Frequency of Discrepancy in Soft Tissue, Bone and Lymphoid Cases Submitted for Second Opinion in Histopathology. Single Institution Experience

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Abstract

Objective: *To determine the frequency and types of discrepancies in the surgical pathological diagnosis of soft tissue lesion, bone and lymphoid tissue submitted for second opinion.*

Study Design: *Cross sectional, Observational.*

Place and Duration: Dept. Of histopathology, Shaukat Khanum memorial cancer hospital and research center, Lahore, Pakistan. 1 year duration.

Material and Method: *All cases of soft tissue, bone and lymphoid neoplasm, irrespective of age and gender, which were referred for second opinion after being reported elsewhere, were included in the study. The cases were divided into 3 categories*

1. ***Non discrepant,***
2. ***Discrepant:*** *Where there was disagreement in the specific diagnostic entity and this is further divided into, a) major discrepancies, b) minor discrepancies and*
3. ***Undiagnosed****, includes those cases where definitive diagnosis could not be made in primary report. Role of immunohistochemistry is also compared in discrepant and non-discrepant cases.*

Results: *During the study period, total 488 cases of soft tissue, bone and lymphoid tissue were received for review and 2nd opinion. 177 (36.2%) were soft tissue and bone cases and 311 (63.7%) were lymphoid malignancies. Total number of discrepant/undiagnosed cases in all three categories were 175 (35.8%).*

In Lymphoma Cases: *120/311 (38.5%) cases were discrepant. Major discrepancies were 26/120 (21.6%). Minor discrepancies were 6/120 (5%). Undiagnosed cases were 88/120 (73.33%). Immunohistochemistry performed before submission in discrepant cases were 14/120 (11.6%).*

In Soft Tissue/Bone Cases: *Total number of discrepant cases was 55/177 (31%). Major discrepancies were 23/55 (41.75%). Minor discrepancies were 11/55 (20%). Undiagnosed cases were 21/55 (38.1%). Immunohistochemistry done before submission for review in discrepant cases were 5/55 (9.09%).*

Conclusion: *Unavailability of Immunohistochemistry in many centers was found to be the main reason for disagreement in the diagnosis in both categories but more pronounced in lymphoid disorder. However, morphological features were also misinterpreted in sarcoma cases.*

Introduction

In recent years, there has been an increasing awareness of patient safety in all fields of medicine and definitely pathology is not an exempted area. A search of National Library of Medicine reference listings using "Error and Pathology Diagnosis" found 3992 citations, the first in 1966. Although not all of these publications are directly related to surgical pathology or cytopathology, 83 of them seem to be relevant to the discussion of diagnostic error or variation. An additional incentive for pathology to examine errors may be the increasing awareness and knowledge of malpractice involving pathologists, which became more apparent in the early 1990s with high-profile cases of false-negative reports of Papanicolaou tests [1].

Anatomic pathology errors are reported to occur in 1% to 43% of all anatomic pathology specimens, and this exceptionally wide range depends on the methods of detection and the definition of what counts as an error. On review of the literature, Raab estimated that the mean anatomic pathology error frequency ranged from 1% to 5%, although this frequency was largely based on studies using single-institution data [2]. No large-scale, multi-institutional anatomic pathology error studies have been conducted, and information on the effect of anatomic pathology error on patient outcome is generally deficient. Error detection in anatomic pathology most often depends on some form of secondary case review. Secondary case review has been proposed into some pathology quality assurance practices [3].

Material and Methods

Shaukat Khanum Memorial Cancer Hospital (SKMCH) is a tertiary care cancer hospital and research centre with an annual specimen load in histopathology which alone is approximately more than 70,000. Out of these cases around 6000 cases are review cases, which are submitted for secondary review/second opinion.

All cases of soft tissue, bone and lymphoid related lesions, irrespective of age or gender, which were referred for second opinion or review after being reported elsewhere, were included in the study. The data is collected from work orders, which is a computer generated request paper on which patients bio data along with a primary pathology diagnosis is mentioned. This work order is submitted to a consultant pathologist along with slides for review. A panel of antibodies is applied according to the requirement of each case. The cases were divided into 3 categories categorized as,

Non discrepant: Where there was concurrence between initial diagnosis and diagnosis at review.

Discrepant: Where there was disagreement in the specific diagnostic entity and this is further divided into

- major discrepancies,
- minor discrepancies.

Undiagnosed: This category includes those cases in which no definitive diagnosis is given by a primary pathologist. Definitive diagnosis means a diagnosis on which physician can start treatment. Once this same material was submitted for review, a definitive diagnosis was rendered.

The classification of discrepancies/errors provided in the Royal College of Pathologists publication entitled 'Concerns about performance in pathology: guidance for healthcare organizations and pathologists' (2006) is,

Category 1: A diagnostic error, which is likely to have a definite influence on clinical management and possible outcome.

Category 2: A misinterpretation or oversight, which has the potential to affect clinical management or outcome.

Category 3: A minor discrepancy of disease categorization, which is likely to be of little clinical significance.

Category 1 and Category 2 are considered as major discrepancies and category 3 considered as minor.

The discrepancies were measured separately in all 3 areas including soft tissue, bone, and lymphomas. The role of IHC is also compared in discrepant and non-discrepant cases whether it was performed by the primary laboratory or not.

Results

A total of 488 cases submitted in the soft tissue/bone and lymphoid neoplasm category are reviewed. Out of these 488 cases, 177 (36.2%) are soft tissue and bone cases, 311 (63.8%) are lymphoid neoplasm. Total number of discrepant cases including all 3 categories are 175 (35.8%). IHC performed by the primary lab before submission in all discrepant cases is only 19/175 (10.85%).

In soft tissue and bone cases, the total number of discrepant cases are 55/177 (31%). Out of these 55 discrepant cases, major discrepancy is noted in 23/177 (13%) cases, minor discrepancy in 11/177 (6%) and undiagnosed cases are 21/177 (12%), (Figure 1). Immunohistochemistry is performed in 1/23 major discrepant cases, in 3/11 minor discrepant cases and in 3/21 non diagnostic cases, before submission in SKMCH for second opinion (Figure 2). Morphology is misinterpreted in many of major discrepant cases, e.g. aneurysmal bone cyst reported by a primary pathologist is actually called Osteosarcoma on bases of morphology and radiological review. Another example is leiomyoma vs. leiomyosarcoma or osteochondroma vs. chondrosarcoma (Table1).

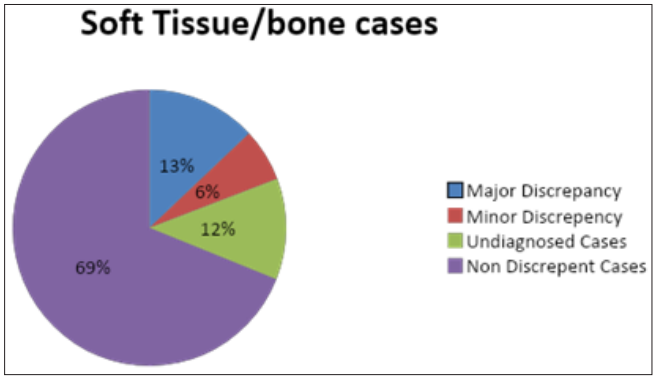

Figure 1: Discrepant cases percentages in soft tissue and bone.

Categories	Primary Lab	SKMCH
Benign to Malignant	Phylloides Tumor Inflammatory Cells Leiomyoma Solitary Fibrous Tumor Aneurysmal Bone Cyst Fibroma Osteochondroma Chronic Inflammation Osteomylitis Dermatofibroma	Myxoid Liposarcoma Malignant/Sarcoma Leiomyosarcoma Synovial Sarcoma Osteosarcoma Synovial Sarcoma Chondrosarcoma De-diff. Liposarcoma Chondrosarcoma DFSP
Malignant to Benign	Kaposi Sarcoma	Hemangioma
No Change in Category	Neuroblastoma NHL Alveolar Rhabdomyo Sarcoma Renal Cell CA Lymphoma	Ewings Sarcoma Ewings Sarcoma PNET Ewings Sarcoma PNET

Table 1: Primary pathologist diagnosis vs. change of diagnosis after review in SKMCH of some of the major discrepant soft tissue/bone cases is mentioned above.

In lymphoma cases, the total number of discrepant cases are 120/311(38.5%), major discrepancy 26/311 (8%), minor discrepancy 6/311 (2%) and undiagnosed 88/311 (28%) (Figure2). IHC was performed in 2/26 major discrepant cases, in 0/6 minor discrepant cases and in 11/88 undiagnosed cases before submission of these cases in SKMCH for second opinion . An important reason for misdiagnosis in lymphoma cases is both misinterpretation of morphology as well as non-availability of immunohistochemistry in many centers from where cases are submitted for review (Table 2).

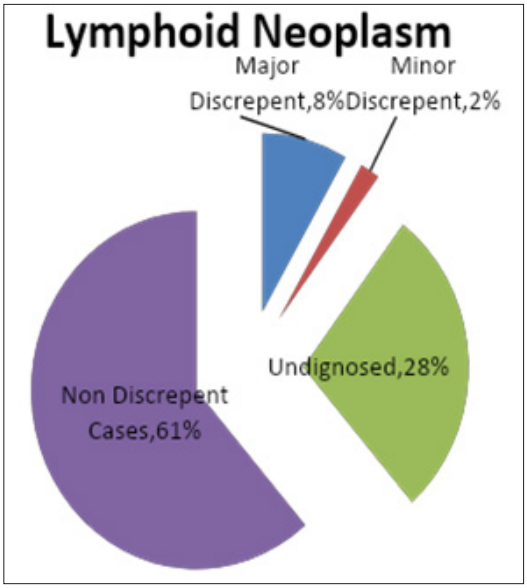

Figure 2: Discrepant cases percentages in lymphoid tissue.

Categories	Primary	SKMCH Diagnosis
Benign to Malignant	Kikuchi Lymphadenitis Inflammation Chronic Gastritis Reactive Lymphoid Hyperplasia Tuberculosis Lymphadenitis	DLBCL with Necrosis NHL DLBCL Low grade B cell NHL DLBCL
Malignant to Benign	None	None
No Change in Category	NHL Metastatic CA HD Carcinoid CLL/SLL ALCL	HD ALCL Follicular Lymphoma NHL HD HD

Table 2: Primary pathologist's diagnosis vs. change of diagnosis after review at SKMCH of some of the major discrepant lymphoma cases is mentioned above.

Discussion

Measurement of discrepancy and its categorization is important because it has an effect on patient management and associated clinical implication. The impact of discrepancy on patient management was classified into 3 categories based on patient outcome, 1) Harm (significant event): A discrepancy that resulted in patient harm (e.g., inappropriate treatment, loss of life or limb, psychological event). The effect of the significant event on the patient outcome was assessed using a 3-point Likert scale (1 = severe effect, 2 = moderate effect, 3 = mild effect). The pathologists performing the review judged the significance of the event, 2) **Near miss:** A discrepancy that was detected before harm occurred, such as a discrepancy that was detected at a clinical pathologic conference before treatment was initiated, 3) **No harm:** A discrepancy that did not result in patient harm, such as a typographic error that had no bearing on patient management [3].

The aim of this study is to measure discrepancies and type of discrepancies in the soft tissue/bone and lymphoma category. We have selected soft tissue and lymphoid neoplasm because these tumors are challenging to diagnose, in the soft tissue domain, especially where histopathological criteria is constantly evolving, particularly concerning ancillary investigations such as immunohistochemistry and molecular genetics. Much of the diagnostic challenge is due to their rarity.

The availability of ancillary tests was not, as might be expected, a cause of significant discrepancies. Virtually all common immunohistochemical markers for soft tissue tumor diagnosis are routinely available within the laboratories of district health general and teaching hospitals, and no diagnostic discrepancies were knowingly noted to occur due to a department lacking a particular antibody. Similarly, no discrepancies occurred because of a subsequent positive result on molecular genetic analysis. In both major and minor discrepancy groups, the majority of

specimens were excisions, meaning there was sufficient lesional material for diagnosis. No difference in rate of error was noted between referrals from district level laboratories and teaching hospitals.

Almost all discrepancies therefore occurred due to differences in interpretation, of either morphology or immunohistochemistry. Appropriate management of patients with lymphoma depends on an accurate and precise pathologic diagnosis as natural history and optimal treatment vary widely among the different subtypes of lymphoma. However, diagnosis is made challenging by the clinical rarity of individual subtypes of lymphoma in most pathologists' practices, small diagnostic specimens, and morphologic overlap across subtypes.

Total discrepancy in our study is 35.8%, which is much higher if we compare our study with Stephen S. Raab's study, published in Arch Pathol Lab Med—Vol 129, April 2005. In which their percentage of discrepant cases is 6.7% [3]. If we compare our study results separately in lymphoma and sarcoma cases, we still have higher figures compared to international data in soft tissue cases Total number of discrepant cases are 55/177(31%), same study done by Khin Thway and Cyril Fisher showed discrepancy in 26.6% cases, minor diagnostic discrepancy in 55 cases (15.7%) and major discrepancy in 38 cases (10.9%) [4]. Our major discrepancy rate in soft tissue area is 13% and minor is 20%, reflecting a worse situation in this area of expertise. A study done by Lavinia P showed 6.2% major discrepancy, which is significantly lower than our study [5]. Our results are more similar with the AFIP Rawalpindi study done by Sharif MA et al. [6] in which total discrepancies in soft tissue cases were 47%, major in 8.8% cases and minor in 11.8% cases. The most important reason for errors is unavailability of IHC in many labs in Pakistan, although in some cases morphological parameters were also overlooked.

The World Health Organization (WHO) classification of hematologic malignancies, published in 2000, was designed to improve diagnostic accuracy by incorporating latest scientific understanding. The impact of the WHO classification on the frequency of diagnostic discrepancy in lymphoma is unknown. Major diagnostic revision was rendered in 65 of the 365 cases (17.8%) in 2001 and 58 of the 354 cases (16.4%) in 2006 (P = NS). Including cases reviewed and revised beforehand at another NCI-CCC, rates of major diagnostic revision were 21.4% and 18.6%, respectively (P = NS). Clinically meaningful diagnostic revision occurs frequently with the expert pathology review for the diagnosis of lymphoma. Despite the WHO classification, rates of diagnostic revision at our institution in 2001 and 2006 did not differ significantly. Given the potential harm from misdiagnosis, a hematopathology review given by an expert should be considered as the standard of care [7].

Unawareness of newly described entities or modification is recently made by WHO in lymphoma as well as sarcoma is found to be another reason for errors. Lack of regular CME or MDT activities is another factor for diagnostic errors as in multidisciplinary meetings; clinical as well as radiological details are very helpful in making the right pathological diagnosis.

A study published by Dr. Asim Qureshi shows only 0.7% true interpretational error in the histopathology department of our hospital in the last 10-year period which reflects a strong peer review system in the pathology department [8].

Discrepancies can be an interpretative error by pathologist, sampling error, lack to integration of clinical findings properly. Many other domains of anatomical pathology effected by diagnostic error issues, a study done by Karen M, describes 67% discrepancies in gynecological cytology and 34% in nongynecologic cases [9]. There are many recommendation in various studies focusing that measuring discrepancy should be part of quality control program of a laboratory and as a performance indicator [10]. Another study done in soft tissue area by Arbiser ZK reflected minor discrepancy in 7%, and major discrepancy in 25% of soft tissue cases [11]. Lymphoid neoplasm always remained a challenging diagnostic area, because of complexities of lymphoid neoplasm, WHO revision 2001 to 2006 edition and lack of availability of ancillary studies as reflected by Kukreti V and Hamdani SN studies [12, 13].

Other quality control measures including random internal or external case audits, which is a routine practice in our hospital, is another useful remedy to avoid errors and to standardize pathology practice in an institution.

In 1992, the Association of Directors of Anatomic and Surgical Pathology published its recommendation that a complete review of outside pathology be a standard quality improvement policy before commencement of treatment at a different institution [14]. Like many other institutions, this is also a policy that the biopsy of every new cancer patient registered at our hospital for treatment should get pathology reviewed in our own pathology department. Multiple studies have reported the clinical management benefits of a pathologic second-review process when patients are referred for treatment from a different hospital, and several large studies of interinstitutional pathology reviews have reported overall discordance rates of 1.4% to 9% [15-18].

Although this is the era of molecular genetics and targeted therapy, morphology has always remained the gold standard in surgical pathology. A recently published study by Cyril Fisher is a true reflection of this statement [19]. In his study he actually re-audited his own study 6 years later, assessing changes in discrepancy patterns, particularly in relation to the widespread use of ancillary molecular diagnostic techniques which were not prevalent in his original study [4] and frequency of discrepancy remain the same in both audits reflecting a possible reason is the increasing lack of exposure to soft tissue cases in non specialized centers. One recent publication also reflecting diagnostic difficulties and discrepancies more marked in soft tissue surgical biopsies [20].

Conclusion

Like any other section of medical practice, pathology is not free of error, the important thing is to identify the reason and work hard as a team to minimize and overcome the problems so that safe reporting with minimal or no harm on patient management can become possible.

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