedded in a “dense” basophilic matrix. Some EMC may be predominantly spindled. Unlike myoepithelioma, EMC do not
produce cartilage, bone or fat. Although some EMC may show prominent rhabdoid change, plasmacytoid, glomoid, hepatoid and vacuolated cells are not seen. By immunohistochemistry, EMC lack expression of epithelial markers and smooth muscle actin, and are only rarely S100 protein-positive. Although both tumors may show EWSR1 rearrangements, NR4A3 rearrangements are specific to EMC.

Case 14: Calcified synovial sarcoma

Case 15: Embryonal rhabdomyosarcoma with cartilage

Case 16: Malignant peripheral nerve sheath tumor with cartilage

It should always be remembered that a variety of other sarcomas may on occasion show production of calcified matrix, woven bone, or cartilage. Examples of this phenomenon include heavily calcified synovial sarcomas, which may at times contain frank bone, low-grade fibromyxoid sarcomas with metaplastic bone, epithelioid malignant peripheral nerve sheath tumors with bone production, embryonal RMS with cartilaginous differentiation, MPNST with heterologous osteo/chondrosarcomatous differentiation, and dedifferentiated liposarcoma with heterologous elements. In all of these cases, the key to making the correct diagnosis is recognition of the more typical morphological features of the non-matrix producing areas, as well as application of appropriate immunohistochemical and molecular genetic markers (covered in other handouts).

Case 17: Angiosarcoma arising in a gouty tophus

This case is a curiosity, but an interesting one. To the best of my knowledge, it is the only example of this phenomenon. Conceivably the pathogenesis of this angiosarcoma was similar to that of other foreign material-associated angiosarcomas. Angiosarcomas are well-recognized to arise in association with implanted foreign materials, including shrapnel, vascular grafts and prostheses.

Suggested References

Given the scope of this Interactive Microscopy session, I have elected not to provide an exhaustive list of primary peer-reviewed articles. Instead I highly recommend the relevant chapters in the 6th Edition of Enzinger and Weiss’s Soft Tissue Tumors, the