**ORIGINAL ARTICLE**

**Retrospective analysis of spectrum of soft tissue tumors in a tertiary care center in Pakistan**

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**ABSTRACT**

**Background:** It is of uttermost importance to compile soft tissue tumor spectrum in the current study population which would not only aid in patient’s diagnosis but also open query for new molecular targets. Hence, this article aimed to study the frequency of different types of soft tissue tumors in a tertiary care hospital and to assess the correlation of the tumor with clinical parameter including gender, age, laterality, and site of soft tissue tumors. In addition, to generate national level statistics and estimate burden of disease.

**Methods:** A retrospective study was carried out at Dow Diagnostic Research and Reference Laboratory (DDRRL) in Karachi, Pakistan from 2013 to 2019. All specimens related to soft tissue tumors received in DDRRL were recruited by PACS link software and through departmental records. Further, with the help of a clinical history, radiological work, morphology and IHC staining, diagnosis was made.

**Results:** A total of 374 soft tissue tumor cases with 16 different types of tumors were identified. Of which Fibrous histiocytoma and rhabdomyosarcoma represented majority of cases (12.8% each). A total of 22 tumor sites were recognized, of which most types of tumors were found in bone mass (13.1%) and 27.3% cases represented left laterality. When the tumor type was assessed in association with clinical parameters, significant results were achieved for age (P-value = 0.000) and tumor site only (P-value = 0.000).

**Conclusion:** This article provided the frequency of some major soft tissue tumor types found in Karachi, Pakistan. This study would not only aid in presenting the estimation of soft tissue tumor burden but would also provide awareness to the general population to seek help at early stage.

**Keywords:** Retrospective, spectrum, soft tissue, tumors, Pakistan.

**Introduction**

At national level, population-based cancer data is being published recently and in recent literature larynx, esophagus, breast, and oral cavity have highest incidence of neoplasms to be reported from Karachi, Pakistan compared to any other Asian populations 1, 2. However, data related to spectrum of soft tissue tumor in Pakistan is least mentioned at national level 3. Soft tissue tumors arise from connective tissues like fat, muscles, nerves, blood vessels, fibrous tissue or deep skin tissue. It comprises of heterogeneous group of diseases and considered as the most difficult area to exactly delineate the diagnosis 4.

As soft tissue tumor comprises of heterogeneous group of diseases with varying complex morphological patterns, it makes them further difficult to diagnose.

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There are various groups of tumors which are age, gender and site specific, although ample data available is based on the finding of western population. However there are lacunae in the data regarding soft tissue tumor frequency and correlation with other parameters to generate statistic**s** in the current study population.

Due to limited resources cases were not submitted for molecular profiling. The diagnosis and characterization of lesion is solely depends on the morphology and immunohistochemistry (IHC) staining of the tissue received in histopathology laboratory. Therefore, it is of uttermost importance to compile soft tissue tumor spectrum in the current study population which would not only aid in patient’s diagnosis but also open query for new molecular targets.

Due to its intricacy, various subtypes and paucity, this group of tumor are under intense research 5. It is therefore imperative to generate national level statistics to calculate the disease burden in order to implement awareness, screening programs and early detection. Hence, this article aimed to study the frequency of different types of soft tissue tumors in a tertiary care hospital and to assess the correlation of the tumor with available clinical parameter including gender, age, laterality, and site of tumors.

**Methods**

A retrospective study was carried out in the department of Histopathology, Dow Diagnostic Research and Reference Laboratory (DDRRL), Dow University of Health Sciences, Karachi from the year 2013 to 2019 through convenience sampling technique. After taking the approval from the International Review Board of the institute via approval number IRB 159 4/DUHS, Approval 2020, cases were recruited in the study as per the inclusion criteria.

All cases were evaluated according to following parameters including age, sex, site of biopsy, and specimen laterality and all available clinical history including radiological and ultrasonography findings.

All the biopsies (core, trucut, incisional, excisional and large resection) specimen related to soft tissue tumors (benign and malignant) of all the organs were included in the study along with relevant radiological workup in DDRRL, recruited by PACS link ® software and through Departmental maintained records. Subsequently, Hematoxylin and Eosin (H&E) and ancillary studies were analyzed and histological types of tumor, subtyping and tumor grade were recorded according to College of American Pathologist (CAP) protocol. Further, tumors were classified according to the WHO classification of soft tissue tumors6. For further sub typing IHC panel was used (Table 1).

**Table 1: Subtyping and characterization of soft tissue tumors based on IHC panel**

|  |  |  |
| --- | --- | --- |
| **Sr. #** | **Types of soft tissue tumors** | **IHC panel used** |
| 1 | Adipocyte Tumor | CD34 (Specifically polymorphic spindle cell) |
| 2 | Fibroblastic and Myofibroblastic Tumor | SMA, CD34, BCl2, S-100, B-Catenin |
| 3 | Fibrohistiotic Tumor | CD68, CD163, p63, Ki67, SMA, Myogenin |
| 4 | Vascular Tumor | CD34, CD31, FLI1, SMA, Vimentin, Calponin, Caldesmon |
| 5 | Smooth Muscle Tumor | ASMA, Desmin, Caldesmon |
| 6 | Skeletal Muscle Tumor | Myogenin, MyoD1 |
| 7 | Chondro-Osseous Tumor | S-100, ERG |
| 8 | Peripheral Nerve Sheath Tumors | S-100, CD34, CD63, Calretinin |
| 9 | Undifferentiated Tumors | CK, S-100, ASMA, LCA, CD68, Desmin, Synaptophysin, Myogenin, BCl2, B-Catenin, Vimentin, Tdt, HMB-45, WTI, Chromogranin |
| 10 | Undifferentiated Small Round Cell Sarcoma of Bone and Soft Tissue | CD99, FLI1, ERG, SATB2, WTI, p40, p63, Myogenin |

All the biopsies were further assessed after the IHC sub typing and the biopsies showing metastatic tumors, were of uterus, had any inflammatory condition and simple cysts of bone were excluded from the study. All other biopsies included were then sent to H and E staining for morphological diagnosis, for further subtyping and characterization relevant IHC staining panels were used.

Statistical software for social sciences (SPSS) ® version 21 was used to analyse the data. Different types of soft tissue tumors and all variables like sex, site of biopsy, and specimen laterality were presented as frequency and percentages while continuous variables like age were presented as means and standard deviation. Further, the correlation of the tumor with clinical parameters including gender, age, laterality, and site of soft tissue tumors were assessed using the 2\*2 cross-tab contingency table and chi-square test. A p-value of less than and equal to 0.05 was considered as significant.

**Results**

A total of 374 soft tissue tumor cases were included with a mean age of 33.72 ± 18.50 years, with age range from minimum 0.5 years to maximum 85 years. Most of the participants were males (61.8%). The current study represented 16 different types of soft tissue tumors. Of which, fibrous histiocytoma and rhabdomyosarcoma represented majority of the cases (12.8% each).Regarding laterality only 182 cases were assessed, of which 56.04% cases represented left sided tumor (Table 2).

**Table 2: Clinical parameters of the study participants (n=374)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Clinical Parameters** | | **N** | **%** | |
| **Age (Years)** | | 0.5 to 20 years | 110 | | 29.4 |
| 21 to 40 years | 137 | | 36.6 |
| 41 to 60 years | 97 | | 25.9 |
| Above 60 years | 30 | | 8.0 |
| **Gender** | | Male | 231 | | 61.8 |
| Female | 143 | | 38.2 |
| **Tumor Type** | | Aneurysmal Bone cyst | 38 | | 10.2 |
| Angiosarcoma | 9 | | 2.4 |
| Chondrosarcoma | 9 | | 2.4 |
| Dermatofibrosarcoma protuberans | 28 | | 7.5 |
| Ewing sarcoma | 35 | | 9.4 |
| Fibrous histiocytoma | 48 | | 12.8 |
| Hemangioendothelioma | 7 | | 1.9 |
| Hemangiopericytoma | 16 | | 4.3 |
| Inflammatory myofibroblastic tumor | 6 | | 1.6 |
| Liposarcoma | 32 | | 8.6 |
| Myoepithelioma | 4 | | 1.1 |
| peripheral nerve sheath tumor | 32 | | 8.6 |
| Rhabdomyoma | 6 | | 1.6 |
| Rhabdomyosarcoma | 48 | | 12.8 |
| Solitary fibrous tumor | 20 | | 5.3 |
| **Tumor Laterality (n=182)** | | Right | 80 | | 43.96 |
| Left | 102 | | 56.04 |

Frequency of soft tissue tumors according to topography was also assessed. Hence, making a majority of 172 out of 374 cases (45.98%) from extremities (Table 3).

**Table 3: Frequency of soft tissue tumors according to topography (n=374)**

|  |  |  |
| --- | --- | --- |
| **Tumor Site** | **Frequency** | **Percent** |
| **paraffin blocks received for second opinion** | 35 | 9.4 |
| **bone mass (tumor of osseous cells)** | 49 | 13.1 |
| **humerus** | 15 | 4.0 |
| **femur** | 17 | 4.5 |
| **knee** | 8 | 2.1 |
| **Hand (including finger, phalanges, wrist)** | 6 | 1.6 |
| **Tibia** | 5 | 1.3 |
| **Fibula** | 2 | 0.5 |
| **Foot (including toes, heal, ankle)** | 14 | 3.7 |
| **Hip** | 7 | 1.9 |
| **chest wall** | 15 | 4.0 |
| **Thigh** | 35 | 9.4 |
| **Leg** | 14 | 3.7 |
| **breast** | 7 | 1.9 |
| **abdomen** | 23 | 6.1 |
| **Lung** | 11 | 2.9 |
| **Back** | 7 | 1.9 |
| **Neck** | 10 | 2.7 |
| **vertebral column** | 9 | 2.4 |
| **Eye** | 27 | 7.2 |
| **Mouth (including submandibular, parotid, hard palate, soft palate, tongue)** | 15 | 4.0 |
| **mandible** | 8 | 2.1 |
| **Others (scrotum, skin, shoulder, nose, forehead, lymph node, prostate gland, head, liver, brain)** | 35 | 9.4 |

When the tumor type of the participants was assessed in association with gender (P-value = 0.230), non-significant results were achieved. However, it was found that males mostly represented rhabdomyosarcoma (n=33), while females mostly represented fibrous histiocytoma (n=24). Regarding laterality, non-significant results were found (P-value = 0.467). Rhabdomyoma (n=13) was mostly represented as right laterality, while fibrous histiocytoma (n=15) was represented mostly as left laterality. Further, significant results were achieved for age (P-value = <0.001). Indicating most cases of rhabdomyosarcoma (n=26) in the age group of 0.5 to 20 years. While the age group of 21 to 40 years represented most cases of fibrous histiocytoma (n=26) and advancing age groups like 41 to 60 years and above 60 years represented dermatofibrosarcoma protuberans & peripheral nerve sheath tumor (n= 13 each), respectively (Table 4).

**Table 4: Type of soft tissue tumor in association with the clinical parameters of the participants (n=374)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical Parameters** | | **Aneurysmal Bone cysts** | **Angiosarcoma** | **Chondrosarcoma** | **Dermatofibrosarcoma protuberans** | **Ewing sarcoma** | **Fibrous histiocytoma** | **Hemangioendothelioma** | **Hemangiopericytoma** | **Inflammatory myofibroblastic** | **Liposarcoma** | **Myoepithelioma** | **peripheral nerve sheath tumor** | **Rhabdomyoma** | **Rhabdomyosarcoma** | **Solitary fibrous tumor** | **Synovial sarcoma** |
| **Age (Years)** | 0.5 to 20 years | 25 | 0 | 1 | 1 | 20 | 11 | 3 | 5 | 2 | 0 | 1 | 2 | 1 | 26 | 3 | 9 |
| 21 to 40 years | 12 | 4 | 0 | 14 | 9 | 26 | 1 | 7 | 0 | 14 | 0 | 13 | 1 | 9 | 8 | 19 |
| 41 to 60 years | 1 | 3 | 5 | 13 | 4 | 10 | 2 | 4 | 3 | 10 | 2 | 13 | 3 | 9 | 8 | 7 |
| Above 60 years | 0 | 2 | 3 | 0 | 2 | 1 | 1 | 0 | 1 | 8 | 1 | 4 | 1 | 4 | 1 | 1 |
| **Gender** | Male | 20 | 4 | 6 | 22 | 25 | 24 | 3 | 10 | 4 | 20 | 1 | 20 | 4 | 33 | 9 | 26 |
| Female | 18 | 5 | 3 | 6 | 10 | 24 | 4 | 6 | 2 | 12 | 3 | 12 | 2 | 15 | 11 | 10 |
| **Laterality (n=182)** | Right | 9 | 1 | 1 | 3 | 10 | 12 | 1 | 4 | 2 | 5 | 8 | 1 | 13 | 2 | 8 | 9 |
| Left | 13 | 4 | 4 | 9 | 5 | 15 | 1 | 2 | 2 | 8 | 7 | 2 | 9 | 7 | 14 | 13 |

When the tumor type of the participants was assessed in association with site of soft tissue tumors, significant results were achieved (P-value = <0.001). It was found that fibrous histiocytoma and rhabdomyosarcoma (n=7 each) were represented mostly as paraffin blocks that were received for second opinion. Aneurysmal bone cyst was found commonly in femur (n=11), hand (n=3), tibia (n=4), and mandible (n=3). Liposarcoma was found commonly in humerus (n=4), and abdomen (n=7). Synovial sarcoma was found commonly in knee (n=4). Fibrous histiocytoma was found commonly in foot (n=4), hip (n=4), thigh (n=8), leg (n=3), and other sites (n=9). Angiosarcoma was also found in breast (n=3). Solitary fibrous tumor was commonly found in lungs (n=3). Ewing sarcoma is commonly found in neck and vertebral column (n=3 each). Rhabdomyosarcoma was commonly found in eye (n=10). Peripheral nerve sheath tumor was commonly found in mouth (n=4) (Table 5).

**Table 5: Type of soft tissue tumor in association with the site of tumor (n=374)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Tumor Site** | **Aneurysmal Bone cyst** | **Angiosarcoma** | **Chondrosarcoma** | **Dermatofibrosarcoma protuberans** | **Ewing sarcoma** | **Fibrous histiocytoma** | **Hemangioendothelioma** | **Hemangiopericytoma** | **Inflammatory myofibroblastic** | **Liposarcoma** | **Myoepithelioma** | **peripheral nerve sheath tumor** | **Rhabdomyoma** | **Rhabdomyosarcoma** | **Solitary fibrous tumor** | **Synovial sarcoma** |
| **paraffin blocks** | 2 | 1 | 0 | 7 | 4 | 4 | 0 | 1 | 2 | 2 | 0 | 1 | 0 | 7 | 0 | 4 |
| **bone mass**  **(Osseous cell tumor)** | 9 | 1 | 3 | 4 | 4 | 6 | 1 | 2 | 0 | 0 | 0 | 5 | 2 | 5 | 1 | 6 |
| **humerus** | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 4 | 0 | 1 | 0 | 2 | 2 | 0 |
| **femur** | 11 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| **knee** | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 4 |
| **Hand** | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **tibia** | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **fibula** | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Foot** | 1 | 0 | 0 | 2 | 2 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **hip** | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **chest wall** | 1 | 0 | 1 | 3 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 3 | 0 | 1 |
| **thigh** | 0 | 0 | 1 | 4 | 3 | 8 | 0 | 0 | 0 | 4 | 0 | 4 | 0 | 5 | 1 | 5 |
| **leg** | 0 | 1 | 0 | 1 | 0 | 3 | 0 | 1 | 0 | 2 | 0 | 1 | 1 | 1 | 0 | 3 |
| **breast** | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| **abdomen** | 0 | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 7 | 0 | 2 | 0 | 4 | 1 | 2 |
| **lung** | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 3 | 2 |
| **back** | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 1 |
| **neck** | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| **vertebral column** | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 1 | 0 | 0 |
| **eye** | 0 | 0 | 0 | 0 | 1 | 3 | 0 | 4 | 0 | 0 | 0 | 1 | 0 | 10 | 5 | 3 |
| **Mouth** | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 2 | 3 | 4 | 0 | 0 | 2 | 0 |
| **mandible** | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 |
| **Others** | 0 | 0 | 0 | 3 | 3 | 9 | 3 | 1 | 0 | 4 | 0 | 2 | 0 | 6 | 3 | 1 |

**Discussion**

According to the WHO classification, tumor of soft tissues are categorized as adipocytic tumors, fibroblastic and myofibroblastic, fibrohistioticytic, vascular, pericytic, smooth muscle, skeletal muscle, gastrointestinal, stromal, chondro-osseous, and peripheral nerve sheath tumors, in addition to tumors with undifferentiated differentiation and undifferentiated small round cell sarcomas of bone and soft tissue 6. Tumors of soft tissue are really rare and very challenging from diagnostic point as they have varying lines of differentiation. Hence, accurate diagnosis is essential for proper prognostication and treatment 7, 8.

However, there are data gaps regarding the frequency of soft tissue tumors and correlation with other parameters in the Southeast Asian region 8, 9. Therefore, the aim of this article was to study the

frequency of different types of soft tissue tumors in a tertiary care hospital in Karachi, Pakistan and to assess tumor correlation with clinical parameter. Where, diagnosis and outcome depend solely on morphology and IHC staining of tissue.

Fibrous histiocytoma and rhabdomyosarcoma represented majority of cases (12.8% each), followed by aneurysmal bone (10.2%) and synovial sarcoma (9.6%) among the current study participants. However, in a study conducted in Turkey most common soft tissue tumor was found to be Liposarcoma, followed by synovial sarcoma and malignant mesenchymal tumor 10. This disparity of results might be due to lack of pathological outcome stratification among the current study participants. Where, molecular profiling was not conducted due to lack of resources in the current study.

Additionally one more study conducted in Karachi, Pakistan reported Liposarcoma (24%) as the most commonly occurring type of soft tissue tumor followed by myxofibrosarcomas, synovial sarcoma and Leiomyosarcoma (12% each).Less common types of soft tissue tumors present were malignant peripheral nerve sheath, pleomorphic sarcoma, and rhabdomyosarcoma (8% each) 11. In contrast, the current study found Fibrous histiocytoma and rhabdomyosarcoma as the most common type (12.8% each). Likewise, another study reported Fibrous histiocytoma as the most common type (28%) 12.

Soft tissue and bone tumors can affect both the genders at any time of their life regardless of their age 4,8. When the tumor type of the participants was assessed in association with age, significant results were achieved (P-value = <0.001). Most cases were reported in the age group of 21 to 40 years (n=137) followed by 0.5 to 20 years (n=110).Two other studies reported the common age range of 11 to 20 years for the soft tissue tumors 10, 13, 14. Another study conducted in Karachi showed that soft tissue tumors were mostly associated with the adult age group that is 25-60 years (67.5%) 8.

Further, it was found that most cases of rhabdomyosarcoma (n=26) followed by aneurysmal bone cyst (n=25) were found in the age group of 0.5 to 20 years. Similarly, a recent study also found that rhabdomyosarcoma commonly occurs in childhood 8.

According to the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC) 8th edition, soft tissue tumors could be present at four major sites including extremities and trunk, head and neck region, retro peritoneum and viscera’s 15.

It was found that soft tissue tumors were found commonly in upper and lower extremities making 172 out of 374 cases (45.98%) from extremities. Likewise, a study reported that both extremities were the commonest site for the development of soft tissue tumors16. Similarly a recent study also demonstrated that lower extremity is the most common site of soft tissue tumor 8. Studies have also demonstrated that sarcomas of primary bones are really rare and contribute to approximately 0.2% of all cancers 17. Nevertheless, the estimation of their exact incidence is difficult because of lack of resources and awareness in general population, especially in rural patients to seek help. Therefore, major cases remain undocumented.

Another study reported that extremities are the most common site for the development of soft tissue tumors involving thigh as the most common site 18. In concordance, the current study also reported both the extremities as the commonest site for the development of soft tissue tumors involving thigh to be the most common site in the lower extremity representing 35 cases.

Moreover, 72 (19.25%) cases were reported from the head and neck region. Around 33 (8.82%) cases were reported from the trunk area, while the third common site for the soft tissue tumors was found to be abdominal cavity with 23 (6.14%) cases. However, in contradiction to this, study reported common site for soft tissue tumor as trunk followed by abdomen and on third the head and neck region 19.

According to the epidemiological study, it has been demonstrated that dermatofibrosarcoma protuberance accounts for 2-6% of all soft tissue tumors.2 Similarly, in the current study dermatofibrosarcoma protuberance accounts for almost 7.48% of all soft tissue tumor cases.

When the tumor type of the participants was assessed in association with gender (P-value = 0.230), non-significant results were concluded. However, it was found that it is most common in males. In agreement, a study conducted in Tertiary Cancer Institute in Eastern India also showed male dominance as compared to females 4. Other studies also reported contrasting results where some reported soft tissue tumors to be common in males 21, 22. However there are studies in which female dominance has been shown 10, 13, 14. A recent study from Pakistan also showed male predilection, similar to the current study results 8. This is because of female reluctance to seek medical help until they have major physical disability.

Although this study contributed widely in determining the frequency of soft tissue tumor and its association based on history, radiology, morphology and IHC. However, it had some limitations. Firstly, several clinical parameters like tumor size, functional outcomes etc. might not have been controlled which might have influenced the results. Further, multivariate analyses have not been performed due to lack of information of prognostic factors. Moreover, retrospective nature of the study, itself is the limitation of the study. Despite these limitations, it was believed that the current study is a valuable contribution to assess the current burden of the major problem and definitely open new avenue for future research.

**Conclusion**

This article provided the frequency of some major soft tissue tumor types conducted in a single tertiary care hospital in Karachi, Pakistan. This study reflects that environment, culture, lifestyle which might be of much importance for the diagnosis, classification and prognosis of these soft tissue tumors.

**Recommendations**

Further, future studies are recommended to consider the further subtyping of specific entity, incorporate molecular studies for definitive diagnosis and identify the genetic and epigenetic alteration and their correlation with morphology and IHC.

**Conflict of Interest:** There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

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