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ORIGINAL ARTICLE

Histopathological diagnoses in soft tissue tumours: an experience from a tertiary centre in Malaysia

Nur Dini JALALUDIN *MB Bch BAO*, Noraini MOHD DUSA* *MD, MPath,* Mohd Rohaizat HASSAN** *MD, M.Comm.Med* and Nordashima ABD. SHUKOR *MD, MPath*

*Department of Pathology, Universiti Kebangsaan, Malaysia Medical Centre, Kuala Lumpur, Malaysia, *Department of Pathology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, and **Department of Community Health, Universiti Kebangsaan, Malaysia Medical Centre, Kuala Lumpur, Malaysia*

Abstract

Soft tissue tumours are a group of remarkably diverse neoplasms that frequently pose significant diagnostic challenges to general pathologists. This study aimed to compare the agreement of histopathological diagnoses between general pathologists from various referral institutes and the referred soft tissue pathologist in a tertiary centre. The common discrepancies and their causes are also presented here. A retrospective study was conducted on 243 cases of potential soft tissue tumours referred to Hospital Kuala Lumpur, Malaysia over a period of 5 years. Reports by the referring pathologists and the soft tissue pathologist were compared based on tumour classification and tumour behaviour. Overall, there was moderate agreement in soft tissue tumour diagnoses in both tumour classification (weighted $\kappa = 0.423$) and tumour behavior (weighted $\kappa = 0.548$). The highest agreement of tumour classification was seen in the adipocytic tumours (21/28 cases), Ewing sarcoma (5/7 cases) and smooth-muscle tumours (3/5 cases). The highest rates of discrepancies were the so-called fibrohistiocytic tumours (7/11 cases), vascular tumours (9/15 cases) and undifferentiated/ unclassified sarcomas (19/32 cases). Full agreement for tumour behaviour was seen in 178 cases and there were 21 cases of zero agreement. Liposarcoma, alveolar soft part sarcoma and benign fibrous histiocytoma were the most frequent benign/malignant diagnostic discrepancies. The most common causes of discrepancy were wrong morphological interpretation followed by insufficient immunohistochemical stains performed. In conclusion, review of diagnosis by a pathologist specialized in soft tissue improves the quality of diagnosis in these heterogenous and rare tumours. A good panel of immunohistochemical stains with additional molecular study is crucial in the general hospital laboratories practice.

Keywords: histopathology, diagnosis, soft tissue tumours, agreement, discrepancies

INTRODUCTION

Soft tissue tumours represent a heterogenous group of neoplasms that can occur at any anatomical sites. According to WHO, the estimated annual incidence of soft tissue tumours is 3000 per million population.[1] The rarity of soft tissue tumours and its constantly evolving histopathological criteria, poses a challenge for general pathologists resulting in referral to centres with a soft tissue pathologist.

Over the past two decades, a few studies have shown that diagnostic agreement in soft tissue neoplasm between primary institutional diagnosis and reviewer diagnosis ranges from 53% to 73%.[2] Overall diagnostic discrepancies range from 28% – 35%, of which minor discrepancies constitute 7% to 16% and major discrepancies 11% to 25%.[2]

The gold standard in the diagnosis of a soft tissue tumour is histopathological assessment which is often difficult and requires further ancillary techniques including immunohistochemistry, cytogenetic and molecular genetics testing.[3] The latest WHO Classification (4th edition) on soft tissue tumour has incorporated more detailed cytogenetic and molecular data in the diagnosis of soft tissue tumours.[4] However, despite the increasing use of ancillary molecular

Address for correspondence: Dr Nordashima Abd Shukor, Pathology Department, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia. Email: nordashima@ppukm.ukm.edu.my

and molecular cytogenetic testing, significant discrepancy still exists between the referring pathologist's diagnosis and the final diagnosis by a soft tissue pathologist.[2] To date, there is no study done in Malaysia to evaluate the degree of agreement or discrepancies in the diagnoses of soft tissue neoplasm.

Hospital Kuala Lumpur (HKL) is a tertiary referral centre in Malaysia and the histopathology department receives soft tissue tumour referral cases from other Ministry of Health hospitals and institutions. The referral cases are reviewed by a histopathologist trained in soft tissue tumours. In this study, we aimed to determine the diagnostic agreement and causes of diagnostic discrepancies in the reporting of soft tissue tumour cases between general hospital laboratories and a tertiary centre.

MATERIALS AND METHODS

Study design

A retrospective study was performed on soft tissue tumours cases referred to a soft tissue pathologist (N.M.D) over a period of 5 years. The record files within the Department of Histopathology at Hospital Kuala Lumpur were examined from 1st February 2011 to the 31st December 2015. The cases were referred for second opinion either by general pathologists from various states and institutions in Malaysia or by treating physicians or surgeons in HKL. All cases without a complete histopathology impression/diagnosis or referral with morphological description only were excluded. Each referral impression/diagnosis was compared with the final diagnosis and panel of immunohistochemical (IHC) studies performed. The diagnoses were classified according to the classification established in the 4th edition of 'WHO Classification of Tumours of Soft Tissue and Bone' blue book. This classification is based on the tissue origin of the soft tissue neoplasia. There are 12 classes of tumour types: adipocytic tumours, fibroblastic/myofibroblastic tumours, so-called fibrohistiocytic tumours, smooth-muscle tumours, pericytic (perivascular) tumours, skeletal-muscle tumours, vascular tumours, chondro-osseous tumours, gastrointestinal stromal tumours, nerve sheath tumours, tumours of uncertain differentiation and undifferentiated/unclassified sarcomas.[4] For the purpose of this research, these tumour classes were labeled as 1 to 12 respectively. Ewing sarcoma (which is classified under bone tumour) and general diagnoses of soft tisssue tumour without any specific tissue classification as per WHO, were grouped and labeled as 13. Non-soft tissue tumour diagnoses or no specific diagnosis were labeled as group 14. The tumour behaviour were recorded based on WHO disease behaviour as benign (0), intermediate (locally aggressive/rarely metastasising) (1) and malignant (3) tumours.[4]

Statistical method for degree of agreement

The degree of agreement for tumour classification and tumour behaviour were measured by linear weighted kappa using the MedCalc software version 11.6.0. The linear weighted kappa value obtained would confer the degree of agreement between the referring pathologists' and the final (referral) pathologist's diagnoses as poor (< 0.2), fair (0.21 - 0.4), moderate (0.41 - 0.6), good (0.61 - 0.8) and very good (0.81 - 1.0).[5]

Analysis of discrepant cases

Among the cases with discrepant diagnoses, those which showed benign/malignant discrepancies or soft-tissue/non soft tissue discrepancies were analysed further as 'zero agreement' cases. In these cases, the morphological interpretation, panel of immunohistochemical stains performed as well as their interpretation by the referring pathologists and the final pathologist were compared.

RESULTS

A total of 342 referral cases were received by the soft tissue pathologist in HKL over a period of 5 years. The cases were mostly referred by pathologists from various states and institutions in Malaysia. A minority of the cases were sent by the orthopaedic oncology surgeon from the Department of Orthopaedics or oncologist from the Department of Oncology in HKL. The materials sent comprised of either paraffin blocks, unstained slides, stained slides (haematoxylin & eosin, immunohistochemical stains) or a mixture of these. The nature of the specimens included core needle biopsies as well as resected specimens. Ninety-nine cases were excluded, of which most were referred as non-soft tissue tumours (15 bone tumour and 40 other tumours). Others were cases where the referring pathologists did not provide their impression or diagnoses (28 cases), the referred diagnoses were too general such that benign/malignant tumour behaviour could not be ascertained (5 cases), diagnoses could not be provided by the soft

tissue pathologist due to insufficient tissue (5 cases), biopsies were deemed not representative (4 cases) and marked burn artefact (2 cases).

Patient characteristics

Two hundred forty-three (243) cases were included in this study, of which 132 patients were male and 111 patients were female. The median age at diagnosis was 46 years (range 3 - 88 years). Malay patients was the highest in number consistent with the Malaysian ethnic distribution, comprising 156 cases, followed by Chinese 46 cases, Indian 21 cases and others 20 cases.

Analysis of diagnoses by tumour classification

The referring pathologists and the soft tissue pathologist agreed on 109 cases, in that their diagnoses were concordant in terms of tumour classification (Table 1). Among the 134 discrepant cases, 108 cases differed groups of tumour classification (Table 1). The rest of the cases (26 cases) were those referred as soft tissue tumours where a final diagnosis of tumours of non-soft tissue origin or reactive conditions were rendered (Table 1). The overall agreement for tumour classification was moderate, $\kappa = 0.423$ (95% CI, 0.333 to 0.512), $p < 0.0005$.

Analysis of diagnoses by tumour behaviour

The referring pathologists and the soft tissue pathologist agreed on 178 cases in that they concurred on 27 cases as benign, 17 cases as intermediate (locally aggressive/rarely metastasising) behaviour and 134 cases as malignant (Table 2). However, there were 9 cases which the referring pathologists diagnosed as benign tumours but the soft tissue pathologist diagnosed as malignant and 12 cases which the referring pathologists diagnosed as malignant tumours but the soft tissue pathologist diagnosed as benign (Table 2). Overall, there was moderate agreement between the pathologists' diagnoses in terms of tumour behaviour, weighted $\kappa = 0.548$ (95% CI, 0.451 to 0.644), $p < 0.0005$.

Analysis of discrepant cases

On considering the discrepancies in soft tissue/non-soft tissue tumour classification and benign/malignant behaviour, a total of 46 cases were identified as showing zero agreement (Table 3). These cases include 25 with discrepancy in soft tissue/non-soft tissue tumour classification and 20 with discrepancy in terms of benign/malignant tumour behaviour. There was one case which showed discrepancy in both soft tissue/non-soft tissue tumour classification and benign/malignant behavior.

The most frequent causes of discrepancies in diagnoses was wrong morphological interpretation with insufficient IHC stains performed (32 cases or 69.57%). This is followed by morphological interpretation alone (without any supporting immunohistochemical studies) in 13 cases (28.26%).

DISCUSSION

Previous studies have shown that more than 40% of first histological diagnoses of soft tissue tumours were modified at second reading, leading to different treatment decisions.[6] Any patient with a provisional diagnosis of bone or soft tissue sarcoma is highly recommended to be referred to a specialist sarcoma pathologist for diagnostic review.[2] Besides morphology and immunohistochemistry, the diagnosis should also be complemented by molecular pathology such as fluorescent in situ hybridisation or reverse transcription-polymerase chain reaction.[7] There are a few centres in Malaysia which offer soft tissue specialist multidisciplinary teams. Unfortunately, not all of these centres have the privilege of a soft tissue pathologist to cater for their diagnostic services. HKL is the largest hospital under the Ministry of Health of Malaysia. It is also one of the few centres in Malaysia with a soft tissue pathologist and receives a variety of referral cases including soft tissue tumours.

In our study, the most commonly referred soft tissue tumours were fibroblastic-myofibroblastic tumours (50/243 or 20.58%), undifferentiated/unclassified sarcomas (32/243 or 13.17%), adipocytic tumours (28/243 or 11.52%) and tumours of uncertain differentiation (25/243 or 10.29%). A study in 2001 by Zoya *et al* showed that problematic areas of diagnoses were nodular fasciitis and its variants, lipoma and its variants, fibrous histiocytoma and desmoplastic-neurotropic melanoma.[8] However, in our study, tumours that showed the highest rates of discrepancies were the so-called fibrohistiocytic tumours (7/11 or 63.64% discrepancy), vascular tumours (9/15 or 60%) and undifferentiated/unclassified sarcomas (29/32 or 59.37%). The highest agreements were seen in the adipocytic tumours (21/28 or 75%), Ewing sarcoma (5/7 or 71.43%) and smooth-muscle tumours (3/5 or 60%). There was only one case of gastrointestinal

TABLE 1: Cross tabulation of tumour classification between referred diagnoses and final diagnoses

Final diagnoses	Referred diagnoses													Total
	1	2	3	4	6	7	8	9	10	11	12	13	14	
1	21	2	0	1	0	1	0	0	1	0	1	1	0`	28 (11.5%)
2	3	28	1	4	4	1	2	0	1	2	1	3	0	50 (20.6%)
3	0	1	4	0	0	1	0	0	0	1	1	3	0	11 (4.5%)
4	0	1	0	3	1	0	0	0	0	0	0	0	0	5 (2.1%)
6	0	1	0	1	4	0	0	0	0	0	1	0	0	7 (2.9%)
7	2	3	0	0	0	6	0	0	0	2	2	0	0	15 (6.2%)
8	0	0	0	0	0	0	0	0	0	0	1	0	0	1 (0.4%)
9	0	0	0	0	0	0	0	1	0	0	0	0	0	1 (0.4%)
10	4	3	1	2	0	0	1	0	12	1	1	1	0	26 (10.7%)
11	0	3	0	0	1	2	0	0	4	11	1	3	0	25 (10.3%)
12	0	5	1	1	1	2	1	0	2	3	13	3	0	32 (13.2%)
13	0	3	0	0	0	1	0	0	1	2	3	6	0	16 (6.6%)
14	3	7	1	0	0	3	1	0	2	4	1	4	0	26 (10.7%)
Total	33 (13.6%)	57 (23.5%)	8 (3.3%)	12 (4.9%)	11 (4.5%)	17 (7%)	5 (2.1%)	1 (0.4%)	23 (9.5%)	26 (10.7%)	26 (10.7%)	24 (9.9%)	0 (0.0%)	243

Adipocytic tumours (1), Fibroblastic/ myofibroblastic tumours (2), So-called fibrohistiocytic tumours (3), Smooth-muscle tumours (4), Skeletal-muscle tumours (6), Vascular tumours (7), Chondro-osseous tumours (8), Gastrointestinal stromal tumours (9), Nerve sheath tumours (10), Tumours of uncertain differentiation (11), Undifferentiated/ unclassified sarcomas (12), Ewing sarcoma/ non-specified soft tissue tumour (13), Others (14)

TABLE 2: Cross tabulation of tumour behaviour between referred diagnoses and the final diagnoses

Final diagnoses	Referred diagnoses			Total
	0	1	3	
0	27	16	12	55 (22.6%)
1	6	17	5	28 (11.5%)
3	9	17	134	160 (65.8%)
Total	42 (17.3%)	50 (20.6%)	151 (62.1%)	243

Benign (0), Intermediate (locally aggressive/rarely metastasizing) (1), Malignant (3)

stromal tumour (GIST) referred and full agreement was achieved (100%).

Regarding the soft tissue/non-soft tissue discrepant diagnoses, most of the final diagnoses turned out to be tumours of other origins (19 out of 25 cases) with only six cases interpreted as reactive conditions. Such finding whereby the change after review was largely to other types of tumour has also been documented in a study done in the United Kingdom, however that particular study involved peer review rather than expert opinion.[9]

Accurate diagnosis is crucial in choosing the correct treatment given.[10,11] In this study we found three examples of cases which showed major changes in treatment due to misinterpretation of the diagnoses. One of the cases was diagnosed and treated as osteosarcoma. Unfortunately, there was no response to treatment and the case was reviewed by the resident pathologist who interpreted the case as possible Ewing sarcoma. However, the final diagnosis was mesenchymal chondrosarcoma. The other two cases were requested for second opinion by the treating orthopaedic surgeons either because the patient showed unexpected tumour behaviour (in a case of fibrous histiocytoma) or absence of SYT gene translocation (for a case initially diagnosed as synovial sarcoma). In contrary, their final diagnoses by the soft tissue pathologist were spindle cell squamous carcinoma and tenosynovial giant cell tumour, localized type (so-called giant cell tumour of tendon sheath) respectively. In these cases, failure to recognize the diagnostic features had led to an inappropriate panel of IHC stains performed and inaccurate interpretation.

In terms of the benign/malignant discrepancies, areas of difficulties were identified in the diagnoses of liposarcoma, alveolar soft part sarcoma and benign fibrous histiocytoma. A case of myxoid liposarcoma was referred as chondroid lipoma, in which the referring report did not elaborate on the morphological feature of arborising blood vessels which is a characteristic feature in myxoid liposarcoma. In another case of liposarcoma, the referred diagnosis of neurofibroma with cystic degeneration was concluded based on the so called positivity of S100 IHC stain and cystic formation which actually represent the adipocytes. Another difficult case was a retroperitoneal tumour with features of haemangioma and inflammatory myofibroblastic tumour. However, the final diagnosis was dedifferentiated liposarcoma with sclerosing and inflammatory elements.

With regards to alveolar soft part sarcoma, there were two cases referred as rhabdomyoma and granular cell tumour, in which both the referring pathologists did not recognise the cytoplasmic crystals and hence did not perform PAS and PAS-diastase special stains. We also found four cases of benign fibrous histiocytoma (BFH) which were referred as low grade fibrosarcoma, poorly differentiated malignant tumour, undifferentiated pleomorphic sarcoma and histiocytic sarcoma. The first two cases were not accompanied by tumour description by the referring pathologists for further comparison and discussion. The morphologic changes in the case of possible undifferentiated pleomorphic sarcoma were described as necrotic tumour with multinucleated tumour cells. However, the soft tissue pathologist came to a diagnosis of BFH and described the presence of haemorrhage, haemosiderin-laden macrophages and Touton giant cells. The fourth case was initially perceived as a sarcomatous lesion with histiocytic sarcoma as the first differential (the referring pathologist found CD68 positivity). However, further review of morphology by the soft tissue pathologist supported a benign spindle cell lesion most likely BFH. Repeat CD68 was found to be negative and in addition, CD10 was positive.

One of the limitations in this study was that we did not include those cases of malignant soft

TABLE 3: List of cases showing zero agreement (discrepancies in tumour soft tissue/ non-soft tissue tumour classification and benign/malignant behaviour)

Referral diagnosis	Final diagnosis
Soft tissue tumour	*Non-soft tissue tumour*
Benign lipomatous tumour	Skin ulcer with fat necrosis
Liposarcoma (spindle cell type)	Hematoma
Pleomorphic liposarcoma	Malignant mesothelioma
Inflammatory myofibroblastic tumour	Castleman's disease
Inflammatory myofibroblastic tumour	Plasmacytoma with lambda light chain restriction
Inflammatory myofibroblastic tumour	Haemorrhagic inflammatory process
Inflammatory myofibroblastic tumour	Erdheim Chester disease
Inflammatory myofibroblastic tumour	Acute on chronic inflammation with granulation tissue
Anaplastic haemangiopericytoma	Mesenchymal chondrosarcoma
Dermatofibrosarcoma protuberans	Dermatofibroma
Benign fibrous histiocytoma	Spindle cell squamous carcinoma
Haemangioendothelioma	Lobular capillary haemangioma
Intramuscular haemangioma	Infected intramuscular haematoma
Epithelioid haemangioma	Lobular capillary haemangioma
Extraskeletal chondroma	Bizarre parosteal osteochondromatous proliferation
Malignant peripheral nerve sheath tumour	Chondroblastic osteosarcoma
Malignant peripheral nerve sheath tumour	Ganglioneuroblastoma
Synovial sarcoma	Metastatic squamous cell carcinoma; poorly differentiated
Synovial sarcoma	Undifferentiated carcinoma
Synovial sarcoma	Metastatic carcinoma
Epithelioid sarcoma	Metastatic carcinoma
Unclassified sarcoma	Ameloblastoma
Ewing sarcoma	Mesenchymal chondrosarcoma
Ewing sarcoma	Metastatic carcinoma
Soft tissue sarcoma	Malignant melanoma
Benign	*Malignant*
Benign fibrous histiocytoma	Spindle cell squamous carcinoma
Chondroid lipoma	Myxoid liposarcoma
Rhabdomyoma	Alveolar soft part sarcoma
Haemangioma	Dedifferentiated liposarcoma
Schwannoma	Spindle cell sarcoma
Neurofibroma with cystic degeneration	Liposarcoma
Granular cell tumour	Alveolar soft part sarcoma
Myxoma	Extraskeletal myxoid chonsrosarcoma
Ossifying chondromyxoid tumour	Sclerosing epithelioid fibrosarcoma
Malignant	*Benign*
Myxoid liposarcoma	Schwannoma
Low grade myofibroblastic sarcoma	Nodular fasciitis
Low grade fibrosarcoma	Benign fibrous histiocytoma
Well differentiated fibrosarcoma	Desmoplastic fibroma
Sclerosing epithelioid fibrosarcoma	Cellular neurothekeoma
Leiomyosarcoma	Nodular fasciitis
Well-differentiated angiosarcoma	Haemangioma
Synovial sarcoma	Giant cell tumour of tendon sheath/ tenonodular synovitis, localized type
Pleomorhic sarcoma (MFH)	Benign fibrous histiocytoma
Myxoid sarcoma	Intramuscular myxoma
Histiocytic sarcoma	Benign fibrous histiocytoma
Poorly differentiated malignant tumour	Benign fibrous histiocytoma

tissue referral cases being reviewed to another malignant soft tissue tumours of different classification or vice versa as part of the zero agreement cases. For example, in vascular tumour discrepancies, misinterpretation of the tumour morphology and IHC performed or limited IHC panels had led to the change in diagnosis. These cases included dermatofibrosarcoma protuberance, undifferentiated sarcoma, solitary fibrous tumour and epithelioid sarcoma being reviewed as angiosarcoma after repeating CD31 and CD34 IHC stains with additional Fli1 immunostains.

Another limitation was that we did not separate the types of specimens sent for referral. Some of the referred cases provided more than one tissue block for the soft tissue pathologist's evaluation whereas in other cases limited biopsy materials were provided. To our knowledge, no statistically significant relationship has been documented with regards to the association of needle core biopsies versus larger biopsies or even resected specimens with major diagnostic discrepancies.[8] Hence we did not analyze the rate of agreement/ discrepancy in association with specimen type. In the future, this may be a potential aspect to analyze in view of the current trend of needle core biopsies in soft tissue tumours workup. In malignant cases, histologic grading should be provided whenever feasible.[12] Thus, another limitation identified in our study was that we did not analyse the discrepancies in tumour grading, which have been shown by other authors to cause major discrepancies and significant management change.[2]

The statistical reliability measurement of agreement was calculated using linear weighted kappa analysis. Kappa statistics analyses the degree of agreement above chances, however kappa does not take into account the degree of disagreement between observers and all disagreement is treated equally as total disagreement. Therefore the usage of weighted kappa was to enable greater emphasis to large differences between ratings than to small differences.[13]

In conclusion, there was moderate agreement in the diagnoses of soft tissue tumours between referring pathologists and the soft tissue pathologist in Malaysia. Our study confirmed the findings observed in other parts of the world where basic morphological interpretation, associated with lack of familiarity, is the most important factor in diagnostic discrepancies of soft tissue tumours. The implication of this is that an inappropriate panel of IHC stains would be performed, with or without IHC misinterpretation. Unfortunately, none of our data included confirmatory molecular studies in reaching the histological diagnoses, reflecting the lack of molecular facilities in the referral centre where this study was conducted. Outsourcing to a molecular diagnostic service could be an option. It would be interesting to expand this study to a larger scale to look at more aspects that could possibly contribute to the agreement or discrepancies of soft tissue tumour diagnoses. It is also hoped that molecular studies will become more available in the general hospital laboratories, especially in the referral centre.

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