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 al 1986, Fletcher 1991, Costa et al 1990, 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 date 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 VIIIrAg, 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,
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. Two cases had marked 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 fascitis 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, Hanrahan 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, Hanrahan 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 (Kiuru-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, COLA1A-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, Pedeutour et al. 1996, 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 HPCLike 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 intralesional 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
3. Taylor RW. Sarcomatous tumors resembling in some respects keloids Arch Dermatol 1890;8:384-387.


