Original Research Paper

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Histopathology

HISTOMORPHOLOGICAL SPECTRUM OF PERIPHERAL NERVE SHEATH TUMORS FROM A SECONDARY CARE HOSPITAL

Jahnavi Marachapu Specialist grade -2, ESIC,Delhi.

ABSTRACT **Background** The peripheral nervous system tumours exhibit a diverse range of morphological characteristics and biological behaviour, ranging from benign to locally aggressive such as plexiform neurofibroma to highly malignant (MPNST) **Aims and Objectives** This study aims to examine the morphological variations of PNST and investigate the accompanying degenerative changes. The study also aims to determine the relative incidence of benign, locally aggressive, and malignant tumours, including their location, age of presentation, and gender distribution. **Materials and Methods** This study was conducted at the Department of Pathology, ESIC Hospital, from January 2020 to December 2022. It includes 29 cases presented and diagnosed at our institute on both clinical and pathological basis. The slides stained with hematoxylin and eosin were evaluated, and the lesions were categorized and classified following the World Health Organization's 2020 classification of soft tissue and bone tumours. The tumours were also assessed for secondary degenerative changes. **Results** Out of 29 cases, 28 were benign, and only one case (%) was malignant in nature. The commonest age group was 14-62 years, Male and female ratio being 1.64:1. Our study comprised 29 cases of PNST. The age range with the highest frequency of occurrence was found to be 21 to 30 years, with the head and neck region being the most commonly affected site. The peripheral nerve sheath tumours (PNSTs) analyzed in the study included neurofibroma (62.07%), schwannoma (31.03%), and malignant PNST (6.90%). Approximately 10% of neurofibromas met the criteria for neurofibromatosis type 1 (NF1). Malignant tumours were larger in dimension than benign ones. Myxoid, cystic, and hyaline changes were commonly associated with benign tumours, while necrosis, haemorrhage, and mitotic activity were seen with malignant tumours. **Conclusion** This study emphasizes the different pathological forms of PNST and the morphological modifications and association with NF1. Familiarity with the various forms of PNST is crucial for precise diagnosis due to their varying biological characteristics.

KEYWORDS :

INTRODUCTION

Peripheral nerve sheath tumours (PNSTs) are a commonly occurring type of neoplasm with well-known clinicopathological features. However, diagnosing these tumours can be challenging in some cases. These peripheral nerve sheath tumours (PNSTs) have a neuroectodermal origin [1] . These tumours range from benign, such as neurofibromas or schwannomas, to the rare and malignant type known as malignant PNST (MPNST) [2]. Approximately 90-95% of PNST cases are benign, but MPNST is a rarer form with a reported incidence of 0.001%. Patients with neurofibromatosis 1 (NF1) have an increased incidence of MPNST at 4-4.6%[1]. Benign PNSTs (BPNST) Variants are not studied much, while malignant PNSTs (MPNST) are more aggressive and often associated with neurofibromatosis type 1, Carey-carney complex and schwannomatosis [3,4]. According to the literature, around 70% of nerve tumours appear sporadically. However, individuals with a genetic predisposition, such as neurofibromatosis 1 and 2 or schwannomatosis, have a 20% higher likelihood of developing nerve sheath tumours. Furthermore, individuals who underwent radiation therapy for cancer may experience an elevated risk of developing these tumours, estimated at approximately 10%, within one year after treatment [5,6] .

Materials and Methods

This is a retrospective study conducted at our Hospital from January 2020 to December 2022. Histopathologically diagnosed cases of PNSTs during the study period were included. The demographic profiles of the patients, such as age, sex, and site of the tumour and gross findings, such as size and other details, were noted from the pathology case files. The hematoxylin and eosin (H and E) stained slides were retrieved from the archives, and in cases where H and E slides were not available, the paraffin block was removed, and 3–4 µ thick sections were cut and stained by H and E. The slides were reassessed, and the lesion was categorized and classified as per the WHO 2020 classification. The tumours were assessed for morphological features such as (a) variants, (b) mitotic activity, (c) necrosis, (d) cystic change, (e) verocay body, (f) haemorrhage, (h) myxoid change, (i) pigment, and (j) calcification. The diagnosis of MPNST was made on the criteria, based on mitotic activity, French system (FNCLCC) for grading soft tissue sarcomas [6] .

Results

The present study comprised 29 cases of PNSTs ranging in age from 14 to 62 years. These tumours were most commonly encountered in the age group of 21–30 were 10 cases (34.48%)years, followed by 31–40 years 9 cases (31.03%). Head and neck 13 (44.83%) were the most common location, followed by lower extremities 6 (20.69%) and upper extremities 2 (6.90%). Acoustic neuroma/vestibular schwannoma was not included in the current study. This tumour requires a neurosurgical removal approach, which is unavailable at our institute. The PNSTs observed in the present study are NF (18 [62.07%]), schwannoma (10[31.03%]), and MPNST (1 [6.90%]). Malignant and benign nerve sheath tumours differ in terms of size and other features like mitosis and necrosis. It states that malignant tumours were larger than benign tumours. Schwannomas were well-encapsulated, while neurofibromas (NF) were poorly encapsulated. Among NF, the diffuse variant was most common 14 (48.28%) followed by localized 2 (6.90%) and plexiform 2 (6.90%). Diffuse and localized variants are most commonly observed in the second and third decades. The head and neck extremities are the most commonly involved sites. The plexiform neurofibromas were more common in multiple locations and occurred most frequently in the first and second decades. Diffuse neurofibromas have an infiltrative type of growth that invades surrounding structures, while localized neurofibromas have a localized type of growth. Myxoid change is the most common secondary change associated with neurofibromas, followed by cystic change and lymphocytic infiltration. Among 29 cases of PNST, 3 cases (10%) fulfilled the criteria for NF1; the common associated finding was café au spots; in addition, one case of plexiform NF had a family history. Like NF, schwannomas were also most commonly located in the head and neck, followed by extremities, and in contrast, they are observed a decade later. Classic variant is most common 8 (27.59%) followed by ancient 1 (3.45%) and plexiform 1 (3.45%) [Table 2].

Classical schwannomas have both hypercellular (Antoni A) and hypocellular (Antoni B) areas in varying proportions. The ancient variant showed predominantly hypocellular areas. The characteristic verocay bodies are seen in 6 cases of classical schwannoma. A single case of the ancient plexiform schwannomas didn't show verocay bodies. Compared to NF, secondary degenerative changes were more evident in schwannomas. One case of MPNST, which is low grade, was included in the present study. In contrast to BPNST, MPNST was seen in the sixth decade, which showed mitotic activity in the range of 7/10HPF (low grade), myxoid change, haemorrhage, and Grade 1 necrosis.

Table 1: Age-wise distribution of Peripheral nerve sheath tumours

Age	Neurofibroma (18 (62.07%))			Schwannoma (10 (31.03%))			MPNST	Total N (%)
	Diffuse (14(48.28%))	Localized (2(6.90%))	Plexiform (2(6.90%))	Classical (8(24.14%))	Ancient (1(3.45%))	Plexiform (1(3.45%))	(1 (6.90%))	

11-20	2 (14.29%)	0	0	2 (28.57%)	0			4 (13.79%)
21 - 30	6 (42.86%)	1 (50.00%)	1 (50.00%)	2 (28.57%)	0			10 (34.48%)
31 - 40	3 (21.43%)	1 (50.00%)	1 (50.00%)	3 (42.86%)	0	0	1 (50.00%)	9 (31.03%)
41 - 50	1 (7.14%)	0	0	0		0	0	2 (6.90%)
51 - 60	1 (7.14%)	0	0	0	0		0	2 (6.90%)
61 - 70	1 (7.14%)	0	0	0	0	0	1 (50.00%)	2 (6.90%)
Total	14 (48.28%)	2 (6.90%)	2 (6.90%)	7 (24.14%)	1 (3.45%)	1 (3.45%)	2 (6.90%)	29 (100%)

Table 2: Site-wise distribution of Peripheral nerve sheath tumours

Site	Neurofibroma (18 (62.07%))			Schwannoma (10 (34.48%))			MPNST (1 (3.45%))	Total N (%)
	Diffuse (14 (48.28%))	Localized (2 (6.90%))	Plexiform (2 (6.90%))	Classical (8 (27.59%))	Ancient (1 (3.45%))	Plexiform (1 (3.45%))		
Head Neck	7 (24.14%)	0 (0.00%)	0 (0.00%)	6 (20.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (44.83%)
Thorax	1 (3.45%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (10.34%)
Upper Extremity	0 (0.00%)	1 (3.45%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)
Lower Extremity	2 (6.90%)	1 (3.45%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (3.45%)	6 (20.69%)
Back	2 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	3 (10.34%)
Multicentre	2 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)
Total	14 (48.28%)	2 (6.90%)	2 (6.90%)	8 (27.59%)	1 (3.45%)	1 (3.45%)	1 (3.45%)	29 (100%)

Table 3: Sex-wise distribution of Peripheral nerve sheath tumours

Sex	Neurofibroma	Schwannoma	MPNST	Total (%)
Male	10 (34.48%)	7 (24.14%)	1 (3.45%)	18 (62.07%)
Female	6 (20.69%)	5 (17.24%)	0 (0.00%)	11 (37.93%)
Total	16 (55.17%)	12 (41.38%)	1 (3.45%)	29 (100%)

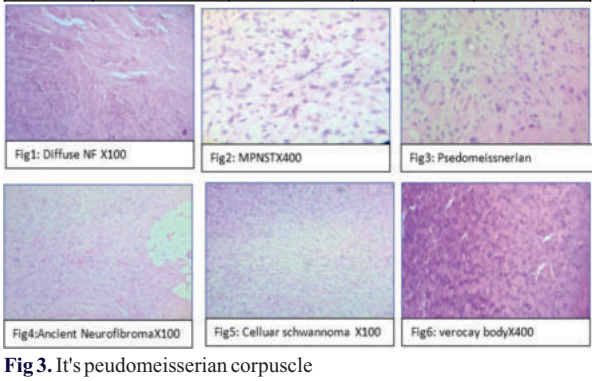

Fig 3. It's peudomeisserian corpuscle

Table 4: Gross and Histological distribution of peripheral nerve sheath tumours

Tumour	Variants	Height (Cm.)			Width (Cm.)			Capsule
		Maximum	Minimum	Mean	Maximum	Minimum	Mean	
Neurofibroma	Diffuse (14)	4	0.8	2.4	3	0.8	1.9	4
	Localized (2)	3.2	0.5	1.85	2.4	1	1.7	1
	Plexiform (2)	3.5	0.8	2.15	2.5	0.8	1.65	1
Schwannoma	Classical (8)	3	0.5	1.75	1.8	0.8	1.3	7
	Ancient (1)	3.5	0.8	2.15	2.3	1	1.65	1
	Flexiform (1)	2.8	0.7	1.75	1.4	1	1.2	1
MPNST		12	2.5	7.25	10	5	7.5	1

DISCUSSION

The improvement in diagnostic methods, such as immunohistochemistry (IHC) and molecular diagnostics, has contributed to a deeper understanding of the origin of tumours and has resulted in increased identification of nerve sheath tumours. This has resulted in the expansion of the WHO classification of soft tissue tumours to include new variants, both benign and malignant. Benign tumours are perineuronal, schwannoma, neurofibroma, Granular cell tumours, Dermal nerve sheath myxoma (DNM), solitary circumscribed neuroma (SCN), ectopic meningioma/meningothelial hamartoma, benign triton tumour (BTT), and hybrid nerve sheath tumours. Malignant peripheral nerve sheath tumours and malignant melanotic nerve sheath tumours are malignant tumours now proven to be of neural origin[7]. Neurofibroma and schwannoma are benign tumours of the peripheral nerve sheath and are often considered to be derived from Schwann cells. However, some studies suggest that dermal neurofibromas may arise from neural crest cells[1,2]. A study by Erlandson and Woodruff 8 on 23 schwannomas, 10 NFs, and 10 MPNST concluded that schwannoma is composed of well-differentiated Schwann cells, making the cell of origin a Schwann cell. The gross appearance of schwannoma is usually solitary and has light-tan cut surfaces surrounded by a fibrous capsule. The appearance may be yellow due to lipid content or lipid-laden macrophages. It also contains cysts and haemorrhagic changes of varying sizes. The subtypes are Ancient schwannoma, Cellular schwannoma, plexiform schwannoma, epitheliod schwannoma and microcystic /reticular schwannoma. The common sites of origin are peripheral nerves in the skin, subcutaneous tissue of the head and neck, or along the flexor surfaces of extremities, and spinal intradural extramedullary tumours are also referred to as "dumbbell tumours." these tumours are slow-growing. Multiple schwannomas are a feature of NF2 and schwannomatosis. Classical schwannomas are easily diagnosed, with alternating areas of hypercellular areas consisting of spindle cells arranged in a palisade formation, forming Verocay bodies, and hypocellular areas consisting of myxoid material, macrophages, and cystic change. The presence of hyalinized blood vessels is a constant finding[2,10] .Cellular variant will have more hypercellular areas ,Antoni A with minimal hypocellular areas, but verocay bodies are absent. It involves large nerves and nerve plexus. In ancient variants, atypical bizarre appearing nuclei and secondary degenerative changes are more evident, along with the extreme degree of hyalinization or central ischemic changes. Verocay bodies are usually absent Plexiform variant is rare, mostly sporadic and less commonly associated with NF2. It usually occurs in the skin and subcutaneous tissue; however, deep visceral sites are also observed. These tumours arise from nerve plexuses or fascicles, less circumscribed and unencapsulated (as observed in our cases). Microscopically, they contain predominantly Antoni A areas. They have low malignant potential, and local recurrence is high [10,12]. Microcystic/reticular schwannoma is a variant of schwannoma; it arises mostly from visceral sites, mostly the gastrointestinal tract. Microscopically, they consist of a microcyst-rich network of interconnected bland spindle cells with myxoid, fibrillary collagenous stroma, and Antoni A areas that are common [2]. Epithelioid schwannoma is sporadic and arises in the setting of schwannomatosis. Loss of SMARCB1 expression is noted in approximately 40% of cases[13,14]. Neurofibroma is a benign peripheral nerve sheath tumour that also develops from neoplastic Schwann cells; in addition, it contains non-neoplastic components, including fibroblasts, mast cells, perineurial-like cells, and residual axons. The variants of neurofibromatosis (NF) can present differently and have distinct characteristics. The sub types are Ancient neurofibroma, Cellular neurofibroma, Atypical neurofibroma, and plexiform neurofibroma. In some studies, the localized variant is the most common, while in others, the diffuse variant is the most frequent [1,2].The diffuse variant presents as a plaque-like enlargement of the nerve, while the localized variant appears as a fusiform enlargement of the nerve. The cut surfaces are variably yellow and translucent depending on the extent of

the myxoid stroma. The microscopic features of neurofibromas are similar regardless of subtype and include a predominance of Schwann cells with thin, wavy nuclei embedded in a myxoid matrix with variable amounts of collagen arranged haphazardly. Other cell components, including mast cells, lymphocytes, fibroblasts, and EMA-positive perineurial cells, are present in varying amounts and contribute to the tumour microenvironment. Microscopically, it is composed of a mixture of diffuse and localized areas [2,15].It does not typically result in secondary degenerative changes[1,2]. The study conducted by Gabhane et al. [1] found that 14% of their cases showed evidence of capsule, while 18% showed myxoid change and 5.5% showed pigment. In the present study, 16 cases showed capsulation, while secondary degenerative changes such as myxoid change were predominantly seen, followed by cystic change and lymphocytic infiltration. In our study, neurofibroma (NF) and schwannoma are commonly found in the head and neck region. But schwannoma occurs a decade later in life, typically between the ages of 20 to 501,2 Unlike NF, schwannomas are typically well-defined and easy to identify due to their characteristic capsulation and prevalence of secondary changes. In our study, we found that conventional or classic schwannomas are the most common type, followed by other variants. Among the variants of NF, we observed that the diffuse variant was the most prevalent, followed by the localized and plexiform variants. The atypical neurofibroma/atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP) and plexiform NF were primarily associated with neurofibromatosis type 1 (NF1). Plexiform NF often involves large nerves imparting a bag of worms or ropy gross appearance. The malignant tumour, which is MPNST arises from pre-existing benign nerve sheath tumour or is associated with NF1; microscopically, it shows areas of geographical necrosis and hyperchromatic nuclei with conspicuous mitotic figures. The present case showed increased mitosis7/10HPF (low grade) and Grade 1 necrosis.

Diagnosis of schwannoma and NF is straightforward and requires IHC rarely. S-100 is found to be constantly expressed in schwannoma and NF [16]

CONCLUSION

The spectrum of PNSTs is wide and rapidly evolving, which requires multidisciplinary collaboration [17]. Most PNSTs can be removed surgically, and they are not radiosensitive, but some are associated with inherited tumours. Accurate diagnosis requires awareness of all variants and a combination of clinical, histological, and cytological studies. The increasing availability of molecular techniques is expected to play a more important role in diagnosis in the future [18]

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