

The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives

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Summary

Mesenchymal tumours represent one of the most challenging field of diagnostic pathology and refinement of classification schemes plays a key role in improving the quality of pathologic diagnosis and, as a consequence, of therapeutic options. The recent publication of the new WHO classification of Soft Tissue Tumours and Bone represents a major step toward improved standardization of diagnosis. Importantly, the 2020 WHO classification has been opened to expert clinicians that have further contributed to underline the key value of pathologic diagnosis as a rationale for proper treatment. Several relevant advances have been introduced. In the attempt to improve the prediction of clinical behaviour of solitary fibrous tumour, a risk assessment scheme has been implemented. NTRK-rearranged soft tissue tumours are now listed as an “emerging entity” also in consideration of the recent therapeutic developments in terms of NTRK inhibition. This decision has been source of a passionate debate regarding the definition of “tumour entity” as well as the consequences of a “pathology agnostic” approach to precision oncology. In consideration of their distinct clinicopathologic features, undifferentiated round cell sarcomas are now kept separate from Ewing sarcoma and subclassified, according to the underlying gene rearrangements, into three main subgroups (CIC, BCLR and not ETS fused sarcomas) Importantly, In order to avoid potential confusion, tumour entities such as gastrointestinal stroma tumours are addressed homogenously across the different WHO fascicles. Pathologic diagnosis represents the integration of morphologic, immunohistochemical and molecular characteristics and is a key element of clinical decision making. The WHO classification is as a key instrument to promote multidisciplinary, stimulating pathologists, geneticists and clinicians to join efforts aimed to translate novel pathologic findings into more effective treatments.

Key words: WHO classification, soft tissue sarcoma, new entity, molecular genetics, morphology

Introduction

The publication of the new WHO classification always generates within the sarcoma community great expectations. Mesenchymal tumours are in fact regarded as one of the most challenging fields of diagnostic pathology and refinement of classification schemes is perceived as the cornerstone around which improving the quality of both pathologic diagnosis and therapeutic options ¹. Published data indicate in sarcoma a rate of diagnostic inaccuracy ranging between 20 and 30% ²⁻⁴. However, this is not at all due to pathologists' negligence. As a matter of fact, there exist objective factors that appear to impact negatively over both the accuracy and the reproducibility of pathologic diagnosis, factors the pathologist have always tried to overcome through specific strategies, most of all by implementation of diagnostic second opinion in expert centers or within collaborative networks ⁵. Four main sources of challenge can be identified.

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Conflict of interest

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- 1 **Rarity.** Sarcomas as a whole are characterised by an incidence of approximately 5 cases/100,000 thus matching the formal definition of a rare tumour⁶. However, soft tissue malignancies are further subclassified in approximately 70 subtypes, each characterized by a distinct morphology, that often translates into a specific clinical behaviour as well as into specific therapeutic approaches. Moreover, many histotypes are exceedingly rare (in the range of 0.1 cases/100,000), to the extent that a pathologist not working in a high-volume centre may not encounter them for years. In this scenario, achieving specific expertise represents undoubtedly a challenge.
- 2 **Intrinsic complexity.** Mesenchymal tumours are characterised by specific diagnostic peculiarities. First of all, the mere application of morphologic criteria of malignancy used for epithelial cancer are not always applicable. The best example is represented by nodular fasciitis, a benign condition most often occurring in the forearm of a young adults, who exhibits clinicopathologic features (rapid growth, hypercellularity and high mitotic activity) that in the context of an epithelial cancer would be highly supportive of a diagnosis of malignancy. The relatively frequent violation of diagnostic criteria of malignancy appears to represent a unique feature of mesenchymal tumours and represents one of the major reasons for diagnostic inaccuracy.
- 3 **Technological complexity.** The diagnostic process of mesenchymal tumours relies upon a complex combination of conventional microscopic morphology, immunohistochemistry, and molecular genetics⁷. This requires state of the art molecular technology that more and more includes Next Generation Sequencing approaches⁸. In contrast with popular belief molecular genetics requires high professional expertise coupled with even higher quality control standards (as compared for example to immunohistochemistry). In this perspective, it is quite intuitive that centralisation of molecular diagnostics in high volume centres is mandatory on order to maintain high analytic quality⁹.
- 4 **Lower impact of educational efforts.** Even if education still plays a fundamental role in increasing diagnostic expertise, it has to be admitted that in the field of rare cancers its efficacy is somewhat hampered. Unless a pathologist is continuously exposed to soft tissue tumours diagnostics, the expertise developed through educational efforts is at risk of being gradually lost.

The field of sarcoma oncology is rapidly evolving through the development of an even close correlation between pathologic diagnosis and tailored treat-

ments¹⁰⁻¹⁶. The WHO classification of soft tissue tumours, since 1999¹⁷⁻¹⁹, has introduced a profound change in its methodological approach aimed to support a more rational therapeutic approach. Major changes can be summarised as follows:

- 1 **Integration of morphology with immunohistochemistry and molecular genetics.** The marriage between morphology and genetics by direct involvement of cytogeneticists has certainly represented a major step forward.
- 2 **Involvement of a broad number of sarcoma expert pathologists.** This approach has minimised the risk of generation of “opinion-leader” bias and has led to a broader diffusion of the classification among pathologists.
- 3 **Precise definition of clinicopathological categories.** It is now broadly accepted that in between benign and malignant categories there exists an “intermediate” category of lesions that can be either locally aggressive (i.e. desmoid fibromatosis) or rarely metastasizing (i.e. plexiform fibrohistiocytic tumour).
- 4 **Involvement of clinicians.** For the first time the 2020 WHO classification of soft tissue and bone tumours, representatives of clinical disciplines such as medical, surgical and radiation oncology have been directly involved. This close interaction has strongly enhanced the clinical value of pathological diagnosis.

The aim of this paper is to review the main advances contained in the current classification and also discuss new perspectives that most likely will generate some debate in the years to come. In consideration of the complexity of the new classification and despite the fact that some soft sarcomas can rarely arise primarily in bone²⁰, with the exception of undifferentiated round cell sarcoma that can occur both in soft tissue and bone, we will focus on tumours of the soft tissue.

Advances in classification

ADIPOCYTIC TUMOURS

The entities characterised by adipocytic differentiation are listed in Table I. Newcomers are represented by *atypical* spindle cell/pleomorphic lipomatous tumour and myxoid pleomorphic liposarcoma. Importantly, both lesions are now regarded as benign and therefore treated with simple surgical excision.

The label *atypical spindle cell lipomatous tumour* represents a new name for the entity formerly known as spindle cell liposarcoma^{21,22} and at the time of first description regarded as a variant of well differentiated liposarcoma. The entity is now defined as an ill-circumscribed, moderately atypical spindle cell tumour fea-

Table I. Adipocytic tumours.

Benign
Lipoma and lipomatosis
Lipomatosis of nerve
Lipoblastoma and lipoblastomatosis
Angiolipoma
Myolipoma of soft parts
Chondroid lipoma
Spindle cell/pleomorphic lipoma
Atypical spindle cell/pleomorphic atypical lipomatous tumor
Hibernoma
Intermediate (locally aggressive)
Atypical lipomatous tumor
Malignant adipocytic tumours
Well differentiated liposarcoma: lipoma-like, sclerosing, inflammatory
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma
Myxoid pleomorphic liposarcoma

turing the presence of a variable number of lipoblasts. Matrix can vary from fibrous to myxoid (Fig. 1A). A remarkable tendency to occur superficially is observed. The new label is justified by the distinctively indolent clinical course. Separation from the group of well differentiated liposarcoma/atypical lipomatous tumour is also justified by the fact that atypical spindle cell tumour is not driven genetically by the amplification of *MDM2* and/or *CDK4* genes. In further contrast dedifferentiation (i.e. transition from low grade to high grade histology) seems not to occur.

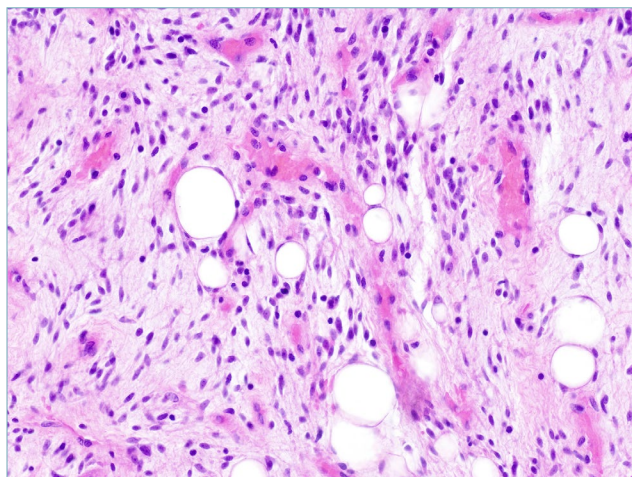


Figure 1A. Atypical spindle cell lipomatous tumor. The tumor is composed of mildly atypical, hyperchromatic, spindle cells, and adipocytic cells set in a myxocollagenous stroma. A bivacuolate lipoblast is seen.

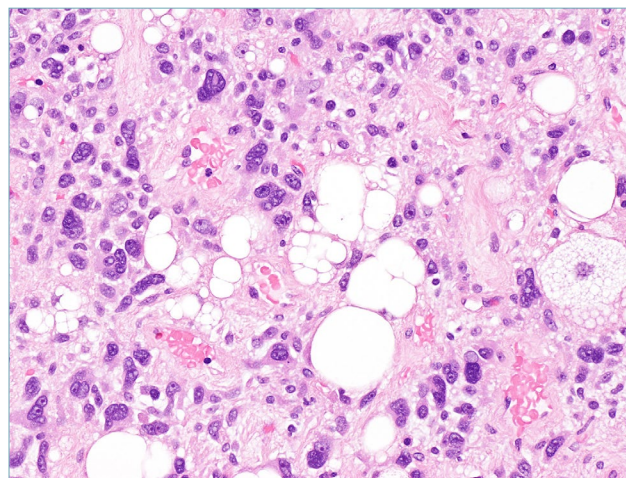


Figure 1B. Atypical pleomorphic lipomatous tumor. The presence of multivacuolated lipoblasts is accepted.

Atypical pleomorphic lipomatous tumour has been recently introduced to recognise the existence of examples of pleomorphic lipoma that, while keeping some key diagnostic features (presence of florette-like multinucleated giant cells as well as of coarse eosinophilic collagen bundles) exhibit higher cellularity, increased mitotic activity and presence of numerous lipoblasts, however without reaching histologic criteria consistent with the diagnosis of pleomorphic liposarcoma²³ (Fig. 1B). Atypical pleomorphic lipomatous tumour, despite alarming morphology, is characterised by a benign clinical behaviour that contrasts with the remarkable aggressiveness of pleomorphic liposarcoma.

Both spindle and pleomorphic atypical lipomatous tumours occur most often in the limbs and limb girdles of middle-aged patients. Importantly, they can rarely arise at visceral locations including the retroperitoneum. From a molecular standpoint *RB1* gene loss is frequently observed that translates into loss of nuclear *RB1* immunoreactivity. As mentioned, both lesions tend to exhibit a low rate of recurrence that seems to be limited to lesions excised incompletely.

Myxoid pleomorphic liposarcoma is an exceedingly rare adipocytic malignancy, and is characterised by occurrence in children and adolescents with female predominance²⁴. Most common anatomic sites are represented by the mediastinum followed by the limbs and the head and neck region. Morphologically myxoid pleomorphic liposarcoma shows features of both myxoid (presence of a rich capillary size vascular network set in myxoid background) and pleomorphic liposarcoma (presence of pleomorphic lipoblasts

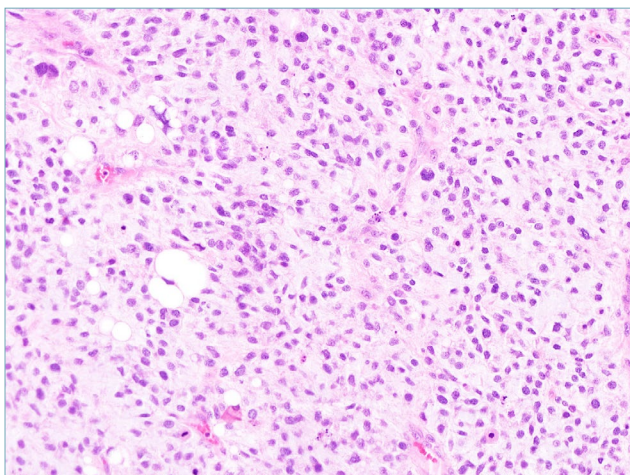


Figure 1C. Myxoid pleomorphic liposarcoma. Neoplastic cells are set in a myxoid stroma with plexiform vascular pattern. Rare pleomorphic lipoblasts can be observed.

(Fig. 1C). No specific genetic aberrations have been so far detected. Clinical behaviour is aggressive with a high recurrence rate and early metastatic spread to the lungs, bone, and soft tissues. It should be remembered that true myxoid liposarcomas almost never occurs in children, those reported case most likely representing examples of lipoblastoma^{25,26}.

FIBROBLASTIC/MYOFIBROBLASTIC TUMOURS

The entities characterised by fibroblastic/myofibroblastic differentiation are listed in Table II. Despite representing one of the larger groups, only three new benign entities are considered in the new classification: angiofibroma of soft tissues²⁷, EWSR1-SMAD3 positive fibroblastic tumour²⁸, and superficial CD34-positive fibroblastic tumour²⁹.

Angiofibroma of soft tissue is a benign lesion most often occurring in the subcutaneous soft tissues of the extremities of adult patients. Morphologically it is composed of a uniform spindle cell proliferation set in a variably myxoid and collagenous background, and associated with a remarkably rich thin-walled vascular network (Fig. 2A). Neoplastic cells express CD34 and EMA. Desmin positivity is often observed in dendritic cells. The presence of an *AHRR-NCOA2* fusion gene is reported in the majority of cases³⁰.

EWSR1-SMAD3 fibroblastic tumour represents one of the new entities in which the name is determined by the involved fusion gene. It is a benign neoplasm most often occurring in the hands and feet with a broad age range. Morphologically it is composed of intersecting cellular fascicles of cytologically bland monomorphic

Table II. Fibroblastic/myofibroblastic tumours.

Benign
Nodular fasciitis
Proliferative fasciitis and proliferative myositis
Myositis ossificans and fibro-osseous pseudotumor of digits
Ischaemic fasciitis
Elastofibroma
Fibrous hamartoma of infancy
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Myofibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
EWSR1-SMAD3-positive fibroblastic tumour (emerging)
Angiomyofibroblastoma
Cellular angiofibroma
Angiofibroma NOS
Nuchal fibroma
Acral fibromyxoma
Gardner fibroma
Intermediate (locally aggressive)
Palmar/plantar-type fibromatosis
Desmoid-type fibromatosis
Lipofibromatosis
Giant cell fibroblastoma
Dermatofibrosarcoma protuberans
Intermediate (rarely metastasising)
Dermatofibrosarcoma protuberans, fibrosarcomatous
Solitary fibrous tumour
Inflammatory myofibroblastic tumour
Low-grade myofibroblastic sarcoma
Superficial CD34-positive fibroblastic tumour
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma
Malignant
Solitary fibrous tumour, malignant
Fibrosarcoma NOS
Myxofibrosarcoma
Low grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma

spindle cells, alternating with hypocellular, hyalinised areas (Fig. 2B). Immunohistochemically it is characterized by nuclear expression of ERG.

Superficial CD34-positive fibroblastic tumour occurs most often skin and subcutis of the lower extremities of middle-aged patients. Morphologically is composed of spindle and epithelioid cell proliferation, often featuring striking cytologic atypia that is associated with insignificant mitotic activity. Neoplastic cells invariably express CD34 (Fig. 2C). Importantly, despite alarming

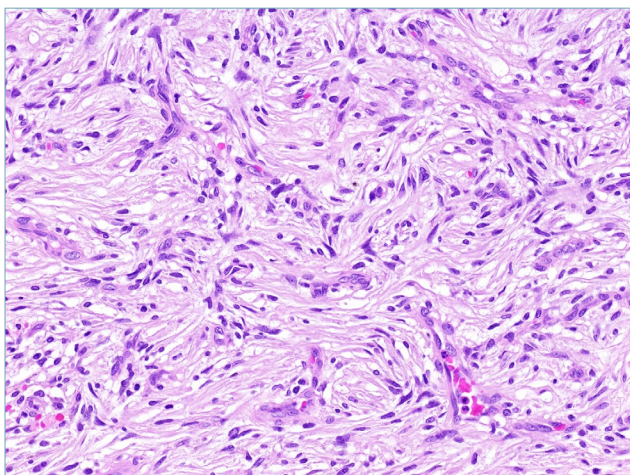


Figure 2A. Angiofibroma of soft tissue. A prominent vascular network composed of thin walled branching vessels represents one of the main features of this entity. The neoplastic spindle cells show inconspicuous pale eosinophilic cytoplasm.

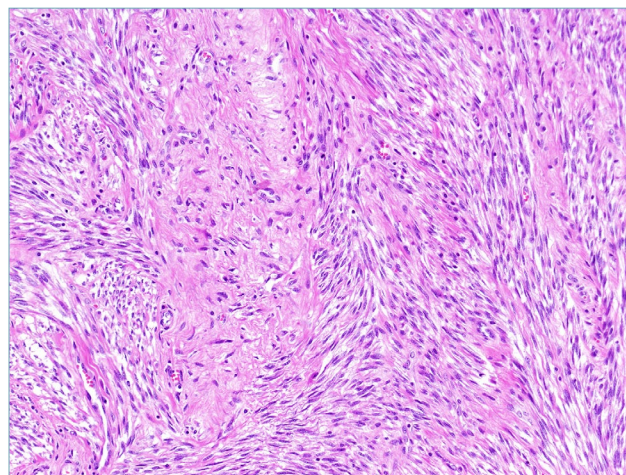


Figure 2B. EWSR1-SMAD3 fibroblastic tumour. Alternation of hyalinised hypocellular areas and more cellular areas composed of intersecting fascicles of monomorphic spindle cells is most often observed.

morphologic features no recurrences are reported following complete excision.

SO-CALLED FIBROHISTIOCYTIC TUMOUR

The category of fibrohistiocytic tumours is the group that through the last three editions of the WHO classification has lost most of the tumour entities. Currently recognised lesions are listed in Table III. The very concept of fibrohistiocytic differentiation is rather elusive as in most cases the histiocytic component is actually non-neoplastic. However, as happens in giant cell tumour, the histiocytic component contributes significantly to the development of the lesion. The most relevant entity that has disappeared since 2013 is represented by the family of so called malignant fibrous histiocytoma (MFH), a group of lesions that until the early 2000 accounted for approximately 50% of sarcoma diagnoses³¹⁻³³. Undifferentiated pleomorphic sarcoma currently represents the correct label for the prototypical storiform and pleomorphic variant of MFH. Giant cell MFH is currently replaced by three distinct tumour types: giant cell tumour of soft tissues, extraskeletal osteosarcoma and giant cell rich osteosarcoma. Myxoid MFH is currently recognised as a purely fibroblastic tumour identified with the original name myxofibrosarcoma³⁴⁻³⁶. So called inflammatory MFH overlaps entirely with the inflammatory variant of dedifferentiated liposarcomas³⁷, and so called angiomatoid MFH (a clinically indolent lesion most often harbouring a *EWSR1-CREB1* fusion gene and, more rarely a *EWSR1-ATF1* or a *FUS-ATF1*) is currently list-

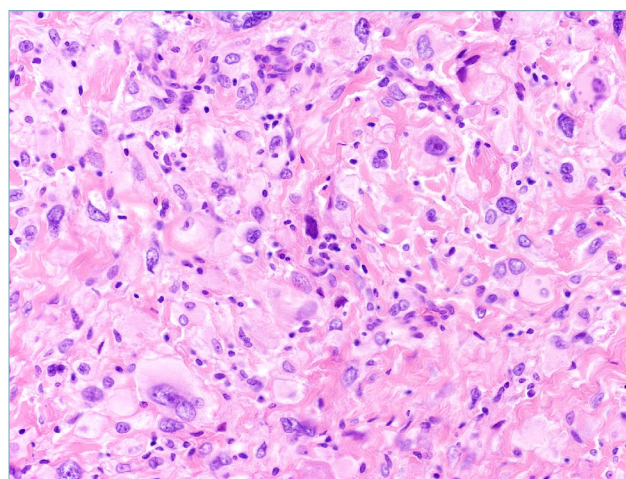


Figure 2C. Superficial CD34-positive fibroblastic tumour. Striking cytologic atypia in absence of mitotic figures and necrosis is often present.

Table III. So-called fibrohistiocytic tumours.

Benign
Tenosynovial giant cell tumour
Deep benign fibrous histiocytoma
Intermediate (rarely metastasising)
Plexiform fibrohistiocytic tumour
Giant cell tumour of soft parts NOS
Malignant
Malignant tenosynovial giant cell tumour

ed within the group of soft tissue lesion of unknown differentiation³⁸.

VASCULAR TUMOURS

The group of neoplasms featuring endothelial differentiation is also very heterogenous both in terms of degree of vasoformative morphology and biological behaviour (Tab. IV). It is worth stressing that despite the label implying an intermediate behaviour, epithelioid haemangioendothelioma (EHE) is actually ranked among vascular malignancies. This is the consequence of an overall metastatic rate of approximately 15%, and the tendency to be remarkably aggressive in specific anatomic locations such as lungs and pleura. Two morphological and molecular variants (*CAMTA1* and *TFE3*-related) are recognised however at the moment no statistically significant differences in terms of clinical behaviour seems to emerge³⁹.

The single new entity appearing among vascular lesions is represented by a benign lesion named *anastomosing haemangioma (AH)*. Initially reported in the male genital tract^{40,41}, anastomosing haemangioma most commonly occurs in the kidney and in the retroperitoneum of adults. Morphologically AH is composed of anastomosing capillary-sized vessels featuring scattered hobnail endothelial cells (Fig. 3). Anastomosing haemangioma is frequently misinterpreted as angiosarcoma, however if present endothelial atypia is mild, and is never associated with multilayering as is typically observed in angiosarcoma.

PERICYTIC (PERIVASCULAR) TUMOURS

This group of lesions share morphologically the presence of a distinctive perivascular pattern of growth (Tab. V). Cell shape varies from epithelioid (such as in glomus tumour) to spindle as observed in myopericytoma/myofibroma and angioleiomyoma. It seems likely the whole group represents a spectrum of perivascular neoplasia exhibiting a variable contractile phenotype. Most of the lesions tend to exhibit a benign clinical course. The diffuse variants (glomangiomas and myofibromatosis) however are associated with significant local morbidity. Malignancy represents an extremely rare condition.

Since 2013 the major advance is represented by the abolition of haemangiopericytoma⁴². The original intuition of Arthur Purdy Stout represented by the recognition of neoplasms composed of perivascular contractile cells, remains absolutely valid, and is currently encompassed by myopericytoma. Unfortunately, through the decades hemangiopericytoma became the preferred label for unrelated lesions sharing an hemangiopericytic vascular pattern, namely the presence of dilated, branching, thin walled blood vessels. Most

Table IV. Vascular tumours.

Benign
Synovial haemangioma
Intramuscular haemangioma
Arteriovenous malformation/haemangioma
Venous haemangioma
Anastomosing haemangioma
Epithelioid haemangioma
Lymphangioma and lymphangiomatosis
Acquired tufted haemangioma
Intermediate (locally aggressive)
Kaposiform haemangioendothelioma
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma
Pseudomyogenic haemangioendothelioma
Malignant
Epithelioid haemangioendothelioma
Angiosarcoma

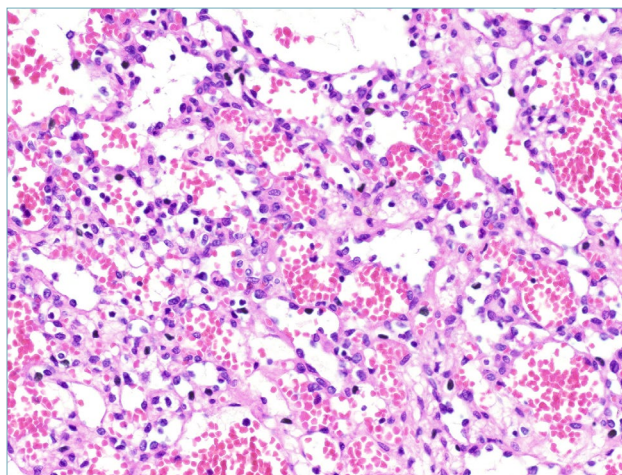


Figure 3. Anastomosing haemangioma. Anastomosing capillary-sized vessels are lined by hobnail endothelial cells in absence of significant nuclear atypia.

Table V. Pericytic (perivascular) tumours.

Benign and intermediate
Glomus tumour NOS
Myopericytoma, including myofibroma
Angioleiomyoma
Malignant
Glomus tumour, malignant

haemangiopericytomas are now recognized as examples of solitary fibrous tumours, however the list of lesions featuring haemangiopericytomas-like vessels

is broad and includes among others myopericytoma/myofibroma, synovial sarcoma, malignant peripheral nerve sheath tumours, endometrial stroma sarcoma, and mesenchymal chondrosarcoma. Solitary fibrous tumour still represents a diagnostic challenge because as mentioned above can mimic many mesenchymal and non-mesenchymal unrelated tumour entities⁴³. The availability of STAT6 immunostaining has certainly contributed to improve diagnostic accuracy⁴⁴ and, most importantly, for the first time the prediction of the outcome of is not simply determined by mitotic count⁴⁵, but by a risk assessment scheme that considers, patient's age, tumour size, depth of location, and mitotic index⁴⁶.

SMOOTH MUSCLE TUMOURS

The changes introduced in the category of soft tissue tumours featuring smooth muscle differentiation are represented by the inclusion as distinct entities of both EBV-associated smooth muscle tumours, and inflammatory leiomyosarcoma (Tab. VI).

EBV-associated smooth muscle tumours are intimately associated with EBV infection most often in the context of immunosuppression⁴⁷. Age range is broad as anatomic location. HIV-associated lesions however tend to occur most often in the central nervous system whereas post-transplant proliferations feature a remarkable tropism for the liver, followed by the lungs and the gastrointestinal tract. Prognosis tends to be more related to the evolution of the state of immunosuppression

Most cases of *inflammatory leiomyosarcoma* occur in the deep soft tissues of the lower limbs, trunk and retroperitoneum of adult patients, with a peak incidence between the third and the fourth decade⁴⁸. Microscopically smooth muscle cells are most often low grade and associated with a lymphoplasmacytic infiltrates that tend to be so prominent to overshadow the neoplastic component. Less often a histiocytic population predominates sometimes assuming a xanthomatous appearance. Inflammatory leiomyosarcoma seems to behave less aggressively than ordinary leiomyosarcoma however follow-up data are still very limited.

Table VI. Smooth muscle tumours.

Benign
Leiomyoma
Intermediate
Smooth muscle tumour of uncertain malignant potential
EBV-associated smooth muscle tumour
Malignant
Inflammatory leiomyosarcoma
Leiomyosarcoma

Table VII. Skeletal muscle tumours.

Benign
Rhabdomyoma
Malignant
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Spindle cell / sclerosing rhabdomyosarcoma
Ectomesenchymoma

SKELETAL MUSCLE TUMOURS

No major changes are reported within this subgroup (Tab. VII). A notable exception is however the recognition that rhabdomyosarcoma can occur primarily in bone as a spindle cell and epithelioid cell neoplasm (Fig. 4) that is most often associated with fusion of the *TFCP2* gene with *FUS* or *EWSR1* and expression of ALK (in absence of *ALK* gene rearrangement)⁴⁹⁻⁵¹. Recently an alternative *MEIS1-NCOA2* gene fusion has been reported⁵². With the bias determined by their extreme rarity, the clinical behaviour appears to be very aggressive.

GASTROINTESTINAL STROMAL TUMOURS (GIST)

One major step forward is that in the 5th series GIST is covered by the same authors in both the gastrointestinal and soft tissue fascicles, therefore ensuring a more homogenous diagnostic approach (Tab. VIII). In comparison with previous editions SDH-deficient GISTs are now discussed in greater detail. This distinct subset (accounting for approximately 5 to 10% of all GIST) is characterised by occurrence in children

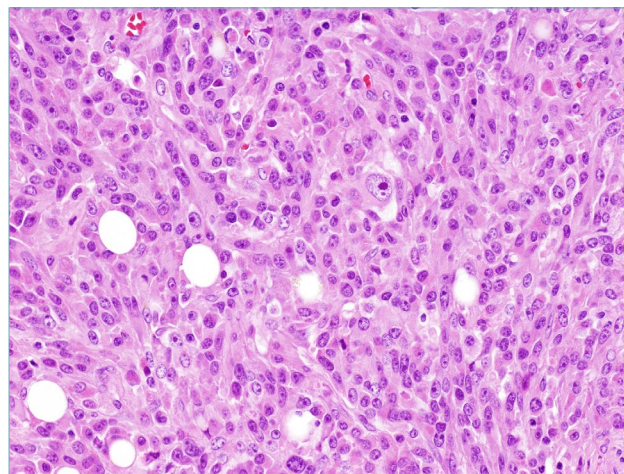


Figure 4. Intraosseous rhabdomyosarcoma. In this example an epithelioid atypical neoplastic cell population predominates.

Table VIII. Gastrointestinal stromal tumours.

Benign
MicroGIST
Malignant
Gastrointestinal stromal tumors

and adolescents, with female predominance⁵³. Relatively often SDH-deficient GISTs feature a distinctive multinodular pattern of growth associated with predominantly epithelioid morphology (Fig. 5A). The presence of *SDH* subunit genes mutations is observed in approximately 60% of cases (*SDHA* mutations are the most frequently observed) and, whatever the subunit involved is predicted by immunohistochemical loss of SDHB expression⁵⁴ (Fig. 5B). In 40% of cases SDHC promoter methylation (epimutation) is detected. Importantly SDH-deficient GIST appears to be resistant to tyrosine kinase inhibitors. In this context the risk assessment schemes utilised for *KIT/PDGFR*A mutated GIST is not applicable.

CHONDRO-OSSEOUS TUMOURS

As exemplified in Table IX no new entries have been included. Both soft tissue chondroma and extraskele-

Table IX. Chondro-osseous tumours.

Benign
Chondroma
Malignant
Osteosarcoma, extraskeletal

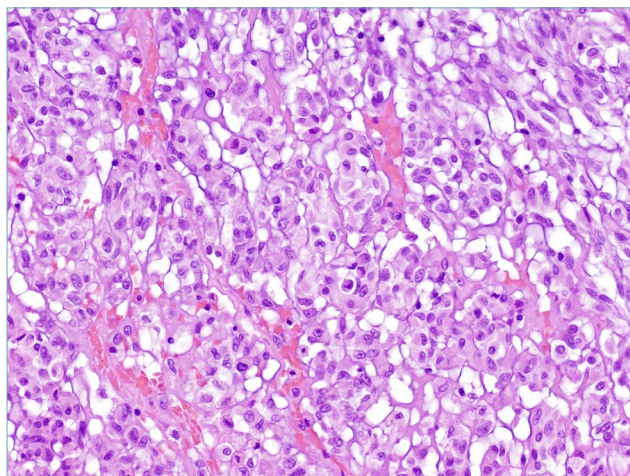


Figure 5A. SDH-deficient GIST. Most cases are predominantly composed of epithelioid cell with pale eosinophilic cytoplasm.

tal osteosarcoma represent exceedingly rare lesions. In approximately 50% of soft tissue chondroma FN1 gene rearrangements have been documented. Extraskeletal osteosarcoma remains an extremely aggressive neoplasms of elderly patients, often presenting with lung metastases at diagnosis.

PERIPHERAL NERVE SHEATH TUMOURS

The single major change introduced by the 2020 WHO classification is the recognition that so called melanotic schwannoma actually represents a clinically aggressive neoplasm (not belonging anymore to the intermediate category) being consequently relabelled as *malignant melanotic nerve sheath tumour*⁵⁵ (Tab. X). It most often occurs in a midline location within spinal and autonomic nerves of adult patients. A subset of lesions occurs in context of Carney complex. Microscopically is composed by spindle and epithelioid neoplastic cells organised in sheets and short fascicles. Cytoplasm vary from eosinophilic to amphophilic and contain round nuclei often featuring pseudoinclusions. The amount of pigment varies from focal to massively abundant (Fig. 6). Approximately half of cases contain psammoma bodies. Presence of necrosis and mitotic activity can be observed that however does not seem to predict outcome. Immunohistochemically, malignant melanotic nerve sheath tumour express S100, SOX10, HMB45 and MelanA. Pathogenetically, the vast majority of tumour are associated with inactivating mutation of the *PRKAR1A* gene leading to the loss of expression of the protein thereof⁵⁶. It has become evident that this lesion is associated with high risk of both local recurrence and metastatic spread, even

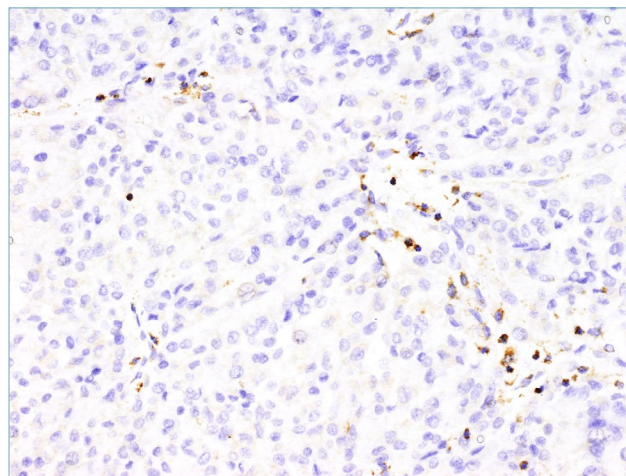


Figure 5B. SDH-deficient GIST. The neoplastic cells show loss of staining for SDHB. Endothelial cells and lymphocytes represent the internal positive control.

Table X. Peripheral nerve sheath tumours.

Benign
Schwannoma
Neurofibroma
Perineurioma
Granular cell tumour
Nerve sheath myxoma
Solitary circumscribed neuroma
Meningioma
Hybrid nerve sheath tumour
Malignant
Malignant peripheral nerve sheath tumour
Melanotic malignant nerve sheath tumour
Granular cell tumour, malignant
Perineurioma, malignant

many years from resection of the primary lesion. As a consequence, long term follow-up is strongly advised.

TUMOURS OF UNCERTAIN DIFFERENTIATION

The inclusion within this tumour category (Tab. XI) as an emerging entity of the category of *NTRK-rearranged spindle cell neoplasm* (excluding infantile fibrosarcoma that represent a distinct clinicopathologic entity defined molecularly by the presence of *NTRK3-ETV6* fusion gene), represents one of the most relevant innovation. The availability of a new class of drugs characterised by NTRK inhibitory action (Entrectinib and Larotrectinib) has in fact generated a remarkable interest towards any neoplasm harbouring a rearrangement of any of *NTRK 1, 2* and *3* genes⁵⁷. NTRK-rearranged spindle cell neoplasms appear

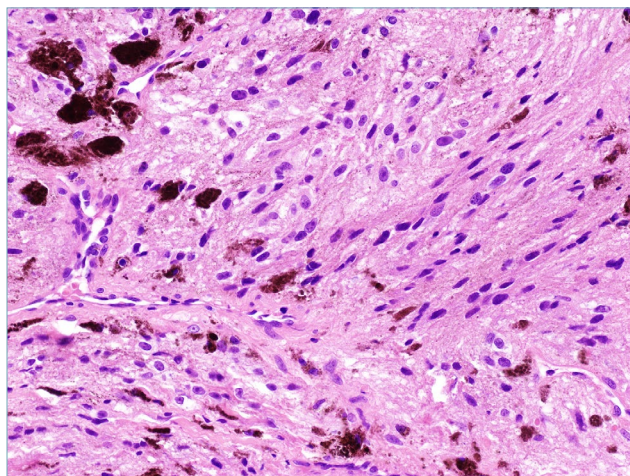


Figure 6. Malignant melanotic nerve sheath tumour. Spindle cell set in a fibrous stroma with heavy melanin pigment deposition is seen.

Table XI. Tumors of uncertain differentiation.

Benign
Myxoma (cellular myxoma)
Deep (aggressive) angiomyxoma
Pleomorphic hyalinising angiectatic tumour
Phosphaturic mesenchymal tumour
Perivascular epithelioid tumour, benign
Angiomyolipoma
Intermediate (locally aggressive)
Haemosiderotic fibrolipomatous tumour
Angiomyolipoma, epithelioid
Intermediate (rarely metastasising)
Atypical fibroxanthoma
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumour
Myoepithelioma
Malignant
Phosphaturic mesenchymal tumour, malignant
NTRK-rearranged spindle cell neoplasm (emerging)
Synovial sarcoma
Epithelioid sarcoma: proximal and classic variant
Alveolar soft part sarcoma
Clear cell sarcoma
Extraskeletal myxoid chondrosarcoma
Desmoplastic small round cell tumour
Rhabdoid tumour
Perivascular epithelioid tumour, malignant
Intimal sarcoma
Ossifying fibromyxoid tumour, malignant
Myoepithelial carcinoma
Undifferentiated sarcoma
Spindle cell sarcoma, undifferentiated
Pleomorphic sarcoma, undifferentiated
Round cell sarcoma, undifferentiated

to form a morphological spectrum that occurs most often in the superficial or deep soft tissue of the extremities of children and adolescents. The molecular pathogenesis is most often related to rearrangement of the *NTRK1* gene with a variety of partners. More rarely *NTRK2* and *NTRK3* aberrations have been detected. At one end of this spectrum is the so-called *lipofibromatosis-like neural tumour* (LLNT), composed of monomorphic spindle cells co-expressing S100 and CD34, featuring a highly infiltrative pattern within subcutaneous fat, therefore closely resembling lipofibromatosis (Fig. 7A). From the clinical standpoint LLNT can recur locally but seems not to possess metastatic potential⁵⁸.

A second subset of cases features a predominantly solid pattern of growth, and is composed of a cellular proliferation of uniform spindle cells that in higher grade examples resemble malignant peripheral nerve

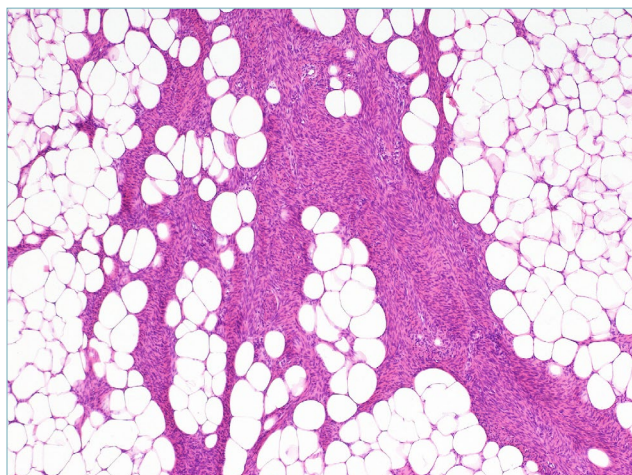


Figure 7A. Lipofibromatosis-like neural tumour. Spindle cells infiltrate adipose tissue resembling lipofibromatosis.

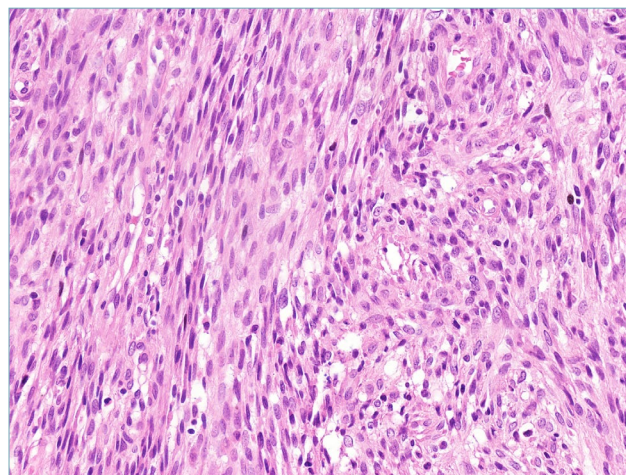


Figure 7B. NTRK-positive tumor resembling peripheral nerve sheath tumour. A highly cellular spindle cell proliferation organised in fascicles is seen.

sheath tumours and therefore labelled as *NTRK-rearranged neoplasm resembling peripheral nerve sheath tumours* (Fig. 7B). Prominent deposition of hyalinised collagen is often observed^{59,60}. Rarely, a myopericytoma-like architecture is detectable⁶¹. Outcome seems to correlate with morphology. Lesions with high grade features tend to behave aggressively often featuring distant spread to the lungs. All these entities share the expression (that is not of course specific) of anti-pan-TRK antibodies. Hopefully, the accrual of more cases will allow in the future to better define the clinicopathologic boundaries of this group of lesions.

UNDIFFERENTIATED SMALL ROUND CELL SARCOMAS OF BONE AND SOFT TISSUES

The creation of a separate chapter encompassing round cell sarcoma of soft tissue and bone also represents a major step forward of the 2020 WHO classification (Tab. XII). This new section contains not only the prototypical round cell sarcoma named Ewing's sarcoma, but also three distinct subsets that differs from Ewing's sarcoma clinically, pathologically and molecularly^{49,62}: 1. Round cell sarcomas with *EWSR1* gene fusion with non-ETS family members⁶³⁻⁶⁵, 2. CIC-re-

arranged sarcomas⁶⁶⁻⁶⁸, and 3. BCOR-rearranged sarcomas⁶⁹. Interestingly, despite significant morphologic overlap, most of these entities tend to exhibit some morphologic features predictive of the underlying molecular alteration. If Ewing sarcoma represents the prototype of round cell sarcoma, CIC sarcomas always exhibits focal pleomorphism, and at times epithelioid morphology can predominate (Fig. 8A). BCOR sarcomas (despite being allocated to the round cell sarcoma family) more often tend to exhibit a spindled morphology (Fig. 8B). NFATC2 sarcoma may exhibit remarkable epithelioid features (Fig. 8C), and PATZ1 sarcomas are composed of a rather undifferentiated round to ovoid cell population (Fig. 8D), often characterised by the presence of a sclerotic background. The differential diagnosis for these tumours is rather broad, and among round cell sarcomas includes alveolar rhabdomyosarcoma, desmoplastic small round cell tumour, poorly differentiated round cell synovial sarcoma, small cell osteosarcoma, and mesenchymal chondrosarcoma. A combination of morphologic, immunohistochemical, and molecular findings allows accurate classification in most cases. A granular diagnostic approach to Ewing sarcoma and Ewing-like sarcomas is justified by significant differences in terms of both response to chemotherapy and overall survival^{68,69}. As all these entities are in part defined by specific fusion genes, a molecular diagnostic approach based on NGS technology should be preferred⁸. In consideration of the extreme rarity of many of these tumour entities, referral to expert rare cancer centres or to rare cancer networks represents the best strat-

Table XII. Undifferentiated small round cell sarcomas of bone and soft tissue.

Ewing sarcoma
Round cell sarcoma with EWSR1-non-ETS fusions
CIC-rearranged sarcomas
Sarcoma with BCOR genetic alterations

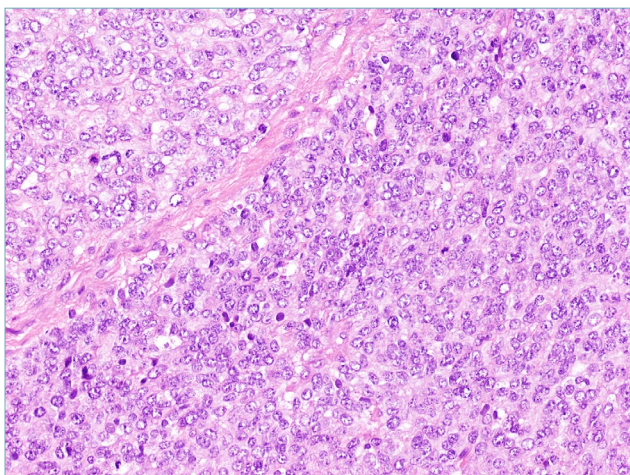


Figure 8A. CIC-rearranged sarcoma. Highly atypical undifferentiated neoplastic cells are organised in a diffuse pattern of growth.

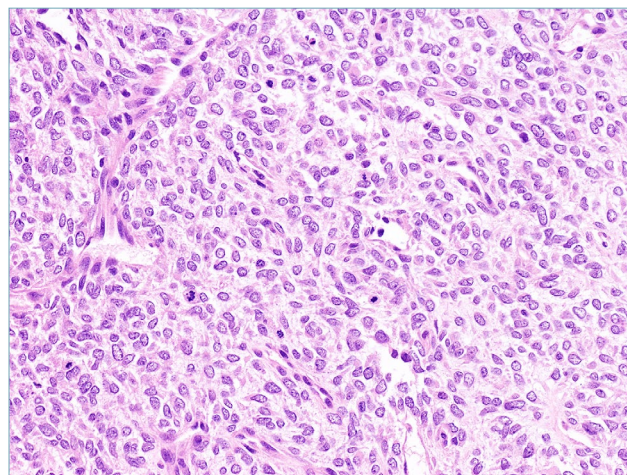


Figure 8B. BCOR-rearranged sarcoma. Neoplastic cell population tends to assume a spindle morphology.

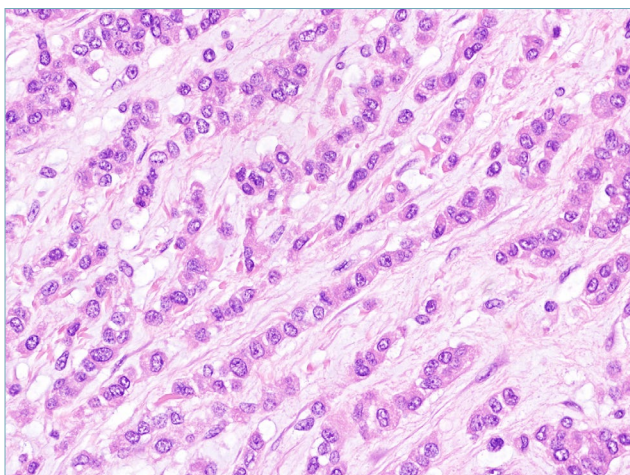


Figure 8C. NFATC2-rearranged sarcoma. Striking epithelioid morphology characterises the majority of cases.

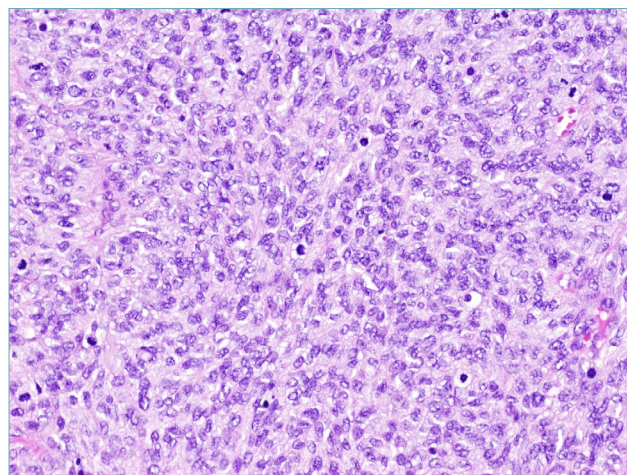


Figure 8D. PATZ1-rearranged sarcoma. Neoplastic cells feature round to ovoid nuclei and are organised in a diffuse pattern of growth.

egy in order to minimise diagnostic inaccuracy, and allow proper patient management.

Standing Issues

DIAGNOSTIC ROLE OF MOLECULAR PATHOLOGY

The integration of morphology and genetics represents one of the major advances introduced by WHO classification since 2000, to the extent that the “blue Book” was labelled as “Pathology and Genetics”¹⁷. In

the last 20 years descriptions of genetic aberrations (particularly new fusion genes) have increased exponentially. Many of these genetic abnormalities are linked with specific histotypes (i.e. *MDM2* gene amplification and well differentiated/liposarcoma; *SYT* gene rearrangement in synovial sarcoma etc.) whereas many others (particularly fusion genes) seem to represent non-driver (stochastic) molecular events the detection of which has been enhanced by extensive use of NGS-based molecular approaches⁷⁰. Moreover, some histotypes are currently defined on

the basis of their genetics (i.e. *NTRK*, *CIC* and *BCOR* sarcomas). Whether molecular analysis should be mandatorily associated with conventional microscopic examination is still source of debate. The WHO expert panel has decided to report in the “blue book” all pertinent genetic aberrations not making them diagnostically obligational. Two main reasons are: 1. Accurate pathologic diagnosis can be reached (in expert hands) without the support of molecular diagnostics. 2. WHO classification is meant to be used globally, including those countries in which molecular pathology is not implemented. Both arguments are of course valid. There exists however one contradiction represented by the introduction of entities labelled based on “specific” fusion genes. In our opinion, it sounds for instance somewhat illogical to make a diagnosis of EWSR1-SMAD3 positive fibroblastic tumour in absence of a formal demonstration of the associated genetic aberration.

DEFINITION OF A TUMOUR ENTITY

An unavoidable consequence of using molecular genetics as the main driver for tumour classification is to generate a debate regarding the principles behind the definition of a tumour entity. Moreover, the advent of “precision oncology” has generated the (mis) concept that extensive molecular profiling of cancer is the only way to improve patients’ outcome⁷¹. The underlying ambition would be the generation of a new taxonomy of human cancer based on molecular genetics, aimed to replace histology-based classifications. Certainly, molecular characterisation can allow to predict sensitivity to treatments, especially molecularly targeted therapies. In the sarcoma field, this has proved extremely effective with tyrosine kinase inhibition in GIST. The principle of precision oncology is however based on the concept that medical therapies should focus on the predictive molecular biomarker rather than on the histotype^{72,73}. This “histological agnosticism” has led for the first time to the approval of anticancer agents based solely on the availability of a molecular target. The prototypical example is in fact represented by neurotrophic tyrosine receptor kinase (NTRK) inhibitors, the concept being that a NTRK-inhibitor may be effective against different malignancies as long as they harbour a *NTRK* gene fusion⁵⁷. As discussed previously, the 2020 WHO classification has introduced an “emerging entity” named NTRK-rearranged spindle cell neoplasm¹⁹. This seems apparently a timely decision however it should be considered that several factors will necessarily influence the actual use of these new agents:

1 The clinical positioning of the drug that may vary

based on the natural history of the cancer type.

2 The actual need for a medical therapy when the stage of the disease is considered.

3 The availability of alternative effective agents.

An NTRK-inhibitor will be used for instance as a last-line therapy in one malignancy and as a first-line therapy in another one. In other words, the regulatory approval of a drug may be histologically agnostic, but its clinical use will never be. Irrespective of its predictive power, a molecular biomarker aimed to select medical therapies should never become the key element to define a disease. In the case of NTRK rearranged spindle cell sarcomas one may suppose that these tumours are sensitive to the new NTRK-inhibitors, however their epidemiology, clinical presentation, natural history and prognosis seems to be extremely variable and somewhat unspecific. If the only common denominator, is the potential activity of a class of drugs, actually many other unrelated non-mesenchymal cancers will be sensitive to the same drugs. On the contrary, a time-honoured entity such as infantile fibrosarcoma, in addition to be pathogenetically related to a gene fusion involving *NTRK3*, clearly features epidemiological, clinical and pathologic characteristics which are highly specific. Its sensitivity to NTRK-inhibitors is just a complement to all that. Thus, while there is no reason to challenge the existence of a disease called infantile fibrosarcoma, one could for instance consider premature (this may change in the future as more data are collected) to consider NTRK-rearranged spindle cell neoplasm as a distinct nosological entity, and this may in principle apply to other “new” sarcoma entities. For these reasons, the concept that a new entity in the sarcoma field should never reflect just the mere presence of a predictive molecular biomarker has been recently proposed to the sarcoma community⁷⁴.

Conclusions

The publication of a new WHO classification represents a major step towards standardization of cancer diagnostics. In the case of rare diseases such as soft tissue tumours its value is even greater as it contributes significantly to improve diagnostic accuracy. Pathologic diagnosis of cancer represents the result of a complex integration of microscopic, immunophenotypic and molecular features and, with rare exceptions is the cornerstone of clinical decision making. WHO classification appears more and more as the field wherein the joint efforts of pathologists, geneticists and clinicians can translate novel findings into more rationale as well as more effective treatments.

Authors' contributions

MS drafted the manuscript. EB selected the illustrations and drafted the tables. APTD edited the final version of the manuscript. All authors approved the manuscript.

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