Ossifying Fibromyxoid Tumor
Something New to Mull Over

During the past 20 to 25 years, the field of soft tissue tumor pathology has been a fertile one for surgical pathologists, with the description of a variety of new and intriguing diagnostic entities. Among the most successful "gardeners" have been the staff of the Soft Tissue Branch of the Armed Forces Institute of Pathology (AFIP), under the able leadership of Drs. Franz Enzinger and Sharon Weiss. From their extensive collection of soft tissue lesions they have brought forth a bountiful harvest, including such now well-known lesions as fibrous hamartoma of infancy, clear cell sarcoma, epithelioid sarcoma, myxoid and angiomatoid malignant fibrous histiocytoma, spindle and pleomorphic lipoma, fibroma of tendon sheath, spindle cell hemangioidoendothelioma, and plexiform fibrous histiocytoma. Many of these entities were either not previously described or so rarely described that it was not until the publication of the AFIP report that they became recognized as distinctive lesions.

Despite the fact that the Soft Tissue Branch at the AFIP is the repository of consultative cases from around the world, many of these newer tumors were exceedingly rare. As examples, the description of clear cell sarcoma was based on only 21 cases seen in 25 years and that of spindle cell hemangioidoendothelioma on only 26 cases accumulated in 30 years. Of added interest regarding these tumors was that at the time of initial publication, their histogenesis, or more properly their current state of differentiation, was unclear. Such is the case with the newest "harvest" from the AFIP, entitled "Ossifying Fibromyxoid Tumor of Soft Parts," by Enzinger, Weiss, and Liang, to which Miettinen addresses himself in this issue. Despite the usual rarity of the soft tissue lesions reported by the AFIP authors (and ossifying fibromyxoid tumor (OFMT) is no exception, with only 59 cases found in 25 years) it has always suprised this writer at how quickly secondary re-reports appear in the literature. In this regard, Miettinen's report may set a record, with only four months elapsing since the original publication of OFMT and the submission of his current article describing four cases collected since the original publication of OFMT and the submission of his current article describing four cases collected since the original publication of OFMT and the submission of his current article describing four cases collected since the original publication of OFMT and the submission of his current article describing four cases collected since the original publication of OFMT and the submission of his current article describing four cases collected since the original publication of OFMT. Miettinen indicates that two of the four tumors had a peripheral rim of bone, the implication being that none of the four had any bone within the lesion proper. In a single example of OFMT supplied to our staff by Dr. Weiss, the bone was confined to the capsule of the lesion.

One might expect that a bone-forming tumor would have roentgenographic correlates. Indeed, a roentgenogram is illustrated in the AFIP report, and the authors indicate that soft tissue matrix information was present in two of nine cases for which roentgenograms were available, but no information is provided on the other seven cases. Miettinen is silent on this issue.

Miettinen also adds little to the light microscopic characterization of the tumor cells or their arrangement, agreeing with the original description of a tumor composed of uniform, oval to round cells residing in a mucoid, fibromyxoid, or fibrous stroma. Cell nuclei are bland with small nucleoli, and the cytoplasm is eosinophilic with indistinct cell borders. In some areas the cells are set off into lobules by thick collagenous septa. In some foci, the tumor cells are arranged in rows or files resembling the pattern in myxoid chondrosarcoma. Regions also are present where the cells have a clear to vacuolated cytoplasm and a spindle cell arrangement. Miettinen did find areas where a lacunar pattern was created by pericellular
spaces about the tumor cells. Periodic acid-Schiff (PAS) stains for glycogen were negative, and the mitotic activity was low. The lesion is richly vascular, with blood vessels frequently having hyalinized walls. Calcification and cartilage were found in a small number of the original cases but not mentioned by Miettinen.

Although Miettinen's cases were examined by electron microscopy, their fixation was not optimal, being based on formalin-fixed tissues in two and prior paraffin-embedded tissue in the other two cases. The type of fixation used in the eight AFIP cases studied by electron microscopy was not stated. The results obtained in both studies overlap, but some differences are present. The tumor cells have irregular borders with elongated cell processes. A partial or discontinuous basal lamina, reduplicated in some instances, was found in some cases and not in others, and when present, not all cells had it. Nuclei were bland with an even chromatin pattern. Significantly, no mention is made in either study of a dense fibrous nuclear lamina, as may be seen in the cells of some cartilage tumors. No cytoplasmic glycogen was found. The AFIP group found scarce and small mitochondria, numerous microfilaments, few endoplasmic reticulum segments, and no microtubules, pinocytic vesicles, desmosomes, or intercellular junctions. However, Miettinen found no microfilaments but found numerous profiles of rough endoplasmic reticulum (RER), occasional plasma membrane pinocytic vesicles, moderate numbers of mitochondria, prominent arrays of intermediate filaments, and in one case, primitive cell junctions. No microtubule-RER aggregates were found.

The strength of the paper by Miettinen is its immunohistochemical section. Although the AFIP report indicated variable S-100 protein positivity in three-fourths of 46 cases tested, and the absence of cytokeratin and glia fibrillary acidic protein (GFAP) in 9 and 5 cases, respectively, no information is given on the type of antibodies used, monoclonal or polyclonal, their source, dilutions, or the immunohistochemical technique employed. Miettinen clearly provides all of these data and significantly extends the immunologic panel to include testing for vimentin, cytokeratin, epithelial membrane antigen (EMA), desmin, muscle-specific actin, melanoma-specific antigen, and Leu-7. Unlike the AFIP study, S-100 protein was strongly positive in all four cases, as were stains for vimentin. Positive results for Leu-7 were found in three cases, and one case was GFAP positive. Negative results were obtained for all of the other markers tested.

Based on the foregoing light and electron microscopic, and immunohistochemical results, what can be said about the taxonomic classification of this lesion? This question is of obvious importance in light of the 14 different benign and malignant diagnoses submitted by the pathologists who contributed to the AFIP series. Although we are not told which of these various diagnoses was the most common, the authors of the two studies on OFMT concentrated their differential diagnostic considerations on two broad groups of tumors, chondroid or chondroid-like lesions and neural crest-derived lesions, principally those of Schwann cell origin.

In favor of a cartilaginous origin was the S-100 positivity of the tumor cells, the lobulation of the tumor, the presence of sulfated glycosaminoglycans, and the electron microscopic presence of irregular cell borders and microfilaments within some of the cells. Among the tumors considered were extraskeletal examples of chondroblastoma, chondromyxoid fibroma, and myxoid chondrosarcoma. Although the authors do not felt impelled to mention the first two of these entities, their light microscopic patterns are not closely allied with that of OFMT. While chondroblastoma has rarely been reported as originating in the soft tissue, we are unaware of any such extraskeletal examples of chondromyxoid fibroma. The ossification pattern noted in OFMT also is not found in either of these two chondroid lesions where ossification of any type is uncommon. Extraskeletal myxoid chondrosarcoma was a significant diagnostic consideration because of the pattern of linear row-like arrangement of some tumor cells in OFMT. The presence of a basal lamina, not usually associated with chondroid cells, and the absence of microtubular-RER aggregates were points used to disregard myxoid chondrosarcoma as a diagnostic consideration. However, a pericellular basal lamina has been found by some authors in both skeletal and extraskeletal myxoid chondrosarcomas, and microtubular-RER arrays are not found in all myxoid chondrosarcomas. Their demonstration being dependent upon the type of fixation used.

Also against OFMT being some variant of myxoid chondrosarcoma is the presence of bone, which is virtually never found in extraskeletal chondrosarcoma. Of more importance in eliminating myxoid chondrosarcoma, as well as other chondroid lesions, including myxoid chondroma, which is the lack of cytoplasmic glycogen, by either PAS staining or by electron microscopic examination, and the absence of an abundant endoplasmic reticulum that is frequently dilated and contains a finely granular material. The lack of these two features, which are so characteristic of cartilage lesions, is strong evidence against OFMT being a chondroid tumor.

Other, and even less likely candidates in the differential diagnosis, were clear cell sarcoma and chondroid syringoma (cutaneous mixed tumor). Although one of Miettinen's cases originally was diagnosed as a clear cell sarcoma, this tumor's light microscopic pattern of clear cells with prominent basophilic nucleoli, occasional multinucleated giant cells, cytoplasmic melanin, positive mel-
anin stains, and electron microscopic presence of pre-
melanosomes or melanosomes should serve easily to dis-
tinguish it from OFMT.21-23 Chondroid syringoma may
at times have a light microscopic appearance indistin-
guishable from myxoid chondrosarcoma. However, elec-
tron microscopic studies show evidence of epithelial and
myoepithelial differentiation,24 and immunohistochemi-
cal studies demonstrate cytokeratin positivity, all of which
are lacking in OFMT.

The most likely diagnosis considered by both the AFIP
authors and Miettinen was that OFMT was a form of
Schwann cell tumor. Indeed, with its myxoid stroma and
plexiform pattern, the low power illustrations of OFMT
resemble either a dermal nerve sheath myxoma (neuro-
thekeoma; pacinian neurofibroma25-29) or a myxoid neu-
rofibroma.10,30 The presence of S-100 protein in the cells
of OFMT, as well as Leu-7 and GFAP as demonstrated
by Miettinen in some of his cases, is in keeping with a
nerve sheath tumor.31-36 However, the electron micro-
scopic results are not totally classic for Schwann cells,
which usually show a continuous basal lamina, mesaxon
inclusions, absence of pinocytotic vesicles, long and en-
tangled cell processes, rare cell junctions, a moderate
number of cytoplasmic organelles, and microtubules and
microfilaments within the cell processes.37 The presence
in some of the tumor cells of pinocytotic vesicles, the
presence of only a partial basal lamina, and primitive cell
junctions in one case, suggest the possibility of perineural
cells as being a component of OFMT. Against the latter
are the recent immunohistochemical results that indicate
that perineural cells contain EMA39 which Miettinen
found to be absent from his cases.2 However, whether all
perineural cells, such as appear to be present by electron
microscopy in nerve sheath myxomas,25,29 lack EMA must
await further reports because the number of such cases
tested thus far is limited.39

The positive results for sulphated glycosaminoglycans
also are not inconsistent with a Schwann cell origin be-
cause like cartilaginous lesions, nerve sheath tumors have
been shown to produce such substances.10,40 Although
both Miettinen and the AFIP group appear to lean toward
a neural origin for OFMT, their inability to find the lesion
in intimate contact with a peripheral nerve made them
hesitant to accept outright a Schwann cell origin. However,
it is not common to find a peripheral nerve of origin in
cutaneous neurofibroma or in many cases of malignant
peripheral nerve sheath tumors, yet we have no hesitation
about making such diagnoses when the morphologic or
immunohistochemical data support such interpretation.

If OFMT is a neural lesion, how do we account for the
high incidence of ossification within it? The pleuropoten-
mors, a variety of tissues, including bone, cartilage, fat,
muscle, and even epithelial elements, is well known.41
This being said, however, the occurrence of such tissues
in benign nerve sheath tumors is exceedingly rare.42-45
Indeed, to emphasize this rarity, Enzinger, Weiss, and
Liang go so far as to mention that they had seen one
case of a shell of ossification in a neurilemoma.1 Apparent­
ly, nerve sheath tumors arising from the cranial nerves are
more prone to such divergent differentiation as reviewed
by Kasantikul and colleagues.40 This writer disagrees with
Miettinen’s implication that the bone formation in OFMT
is no more specific than that found in scar tissue.1 We
are not dealing here with scar tissue, and the frequency of
the ossification in OFMT, as well as the rare presence of car-
tilage, suggests that if OFMT is a tumor of Schwann cell
origin, then this mesenchymal differentiation is specific
and reflects some altered differentiation pattern in the cells
of this lesion in contrast to those of other Schwann cell
lesions.

Although this writer also believes that OFMT probably
is of Schwann cell origin, the issue of its histogenesis is of
secondary importance to that of its biologic significance,
and I agree with the conservative view of the authors of
these papers that there is no need for a rush to judgment
on this issue.

Whether OFMT is a benign lesion or one with a low-
grade malignant potential is far from clear, and the ques-
tion is not directly addressed by Miettinen. There were
no recurrences in any of Miettinen’s patients at intervals
of 1, 3, 8, and 11 years after therapy. Three of the patients
had local excisions, and one, who was misdiagnosed as
having a clear cell sarcoma, received adjuvant radiation
therapy. In the larger AFIP series, there was a local re-
currence rate of 27%, with multiple recurrences in three
patients, one of whom had three recurrences in 32 years.
Unfortunately, no information is given as to the recur-
rence rate for those tumors arising in the deep soft tissue
versus those arising in the subcutaneous tissue. Further-
more, due to the nature of the consultation practice at
the AFIP, details on therapy are largely absent, although
local excision was used in the “majority” of patients.
Wide, radical, or en bloc excisions, including amputation
disarticulation, also were employed, but it is unclear
how many of the these were employed for primary or
recurrent lesions, and no reasons were given for the am-
putations. One can only guess that they were done because
of initial misdiagnoses of malignancy. Two patients in
the AFIP series are of particular interest in evaluating
the malignant potential of OFMT. One developed a contra-
lateral OFMT following the third recurrence of an OFMT
first excised 20 years previously. This contralateral tumor
was considered to be a metastases by the authors. No pul-
monary lesions were noted. Unfortunately, this patient

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committed suicide shortly after the onset of this supposed metastases. The second patient developed a recurrence that was notable for its high cellularity and the appearance of a low-grade (well-differentiated) osteosarcoma in many areas. However, the low power illustration of this case is not convincing. Miettinen may have unintentionally muddied the waters on this issue by stating that OFMT may include histologically malignant variants that might be classified as extraskeletal osteosarcomas, two of which he excluded from his series. Unfortunately, it is not clear whether these two cases were simple examples of extraskeletal osteosarcomas or whether they had any relationship to OFMT.

We are, therefore, faced with a tumor that has a reasonable rate of local recurrence, but for which we have little definitive data on how the lesions were treated. Benign tumors, when inadequately excised, can recur. It is obvious that the true biologic potential of OFMT is unknown, and the clarification of this issue must await further reports. It is hoped such reports will deal with new information that either helps elucidate the histogenesis or differentiation of OFMT or deal with patients with whom have been followed for a sufficient period of time to determine whether some ossifying fibromyxoid tumors are low grade malignancies. In this regard, the name chosen for this entity, although aptly descriptive, runs up against the tumor recently described by Evans as “low-grade fibro-myxoid sarcoma” (that tumor has no histopathologic similarity to OFMT).

It is hoped that if a Schwann cell origin of OFMT were ever established, a name such as “ossifying schwannoma” might be adapted to avoid any confusion with the lesion described by Evans.

**REFERENCES**


