Franz M. Enzinger: His Life and Work

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There was never any question in Franz Enzinger’s mind he would become a doctor. Growing up the younger of two children in Austria, he remembers fondly his family physician and the great admiration he had for the gentleman. That and the generous support from his father, a government worker and his mother a dedicated homemaker conspired to make his path to medicine more of a calling than a conscious decision. However, World War II interrupted his studies and he found himself working as a medical orderly in the German army. It was from a radar station in Cherbourg that he, a mere 20 year old, witnessed the Normandy invasion on that fateful day in June of 1944 knowing it might be his last. Fortunately, with the conclusion of the war he was both alive and able to return to medical school at the University of Innsbruck where he gravitated toward anatomy and histology and eventually became an anatomy instructor there. He arrived in the United States in 1951 to take a rotating internship at Northern Westchester Hospital, a position he had learned about from a colleague. Following this year he decided he would like to do a pathology residency under the illustrious Arthur Purdy Stout. He recalled that Dr. Stout was “very nice to him” during the interview but ultimately did not accept him. Instead, he went to the University of Iowa where he trained under the late Dr. Emory Warner, who later described his appointment of Franz Enzinger as the best decision he ever made as departmental chair.
Franz as a young man

It was his friend Jim Butler, a hematopathologist, who convinced Franz he should apply to the Armed Forces Institute of Pathology, a recreation of the old Army Medical Museum staffed by the best diagnosticians in a new building situated on the grounds of the Walter Reed Army Medical Center. Although the AFIP was created as a consultation center for the military, it soon became a consultation center for the world. On his arrival in 1957 he was assigned to the Pulmonary, Mediastinal, ENT Branch headed by Dr. Samuel Rosen. During that first year he participated in the classic description of pulmonary alveolar proteinosis along with Drs. Rosen, Castleman, and Liebow. In his second year he found himself in Dr. Helwig’s Dermatopathology/Gastrointestinal Branch and in his third year the Department of Soft Tissue Pathology where he became chair after a mere 18 months (at the age of 37) when the former chair, Dr. Winslow, decided to leave. This appointment marked the beginning of Franz’s illustrious career in soft tissue pathology, for here, drawing on his remarkable visual abilities and the unparalleled archives of the Institute, Franz wrote prodigiously on nearly every known soft tissue lesion as well while describing many new ones.

His first major work was “Liposarcoma: A study of 103 cases.” in which he drew sharp lines among the various histologic subtypes and illustrated the close correlation between subtype and behavior in that disease. The clairvoyance of his opening stating that the subtypes of liposarcoma should be regarded as groups of closely related tumors rather than as one disease presages by nearly 30 years the molecular classification of liposarcoma which firmly validated all the principles in that paper. Over the next 10 years nearly every paper he wrote became a classic such as: musculoaponeurotic fibromatosis of the shoulder region, proliferative myositis, and juvenile aponeurotic
fibroma to name a few. In “Alveolar Rhabdomyosarcoma: an analysis of 110 cases.”
Franz called attention to the fact that nearly one half of cases contained “solid or medullary” areas which closely resembled lymphoma. This fact seemed largely forgotten until modern classifications re-emphasized the solid variant of alveolar rhabdomyosarcoma. However, it was his next two major papers that clearly established him as one of the most original surgical pathologist—one who had the capacity to recognize lesion which others had never seen or had seemingly overlooked. In his paper on clear cell sarcoma of tendon and aponeurosis published in 1965 he described a distinctive clear cell tumor of the distal extremities which he pointed out was neither a classic synovial sarcoma nor a malignant melanoma. Interestingly, although he observed the presence of Fontana positive pigment within the lesion, he chose to interpret it as hemosiderin, probably accounting for the relative ease with which he concluded that these tumors were not melanomas. Of all his papers epithelioid sarcoma paper probably stands as his masterpiece. Written with great detail and precision, illustrated with great beauty and buttressed with follow up information, this paper describes a lesion which virtually no one was aware of at the time of its publication, yet many would recall a probable case from the past. Even today, no one has improved on the fundamental description laid out by Franz in that 1970 publication. It was no wonder that Richard Reed dubbed the tumor a “franzoma.” Yet in his usually modest way, when I asked him if he thought his epithelioid sarcoma was his finest paper, he said, “It was good.”

It was during this period of incredible productivity that Franz was also asked to direct the First World Health Organization for the Classification of Soft Tissue Tumors. His committee consisted of a panel of international experts who not only produced the first

The First WHO Committee for the Classification of Soft Tissue Tumors c. 1960-62
Franz is seated at the head of the table
“Blue Book” but also a magnificent set of glass slides with accompanying syllabus. He magnanimously gave sets to visiting residents and scientists at the AFIP and distributed many world wide, a gesture that accounted for the rapid assimilation of this first classification. I still have and cherish the set he gave me.

With the publication of the “Blue Book,” Franz quickly became the leading diagnostic soft tissue pathologist of his generation. His earlier papers were followed by several other classics including “Fetal Rhabdomyoma,” a paper co-authored with Peper Dehner, then a young pathologist at the AFIP, “Extrasketal myxoid chondrosarcoma: an analysis of 34 cases,” “Malignant Giant Cell Tumor of Soft Parts,” a tumor subsequently to become part of the spectrum of malignant fibrous histiocytoma, “Proliferative fascitits,” co-authored with his long time collaborator Ed Chung, Hemangiopericytoma, and “Extrasketal neoplasm resembling Ewing’s sarcoma,” which he wrote with his long time Swedish friend, Lennert Angervall. “Spindle Cell Lipoma” and the closely related “Pleomorphic Lipoma,” were clearly identified as benign lesions the latter of which had probably been diagnosed as a liposarcoma for many years. A series of publications in the 1970’s and 80 led to the concept of intermediate fibrohistiocytic tumors. These included the giant cell fibroblastoma a lesion, a lesion correctly identified as a variant of dermatofibrosarcoma protuberans years before the characteristic ring chromosome linked them to one another, “Angiomatoid Malignant Fibrous Histiocytoma: a Distinct Fibrohistiocytic Tumor of Children and Young Adults simulating a vascular neoplasm,” and “Plexiform fibrohistiocytic tumor presenting in children and young adults: an analysis of 65 cases” Interestingly, although all of these papers obviously relied heavily on Franz’s insights, he was always generous including others in these efforts even when he himself had to do much of the work.
By the time I had finished my residency and brief tenure as a faculty member at the Johns Hopkins Hospital in nearby Baltimore, there seemed no better place to train than at the AFIP with Franz Enzinger even though it entailed a 100 mile round trip commute on a daily basis. It was 13 year association I have never regretted. During this time we published two major articles on malignant fibrous histiocytoma, “Myxoid malignant fibrous histiocytoma” and “Malignant Fibrous Histiocytoma: An analysis of 200 cases.” which have been both embraced and dismissed over the years. The importance in these articles, I have always maintained, was not to support the concept of the histiocytic origin of these pleomorphic sarcomas but rather to detail their behavior as it relates to the parameters of size and depth. In fact, Franz and I had vastly different ideas about the origin or differentiation of theses lesions. We fought for weeks over this issue. It seemed we were not destined to finish the paper. Finally, to compromise we concluded with the statement that these tumors showed “partial histiocytic and fibroblastic differentiation.” Fortunately, writing the first edition of our textbook *Soft Tissue Tumors* led to far fewer disputes. Franz afforded me great latitude in this endeavor. He assigned me one half the chapters and generously granted me one half of the royalties as well, something I have long remembered.

It was a very sad day in October 1987 when Franz announced his intention to retire from the AFIP. He was barely 64, far younger than many other chairs such as Drs. Mostofi and Helwig who desperately tried to convince him to reconsider his decision. When I asked him why he chose such an early retirement he said, “I want to retire when everyone still thinks I am great.”

The Soft Tissue Department
Franz’s Retirement Ceremony
1988
Although he remained true to his intentions, he returned often over the ensuing years as a consultant to assist the department under the new leadership of Jeanne Meis-Kindblom and later Markku Miettinen. Even at this point in his career he continued his mentoring. He co-authored with Jeanne Meis-Kindblom and others in the department several important papers including “Inflammatory Fibrosarcoma of the Mesentery and Retroperitoneum: a Tumor Closely Simulating Inflammatory Pseudotumor,” an important early description of the inflammatory myofibroblastic tumor.

Franz has been truly one of the most remarkable individuals to cross my path during my career as a pathologist. From his own career one can learn much. He was an individual who always remained focused on his work and the pursuit of excellence. He had little regard for the politics of pathology and probably for that reason had no enemies. He once admonished me to “pay attention to pathology and not the personalities in pathology.” He insisted it was better to write one excellent paper than 12 mediocre ones. His own curriculum vitae had about 75 papers when he retired, but each was a classic. He was kind and generous to other pathologists. I once asked him why he took so long to look at slides which others brought him when I knew how easy the cases must have been for him—because he wished them to think he, too, had struggled over the case, he said. He had calm perspective on life once telling me that if he had a sarcoma he would not venture to a major medical Mecca, but rather Tahiti for a long vacation. He has always enjoyed life to the fullest in the companionship of his lovely wife Inge, a former Fulbright Scholar, whom he married over 40 years ago and his son Peter, a medical oncologist at Brigham and Women’s Hospital in Boston. It is, indeed, a privilege for our society to honor this man who has meant so much to our discipline and for me personally to acknowledge how influential he has been to my life and career.
References:


Clear Cell Sarcoma: A Historical Perspective with Personal Comments

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Recognition of a New and Distinct Entity

In 1965, Dr. Franz Enzinger published the first description of clear cell sarcoma of tendons and aponeuroses (9). His series of 21 cases was culled from the archives of the Armed Forces Institute of Pathology (AFIP) over a 25-year period. Two of the cases had previously been included in another publication from the AFIP on synovial sarcomas (2).

The cases described by Dr. Enzinger typically occurred in the foot and knee of young adults, especially women, and were intimately associated with tendons. The main symptom was a mass associated with pain in half of the cases, usually of long duration. The median age at onset of symptoms was 24 years, and the median age at initial surgery 26 years. All masses were solitary at presentation. No joint or bursal involvement was noted and bone erosion was seen in only one case. Tumor sizes ranges from 2 – 6 cm. (median, 4 cm.).

The salient histological features of the entity, illustrated in 7 of 21 cases, included fascicles and nests or cellular aggregates of pale, fusiform, epithelioid cells with clear to finely granular cytoplasm and round nuclei with very prominent nucleoli. The cellular aggregates were encased by delicate fibrous septa and were intimately associated with tendons and aponeuroses. Multinucleated tumor giant cells with 10 – 15 nuclei per cell were seen in two-thirds of cases. Mitoses were generally sparse and necrosis and hemorrhage were rare. Eight histochemical stains were performed; these showed intracellular glycogen in 8 of 15 cases and extra- and intracellular iron located primarily within dense fibrous tissue or septa. Intriguingly, small amounts of granular Fontana positive pigment not abolished by melanin bleach were found in 7 of 15 cases. The same areas were usually associated with hemorrhage and the pigment was also weakly positive with Gomori’s iron stain.

Follow-up information was available in 19 of 21 cases, with follow-up periods of 10 or more years in five cases and autopsies in six. Clinically the cases were characterized by a slow relentless growth, with repeated local recurrences and eventual metastases. Sixteen of 19 patients had local recurrences, usually within one year. Metastases occurred in 12 of 19 patients; all patients with metastases died of tumor. Fourteen of 19 patients died at a median interval of 4.5 years after diagnosis. Metastases were usually to regional lymph nodes and lungs, followed by the heart, liver and brain.

Prognostic factors were not clear at the time, aptly summed up by Dr. Enzinger’s comment that “…attempts to correlate the prognosis with the gross and microscopic features have been
unrewarding.” Survivals were shorter in larger tumors, but did not clearly correlate with prognosis. There was no clear correlation of outcome with mitotic rate or type of surgery.

Dr. Enzinger concluded that the cell of origin of clear cell sarcoma was unclear, stating that “…the term clear cell sarcoma of tendons and aponeuroses … is purely descriptive and reflects the uncertainty of histogenesis.” He further stated that it was not related to fibrosarcoma or synovial sarcoma (the most commonly rendered diagnosis), that it should not be categorized as tenosynovial sarcoma, and even more astutely, that it was not a spindle cell melanoma.

Forty years after its initial description, one cannot help but marvel at the precision with which this study was executed – on all levels, not to mention the creative genius involved in recognizing and accurately describing an entity that has withstood the scrutiny and analysis of time, several investigators, and ever evolving new technologies. The clinical histories are incredibly detailed; the completeness of the tables are exemplary with utmost attention to dates of treatment, local recurrences, metastases and treatment type; the results of intricate histochemical studies in the pre-immunohistochemical era are painstakingly documented and eerily accurate; and the follow-up is remarkably complete for a referral center (privacy laws hadn’t been implemented yet). The writing has a beautiful simplicity; it is clear and detailed yet concise. The measured nature of the conclusions regarding clear cell sarcoma's histogenesis is a quality that runs through all of Dr. Enzinger’s original works; the balance between observation and conclusion is always rigorously scientific – never speculative or pontificating.

Reaffirmation and Further Investigations Regarding Differentiation
After the original detailed description of clear cell sarcoma, several small and large clinicopathologic studies appeared in the literature, reaffirming its existence and uniqueness as a clinicopathologic entity (6-8, 10, 13-15, 17, 18, 20, 27). Additionally, many of these addressed the histogenesis / differentiation of clear cell sarcoma, using first ultrastructural and later immunohistochemical techniques to investigate the mysterious Fontana positive granular material found within the cell cytoplasm. Thus, ultrastructural evidence of melanocytic differentiation was reported by several authors within one to two decades of the seminal description of clear cell sarcoma (1, 8, 12, 13, 16). This information was most clearly assimilated and cogently presented in 1983 by Kindblom et al. in their report of 15 cases of clear cell sarcoma (13). In six of the cases studied ultrastructurally, variable amounts of intracytoplasmic glycogen and external lamina surrounding groups of cells or individual tumor cells were seen. Bizarre were melanosomes found in one case. S100 protein was detected in all 15 cases. They concluded that clear cell sarcoma was indeed a homogeneous tumor entity of probable neural crest origin and not part of the nebulous group of tenosynovial sarcomas.

Reassessment of the Clinical Course and Differentiation
In 1983, Chung and Enzinger reported the accumulated experience of 141 cases of clear cell sarcoma retrospectively gathered from the archives of the AFIP from 1942 – 1980 (6). This study included the original 21 cases described by Dr. Enzinger in 1965 (7). Interestingly, the data had preliminarily been presented at the 67th Annual USCAP Meeting in Atlanta in 1978.
Although the follow-up period of this study was longer than the smaller series reported in 1965, the clinical findings in terms of tumor sites, presenting symptoms and sex distribution were similar. The median tumor size was less, as were the number of local recurrences, metastases and tumor deaths, probably due in part to the heightened awareness of the entity since its description in 1965. However, the authors pointed out that these tumors frequently developed recurrences and metastases 5 or more years after initial therapy, indicating the need for long-term follow-up with respect to treatment strategies.

New findings in this paper included the detection of intracellular melanin demonstrated in 72% of tumors with the more sensitive Warthin-Starry stain at pH 3.2. Again, iron and melanin were occasionally noted in the same cells. Additionally, intracytoplasmic glycogen was detected in two-thirds of cases. S100 immunostains were performed on a minority of cases and found to be positive in slightly more that two-thirds of cases. Notably, some of the cases of clear cell sarcoma bore a close resemblance to spindle cell melanomas of the ocular choroid, an observation that may well have been related to the presence of Dr. Zimmerman, the then current chairman of the Department of Ophthalmic Pathology at the AFIP.

In this paper, Drs. Chung and Enzinger stated that “…the presence of melanin was overlooked…”, not only by themselves, but by others. They capitulated to previous reports demonstrating melanogenesis in clear cell sarcoma, stating “…it is safe to conclude that: 1) clear cell sarcoma represents a malignant neuroectodermal tumor derived from potentially melanogenic cells that have migrated from the neural crest during embryonal life and 2) that the tumor is in many aspects akin to malignant melanoma and malignant blue nevus.” They thus concluded that a more appropriate term would be “…malignant melanoma of soft parts, rather than the purely descriptive term of clear cell sarcoma.”

Later, other authors stated that clear cell sarcoma was a preferable term, since clear cell sarcoma was clinically very unlike cutaneous melanoma (15). As we shall see, subsequent molecular genetic studies have confirmed this contention, illustrating the distinctness of the two tumors.

**Prognostic Studies**

Several relatively large studies on clear cell sarcoma were carried out within the next 25 -30 years following its description. The clinical features of some of the more significant studies are compared in Table 1. Oddly, studies focusing on prognosis were not performed until the statistical analysis published from MD Anderson Cancer Center in 1990 (27). Similar to Dr. Enzinger’s original study, no correlation between histological appearance and clinical outcome was found. Only tumor size \(\geq 5 \text{ cm.} \) was found to correlate with outcome (Table 2). Similar results were found in a Mayo Clinic series with respect to tumor size; any microscopic necrosis was also found to be an independent adverse prognostic factor (15). The following year, a rigorous statistical analysis of 58 cases that had not been previously reported from the AFIP was published (20). In that study, the authors found that larger tumor size as a continuous variable and any tumor necrosis were independent adverse prognostic factors. Interestingly, the tumors in their series were significantly smaller than those of other series (see Table 1), probably reflecting the relatively unbiased nature of the AFIP material seen at that time compared to major treatment referral centers. Again, no correlation between
clinical course, histological or immunohistochemical features, including proliferative activity, was found.

Subsequent prognostic studies have confirmed that size is the most important factor in the prognosis of clear cell sarcoma (7, 10, 17) and that radical surgery is the treatment of choice (10, 15). Chemotherapy still has little role to play in the treatment of this tumor (10).

Table 1. Comparison of Clinical Data of Major Studies on Clear Cell Sarcoma

<table>
<thead>
<tr>
<th>NO. CASES</th>
<th>SEX RATIO M:F</th>
<th>AGE (YRS), MEDIAN &amp; RANGE</th>
<th>TUMOR SIZE (CM.), MEDIAN &amp; RANGE</th>
<th>% CASES WITH FOLLOW-UP / MEDIAN &amp; RANGE</th>
<th>LOCAL RECURRENCES</th>
<th>METS, MEDIAN TIME TO METS &amp; SITES</th>
<th>% PATIENT TUMOR DEATHS &amp; MEDIAN INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENZINGER 1965</td>
<td>21</td>
<td>3:4</td>
<td>26 yrs 1 – 65</td>
<td>4 cm 2 – 6</td>
<td>95% 48 mos 1 – 36 yrs</td>
<td>84%</td>
<td>63% 7 yrs lung &amp; nodes</td>
</tr>
<tr>
<td>CHUNG &amp; ENZINGER 1983</td>
<td>141</td>
<td>6:7</td>
<td>27 yrs 7 – 83</td>
<td>3.3 cm 1 – 15</td>
<td>82% 68 mos (ave) 1 – 36 yrs</td>
<td>39%</td>
<td>50% 8 yrs (ave) lung&gt; nodes&gt; bone</td>
</tr>
<tr>
<td>SARA &amp; EVANS 1990</td>
<td>17</td>
<td>1:1</td>
<td>28 yrs 70 – 90</td>
<td>4.5 cm 2 – 9.5</td>
<td>100% 49 mos 3 – 158 mos</td>
<td>24%</td>
<td>59% 25 mos lung &gt; nodes</td>
</tr>
<tr>
<td>LUCAS, NASCIMENTO, SIM 1992</td>
<td>35</td>
<td>2:3</td>
<td>30 yrs 10 – 64</td>
<td>4.5 cm 1 – 14</td>
<td>100% 74 mos. 7 – 258 mos</td>
<td>14%</td>
<td>63% 5 yrs (ave) lungs &gt; nodes &gt; bone</td>
</tr>
<tr>
<td>MONTGOMERY, RAMOS, MEIS ET AL. 1993</td>
<td>58</td>
<td>1:1</td>
<td>31 yrs 7 - 78</td>
<td>2.5 cm 0.6 – 9</td>
<td>84% 48 mos 2 – 264 mos</td>
<td>26%</td>
<td>44% 26 mos. lungs &gt; bone &gt; nodes</td>
</tr>
</tbody>
</table>

Table 2. Adverse Prognostic Factors Affecting Survival in Clear Cell Sarcoma Patients

<table>
<thead>
<tr>
<th>TUMOR SITE</th>
<th>TUMOR SIZE (CM)</th>
<th>NECROSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARA &amp; EVANS 1990 *</td>
<td>No</td>
<td>≥ 5 cm.</td>
</tr>
<tr>
<td>LUCAS, NASCIMENTO, SIM 1992 §</td>
<td>No</td>
<td>≥ 5 cm.</td>
</tr>
<tr>
<td>MONTGOMERY, RAMOS, MEIS ET AL. 1993</td>
<td>No</td>
<td>Yes, as a continuous variable</td>
</tr>
</tbody>
</table>

Table 2. Other factors analyzed but not found to be statistically significant:
*Age, sex, race, tumor site, symptom duration, initial therapy, mitotic rate, tumor necrosis, proportion of epithelioid cells, nuclear pleomorphism
§ Mitotic rate, nuclear pleomorphism, symptom duration, age, sex, tumor location and ploidy
Tumor size as a dichotomous variable, vascular invasion, presence of multinucleated giant cells, average and maximum mitotic rate, %PCNA positivity, immnostaining for HMB45 or S100 protein, age, race, sex, tumor site, pushing vs. infiltrative tumor margins, packeted vs. spindle cell patterns, tinctorial features of the cytoplasm (clear vs. eosinophilic)

**Cytogenetic and Molecular Genetic Studies**

The late 1980’s and 1990’s heralded the discovery of many tumor specific translocations for soft tissue sarcomas (19). The cytogenetic hallmark of clear cell sarcoma of tendons and aponeuroses is t(12;22)(q13;q12), resulting in a chimeric EWS/ATF1 gene in which the 3’-terminal part of EWS at 22q is replaced by the 3’-terminal part of ATF1 at 12q (3, 4, 14, 19, 21, 24 – 26, 28 – 30). This translocation has been detected cytogenetically in about 70% of reported cases of clear cell sarcoma. Many cases of clear cell sarcoma also display additional chromosomal aberrations including extra copies of chromosomes 8 and 7 and 2, and structural and numerical aberrations of chromosome 22 other than t(12;22) (3, 4, 26, 28, 29). To date, no cryptic translocations resulting in the EWS/ATF1 fusion transcript have been reported.

The EWS/ATF1 fusion transcript can be detected using RT-PCR and FISH techniques in about 50 – 75% of cases of clear cell sarcoma (14). Four types of EWS/ATF1 chimeric transcripts, designated types 1 – 4, have been identified in clear cell sarcoma and well characterized (21). These occur with different frequencies and sometimes simultaneously in a given tumor; type 1 seems to be the most common of these.

The histological and immunohistochemical features of clear cell sarcoma overlap significantly with those of cutaneous melanoma and occult metastatic melanoma, hence the differential diagnosis between these two entities still is problematic with profound clinical consequences (5, 23). Application of the aforementioned techniques in selected instances is potentially useful for definitive diagnosis.

Molecular genetic techniques have had an even greater impact on the ongoing controversy regarding the relationship of clear cell sarcoma to melanoma, and have unequivocally shown that clear cell sarcoma of tendons and aponeuroses is genetically distinct from cutaneous melanoma. Additional studies to detect mutations of exon 11 and 15 of the BRAF gene, which is commonly mutated in melanoma, are consistently negative in clear cell sarcoma (22). Thus, these tumors seem to develop through different genetic pathways.

Recently, t(12;22)(q13;q12) has been shown to not be unique for clear cell sarcoma of tendons and aponeuroses. We have recently reported a case of angiomatoid fibrous histiocytoma that displayed t(12;22)(q13;q12) as the sole cytogenetic abnormality (11). FISH, RT-PCR and sequence analyses revealed an EWSR1-ATF1 fusion gene that has previously been reported in clear cell sarcoma; no microphthalmia transcription factor (MITF-M) transcript was found. This study shows that:

1) The EWSR1-AFT1 chimera can be seen in tumors other than clear cell sarcoma, namely angiomatoid (malignant) fibrous histiocytoma.

2) The MITF-M transcript is not present in angiomatoid (malignant) fibrous histiocytoma, suggesting that its presence in clear cell sarcoma may be a reflection of its cellular origin rather than a consequence of transactivation by EWSR1-AF1 as proposed by others.
3) Activation of the EWSR1-ATF1 oncogene is probably an early step in the transformation process of clear cell sarcoma and other tumors. Overall gene expression patterns undoubtedly vary a great deal between different types of sarcomas with activation of EWSR1-ATF1.

**Concluding Remarks**

Forty years and many papers have passed by since the original description of clear cell sarcoma of tendons and aponeuroses by Dr. Enzinger. None of them have disproven his original observations or conclusions. This paper has withstood the acid test of time! Its uniqueness has been genetically confirmed. It is still viewed as a tumor of uncertain differentiation despite the detection of intracellular melanin.

Clear cell sarcoma of tendons and aponeuroses probably is the best name for this tumor. It has clearly been shown to be distinct from cutaneous melanoma. It is not to be confused by the uninformed with other “clear cell” tumors, including clear cell sarcoma of kidney, clear cell myelomelanocytic tumor and clear cell carcinomas.

The original description of clear cell sarcoma of tendons and aponeuroses is, quite simply, a stroke of genius. It is one of many strokes of genius by Dr. Enzinger, who laid the first sound foundations for the classification of soft tissue tumors that have withstood the test of time, advanced medical technology, and critics. This paper also illustrates the remarkable gift that Dr. Enzinger has not only as a pathologist with superb observational skills, but as a physician with a broad perspective and as a superb writer. Dr. Enzinger is, without a doubt, one of the greatest figures in surgical pathology. His original works in soft tissue pathology will remain the indisputable gold standard by which future works are measured.
Bibliography


EPITHELIOID SARCOMA

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Introduction Epithelioid sarcoma is a tumor of mesenchymal cells displaying differentiation that is multidirectional but predominantly epithelial. Soft tissue tumors composed of large polygonal cells resembling carcinomas were observed from time to time under a variety of names in the early literature on synovial sarcoma\(^1\) or giant cell sarcomas. In 1961, Laskowski reported examples of ‘aponeurotic sarcoma’ in an account which was published first in Polish\(^2\) and republished in English a decade later.\(^3\) Enzinger, while noting the prior accounts, then described 62 cases in 1970 as epithelioid sarcoma,\(^4\) the term which has been used ever since. Chase and Enzinger followed this 15 years later with a definitive study of 241 cases which emphasized the behavior and assessed in detail the prognostic factors for 202 cases of this rare sarcoma.\(^5\)

The usual-type epithelioid sarcomas, located most commonly in the distal extremities, have cells with only mild atypia, although they can appear more pleomorphic in recurrences or metastases. A group of more proximally- or axially-located tumors which are pleomorphic and aggressive from the outset have been termed proximal-type (aggressive, large cell) epithelioid sarcoma. Over 70 examples of this variant have now been reported; their existence as a subset was acknowledged in (but excluded from) the AFIP’s 1985 series of 241 epithelioid sarcomas.\(^5\)

Clinical features Epithelioid sarcoma occurs at any age with a peak in young adults and more frequently in males. A higher than usual proportion of cases (up to 20\%-27\%) have been associated with antecedent trauma, including origin in scar tissue\(^7,8\) although any causal relationship is obviously speculative. A majority of cases occur in the extremities, especially the arm and hand, as a subcutaneous or more deeply located nodule which grows slowly and can ulcerate. The ulcers have raised margins and are non-healing and clinically can resemble granuloma annulare. Deeper lesions can extend along tendon sheaths or aponeuroses.

Epithelioid sarcoma: Age and Sex

![Epithelioid sarcoma: Age and Sex](Data from Chase and Enzinger, 1985)
The proximal variant occurs in adults (range 13 to 80 years, median 40 years), with a slight predominance in males, and mainly in proximal or axial regions including limb girdles, pelvis, perineum or genital tract, mediastinum and trunk. The usual presentation is with symptoms of an infiltrative mass in deep soft tissue, and less frequently in skin or subcutis, which can attain a large size, up to 20cm in diameter, and which commonly displays hemorrhage and necrosis.

**Microscopic features** Enzinger’s original paper described comprehensively the features of this tumor, including some variations which have since been expanded as subtypes. The tumor forms nodules with central necrosis, and ulceration in cutaneous examples, composed of relatively uniform polygonal cells, often with loss of cohesion, which merge peripherally into spindle cells without demarcation. The cells have minimal pleomorphism but occasional mitoses and relatively abundant deeply eosinophilic cytoplasm. Stromal changes include hemorrhage into spaces (subsequently noted as the angiomatoid or angiosarcoma-like variant), desmoplasia with cords of bland spindle cells sometimes with storiform pattern (the fibroma-like variant with an affinity for involving bone), and focal calcification or metaplastic ossification in some cases. The larger 1985 series excluded pleomorphic examples, added new observations and quantitated the occurrence of some of the features: intracytoplasmic vacuoles, multinucleated giant cells (5%), storiform pattern (5%), calcification (19%), osseous metaplasia (10%), chondroid metaplasia (1 case), lymphocytic reaction, vascular invasion (11%), and neural invasion (7%).

In the proximal variant, there is a multinodular pattern of large polygonal cells with vesicular pleomorphic nuclei and prominent nucleoli. There is often rhabdoid cytomorphology, which can be focal or predominant. Sometimes there is a signet-ring-like vacuolation, or a minor spindle cell component but this is less common than in usual-type epithelioid sarcoma. The nodules frequently have central necrosis, with or without a ‘geographic’ pattern, as in usual epithelioid sarcoma, and a pseudoangiomatous architecture is occasionally seen. Rarely, a tumor has features of both variants. It should also be noted that the usual and proximal types can each occur in either proximal or distal locations.

**Immunohistochemical findings** Cytokeratin positivity in epithelioid sarcoma was observed by Chase et al in 1984 and in the subsequent 1985 AFIP series 75% of cases were found to be CK positive. Also, 38% of cases expressed CEA, and 53% alpha-1 antitrypsin, but these markers are no longer used routinely in this context.

It has since been amply confirmed that virtually all cases are positive for cytokeratin and for EMA (usually with membranous staining). Most cases co-express vimentin as well as cytokeratin, but a few are vimentin-negative. SMA and neurofilament are also detectable, especially in the spindle cells. CD34 is positive in over half of epithelioid sarcomas unlike in carcinoma which is almost always CD34-negative. Two large studies from AFIP have further defined the immunophenotype of epithelioid sarcoma, which expresses cytokeratins 8 (94%), CK14 (48%) and CK19 (72%), but rarely CK7 (22%), CK20 (15%) or CK5/6 (30%, focal). No single marker was able to distinguish the main 4 histologic subtypes of epithelioid sarcoma. Desmin was positive in several cases in one study but negative in all variants of epithelioid sarcoma examined in a larger series. An important negative is S100 protein although HMB45 was found in a minority of cells in 3 cases of proximal epithelioid sarcoma.
et al found positivity in the proximal variant for EMA in 85%, CD34 in 45%, CD99 in 25% and desmin or SMA in 15%. These findings are depicted below:

![Epithelioid Sarcoma: Immunohistochemistry](image)

**Ultrastructural findings**  Electron microscopy reveals a spectrum of appearances from undifferentiated cells to carcinoma-like epithelial differentiation. Enzinger originally described cells with filopodia, junctions and intermediate filaments. Subsequent accounts have confirmed these observations and extended them to include desmosomes, surface microprocesses, and interdigitating cell membranes indicating epithelial (sometimes interpreted as synovial sarcoma-like) differentiation. In addition, cells with dilated rough endoplasmic reticulum and peripheral myofilament bundles, the latter especially seen in spindle cells at the periphery of the nodules, have been observed, resembling ‘fibrohistiocytic’, fibroblastic or myofibroblastic differentiation and mimicking the appearances seen in pleomorphic sarcomas of MFH type or pleomorphic myofibrosarcoma. The rhabdoid cells contain abundant cytoplasmic whorls of intermediate filaments.

**Genetic findings** There are no consistent or specific findings. Some tumors are diploid and others polyploid. Abnormalities involving 18q11 and 22q11 (including 22q deletions) have been observed. Chromosomal rearrangements t(8;22)(q22;q11) in usual-type epithelioid sarcoma and t(10;22) in two cases of proximal epithelioid sarcoma have been described. In addition, inactivation of a tumor suppressor gene SMARCB1/INI1 located at 22q11 has been found in proximal but not usual-type epithelioid sarcoma. The 22q region, which carries the locus of the NF2 tumor suppressor gene is also affected in neurofibromatosis type 2, in association with which one example of usual-type epithelioid sarcoma has been reported.

**Differentiation** The morphologic observations have been the basis of several hypotheses about the lineage or nature of epithelioid sarcoma. Enzinger considered but rejected epithelioid sarcoma as a variant of synovial sarcoma. He suggested that epithelioid sarcoma was a mesenchymal tumor differentiating along fibroblastic or histiocytic lines, and noted the resemblance to cells of epithelioid granuloma. Later observers emphasized histiocytic, fibroblastic or myofibroblastic differentiation, and the discovery of epithelial marker positivity was used as additional support for a relationship with synovial sarcoma which some had postulated based on ultrastructure. The possibilities of endothelial and perineurial differentiation have also been raised. In truth, because of the multidirectional differentiation and the variation in features from case to case, all these suggestions except synovial sarcoma might be appropriate.
Notwithstanding its epithelial differentiation, epithelioid sarcoma differs from synovial sarcoma in many respects. Clinically, epithelioid sarcoma is often dermal and presents in the finger or hand, features which would be exceptional for synovial sarcoma. Epithelioid sarcoma is not truly biphasic but the spindle cells emerge at the edge of the tumor nodules with continuous transition from the polygonal cells. There is no glandular formation, morphologically or ultrastructurally, and no external lamina. Synovial sarcomas display epithelial markers more focally, express CK7, which is usually absent from epithelioid sarcoma\textsuperscript{12, 37} and are almost always CD34-negative.\textsuperscript{38} Genetically, the t(X;18) with SYT-SSX fusion genes which is characteristic of synovial sarcoma\textsuperscript{39} is never found in epithelioid sarcoma which has variable abnormalities including most commonly those of the 22q region.

In the current WHO classification, epithelioid sarcoma is categorized as a tumor of uncertain differentiation and described as being of unknown lineage.\textsuperscript{40}

**Behavior** Epithelioid sarcoma recurs persistently, often with successive lesions appearing more proximally, and eventually metastasizes. Of Enzinger’s original cases, 87\% recurred (increasing to 93\% of those with longer than 5 years follow up), and 30\% metastasized. With a mean follow up period of 7 years, 20\% died of disease. In the large series of Chase and Enzinger, of 202 cases with follow-up 77\% recurred, and 45\% metastasized – predominantly to lungs (51\%), local lymph nodes (34\%), scalp (22\%) (especially in males) and other skin areas, bone, brain, liver and pleura. Adverse prognostic factors include proximal location (71\% metastasized vs. 38\% of distal cases), amount of necrosis and vascular invasion, and inadequate excision. Favorable factors are young age at first diagnosis, female sex (78\%-80\% survival rate vs. 40\%-64\% for males), and small size (<2cm). Spillane et al\textsuperscript{42} found a five year survival of 70\% and a 10 year survival of 42\%, in a series with a metastatic rate of 40\%. Because of the relatively indolent behavior, the incidence of late recurrence, and the continuing death rate, long term follow up is indicated.\textsuperscript{5}

Proximal epithelioid sarcoma is an aggressive neoplasm. In the series of Guillou et al,\textsuperscript{9} six of 14 patients with up to 8 years follow up developed metastases, and five died of tumor. However, six patients were alive and well at last follow up including one with local recurrence at 2 months who was disease free at 8 years. In a second series of 20 cases, 65\% developed local recurrence and 75\% metastases, with 65\% dead of disease.\textsuperscript{10}

**Differential diagnosis** Epithelioid sarcoma has a wide range of appearances and immunophenotype and, as noted in the title of Enzinger’s original paper, it can resemble a number of non-neoplastic lesions as well as benign and malignant neoplasms. Among the most common benign diagnoses suggested by pathologists referring cases to the AFIP were fibrous histiocytoma, nodular fasciitis and other reactive proliferations, fibromatosis and giant cell tumor of tendon sheath.\textsuperscript{5} Apart from their discriminating morphologic features, all of these, however, lack cytokeratin and EMA. The bland cytology of epithelioid sarcoma can lead to misinterpretation as granuloma annulare or other necrotizing granuloma.\textsuperscript{43} The presence of mitotic activity, however, should raise the index of suspicion and epithelial marker positivity indicates the correct diagnosis.

Carcinomas, both primary (including those of adnexal origin) and metastatic, can have a similar presentation. Immunohistochemistry can be helpful in diagnosis since CK5/6 \textsuperscript{18, 44} and p63 \textsuperscript{18} are more commonly expressed in carcinomas than in epithelioid sarcoma. Furthermore, carcinomas are nearly always CD34 negative,\textsuperscript{45} and this marker, though only expressed in about half of the cases, is particularly useful for the deep-seated
proximal variant of ES which can be misdiagnosed as metastatic carcinoma of unknown primary site. Melanoma with rhabdoid features can acquire cytokeratin and even desmin expression. The diagnosis is even more confusing since such melanomas can lack S100 protein and HMB45. Thus, it might not be possible to distinguish S100 protein negative rhabdoid melanoma from proximal epithelioid sarcoma, especially as some of the latter have been reported to be HMB45 positive. Clear cell sarcoma can rarely express cytokeratin but is almost always positive for S100 protein and HMB45.

Rhabdomyosarcoma is readily excluded by immunohistochemistry showing positive epithelial markers and absence of desmin, myogenin and MyoD1 as well as by the clinical picture. Synovial sarcoma can have plump epithelioid and even rhabdoid cells on occasion. However, it is rarely located superficially and when biphasic has discrete spindle and epithelial components. The immunoprofile of the two tumors can overlap but synovial sarcoma is often S100 protein-positive and only very rarely CD34 positive. Finally, the specific t(x;18) of synovial sarcoma is not found in epithelioid sarcomas.

Epithelioid vascular tumors can resemble epithelioid sarcoma, and additionally some express cytokeratins. Epithelioid hemangioendothelioma, which can occur in skin and soft tissues and has eosinophilic cells in cords and nests in a fibromyxoid stroma, can resemble the fibroma-like variant of epithelioid sarcoma. Many of the cells, however, have vacuoles (some with a thin septum traversing the vacuole) and in addition to the other markers react for CD31 and FVIIIIRAg. The recently described epithelioid sarcoma-like hemangioendothelioma, which is cytokeratin-positive, differs from epithelioid sarcoma in being positive for CD31 but not CD34, and in its indolent behavior. Distinction of epithelioid sarcoma from epithelioid angiosarcoma is aided by lack of hemorrhage or significant pleomorphism, and of CD31 and FVIIIIRAg.

Many tumors formerly diagnosed as malignant rhabdoid tumor are now classified as proximal epithelioid sarcoma. Malignant rhabdoid tumor, composed predominantly of rhabdoid cells, occurs principally in infancy or childhood, and was recognized first in the kidney and central nervous system, and later also in various soft tissue sites. Extrarenal malignant rhabdoid tumor, however, is more difficult to define because rhabdoid cells are found in varying proportions in a number of other, more specific tumor types. These include epithelioid sarcoma, melanoma, rhabdomyosarcoma and carcinoma, and some examples of poorly differentiated synovial sarcoma, extraskeletal myxoid chondrosarcoma, desmoplastic small round cell tumor, peripheral primitive neuroectodermal tumor, epithelioid malignant peripheral nerve sheath tumor, mesothelioma, and endometrial stromal sarcoma. It seems, therefore, that many if not most examples of MRT can be classified as other tumors and that, like malignant fibrous histiocytoma and hemangiopericytoma, it is predominantly a pattern and only rarely an entity which is essentially a diagnosis of exclusion.

Conclusion Enzinger’s original descriptions represent the definitive accounts of epithelioid sarcoma, encompassing its clinical, morphologic and behavioral features. 35 years after Enzinger’s first report, epithelioid sarcoma, a mesenchymal tumor with coexistent epithelial differentiation, is still of uncertain nature (i.e. without a normal counterpart cell), and without a conclusive genetic basis. It remains, however, a distinct entity with characteristic appearances, ultrastructure and immunophenotype.
References
Lipomatous tumors - how we have reached our present views, which controversies remain and why we still face diagnostic problems

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Lipomatous tumors are one of the most complex areas of soft tissue pathology. The different subtypes vary greatly with regard to incidence, clinical presentation, morphologic appearance, and behavior. Hence, this tumor group includes some of the most common human neoplasms as well as exotic rarities, minute superficial lesions indistinguishable from normal fat to deep-seated masses - among the largest ever seen, without any resemblance to normal or embryonal fat.

To a large extent, Dr. Franz Enzinger’s work in this area of soft tissue pathology over the last four decades has shaped our present classification and concepts of fatty tumors (as in so many other areas of soft tissue pathology). In addition to clearly defining the different main subtypes of liposarcoma and their morphologic spectrum, he has identified several previously unknown entities that in the past caused frequent overdiagnosis of malignancy.

This brief overview does not attempt to summarize all current views on lipomatous tumors, but rather highlight some of Dr. Enzinger’s important contributions, what we have learned, and what problems and controversies still remain.

The WHO classification of adipocytic tumors
The current WHO classification (2002) includes 12 benign subtypes, one intermediate and 5 main types of malignant lipomatous tumors.

Benign adipocytic tumors
These include the very common lipomas (with a very wide spectrum in terms of site, size, growth characteristics, and clinical significance)(Kindblom et al. 1974), the relatively common angiolipomas, spindle cell lipomas and pleomorphic lipomas, as well as the rare lipomatosis, myolipomas, chondroid lipomas, extra-renal angiomyolipomas, extra-adrenal myelolipomas and hibernomas.

Of particular diagnostic importance has been the recognition of spindle cell and pleomorphic lipoma and chondroid lipoma, since they have frequently in the past been misdiagnosed as liposarcoma or other sarcoma types. In addition, Dr. Enzinger and coworkers have also described abdominal myolipoma, lipofibromatosis occurring in the pediatric age group and the largest and best defined series of childhood liposarcomas (Shmookler and Enzinger, 1983),
lipoblastomatosis (Chung and Enzinger, 1973) and fibrolipomatous hamartoma of nerve (lipomatosis of nerve) (Silverman and Enzinger, 1985).

**Spindle cell lipoma and pleomorphic lipoma**

These were first defined by Enzinger and Harvey in 1975 and by Shmookler and Enzinger in 1981, respectively and are today recognized as some of the most common pseudosarcomas. Because of their overlapping morphologic features, the occurrence of hybrid forms and the very similar clinical presentation in terms of age, gender, and site distribution (typically middle-aged and elderly men, in the subcutis of neck, shoulders, and back), they are currently viewed as representing different ends of a continuous spectrum. Even for experienced soft tissue tumor pathologists, these tumors sometimes continue to cause problems, particularly the entirely myxoid variants and the very cellular, fascicular variants of spindle cell lipoma that may virtually lack any lipomatous component (Angervall, Kindblom, Dahl, 1976; Fletcher, 1987). Difficulties also arise with pleomorphic lipomas that in addition to the characteristic floret-like giant cells may contain multivacuolated lipoblasts. Another problem is those the tumors that don’t follow the book and occur at unusual, even deep-seated, sites. Both sporadic and familial cases of multicentric spindle cell lipomas have been reported (Fanburg-Smith, Devaney, Miettinen et al, 1998).

In 1993, Meis and Enzinger described and defined **chondroid lipoma** as a unique, benign lipomatous tumor simulating myxoid/round cell liposarcoma or extraskeletal myxoid chondrosarcoma. These rare tumors can occur both superficially and deep and tend to involve extremities and limb girdles. They may reach considerable size, adding to the risk of misdiagnosing them as sarcomas. There is a predilection for adult women but pediatric cases also occur. Subsequent ultrastructural and immunohistochemical studies have shown that chondroid lipomas are truly biphenotypic with both lipoblastic differentiation and features of primitive cartilage (Kindblom, Meis-Kindblom, 1995).

**Myolipoma**, first described by Meis and Enzinger in 1991, is a rare lesion predominantly seen in women and mostly in deep soft tissues, particularly within the abdomen and retroperitoneum, but occasionally also occurring more superficially in the abdominal wall and groins. This entirely benign lesion, composed of a usually dominating bland smooth muscle component intermingled with mature looking fat, should not be mistaken for angiomylipoma, dedifferentiated liposarcoma with a smooth muscle component or the so called lipoleiomyosarcoma (Folpe and Weiss, 2002).

**Lipofibromatosis** has been suggested as a unifying term for a group of lesions predominantly occurring in the hands and feet of pediatric patients (Fetsch, Miettinen, Laskin, Michal and Enzinger, 2000). These lesions, composed of adipose tissue and spindled fibroblastic elements, involving fibrous septae in fat and skeletal muscle, had previously been classified as various types of infantile or juvenile fibromatosis, fibrous hamartoma of infancy or fibrosing variants of lipoblastoma. Recurrent or persistent tumor was seen in almost three-fourths of patients.

**Intermediate and malignant adipocytic tumors**

Traditionally, **liposarcoma** is defined as a malignant mesenchymal neoplasm exhibiting features of adipocytic differentiation usually in the form of tumor cells resembling embryonal
fat cells, so called lipoblasts (complications of this diagnostic approach are outlined below). However, the diversity and complexity of this group of sarcomas, being one of the most common among soft tissue sarcomas, is such that the term liposarcoma becomes meaningless unless qualified by subtype and indication of their malignant potential. In the early literature (starting with Virchow in 1857), the terminology for various subtypes is quite confusing (for a review see Kindblom et al., 1975). In the classical work of Enzinger and Winslow (1962), they state that “among mesenchymal tumors, liposarcomas are probably unsurpassed by their wide range in structure and behavior” and that they should rather be regarded as a group of related neoplasms than a well defined entity. Their proposed classification of liposarcomas into the subtypes of well-differentiated liposarcoma, myxoid and round cell liposarcoma and pleomorphic liposarcoma was shown to be of great prognostic significance and is largely unchanged in the current WHO classification. So-called dedifferentiated liposarcoma, now added to the classification, is a variant of well-differentiated liposarcoma with progression to a usually high grade, non-lipogenic sarcoma.

Atypical lipoma, atypical lipomatous tumor and well-differentiated liposarcoma are all terms that have been used for the most well-differentiated liposarcomas without progression (“dedifferentiation”) that never metastasize. In the current WHO classification, these tumors have been grouped under the “intermediate malignancy” label. The terms atypical lipoma and atypical lipomatous tumor were originally introduced to emphasize their almost invariably non-aggressive behavior, as long as they occurred outside the abdomen/retroperitoneum (Evans, Soule, Winkelman, 1979; Kindblom, Angervall, Fassina, 1982; Evans, 1988 ). The striking tendency for tumors in the abdomen/retroperitoneum and groin areas to recur and not infrequently progress to higher grade sarcomas that eventually lead to the patient’s death has motivated most soft tissue pathologists to retain the term well-differentiated liposarcoma (Weiss, Rao,1992; Lucas, Nascimento, Sanjay, Rock,1994). Also the deep-seated extremity tumors may, less frequently, show repeated recurrences and occasionally dedifferentiation. It has therefore been suggested to use the term atypical lipomatous tumor only for the superficial, subcutaneous lesions. Regardless of terminology, pathologists need to convey to the clinicians the current knowledge of the lesion’s behavior. Whether the dramatic difference in prognosis between the superficial atypical lipomatous tumors and the retroperitoneal tumors with an identical morphology is only a time-dependent phenomenon or indicate some true biologic differences remains unclear.

Four main subtypes of atypical lipomatous tumor/well-differentiated liposarcoma are recognized in the current WHO classification: the common lipoma-like and sclerosing subtypes that frequently are mixed and the much rarer inflammatory (Argani, Facchetti, Inghirami, Rosai, 1997; Kraus, Guillou, Fletcher, 1997) and spindle cell variants (Dei Tos, Mentzel, Newman, Fletcher,1994). Interestingly, the textbook of Enzinger and Weiss illustrates spindle cell liposarcoma (seemingly indistinguishable from those illustrated by Dei Tos et al.). as part of the spectrum of myxoid liposarcoma. Whether spindle cell liposarcoma truly represents a distinct subgroup or only a pattern occurring in different types of liposarcoma remains somewhat unclear. We have also seen such low grade spindle cell liposarcoma areas as part of pleomorphic liposarcoma as well as low grade areas of dedifferentiated liposarcoma with sometimes gradual transition to high grade fibrosarcomatous areas. Well-differentiated liposarcoma within the retroperitoneum and deep soft tissues of the extremity may contain areas indistinguishable from spindle cell and pleomorphic lipoma (Kindblom et al. 1975).
Dedifferentiated liposarcoma (DDLS) was originally defined as a well-differentiated liposarcoma juxtaposed to a high grade non-lipogenic sarcoma component (Evans, 1979). Such tumors had earlier been described in descriptive terms as well-differentiated liposarcomas mixed with various types of high grade sarcoma patterns (Enzinger & Winslow, 1962; Kindblom et al.1975). DDLS are by far most commonly seen in the retroperitoneum, followed by deep soft tissues of the extremities, trunk, and head and neck areas; they are virtually never seen in the subcutis (Weiss & Rao,1992, Henricks et al.1997). In most cases, the high-grade areas are recognized from the onset; in some cases, however, they are seen in recurrences. Many times the high-grade areas dominate and the well-differentiated lipoma-like areas can only be found after careful search (generous sampling is therefore important!). When diagnosing abdominal/retroperitoneal tumors in needle biopsies, close review of imaging studies are essential in order to detect the composite nature of DDLS (Kransdorf, Meis, Jelinek,1993). The high-grade components can display a wide range of appearances; MFH, myxofibrosarcoma and fibrosarcoma-like features are the most common; both leiomyosarcomatous and rhabdomyosarcomatous differentiation can be seen as well as hemangiopericytoma-like areas and cartilage and osteoid/bone matrix producing tumor components. A peculiar morphologic variant is the neural-like or meningothelial-like whirling pattern that can be seen associated with metaplastic bone formation (Fanburg-Smith et al. 1999; Nascimento et al. 1998). In rare instances the dedifferentiated component has had features of so called inflammatory MFH; such cases have presented with a leukemoid blood reaction (Hisaoka et al. 1997).

More recently the concept of DDLS has widened since it has been recognized that the dedifferentiated component may be of lower grade, resembling fibromatosis and low-grade fibrosarcoma (Elgar et al. 1997, Hendricks et al. 1997). It is not always obvious where to draw the line between low grade variants of DDLS and well-differentiated liposarcomas with focal progression to somewhat higher grade spindle type liposarcomas.

The outcome of DDLS depends largely on tumor site; the most common retroperitoneal tumors tend to recur repeatedly and patients often succumb to local complications. Extra-abdominal and retroperitoneal metastases are surprisingly rare for such high-grade sarcomas, suggesting a divergent biology (McCormick et al. 1994). It has been argued, however, that the low metastatic rate in dedifferentiated liposarcoma may be partially time related since many patients die relatively early in the course of disease of local complications (Henricks et al., 1997). Patients with DDLS in the extremity have a significantly better survival.

The myxoid/round cell liposarcoma (MRCLS) group is the most common subtype and represents close to half of all liposarcomas. As pointed our already in Enzinger’s and Winslow’s original work, the purely myxoid and solid round cell patterns represent different ends of a continuous spectrum. The similar clinical characteristics, the frequent occurrence of intermediate and hybrid forms and more lately the unique karyotypic and molecular genetic findings indicate that these tumors all belong to the same family (see below). The vast majority of these tumors have features of classical myxoid liposarcoma or mixed/intermediate myxoid-round cell liposarcoma, while the purely round cell type is extremely rare.

In very rare instances MRCLS may have cartilage, osseous and leiomyomatous and exceptionally even rhabdomyoblastic differentiation. A few MRCLS have also been reported
to contain dedifferentiated areas similar to that seen in well-differentiated liposarcoma (Mentzel et al. 1997).

A puzzling phenomenon, described and discussed in detail already in Enzinger’s and Winslow’s original work, is the so called multicentric MRCLS. In this condition, numerous tumors occur in various soft tissue sites and at other locations rarely affected by metastases. We have seen such patients develop up to 31 tumors over a 10 year period. Molecular genetic confirmation of monoclonality of such tumors in a single patient has confirmed that this indeed is an unusual presentation of metastatic disease (Antonescu et al., 2000).

There is extensive literature testifying to the adverse prognostic impact of increasing cellularity and occurrence of a round cell component in these tumors. Enzinger and Winslow (1962) reported a 5-year survival of 77% for the purely myxoid subtype as opposed to 18% for the mixed myxoid-round cell and purely round cell types. We (Kindblom et al. 1975) found 5-year survivals for purely myxoid, mixed myxoid/round cell and purely round cell liposarcomas to be 80%, 40% and 15%, respectively. Many have subsequently attempted to refine the prognostication of these tumors by introducing different criteria for where to draw the line between cellular myxoid liposarcoma and round cell liposarcoma; in particular a number of different percentage cut off points for the round cell component have been suggested. A drastically worse prognosis has been seen in tumors with round cell components ranging from 5 to 25% (Kilpatrick et al., 1996; Smith et al. 1996; Antonescu et al., 2001). A disadvantage of simply applying a percentage approach is of course that this does not take into account the size factor that is probably of great importance, as in most high grade sarcomas.

**Pleomorphic liposarcoma** is the rarest subtype and constitutes probably less than 10% of all liposarcomas. These typically deep-seated sarcomas occur predominantly in the extremities, more rarely in the trunk and retroperitoneum, and involve mostly the elderly. Histologically, a number of patterns have been reported including the most common MFH-like, the lipoblastic type with numerous smaller and gigantic, multinucleated, bizarre lipoblasts, the epitheloid type, and the myxofibrosarcoma-like types (Enzinger & Winslow, 1962; Kindblom et al.1975; Downes et al. 2001; Miettinen & Enzinger, 1999; Hornick et al. 2004). We have also seen an unusual small cell variant that may resemble round cell liposarcoma, but that is clearly distinguished from it by the cytogenetic findings (Meis-Kindblom et al, 2001). Pleomorphic liposarcoma has an aggressive behavior with 5-year disease free survival figures ranging from 40 to virtually 0%.

**What have we learned from adjunctive techniques?**

Over the years and depending on the popularity and availability of different techniques, lipomatous tumors have been extensively studied with histochemistry (in particular to identify fat content and to characterize the nature of the myxoid matrix), electron-microscopy (for example, to show similarities with normal embryonal adipogenesis and documenting complex lines of differentiation) and immunohistochemistry (purportedly showing the usefulness of S-100 protein and CD34 as markers). Overall, however, such techniques play little role in the everyday diagnosis of lipomatous tumors; traditional evaluation of histology combined with careful clinical correlation remains the basis for most diagnoses. The details of such adjunctive studies are not in the scope of this short summary.
In contrast, the more recent cytogenetic and molecular genetic studies of lipomatous tumors have been remarkably successful in giving new insight into the biologic relationship between different morphologic variants, have helped to support the correctness of morphologic classifications and have, in some instances, revealed pathogenetic mechanisms. Cytogenetic techniques have become useful diagnostic tools. An example is the t(12;16)(q13;p11) causing the FUS/CHOP fusion that is highly sensitive and specific for MRCLS. Some of the more important and confirmed genetic findings in this tumor group are summarized in the following table:

**Summary of karyotypic and molecular genetic characteristics of lipomatous tumors**

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>KARYOTYPE</th>
<th>MOLECULAR GENETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoma</td>
<td>Ab.12q13-15</td>
<td>HMGIC involvement</td>
</tr>
<tr>
<td></td>
<td>t(3;12)(q27-28;q13-15)</td>
<td>HMGIC/LPP fusion transcript</td>
</tr>
<tr>
<td></td>
<td>Ab.6p21-23</td>
<td>HMGIY transcript activation</td>
</tr>
<tr>
<td></td>
<td>13qdel</td>
<td></td>
</tr>
<tr>
<td>Lipoblastoma</td>
<td>Ab. 8q11-13</td>
<td>HAS2/PLAG1 and COL1A2/PLAG1 fusion transcript</td>
</tr>
<tr>
<td>Chondroid lipoma</td>
<td>t(11;16)(q13;p12-13)</td>
<td></td>
</tr>
<tr>
<td>Spindle cell/pleomorphic lipoma</td>
<td>Hypodiploid, loss or del. of chr.13 and/or 16</td>
<td></td>
</tr>
<tr>
<td>Hibernoma</td>
<td>Near-pseudodiploid, Ab.11q13-21</td>
<td>Homozygous del. MEN1 and PPP1A?</td>
</tr>
<tr>
<td>Atypical lipoma/ well-differentiated liposarcoma</td>
<td>Ring and giant marker chromosomes (chr.)</td>
<td>12q14-15 ampl., incl. MDM2, SAS, CDK4, CMGIC</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>Ring and giant marker chr.</td>
<td>12q13-21 ampl. MDM2 ampl. in retroperitoneal/TP53 mutations in non-retroperitoneal</td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;16)(q13;q12)</td>
<td>FUS/CHOP fusion transcript</td>
</tr>
<tr>
<td></td>
<td>t(12;22)(q13;q12)</td>
<td>EWS/CHOP fusion transcript</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>Complex, polyploidy, ring and marker chr.</td>
<td>TP53 mutations or MDM2 ampl.</td>
</tr>
</tbody>
</table>

For extensive references regarding this table, please see “Pathology and Genetics: Tumours of Soft Tissue and Bone”, WHO Organization Classification of Tumours (eds. C.D.M. Fletcher, K.K. Unni and F. Mertens), 2002.
Why do we still face diagnostic problems?

The reasons for continuous diagnostic problems are many - the rarity and complexity of some of these lesions, the occurrence of lesions that do not fit well into our present ideas of tumor classification, the sometimes unpleasant feeling of being at the mercy of a surgeon that has taken a potentially non-representative biopsy, etc., etc. From our experience of consultation cases the main reasons seems to be:

1). The beliefs that a diagnosis of liposarcoma requires the demonstration of lipoblasts and that the presence of lipoblasts is synonymous with the diagnosis of liposarcoma. True lipoblasts (not lipoblast-like cells or pseudolipoblasts!) are seen in a number of benign lesions such as spindle cell/pleomorphic lipoma, chondroid lipoma and, of course, lipoblastoma. Conversely, lipoblasts may be totally absent in well-differentiated liposarcomas, some myxoid liposarcomas and occasionally very primitive round cell liposarcomas (the true nature of which may be revealed by cytogenetic analysis). At times the MFH-like pleomorphic liposarcomas contain only occasional bizarre lipoblasts found after painstaking sampling, this suggests that they are underdiagnosed.

2). Lipoblast-like cells can occur in a number of neoplasms and reactive conditions. Particularly common are juicy looking areas with vacuolated macrophages in fat necrosis that may be seen in lipomas, reactions around ruptured silicone implants and other injected compounds. Severely atrophic fat may have a worrisome appearance as may fat invaded by various neoplasms. Mucin-containing cells in carcinomas and tumor cells of myxofibrosarcoma and acral myxoinflammatory fibroblastic sarcoma may very closely simulate lipoblasts. Fixation artifacts may lead to a morphology resembling lipoblasts. A number of these examples have been illustrated in detail in the latest version of the Enzinger and Weiss’s Soft Tissue Tumor book.

3). Interpreting biopsies from lipomatous tumors, particularly needle biopsies, is treacherous if not done in close conjunction with all pertinent clinical information, including imaging studies. Always think twice before making a liposarcoma diagnosis in children as well as superficial lesions, but remember that pediatric liposarcomas (almost exclusively MRCLS) do occur as do superficial liposarcomas. Another good rule is to think twice before making a benign lipoma diagnosis in large fatty tumors of the retroperitoneum, groin and funicle and paratesticular areas.

4). Liposarcoma can be seen as part of the spectrum of heterologous components of carcinosarcoma and malignant mixed Mullerian tumors.

Conclusion

The lipomatous tumors constitute an unusually variegated and complex mosaic. A great deal of progress of vast clinical importance over the last four decades has been made recognizing patterns in this virtual maze of tumors. Dr. Franz Enzinger has, through his sharp eyes, analytical and scientific mind, and didactic skills played the key role in this development. The recent genetic discoveries in this field have confirmed morphologically-based theories and added new insight into pathogenetic mechanisms.
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Introduction

It is an honor and pleasure to present at this symposium in the presence of Dr. Franz Enzinger and his family members Inge and Peter, who have all had a great positive impact on our department. First, I would like to share a few words on my personal experience working with Dr. Enzinger in the 1990s and my exposure to Dr. Enzinger’s legend at the Armed Forces Institute of Pathology (AFIP).

Dr. Enzinger has truly had a remarkable career. He created the foundation on which soft tissue pathologists currently build. Dr. Enzinger’s recorded diagnoses and comments on hundreds of thousands of cases at AFIP continue to educate staff and visiting pathologists in our department.

This lecture will discuss seminal observations made by Dr. Enzinger on three “fibrohistiocytic” tumors of intermediate or borderline malignant potential. It will also highlight additional observations on these tumors, which could not have been made without the forethought of our great mentor.

Category of “Intermediate Malignant Potential,” as suggested in 1969 by Dr. Enzinger

Dr. Enzinger was the primary editor of the first soft tissue World Health Organization (WHO) book in 1969, entitled “Histological Typing of Soft Tissue Tumours.” Although he had not yet described angiomatoid “malignant” fibrous histiocytoma (A(M)FH), giant cell fibroblastoma (GCF), or plexiform fibrohistiocytic tumor (PFHT), he had already considered the concept of a fibrous tumor of intermediate malignant potential category. Therefore, dermatofibrosarcoma protuberans (DFSP) was independently described and separated from benign tumors of fibrous tissue and from fibrosarcoma. Even then Dr. Enzinger classified DFSP as we know this tumor today: “A cellular tumor of disputed histiocytic or fibroblastic origin composed of small uniform cells arranged in a cartwheel pattern. It usually forms a protruding nodular or multinodular mass by infiltration of the entire dermis and the subcutaneous fat. The tumor has a tendency to recur locally after simple excision. Cases with metastases have been recorded.”
The category of “fibrohistiocytic tumors of intermediate malignancy” was further developed in the first and second editions of Drs. Enzinger and Weiss’ Soft Tissue Tumors textbooks in 1983 and 1988, respectively. When Dr. Enzinger described PFHT in his seminal paper in 1988, he referred to these tumors as “borderline” and recommended wide excision.

The concept of borderline malignancy was expanded in the 1994 second edition of the soft tissue WHO book, also entitled “Histological Typing of Soft Tissue Tumours,” edited by Dr. Sharon Weiss and nine international colleagues, including Dr. Franz Enzinger. This classification included atypical fibroxanthoma (AFX), DFSP, GCF, PFHT, and AFH (officially omitting the “malignant” from the name). The category of “fibrohistiocytic tumors of intermediate malignancy” in the third edition of Enzinger and Weiss’ Soft Tissue Tumors also included DFSP and Bednar Tumor, GCF, AFH, and PFHT. In the 2002 third and current WHO series edited by Drs. Fletcher and Unni and entitled “Pathology and Genetics: Tumours of Soft Tissue and Bone Pathology,” plexiform fibrohistiocytic tumor and giant cell tumor of soft parts were retained in this category. AFH was also retained as “intermediate” category as a tumor of “uncertain differentiation.”

Today, all three tumors are considered to have “intermediate” malignant behavior. All three, AFH, GCF, and PFHT, are rare but have distinctive clinicopathologic features. Interestingly, all three lesions occur mainly in young patients (although extremes of age have been described for all three lesions); are generally nodular, painless and slow growing; are generally superficial (deep dermis, subcutis and rarely superficial skeletal muscle involvement); and most importantly, while local recurrence can be in up to one half of cases, these tumors have exceedingly rare potential for lymph node or systemic metastases. In fact, GCF, in its pure form, has not been reported to metastasize.

**Angiomatoid “Malignant” Fibrous Histiocytoma**

*Dr. Enzinger defined this entity of “angiomatoid malignant fibrous histiocytoma” in his seminal paper in 1979.* He described 41 cases in the extremities of young patients, ages 5-25 (median 13 years). These lesions were mainly nodular, subcutaneous, painless, and simulated hematoma. He noted patients with associated severe anemia, fever, and weight loss in several cases and occasionally with increased gamma globulins. These grossly circumscribed, multicystic, and hemorrhagic masses measured 0.7-10 cm (median 2.5 cm). Three key microscopic components included: fibrohistiocytic nests with some lipid or hemosiderin; hemorrhagic non-endothelial lined cystlike spaces; and aggregates of chronic inflammatory cells, often with lymphoid follicles. Of 24 cases with follow-up, 20 were alive, 11 with recurrence (two with two recurrences, one with 5 recurrences over 3 years and one with 9 recurrences over 21 years). Two patients had proximal lymph node metastasis at 18 months and one year, respectively. Three patients died of metastatic disease at 12 months, 3 years, and 13 years (the latter after 9 recurrences). Two cases that metastasized showed a greater degree of cellular pleomorphism and necrosis than the other cases.

Additional follow-up observations on A(M)FH resulting in dropping “malignant” from the terminology: In the above seminal paper, Dr. Enzinger already noted the difference between
A(M)FH and other malignant fibrous histiocytomas (MFH) based on younger patient age, distinctive histologic features, and better behavior of A (M) FH. With additional studies on these tumors, we have observed good overall outcome for these patients, resulting in dropping the term “malignant” from angiomatoid fibrous histiocytoma in the 1994 WHO classification. These tumors have better behavior than previously recognized, especially with complete excision of the original tumor and involved regional lymph node. Regional and proximal draining lymph nodes may be affected, like a field effect, however, in most patients, when these lymph nodes are removed the patient does well.

Costa and Weiss (series of 108 cases, 94 with follow up, 1990) had 12% recurrence and 4 patients with regional metastasis who did well and only 1 patient with distant metastasis and death. Pettinato also had one patient who developed regional lymph node metastases and eventually died of disease (series of 20 cases, 9 with follow-up, 1990). Fletcher (series of 6 cases, 1991) only reported one patient with local recurrence, metastasis, and death from tumor. Since the change in classification, additional studies continue to support good overall outcome for these patients. Excluding 31 cases from the AFIP files from 1979 to 1995 due to lack of material or criteria for A(M)FH, Fanburg-Smith and Miettinen (154 cases, 86 with follow-up, 1999) demonstrated only 1% metastasis to a local lymph node. Frequent and recent updates show that the patient is currently doing well. Wide excision in absence of adjuvant therapy is the primary management for A(M)FH.

Additional clinical findings in A(M)FH: These additional reports of A(M)FH also demonstrated that extremes of age may be involved (congenital and elderly) (Argenyi 1988, Costa 1990, Fanburg-Smith 1999). Head and neck location may have higher recurrence potential due to inability to completely excise the lesion (Costa 1990). Sixty-six percent of cases appear to occur in regions of normal lymphoid tissue such as neck, antecubital fossa, axilla, etc… (Fanburg-Smith 1999). Occasional cases are preceded by trauma (Fanburg-Smith 1999).

Additional morphologic findings in A(M)FH: Dr. Enzinger and others later reported round as well as spindled features of the fibrohistiocytic cells. This finding of round cell or epithelioid morphology was found in approximately one half of cases. Many were, interestingly, positive for CD99, which should not be confused with PNET/Ewing Sarcoma. No distinctive morphologic features can predict outcome. Depth and infiltrative growth pattern were related to increased recurrence (Costa 1990).

With the advent of additional antibodies for immunohistochemistry, particularly desmin, it was observed that approximately one half of A(M)FH cases are positive for this marker, supporting a myoid phenotype (Fletcher 1990, Smith 1991, Fanburg-Smith 1999). Importantly, A(M)FH are negative for myoD1 and myf4 refuting skeletal muscle phenotype. Additional immunohistochemistry performed in A(M)FH showed that several other non-specific markers, such as CD99, CD68, EMA, synaptophysin, NSE, and Leu-7 (Hasagawa et al. 2000) may be positive but do not indicate specific phenotype. Finally, all melanocytic markers are negative in these tumors.

The recent molecular data of A(M)FH are quite exciting: Two cases originally demonstrated t(12;16)(q13;p11) translocation, leading to a fusion product FUS-ATF1 gene (Waters 2000,
Raddaoui et al 2002). FUS is the N-terminus of myxoid liposarcoma and ATF1 is the DNA-binding domain of clear cell sarcoma. However, more recently, a t(12;22) translocation, specific for clear cell sarcoma, and its fusion product EWSR1-ATF1, was detected in A(M)FH. While the latter is specific for clear cell sarcoma, we know that A(M)FH is clinically, morphologically and immunophenotypically (melanoma marker negative) distinctive from clear cell sarcoma (aka malignant melanoma of soft parts).

The differential diagnosis of A(M)FH includes “aneurysmal” FH (Calonje 1995), mostly because of confusing terminology, PNET with epithelioid cases, true intra-nodal tumors, vascular neoplasms, and other desmin-positive tumors such as rhabdomyosarcoma. Careful attention to morphologic features including pseudocapsule, lymphoid response, angiectoid spaces often filled with blood, and fibrohistiocytic spindled or epithelioid proliferation, as well as desmin reactivity in one half of cases, can help separate these subcutaneous A(M)FH from other tumors.

Proposal of a possible relationship of A(M)FH with fibroblastic reticulum cell tumors: Reticulum cells are nonlymphoid nonvascular cells of lymphoid tissue. Lennert (1978) originally described four types of reticulum cell sarcomas pertaining to the four types of reticulum cells in lymphoid tissue: dendritic, interdigitating, histiocytic, and fibroblastic. Fibroblastic reticulum cells are elongated and often branched and are composed of stromal supporting elements that provide structure and function along parafollicular and deep cortical areas of lymph nodes as well as around vessels. They interact with lymphocytes in vitro and induce B cell adhesion and proliferation (Lisignoli 1996). They can be positive for vimentin, cytokeratins 8 and 18, and desmin. Fibroblastic reticulum cell sarcoma is a stromal myoid tumor that has an intimate association with lymphoid tissue; it can be desmin and actins positive and has good outcome.

Based on the findings that 66% of A(M)FH seem to occur in regions of normal lymph nodes, that desmin positive cells resembling tumor cells are found in the lymphoid proliferations surrounding the tumor cells, that Dr. Enzinger and others since have observed the marked lymphoid response of A(M)FH, and that cytokine production by tumor causes B-symptoms, which resolves after removal of the tumor, a proposed relationship between A(M)FH and fibroblastic reticulum cell tumors has been made (Fanburg-Smith 1999). Dr Enzinger’s original paper and others have also cited patients with paraneoplastic findings of severe anemia, fever, and hypergammaglobulinemia, as well as polyarteritis nodosa and Castlemanlike changes (Enzinger 1979, Seo et al1986, Fletcher 1991, Costa et al1990, Hothi et al 2004), the latter which often occur in tumors of lymphoreticular system (Seo 1986). The fact that A(M)FH spreads to regional lymph nodes seems to support a lymphotrophism of these tumors. It is possible that some of these patients have lymphocytic response to trauma and develop myoid tumors from the myoid cells in lymphoid tissue.

Therefore, A(M)FH is still exactly clinically and morphologically as Dr. Enzinger originally described it. In addition, we now best classify this as a tumor of borderline or intermediate malignant potential. One half of cases are desmin positive and findings suggest a possible relationship with fibroblastic reticulum cell sarcoma, a low grade myxoid tumor of lymph node. Newer molecular data suggest similar findings to clear cell sarcoma, despite very different clinicopathologic features from the entity of A(M)FH.
**Plexiform Fibrohistiocytic Tumor (PFHT)**

*Dr. Enzinger’s seminal 1988 paper* defined plexiform fibrohistiocytic tumor (PFHT) as a distinctive entity. This paper was coauthored by Dr. Renyuan Zhang and covered tumors from the AFIP from 1965 to 1985. The authors described 65 PFHT cases in the dermis and subcutis of children and young adults (median 14.5 years, 2/3 younger than 20 years, but age range 2 months to 71 years). There was a female predominance. These were slow growing, painless, and relatively small tumors. The most common site is the upper extremity (particularly shoulder and forearm), followed by the lower extremities, trunk and rarely head and neck. These tumors are comprised of a plexiform proliferation of histiocytoid mononuclear and osteoclast type giant cells, admixed with a spindled, infiltrative background of fibroblast-like cells. Twenty-eight cases were predominantly histiocytic and 11 others predominantly fibroblastic; 26 cases demonstrated mixed areas. Two predominantly fibroblastic PFHT had metaplastic bone formation. Absence of cellular pleomorphism and low mitotic activity were noted. Dense hyalinization was described. Hemorrhage and chronic inflammation were common. Tumors were negative for S100 protein, desmin, cytokeratin, Factor VIII rAg, and lysozyme. Vascular invasion was present in one recurrent, yet non-metastatic, case. Sixty-two and one half percent (20) patients were alive and without disease up to 60 years after excision. Thirty-seven and one half percent (i.e. 32 cases) with follow-up recurred and two of those patients had regional lymph node metastasis at 9 and 36 months, respectively. One of these patients was well at 10 months after lymph node excision. There were no systemic metastases.

Additional studies demonstrate *clinically* that congenital PFHT cases have also been identified (one from a series of 14 PFHT cases, Hollowood 1991; one from a series of three cases, Leclerc 2005). Subsequent *follow-up* data demonstrate systemic metastasis for PFHT (Remstein 1999, Salomao 1997). Remstein et al (1999) in a series of 22 PFHT cases report 19% (3) cases with pulmonary metastases to subpleural and peribronchial locations. One patient from the Remstein series who died of metastatic disease may be from Dr. Enzinger’s original series (and was also reported by Salomao 1997), as her material was seen in consultation by Dr. Enzinger early in the course of her disease. Nonetheless, another of these three patients was free of disease 18 years after thoracotomy and chemotherapy. A fourth patient had an unbiopsied pulmonary nodule. Remstein also reports a case of lymph node metastasis without further complications and a patient with regional metastasis who was also one of the systemic metastasis patients. Hollowood et al report a similar 40% recurrence rate to Dr. Enzinger’s original study; none in the Hollowood et al. study metastasized to either regional or systemic locations. Most importantly, the majority of PFHT patients do well, with 88% in the Remstein series without any further disease after complete excision of the primary lesion. Treatment for PFHT should be wide excision. Recently, Mohs micrographic surgery has been successfully used for PFHT (Rahimi 2001).

*Morphologically*, occasional PFHT cases with cellular atypia, pleomorphism, and even atypical mitoses may be observed (Remstein 1999, Fisher 1997). Osteoclast type giant cells are generally present, but PFHT have been reported with absence of giant cells (Chen 2004, Fisher 1997,
In addition to hyalinization, myxoid change occasionally occurs (Hollowood 1991).

Additional immunohistochemical observations reveal that PFHT is positive for CD68 in mononuclear histiocytoid and multinucleated giant cells (Hollowood 1991, Remstein 1999). SMA is often positive in fibroblasts (Hollowood 1991, Giard 1991, Remstein 1999). CD34 is generally negative in PFHT but has occasionally been reported as positive in spindled cells (Remstein 1999, Chen 2004).

Cytogenetic data are available in two PFHT cases; however, the reported abnormalities are strikingly different. One case revealed a simple chromosomal translocation whereas the other had complex chromosomal changes (Smith 1990, Redlich 1999). Therefore, no recurring cytogenetic or molecular genetic abnormalities have been reported in PFHT.

Initial personal observations on 66 new cases out of 80 AFIP cases coded as “PFHT” from 1990 to the present were as follows (with Drs C. Moosavi, P. Jha, and J. C. Fanburg-Smith). These were previously unreported PFHT, not included in Dr. Enzinger’s original series. The remaining cases had unavailable material or were better diagnosed as giant cell tumor of soft parts, lipofibromatosis, desmoid, nodular fasciitis, angiomatoid (m) fibrous histiocytoma, or myofibroma. There were 37 males and 29 females. Patient ages ranged from 1 to 77 years (median 20 years, 53% under the age of 20). Twenty-eight cases were in the upper extremity (mostly forearm), 16 in lower extremity, 11 in trunk and 9 in head and neck (2 currently unknown). 22 cases were predominantly dermal, the rest were predominantly subcutaneous with four superficially involving skeletal muscle. Except for 12 predominantly dermal cases, most cases had an infiltrative growth pattern. Thirty-four cases were predominantly histiocytic, 16 cases were predominantly fibroblastic, and the remaining 16 mixed types. Two fibroblastic cases demonstrated the microfat cells (probably secondary to subcutis infiltration) seen in lipofibromatosis. All cases demonstrated a plexiform growth pattern of small to medium sized sometimes whorling nodules. All but 25 cases had giant cells, mainly osteoclast type. The predominantly histiocytic lesions often had giant cells and hemorrhage. The purely fibroblastic often lacked giant cells and had surrounding inflammation. The purely fibroblastic often lacked giant cells and had surrounding inflammation. Perineural growth was observed in five cases, peri-Pacinian corpuscle growth in 2 cases, adnexal trapping in several cases, and, increased hyalinized collagen in 17 cases. Eight cases demonstrated focal myxoid change. Only one case, surprisingly a histiocytic, had bone formation, suggesting the differential diagnosis of giant cell tumor of soft parts. While increased cytologic atypia and mitotic activity were noted in a few cases, an atypical mitosis was only observed in one case. No cases demonstrated lymphatic invasion or necrosis. The tumors were generally positive for CD68, SMA, occasionally for MSA, and negative for keratin, desmin, HMB45, S100 protein, and CD34. Overall, the observations were very similar to Dr. Enzinger’s original observations, with the minor exceptions of an unexplained male predominance (possibly due to timely referral bias), a few examples with myxoid change and increased inflammation, and the finding of two cases with microfat similar to recently described lipofibromatosis.

The differential diagnosis for PFHT depends on which component predominates. When the histiocytic and osteoclast type giant cells predominate, especially when deep, despite a plexiform growth pattern, one would consider a giant cell tumor of soft parts, malignant fibrous
histiocytoma, or even nodular fasciitis in the differential diagnosis. When the fibroblastic component predominates, one might consider fibromatosis or lipofibromatosis. When both are present, one might consider myofibromatosis or fibrous hamartoma of infancy (FHI) or cutaneous (pilar) leiomyoma. Interestingly, some A(M)FH have even been classified incorrectly as PFHT. Sometimes the abundant hemorrhage can be almost Kaposi-like. FH is generally not infiltrative into fat and only rarely plexiform, generally without osteoclast type giant cells. Kaposi would be in dermis without giant cells and would have intracytoplasmic hyaline globules. Giant cell tumor of soft parts has more osteoclast type giant cells and can also be multinodular, but lacks the infiltrative fibroblastic growth pattern of PFHT. Neurofibroma and nevus would be S100 protein positive (the latter also positive for HMB45), lack osteoclast type giant cells and have a different morphologic appearance than PFHT. Fibromatosis is not plexiform and lacks osteoclast type giant cells. Myofibromatosis has smooth muscle and hemangiopericytoid features, both which are absent in PFHT. Despite growth pattern similarities with FHI, the absence of giant cells like PFHT and components of fat and primitive cells in FHI are absent in PFHT. Giant cell rich malignant fibrous histiocytoma would be multinodular but lacks the infiltrative fibroblastic pattern of PFHT, has more atypia and increased mitoses with atypical forms (all which can occasionally be observed in PFHT), but also has necrosis, not a feature of PFHT.

Cellular neurothekeoma seems to be a related or identical lesion to PFHT, particularly when PFHT is deep dermal or superficial subcutaneous. A probable relationship between these two entities, PFHT and cellular neurothekeoma, was first proposed by Requena in 1995, and subsequently suggested by Jaffer, Eusehi and Rosai in a 2000 USCAP abstract (Modern Pathol 2000, p11A, #45) and by Laskin et al (2000).

While Dr. Enzinger was describing PFHT and colleagues were re-examining this lesion in the soft tissue literature, attention was brought to “cellular neurothekeoma” primarily in the dermatopathology literature. It was actually Drs. Enzinger and Weiss who noted in their 1983 Soft Tissue Tumors textbook that some neurothekeomas are very cellular with little myxoid background and a combination of epithelioid and histiocytic cells in this cellular lesion could pose a problem with differentiation from histiocytic skin tumors. In 1986, Rosati et al described three cases of cellular neurothekeoma occurring in young adult females (upper extremity, trunk, and face) with excellent follow-up 2 to 5 years. In retrospect, except for a relative paucity of giant cells, the microphotographs of these cases look identical to PFHT, with one case even involving subcutis, not just dermis.

Like PFHT, cellular neurothekeoma has also been described in very young patients, also has a female predominance (Pasquier1994, Busam 1998, Zelger 1998, Barnhill 1990, Hanraran 2002, Chatelain 2000, Bhatia 2003, Cohen 2004, Page 2004, Pasquier 1994), and is reported in extremity and trunk locations as well as face (Laskin 2000, Barnhill 1990, Hanraran 2002, Akhtar 2004, Fernandez 2000, Cohen 2004, Page 2004). While cellular neurothekeoma is thought to be dermal and PFHT subcutaneous, pure dermal variants of PFHT have been reported (Zelger 1997, Herring 1993) and cellular neurothekeoma may infiltrate subcutis (Rosati 1986). There does appear to be in paucity of osteoclast type giant cells in cellular neurothekeoma compared with PFHT, however, multinucleated and even osteoclast type cells are observed in many cellular neurothekeoma cases (Laskin 2000, Barnhill 1990, Chang 1999, Zelger 1998).
Cellular pleomorphism, mitotic activity, and even vascular invasion have also been identified in cellular neurothekeoma (Busam 1998), similar to PFHT. Likewise, cellular neurothekeoma has also demonstrated SMA and occasionally CD68 reactivity (Chang et al 1999, Jaffer et al. abstract 2000, Page 2004, Hanrahan et al 2002, Chatelain et al 2000, Misago et al 2004). PGP-9.5 and S100A6 are positive in cellular neurothekeoma (Wang et al 1999, Fullen et al 2003). Further studies have revealed Mitf and NK1C3, also known as CD57 (Calonje et al 1992, Zelger et al 1998, Page et al 2004) reactivity in cellular neurothekeoma. Many of these non-specific markers have also been observed in PFHT (personal observations and communications).

The major difference between PFHT and cellular neurothekeoma appears to be the excellent, non-recurrent behavior of cellular neurothekeoma (Busam 1998, Rosati 1986, Chow 1997, Tomasini 1996, Chang 1999, Hanrahan 2002, Akhtar 2004, Misago 2004, Zelger 1998, Calonje 1992), compared with the recurrent and occasionally regional and systemic metastases of PFHT. However, many reported cellular neurothekeomas have short or absence of follow-up data (Busam 1998, Calonje 1992, Tomasini 1996, Zelger 1998, Bhatia 2003). Most PFHT actually do well. Furthermore, it is possible that cases called cellular neurothekeoma that are in the superficial dermis and have a primary head and neck location may have a better prognosis than deeper subcutaneous and even superficial skeletal muscle lesions called PFHT that involve an extremity or truncal locations. Additional follow-up studies and molecular investigation are required to support the observed morphologic and immunophenotypic overlap between PFHT and cellular neurothekeoma.

PFHT is currently classified as the same morphologic and myofibroblastic tumor of low grade malignant or borderline potential as previously described by Dr. Enzinger and colleague in 1988. There are additionally more follow-up data revealing occasional systemic metastasis and some clinical, morphologic and immunophenotypic evidence to support a group of dermal PFHT variants primarily of the head and neck (aka cellular neurothekeoma).

Giant Cell Fibroblastoma (GCF)

Dr. Enzinger’s seminal contributions in 1982: Dr. Enzinger and Dr. Shmookler presented this new entity as an abstract at the International Academy of Pathology in Boston: Giant Cell Fibroblastoma: A Peculiar Childhood Tumor (Shmookler BM, Enzinger FM. Lab Invest 1982; 76A). The abstract was published as a paper in 1989 (see below).

In the original abstract, there were 20 cases, including 17 children. Patient ages ranged from 4 months to 31 years and 85% were less than 10 years old. There was a male predominance and the back and thigh were the most common locations (20% each), followed by the anterior chest, inguinal region, and clavicular area. Tumor sizes were generally small, mean 3.5 cm. They described in the dermis and subcutis parallel fascicles of wavy uniform spindled cells with wiry collagen fibers and densely sclerosed areas with scattered pleomorphic giant cells, the latter also lining gaping and branching sinusoidal structures. Electron microscopy suggested fibroblastic phenotype. All cases had benign behavior but almost half demonstrated local recurrence over a mean of 6.8 years. The caveat for this tumor was mistaking it for a malignant mimicker.
In 1989, Drs. Enzinger, Shmookler, and Weiss published this abstract as 28 cases from AFIP (1960-1981), including four adults up to age 55 years. They proposed a relationship of this childhood tumor to dermatofibrosarcoma protuberans (DFSP) and mentioned observing cases of DFSP with GCF-like areas, not included in this study. Tumor recurrence of GCF was noted in 47% of 19 cases, but metastasis was not observed.

DFSP had been initially recognized in 1890 by Taylor as a sarcoma resembling keloid. It was then called “progressive and recurrent dermatofibromas or skin fibrosarcomas” by Derier and Ferrand in 1924 and bequeathed Derier-Ferrand tumor in 1985 by Hoffmann. Generally (as above in ST WHO book 1969), DFSP has monotonous storiform growth pattern with honeycomb and parallel patterns of infiltration, adnexal sparing, and generally low mitotic activity. DFSP can have melanin pigment (Bednar tumor), myoid areas (Calonje et al. 1996), and even giant cells. It may undergo fibrosarcomatous transformation, generally in the deep aspect of the tumor, often de novo, giving a slightly worse prognosis. Recurrence potential for DFSP is high, but metastatic potential is around 1% (slightly higher if associated with fibrosarcomatous transformation in some series). Initial cytogenetic observations demonstrated supranumery ring chromosomes (Bridge et al 1990, Mandahl et al 1990). In 1993 and 1994, Pedeutour et al showed that these rings contained chromosome 17 sequences. Subsequently, FISH and comparative genomic hybridization techniques confirm t(17;22) translocation in the ring chromosome (Minoletti et al 1995, Pedeutour et al 1995). The same fusion product COLA1A-PDGFRB and giant ring chromosome is found in the fibrosarcomatous portion of DFSP (Kiuuru-Kuhlefelt et al. 2001).

After Dr. Enzinger and colleagues’ description of GCF, there was additional support, including molecular, for a relationship between DFSP and GCF. Cases have been documented in the literature with hybrid features of GCF and DFSP (Shmookler et al 1989, Connelly et al 1992, Beham et al 1990, Goldblum 1996, Harvell et al. 1998, Maeda et al. 1998, Galiner et al 2000). Despite a mainly younger age for GCF, compared with DFSP, both can occur in newborn patients as well as elderly individuals, suggesting that GCF is not merely the “juvenile” version of DFSP but that these tumors remain on a spectrum of the same entity. GCF has recurred as DFSP and vice versa (Shmookler et al. 1989, Alguacil-Garcia 1991, Allen et al. 1992, Coyne et al.1992, Michal et al.1992, Perry et al. 1993, Pitt et al. 1994) Both DFSP and GCF share common clinical features of male predominance, slow growth, painlessness, anatomic location of mainly trunk or old-fashioned bathing suit distribution, and later protuberant nodule formation. They also share several morphologic features of depth of dermis/subcutis rarely superficial skeletal muscle involvement, honeycomb and parallel growth patterns, adnexal sparing, myxoid change, and prominent vasculature, particularly in areas of myxoid change. Both lesions may demonstrate intralesional melanin pigment, so called “Bednar Tumor” (Dupree et al., De Chadarevian et al. 1993, Zamecnik et al.2002) which occurs in 5% of DFSP. GCF has the added feature of the branching sometimes large pseudocystic or pseudovascular areas lined by giant cells and giant cell in the stroma of the solid GCF areas, with absence of true storiform areas without giant cells. DFSP has true storiform growth pattern with absence of giant cells and can have fibrosarcomatous areas. Mitotic activity is uncommonly high in either tumor but seems to be slightly higher in most DFSP areas (4/10 hpf) compared with GCF. Immunohistochemically, both GCF and DFSP are positive for CD34. GCF has some actins reactivity, suggesting CD34-positive (myo)fibroblastic phenotype. Hormonal influence may
have explained growth of GCF in young patients. Hormonal influence has also been suggested as a reason for increased size of DFSP during pregnancy and in gynecomastia by GCF of a 4 year old male (Nebesio et al. 2005) but neither serologies in GCF nor immunohistochemistry for ER in DFSP has been identified, to date. PR, being rather nonspecific, has been found in an occasional case of DFSP.

Cytogenetically, DFSP has either supernumerary ring chromosome or t(17;22) translocation. The latter seems to be more common in adult than childhood tumors. The same t(17;22) translocation has been reported in GCF. Also, COL1A1-PDGFRB gene fusion product of t(17;22) has been documented in both GCF and DFSP tumors (Dal Cin et al. 1997, Craver et al. 1995, Pe deutour et al. 1995, O’Brien 1998, Vanni et al 2000, Maire et al. 2002, Terrier-Lacombe 2003).

Biologic behavior of both tumors is high local recurrence (GCF in approximately half the cases). In addition, DFSP may metastasize in less than 1% if in pure form and commonly there is an increased incidence of metastasis with a FS transformation, but pure GCF has not yet been reported to metastasize and may, as suggested by Michal and colleagues, represent a more well-differentiated form of DFSP. Treatment for both tumors is wide excision. Mohs surgery has been advocated in GCF. Gleevec (ST1571 or Imatinib), a tyrosine kinase receptor type III family inhibitor, has been partially successful in DFSP and (Shimizu et al. 1999, Sjoblom et al. 2001, Rubin et al. 2002) may prove helpful for metastatic, unresectable cases for both DFSP and GCF.

The differential diagnosis of GCF might include myxofibrosarcoma (generally deeper and in older patients), liposarcoma (especially when giant cells occur in areas of honeycomb infiltration of fat (but the remaining portions of the lesion and absence of widened septa and younger age help separate GCF), papillary intralymphatic angioendothelioma (although vascular markers are not positive and other myxoid and cellular areas of GCF help separate it), myofibroma (especially if myoid areas are present, but absence of HP C like helps separate GCF from this entity) and fibrous histiocytoma with giant cells (not having the infiltrative pattern of GCF), but this tumor is rather distinctive.

Initial personal unpublished observations (with Drs. C. Moosavi, P. Jha, J.C. Fanburg-Smith) on 86 new GCF cases at AFIP: These cases were found from 1981 to present. There were potentially 97 cases coded as “GCF”, but 11 cases were excluded due to insufficient material or better diagnosis as pure DFSP or other tumor. There were 60 males and 26 females. Patient ages ranged from 6 months to 62 years (median 6 years, 62% under the age of 10 and 77% under the age of 20 years, and only 10 patients over 40 years). 39 GCF cases were observed to be protuberant and one manifested as superficial ulceration; other cases were not protuberant or did not have enough epidermal tissue to evaluate. Most cases were dermal and subcutaneous tumors, with three purely dermal and five involving superficial skeletal muscle. Almost all cases demonstrated honeycomb, several parallel growth patterns of infiltration and several with adnexal sparing. Pure GCF areas ranged from solid and collagenized to angiectoid and myxoid, the latter with small to large cystlike spaces. Most cases were relatively hypocellular except one case. One case of pure GCF had atypia and high mitotic activity. GCF demonstrated myoid whorls in two cases, a feature also described in DFSP (Calonje 1996). We also observed collections of stromal spindled and epithelioid non-storiform “whorls,” a feature previously
described in DFSP (Llatjos R et al. 2000), in two cases. Most remarkable is that almost every case of GCF has this peculiar perivascular extravasation of lymphocytes in an onion skin pattern, not observed in DFSP. Furthermore, histologic intraläsional hemorrhage seems to be common in GCF, particularly near the fascia, and true vessels can be quite prominent in GCF, making hemorrhage possible at the time of excision.

**Hybrid cases or GCF recurring as DFSP:** 14 cases of our 86 cases demonstrated 1-70% (median 20%) dense non-giant cell storiform areas, interpreted as hybrid GCF-DFSP. Three of these cases demonstrated hypercellular DFSP. One case with 60% DFSP also had 15% fibrosarcomatous transformation. Two cases of pure GCF recurred as a hybrid tumor with DFSP areas, one of these with hypercellular DFSP. In most cases the DFSP was adjacent to GCF with an abrupt transition but was superficial to GCF in one case. Most interestingly, we did observe one case of GCF with fibrosarcomatous transformation without any evidence for DFSP.

Follow-up has not yet been systematically performed on these GCF and GCF-DFSP hybrid tumors, but 11 were submitted to AFIP as recurrent cases. Most cases studied were positive for CD34 (more intense in DFSP than relatively hypocellular GCF areas) and negative for SMA, desmin, HMB45, keratin, and S100 protein.

Therefore, in summary, GCF is exactly clinically and morphologically as Dr. Enzinger and colleagues originally described it. Additional observations of marked perivascular and onionskinlike chronic inflammation and consistent hemorrhage may aid in diagnosis of this previously well-described tumor. Collectively, we now have even more convincing evidence that GCF is related to or on a spectrum with DFSP, including hybrid cases, one GCF with FS, and new molecular findings. Follow-up on additional cases, including GCF with FS or GCF with hypercellular DFSP, will be interesting.

Dr. Enzinger described most entities in soft tissue and without his original observations of fibrohistiocytic tumors of intermediate malignancy, A(M)FH, PFHT, and GCF, newer studies on these tumors would not have been possible.

References

**Angiomatoid “Malignant” Fibrous Histiocytoma**


**Plexiform Fibrohistiocytic Tumor**


Giant Cell Fibroblastoma


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Symposium honoring Dr. Franz M. Enzinger, M.D., Emeritus Chairman of Department of Soft Tissue Pathology of the Armed Forces Institute of Pathology

CONCLUDING REMARKS

Markku Miettinen, AFIP

It is my great privilege to present in this symposium honoring Dr. Franz Enzinger, one if not the only surviving AFIP chairman who served from the 1960’s and on. His nearly 30 year leadership period in the Department of Soft Tissue Pathology of AFIP left great mark not only to the Institute but also to the field of Soft Tissue Pathology and to the way medicine of soft tissue tumors is practiced today.

Careful and systematic observations and cataloging, unique understanding of morphology, synthesizing ability and phenomenal memory were elements involved in the genesis of Dr. Enzinger’s tumor entities. We all know that great many key entities, as discussed in previous presentations of this symposium, were named and described by Dr. Enzinger, some in collaboration in his world-wide student body. These tumors include fibrous hamartoma of infancy, myofibromatosis, clear cell sarcoma, epithelioid sarcoma, extraskeletal Ewing sarcoma, angiomatoid fibrous histiocytoma, fibroma of tendon sheath, ossifying fibromyxoid tumor, among others. His accomplishments have been recognized by a multitude of institutional, national, and international awards and honorary memberships.

Dr. Enzinger has been directly or indirectly involved in the soft tissue pathology careers of virtually all of us, and we are thankful for that. Some of us have been enjoying direct collaboration with him experiencing his unique generosity and collaborative spirit. Certainly, all of us have enjoyed the first definitive text on soft tissue tumors that Dr. Enzinger authored with Sharon Weiss in 1983. I have heard prominent soft tissue pathologist stating that Dr. Enzinger’s book was a specific source of inspiration for seeking into this field. Dr. Enzinger’s role in helping the future chairmen of AFIP’s Department of Soft Tissue Pathology has been remarkable. His farsighted and systematic collection of tissue (not only slides) into the AFIP files has made possible the present day immunohistochemical and molecular studies.

Although Dr. Enzinger formally retired from Federal service in January 1988, he soon was asked to re-join the Department of Soft Tissue Pathology as a consultant and research collaborator. He obliged, serving more than ten years in that capacity. During this time many new entities were described with his kind collaboration. The following pattern was the rule: someone showed Dr. Enzinger one case of a potential new entity, and he found at least 10 if not 50 similar cases from the files, and sometimes already had the entity named, greatly facilitating the birth of that tumor entity – that already must have existed in his mind years before.

In addition to knowing Dr. Enzinger through his scientific contributions, I have been fortunate to personally know Dr. Enzinger for nearly 20 years. During my first visit to the AFIP, he gave a memorable presentation on then groundbreaking technology, computer-assisted reference bank. He then regretfully informed me that there were no fellow positions in his Department, but some 10 years later, he was helping AFIP’s recruitment efforts for the chair of Soft Tissue Pathology culminating into him a giving a city-wide scenic tour. Broad understanding of a wide variety of topics from scientific details to strategies of survival in sometimes hard climate of a federal institute has made Dr. Enzinger a unique personal advisor and collaborator.

It is my great honor and pleasure to now present Dr. Enzinger A lifetime Achievement Award on behalf of the International Society of Bone and Soft Tissue Pathology. I believe that the membership joins me in congratulations and wishing Dr. Enzinger many more happy years.