Original Research Article

Diagnostic Importance of Clinic-Pathologic Features and p16, CD34, MDM2 Expression in Differential Diagnosis of Tumors

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Abstract

Background: The large majority of soft tissue tumors are benign. Malignant mesenchymal neoplasm amount to less than 1% of the overall human burden of malignant tumors but they are life threatening and may pose a significant diagnostic and therapeutic challenge since there are more than 50 histological subtypes of STS, which are often associated with unique clinical, prognostic and therapeutic features.

Methods: The study was undertaken in department of Pathology, King George's Medical University, Lucknow. The Study Design was Retrospective and prospective study carried over a period of two year from September 2018 to august 2020 including 70 cases. *Results*. Most common diagnosis of malignant cases was Synovial saroma (21.4%) followed by Leiomyosarcoma (19.0%) and Undifferentiated pleomorphic sarcoma & Fibromyxoid sarcoma (11.9% each). Less common diagnosis were Ewing's sarcoma, Liposarcoma and Rhabdomyosarcoma (9.5% each), 1 (2.4%) case each was diagnosed as Chondrosarcoma, MPNST and Myxoid liposarcoma.

Conclusions: Genetic alterations involving the 12q13-15 chromosomal region are common in musculoskeletal sarcomas, and many bone and soft-tissue malignant tumors showed amplification of various genes located in this region**.**

Keywords: synovial sarcoma; ewing's sarcoma ;histopathological.

Introduction

The large majority of soft tissue tumors are benign. Malignant mesenchymal neoplasm's amount to less than 1% of the overall human burden of malignant tumors but they are life threatening and may pose a significant diagnostic and therapeutic challenge since there are more than 50 histological subtypes of STS, which are often associated with unique clinical, prognostic and therapeutic features.[1]The etiology of most benign and malignant soft tissue tumors is unknown. In rare cases, genetic and environmental factors, irradiation, viral infections and immune deficiency have been found associated with the development of usually malignant soft tissue tumours.[2] However, the large majority of soft tissue sarcomas seem to arise de novo, without an apparent causative factor. In this study we analyze the expression of CDK4 and p16 in the various lineages

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of soft tissue sarcoma and their role in differentiating atypical lipomatous tumor/WDL from benign lipomas.[3]

Material and Methods

The study was undertaken in department of Pathology, King George's Medical University, Lucknow. The Study Design was Retrospective and prospective study carried over a period of two year from September 2018 to august 2020 including 70 cases with

Inclusion Criteria:

Histologically diagnosed cases of soft tissue tumors.

Exclusion Criteria:

Inadequate biopsy tissue for immune-histochemistry.

Results

The present study was conducted in the Department of Pathology in collaboration of Departments of Surgical Oncology and Orthopedics, King George's Medical University, Lucknow to study the immunohistochemical expression of p16 and CDK4 markers in various lineages of soft tissue sarcomas. In the present study, 70 histological diagnosed cases of soft tissue tumors fulfilling the inclusion criteria were enrolled in the study.

Age of patients enrolled in the study ranged from 1 to 97 years, mean age was found to be 34.98±19.96 years. Most common age groups were 31-40 years (20.0%) followed by 11-20 years and 41-50 years (18.6% each).

Out of 70 patients enrolled, majority were males (61.4%) and rest 38.6% were females.

Most common site of swelling were lower extremity (34.3%) followed by head and neck (22.9%) and Upper extremity (11.4%) while less common sites of swelling were Back and Trunk (8.6% each) and Pelvic and Retroperitoneum (7.1% each).

Majority of the patients presented with pain (61.4%) and showed progression of swelling (84.3%).

Duration of symptoms in majority of the patients was >6 months (77.1%).

Minimum size of tumour was 1 cm while maximum size was 18 cms. Mean size of tumour was 7.09±4.52 cms. Only 5 (7.1%) cases had tumour size >15 cm, 12.9% had tumour size 11-15 cm, 34.3% had tumour size 6-10 cm and rest 45.7% had tumour size ≤5 cm.

Excisional biopsy was done for majority of the cases (80.0%) and for rest of the cases Incisional biopsy was done (20.0%).

Out of 70 cases enrolled in the study, 42 (60.0%) were histopathologically found to be malignant, 20 (28.6%) as benign and rest 6 (11.4%) as intermediate.

Out of 20 cases histopathologically found to be benign, Lipoma was the most common diagnosis (25.0%) followed by Angiomyolipoma, Benign fibromyxoid neoplasm, Calcifying fibrous tumour and Fibroma (15.0% each), 1 (5.0%) case each was diagnosed as Dermatofibroma, hemangioma and myxoma.

Most common diagnosis of malignant cases was Synovial saroma (21.4%) followed by Leiomyosarcoma (19.0%) and Undifferentiated pleomorphic sarcoma & Fibromyxoid sarcoma (11.9% each). Less common diagnosis were Ewing's sarcoma, Liposarcoma and Rhabdomyosarcoma (9.5% each), 1 (2.4%) case each was diagnosed as Chondrosarcoma, MPNST and Myxoid liposarcoma.

Among histopathologically intermediate cases most common diagnosis was DFSP (62.5%) followed by Well differentiated liposarcoma (25.0%) and Low grade myofibroblastic sarcoma (12.5%).

Age of histologically benign cases ranged between 9 to 56 years of age, mean age was 29.55±15.37 years. Difference in age of benign cases with different diagnosis was not found to be significant statistically.

Range of age of histopathologically malignant cases was 1 to 97 years, mean age of these cases was 36.58±22.56 years. Age of 1 case each of Chondrosarcoma, MPNST and Myxoid liposarcoma was 40, 16 and 74 years respectively. Minimum mean age was observed for cases diagnosed as Rhabdomyosarcoma (1.88±0.85 years) followed

by Ewing's sarcoma (12.25±6.29 years) while mean age was maximum for cases diagnosed as myxoid liposarcoma (74.00±0.00 yrs) followed by Undifferentiated pleomorphic sarcoma (61.60±25.58 years). Difference in mean age of malignant cases with different diagnosis was found to be significant statistically.

Age of histopathologically intermediate cases ranged between 23 to 64 years, mean age was 40.13±13.27 years. Minimum mean age was observed for cases diagnosed as low grade myofibroblastic sarcoma (27.00±0.00 yrs) followed by DFSP (36.60±9.76 years) while maximum age was observed for cases diagnosed as Well differentiated liposarcoma (55.50±12.02 years). Difference in age of intermediate cases with different diagnosis was not found to be significant statistically.

Among benign cases majority were males (70.0%) and rest were females. Male preponderance was found for all the above diagnosis except for Dermatofibroma (33.3% males only). Difference in gender of benign cases with different diagnosis was not found to be significant statistically.

Out of 42 malignant cases 23 (54.8%) were male and rest were females. Male preponderance was seen for cases diagnosed as Chondrosarcoma, MPNST (100.0% each), Lipo sarcoma (75.0%) and synovial sarcoma (66.7%). Ewing's sarcoma and Leiomyosarcoma were present in equal proportion of males and females. Female preponderance was seen for cases diagnosed as Myxoid liposarcoma (100.0%), Fibromyxoid sarcoma (80.0^), Rhabdomyosarcoma (75.0%). Difference in gender of malignant cases with different diagnosis was not found to be significant statistically.

Out of 8 histopathologically intermediate cases 6 (75.0%) were males. Male preponderance was observed for cases diagnosed as DFSP (80.0%) and low grade myofibroblastic sarcoma (100.0%) while male:female ratio was similar cases diagnosed as Well differentiated liposarcoma. Difference in gender of histopathologically diagnosed intermediate cases with above diagnosis was not found to be significant statistically.

Positive p16 expression was observed in majority of the cases (51.4%) while negative p16 expression was observed for 44.3% cases and rest were found to be focal positive (4.3%).

Negative CDK4 expression was observed in majority of the cases (81.4%) while positive CDK4 expression was observed for 10.0% cases and rest were found to be focal positive (8.6%).

Both p16 & CDK4 positive expression was observed in only 12.9% cases, 38.3% had both negative expression and rest 48.6% cases had positive expression either for p16 or CDK4.

Negative p16 expression was observed among higher proportion of Benign as compared to malignant and intermediate cases (75.0% vs. 31.0% & 37.5%) while positive p16 expression was observed among higher proportion of malignant as compared to Benign & intermediate cases (66.7% vs. 20.0% & 50.0%) while focal positive expression was observed in higher proportion of Intermediate as compared to Benign & Malignant cases (12.5% vs. 5.0% & 2.4%). This difference was found to be significant statistically.

Negative CDK4 expression was observed among higher proportion of Benign as compared to malignant and intermediate cases (90.0% vs. 78.6% & 75.0%) while positive CDK4 expression was observed among higher proportion of Intermediate as compared to Benign & malignant cases (25.0% vs. 5.0% & 9.5%) while focal positive expression was observed in higher proportion of malignant cases as compared to Benign & Intermediate cases (11.9% vs. 5.0% & 0.0%). This difference was not found to be significant statistically significant.

Both p16 & CDK4 negative expression was observed among higher proportion of Benign as compared to malignant and intermediate cases (65.0% vs. 26.2% & 37.5%) while among higher proportion of malignant as compared to Benign & intermediate cases had either positive expression (57.1% vs. 35.0% & 37.5%), positive expression was observed among higher proportion of Intermediate as compared to benign and malignant (25.0% vs. 0.0% & 16.7%). This difference was not found to be significant statistically significant.

Out of 45 diagnosed cases of Sarcoma, majority had FNLCC Grade 3 (62.2%), only 11.1% were Grade 2 and rest 26.7% were Grade 1 cases.

TNM Staging was done for 31 cases. Majority of the cases were pT1 and pT2 (67.7%), only 12.9% cases were pT4 and rest 19.4% were pT3 stage.

An increment in p16 negative expression with increase in FNLCC Grade was observed (8.3%, 20.0% & 39.3%) while p16 positive expression was found to be higher in Grade 1 as compared to Grade 2 and Grade 3 (83.3% vs. 60.0% & 60.7%). Association of p16 expression with FNLCC grade was not found to be significant statistically.

Association of p16 expression with TNM staging was not found to be significant statistically.

A decline in CDK4 negative expression with increase in FNLCC Grade was observed (83.3%, 80.0% & 71.4%) while CDK4 positive expression was found to be higher in Grade 2 as compared to Grade 1 and Grade 3 (20.0% vs. 16.7% & 10.7%). Association of CDK4 expression with FNLCC Grade was not found to be significant statistically.

Association of CDK4 expression with TNM staging was also not found to be significant statistically.

For adipocytic tumors, majority of the benign tumours had negative expression of p16 (6/8; 75%) and CDK4 (8/8; 100%) while majority of malignant and intermediate tumours had positive p16 (7/7; 100%) and CDK4 (6/7; 85.7%) expression. These differences were found to be significant statistically (p16; χ^2=8.750; p=0.003; CDK4; χ^2=11.429; p=0.001).

Discussion

In present time apart from clinical and histomorphological picture there are many techniques to differentiate soft tissue tumors specially sarcomas. These techniques are immunohistochemistry, cytogenetics and molecular genetics. Immunohistochemistry is used to identify the differentiation of tumor cells in a particular section.Immunohistochemistry also plays a major role in soft tissue tumor classification, diagnosis, treatment and prognosis.

Genetic alterations involving the 12q13-15 chromosomal region are common in musculoskeletal sarcomas, and many bone and soft-tissue malignant tumors showed amplification of various genes located in this region[10].

p16 is a tumor suppressor gene and it is an important cell cycle regulator. It inhibits cell cycle at G1-S checkpoint by binding to cyclin-dependent kinases 4/6 and prevent inactivation of the Rb protein. p16may be mutated or deleted in many cancers[22,33-36].

Conclusion

Genetic alterations involving the 12q13-15 chromosomal region are common in musculoskeletal sarcomas, and many bone and soft-tissue malignant tumors showed amplification of various genes located in this region.

INFORMED CONSENT: written informed consent was taken from patients .

Ethical Approval: ethical committee approval was taken from the Institutional Committee Of Ethics, VIMS (VIMSE/2022/11-99) .

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