Introduction
Over the past several decades it has become apparent (to the dismay of surgical pathologists, clinicians and patients) that several morphologically benign tumors of soft tissue and bone may on extremely rare occasions metastasize. Recognition of and agreement on this phenomenon has not been universal among pathologists, with some for example claiming that all such cases represent “misdiagnoses” of a malignant tumor as benign (i.e., misdiagnosis of superficially located “malignant fibrous histiocytoma” as cellular fibrous histiocytoma). However, it is safe to say that there is now an evolving consensus that “benign metastasizing” soft tissue and bone tumors do occur.

“Benign metastasizing” soft tissue and bone tumors may be conceptualized as falling roughly into 3 groups. The first group includes tumors widely agreed to be benign, which may on extremely rare occasions metastasize, including benign fibrous histiocytoma (dermatofibroma) of soft tissue, and giant cell tumor and chondroblastoma of bone. The second group encompasses many of those tumors currently classified as being of borderline/intermediate malignancy by the WHO, which have a recognized ~2% risk of metastasis, despite their often very bland appearance (e.g. plexiform fibrohistiocytic tumor). The third group is the least well-defined, and includes a variety of rare mesenchymal tumors which span a histologic spectrum from apparently benign to apparently malignant, but where histologic study does not always accurately predict behavior (e.g., gastrointestinal stromal tumor, soft tissue myoepithelioma, perivascular epithelioid cell tumors).

This handout will cover the clinicopathological features of benign fibrous histiocytoma of soft tissue and giant cell tumor of bone, prototypical “benign metastasizing” tumors in those locations, as well as ossifying fibromyxoid tumor, a tumor originally considered benign but currently thought of as being of borderline malignancy.

Benign fibrous histiocytoma (BFH)
BFH, also referred to as dermatofibroma, is a common lesion of the dermis and subcutis, which are most often located in the extremities of young to middle-aged adults. There is a female predominance. The lesions may be solitary or multiple. Several variants have been described; cellular, aneurysmal, and atypical variants will be discussed in this handout.
BFH consists of a circumscribed, variably cellular monomorphic population of spindle cells arranged in fascicles and storiform patterns, which may be intermixed with multinucleated giant cells (Touton giant cells), foamy macrophages, siderophages and interstitial fibrosis. Thickened collagen bundles are classically observed at the periphery, surrounded by lesional cells. The overlying epidermis is often hyperplastic. Cellular fibrous histiocytomas are highly cellular lesions, showing a storiform or fascicular growth pattern, with little collagen deposition. They tend to be larger (up to 2.5 cm) than common dermatofibroma, often extending into subcutis (30% of cases). Mitoses are numerous, and foci of necrosis and/or vascular invasion may be observed. Intralesional aneurysmal changes are characteristic of the aneurysmal variant of fibrous histiocytoma. Vascular spaces are often bordered directly by multinucleated cells and/or siderophages. The pseudovascular lumina are frequently occupied by foamy siderophages or Touton giant cells containing lipid and hemosiderin. The atypical (pseudosarcomatous) fibrous histiocytoma variant contains numerous pleomorphic (monster) cells with enlarged hyperchromatic nuclei, resulting in a pseudosarcomatous appearance. Mitoses are sometimes numerous in this variant and atypical mitoses are occasionally seen, especially in pleomorphic areas. Recognition of features of typical BFH is the key to the diagnosis of all BFH variants. Deeply situated BFH are often more uniform in appearance, showing a storiform growth pattern and a hemangiopericytoma-like vasculature. They are often well demarcated and can be encapsulated.

Immunohistochemically, BFH are usually negative for CD34 and positive for Factor XIIIa, and KiM1p. The histiocytic cells, including multinucleated giant cells, express CD68 (clone KP1 and/or PGM1). Deep fibrous histiocytomas express CD34, at least focally, in about 30% of cases.

BFH are benign lesions. Recurrences are rare (<5% of cases), often following incomplete local excisions. Cellular, aneurysmal, and atypical variants of fibrous histiocytoma are prone to recur more frequently (up to 25% of cases). Reexcision is usually curative. Approximately 20 cases of metastasizing BFH have been reported, typically to the lungs. The primary tumors in such cases are most often of the cellular variant, although metastases have also been reported in cases of aneurysmal, atypical and conventional BFH. The lesion reported in the pulmonary pathology literature as “cystic fibrohistiocytic tumor” represents metastatic BFH in essentially all instances. There are no pathological features of the primary tumor that are predictive of metastases, although this extremely rare event seems to be somewhat more common in tumors that have recurred locally multiple times.

The differential diagnosis of cellular FH centers on fascicular spindle cell tumors, including dermatofibrosarcoma protuberans, leiomyosarcoma and the fibroma-like variant of epithelioid sarcoma. Leiomyosarcoma typically grows in longer fascicles, shows more diffuse cytoplasmic eosinophilia, lacks inflammatory cells, and is SMA/caldesmon/desmin positive in most instances. Dermatofibrosarcoma protuberans is a more monotonous proliferation of more lightly staining spindled cells arranged in storiform arrays, with diffuse infiltration of adipose tissue, and
strong CD34 expression. Fibroma-like epithelioid sarcomas typically show at least small areas of more conventional epithelioid sarcoma, with infiltrative epithelioid cells, and are cytokeratin-positive/INI-1 negative. Aneurysmal BFH should be distinguished from angiomatoid (malignant) fibrous histiocytoma, a fibrohistiocytic tumor of intermediate malignancy, typified by a fibrous capsule containing lymphoid aggregates, short fascicles and meningothelial-like whorls of histiocytoid cells often containing hemosiderin pigment, intravascular hemorrhage, and a unique desmin/EMA/CD68-positive immunophenotype. Atypical FH should be distinguished from atypical fibroxanthoma, a tumor that arises in sun-damaged skin in much older adults, and lacks the presence of areas of typical BFH at its periphery, and from superficially located pleomorphic sarcomas, in particular myxofibrosarcoma, a tumor that often occurs in the superficial soft tissues and may involve the skin. Clinical correlation with regards to the size and extent of the tumor is often helpful in this regard.

**Giant cell tumor of bone (GCT)**

GCT is relatively common, comprising 5% of all bone tumors and 20% of all benign bone tumors. GCT most often involves the epiphyseal or meta-epiphyseal region of long bones such as the femur, tibia and radius, but may also involve the sacrum, spine and short tubular bones of the hands and feet. Multicentric GCT have been reported but are extremely rare. GCT show a slight female predominance, and most often occur in skeletally mature individuals in the 3rd-4th decades of life. Clinically, GCT present as pain or swelling or with pathological fracture. Radiographically, GCT are purely lytic lesions with either well-defined, non-sclerotic margins, or poorly circumscribed margins. Cortical destruction and soft tissue extension may be present; a shell of reactive bone may be seen in soft tissue extension or in soft tissue recurrences.

Microscopically, GCT are composed of sheets of osteoclast-like giant cells with interspersed round to slightly spindled mononuclear cells. The nuclei of the mononuclear cells are uniformly bland, an important distinction from various osteoclast-rich malignancies, including osteoclast-rich osteosarcoma. Although the nuclei of the mononuclear cells and giant cells are classically described as looking similar, it is now understood that they represent different cell types. Specifically, the mononuclear cells of GCT appear to be primitive osteoblast precursors, which recruit osteoclast-like giant cells through production of RANK-L (osteoclast differentiation factor). A variety of secondary changes may be seen in GCT, including a fascicular to storiform spindle cell proliferation resembling BFH, foamy macrophages, cystic change, hemorrhage and necrosis.

Although GCT are considered benign neoplasms, they may be locally aggressive and recur locally in up to 25% of cases. The adequacy of local resection appears to be the most important predictor of local recurrence, although some authors have suggested that radiographically poorly marginated lesions (Campanacci grade 3) have a higher risk of local recurrence (presumably reflecting tumors in which adequate local resection is more difficult to achieve). Recurrent GCT, particularly those that have been treated with adjuvant radiotherapy, may
progress to high-grade sarcoma, typically resembling fibrosarcoma, undifferentiated pleomorphic sarcoma, or osteosarcoma.

Metastases, almost always to the lungs but rarely to soft tissue or lymph nodes, occur in ~2% of patients with giant cell tumors. These metastases may be solitary or multiple, tend to grow slowly, and are typically amenable to surgical resection with excellent patient outcome. There are no histologic features of the primary tumor that reliably predict metastasis, although it has been recently suggested that intratumoral hemorrhage and thrombosis is more common in GCT with lung metastases than in those without this. Larger studies are required to confirm this. The presence of soft tissue extension has also been associated with a greater likelihood of metastasis in some studies. Telomerase activation, as measured by hTERT immunohistochemistry or TRAP assays, is a common finding in GCT which appears to be associated with a greater likelihood of local recurrence, but not with a greater risk for metastasis.

The differential diagnosis of GCT includes any osteoclast-rich tumor of bone, including chondroblastoma, brown tumor of hyperparathyroidism, aneurysmal bone cyst, and osteoclast-rich osteosarcoma. Chondroblastoma typically occurs in skeletally immature individuals and contains clusters of chondroblasts with grooved nuclei as well as calcified matrix. A history of hyperparathyroidism should be sought in any patient with apparently multicentric giant cell tumors. Aneurysmal bone cyst typically occurs in younger patients in a metaphyseal location and shows a more variable microscopic appearance than does GCT. Giant cell-rich osteosarcoma occurs in the same location as does conventional osteosarcoma (metaphysis or meta-epiphysis), and is distinguished from GCT by the presence of clearly malignant-appearing stromal cells showing osteoid production. In general, bone production in GCT is found at the periphery of the tumor, as a shell of woven bone, whereas osteoclast-rich osteosarcomas show a greater abundance of centrally located bone.

**Ossifying fibromyxoid tumor of soft parts (OFMT)**

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. The stroma of OFMT varies from highly myxoid to fibrous, and may on occasion hyalinize and calcify. A very characteristic feature of OFMT is its even and regular cell-cell spacing. Mitotic activity is usually very low. S100 protein is expressed by over 70% of typical OFMT and by a smaller percentage of atypical and/or malignant OFMT (see below). A minority of OFMT will show focal expression of cytokeratins, smooth muscle actin or desmin. Some OFMT may also rarely express other markers of putative nerve sheath differentiation, such as CD57 (Leu 7), “neuron-specific” enolase, and glial fibrillary acidic protein.
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 (Fig 17-18). Prominent spindling or extensive stromal hyalinization may be present. Bone production may either be absent or may be increased, sometimes within the center of the lesion.

The initial description of OFMT by Enzinger et al emphasized what might be thought of as “typical OFMT” inasmuch as all of the cases were circumscribed, of low cellularity and low nuclear grade, lacked necrosis or vascular space invasion and had mitotic rates of 1-2/10HPF (with one exception). Local recurrences occurred in 7 of 41 cases with follow-up information and were generally similar to the primary lesion with the notable exception of 2 cases that showed increased cellularity and mitotic activity. One of these recurrent lesions was described as showing “a transition to a well-differentiated osteosarcoma”. That case was characterized by moderately increased cellularity and cytologic atypia and increased centrally placed hyaline matrix, but maintained the overall cytoarchitectural features of an OFMT. The other patient whose recurrent lesion showed increased cellularity suffered a contralateral soft tissue metastasis.

In the years immediately following that initial publication a number of additional series and cases were reported that for the most part described OFMT with typical histologic features and a benign clinical course. However, unquestionable examples of OFMT were also reported that either appeared histologically malignant or produced metastasis. For example, Yoshida et al first reported a tumor that lacked overtly malignant features but produced local recurrence, distant soft tissue metastasis and death. Kilpatrick and colleagues reported a series of 6 atypical OFMT, one of which appeared overtly malignant, four of which showed lesser degrees of atypicality, and one of which was a histologically typical OFMT that both recurred locally and metastasized to the lungs. Zamecnik et al described 3 histologically malignant tumors in a series of 17 OFMT, 2 of which developed recurrences and one of which metastasized to the lungs. In 2003 we published a series of 70 OFMT, noting local recurrences and metastases in 12% and 4% of “typical” OFMT (those with low nuclear grade, low cellularity and a mitotic rate < 2/50 HPF), as compared with 60% and 60% of “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 showed similar outcome to “typical” OFMT. Most recently, Miettinen and Fetsch have examined a very large series (104 cases) of purely typical OFMT (excluding all cases with any atypical features) and noted a local recurrence rate of 22%, but no metastases. Putting all of this together, it would appear that entirely banal-appearing OFMT have an approximately 15% risk of local recurrence and a 5% metastatic risk, supporting their reclassification by the WHO as mesenchymal tumors of intermediate/borderline malignancy. Malignant-appearing OFMT behave as high-grade sarcomas. Within the group of histologically typical OFMT, there are no histologic features that are predictive of metastasis.
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.

Conclusions

To answer the question posed by the title of this talk and handout, it would appear that we as pathologists can do several things in response to the frustrating problem of “benign metastasizing” tumors. First and foremost, it is crucial to recognize those truly malignant tumors that may mimic these various benign neoplasms, so as to avoid underdiagnosis. It thus follows that we must also be willing to critically re-evaluate the primary tumors in patients with unexpected metastases for evidence that we may have initially been in error. Assuming that our initial diagnoses were correct, we must also be willing and able to communicate intelligently about these issues with clinicians and patients, many of whom will have great difficulty in understanding the complexities of “benign metastasizing” tumors. Third, although we as a group have not as yet identified any histologic or molecular markers predictive of eventual metastases in “benign metastasizing” tumors, it is hoped that continued study of these rare neoplasms will identify such markers. Finally, it is important that we as a discipline continue to re-evaluate the proper classification of soft tissue and bone tumors, with perhaps the eventual expansion of the borderline/intermediate malignancy category to include tumors of bone, such as giant cell tumor.

Selected references

BFH


**GCT**


**OFMT**


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