Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Research

Histopathological and Immunohistochemical Patterns of Malignant Peripheral Nerve Sheath Tumours in a Tertiary Institution of Northern Nigeria.

***Zainab Ali Adamu[1], Mikhail Olayinka Buhari[2], Abdullahi Mohammed[1].**

[1]Department of Pathology, Ahmadu Bello University Teaching Hospital, Shika- Zaria, Kaduna State, Nigeria.
[2]Department of Pathology, University of Ilorin Teaching Hospital, Ilorin-Kwara State, Nigeria.

Abstract

Background: Malignant peripheral nerve sheath tumours (MPNSTs)are uncommon, aggressive sarcomas arising from a peripheral nerve or extra neural soft tissue and show evidence of nerve sheath differentiation. These tumours exhibit variability in grade and can either occur as familial or sporadic tumours. Immunohistochemistry is a paramount tool in the evaluation of these tumours. This study aimed at analyzing the histopathological and immunohistochemical patterns of these tumours and determining the frequency, demographic and anatomical site distribution.

Methodology: This was a 10-year retrospective hospital-based study. Formalin fixed paraffin embedded tissue blocks were sectioned and the slides werereviewed and interpreted. Morphological features were noted and immunohistochemical analysis was performed using four primary antibodies. Descriptive statistical analysis was used to collate and analyse data, and statistical test was used where necessary. The results were presented on statistical charts and tables.

Results: In this series, 20 cases of MPNSTs were seen with a male predilection. The 3rd and 4th decades were the most frequent decades of occurrence, and most tumours occurred in the gluteal region (eight cases) constituting 40% of all anatomical site's distribution. Borderline/intermediate grade tumours (Grade 2) were the most frequent grade. S100 (25%) and SOX10 (35%) showed low positive immunoexpression. Most of the tumours had low proliferative index or labelling hot spots with Ki67 antibody.

Conclusion: Malignant peripheral nerve sheath tumours are uncommon and tend to be sporadic in our region. Most of these tumours are borderline/intermediate grade tumours (Grade 2) showing low immunoexpression to antibodies employed with varying intensities.

Keywords: Gluteal Region; Histopathological; Immunohistochemical; Intermediate Grade; Male; MPNSTs.

***Correspondence:** Zainab Ali Adamu. Department of Pathology, Ahmadu Bello University Teaching Hospital, Shika- Zaria, Kaduna State, Nigeria. **Email:** superzeea@gmail.com

How to cite: Adamu ZA, Buhari MO, Mohammed A. Histopathological and Immunohistochemical Patterns of Malignant Peripheral Nerve Sheath Tumours in a Tertiary Institution of Northern Nigeria. Niger Med J 2025; 66 (3):1135-1158.https://doi.org/10.71480/nmj.v66i3.898.

Quick Response Code:

Introduction

Malignant peripheral nerve sheath tumours (MPNSTs) are rare neoplastic lesions originating from peripheral nerves, from a pre-existing benign nerve sheath tumour (usually neurofibroma) or in patients with neurofibromatosis type 1 (NF1).[1] Accounting for up to 5% of soft tissue sarcomas, MPNST tends to display highly variable morphological features.[2]Due to their morphological heterogeneity, these tumours were formerly termed; *neurofibrosarcoma, malignant schwannoma,* and *neurogenic sarcoma*.[3] The spectrum of morphological appearance of MPNSTs is variable, recapitulating the morphological features of different cells of the nerve sheath ranging from tumours that resemble a neurofibroma to those resembling a fibrosarcoma. MPNST occur in two primary forms, either as solitary sporadic tumours (70%) or as familial multiple tumours (30%) which are typically associated with the stigmata of NF1 or a family history of NF1.[3,4]Molecular studies have implicated the role of epidermal growth factor receptor (EGFR) overexpression in its pathogenesis.[5]Complex intricate clonal aberrations present in most cases often show homozygous deletion of the *cyclin-dependent kinase inhibitor 2A (CDKN2A)*gene on 9p21, which encodes the cell-cycle regulators *p16INK4a(p16 inhibitor of cyclin-dependent kinase 4)* and *p19ARF (p19 alternative reading frame)*.[6] Generally,10% of MPNSTs can be radiation–induced, with a 10-year or more post-treatment latency period.[7]The presence of heterologous elements is a unique feature displayed in about 10-15% of MPNSTs and its usually seen in tumours arising in NF1 patients.[8]Immunohistochemistry is valuable when histopathological assessments in differential diagnoses are inconclusive.In Nigeria and sub-Saharan Africa at large, few clinicopathological studies have been done on these tumours with most being case reports. Studies on histopathological and immunohistochemical profile of these tumours in a cohort or series are scarce in our region. Based on our current knowledge, this study will be a first attempt at investigating the morphological and immunohistochemical patterns of malignant peripheral nerve sheath tumours in the north-western Nigeria. This study will hopefully provide valuable insight in the diagnostic methods of these tumours in Nigeria and Africa at large. The study aimed at evaluating the histopathological and immunohistochemical patterns of malignant peripheral nerve sheath tumours with the objectives of ascertaining the frequency distribution, demographic characteristics and sites of occurrence of these tumours.

Methods and Materials

Study Area

This study was performed at the Pathology Department of a tertiary health care facility. This facility offers expertise management to myriads of illnesses mainly to patients in the northern part of the country and also serves other geopolitical zones of Nigeria.

Study Design

This was a descriptive retrospective hospital-based study of all histologically diagnosed Malignant Peripheral Nerve Sheath Tumours (MPNSTs) at Pathology Department from 1stJanuary 2010 to 31stDecember 2019.

Study Population

Source Population-All surgical biopsy specimens received in the department within the study period from 1stJanuary 2010 to 31stDecember 2019 constituted the source population.

Study Population-Cases with confirmed histological diagnosis of Malignant Peripheral Nerve Sheath Tumours (MPNSTs) within the study period constituted the study population. All cases of histologically diagnosed MPNSTs that strictly met the inclusion criteria within the study period.

Inclusion Criteria: All cases of malignant peripheral nerve sheath tumours diagnosed in the pathology department during the study period were included.

Exclusion Criteria: All cases with no request forms, missing tissue blocks or slides, incomplete demographic information, unspecified anatomical location of tumour were all excluded from the study. Also, cases with non-representative samples in situations in which repeat biopsies were done were also excluded from the study.

Data Collection Tools and Procedures

All surgical biopsy specimens submitted for histopathological evaluation to the pathology department of the institution over the study period were retrieved from departmental bench books, registry and archives. All cases diagnosed histologically as MPNSTs were extracted from the archival storage. The information collected and evaluated included basic demographic information, clinical features, anatomical location of tumours and morphological characteristics like macroscopical gross description and microscopic features with diagnosis. During collation of data, quality control measures such as data validation, cleaning and double-entry verification were ensured. Most of the archived haematoxylin and eosin-stained slides were either faint or broken, making interpretation challenging. This prompted the production of new haematoxylin and eosin-stained slides for all cases to enhance their proper review. The Formalin-fixed paraffin-embedded (FFPE) tissue blocks of all the cases were retrieved, and sections were made at 3-5 microns with the aid of a rotary microtome. The new slides produced were reviewed for histological diagnoses based on the World Health Organisation (WHO) Classification of Tumours of Soft Tissue and Bone, 4th Edition.[4] Histological grading of the tumours was based on the conventional histological grading system for soft tissue tumours by FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer).[9] In order to achieve proper verification of the diagnosis, the newly produced slides were reviewed and compared with the archived slides.

The immunohistochemical assay employed was the indirect immunoperoxidase detection method (Polymer Based Method- PBM) using the Bio SB (Bioscience IHC Technical Guide) Mouse/Rabbit PolyDetector 3, 3'-Di-amino-benzidine (DAB) horseradish peroxidase (HRP) Brown detector kit, which works on a biotin-based detection system. The staining approach utilized was the conventional streptavidin-biotin-peroxidase. This staining technique was carried out on 3-5 µm thick tissue sections from the formalin fixed paraffin embedded blocks in paraffin. The sections were then placed on positively charged adhesion microscope slides (CITOGLAS^{R}). The immunohistochemical procedures were strictly performed using standard protocols as outlined in the manufacturer's guidelines manual. The tissue sections were initially deparaffinized and rehydrated in water to reduce nonspecific signals which may interfere with the process. The sections were then incubated in citrate buffer at pH 6 for 60 minutes via the water bath method in order to achieve retrieval of antigen or unmask the epitopes. This was then followed by rinsing of sections in water with subsequent pretreatment using hydrogen peroxide for 5 minutes. The process of rinsing and pretreatment with hydrogen peroxide was performed to obstruct or douse the activity of endogenous enzymes or secondary antibodies that could cause nonspecific binding during the assay. These sections were then rinsed in Phosphate Buffered Saline (PBS) and incubated with the primary antibodies at different dilution factors for 60 minutes at room temperature (RT). Another rinse with PBS was performed again and the sections were then incubated in the detection system (Bio SB Mouse/Rabbit PolyDetector DAB HRP Brown, USA detector kit) for 30 minutes at RT. Following the final PBS rinse, sections were submerged in Di-amino-benzidine (DAB) for 5 minutes to visualize the reaction end product and then rinsed again in PBS. Sections counterstaining was then performed using Mayer Haematoxylin for 1 minute, these were again rinsed in water, dehydrated, cleared with xylene, and placed in Dibutylphthalate Polystyrene Xylene (DPX) before thenfinally cover slipping. The primary antibodies utilized in this assay include: (a) S100 protein [Solubility in 100%] (1:100, Bio SB, USA), (b) SOX10 [SRY (sex determining region Y)-box 10 protein] (1:100, Elabscience^{R}, USA), (c) Ki67 [Antigen/Protein Keil 67] (1:100, GenomeMe, Canada), and (d) Desmin (1:100, Bio SB, USA). The

whole staining process was performed and facilitated with an automated slide stainer. Reliability and validity of tests was ensured by including both positive extrinsic and intrinsic control samples which were introduced in the assay alongside the test samples. All reagents and study tools utilized were developed and validated by experts to ensure reliability, consistency, accuracy and completeness of the procedure. Elimination of bias in this retrospective study was also achieved by strictly adhering to the inclusion/exclusion criteria, accurate data collection and ensuring standard quality control and assurance measures. (Table 1) presents the characterization of the immunohistochemical markers.

Table 1: Immunohistochemical Markers Characterization

Characterization	**Immunohistochemical Markers Used**			
	S100	**SOX10**	**Ki67**	**Desmin**
Localization	Cytoplasmic & Nuclear	Nuclear	Nuclear	Cytoplasmic
Extrinsic Control	Schwannoma	Melanoma	Pineoblastoma	Leiomyosarcoma
Intrinsic Control	Melanocytes	Melanocytes		Tunica media
Primary Antibody	Mouse, m	Rabbit, p	Rabbit, m	Mouse, m
Species Reactivity	Human, mouse & dog	Human, mouse & rabbit	Human	Human, Canine
Isotype	IgG2a	IgG	-	IgG1/K

**Abbreviations:* S100- Solubility in 100%, SOX10- SRY (sex determining region Y)-box 10 protein, Ki67- Antigen/Protein Keil 67, m- monoclonal, p-polyclonal, IgG- Immunoglobulin G, IgG1/K- Immunoglobulin G1 Kappa

The histological examination and review of all stained slides were independently evaluated by two consultant pathologistsusing the Leica DM750 LED Biological Microscope Series. Photomicrographs were captured with a Euromex CMEX-12f Pro 12 Megapixel Camera featuring a fast CMOS sensor (Complementary metal oxide semiconductor). The architectural, cytomorphological, and immunohistochemical characteristics of all cases were documented and the grading of these tumours was based on the histological features.

Immuno histochemical Staining intensity scoring systems

In the interpretation of two of the four primary antibodies (S100 and SOX10), a semi-quantitative scale of proportion/distribution, staining intensity and extent, as adapted by Ji Y et al [10], was utilized. All cases were either categorized into a negative group [when less than 5% of neoplastic cells are stained] or a positive group [when more than 5% of neoplastic cells are stained]. The specific localization of these antigens aided interpretation of these antibodies: (a) S100 (Nuclear and cytoplasmic immunopositivity were required for interpretation) while (b) SOX10 (Nuclear immunopositivity was required for interpretation). Within the positive group, the staining intensity was interpreted as (1, weak/mild; 2, moderate; 3, strong/intense). The proportion or percentage in the positive groups were quantified based on the percentage range [5-25%; >25-75%; >75%]) and the staining extent was either focal or diffuse. The evaluation of the antibody Ki67 staining was based on a different method or scale. The staining with Ki67 antibody was not deemed negative even if less than 5% of cells were stained rather, hotspot labeling index or diffuse staining was used. The scale used for evaluation of Ki67 immunoexpression was the Eye-10 method proposed by Kadivar et al. [11] The parameters for interpretation include the Ki67 Labeling Index, which is defined as the percentage of cells with Ki67 positive nuclear immunostaining, and Hot Spots, which is defined as areas where Ki67 staining was notably higher compared to adjacent areas. Based on the definitions stated, the Eye-10 method suggests that a percentage labeling index hot

spot of [<10%] indicates a low-grade tumour, [10-20%] indicates a borderline tumour, and [>20%] indicates a high-grade tumour. Desmin antibody required cytoplasmic immunopositivity for interpretation and this antibody was only utilized in all cases of malignant triton tumour (MTT) to specifically highlight rhabdomyoblasts at various stages of development.

Data Analysis

Data was analysed using descriptive statistical analysis which was conducted on the collected data. This analysis utilized the Statistical Package for the Social Sciences (SPSS) version 20.0 to investigate the demographic characteristics, histopathological features, immunohistochemical features, and histological grading of these tumours. The results were displayed on frequency distribution tables, and statistical charts were created with Microsoft Excel and Microsoft Word version 2020.Correlational study was performed using the Spearman's rank correlation test in order to assess the relationship between tumour grade and Ki67 immunoexpression.

Ethical Consideration

Study Approval: Ethical considerations were strictly adhered to in this study. Approval and consent for the research were obtained from the Health Research Committee of the Department and Institution with D.U.N.S Number: 954524802.

Anonymity and Confidentiality: To ensure anonymity and confidentiality, the complete information retrieved during the study is available only to the investigators. The patient names, histology number or chart numbers were all removed from the data extraction sheet to maintain patient confidentiality. This study did not pose a risk to any of the patients.

Results

Time Trend

A total of 20 cases (0.7%) of MPNSTs that strictly met the inclusion criteria out of 30,267 surgical biopsies received within the study period were identified. Of the total specimen received, 1,502 cases were diagnosed as soft tissue tumours and MPNSTs constituted 1.3% of all soft tissue tumours diagnosed over the study period. (Figure 1) is a multiple line graph depicting the time trend of total specimens received, soft tissue tumours and MPNSTs.

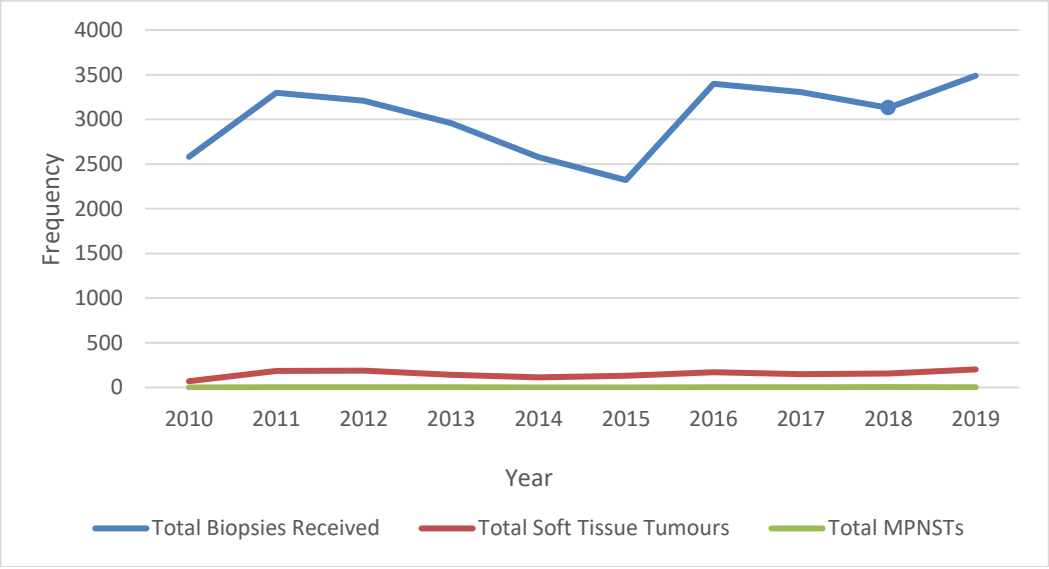

Figure 1: A multiple line graph showing the changing time trend of total biopsies, soft tissue tumours and MPNSTs over the study period.

Age and Gender Distribution

Of the 20 cases seen, 15 cases (75%) occurred in males while five cases (25%) occurred in females and male to female ratio of (3:1) was observed. Patients age ranged from 4-75 years, and the overall mean age was 36.2years [SD=17.9] and inter-quartile range (IQR)= 32years. These characteristics are shown in (Figure 2) and (Figure 3) which are box and whisker plots showing the overall and individual mean and median ages and the inter-quartile ranges (IQR) respectively. The peak age range of occurrence was seen in the third and fourth decades of life and this is shown in (Figure 4).

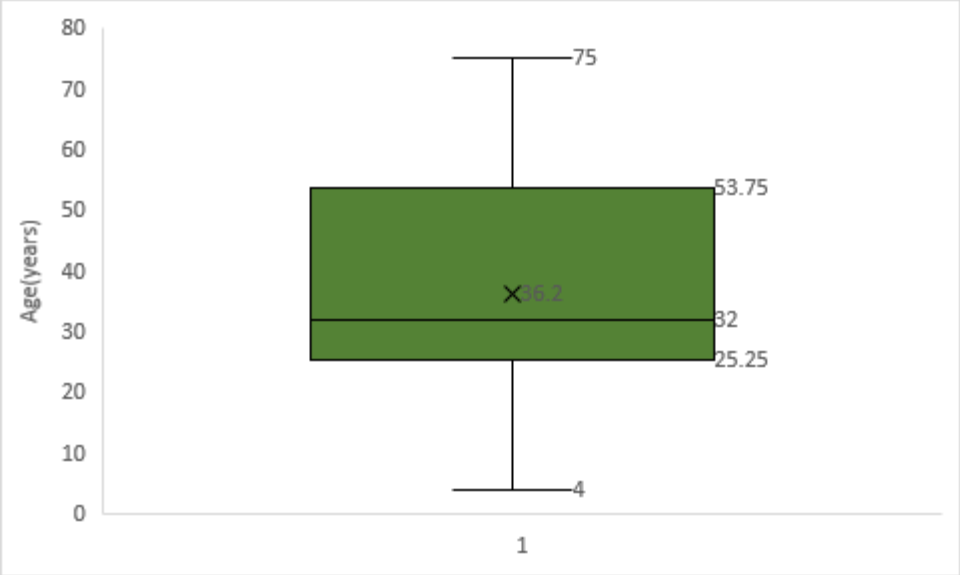

Figure 2: A Box and Whisker plot showing the overall mean and median ages with the inter-quartile ranges (IQR) of MPNSTs over the study period.

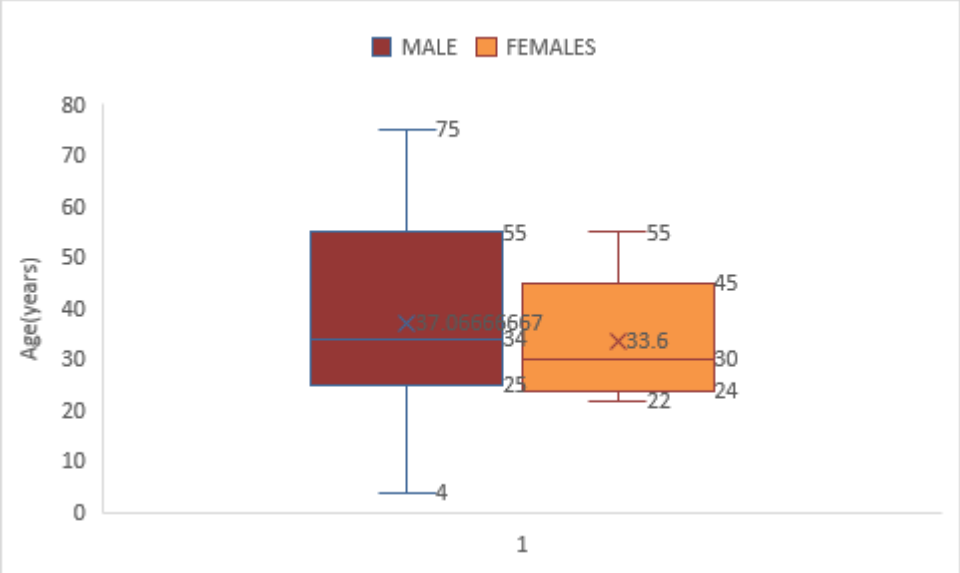

Figure 3: A Box and Whisker plot showing the individual sex mean and median ages with the inter-quartile ranges (IQR) of MPNSTs over the study period.

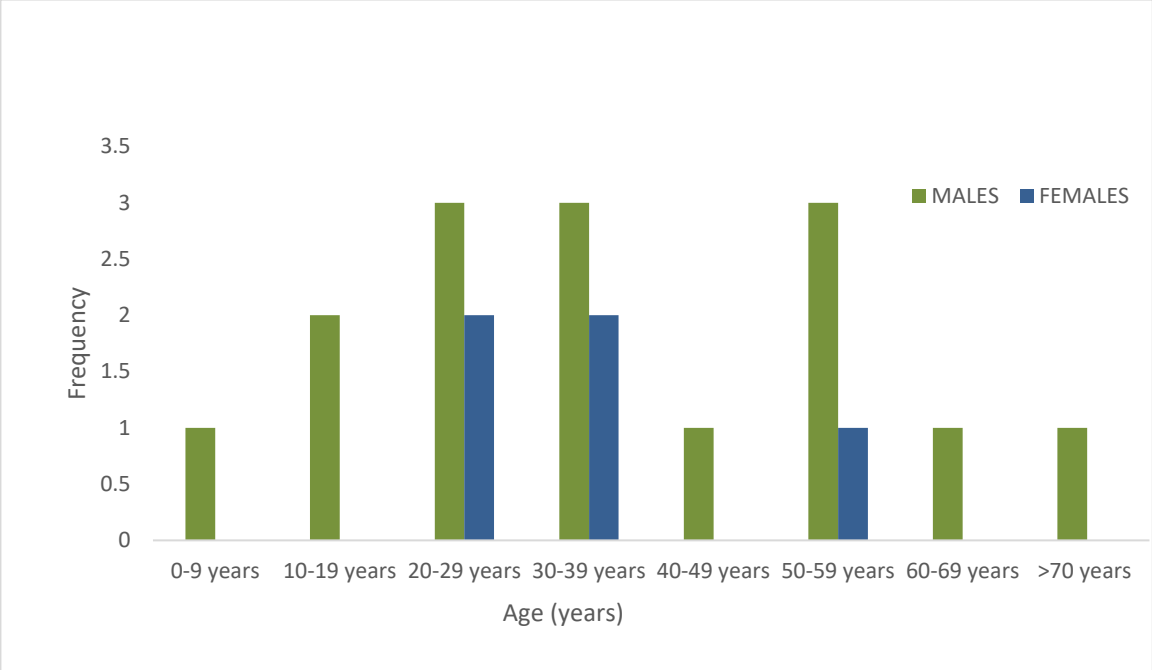

Figure 4: A clustered column showing the sex and age range frequency distribution of MPNSTs over the study period.

Anatomical Sites Distribution

The most common anatomical location of these tumours wasthe gluteal region (8), head and neck (4), trunk (2), upper limbs (1), lower limbs (3) and 2 unusual sites of presentation (anterior chest wall and intra-abdominal). (Figure 5) shows the frequency of anatomical sites distribution of MPNSTs seen within the study period. The demographic and anatomical sites distribution has been summarized in (Table 2)

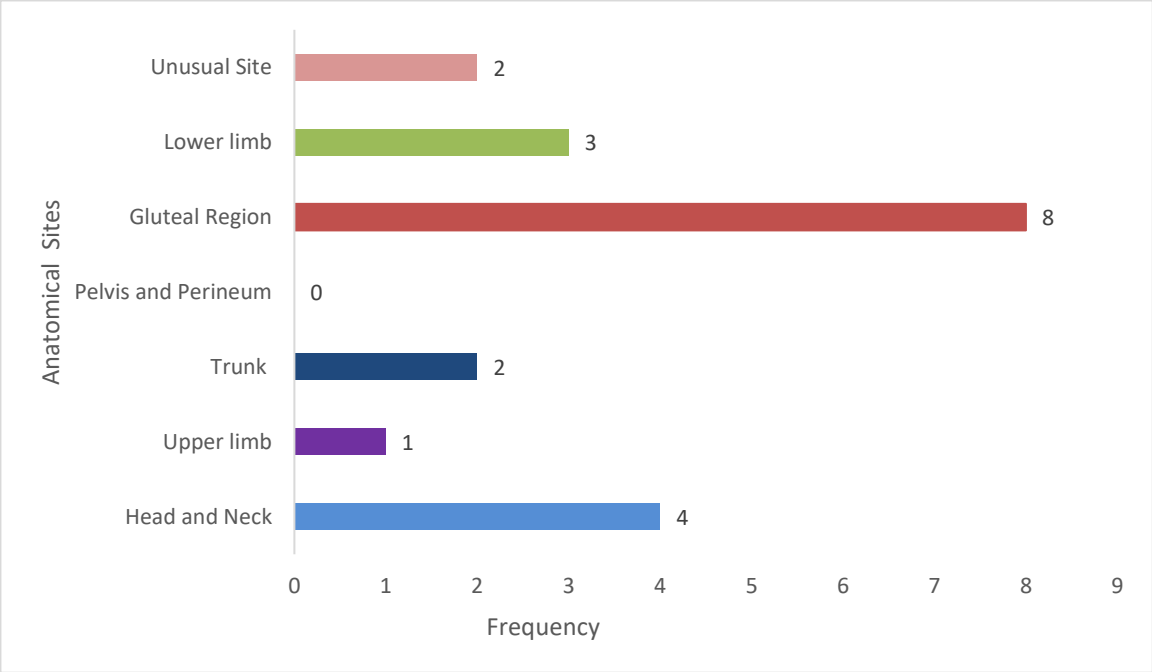

Figure 5: A clustered bar chart showing the anatomical sites frequency distribution of MPNSTs over the study period.

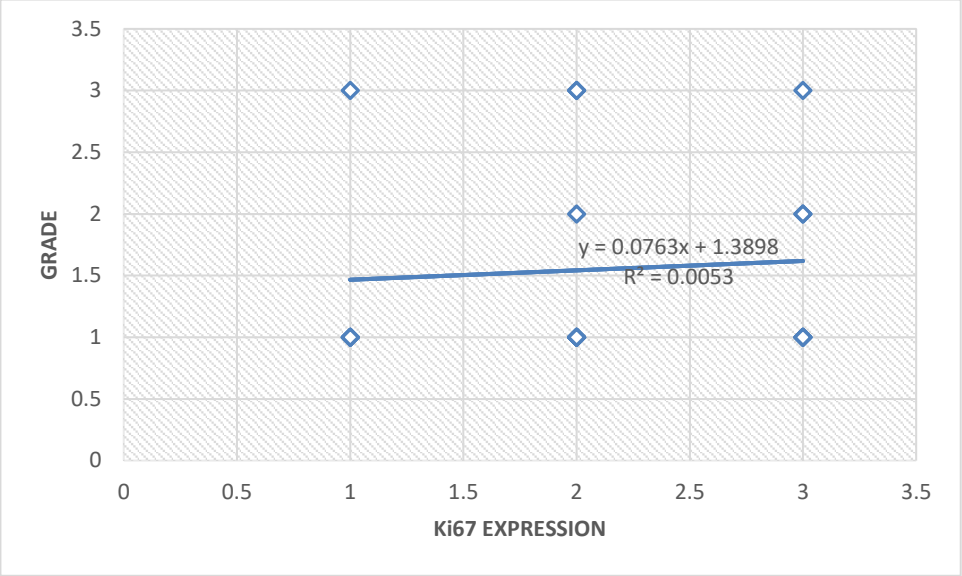

Figure 6: A scatter plot showing the relationship between tumour grades and Ki67 expression of MPNSTs over the study period.

Table 2: Demographic and Anatomical sites distribution of 20 Cases of MPNSTs

Characteristics	**Value**
Sex(M/F)	15/5
Age range with highest frequency	3rd decade (20-29 years) and 4th (30-39years)
Mean age (years) and SD	36.2 [SD=17.9]
Number of cases with NF1	2
Tumour Location	
Head and Neck	4
Upper limb	1
Trunk	2
Pelvis and Perineum	0
Gluteal Region	8
Lower Limb	3
Unusual Site	2

**Abbreviation:* MPNSTs- Malignant Peripheral Nerve Sheath Tumours, SD-Standard Deviation

Morphological features

Haematoxylin and Eosin Stain Morphological features

Twenty MPNSTs were found within the study period and analyzed. The architectural and cytological parameters frequency distribution is seen in (Table 3) and (Table 4). These tumours were further graded using the conventional FNLCC grading system of soft tissue tumours. Most of the tumours were infiltrative (90%) and markedly cellular showing geographic necrosis. Long organized fascicles were

seen in most cases. The Haematoxylin and eosin morphological features are shown in (Figure 7 - Plate 1) and (Figure 8 - Plate2). Four (20%) cases had heterologous (divergent) differentiation in form of osteogenic (25%), chondromatous (25%) and rhabdomyoblastic (50%) elements. (Figure 9 - Plate 3) shows the heterologous osteogenic and chondromatous elements. The two cases with rhabdomyoblastic differentiation were malignant triton tumour -MTT and the histological features are shown in (Figure 10 - Plate 4).

Table 3: Morphological (Architectural) Features of 20 cases of MPNSTs

Architecture	*Number of Cases with the features (%)*
Margins	
Infiltrative	18/20 (90%)
Fair circumscription	2/20 (10%)
Marble Effect	
Present	15/20 (75%)
Absent	5/20 (25%)
Fascicles	
Long sheaves	8/20 (40%)
Short sheaves	3/20 (15%)
Mixed sheaves	9/20 (45%)
Herringbone Pattern	
Present	16/20 (80%)
Absent	4/20 (20%)
Necrosis	
Present	14/20 (70%)
Absent	6/20 (30%)
Heterologous element	
Present	4/20 (20%)
Absent	16/20 (80%)
Perivascular accentuation	
Present	10/20 (50%)
Absent	10/20 (50%)
Pre-existing BPNST	
Present	1/20 (5%)

Absent	19/20 (95%)
Secondary degenerative features	
Present	19/20 (95%)
Absent	1/20 (5%)
Variants	
Conventional	14/20 (70%)
Myxoid	1/20 (5%)
Divergent differentiation	5/20 (25%)

**Abbreviations:* BPNSTs- Benign Peripheral Nerve Sheath Tumours, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

Table 4: Morphological (Cytomorphological) Features of 20 cases of MPNSTs

Cytological Features	*Number of Cases with the features (%)*
Cellularity	
Mild +	1/20 (5%)
Moderate ++	6/20 (30%)
Marked +++	12/20 (60%)
Cell Population	
Variable (mixed population)	0/20
Invariable(monotonous)	20/20 (100%)
Predominant cell type	
Spindle (buckled, wavy, serpentine)	16/20 (80%)
Spindle (elongate/oval)	4/20 (20%)
Nuclear features	
Nuclei	
variable	0/20
monotonous	20/20 (100%)
Pleomorphism	
mild +	1/20 (5%)

moderate ++	13/20 (65%)
marked +++	6/20 (30%)
Hyperchromasia	
mild +	1/20 (5%)
moderate ++	2/20 (10%)
marked +++	17/20 (85%)
Mitoses	
Absent	0/20
Present 5-9/10hpf	9/20 (45%)
Present 10-19/10hpf	6/20 (30%)
Present >20/10hpf	5/20 (25%)

**Abbreviations:* hpf-high power field, + mild, ++ moderate, +++ marked, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

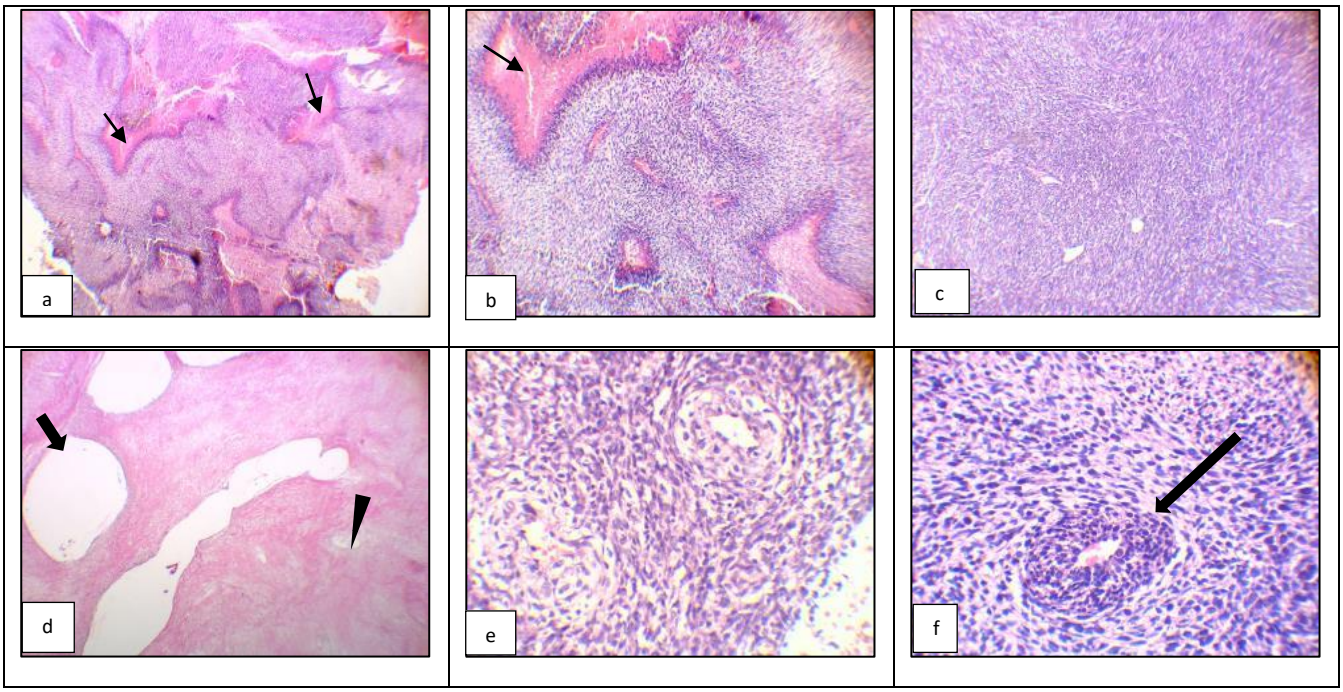

Figure 7: Showing the Haematoxylin and eosin morphological features are shown in - Plate 1[a-f]: Architectural Features of MPNSTs

(a) Photomicrograph with short thin black arrows showing zones of geographic necrosis in MPNSTs, H&E x40 (b) Photomicrograph with a short thin black arrow highlighting palisading necrosis, H&E x100. (c)Photomicrograph showing hyper cellularity with few dilated vessels,H&E x40(d) Photomicrograph with a short thick black arrow and thick arrow head showing cystic and hyaline degenerative changes respectively, H&E x40.(e) Photomicrograph showing perivascular accentuation by tumour cells, H&E x400 (f) Photomicrograph with a long thick black arrow showing perivascular aggregates of tumour cells, H&E x400.

**Abbreviations:* H&E- Haematoxylin and Eosin stain, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

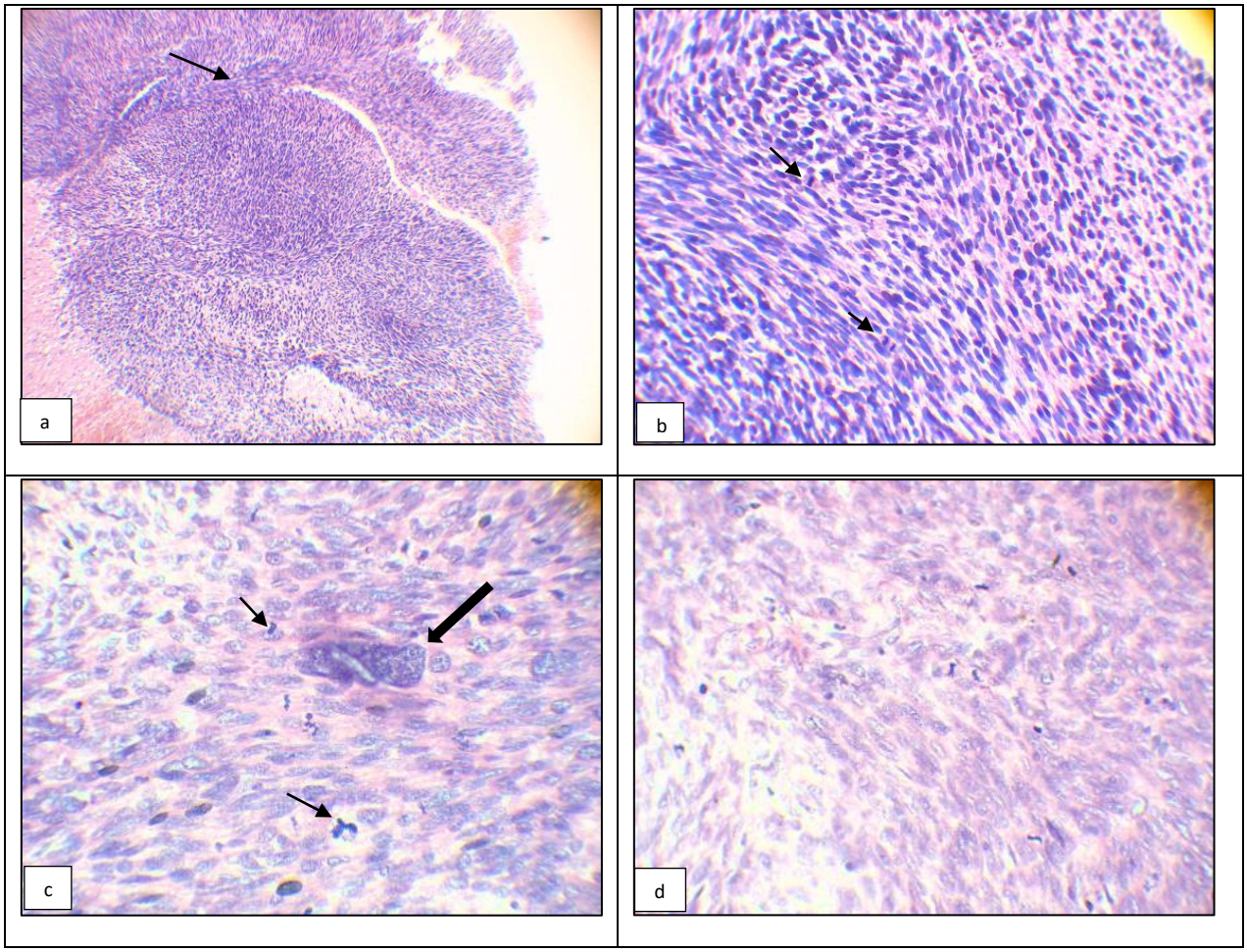

Figure 8 - Plate 2[a-d]: Cytomorphological Features of MPNSTs

(a)Photomicrograph with short thin arrow showing herringbone pattern, H&E x40(b) Photomicrograph showing markedly pleomorphic cells having hyperchromatic nuclei and some mitotic figures highlighted in short black thin arrows, H&E x400.(c) Photomicrograph showing tumour giant cell with a long black thick arrow and short black thin arrows highlighting frequent atypical mitoses in background, H&E x 400 (d) Photomicrograph showing numerous mitotic figures highlighted with arrows,H&E x400.

**Abbreviations:* H&E- Haematoxylin and Eosin stain, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

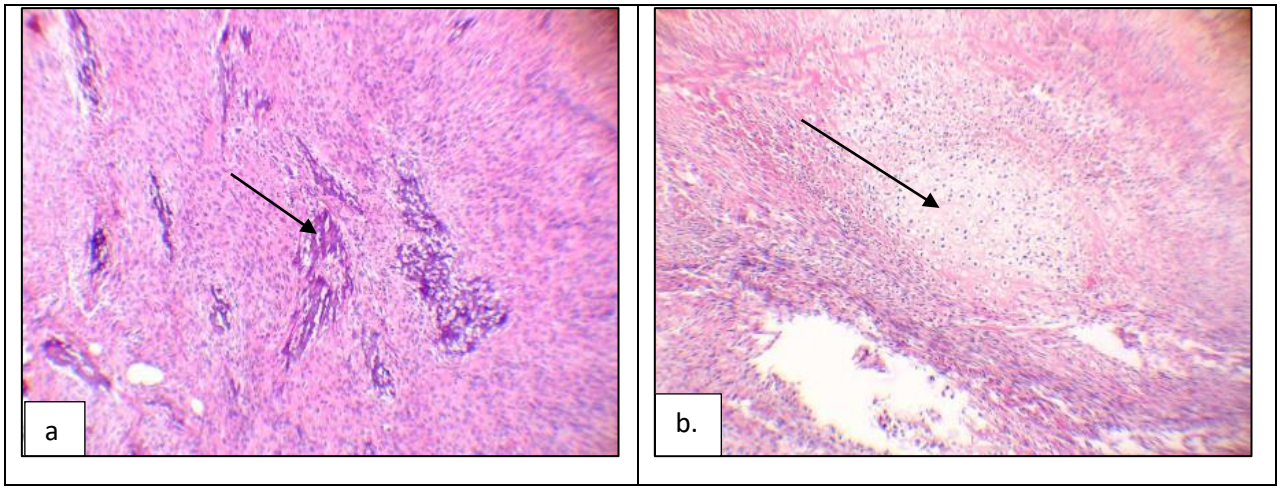

Figure 9 - Plate 3[a&b]: Heterologous (Divergent) differentiation in MPNSTs

(a)H&E x100 showing areas of osteogenic differentiation. (b) H&E x100 showing an area of chondromatous differentiation

**Abbreviations:* H&E- Haematoxylin and Eosin stain, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

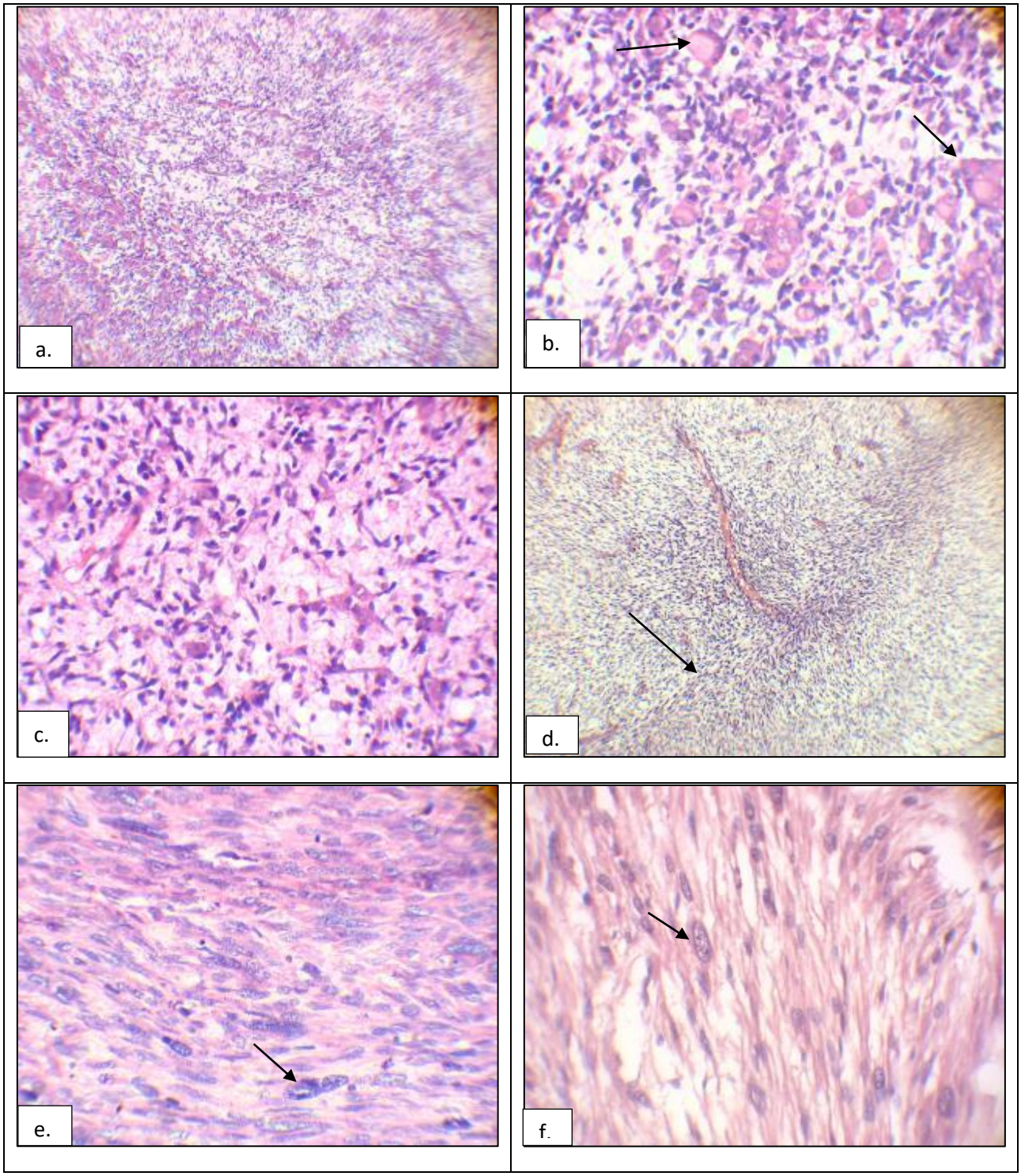

Figure 10 - Plate 4[a-f]: Histological features of Malignant Triton Tumour (MMT)

(a) Photomicrograph of Malignant Triton Tumour,H&E x 100 (b) Photomicrograph with short black thin arrows highlighting rhabdomyoblasts at varying stages of maturation, H&E x400. (c) Photomicrograph showing rhabdomyoblasts at varying stages of maturation,H&E x400 (d) Photomicrograph showing

herringbone pattern, H&E x100.(e) & (f) Photomicrographs showing marked nuclei pleomorphism in MMT, H&E x 400.

**Abbreviations:* H&E- Haematoxylin and Eosin stain, MMT- Malignant Triton Tumour, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

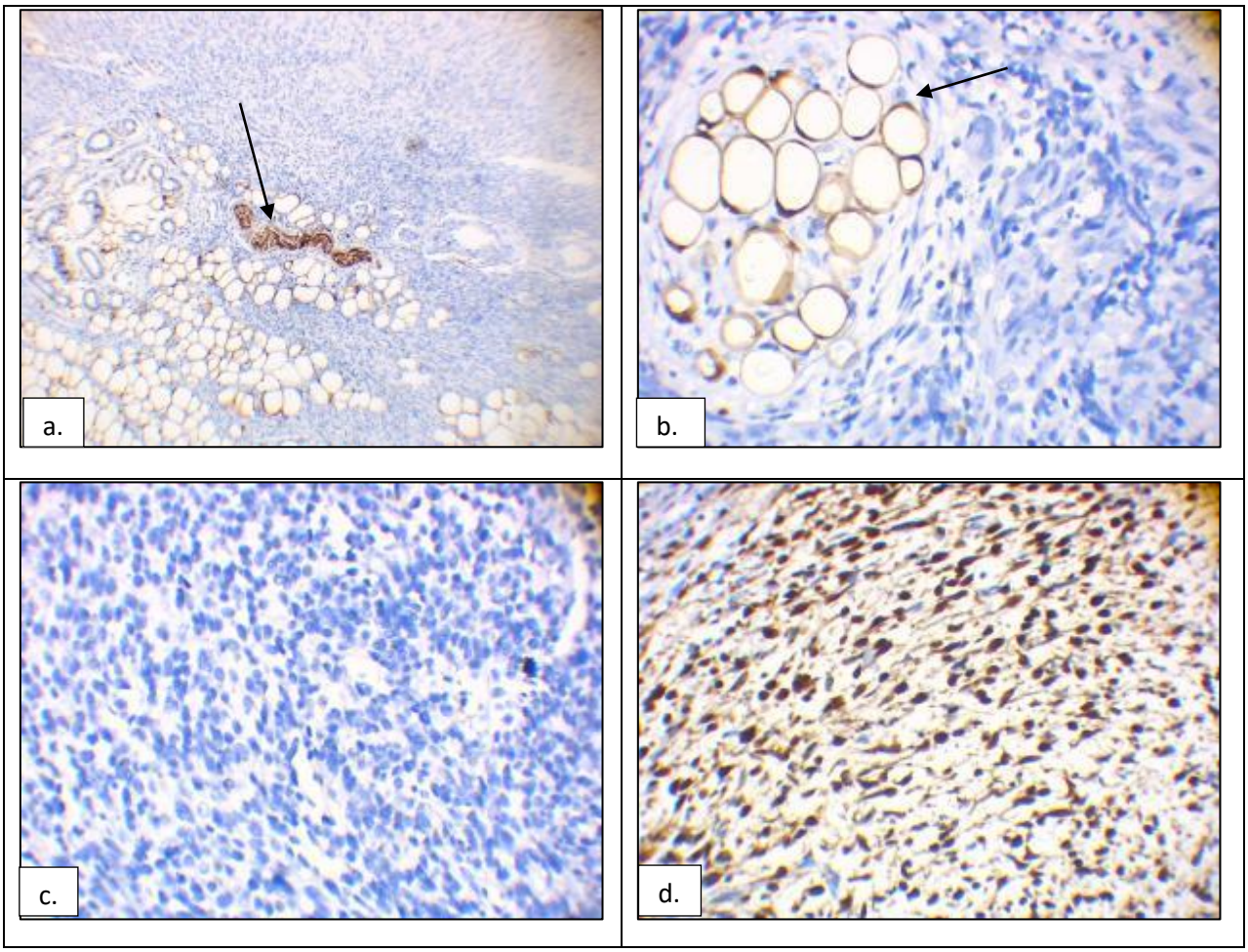

Figure 11 - Plate 5[a-d]: MPNSTs Immunohistochemical Stains; S100

(a) Photomicrograph shows S100 negative stain in neoplastic cells and arrow showing positive staining in adipocytes and normal neurovascular bundles serving as intrinsic control,PBM x100 (b) Photomicrograph showing S100 immunonegativity in the neoplastic cells on the right and arrow showing positivity in lobule of adipocytes on the left as intrinsic control, PBM x400.

(c) Photomicrograph showing negative S100 staining in MPNST,PBM x 400 (d) Photomicrograph showing S100 strong diffuse immunopositivity in one of the tumours,PBM x400.

**Abbreviations:* S100-Solubility in 100%, PBM- Polymer Based Method, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

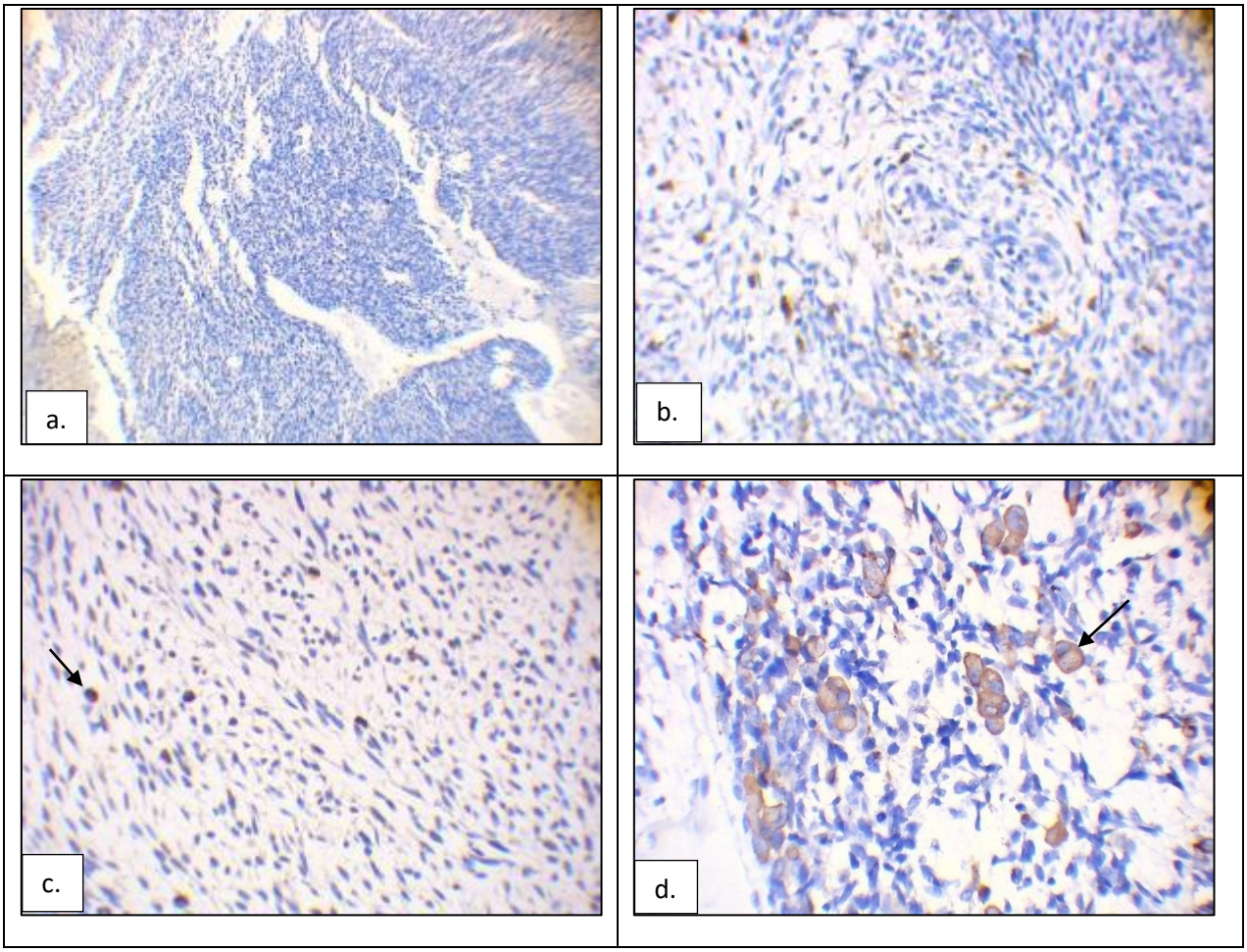

Figure 12 - Plate 6[a-d]: MPNSTs Immunohistochemical Stains; SOX10, Ki 67 and Desmin

(a)Photomicrograph shows SOX10 immunonegativity, PBM x100 (b) Photomicrograph showing S0X10 immunopositivity with moderate (++) patchy focal fashion, PBM x 400.

(c) Photomicrograph of Ki 67 immunostaining labeling few hot spots with arrow highlighting a hot spot in a Grade 2 tumour, PBM x 400 (d) Photomicrograph of Desmin showing cytoplasmic staining in pleomorphic rhabdomyoblasts in MMT, an arrow highlights a rhabdomyoblast, PBM x 400.

**Abbreviations:* SOX10- SRY (sex determining region Y)-box 10 protein, Ki67- Antigen/Protein Keil 67, PBM- Polymer Based Method, MMT- Malignant Triton Tumour, MPNSTs- Malignant Peripheral Nerve Sheath Tumours, ++- moderate

Histological Grading

It was observed that five cases constituting 25% were Grade 1 tumours, eight cases constituting 40% were Grade 2 and seven cases constituting 35% of all cases were Grade 3 tumours. Based on the modified FNCLCC grading system, five cases constituting 25% were low grade tumours while 15 cases constituting 75% were high grade tumours. The grade of these tumours is shown in (Table 5). The different grades of these tumours in relation to demographic characteristics and NF1 status is shown in (Table 6). Eighteen (90%) cases were sporadic occurring mostly as solitary tumours in adults while two cases were familial occurring in the setting of NF1.

Table 5: Histological Grading of 20 cases of MPNSTs According to FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer)

Parameters	*Frequency of cases with the parameters (%)*
Tumour Differentiation	
Score 1(Arising in transition from BPNST)	1/20 (5%)
Score 2(Conventional)	15/20 (75%)
Score 3(With divergent differentiation)	4/20 (20%)
Mitotic count	
Score 1 (0-9/10hpf)	9/20 (45%)
Score 2 (10-19/10hpf)	6/20 (30%)
Score 3 (>20/10hpf)	5/20 (25%)
Tumour necrosis	
Score 0- Necrosis absent	6/20 (30%)
Score 1- <50% necrosis	4/20 (20%)
Score 2- >50% necrosis	10/20 (50%)
Grade	
Grade 1(Low Grade) -Total Score 2-3	5/20 (25%)
Grade 2(Intermediate Grade) -Total Score 4-5	8/20 (40%)
Grade 3(High Grade) -Total Score 6-8	7/20 (35%)

**Abbreviations:* FNCLCC- Fédération Nationale des Centres de Lutte Contre le Cancer, hpf-high power field, MPNSTs- Malignant Peripheral Nerve Sheath Tumours

Table 6: Grading and Demographic Characteristics of 20 cases of MPNSTs

S/No	Age & Sex	Site	NF Status	Pre-existing BPNST	Grade
1.	4years/male	Posterior Thigh	Negative	Absent	2
2.	25years/male	Gluteal	Negative	Absent	3
3.	35years/female	Gluteal	Negative	Absent	2
4.	50years/male	Gluteal	Negative	Absent	3
5.	34years/male	Gluteal	Negative	Absent	2
6.	34years/male	Gluteal	Negative	Absent	1
7.	40years/male	Gluteal	Negative	Absent	2
8.	55years/male	Lower Limb (Leg)	Negative	Absent	2
9.	65years/male	Upper trunk	Negative	Absent	2
10.	30years/female	Anterior chest wall	Positive	Present	3
11.	30years/male	Arm	Negative	Absent	3
12.	75years/male	Submandibular	Negative	Absent	3
13.	29years/male	Facial	Negative	Absent	1
14.	22years/female	Gluteal	Negative	Absent	1
15.	26years/female	Facial	Negative	Absent	2
16.	18years/male	Intra-abdominal	Positive	Present	2
17.	55years/female	Lower Trunk (Lumbar)	Negative	Absent	1
18.	55years/male	Lower limb (Leg)	Negative	Absent	1
19.	16years/male	Gluteal	Negative	Absent	3
20.	26years/male	Neck	Negative	Absent	3

**Foot note*- FNCLCC Grade 1 = Low Grade, FNCLCC Grade 2= Intermediate Grade & FNCLCC Grade 3 = High Grade

Immunohistochemical Findings

All cases of MPNSTs were subjected to immunohistochemical analysis utilizing the following primary antibodies; SOX10, S100, Ki67 and Desmin. The immunohistochemical features of these tumours is shown in (Table7) and (Table 8).

Table 7: Immunohistochemical Profile of 20 cases of MPNSTs in showing staining intensity, percentage of neoplastic cells stained and the extent of neoplastic cells stained

	Parameter	**Antibody Used**	
		SOX10	S100
Staining Intensity	**Intensity**		
	Positivity	7/20(35%)	5/20(25%)
	Strong intensity	1/7(14.2%)	4/5(80%)
	Moderate intensity	3/7(42.9%)	1/5 (20%)
	Mild intensity	3/7(42.9%)	0
	Negativity	13/20(65%)	15/20(75%)
Percentage of Neoplastic Cells Stained	**Percentage (%)**		
	Positives		
	5-25%	5/20(25%)	3/20(15%)
	>25-75%	2/20(10%)	2/20 (10%)
	>75%	0	0
	Negatives		
	<5%	13/20(65%)	15/20 (75%)
Extent in Positive Cases	**Extent in Positives cases**		
	Diffuse	0	1/5(10%)
	Focal	7/7 (100%)	4/5 (80%)

Table 8: Immunohistochemical Profile using Ki67 Antibody of 20 cases of MPNSTs	
Eye -10 Method Percentage (%)	**Frequency of Distribution (%)**
<10%	13/20(65%)
10-20%	3/20(15%)
>20%	4/20 (20%)
Staining Intensity	
Mild +	15/20(75%)
Moderate ++	1/20(5%)
Strong +++	4/20(20%)

SOX10 antibody staining employed in the analysis of MPNSTs required nuclear immunostaining for interpretation. Of the 20 cases subjected to SOX10 antibody staining, only seven cases (35%) were immunopositive while 13 cases (65%) were immunonegative. The seven cases that showed nuclear immunopositivity had mild and moderate staining intensities in three cases each while only one case showed strong staining intensity. The positive cases showed a percentage distribution of {>5-25%} in five (25%) cases and {>25-75% in two (10%) cases. The percentage distribution of these positive cases showed focal patchy nuclear immunopositivity.

For S100 antibody, interpretation was both nuclear and cytoplasmic and only five cases (25%) expressed S100 antibody while the remaining 15 (75%) cases did not express this antibody. Of the five cases that showed immunopositivity, four cases showed strong staining intensity while one case showed moderate staining intensity. The positive cases showed a percentage distribution of {>5-25%} in three (15%) cases and {>25-75%} in two (10%) cases. Out of the five positive cases that showed nuclear immunopositivity, four (80%) cases showed focal patchy immunopositivity while one (20%) case showed diffuse patchy immunopositivity.

In the interpretation of Ki67 antibody expression, the Eye-10 method suggested by Kadivar *et al* was used. [11]. Nuclear staining was required for immunostaining interpretation. Histological analysis of all the 20 cases stained with Ki67 revealed; 13(65%) cases had {<10%} low nuclear immunostaining percentage hot spots, three (15%) cases had {10-20%} borderline nuclear immunostaining percentage hot spots and four cases (20%) had {>20%} high nuclear immunostaining percentage hot spots. The four cases with high labeling hot spots were Grade 3 tumours. Fifteen (75%) of the cases showed focal patchy nuclear positivity with mild staining intensity, one (5%) of the cases showed focal patchy nuclear positivity with moderate intensity and four (20%) cases showed strong diffuse patchy nuclear positive hot spots.

Desmin was utilized to highlight rhabdomyoblasts in MTT at varying stages of development.

Correlation Analysis

The Spearman's rank test was employed to test the strength and direction of the relationship between the histological grade and Ki67 expression of these tumours. It was observed that a weak positive correlation exists between these two categorical variables and r_s= 0.1165. A high Ki67 expression was noted in some

grade 1 tumours while a low Ki67 expression was observed in some grade 3 tumours. A low Ki67 labeling index in some high grade MPNST could indicate that a higher-grade component of the tumour was not sampled. (Figure 6) shows a scatter plot depicting the relationship. The total percentage expression of Ki67 antibody by these tumours was 264% with a mean percentage expression of 13.2 [SD=9.08].

Discussion

MPNSTs are uncommon, aggressive sarcomas that either originate from a peripheral nerve or extra neural soft tissue and may show evidence of nerve sheath differentiation. These tumours are rare constituting about 5% of all soft tissue sarcomas.[2] In this series, 20 cases of MPNSTs were seen and diagnosed within the study period which constituted 1.3% and 9.0% of all soft tissue tumours and all peripheral nerve sheath tumours respectively. These tumours were more prevalent in males with a male to female ratio of 3:1 and a peak age range of occurrence (mode)in the 3rd and 4th decades of life and a mean age of 36.2years. In line with a study carried out by Nthumba PM *et al* in Kenya, in a retrospective study, who reviewed 333 peripheral nerve sheath tumours diagnosed over 16 years. Thirty-one (31) cases in their study were diagnosed as MPNSTs with a frequency of 9.3% and these tumours had slight male predilection. The male to female ratio was 1.06:1 and the patients age range with the highest occurrence (mode) was seen in the 4th decade with a mean age of 34 years.[12] However, the findings in the index study are contrary to a 22-year retrospective clinicopathological review in Ilorin, Nigeria by Odebode *et al* who studied 98 clinically diagnosed NF1 patients with PNSTs of which only three patients(3.1%) had MPNSTs.[13] Their study observed male predilection and the male to female ratio was 3:2.[11] Also, Adeyemi *et al*in Ibadan, Nigeria in a single institutional review of all head and neck cancers showed MPNSTs to represent 6.5% of all head and neck cancers studied and female preponderance was observed.[14] Another contrasting work done by Chikkannaiah P *et al* in Karnataka, India, in a review of 143 PNSTs found three cases (2%) to be MPNSTs and the most frequent occurrence was in the 4th decade with a male predominance.[15] Also, Pekmezci *et al* in California assessed 115 MPNSTs and showed a female preponderance in which 65 cases (56%) occurred in females and 50 cases (44%) of these tumours occurredin males with a male to female ratio of 1:1.3. Mean age of occurrence of these tumours in their study was 38.2 years which is in accordance with this study.[16] Generally, MPNSTs occur more in males and areseen commonly in the fourth and fifth decades, as seen in literatures. These tumours can occur at any age groupbut are more commonly seen in older age groups. [1,9] There are no apparent scientific reasons why these tumours occur more in males as available evidence have shown no hormonal relationship in the pathogenesis of these tumours. A small proportion of cases occur in childhood, in which its association with NF1 has been said to be more common than in adults.[1]MPNSTs are usually seen in adulthood with most tumours occurring in age range of 20 to 50 years with a median age of about 35 years.[1] Patients with NF1 usually present at a slightly earlier age and have larger tumours than those with sporadic lesions. [1] MPNST occur in two primary forms, either as solitary sporadic tumours or as multiple syndromic tumours seen in 30% to 50% of patients which is usually association with NF1. Patients with NF1 have a 5% to 10% range lifetime risk of developing MPNST. [5,8] The index study also observed that most cases of MPNSTs seen within the study period were solitary sporadic cases 18 (90%) while two cases (20%) were syndromic associated with NF1. Also, the mean ages of the sporadic and syndromic cases were 37.5years and 33years respectively in the index study. In contrast, Nthumba PM*et al*found the solitary sporadic forms 16 (52%) slightly outnumbering the syndromic cases 15 (48%) with most of the syndromic forms occurring in females. The NF1 associated MPNSTs occurred in a younger age group as compared to patients with solitary sporadic tumours occurring in the adult age group.[12] Pekmezci *et al* in California, also reported median ages at diagnosis for NF1 associated MPNSTs and those not associated with NF1 to be 33.8 years and 41.7 years respectively.[16] Nthumba PM *et al* revealed that most patients with syndromic or familial MPNSTs presented mainly in the 3rd decade while those with sporadic MPNSTs presented in the 5th decade. This is in concordance with other reports that have shown NF1-associated MPNSTs occurring earlier in life.[12] This study also observed that sporadic

MPNSTs presented in the fourth and fifth decades while the NF1 associated MPNSTs were encountered in the second and fourth decades of life.

MPNSTs usually arise in the upper and lower extremities followed by the trunk and then head and neck area.[10] These tumours tend to involve large nerve plexuses like brachial plexus and sacral plexus. MPNSTs typically occur in the proximal portions of the upper and lower extremities.[1]The most frequent anatomical site of distribution of MPNSTs in this study was the gluteal region with about eight cases seen constituting 40% of anatomic distribution of MPNSTs seen. Most studies have shown MPNSTs commonly involving large nerve trunks, such as sciatic nerve, brachial plexus, and sacral plexus.[1,8] This is in contrast to Nthumba PM*et al*in Kenya who found the most frequent anatomical siteto be the trunk.[12] Gabhane SK *et al*, in India evaluated 126 peripheral nerve sheath tumours of which only eight cases were MPNSTs and most of the tumours occurred in the lower extremity.[28] Also, several literatures have shown that MPNSTs occur in deep soft tissues, involving large nerve trunks, commonly the sciatic nerve or other major nerve plexuses such as brachial and sacral plexuses.[1,12] This may explain why the gluteal region is the most frequent anatomical site of these tumours.

MPNSTs usually vary from low-grade lesions to mostly high-grade tumours displaying high cellularity, brisk mitotic activity and necrosis. [1,9] Most of the MPNSTs seen (eight cases, representing 40% of all MPNSTs) in this study were Grade 2 tumours and two of the MPNSTs were seen arising in pre-existing NF1 patients. The other MPNSTs encountered in the index study were Grade 3 and Grade 1 tumours representing 35% (seven cases) and 25% (five cases) of all MPNSTs. This finding is contrary to a study performed in California, Pekmezci *et al* observed out of all the 115 MPNSTs analyzed, 11 (13%) were low grade tumours (Grade 1) and 102 (89%) were high grade tumours (Grades 2 & 3) including 20% diagnosed as Malignant Triton Tumour (MTT) and they also reported two cases of MPNSTs in patients with clinical diagnosis of NF1.[16]A unique feature displayed by approximately 10% to 15% of MPNSTs, especially in those originating in patients with NF1, is the presence of heterologous differentiations. Indeed, this peculiar feature usually takes the lineage of a rhabdomyosarcomatous component, hence producing the so-called Malignant Triton Tumour, which is typically associated with NF1. [1,4] This current study encountered three cases of MPNSTs with divergent differentiation constituting 15% of all MPNSTs seen. Of the three cases, two had rhabdomyosarcomatous differentiation and diagnosed as MTT while the other case had chondroblastic and osteoid differentiation. Cases of MPNSTs and MTT in uncommon sites have also been reported in the literatures. [17, 18, 19, 20, 21, 22, 23] Most studies have proven that neurofibromas seen in NF1 patients may transform into MPNSTs in about 10% of these patients. [1,9,24.25] This is consistent with the development of MPNSTs in the two patients which were clinically diagnosed with NF1 both having pre-existing multiple neurofibromas in this study.

In the index study, most of the tumours (90%), were infiltrative with two cases (10%) having fair circumscription and devoid of capsule. Fourteen cases (70%) had secondary degenerative changes with extensive geographic necrosis ranging from <50% to >50%. Similarly, Gabhane SK *et al*, in India showed necrosis in 75% of all the MPNSTs seen but contrary to our study he outlineda capsule in three (37.5%) out of the eight MPNSTs seen in their study.[28] Histologically, most cases of MPNSTs are composed of fascicles of spindle cells with distinctive features suggesting neural differentiation. These features include; alternating cellular and myxoid areas with focal areas of perivascular accentuation or whirling of tumour cells around vascular channels which may sometimes directly extend into vascular walls leading to thrombosis.[9]Immunohistochemical analysis of 20 cases of MPNSTs in the index study showed 35% and 25%immunopositivity to SOX10 and S100 respectively with moderate staining intensity in a patchy focal fashion staining mainly {5-25%} of neoplastic cells. Ki67 labeling index using the Eye 10 method showed 13(65%) cases showing mild staining intensity in {<10%} of neoplastic cells. Desmin stain was employed in two cases of Malignant Triton Tumour MTT and it highlighted strongly stained rhabdomyoblasts in a background of high grade MPNSTs. In California, Karamchandani JR, *et al*

did an immunohistochemical analysis of MPNSTs and revealed sensitivities of S100 and SOX10 expression to be 41% and 18%, respectively.[26]S100 protein reactivity in MPNSTs is related to the grade and only 50% of MPNSTs express S100 protein.[9]S100 protein expression in high-grade tumours is typically patchy and mostly seen in individual cells, whereas its expression in low-grade tumours is extensive. The diffuse expression of S100 protein by most MPNSTs is unusual but this is a typical phenomenon seen in the epithelioid variant of MPNST which tends to arise from a preexisting schwannoma.[8]Comparing these results with previous studies, there are strong evidences suggesting the down regulation of schwannian markers in malignant peripheral nerve sheath tumours.[16] Even though, the lack of S100 and SOX10 expression definitely raises the suspicion for other sarcomas, it is relatively specific for diagnosing malignant peripheral nerve sheath tumour in the presence of other benign nerve sheath tumours like cellular neurofibroma or schwannomas versus low grade malignant peripheral nerve sheath tumour.[9] Also,diffuse immunoexpression of S100 or SOX10 may strongly suggest a cellular schwannoma. Interestingly, epithelioid MPNSTs, a high-grade sarcoma typically arising in a pre-existing schwannoma and tend to express S100 diffusely.[8] The sensitivity of SOX10 for MPNSTs varies between studies (27-61%).[27] In California, Karamchandani JR *et al* in a cohort of 78 patients with MPNSTs, showed that S100 had increased sensitivity (31/78, 40%) as compared with SOX10 (21/78, 27%), `but the majority of these cases were negative for both SOX10 and S100 (44/78, 56%).[26]The finding is contrary to that of the index study which revealed less sensitivity to S100 compared to SOX10 implying that SOX10 is a more specific marker. However, most cases of MPNSTs observed in this study were negative for both S100 and SOX10. Ki67 staining was used as a proliferation index in the study, and it was observed that most of the tumours (13/20, 65%) had low proliferative index {<10%} and most (40) % were grade 2 tumours. The low expression of SOX10 and S100 antibodies by MPNSTs seen in this study may also be due to down regulation of schwannian markers in malignant peripheral nerve sheath tumour which is a usual phenomenon. [8,9]

Conclusion

Malignant peripheral nerve sheath tumours are uncommon and tend to be sporadic in our region. These tumours tend to have a male predilection with the gluteal region being the most frequent anatomical site of occurrence. Most of these tumours are borderline tumours (Grade 2) and show low immunoexpression of SOX10 and S100 antibodies. Ki67 antibody expression by these tumours are high with mainly low labelling hot spots index.

References

1) Fletcher DMC. Tumours of the peripheral nervous system. In: Houston M, DeFrancesco K. (eds) Fletcher DMC. Diagnostic histopathology of tumours. 5th ed. Philadelphia: Elsevier; 2021. p2172-2191.
2) Nonaka D, Chiriboga L, Rubin BP. Sox 10: a pan –schwannian and melanocytic marker. *Am J Surg Pathol*. 2008; 32(9): 1291-1298.doi:10.1097/PAS.0b013e3181658c14.
3) Belakhoua SM, Rodriguez FJ. Diagnostic pathology of tumours of peripheral nerve. *Neurosurgery*. 2021; 88(3): 443-456.doi:10.1093/neuros/nyab021.
4) Antonescu CR, Brems H, Legius E, Woordruff JM. Nerve sheath tumours. In: Fletcher CDM, Julia AB, Hogendoorn CW, Fredrik M (Eds). World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC press; 2013: p170-191.
5) Guha D, Davidson B, Nadi M, Alotaibi NM, Fehlings MG, Gentili F, et al. Management of peripheral nerve sheath tumours: 17 years of experience at Toronto Western Hospital. *J Neurosurg*. 2018; 128(4):1226-1234.https://doi.org/10.3171/2017.1.JNS162292.

6) Kang J, Yang P, Zang Q, He X. Traumatic neuroma of the superficial peroneal nerve in a patient: a case report and review of literature. *World J surg Onc*. 2016; 14:242. https://doi.org/10.1186/s12957-016-0990-6
7) Carroll S. Molecular mechanisms promoting the pathogenesis of Schwann cell neoplasms. *Acta Neuropathol*. 2012; 123(3):321-348.https://doi.org/10.1007/s00401-011-0928-6.
8) Jose FGC, Rodrigo SVC. Immunohistochemical markers for schwannomas, neurofibromas and malignant peripheral nerve sheath tumours-what can the recent literature tell us? *Arq Bras Neurocir*. 2018; 37:105-112. https://doi.org/10.1055/s-0038-1667180.ISSN 0103-5355.
9) Weiss WS, Goldblum RJ. Benign and Malignant tumours of peripheral nerve. In: Enzinger and Weiss's Soft Tissue Tumours. 7th ed. Philadelphia: Elsevier Saunders; 2020. p 885-985.
10) Ji Young P, Hoon P, Nam Jo P, June Sik P, Hyun-Jung S, Sang Sook L. Use of Calretinin, CD56 and CD34 for differential diagnosis of Schwannoma and Neurofibroma. *Korean J Pathol*. 2011; 45(1):30.doi:10.4132/KoreanJPathol.2011.45. 1 .30
11) Kadivar M, Aram F. Assessment of Ki 67 in breast cancer: a comparison between the Eye -10 method, stepwise counting strategy, and international system of Ki 67 evaluation. *Iran J Pathol*. 2020; 15(1):13-18.doi: 10.30699/IJP.2019.102290.2017.
12) Nthumba PM, Juma PI. Malignant peripheral nerve sheath tumours in Africa: a clinicopathological study. *ISRN Surgery*. 2011; 2011:526454. doi:10.5402/2011/526454.
13) Odebode TO, Afolayan EAO, Adigun IA, Daramola OOM. Clinicopathological study of neurofibromatosis type 1: an experience in Nigeria. *Int J Dermatol*. 2005; 44(2):116-120. doi:10.1111/j.1365-4632.2005.02386. x.
14) Adeyemi BF, Adekunle LV, Kolude BM, Akang EEU, Lawoyin JO. Head and Neck cancer: a clinicopathological study in a tertiary care centre. *J Natl Med Assoc*. 2008; 100(6): 690-697.doi: 10.1016/s0027-9684(15)31343-2.
15) Chikkannaiah P, Boovalli MM, Nathiyal V, Venkataramappa S. Morphological spectrum of peripheral nerve sheath tumours: an insight into World Health Organization 2013 classification. *J Neurosci Rural Pract*. 2016; 7(3): 346-354.doi:10.4103/0976-3147.182768.
16) Pekmezci M, Reuss DE, Hirbe AC, Dahiya S, Gutmann DH, von Deimling, et al. Morphologic and immunohistochemical features of malignant peripheral nerve sheath tumour and cellular schwannomas. *Mod Pathol*. 2015; 28(2):187-200. doi: 10.1038/modpathol.2014.109.
17) Shih-Wen H, Wei-Chen L, Hui-Jen T, Song-Hsiung C, Kun-Bow T. Immunoprofiles in malignant peripheral nerve sheath tumour: three case reports and literature review. *Kaohsiung J Med Sci*. 2006; 22(3):135-142.https://doi.org/10.1016/S1607-551X(09)70233-5.
18) Herzberg J, Corradinib GM, von Seydewitzc C, Gurayad SY, Stratea T, Honarpisheha H. Malignant triton tumour of the rectum: a case report and review of the literature. *Int J Surg Case Rep*. 2020; 76:517–521.https://doi.org/10.1016/j.ijscr.2020.10.027.
19) Emejulu CJK, Ekwunife OH, Chukwuanukwu TOG, Okpalike VI, Izuora KO, Ekweogwu OC, et al. Malignant peripheral nerve sheath tumour in a 10-year-old: a case report. *JCAN*. 2017; 2(1):36-41.
20) Žaklina M, Dragan M, Nikola Ž, Miloš K, Sladjana Ž, Nebojša S. A rare case of retroperitoneal malignant triton tumour invading renal vein and small intestine. *Vojnosanit Pregl*. 2013; 70(3): 322–325.doi: 10.2298/vsp1303322m.

21) Li Z, Xiang J, Yan S, Gao F, Zheng S. Malignant triton tumour of the retroperitoneum: a case report and review of the literature. *World J of Surg Oncol*. 2012; 10:96. doi: 10.1186/1477-7819-10-96.
22) Biglow LR, Cuda J, Dotson. A rare case of epithelioid malignant peripheral nerve sheath tumour mimicking malignant melanoma. *Cureus*. 2021; 13(2): e13424. doi: 10.7759/cureus.13424.
23) Ugwu JO, Onwukamuche ME, Ekwunife HO,C Emejulu JK, Modekwe V, Osuigwe OA. A case of retroperitoneal malignant triton tumour in a Nigerian boy. *Niger J Surg*. 2017; 23(2):141-144. doi: 10.4103/njs.NJS_57_16.
24) John R. Soft tissue. In: John G, Laura L, Jesse M, Jeffrey M (Eds). Surgical Pathology. 11th ed. Philadelphia: Elsevier; 2018.p1810-1914.
25) Parizel PM, Geniets C. Tumours of peripheral nerves. In: De Schepper AM, Vanhoenacker F, Gielen J, Parizel PM. (eds) Imaging of soft tissue tumours. Springer, Berlin, Heidelberg. 2006. https://doi.org/10.1007/3-540-307923_20.
26) Karamchandani JR, Nielsen TO, van de Rijn M, West RB. Sox10 and S100 in the diagnosis of soft- tissue neoplasm. *Appl Immunohistochem Mol Morphol*.2012; 20(5): 445-450.doi: 10. 1097/PAI.0b013e318244ff4b.
27) Kang Y, Pekmezci M, Folpe AL, Ersen A, Horvai AE. Diagnostic utility of SOX10 to distinguish malignant peripheral nerve sheath tumour from synovial sarcoma. *Mod Pathol* .2014; 27(1):55-61. doi: 10. 1038/modpathol.2013.115.
28) Gabhane SK, Kotwal MN, Bobhate SK. Morphological spectrum of peripheral nerve sheath tumors: A series of 126 cases.*Indian J Pathol Microbiol* 2009; 52:29-33.https://www.ijpmonline.org/text.asp?2009/52/1/29/44958.