ELSEVIER

European Journal of Cancer 40 (2004) 543–548

European Journal of Cancer

www.ejconline.com

Current soft-tissue sarcoma classifications

S. Daugaard*

Department of Pathology 5443, Rigshospitalet, Frederik V's Vej 11, DK-2100 Copenhagen Ø, Denmark

Received 21 July 2003; received in revised form 20 October 2003; accepted 20 November 2003

Abstract

In order to analyse the impact of modern sarcoma classification criteria, pathological material from 281 extremity soft-tissue sarcomas (STS) was reviewed. The cases were originally diagnosed between 1972 and 1994, and the most frequent diagnoses then were malignant fibrous histiocytoma (MFH) (26%), liposarcoma (21%), fibrosarcoma (11%), and leiomyosarcoma (10%). After reclassification, the proportions had changed significantly, with the largest group now being leiomyosarcomas (20%), liposarcomas (17%), synovial sarcomas (14%), and sarcomas 'not otherwise specified' (NOS) (11%). The original diagnosis was changed in 57% of the cases; in particular, the number of fibrosarcomas was reduced from 32 to 6, and MFHs from 72 to 2, with 22 renamed as myxofibrosarcomas; 20 (7%) were found not to be sarcomas. The main reasons for these results are the recent advances in immunohistochemistry (IHC) together with changes in nomenclature. The findings have obvious implications, in particular for retrospective research.

Keywords: Soft-tissue sarcomas; Pathology; Classification; WHO; Review

1. Introduction

Until recently, the clinical importance of histological typing and subtyping of soft-tissue sarcomas (STS) was minor, since their treatment depended more on grade, stage, and technical considerations in relation to the site. The main role of the pathologist was to exclude other types of malignancy (or even benign lesions, 'pseudosarcomas') and to perform a grading, the latter being of more immediate relevance to the surgeon and the radiotherapist, as well as being the most important histopathological prognostic factor in most studies [1]. However, with the accumulating knowledge of molecular mechanisms of growth and oncogenesis, new treatment strategies are gradually becoming possible. This is illustrated in the recent use of the tyrosine kinase inhibitor, imatinib (STI571), in gastrointestinal stromal tumours (GISTs) [2]; these were, until a few years ago, considered to be variants of leiomyosarcomas, but modern immunohistochemical (IHC) techniques have shown them to have a characteristic marker profile (notably positivity for c-kit, or CD117), allowing a confident identification in all but a few cases [3]. Thus, histological typing now has direct implications for therapy at least for intra-abdominal sarcomas [4].

In the new and timely World Health Organisation (WHO) classification of STS published in the autumn of 2002 [5], the importance of correct histotyping has been recognised by the incorporation of IHC into the diagnostic criteria, and in many cases molecular genetic data has also been included. The classification represents a summary of recent pathobiological advances and provides a new baseline for clinical as well as laboratory research.

The present study shows the impact of modern diagnostic criteria on historical material from extremity STS and discusses some of the common problems in differential diagnosis, as well as their implications for retrospective research.

2. Patients and methods

A search of the files of the Department of Pathology, Rigshospitalet, identified 302 patients coded as having a STS (apart from Kaposi's sarcoma) of an extremity in the period of 1972–1994 (this search was not exhaustive; Systematized Nomenclature of Medicine (SNOMED)

* Tel.: +45-3545-5340; fax: +45-3545-6380.
E-mail address: sarcpath@rh.dk (S. Daugaard).

0959-8049/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2003.11.009

coding was not introduced until 1980, and not all cases before this date had been coded subsequently). Of these, one was a coding error, and material was not available for a further 20 (referral or consultation) cases, leaving 281 evaluable tumours, from mainly adult patients (only six were less than 15 years old). The slides were reviewed (from 1998 onwards), and if judged necessary, new sections were cut and IHC performed. A list of the most important antibodies used is shown in Table 1. In a few cases, the paraffin blocks were not available, or no tissue was left in the blocks; the probable diagnosis then had to be made from the slides alone. IHC was used from 1984 onwards (365 stains on 92 cases, with 1–12 stains per case); in the beginning, only a few antibodies were available (polyclonal anti-keratin, S-100, myoglobin). Electron microscopy (EM) was performed with varying enthusiasm during this time period; micrographs were reviewed in seven cases, where it was helpful in reaching the diagnosis.

A second and final review took place from 2001 to 2003, i.e. mainly before the new WHO classification was published, but generally the same nomenclature and diagnostic criteria were used. However, two additional terms were thought to be useful: *Pleomorphic myogenic sarcoma* was used to designate high grade tumours where the differential diagnosis stood between leiomyo- and rhabdomyosarcoma [6], and morphology and IHC were inconclusive; *Myofibrosarcoma* was used as suggested by Mentzel in Ref. [7], especially if supported by EM.

As 'original diagnosis', the first (earliest) diagnostic suggestion has been used; in some cases, this was changed later, especially if recurrences yielded better material, or EM or new IHC stains had become available in the meantime.

If the material made it possible, the tumours were graded according to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [8]. Their location (superficial or deep) was also noted.

3. Results

A total of 5189 slides were reviewed, corresponding to an average of 18.5 slides per case (range 1–96). The average number of paraffin blocks per case was 9.7 (range 1–37). In 60 cases, two events were included, and in 7 cases, three events. No blocks were available in 13 cases; in 2 of these, the diagnosis was changed (an unclassified sarcoma was judged to be an epithelioid sarcoma based on the morphology and reinterpretation of the original IHC stains; and a dermatofibrosarcoma protuberans was reclassified as an aneurismal fibrous histiocytoma, supported by a negative staining for CD34 on a preserved unstained slide). In 82 cases, new IHC stains were performed (1–14 per case, with a total of 462).

The histological diagnoses are shown in Table 2. Among the original diagnoses, the most popular was malignant fibrous histiocytoma (MFH) (26%), followed by liposarcoma (21%), fibrosarcoma (11%), leiomyosarcoma (10%), synovial sarcoma (8%), sarcoma not otherwise specified (NOS) (5%), and neurofibrosarcoma (4%). After review, the most frequent diagnosis was leiomyosarcoma (20%), liposarcoma (17%), synovial sarcoma (14%), sarcoma NOS (11%), and myxofibrosarcoma (8%). The original diagnosis was changed in 160 of the 281 cases (57%). In 42 cases (15%), this was simply a change in nomenclature, but in the remaining 118 cases (42%), there was actual disagree-

Table 1
List of the most important antibodies used and their major reactivity in soft-tissue sarcomas (STS)

Antibody (clone)	No. of times used	Main reactivity
Actin (1A4), alpha-smooth muscle actin	67	Myogenic tumours: MFS, LMS, RMS
Actin (HHF35), muscle-specific actin	25	As above
Bcl-2 (124), oncoprotein	29	Broad; stromal cells in SS
CD31 (JC70A), PECAM-1	5	Endothelium-derived tumours
CD34 (My10)	50	Endothelium-derived tumours; ES; SFT/HPC; DFSP; GIST
CD56 (1B6), NCAM	2	Neural crest-derived tumours; MPNST; RMS; SS
CD68 (KP1)	10	Macrophages; benign FH
CD99 (12E7), MIC2	4	Ewing's sarcoma/PNET; SS
Cytokeratins (AE1/AE3, KP1 or MNF116)	19	Carcinomas; ES; SS
Desmin (D33)	60	Myogenic tumours: LMS; RMS
EMA (E29), epithelial membrane antigen	32	Carcinomas; ES; SS; SEFS
Human melanosome (HMB45)	8	Malignant melanomas; 'PEComas'
Myf-4 (LO26), human myogenin	15	RMS
Myoglobin (polyclonal)	13	RMS
S-100 (polyclonal)	70	Broad; MPNST; SS

ES, epithelioid sarcoma; FH, fibrous histiocytoma; LMS, leiomyosarcoma; MFS, myofibrosarcoma; MPNST, malignant peripheral nerve sheath tumour; RMS, rhabdomyosarcoma; SEFS, sclerosing epithelioid fibrosarcoma; SS, synovial sarcoma; GIST, gastrointestinal stromal tumours; SFT, solitary fibrous tumour; NCAM, neural cell adhesion molecule; PECAM, platelet/endothelial cell adhesion molecule.

Table 2
Histological diagnoses of 281 extremity soft tissue sarcomas

Original (first) diagnosis		Review diagnosis	
Alveolar soft part sarcoma	3	Alveolar soft part sarcoma	4
Angiosarcoma	2	Angiosarcoma	2
'Benign synovioma?'	1	Chondrosarcoma, extraskeletal myxoid	3
Chondrosarcoma, mesenchymal	1	Chondrosarcoma, mesenchymal	2
Clear cell sarcoma	3	Clear cell sarcoma	2
Dermatofibrosarcoma protuberans	5	Dermatofibrosarcoma protuberans	1
Epithelioid sarcoma	4	DFSP with sarcoma	2
Fibrosarcoma	32	Epithelioid sarcoma	7
Haemangioendotheliosarcoma	1	Fibrosarcoma	6
Haemangiopericytoma	2	Leiomyosarcoma	57
Leiomyosarcoma	29	Liposarcoma	49
Lipoma, intramuscular	1	Low grade fibromyxoid sarcoma	2
Liposarcoma	60	Malignant peripheral nerve sheath tumour	9
Malignant fibrous histiocytoma	72	Malignant fibrous histiocytoma	2
Malignant mesenchymoma	1	Myofibrosarcoma	5
Malignant Schwannoma	5	Myogenic sarcoma (high-grade NOS)	11
Myofibroblastic sarcoma	2	Myxofibrosarcoma	22
Myxofibrosarcoma	2	Osteosarcoma, extraskeletal	3
Neurofibrosarcoma	10	Rhabdomyosarcoma	2
Osteosarcoma, extraskeletal	1	Sarcoma NOS	31
Rhabdomyosarcoma	7	Solitary fibrous tumour, malignant	1
Sarcoma NOS	14	Synovial sarcoma	38
Synovial sarcoma	23	Not sarcoma	20

DFSP, dermatofibrosarcoma protuberans; NOS, not otherwise specified.

Table 3
Lesions found not to be sarcomas by review ($n = 20$)

Atypical fibroxanthoma	1
Fat necrosis	1
Fibromatosis	5
Fibrous histiocytoma, dermal	1
Fibrous histiocytoma, deep	2
Fibrous histiocytoma, angiomatoid	1
Inflammatory lesion	1
Lipoma	1
Lipoma, atypical	1
Nodular fasciitis	2
Solitary fibrous tumour, benign	1
Metastases (adenocarcinoma; clear cell carcinoma; malignant melanoma)	3

ment on the classification. Thus, 20 lesions (7%) were found not to be sarcomas at all (Table 3). Best agreement was found within the groups of leiomyosarcomas (86%) and liposarcomas (73%), the poorest among the fibrosarcomas (Table 4) and the MFHs (Table 5).

A histological grade could be assigned in 257 cases: 58 (23%) were grade I, 103 (40%) grade II, and 96 (37%) grade III. These proportions did not differ significantly between superficial and deep locations. 157 tumours were deep, 101 were superficial; depth could not be determined in 23 cases.

Table 4
Review diagnoses of 32 fibrosarcomas

Fibromatosis	5
Fibrosarcoma	4
Leiomyosarcoma	10
Liposarcoma (myxoid)	1
MPNST	1
Myxofibrosarcoma	2
Nodular fasciitis	1
Sarcoma NOS	2
Solitary fibrous tumour, benign	1
Synovial sarcoma	5

MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified.

Table 5
Review diagnoses of 72 malignant fibrous histiocytomas

DFSP with sarcoma	2
Leiomyosarcoma	18
Liposarcoma, pleomorphic	3
Low grade fibromyxoid sarcoma	1
Malignant fibrous histiocytoma	2
Myofibroblastic sarcoma	2
Myogenic sarcoma (high-grade, NOS)	6
Myxofibrosarcoma	14
Osteosarcoma, extraskeletal	2
Sarcoma NOS	20
Solitary fibrous tumour, malignant	1
Synovial sarcoma	1

DFSP, dermatofibrosarcoma protuberans; NOS, not otherwise specified.

4. Discussion

The last twenty years have witnessed significant advances in the diagnosis of soft-tissue tumours, mainly with regard to the application of IHC. There has been an increasing number of antibodies available together with increasingly efficient antigen-retrieval methods, such as heat-induced epitope retrieval (HIER). Recently, cytogenetics have also contributed—a fact reflected in the latest WHO classification [5]. This attempts to minimise the inherent subjectivity of this field by combining these results with morphology and hopefully establishing reproducible diagnostic criteria. The experience from the previous classifications shows that poorly defined entities like fibrosarcomas, haemangiopericytomas and MFHs have a tendency to become diagnostic 'waste baskets'. As long as the clinical management of these tumours was independent of their subclassification, this imprecision could be ignored; however, as the example of the GISTs shows, a correct histological diagnosis, in combination with an analysis of markers such as c-kit (CD117), may very soon have therapeutic implications [2–4].

Fibrosarcoma is defined as a malignant tumour composed of fibroblasts; there are no immunological markers for this cell type, which makes its diagnosis a question of exclusion by IHC. It has consequently become very rare, although it has been boosted by the recent description of an epithelioid sclerosing variant [9], listed as a separate entity by the WHO. Approximately half express epithelial membrane antigen (EMA). Of the six cases that were diagnosed as fibrosarcoma, three were of this subtype; of the remaining three, two were negative by IHC, and in the last case no paraffin blocks were available. The results in Table 4 also reflect a previous controversy of the 1970s: namely, whether to use the term 'aggressive fibromatosis/desmoid tumour' or 'low grade (or even grade 1/2) fibrosarcoma' [10].

Leiomyosarcoma and (monophasic) synovial sarcoma are classical morphological differential diagnoses that today are easily discriminated by IHC. Leiomyosarcomas are positive for at least one of the myogenic markers actin, desmin or caldesmon (a fairly specific, but not very sensitive marker). Synovial sarcomas express EMA and cytokeratins in their epithelial component, while the stromal component is positive for bcl-2, CD56, and S-100 to a varying degree.

The term MFH has been partly abandoned in the 2002 WHO classification. The myxoid MFH is synonymous with myxofibrosarcoma (which is now the preferred term); it is mainly a tumour of the elderly and is often superficially located, i.e. subcutaneous. Its establishment as a separate entity is thus justified by its clinical and morphological features, even though it does not have a characteristic IHC profile and no specific cytogenetic aberrations have as yet been demonstrated. Pleomorphic/giant cell/inflammatory MFHs are now considered to be—in WHO terminology—'undifferentiated pleomorphic sarcomas' (here called NOS for brevity's sake). This change in terminology may appear to be trivial, but it discourages the use of a name that must be considered obsolete and 'pseudo-specific' by today's standards, and it clearly implies that an effort should be made to characterise these tumours as far as the available methods allow. Modern IHC methods can often demonstrate subtle cellular differentiation and help determine the classification. A substantial number of pleomorphic MFHs can thus be proven to be leiomyo-/myogenic sarcomas (Table 5) [11] or, in the case of the retroperitoneum, dedifferentiated liposarcomas [12]. The term MFH was retained in only two instances in this material; both were superficially located (subcutaneous) and exhibited a morphology similar to the dermal fibrous histiocytoma, but were obviously malignant (grade III). Both might arguably have been classified as sarcomas NOS.

The other changes in nomenclature are less important, since the names are self-explanatory. Angiosarcoma is now preferred to the cumbrous haemangioendotheliosarcoma, and the academic distinction between malignant Schwannoma and neurofibrosarcoma has been abandoned in favour of the term malignant peripheral nerve sheath tumour, usually shortened to MPNST.

New entities appearing during the period in question and incorporated in the new WHO classification are the low grade fibromyxoid sarcoma and the solitary fibrous tumour. The latter partly replaces the term haemangiopericytoma, which may still be used for what is now considered to be one end of a morphological spectrum [5].

The 2002 WHO classification uses the term myofibroblastic sarcoma in only one instance: the 'low grade myofibroblastic sarcoma', an almost fibromatosis-like lesion of the head and neck. Unsurprisingly, this type was not identified in the present material of extremity sarcomas; but five cases of intermediate or high grade were nonetheless designated 'myofibroblastic sarcomas'. Since 'Fibrous Tissue Tumours' in the 1994 WHO classification are now termed 'Fibroblastic/Myofibroblastic tumours', one might argue that they may as well be classified as variants of adult fibrosarcoma. However, this author agrees with others [7] that they constitute a recognisable entity with a morphology exhibiting traits of both leiomyosarcomas and classical fibrosarcomas, as well as typical peripheral cytoplasmic IHC staining for actin. With EM, their ultrastructure recapitulates that of the normal myofibroblast. The controversy arises because there are no universally agreed minimum criteria for the diagnosis of myofibroblasts, especially in neoplasia [13]. Molecular genetics may be able to clarify these issues in the future.

The other non-WHO term of 'pleomorphic myogenic sarcoma' was applied because high grade leiomyosarcomas and rhabdomyosarcomas are often indistinguishable on routine light microscopy alone, and ancillary techniques are necessary to separate them. However, EM is time-consuming and prone to sampling errors; and in spite of the claims of some investigators [6], IHC may not be conclusive. For instance, the interpretation of myoglobin staining results is not always straightforward, especially on old material; and it is not always clear what to make of focal or weak nuclear staining for myf-4 (myogenin). Besides, rhabdomyoblastic differentiation in a *bona fide* retroperitoneal leiomyosarcoma has been reported [14].

The number of synovial sarcomas increased significantly in the review diagnosis, from 8 to 14%. Again, this is mainly due to IHC, with markers such as bcl-2 and EMA being particularly useful. In addition, awareness of this diagnostic entity has increased during recent years, particularly with the realisation that it has nothing to do with the synovium proper and may be found far away from the joints, e.g. in the thorax and neck. Some clinicians are still perplexed by this. The designation is thus unfortunate, but attempts to rename these tumours have been met with resistance [5,15].

Even with modern IHC, some 10% of sarcomas turn out to be unclassifiable, or NOS [13]. In this material, the proportion was 11%; this was, in some cases, due to the absence of blocks or small amounts of tissue. While being a significant adjunct in the classification of STS, IHC clearly has its limitations, even with the improved modern detection protocols. Above all, it should be stressed that the results of IHC (and for that matter, data from cytogenetics) must always be interpreted in context with the morphological and clinical findings. Of the markers listed in Table 1, only myoglobin and myf-4 (myogenin) appear to be specific. For a recent balanced review of IHC in the diagnosis of soft tissue tumours, see Ref. [16].

A review like this inevitably finds cases where the original diagnosis is clearly wrong (as opposed to findings that are open to subjective interpretation), e.g. in the case of metastatic carcinomas (Table 3). Again, the advances in IHC are of overwhelming importance in reaching the correct diagnosis. However, in some cases, such as the misinterpretation of nodular fasciitis or fatty tumours with reactive changes, it is clear that the major factor is lack of experience on behalf of the describing pathologist—the usual expert having being absent or the position vacant. This underlines the need for centralisation and multidisciplinary integration of the diagnosis and treatment of these tumours; optimally, key diagnostic functions should not be dependent on a single person [17].

This study also emphasises the need for pathological review whenever historical (i.e. more than a few years old) material is used uncritically and without review in retrospective analyses regarding molecular biology, prognostic markers etc. The occurrence of a significant number of fibrosarcomas, for instance, in such studies must necessarily cast severe doubt on the validity of any conclusions reached, at least with regard to the histotypes. The term MFH should also be avoided, unless qualified by a closer definition. One should also be aware that comparison of modern with older published series of fibrosarcomas and MFHs is methodologically unsound. The accelerating development within IHC and molecular pathology is bound to refine our diagnoses and classifications further in the future. Thus, so far, IHC has been used mainly to demonstrate phenotypical differentiation which can be quite irrelevant when the underlying cytogenetic abnormalities are considered (e.g. synovial sarcomas may vary in their antigen expression, but are characterised by their t(X;18) translocation in more than 90% of cases). However, there is a new trend within IHC: the demonstration of specific gene products with prognostic or therapeutic implications. The best examples are CD117 (c-kit) as mentioned above, and HER-2/neu overexpression which offers the possibility of treatment with trastuzumab (Herceptin) (already a routine treatment for breast cancer). Other potential candidates include the epidermal growth factor receptor (EGFR) or insulin-like growth factor receptor (IGFR). Conventional morphology offers substantial prognostic information, but molecular pathology will increasingly be able to indicate therapeutic strategies.

The optimal tumour classification is one that assures a reproducible diagnosis that is also clinically useful. Whether these goals are best reached by morphology or genetics can be discussed, since both have their limitations. The new WHO classification reflects a balanced view, or perhaps a compromise, between these viewpoints; as such, it represents a step forward in our understanding of STS and provides a new baseline for research. But it may soon be outdated, given the present rate of new discoveries in molecular pathology and pharmacology.

5. Conflict of interest statement

The author is a member of the Pathological Subcommittee of the Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer (EORTC).

References

1. Coindre JM, Terrier P, Guillou L, *et al*. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas. *Cancer* 2001, **91**, 1914–1926.

2. van Oosterom AT, Judson IR, Verweij J, *et al*. Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumours: a report of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2002, **38**(Suppl. 5), S83–S87.
3. Graadt van Roggen JF, van Velthuysen MLF, Hogendoorn PCW. The histopathological differential diagnosis of gastrointestinal stromal tumours. *J Clin Pathol* 2001, **54**, 96–103.
4. Greenson JK. Gastrointestinal stromal tumors and other mesenchymal lesions of the gut. *Mod Pathol* 2003, **16**, 366–375.
5. Fletcher CDM, Unni KK, Mertens F, eds. *Pathology and Genetics of Tumours of Soft Tissue and Bone (World Health Organization Classification of Tumours)*. Lyon, France, IARC Press, 2002.
6. Schürch W, Bégin LR, Seemayer TA, *et al*. Pleomorphic soft tissue myogenic sarcomas of adulthood. A reapprisal in the mid-1990s. *Am J Surg Pathol* 1996, **20**, 131–147.
7. Mentzel T. Myofibroblastic sarcomas: a brief review of sarcomas showing a myofibroblastic line of differentiation and discussion of the differential diagnosis. *Curr Diagn Pathol* 2001, **7**, 17–24.
8. Guillou L, Coindre JM, Bonichon F, *et al*. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997, **15**, 350–362.
9. Meis-Kindblom JM, Kindblom LG, Enzinger FM. Sclerosing epithelioid fibrosarcoma. A variant of fibrosarcoma simulating carcinoma. *Am J Surg Pathol* 1995, **19**, 979–993.
10. Mackenzie DH. *The Differential Diagnosis of Fibroblastic Disorders*. Oxford and Edinburgh, Blackwell Scientific, 1970, 67–102 [chapter 9].
11. Oda Y, Tamiya S, Oshiro Y, *et al*. Reassessment and clinicopathological prognostic factors of malignant fibrous histiocytoma of soft parts. *Pathology Int* 2002, **52**, 595–606.
12. Coindre JM, Mariani O, Chibon F, *et al*. Most malignant fibrous histiocytomas developed in the retroperitoneum are dedifferentiated liposarcomas: a review of 25 cases initially diagnosed as malignant fibrous histiocytoma. *Mod Pathol* 2003, **16**, 256–262.
13. Weiss SW, Goldblum JR. *Enzinger and Weiss's Soft Tissue Tumors*. St Louis, MO, Mosby Inc, 2001.
14. Roncaroli F, Eusebi V. Rhabdomyoblastic differentiation in a leiomyosarcoma of the retroperitoneum. *Hum Pathol* 1996, **27**, 310–313.
15. Ghadially FN. Is synovial sarcoma a carcinosarcoma of connective tissue? *Ultrastruct Pathol* 1987, **11**, 147–151.
16. Coindre JM. Immunohistochemistry in the diagnosis of soft tissue tumours. *Histopathology* 2003, **43**, 1–16.
17. Grimer RJ, Carter SR, Spooner D, Sneath RS. Diagnosing musculoskeletal tumours. *Sarcoma* 2001, **5**, 89–94.