

Schwannoma and its unusual variants – A histopathological study

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Abstract

Background: Schwannomas exhibit histologic features that may overlap with those of benign and malignant peripheral nerve sheath tumours. This can be the challenging in making accurate histopathological diagnosis there by influence clinical management.

Objective: Our study focuses on schwannomas to identify subtypes based on histopathologic attributes and associated clinical features and its variants.

Methods: 37 cases of schwannoma were ascertained using records (2003 to 2006) and also prospectively (2006-2008) at JJM Medical college hospital, Davangere. Case and specimen details, slides and blocks were collected from department archives. The specimens were fixed in 10% formalin for 24-48 hours and sampled for detailed histopathological examination. Slides were stained with hematoxylin and eosin. Microscopic findings were noted in a detailed manner in a proforma. Special staining with Perl's Prussian blue, toluidine blue and immunohistochemistry were performed wherever needed.

Results: Classical schwannomas comprised most cases, 31 (83.8%). Histological variants encountered were cellular schwannoma, plexiform schwannoma, ancient schwannoma, schwannoma with pseudoglandular elements, cystic schwannoma and psammomatous schwannoma. Most common locations of classical schwannomas were head & neck region followed by extremities, seen over a wide age range. In only one case of classical schwannoma, histopathological diagnosis correlated with clinical diagnosis.

Conclusion: Schwannomas show an interesting histologic variety despite being composed of a limited array of cellular constituents. Key issue for the pathologist includes distinguishing schwannomas from neurofibromas, and MPNSTs from cellular schwannoma or neurofibromas.

Keywords: Schwannoma, Peripheral nerve, Histopathology

Introduction

Most peripheral nerve sheath tumors are histologically benign, schwannomas and neurofibromas, however, they may experience malignant degeneration especially in the setting of neurofibromatosis. Malignant neurosarcomas are a rarity and comprise very small proportion of soft tissue sarcomas but are challenging to treat. Surgical excision and radiotherapy form the mainstay of treatment. Various subtypes in schwannomas and atypical neurofibromas can pose difficulties in histopathologic diagnosis. Treatment in the form of gross total surgical removal is therefore indicated in most nerve tumors for histologic diagnosis as well as for relief of symptoms. Our study focuses on most common primary neoplasms of peripheral nerve sheath, schwannomas, to identify subtypes based on histopathologic attributes and associated clinical features. The present study aids a pathologist in becoming familiar with these entities and to establish their accurate pathological diagnosis in view of their varying biologic behavior.¹⁻³

Materials and Methods

The material for the present study comprised of schwannomas diagnosed in the Department of Pathology, J.J.M. Medical College, Davangere, over a period of 5 years, between 2003 and 2008, of patients

admitted to Bapuji Hospital, Chigateri General Hospital and also received from Private Hospitals. Clinical history and findings were recorded in each case from the available requisition forms/ case records. For the cases from March 2003 to May 2006, case and specimen details, slides and blocks were collected from department archives. Between June 2006 to February 2008 cases were ascertained prospectively. The specimens were fixed in 10% formalin for 24-48 hours and sampled for detailed histopathological examination. Slides were stained with hematoxylin and eosin. Microscopic findings were noted in a detailed manner in a proforma. Special staining with Perl's Prussian blue, toluidine blue and immunohistochemistry were performed wherever needed. FNAC correlation was not attempted, as it was not considered in the aim of the study. Further it was not performed as a preoperative procedure in all the cases. Absolute numbers of cases and proportions are used to present the results in the tables. Results are prepared using MS office excel software. Ethical clearance was obtained from Rajiv Gandhi University of health sciences ethical review committee, Bangalore.

Results

A total of 37 cases of schwannoma were diagnosed between 2003 and 2008. Classical schwannomas

comprised most cases, 31 (83.8%). Of the 6 remaining, 3 were ancient, 2 cellular and one case of plexiform schwannoma. Table 1 shows the distribution of conventional schwannomas by gender, age-group and location. Schwannomas showed equal predilection for both the sexes. Schwannomas occurred over a wide age range. Classic schwannomas were more common in the 2nd – 4th decade of life. The youngest patient was of 13 years and oldest of 80 years.

Majority of the schwannomas in our study occurred in head and neck region (13/31 conventional schwannomas) followed by in extremities (9/31). One each of conventional schwannoma occurred in parotid gland region, submandibular gland region and palate. In other sites, one case was from retroperitoneum, 2 from back, one from cervical spine nerve root and one from scrotum. In 4 conventional schwannomas site of tumor origin was not known.

Clinical Diagnosis: In 27 out of 31 classic schwannomas a clinical diagnosis was made. Only in one case out of 27, clinical diagnosis correlated with histopathologic diagnosis. 5 were clinically considered as neurofibroma. In 4 out of 31 cases no clinical impression was given. Most of the schwannomas in the neck region were clinically suspected to be lymphadenitis and in one case as lymphoma. Schwannoma of lip was clinically considered as mucocele and palatal lesion as minor salivary gland tumor. In 2 cases of salivary gland schwannoma one was clinically suspected to be malignancy and the other one as sialadenitis. In retroperitoneal schwannomas, classical schwannoma was clinically considered as mesenteric cyst/ dermoid cyst and the cellular schwannoma was suspected to be a leiomyoma. Schwannoma with pseudoglandular elements in the neck was clinically mistaken for cystic hygroma and cystic schwannoma for ganglion. In none of the schwannoma variants clinical diagnosis correlated with the histopathological diagnosis except for one of the cellular schwannoma which was clinically diagnosed as schwannoma.

Table 2 shows the clinical data of non-classical schwannomas (unusual variants). **Ancient Schwannomas:** Two ancient schwannomas occurred in the arm region and one in the neck region. Grossly, all the 3 were gray white globular encapsulated mass with smooth surface and cut section showed homogenous gray white areas. One case showed tiny foci of yellow areas. On Microscopy, apart from Antoni A, Antoni B and Verocay bodies, pleomorphic nuclei were seen in two and smudged nuclei in one. Giant cells were seen in one case. None of them showed mitosis. One case showed thrombosed blood vessel. Hemosiderin macrophages and foamy histiocytes were seen in one case. Mast cells were seen in one. Two cases showed areas of hyalinization and myxoid change.

Cellular Schwannoma: One case of cellular schwannoma was seen in young female and the other one was seen in a middle aged male. One occurred on the face and other in the retroperitoneum. Grossly, Retroperitoneal cellular schwannoma was encapsulated, globular gray white mass with smooth surface. Cut surface showed non-homogenous gray white to yellow (xanthomatous foci). Hemorrhagic foci and areas of cystic changes were seen. And the other one was received as gray white multiple, irregular bits. On Microscopy, Retroperitoneal cellular schwannoma was encapsulated, showed high cellularity. It predominantly consisted of Antoni A with spindle tumor cells arranged fascicles, nuclear palisading was seen. No mitosis was evident. Along with hyalinised blood vessels, few dilated and congested blood vessels were seen. At places myxoid areas were seen. Hemosiderin macrophages were seen in small clusters and sheets. Foamy histiocytes, lymphocytic infiltration and mast cells were seen scattered in the lesion. The lesion showed pseudoglandular element (type A). Similarly, other case showed high cellularity with spindle tumor cells arranged in fascicles and predominant Antoni A areas. Both the cases did not show any infiltration into adjacent tissue.

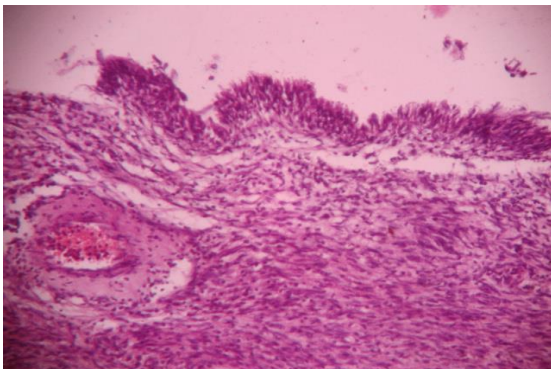
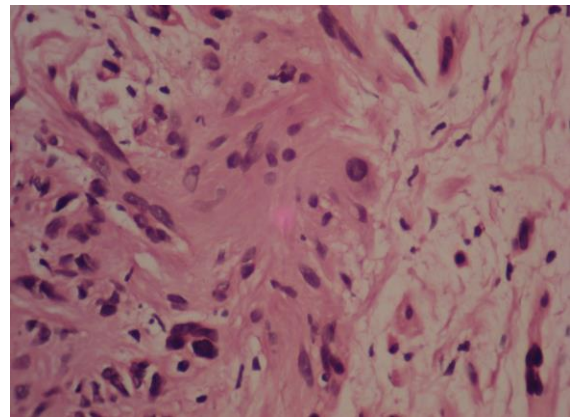
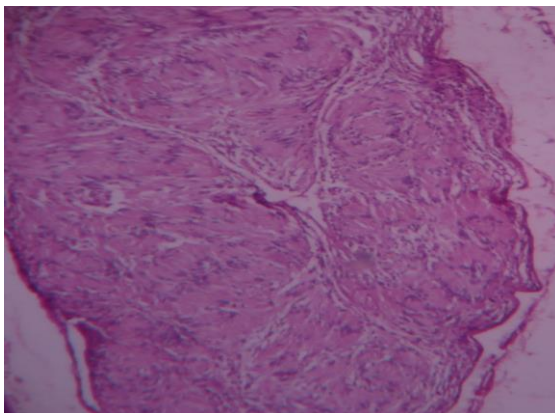
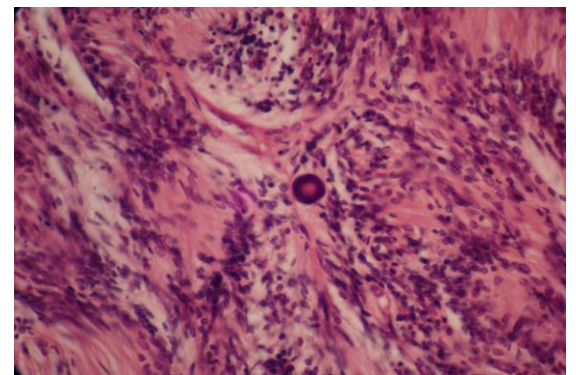
Plexiform Schwannoma: Plexiform schwannoma was seen in a 13-year-old boy, in the scrotal region. Clinically it presented as multinodular mass in the superficial soft tissue in scrotal region. Neurofibromatosis status in patient was not known. Grossly, it was firm, gray-white encapsulated multinodular with bosselated surface. Cut surface showed homogenous gray-white nodules. On microscopy, it was well encapsulated, showed multiple nodules composed of spindle schwann cells separated by fibrous tissue. These nodules showed varying cellularity. Antoni A, Antoni B areas, nuclear palisading and Verocay bodies were seen.

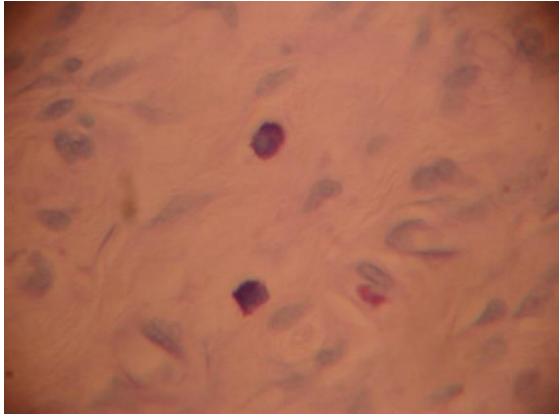
Table 1: Distribution of conventional schwannomas by gender, age-group and location (N=29)

Characteristic	Categories	Number	%
Gender	Male	15	51.7
	Female	14	48.3
Age-group (in years)	11-20	7	24.1
	21-30	8	27.6
	31-40	8	27.6
	41-50	1	3.4
	51-60	3	10.3
	61-80	2	6.9
Location (N=27)	Head & Neck	13	48.2
	Extremities	9	33.3
	Other region	5	18.5

Table 2: Clinical data of non-classical schwannomas in the study

Sl. No.	Schwannoma (unconventional)	Sex	Age	Location	Clinical Diagnosis
1	Ancient	F	55	Arm	Lipoma
2	Ancient	F	20	Neck	TB Lymphadenitis
3	Ancient	M	60	Arm	Lipoma
4	Cellular	M	36	Face	Schwannoma
5	Cellular	F	16	Retroperitoneum	Leiomyoma
6	Plexiform	M	13	Scrotal region	Fibrolipoma
7	with pseudoglandular elements	F	49	Neck	Cystic hygroma
8	with pseudoglandular elements	F	16	Retroperitoneum	Leiomyoma

**A: Cellular schwannoma with pseudoglandular element****C: Ancient schwannoma****B: Gross and microscopy of plexiform schwannoma****D: Psammomatous schwannoma**



E: Mast cells in toluidine blue stain

Discussion

Benign peripheral nerve sheath tumors of schwann cell origin, schwannomas or neurilemmomas, may have a highly variable morphologic appearance. Although the classic benign schwannoma usually causes few differential diagnostic problems, there are variants that may be difficult to recognize as schwannian and they may even be misinterpreted as malignant. Well known examples include cellular schwannoma, so called ancient schwannoma with marked pleomorphism, melanotic schwannoma, granular cell schwannoma, plexiform schwannoma, and neuroblastoma-like schwannoma.⁴

In cytopathology many of the characteristic light microscopic features that assist in the diagnosis of schwannoma are absent from smears. These include no method for assessing the presence of a capsule, inability to appreciate hyalinization of tumor vasculature, and under sampling of mitotic activity on smears. In addition to lacking many of these helpful diagnostic clues, schwannomas are heterogeneous and contain areas that are potentially very misleading if they are the only ones sampled by a thin needle.⁵

A case of cystic schwannoma seen in our classical schwannomas was noted with similar clinical presentation as the one described in Agarwal et al study. In both the studies, it occurred in upper extremity in elderly patients. However, the clinical diagnosis in our case was ganglion and in the Agarwal study it was soft tissue sarcoma.⁶ Cystic spaces resemble glands or dilated lymphatics on histopathological examination.⁷ Cystic schwannomas are a cause of diagnostic difficulty because the imaging characteristics and FNAC may not be sufficiently reliable to give a correct diagnosis.⁶

Schwannoma rarely occur in the retroperitoneum. They are usually asymptomatic but they enlarge and may compress adjacent structures, which leads to a wide spectrum of non-specific symptoms.⁸ In our study one of the cellular schwannoma cases was encountered in retroperitoneum in a 16-year-female. MRI confers the presence of a solid, homogenous mass and shows its

relation to adjacent structures in greater detail. Usually these represent no invasive process and have regular margins. These features on MRI are convincing that the mass is benign in nature.⁸ But there are no distinct diagnostic features of schwannoma and there still may be difficulties in differential diagnosis from other tumors in the retroperitoneum.⁹ But the definite diagnosis is made during histopathological examination.⁸

According to two large clinico-pathologic series, cellular schwannomas occur in a wide age range with predominance in young and middle aged adults, with the peak incidence in the fourth decade and median and mean ages between 40 and 54 years. They reported significant female predominance (63-72%).¹⁰⁻¹¹ A majority of cellular schwannomas occur in the retroperitoneum and posterior mediastinum, whereas few are seen in head and neck and the extremities.¹²

It is important to recognize that cellular schwannomas can histologically mimic malignant peripheral nerve sheath tumours (MPNSTs) because of their high cellularity and mitotic activity, but they are relatively benign tumors with a tendency to recur but not to metastasize.¹³ Incomplete excisions with an elevated mitotic index appear to be particularly prone to recurrences. The variation in mitotic index observed in recurrent tumors was such that no definite level of mitotic activity could be established as a predictor of recurrence.¹¹

Pediatric plexiform schwannomas are likely to be syndrome-associated.¹⁴ It may be that our case is Neurofibromatosis 2 because of young age. No other stigmata were seen in our case and needs to be investigated. Deep seated plexiform schwannoma is a rare, under-recognized peripheral nerve sheath tumour of deep soft tissue, whereas superficial ones are much more common tumours and occur in the extremities.¹⁵ Lesions with increased cellularity, presence of nuclear pleomorphism, mitoses or necrosis can be extremely challenging and worrisome. They can recur locally due to their multinodular growth pattern. It is important to differentiate these tumors from plexiform neurofibromas and MPNSTs as they follow a benign clinical course, with complete surgical excision being curative.¹⁵ Misinterpretations due to limited biopsy material or the unsettling finding of a cellular, hyperchromatic, mitotically active, often sizable tumor can easily lead to an over diagnosis.¹⁶

When pseudoglandular schwannoma shows high cellularity, an erroneous diagnosis of sarcoma, malignant glandular PNST can be made. The presence of areas showing more typical features of schwannoma, diffuse and strong S100 protein immunoreactivity, and lack of cytokeratin expression should suggest the correct diagnosis.¹⁷ One of our cases with pseudoglandular elements was retroperitoneal cellular schwannoma, and other case was a conventional schwannoma in neck in a 49-years-female.

In Robinson et al study, 16 cases characteristically revealed pseudoglandular elements around the degenerative cysts. On electron microscopy, cells which were lining the cysts represented degenerated schwannian cells. The author concluded that a previously designated entity of so called “pseudoglandular schwannoma” is indeed a non-existent entity.¹⁸ Pseudoglandular elements are type A in our 2 cases. One presented as cystic lesion and other as retroperitoneal lesion.

Histologically, the pigmented cells in psammomatous melanotic schwannoma tend to be somewhat large and more epithelioid than the pigmented cells in melanotic neurofibroma, and they sometimes have a large nucleus with an open chromatin pattern, and a distinct melanoma-like nucleolus. Laminated calcific concretions and metaplastic ossification are noted features of psammomatous melanotic schwannoma. Psammomatous subtype of melanotic schwannoma occur as a part of Carney complex.¹⁹ In one case of schwannoma, we found a psammomatous body but no melanin pigment. Our case was peculiar for its absence of pigment.

The distinction between schwannoma and neurofibroma is important because the latter shows a small but non-negligible potential for malignant transformation. In addition, neurofibromas are also much more often diagnosed in association with von Recklinghausen disease than are schwannomas.²⁰

Conclusion

Schwannomas show an interesting histologic variety despite being composed of a limited array of cellular constituents. Key issue for the pathologist is a definitive diagnosis in this histologic diversity for better management. Peripheral nerve sheath neoplasms exhibit histologic features that overlap with those of many other benign and malignant soft tissue tumors. The correct diagnosis relies mainly on histologic findings and IHC profile, but ultrastructural studies can be used in difficult cases. Key issue for the pathologist includes distinguishing schwannomas from neurofibromas, and MPNSTs from cellular schwannoma or neurofibromas.

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