HOW MAY THE CLASSIFICATION OF SOFT TISSUE TUMORS EVOLVE?

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Dr. Fletcher has no conflict of interest or disclosures to make.

CURRENT STATUS
• Huge steps towards consensus classification schemes and more rational/reproducible diagnoses over the past 20-25 years
• Cytogenetic/molecular genetic data have facilitated objectivity and reproducibility – but have begun to pose new questions
• Better-defined concepts regarding biologic potential have emerged
• Classification now based on line of differentiation (not „histogenesis“, which is largely unknown)
WHO CLASSIFICATION 2002
MAJOR CHANGES

• Clearer definitions of biologic potential
• Acknowledgement of problems with “MFH” terminology (“undiff pleomorphic sarcoma”)
• Acknowledgement that hypercystoma was formerly a wastebasket with most tumors being unrelated to pericytes (SFT)
• Major restructuring of intermediate vascular tumors
• More lesions classified as „Tumors of Uncertain Differentiation“

ISSUES STILL TO ADDRESS

• Outdated diagnostic concepts
• Nomenclatural anomalies
• Lack of biologic understanding in some broad areas
• Genetic uncertainties
OUTDATED DIAGNOSTIC CONCEPTS

- “Malignant fibrous histiocytoma”
- “Haemangiopericytoma”
- “Fibrosarcoma” (at least in adults)

Challenges posed by major change
Power of existing literature across multiple disciplines

“MALIGNANT FIBROUS HISTIOCYTOMA”

- Myxofibrosarcoma and angiomatoid “MFH” have been reallocated (WHO 2002)
- Pleomorphic, giant cell and inflammatory “subtypes” are unrelated
- “Undifferentiated pleomorphic sarcoma” facilitates transition but is neither a specific nor a common diagnosis
**PLEOMORPHIC SARCOMAS**
APPROX RISK OF METASTASIS AT 5 YRS

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Approx Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>15-20%</td>
</tr>
<tr>
<td>High grade myxofibrosarcoma</td>
<td>30-35%</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>40-50%</td>
</tr>
<tr>
<td>Pleomorphic leiomyosarcoma</td>
<td>60-70%</td>
</tr>
<tr>
<td>Pleomorphic rhabdomyosarcoma</td>
<td>80-90%</td>
</tr>
</tbody>
</table>

• Not an „entity“ – but synonymous with undifferentiated pleomorphic sarcoma
• Diagnosis of exclusion
• Accounts for no more than 5% of adult sarcomas
• Subclassification of pleomorphic sarcomas has clinical relevance (myogenic is bad…)
• MFH terminology should now disappear (WHO 2013), but clinicians may need to understand why

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**PLEOMORPHIC „MFH“**
KEY POINTS

- Not an „entity“ – but synonymous with undifferentiated pleomorphic sarcoma
- Diagnosis of exclusion
- Accounts for no more than 5% of adult sarcomas
- Subclassification of pleomorphic sarcomas has clinical relevance (myogenic is bad…)
- MFH terminology should now disappear (WHO 2013), but clinicians may need to understand why

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**„MALIGNANT FIBROUS HISTIOCYTOMA“**
WHAT TO DO NEXT ?

- No continuing rationale for maintaining the term, other than “clinical convenience”
- No good definition for fibrohistiocytic differentiation
- Need to begin to acknowledge existence of undifferentiated or unclassified sarcomas as a routine clinical problem
- Create category of undifferentiated sarcomas with criteria for inclusion/exclusion

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HEMANGIOPERICYTOMA
CONCERNS RAISED (early 1990s)

• No convincing immuno or EM evidence of true pericytic differentiation
• Branching thin-walled vessels notably non-specific among mesenchymal tumors
• Striking morphologic overlap with certain specific tumors, including solitary fibrous tumor (increasingly recognised at that time)
• Uncertain relationship (if any) between the originally defined subsets
HEMANGIOPERICYTOMA
REVISED DEFINITION

“The... group of lesions, previously combined under the term hemangiopericytoma, which closely resemble cellular areas of solitary fibrous tumor (SFT) and which appear fibroblastic in type. It has a range of clinical behavior and is closely related to, if not synonymous with, SFT.”

WHO Classification 2002

“HEMANGIOPERICYTOMA”

- Diagnosis was formerly based largely on thin-walled branching vascular pattern – which is shared by multiple tumour types
- Most tumours formerly labelled as “hemangiopericytoma” are fibroblastic – specifically solitary fibrous tumours
- Pericytic neoplasms undoubtedly exist (e.g. myopericytoma spectrum, sinonasal HPC) – but need to be separated clearly from the old concept of HPC
HEMANGIOPERICYTOMA

MODERN PERSPECTIVE

Adult hemangiopericytoma
- most are solitary fibrous tumors

Infantile hemangiopericytoma
- is part of the myopericytoma spectrum

Meningeal hemangiopericytoma
- is indistinguishable from cellular / malignant SFT

Sinonasal hemangiopericytoma
- is a myopericytic neoplasm

WHAT TO DO NEXT?

- ? Remove as synonym for SFT
- ? Reintroduce as synonym for myopericytoma
- ? Redefine as preferred term for myopericytoma
- Nothing….
ADULT FIBROSARCOMA
CURRENT STATUS

- Most lesions so classified in the past would nowadays be relabelled synovial sarcoma or MPNST
- Malignant fibroblastic tumors in adults do exist — eg myxofibrosarcoma, LGFMS, fibrosarcomatous DFSP
- Other less well-defined tumors may well belong in this category, but fibrosarcoma NOS is not currently a useful concept
- Our ability to define fibroblasts/fibroblastic neoplasms is currently very limited
- The fact that some but not all fibroblastic tumors form a continuum with myofibroblastic tumors adds complexity
FIBROBLASTIC SARCOMAS
PROBLEMS TO CONSIDER

• Virtual non-existence of adult-type fibrosarcoma as presently defined
• Difficulties in reproducibly defining fibroblastic differentiation
• Undoubted existence of fibroblastic sarcomas, some with reproducible features, some without

NOMENCLATURAL ANOMALIES
Practical considerations vs scientific accuracy
How best to determine nomenclature?
Historical precedent vs line of differentiation
(which may be unknown) vs genetics
Potential consequences for patient care
(Isn’t it our job to re-educate clinicians?)
Fossilising sociologic issues …..

Are there other branches of science that are quite so slow to evolve or correct themselves?
H'ENDOTHELIOMA (retiform)

NOMENCLATURAL ANOMALIES
POSSIBLE WAYS FORWARD

• Openness to gradual revision on the basis of good/rational evidence
• Willingness to accept genetic definitions (as with leukemias)
• Commitment to bringing clinicians along with us (perhaps thru’ consensus conferences)
• ? „Radical” approaches, dismissing time-honored terminology - ? Less likely to succeed
• ? WHO Working Groups should formally validate/approve terminology

LACK OF BIOLOGIC UNDERSTANDING

Vascular tumours – par excellence!
Neoplasm vs malformation / hamartoma
How to define a neoplasm?
Relevance of clonality / mixed cell types
Limited genetic data
Blood vascular vs lymphovascular
Problem of “intermediate” lesions
Potential to be overtaken by clinicoradiologic classification
IMPACT OF GENETICS
CURRENT STATUS

• Important impact on classification
• Valuable diagnostic adjunct in selected tumor types
• Uncertain/limited prognostic value
• Limited but increasing impact on understanding pathogenesis
**CYTOGENETIC ABERRATIONS IN SOFT TISSUE SARCOMAS**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Cytogenetic changes</th>
<th>Gene fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing's sarcoma/primitive neuroectodermal tumor</td>
<td>t(11;22)(q24;q12)</td>
<td>FLI1-EWSR1</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(21;22)(q22;q12)</td>
<td>ERG-EWSR1</td>
</tr>
<tr>
<td>Neuroepithelial tumor</td>
<td>t(7;22)(p22;q12)</td>
<td>ETV1-EWSR1</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(17;22)(q12;q12)</td>
<td>EIAF-EWSR1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(2;22)(q33;q12)</td>
<td>FEV-EWSR1</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FOXO1A</td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;16)(q13;q11)</td>
<td>DDIT3-FUS</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>t(12;22)(q13;q11)</td>
<td>DDIT3-EWSR1</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)(p13;q12)</td>
<td>WT1-EWSR1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)(p11.2;q11.2)</td>
<td>SSX1-SS18</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>AT1-EWSR1</td>
</tr>
<tr>
<td>Giant cell fibroblastoma</td>
<td>t(9;22)(q22;q12)</td>
<td>NR4A3-EWSR1</td>
</tr>
<tr>
<td>Nodular fasciitis</td>
<td>t(17;22)(p13;q12.3)</td>
<td>USP6-MYH9</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>t(8;8)(q21.1;q13.3)</td>
<td>HEY1-NCOA2</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>t(1;3)(p36.3;q25)</td>
<td>WWTR1-CAMTA1</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>t(15;17)(q25;p13)</td>
<td>ETV6-NTRK3</td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma</td>
<td>t(1;10)(p22;q24)</td>
<td>TGFBR3-MGEA5</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>t(1;10)(p22;q24)</td>
<td>TGFBR3-MGEA5</td>
</tr>
</tbody>
</table>

**RECENTLY IDENTIFIED SPECIFIC CYTOGENETIC / MOLECULAR GENETIC ABERRATIONS IN SOFT TISSUE TUMORS**

- Myoepithelial tumors: EWSR1 and various fusion partners
- Nodular fasciitis: t(17;22)(q13;p12.3)
- Mesenchymal chondrosarcoma: t(8;8)(q21.1;q13.3)
- Epithelioid hendothelioma: t(13;31p36.5;q25)
- Pseudomyogenic hemangioendothelioma: t(7;19)(q22;q13)
- Soft tissue angiofibroma: t(5;8)(p15;q31)
- Undifferentiated (Ewing-like) sarcoma: t(4;10)(q26)
- Ossifying fibromyxoid tumor: Rearrangement of PHF1 at 6p21

**IMPACT OF GENETICS POSSIBLE INFLUENCE ON NOMENCLATURE AND / OR CLASSIFICATION?**

- DFSP: Giant cell fibroblastoma
- Spindle cell lipoma: Mammary-type myofibroblastoma, Cellular angiofibroma

Just „related“? Or variants of a single „entity“?
DERMATOFIBROSARCOMA PROTUBERANS AND GIANT CELL FIBROBLASTOMA CYTOGENETIC FEATURES

t(17;22)(q22;q13)
Leading to PDGFB-COL1A1 fusion
Ring chromosomes in DFSP – composed of amplified elements of same regions of 17 and 22
Same also (with additional genomic gains) in fibrosarcomatous DFSP

RELATIONSHIP BETWEEN DFSP AND GIANT CELL FIBROBLASTOMA

• Similar anatomic sites – but usually different ages at presentation
• Similar infiltrative pattern / recurrence
• Morphologic hybrids
• GCF may recur as DFSP (and vice versa)
• ? Neither metastasises without progression to “fibrosarcoma”
• Same translocation / fusion gene - but ? role of different copy numbers
RELATIONSHIP BETWEEN SPINDLE CELL LIPOMA, MAMMARY-TYPE MYOFIBROBLASTOMA & CELLULAR ANGIOFIBROMA

- Generally different anatomic sites - does this influence the phenotype?
- Morphologic overlap with subtle differences
- Immunophenotypic differences
- Same rearrangement/loss of 13q14
- All benign/rarely recur
- Cellular angiofibroma may perhaps have potential for progression

HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR
(aka “haemosiderotic fibrohistiocytic lipomatous lesion”)

CLINICAL FEATURES
- Adults > children
- Females slightly > males
- Ankle / foot ++
- Subcutaneous / poorly marginated
- Usually < 5 cm
- Local recurrence 30%
- Possible potential to progress (?)
Female aged 46 with lesion on dorsum of foot – 2 different components

MYXOINFLAMMATORY FIBROBLASTIC SARCOMA
AND
HEMOSIDEROTIC FIBROLIPOMATOUS TUMOR
SHARED CLINICOPATHOLOGIC & GENETIC FEATURES

Predilection for distal extremities, esp. feet
Recur ++ but almost never metastasise
Isolated cases show hybrid morphologic features
Both show reciprocal t(1;10)(p22;q24)
Gene fusion TGFBR3 – MGEA5
Leads to up-regulation of FGF8
Also amplified 3p in ring chromosomes

Lambert et al, Virchows Arch 2001; 438:509-512
Wettach et al, Cancer Genet Cytogenet 2008; 182:140-143
Hallor et al, J Pathol 2009; 217:716-727
Antonescu et al, Genes Chromosomes & Cancer 2011; 50:757-764
IMPACT OF GENETICS
SHARED GENE REARRANGEMENTS

- *EWSR1*
- *FUS*
- *CREB1*
- *ATF1*
- *HMGA-2*

[Dal Cin 1995]

[2001]
SHARED FUSION GENES IN SOFT TISSUE SARCOMAS

ETV6-NTRK3

- Infantile fibrosarcoma
- Cellular mesoblastic nephroma
- Secretory carcinoma of breast (and now salivary gland)
- Rare cases of AML (M2) & CML
EWSR1-ATF1
EWSR1-CREB1

- Clear cell sarcoma
- Melanocytic
- Deep soft tissue/GI
- Adults (mainly young)
- > 50% metastasise
- Angiomatoid “MFH”
- Lineage unknown
- ?? dendritic cell
- Mostly subcutaneous
- Commonest < 20 years
- < 2% metastasise

IMPAKT OF GENETICS
THE STORY CONTINUES...
MYOEPITHELIAL TUMORS OF SOFT TISSUE

- 45% have EWSR1 gene rearrangement
- New fusion gene partners - POU5F1, PBX1, ZNF444
  - with apparent morphologic correlates
- Skin lesions seem different/mostly lack EWSR1 involvement
- As with salivary gland lesions, PLAG1 involvement
  in some mixed tumors of skin and soft tissue

Antonescu et al. Genes, Chromosomes & Cancer 2010; 49: 1114-1124
Bahrami et al. Genes, Chromosomes & Cancer 2012; 51: 140-148

IMPAKT OF GENETICS
WHERE NEXT ?

- Need to more sharply define diagnostic role
- Need to reassess role in classification – how best to reconcile/prioritise genotype with phenotype?
- Need to determine significance (pathogenetic and perhaps clinical) of such prominently shared fusion genes
- Need to actively maintain this work since valuable and remarkable new data continue to emerge
WHO CLASSIFICATION 2012/2013

MAJOR CHANGES

- Introduction of undifferentiated / unclassified sarcomas
- Disappearance of malignant fibrohistiocytic tumors
- Disappearance of hemangiopericytoma
- Introduction of some "new" entities
- Inclusion of GIST and nerve sheath tumors in soft tissue volume

WHO CLASSIFICATION 2012/2013

"NEW ENTITIES"

- Pseudomyogenic hemangioendothelioma
- Hybrid nerve sheath tumors
- Acral fibromyxoma
- Hemosiderotic fibrolipomatous tumor
- Phosphaturic mesenchymal tumor
WHO CLASSIFICATION 2012/2013
CONCEPTUAL SHIFTS
• Separate classification of spindle cell / sclerosing rhabdomyosarcoma
• Acceptance of nodular fasciitis as neoplastic (now has ICD-0 code!)
• Co-classification of myofibroma / myopericytoma

OTHER UNANSWERED QUESTIONS WHICH MIGHT IMPACT TAXONOMY
• Cell of origin in many/most tumor types?
• Line of differentiation in many tumor types?
• Nature of multistep process in mesenchymal tumorigenesis?
• Relevance of “mesenchymal stem cell”?
For these questions, what insights can we gain from molecular genetic data?

CONCLUSIONS
• There remain important opportunities to improve the classification of soft tissue tumours
• Objectivity and diagnostic reproducibility are both the goals as well as the validation of any classification scheme (WHO 2012 hopefully improves on WHO 2002…)
• Cytogenetics / molecular genetics have been invaluable thus far, but their impact has become more complex and confusing
• Old habits die hard ……..