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Original Research Article

Clinical and cytohistomorphological evaluation of peripheral nerve sheath tumours with special reference to immunohistochemical diversity in a tertiary care hospital

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ABSTRACT

Background: Peripheral Nerve Sheath Tumours (PNST), though have a frequent prevalence, are diagnostically challenging. There is a wide spectrum of lesions ranging from benign entities like neurofibroma, Schwannoma, perineurioma to malignant entities like malignant peripheral nerve sheath tumours (MPNST), malignant granular cell tumour and malignant perineurioma. Since there is an overlap with other spindle and round cell tumours, IHC and molecular studies are needed to provide a clear distinction between different tumour types.

Materials and Methods: It was a 5 years observational study (3 years retrospective and 2 years prospective) conducted in the Department of Pathology, JNMCH, AMU from 2015-2020. . History and relevant clinical findings were retrieved from the archives of both the Histopathology and Cytopathology Lab. Imprints as well as FNA smears were included from Cytopathology Lab and biopsies and resection specimen from Histopathology Lab. Immunohistochemistry was applied wherever necessary.

Results: A total of 82 cases were diagnosed over a 5 year period out of which 70 were benign and 12 malignant. Male preponderance was seen. Benign tumours comprised mostly of Neurofibroma and Schwannoma and there were 12 cases of MPNST. Correlation was established between Cytopathological and Histopathological findings and IHC, mostly S100 proved useful in differentiating it from other malignant spindle cell tumours.

Conclusion: The differential diagnoses of these tumours has always posed a problem given their monotonous appearance and clinical overlap. This study, therefore, aims to analyse the diverse morphological features of Peripheral Nerve Sheath Tumours in the light of cytopathological and histopathological findings and immunohistochemistry.

1. Introduction

Peripheral nerve sheath tumors constitute a diverse group of neoplasms that are derived from cells accompanying peripheral nerve fibers. These include Schwann cells that form the innermost layer of endoneurium, characterised cytologically by wavy nuclei and expression of S100 protein; perineurial cells, nerve sheath dendritic cells as well as fibroblasts.[1]

In the recent 2020 WHO Classification, nerve sheath tumours included under benign category are schwannoma, neurofibroma, perineurioma, granular cell tumour, nerve sheath myxoma, solitary circumscribed neuroma and hybrid nerve sheath tumour. These tumours exhibit a wide range of diagnostically challenging cytomorphologic features like spindle cells, hypercellularity, myxoid change, epithelioid

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morphology and degenerative atypia and hence differential diagnoses with leiomyoma, fibromatosis, solitary fibrous tumor and low-grade fibromyxoid sarcoma, at times, becomes difficult. Malignant peripheral nerve sheath tumor (MPNST), malignant granular cell tumour and malignant perineurioma are the malignant counterparts and can be confused with high-grade soft tissue neoplasms, i.e., synovial sarcoma, fibrosarcoma, leiomyosarcoma, sarcomatoid carcinoma, and melanoma.[2] Therefore, a comprehensive clinicopathological, morphological and immunohistochemical approach is necessary for arriving at definitive diagnosis.

2. Aims and Objectives

1. To analyse the clinical spectrum of peripheral nerve sheath tumours over a period of 5 years.
2. To study the histomorphological features of peripheral nerve sheath tumours along with cytopathological and immunohistochemical correlation.

3. Materials and Methods

It was a 3 years retrospective and 2 years prospective study from 2015-2020 conducted in the Department of Pathology of JawaharLal Nehru Medical College, AMU, Aligarh. Prior ethical approval and clearance was taken from the University Ethical Review Board. Informed consent was taken in all cases. History and clinical findings were collected from the archives of Histopathology and Cytopathology Lab and both FNA as well as Imprint smears were included in the Cytopathology cases. The biopsies and resected histopathological specimen were fixed in 10% neutral buffered formalin and processed routinely and stained by H and E staining.

Immunohistochemical staining was done using automated VENTANA BENCHMARK XT. The immunophenotypic panel of markers which were used in the study to differentiate and categorise the peripheral nerve sheath tumours were- S100, EMA, Pan CK, Desmin, SMA, TLE -1, HMB -45, GLUT -1, CD 31, CD 34 and Ki 67.

4. Results

A total of 82 cases of Peripheral Nerve Sheath Tumours (PNSTs) were subjected to FNAC over a period of 5 years (2015-2020) accounting for 45.8% of the total soft tissue tumours. Out of 82 cases, 70 (85.4 %) were diagnosed as benign and 12 (14.6 %) as malignant. The male to female ratio was 1.5:1. Cytologically diagnosed cases were confirmed on histopathology and after the application of immunohistochemistry. Benign cases comprised of Neurofibroma (52.5%) and Schwannoma (47.5%) and their variants namely plexiform neurofibroma, cellular neurofibroma, cellular schwannoma and ancient schwannoma while malignant cases included MPNST.

4.1. Neurofibroma (38 cases – 46.4%)

It was seen over a wide age range with maximum cases in 2^{nd} decade. With a male to female ratio of 1.9:1, head and neck region was the most common site. Clinically, most tumours were slow growing and painless, solitary lesions with a soft to rubbery consistency. The mean size was around 2-3 cm. On Cytopathology, low to moderate cellularity was seen, comprising of sheets as well as singly scattered spindle cells with characteristic wavy nuclei set in a pink matrix background were seen. Grossly, the tumours were lobulated or well circumscribed masses. Most of them were skin covered with glistening, tan white cut surface. Microscopic examination revealed small bland spindle cells with wavy nuclei and cytoplasmic processes set in a loose myxoid stroma. No mitosis or necrosis was seen. The differential on histopathological examination was Schwannoma and S100 was diffusely positive in all the cases . Grossly, plexiform neurofibroma showed enlarged tortuous and fusiform nerves and microscopically disordered proliferation of Schwann cells in a myxoid matrix was seen.

4.2. Schwannoma (32 cases – 39%)

Schwannoma showed a female preponderance presenting in the 3^{rd} decade with head and neck as the most commonly involved site (62.5%). FNA smears showed clusters of bland spindle cells with wavy pointed nuclei. Grossly, the tumours were mostly solitary, well-circumscribed, and encapsulated. Microscopically, there were compact Antoni A areas with cells showing moderate amount of eosinophilic cytoplasm and elongated tapered nuclei with occasional nuclear palisading (Verocay bodies), alternating with loosely arranged Antoni B areas. Diffuse nuclear as well as cytoplasmic S100 positivity was seen with greater intensity in Antoni A areas. One case of cellular schwannoma showed cellular Antoni A areas and no Verocay bodies or Antoni B areas. Scattered aggregates of foamy macrophages along with increased mitotic activity and focal atypia were also seen. There were 2 cases of ancient Schwannoma showing hyalinisation, nuclear atypia and hemosiderin deposition.

4.3. Malignant peripheral nerve sheath tumour (12 cases- 14.6%)

MPNST occurred in the second and third decade of life, with a male to female ratio of 2:1, in the head and neck region and lower extremity. Almost all patients presented with a palpable swelling which was painful in 60% cases. The mean size was about 6 cm. On Cytopathology, the smears were highly cellular showing clusters of malignant spindle cells with increased nucleocytoplasmic

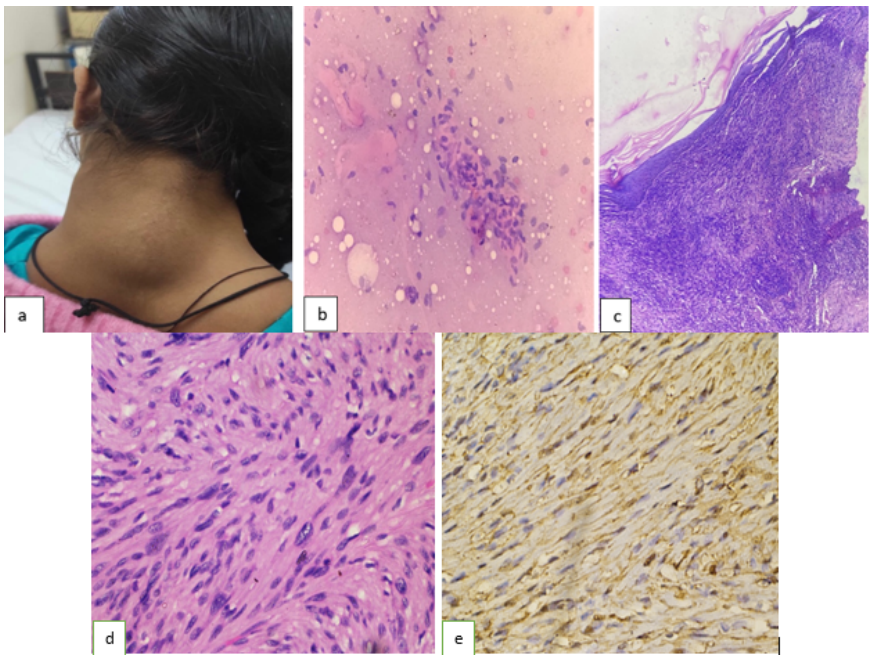

Fig. 1: a: Clinical Photograph of a patient showing swelling on the back of neck; **b:** FNA smear showing sheets as well as singly dispersed bland spindle cells. H & E (x100); **c:** Section showing skin covered tissue with underlying tissue showing proliferation of spindle cells; **d:** Section showing small bland spindle cells set in a loose stroma. H & E (x400); **e:** S100 showing diffuse cytoplasmic positivity.

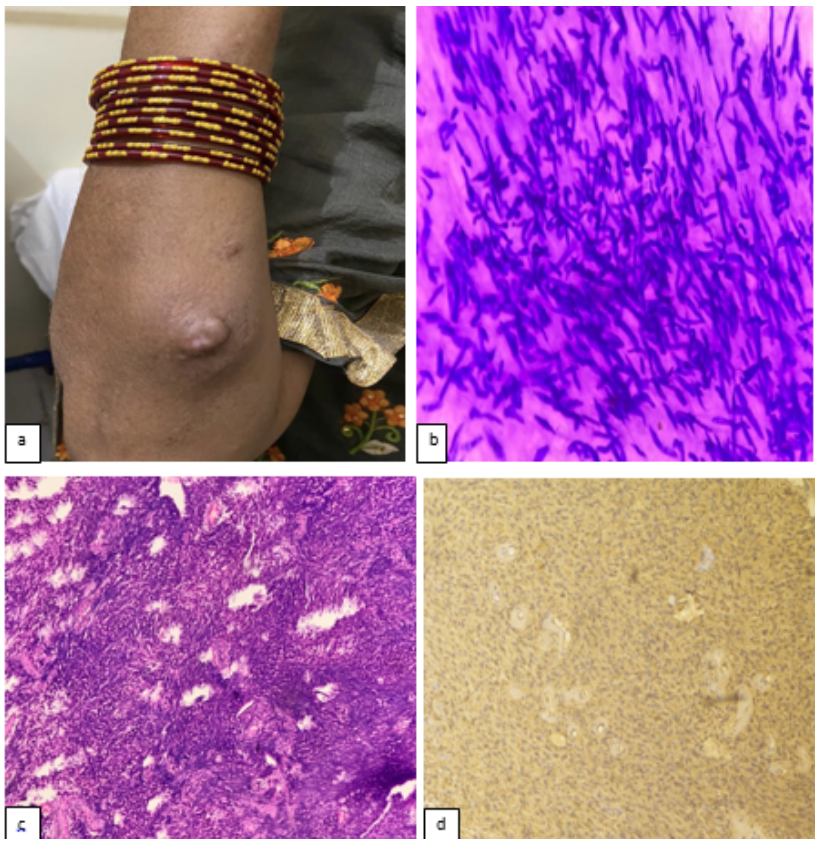

Fig. 2: a: Clinical Photograph of a 24 years old female patient showing swelling on the extensor aspect of forearm; **b:** FNA smear showing cluster of spindle cells with characteristic wavy nuclei. H & E (x400); **c:** Section showing compact Antoni A areas alternating with loosely arranged Antoni B areas. H & E (x40); **d:** S100 showing diffuse cytoplasmic positivity (x400).

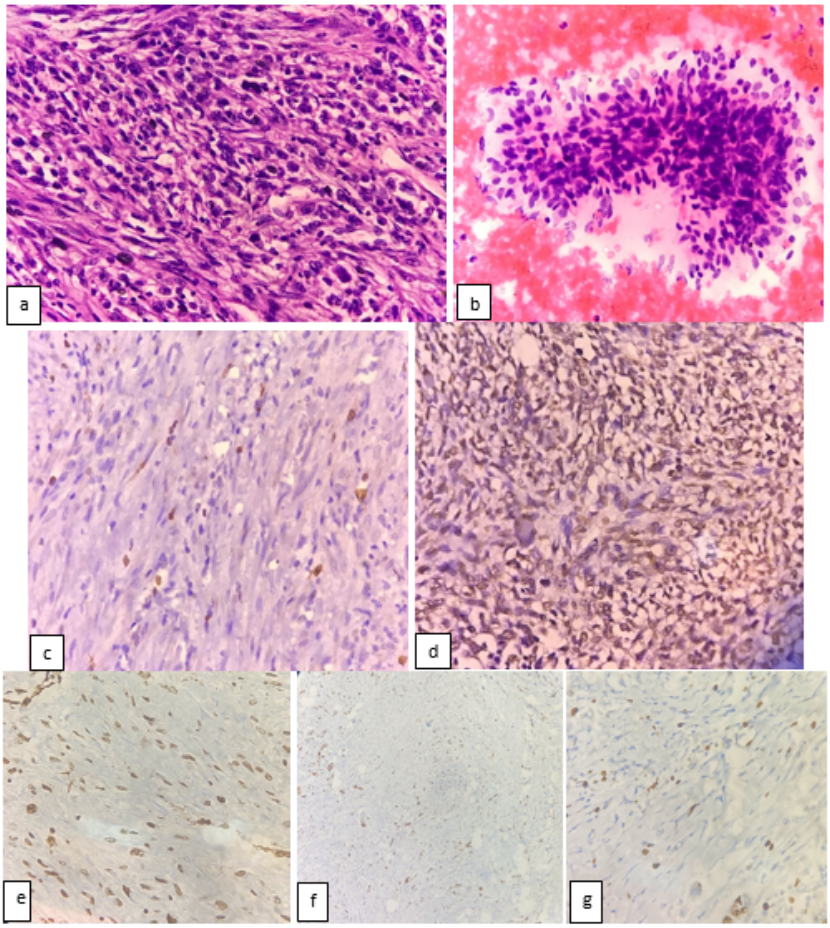

Fig. 3: a: FNA smear showing cluster of malignant spindle cells with increased nucleocytoplasmic ratio, prominent nucleoli and scant cytoplasm against a hemorrhagic background. H & E (x400); **b:** Section showing marked nuclear atypia, hyperchromasia and irregular nuclear membrane. H & E (x400); **c:** S100 showing focal cytoplasmic positivity (x400); **d:** Vimentin showing strong cytoplasmic positivity; **e:** Ki67 index >40%; **f:** INI 1 showing nuclear positivity (x100); **g:** H3K27me3 showing diffuse nuclear positivity (x400)

Table 1: Comparative analysis of incidence, age, sex and site distribution of peripheral nerve sheath tumors

	Number of cases	Age (in years)	M:F ratio	Site
Vahini., 2015[3]	32.38%	21-30	1:1	Head and neck
Harpal et al. 2016[4]	10.5%	11-30	0.9:1	-
Naik et al., 2018[5]	13.27%	61-70	0.6:1	Head and neck
Present study,2020	45.8%	11-20	1.48:1	Head and neck

ratio, prominent nucleolus and scant cytoplasm against a hemorrhagic and necrotic background. Grossly, it was a large infiltrative tumour seen in association with major nerves. On microscopy, tumours were composed of fascicles of alternating hyper- and hypo-cellular spindle-shaped cells with hyperchromatic nuclei and pale wavy cytoplasm along with areas of geographical necrosis and increased mitotic activity. Immunohistochemically, SMA, EMA, vimentin and Pan CK were negative and focal S100 positivity was seen. H3K27me3, SOX10 and INI1 were applied also applied. FNCLCC grading was done and 6 tumours were grade 2 while remaining 6 were grade 3. Staging was done using AJCC system. 6 tumours were Stage II and 6 were Stage III.

5. Discussion

Neurofibroma and schwannoma are common benign peripheral nerve sheath tumours that occur as isolated sporadic lesions or in syndromic association with Neurofibromatosis.[6] The incidence of MPNSTs is 0.001%.[7]

The frequent sites of involvement of benign peripheral nerve sheath tumours were the head and neck.[8] Maximum cases of neurofibroma in our study were also located in

head and neck region and were commonly seen in the second decade with a high male to female ratio. In a study by Rao BS.,et al., 2016[9] neurofibroma constituted 8 cases (44.4%) out of 18 cases of peripheral nerve sheath tumours with male predominance, similar to our study while Naik V., et al.,2018[5] reported a much higher incidence of 80%.Cimino -Mathews AM.,2011[10] reported that scattered nuclear atypia can be seen in neurofibroma but necrosis and brisk mitotic activity were absent, a finding similar to our study. In few cases, mild nuclear pleomorphism was seen but frank mitosis and necrosis were absent.

Bishop JA., 2011[11] observed that although schwannomas can occur at any age but most commonly involve patients in the age group 20-50 years and are often located in the head and neck and extremities. In our study, schwannoma also showed site predilection for head and neck with maximum incidence in the third decade and a female predilection. Schaefer and Fletcher CD.,2015,[12] also observed that middle aged women are more commonly affected. Bishop JA.,2011[11] also observed that cellular schwannomas can be confused with sarcomas especially MPNST because of high cellularity and mitosis but strong and diffuse positive S100 staining was very reassuring. We did face this problem with cellular and ancient schwannomas, but a strong and uniform S100 positivity confirmed the diagnosis.

MPNST showed equal distribution in head and neck and lower extremity and were more commonly seen in males. All 12 cases were seen in the second and third decade.

Fisher C.,2011[13] observed that the commonest sites of MPNST are proximal limbs, trunk, or head and neck and younger age at presentation is associated with Neurofibomatosis type 1 with a peak in 4^{th} decade. In our study, none of the patients clinically showed any signs and symptoms of NF-1. We also observed herringbone pattern in one of the cases. This was in accordance with report published by Hirose T.,et al., 1998[14] in which he described MPNSTs to have a herringbone pattern with wavy, serpiginous buckled nuclei with scant cytoplasm. A study by Senthilkumar AC.,2019[15] also highlighted focal areas with rhabdoid differentiation. However, in our study, we have included only those cases that exhibited spindled morphology.

6. Conclusion

Tumors arising from peripheral nerves may cause difficulties in diagnosis, in classification and in management. There is a wide differential diagnosis, especially with malignant tumours in which overlap with other spindle cell tumours is seen. Hence, a clinical as well as cyto-histopathological correlation is necessary along with judicious use of immunohistochemistry to arrive at a definitive diagnosis.

7. Conflicts of Interest

There are no conflicts of interest.

8. Conflict of Interest

None.

References

1. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathol*. 2012;123(3):295–319.
2. Lokuhetty D, White VA, Cree IA. WHO Classification of Soft Tissue Tumours. WHO Classification of Tumours, Soft Tissue and Bone, 5th Edn. Lyon: IARC; 2020. p. 2–3.
3. Vahini G. A clinicopathological study of soft tissue tumours in correlation with immunohistochemistry. *IOSR J Dent Med Sci*. 2015;14(1):31–40.
4. Harpal S, Richika R, K R. Histopathological pattern of soft tissue tumours in 200 cases. *Ann Int Med Dent Res*. 2016;2(6):6.
5. Naik V, Hoogar MB, Sahu S, Khadayate R. Histomorphological Profile and Clinicopathological Correlation of Soft Tissue Tumours-A Study at a Tertiary Care Teaching Hospital. *J Health Sci Res*. 2018;8(9):35–42.
6. Gilchrist JM, Donahue JE. Peripheral nerve tumors. UpToDate, Post TW. Waltham. 2018 May. Available from: https://www.mayoclinic.org/diseases-conditions/peripheral-nerve-tumors/symptoms-causes/syc-20355070.
7. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer*. 1986;57(10):2006–21.
8. Biswas D, Marnane C, Mal R, Baldwin D. Benign extracranial nerve sheath tumors of the skull base: postoperative morbidity and management. *Skull Base*. 2008;18(2):99–106.
9. Rao BS, Grandhi B, Shanthi V, Bheemaraju V, Rao NM, Goel A, et al. Clinicopathological Evaluation of Benign and Malignant Soft Tissue Tumours -2 Years Retrospective Study. *JMSCR*. 2016;4(6):10822–32.
10. Cimino-Mathews AM. Peripheral Nerve Sheath Tumors. *Surg Pathol Clin*. 2011;4(3):761–82.
11. Bishop JA. Soft tissue pseudosarcomas. *Surg Pathol Clin*. 2011;4(3):699–19.
12. Schaefer IM, Fletcher CD. Diagnostically challenging spindle cell neoplasms of the retroperitoneum. *Surg Pathol Clin*. 2015;8(3):353–74.
13. Fisher C. Immunohistochemistry in diagnosis of soft tissue tumours. *Histopathology*. 2011;58(7):1001–12.
14. Hirose T, Scheithauer BW, Sano T. Perineurial malignant peripheral nerve sheath tumor (MPNST): a clinicopathologic, immunohistochemical, and ultrastructural study of seven cases. *Am J Surg Pathol*. 1998;22(11):1368–78.
15. Senthilkumar AC, Sridharan S, Mahendra B, Chander V. Malignant peripheral nerve sheath tumour—A case report. *Int J Surg Case Rep*. 2019;64:161–4. doi:10.1016/j.ijscr.2019.10.004.

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