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RESEARCH ARTICLE

Discordance of Histo-pathological Diagnosis of Patients with Soft Tissue Sarcoma Referred to Tertiary Care Center

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Abstract

Background: Reaching the correct histo-pathological diagnosis of soft tissue sarcomas (STS) is a great challenge and is cornerstone for treatment planning. Need of expertise for diagnosis is limited due to the lack of dedicated expert sarcoma pathologists and oncologists in India. In this study, we highlight the pattern of pathological diagnosis and its accuracy outside specialist centre. **Methods:** We performed retrospective analysis of all patients referred to us with a clinical or histopathologic diagnosis of STS over the period January 2016 to December 2017. According to the protocol, all patients had a review of histopathology diagnosis from our institute. The tissue blocks if available were reviewed and a fresh biopsy was performed when required. The histopathologic diagnosis was also reviewed in the joint clinic, giving clinics-radiological inputs to sarcoma pathologists. For the patients with outside diagnosis and discordant report, we divided them into major discrepancy (including change of diagnosis of sarcoma to benign or other histological entity that could potentially change the treatment plan) or minor discrepancy (like mild change in grade or histopathological diagnosis not affecting the treatment plan). Statistical analysis was done by SPSS ver 23. **Results:** There were 149 patients with median age of 36 years (range 14-77 years), and 93 patients (62.4%) were males. About 57% (85 cases) of patients had localized disease. Most common subtypes were synovial sarcoma (16%), liposarcoma (9%), soft tissue ewings sarcoma (9%), MPNST (9%), leiomyosarcoma (8%), and undifferentiated pleomorphic sarcoma (8%). Of 149 patients, 47 (31.5%) had not been worked up outside by immunohistochemistry or other molecular studies and thus comparison was not possible; while 4 patients couldn't retrieve blocks and repeat biopsy could not be performed. Of 97 patients (biopsy = 84, FNAC = 13) who had diagnosis from outside, 37% had major discrepancy and 24% had minor discrepancy as compared with our diagnosis from the sarcoma specialists. Univariate analysis revealed that the major discrepancy was more in non-extremity than extremity STS (p = 0.003). **Conclusion:** Histopathologic diagnosis in more than half of patients referred from outside centers was discordant with respect to the diagnosis of our centre with major implications on 37% of cases. We believe this is due to the lack of sarcoma pathology experts, and they are virtually non-existent in the multidisciplinary clinic set up outside the tertiary care centres.

Keywords: Soft tissue sarcoma- histopathology- pathology- sarcoma- discordance

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Introduction

Soft tissue sarcoma (STS) is an exceedingly complex disease mainly because of its heterogeneity, rarity, and ability to arise from different locations in the body. The treatment of soft tissue sarcoma essentially requires dedicated sarcoma pathologists, surgeons, medical oncologist, radiation oncologist, palliative care team etc.

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as a part of multi-disciplinary team [1]. Expert pathology unarguably is the cornerstone of the management of STS. Pathology of sarcoma is far more challenging than epithelial tumors because of rarity and multitude of subtypes [2]. The advent of specialized molecular testing has further complicated the scenario. The rarity of disease and non-specialized pathology reporting might lead to inappropriate treatment and thus poor outcomes [3-5].

Most of the data, literature and guidelines regarding pathology of sarcoma come from the western studies. In a report from Royal Marsden Centre, Thway et al [6] compared sarcoma unit's histopathology reports with referring reports on 349 specimens in patients with suspected or proven soft tissue sarcoma. Major discrepancy was defined by the discordance that could lead to change in treatment; while, minor discrepancy was defined as discordance that was not thought to provoke significant treatment change. On comparison from outside report, diagnostic concordance was found in 73.4% (n=349) of cases with minor diagnostic discordance in 15.7% of cases,, and major discordance in 10.9% of cases. Furthermore, the cause of this discrepancy was the different opinion of general or non-soft tissue sarcoma pathologists and pathologists at the specialist unit [6]. The rate of error in the diagnosis of soft tissue sarcoma in literature varies widely between 25-40% which further gives impetus to the fact that the review should be done by a bone and soft tissue pathologist, who evaluates soft tissue sarcoma regularly [6-9].

We believe that this discrepancy could be more in developing countries like India due to various factors. Thus a strategy should be developed to review all the cases or suspected cases of sarcoma from dedicated sarcoma pathologists. We conducted retrospective analysis of patients referred to our sarcoma clinic with an outside diagnosis and compared with our diagnosis that was made by specialists in bone and soft tissue pathology.

Materials and Methods

We retrospectively analysed patients referred to us with a diagnosis of soft tissue sarcoma (STS) in dedicated Sarcoma Medical Oncology clinic in All India Institute of Medical Sciences from January 2016 to December 2017. Many times, patients are referred to us from other clinics like hematolymphoid or pulmonary departments when the pathology unsuspectingly turns out to be sarcoma (intrainstitutional referral) or we get patients referred from outside directly when the outside biopsy is suggestive of sarcoma. As per institutional protocol we review histopathology diagnosis of outside institute by our bone and soft tissue pathology experts in all cases irrespective of that being reported from outside sarcoma specialized centers. If blocks were available, they were reviewed, and when necessary, a repeat biopsy was taken. Repeat biopsy was done in all patients who had only FNAC diagnosis from outside. The data for the study were collected during the course of common clinical practice. Signed informed consent was obtained from each patient for any procedure.

For the cases diagnosed outside and had discordant reports as compared to our (institutional) histopathology diagnosis we divided them into major discrepancy (including change of subtype/grade of sarcoma effecting further treatment, change to histopathology other than sarcoma or change to benign histopathology) or minor discrepancy like change in grade/subtype not affecting further management plan. When actual diagnosis was one of the differential diagnoses of the outside provisional report we considered that as minor discrepancy. For example, if the outside report for soft tissue ewings sarcoma was given as ? round cell tumor ? ewings sarcoma then we included those cases in minor discrepancy category.

Sarcoma Pathology reporting in AIIMS

We have two committed sarcoma pathologists at our institute and there is weekly pathology meeting during which all atypical/ rare cases are discussed and correlated with radiology as well. Molecular testing like translocation study was done wherever available and, in cases when the test was performed in outside laboratory the cost was borne by patient.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences Inc., version 18.0 for Windows. Nominal data are provided as number (%) and continuous data as median (range). Univariate analysis was done to delineate the characteristics of sarcoma in which discrepancy was there.

Results

There was total of 149 soft tissue sarcoma patients registered during this time. Patient characteristics are shown in Table 1 (median age, male:female, range, metastatic, truncal, extremity, non-extremity). Of 149 patients, 102 patients had diagnosis from outside; while 47 patients were not worked up outside for providing diagnosis. Out of 102 cases, 4 patients refused to undergo a repeat biopsy. Hence, treatment was continued on the basis of previous diagnosis; while data were unavailable in another 1 case.

Diagnostic correlation was done in 97 patients who had a diagnosis available from both outside and our centre. Outside diagnosis was given on biopsy in 86.5% (84 cases) and FNAC in 13.4% (13 cases) of cases. Immunohistochemistry report in outside diagnosis was available in 27.8% (27 cases) of patients. Complete data were available in 81 patients, 76.5% (62 cases) of them were worked up in private centre, while 19 patients in government set up (medical college). Grade of sarcoma in outside report was given only in 13% of patients. Major discrepancy was present in 37.1% (36 patients); while, minor discrepancy was present in 23.7% (23 patients) of cases. Of those patients who had immunohistochemistry report from outside the major discrepancy was seen in 33% (9 cases) of patients.

We further divided major discrepancy into

Table 1. Showing Characteristics of All Patients

Characterstics	(n=149)
Median Age	36 years
Age Range	14-77 years
Sex	
Males	93
Females	56
Extent of disease	
Metastatic	64
Non metastatic	85
Subtypes (after review from our institute)	
Synovial sarcoma	25 (16.8%)
Liposarcoma	13 (8.7%)
Malignant Peripheral Nerve Sheath Tumor	13 (8.7%)
Soft tissue Ewings Sarcoma	13 (8.7%)
Leiomyosarcoma	12 (8.1%)
Pleomorphic undifferentiated sarcoma	12 (8.1%)
Gastrointestinal stromal tumor	9 (6%)
Others	52 (34.8%)
Diagnostic test done outside (biopsy or FNAC)	
Yes	102
No	47
Extremity vs non Extremity primary	
Extemity	52 (34.9%)
Non extremity	
Retroperitoneum	23 (15.4%)
Trunk	20 (13.4%)
Visceral	14 (9.4%)
Head and neck	22 (14.8%)
Mediastinum	10 (6.7%)
Others (pelvis, paraspinal and spinal)	8 (5.4%)

a. Sarcoma outside to some other tumor inside (n=3, 8.3%)

b. Benign or other histopathology outside to sarcoma in our institute (n=15, 41.6%)

c. Change in histopathology diagnosis from one sarcoma to another sarcoma type (n=18, 50%)

a. Sarcoma outside to another tumor inside

1. Undifferentiated sarcoma to lymphoma (thigh mass)
2. Undifferentiated sarcoma to lymphoma (chest wall mass with paraspinal component)
3. Liver ewings sarcoma to Neuroendocrine tumor

b. Benign and other histopathology to sarcoma in our institute

1. Arm fibromatosis to synovial sarcoma
2. Parapharyngeal adenocarcinoma to MPNST
3. Lymphoma of pelvis to ewings sarcoma (translocation proven)
4. Granulosa cell tumor ovary to ewings sarcoma ovary (translocation proven)
5. Tuberculosis knee to clear cell sarcoma

Table 2. Univariate Analysis for the Major Discrepancy in Pathology in Soft Tissue Sarcoma

Characteristics	Percentage of major discrepancy	P value
Types of outside hospital	35.7%	0.867
Private	40%	
Public		
Location of the tumor		
Extremity	19.4%	
Non extremity	48%	0.005
Type of sample done outside		
Biopsy	34.5%	
FNAC	53.8%	0.18
Age at presentation		
Less than or =40 years	41%	
More than 40 years	31%	0.32

6. Hemangioma to ewings sarcoma thigh
7. Kidney NHL changed to kidney ewings sarcoma
8. Lymphoma to mediastinal liposarcoma
9. Spindle cell thymoma to synovial sarcoma (X 18 positive)
10. Schwannoma to MPNST
11. Adenocarcinoma lung to pulmonary intimal sarcoma
12. Benign spindle cell tumor of lung to pulmonary myxoid sarcoma
13. Germ cell tumor to rhabdomyosarcoma
14. Plexiform neurofibroma to synovial sarcoma
15. Small cell carcinoma to synovial sarcoma

c. One sarcoma subtype to another sarcoma subtype

1. Abdominal myxofibrosarcoma to abdominal rhabdomyosarcoma
2. Pleomorphic sarcoma to MPNST
3. Pleomorphic rhabdomyosarcoma to pleomorphic leiomyosarcoma
4. Spindle cell carcinoma to rhabdomyosarcoma
5. Scalp rhabdomyosarcoma to Alveolar soft part sarcoma
6. Angiosarcoma to dendritic follicular cell neoplasm
7. Synovial sarcoma to epitheloid sarcoma
8. Extraskeletal chodrosarcoma to extraskeletal osteosarcoma
9. Fibrosarcoma to GIST
10. Pleomorphic undiffentiated sarcoma to GIST
11. Myofibroblastic tumor to GIST
12. MPNST to GIST
13. Rhabdomyosarcoma to leiomyosarcoma
14. Pleomorphic undifferentiated sarcoma to solitary fibrous tumor
15. Dediffentiated liposarcoma to pleomorphic liposarcoma
16. Fibrosarcoma to solitary fibrous tumor
17. Fibrosarcoma to synovial sarcoma
18. Pleomorphic liposarcoma to Well differentiated liposarcoma

Minor discrepancy was all due to change in histopathology from one sarcoma to another sarcoma subtype except in one case which was due to change

Table 3. Showing Minor Discrepancy Detail

1. Ewings sarcoma/ synovial sarcoma ?	1. Ewings sarcoma soft tissue
2. Small round cell tumor?	2. Desmplastic round cell tumor
3. Round cell tumor? Sarcoma	3. Low grade sarcoma
4. Pleomorphic sarcoma NOS	4. Myxoid liposarcoma
5. Undifferentiated sarcoma	5. Leiomyosarcoma
6. Undifferntiated sarcoma	6. Leiomyosarcoma
7. Round cell tumor (? Neuroblastoma/ ? Ewings sarcoma)	7. Ewings sarcoma soft tissue
8. Synvial sarcoma/ ewings sarcoma malignant mesenchymal tumor	8. Soft tissue ewings sarcoma
9. ? Sarcoma	9. Undifferentiated sarcoma
10. Ewings/ synovial sarcoma	10. Ewings sarcoma soft tissue
11. Mesenchymal tumor (? Benign/ ? malignant)	11. Fibromatosis
12. MPNST / SFT (solitary fibrous tumor)	12. MPNST
13. ? Round cell tumor	13. Soft tissue ewings sarcoma
14. Spindle cell tumor	14. Synovial sarcoma
15. ? round cell tumor	15. Ewings sarcoma
16. Spindle cell sarcoma	16. Synovial sarcoma
17. Spindle cell sarcoma	17. Myxofibrosarcoma
18. Spindle cell sarcoma	18. Pleomorphic undifferentiated sarcoma
19. Myxofibrosarcoma	19. Dedifferentiated liposarcoma
20. Myxoid liposarcoma grade 1	20. Myxoid liposarcoma grade 2
21. Non malignant mesenchymal tumor ? DFSP	21. Dermatofibrosarcoma protuberans
22. Soft tissue sarcoma	22. MPNST
23. Leiomyosarcoma	23. Undifferentiated sarcoma

in the grade (this may be due to very few numbers of cases where grade was given in outside report) and are summarized in Table 3.

In univariate analysis the major discrepancy was correlated with the factors such as location of tumors, type of sample (FNAC vs biopsy), age at presentation 40 years or less vs more than 40 years, reported outside in private vs government centre. The only factor which showed statistical significance was location of tumor (Table 2), and the discrepancy was significantly more in non-extremity tumors. Though the percentage was relatively higher in patients diagnosed by FNAC, yet it was not statistically significant. Besides, the type of outside institute where patient had been worked up was immaterial.

Discussion

This paper underscores several important aspects in the diagnosis of soft tissue sarcoma. Firstly, the younger presentation in our setting which could be due to relatively younger population pyramid in India. Secondly, most of the patients 102/149 (68%) before presenting to us already had diagnostic workup elsewhere including biopsy or FNAC. There were 13 patients (12.7% of all with any tissue workup outside) in whom FNAC was done outside. FNAC is not recommended in soft tissue sarcoma and might be responsible for delay in the diagnosis and diagnostic discrepancy in many cases leading to inadequate information and thus treatment [10].

The main purpose of this study is to discuss the importance of highly specialized skills in pathology to ensure accurate diagnosis of sarcoma in India. Our data shows alarming discrepancy of 60.8% in the histopathological diagnosis outside tertiary care centre. This discrepancy is certainly more than that stated in western literature (ranging 25-40%) in various reports [6-11-12]. In a similar report from Pakistan [13], major discrepancy on second review (which had potential to change treatment) was 35.2% while minor discrepancy was 23.5% which is very similar to what we have reported (37.1% and 23.7% respectively). We had no cases that were reported malignant outside but turned out to be benign unlike other reports where they exist in the tune of 5%. Besides, we had 6 cases (6.1%) that were referred to the other department as benign and found to have sarcoma on institutional review.

Though we have divided discrepancy into major and minor discrepancy according to decision change in individual patient, yet even minor discrepancy can lead to decision change in different setting. For example, in adjuvant setting large high-grade myxoid liposarcoma will have same treatment as pleomorphic undifferentiated sarcoma but in metastatic setting the treatment of myxoid liposarcoma includes promising newer drugs like trabectidin and eribulin which physician might not use in PUS. Thus, even minor discrepancy can't be taken trivially as it might altogether affect the treatment strategy.

The frequency of major discrepancy was significantly higher in non-extremity sarcoma and this could be because pathologist and clinicians don't suspect sarcoma in visceral sites. To the best of our knowledge, this has not been previously reported in literature and might be useful indicator for guiding second review in resource constrained setting.

We believe in time to come this discrepancy can be lessened by reviewing histopathology in tertiary care centre as a part of treatment paradigm in soft tissue sarcoma. Given the population of India and numerically high burden of patients with sarcoma, Indian government must focus on opening dedicated sarcoma units in tertiary care centres. Even though sarcoma is a rare disease but the sheer volume of patients having this disease certainly deserve attention. Misdiagnosis of tumors like GIST also needs attention as GIST has good outcomes even in metastatic settings as compared to other soft tissue sarcomas. As of now, there is no standard guidelines in Indian setting however looking at guidelines issued by various expert groups we must incorporate those for our nation as well. The Guidance on Cancer Services issued by the National Institute for Health and Clinical Excellence (NICE) for soft tissue sarcoma explicitly state that all pathology should be either first reported or reviewed by a specialist soft tissue sarcoma pathologist [14].

We also believe that the unavailability of immunohistochemistry or the cost of immunohistochemistry is probably not the limiting factor as of patients who had immunohistochemistry report from outside (n=27), 9 patients still had major discrepancy, further reinforcing the fact that immunohistochemistry is not a good substitute for expert pathology. We didn't have data for the translocation tests for the study as it is not done in our centre and was done in case to case basis at the discretion of the physicians.

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