A new classification of sarcomas

Interview to A.P. Dei Tos[1] *by* R. Sanfilippo[2]

Last January, the latest WHO classification of Tumors of Soft Tissue and Bone, was published [1]. WHO classifications traditionally exert a profound impact not only among the pathologist community, but also among clinicians. Concerning this important new classification, on behalf of *Cancer Breaking News* Roberta Sanfilippo interviewed Angelo Paolo Dei Tos, Department of Oncology, General Hospital of Treviso, panel member for the WHO Working Group for the Classification of Tumours of Soft Tissue and Bone. He also participated in the WHO classification final Consensus Conference (held in Zurich, May 2012) when the 2002 WHO classification of sarcomas was finally updated.

1. Why was needed a new classification of sarcomas?

The last WHO classification of tumours of soft tissue and bone was published more than 10 years ago [2]. That classification certainly represented a major step forward. In fact, for the first time it included not only conventional, haematoxylin- and eosin-based morphology, but also both immunohistochemistry and molecular genetics. This integrated approach brought about significant advances allowing a more rational allocation of tumour entities to well-defined histogenetic groups. For the first time, mesenchymal tumours were also approached clinically, with the classification attempting to provide a clear definition of benign, intermediate malignancy and malignant tumours. Most importantly, this classification began an extensive reappraisal of popular labels such as 'malignant fibrous histiocytoma' and 'hemangiopericytoma' that had originated from a decade of sharp debate. Another relevant conceptual advance was represented by the proposal to replace the term 'well differentiated liposarcoma' with 'atypical lipomatous tumour' for lesions arising in surgically amenable soft tissue. This decision represented an important step towards the use of a terminology more fitting to the clinical reality of some tumour entities. It has also to be underlined that the 2002 WHO classification (as it was the latest one) represented the efforts of more than one hundred contributors, further elaborated within a 4-day consensus conference aimed at eliminating all controversies. Ten years later it was felt that enough new data had been published and that an updated WHO classification was necessary.

2. What are the main changes introduced by the 2013 WHO classification?

There are several important changes. First of all, the terms 'hemangiopericytoma' and 'malignant fibrous histiocytoma' were entirely abolished [1]. Both entities represented a 'top-seller' during the '80s and '90s. Then it became clear that both represented an irrational conglomerate of unrelated diseases. Hemangiopericytoma included benign lesions currently renamed myopericytomas, as well as malignant lesions, such as synovial sarcoma and peripheral nerve sheath tumours (MPNST). Above all, it is now clear that most hemangiopericytomas actually represented examples of a morphologically as well as genetically distinctive tumour known as a solitary fibrous tumour [1].
For a long time, malignant fibrous histocytomas accounted for approximately 50% of sarcoma diagnosis. It took several years to understand that this label not only included distinctive subtypes of pleomorphic sarcomas (leiomyosarcomas, rhabdomyosarcomas, dedifferentiated liposarcoma and others), but also unrelated diseases such as lymphomas, malignant melanomas and sarcomatoid variants of carcinomas, which deserve specific treatments [3, 4].
The definition of tumours also changed. In fact it was felt that the term 'intermediate malignancy' had generated significant confusion both among pathologists and clinicians. In particular, such lesions were mistakenly associated with grade 2 sarcomas. Now the former intermediate malignancy category has been split into:

a. locally aggressive non metastasizing tumours (i.e. desmoid fibromatosis);
b. rarely metastasizing lesions (i.e. plexiform fibrohistiocytic tumour).

Several new entities have been added. One good example is represented by 'pseudomyogenic hemangioen-

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dothelioma' [5]. This is a lesion often characterized by multifocal presentation, significant recurrence rate and a low tendency for distant metastasis. Its recognition is important particularly because of the stark contrast between its rather alarming morphology, and its relatively indolent clinical course.

Another major problem was represented by the fact that the 2002 WHO classification did not include the whole group of neural neoplasms. Also some entities, such as atypical fibroxanthoma, had been 'forgotten' and left out from all WHO tumour fascicles. It was also felt that the classification of bone tumours required a major reappraisal.

The same reasoning used for well-differentiated liposarcoma was applied to G1 chondrosarcomas that now may be less aggressively labelled as atypical cartilaginous tumours. In addition, genetic data have been extensively added whenever available. A summary of the new classification (excluding benign lesions) is available in Tables 1 and 2.

Table 1. Updated WHO classification of malignant and intermediate malignancy soft tissue neoplasms

Adipocytic tumours
• Atypical lipomatous tumours/well differentiated liposarcoma (lipoma-like, sclerosing, and inflammatory variants)
• Spindle cell liposarcoma
• Myxoid/round cell liposarcoma
• Pleomorphic liposarcoma
Fibroblastic/myofibroblastic tumours
• Desmoid fibromatosis
• Dermatofibrosarcoma protuberans (DFSP)
• Fibrosarcomatous DFSP
• Atypical fibroxanthoma
• Solitary fibrous tumour
• Inflammatory myofibroblastic tumour
• Low grade myofibroblastic sarcoma
• Infantile fibrosarcoma
• Myxofibrosarcoma
• Myxoinflammatory fibroblastic sarcoma
• Low grade fibromyxoid sarcoma
• Sclerosing epithelioid fibrosarcoma
So-called fibrohistiocytic tumours
• Plexiform fibrohistiocytic tumour
• Giant cell tumour of soft tissue
Smooth muscle tumours
• Leiomyosarcoma
Pericytic (perivascular) tumours/muscle tumours
• Malignant glomus tumour
Skeletal muscle tumours
• Embryonal rhabdomyosarcoma
• Alveolar rhabdomyosarcoma
• Pleomorphic rhabdomyosarcoma
• Spindle cell/sclerosing rhabdomyosarcoma

Vascular tumours
• Kaposiform haemangioendothelioma
• Retiform haemangioendothelioma
• Papillary intralymphatic angioendothelioma
• Composite haemangioendothelioma
• Kaposi sarcoma
• Pseudomyogenic 'epithelioid sarcoma-like' haemangioendothelioma
• Epithelioid haemangioendothelioma
• Angiosarcoma of soft tissue
Chondro-osseous tumours
• Extraskeletal osteosarcoma
Gastrointestinal stromal tumour
Nerve sheath tumours
• Malignant peripheral nerve sheath tumours
• Malignant granular cell tumour
Tumours of uncertain differentiation
• Angiomatous fibrous histiocytoma
• Hyalinizing angiectatic tumour of soft parts
• Ossifying fibromyxoid tumour
• Mioepithelioma
• Phosphaturic mesenchymal tumour
• Synovial sarcoma
• Epithelioid sarcoma
• Alveolar soft part sarcoma
• Clear cell sarcoma
• Extraskeletal myxoid chondrosarcoma
• Mesenchymal chondrosarcoma
• Desmoplastic small round cell tumour
• Extrarenal rhabdoid tumour
• PEComa (perivascular epithelioid cell tumour)
• Intimal sarcoma
• Undifferentiated sarcomas (pleomorphic, epithelioid, spindle cell and round cell)

Table 2. Updated WHO classification of malignant and intermediate malignancy bone neoplasms

Cartilage tumours
• Chondrosarcoma
• Dedifferentiated chondrosarcoma
• Mesenchymal chondrosarcoma
• Clear cell chondrosarcoma
Osteogenic tumours
• Low grade central osteosarcoma
• Conventional osteosarcoma
• Teleangiectatic osteosarcoma
• Small cell osteosarcoma
• Secondary osteosarcoma
• Paraosteal osteosarcoma
• Periosteal osteosarcoma
• High grade surface osteosarcoma
Fibrogenic tumours
• Desmoplastic fibroma of bone
• Undifferentiated high grade pleomorphic sarcoma
Ewing sarcoma
Notochordal tumours
• Chordoma
Vascular tumours
• Epithelioid haemangioendothelioma
• Angiosarcoma
Smooth muscle tumours
• Leiomyosarcoma
Adipocytic tumours
• Liposarcoma
Epithelial tumours
• Adamantinoma

3. Why has genetics become so important in the field of sarcomas?

Genetics has proved tremendously important to all pathology subspecialties. Haematopathology was the first to integrate cytogenetics/molecular genetics into classification schemes. Soft tissue and bone tumours came second, but the list of genetic aberrations associated with specific groups of tumours has grown exponentially. Table 3 includes some of the most relevant neoplasms with the associated genetic alteration. Both cytogenetics and molecular genetics have substantially contributed to the evolution of mesenchymal tumour classification. The fact that entities that were once separated, such as myxoid liposarcoma and round cell liposarcomas, are currently regarded as a single spectrum of myxoid lipogenic sarcomas, received final confirmation with the observation of identical chromosome translocation in both lesions [6]. Examples were so numerous that during the WHO classification final consensus conference (held in Zurich in May 2012), we decided to include the pertinent genetic aberration in the tumour type definition. As an example, dedifferentiated liposarcoma is now also defined as an MDM2-amplified lipogenic sarcoma [7].

4. In consideration of the relevance of genetics do you believe that in the future morphology will be abandoned in favour of genetic classification of sarcomas?

Not at all, and the reason is very simple. The dream that genetic aberrations were 100% specific for given entities could not persist with more extensive tumour molecular genetic analysis. Now, we are aware that the same aberration of the ALK gene can be seen in mesenchymal tumours such as inflammatory myofibroblastic tumours and also in anaplastic large cell lymphoma and lung carcinoma. ETV6 aberrations are seen in infantile fibrosarcoma, in secretory breast carcinoma, and in leukaemia. Even more intriguing is the fact that the same translocation can be seen in a high-grade malignancy such as clear-cell sarcoma and in a quasi-benign entity named 'angiomatoid fibrous histiocytoma' [8]. Trying to set genetics in opposition to morphology is a sterile exercise. Morphology will remain the mainstay of tumour classification for many years; however, genetics will play an increasing role. The marriage between pathology and genetics has proved extremely fruitful and will certainly persist.

5. What can we expect for the future?

It is always hard to predict the future. However, as it was for the 2002 WHO classification, we need to make the use of the 2013 update as widespread as possible. The amazing success of the WHO tumour fascicles would suggest that this represents an achievable objective. Most likely a new classification will be released within a shorter time compared with the previous one, and an update could be expected in 5 or 6 years. Certainly more genetic data will be added and it is also possible that genetic aberrations (as

Table 3. Common genetic aberrations occurring in mesenchymal tumours of bone and soft tissue

Tumour	Genetic mutation	Gene involved
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	PAX3-FOXO1A PAX7-FOXO1A
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	ASPL-TFE3
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12) t(2;22)(q34;q12)	ATF1-EWSR1 CREB1-EWSR1
Aneurysmal bone cyst	t(16;17)(q22;p13)	CDH11-USP6
Atypical lipomatous tumour/ dedifferentiated liposarcoma	Amplification	MDM2
Central/periosteal osteosarcoma	Point mutation	IDH1/IDH2
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q34;q12)	ATF1-EWSR1 CREB1-EWSR1
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1-PDGFB
Desmoid type fibromatosis	Activating mutation	BCTN1
Desmoplastic round cell tumour	t(11;22)(p13;q12)	WT1-EWSR1
Endometrial stromal sarcoma	t(7;17)(p15;q21) t(6;7)(p21;p15) t(6;10)(p21;p11)	JAZF1-JJAZ1 PHF1-JAZF1 PHF1-EPC1
Ewing sarcoma/PNET	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) t(16;21)(q13;q22) t(2;22)(q33;q12)	EWSR1-FLI1 EWSR1-ERG ETV1-EWS EIAF-EWS FUS-ERG FEV-EWS
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;15)(q22;q21)	EWSR1–NR4A3 TCF12–NR4A3 TFG–NR4A3
Fibrous dysplasia/intramuscular myxoma	Activating mutation	GNAS1
Infantile fibrosarcoma	t(12; 15)(p13;q25)	ETV6-NTRK3
Inflammatory myofibroblastic tumour	t(2;19)(p23;p13.1) t(1;2)(q22-23;p23)	ALK-TPM4 TPM3-ALK
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11) t(11;16)(p11;p11)	FUS-BBF2H7 CREB3L1-FUS
Myxoid-round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	FUS-DDIT3 EWSR1-DDIT3
Pericytoma with t(7;12)	t(7;12)(p22;q13)	ACTB-GLI
Pigmented villonodular synovitis	t(1;2)(p13;q37)	COL6A-CSF1
Soft tissue and bone myoepithelioma	t(1;22)(q23;q12) t(19;22)(q13;q12)	EWSR1-PBX1 EWSR1-ZNF444
Synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1 SS18-SSX2 SS18-SSX4

in some hematologic neoplasms) may become the defining feature of some tumour entities. The first example that crosses my mind is those surrounding cell sarcomas harbouring the CIC-DUX4 translocation [9]. In addition, new entities keep being reported, which means that we need to keep our eyes and minds wide open.

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