



ARAŞTIRMA / RESEARCH

Hybrid peripheral nerve sheath tumors

Hibrid periferik sinir kılıfı tümörleri

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Abstract

Purpose: The aim of this study was to evaluate patients formerly diagnosed as neurofibroma and schwannoma in terms of hybrid peripheral nerve sheath tumors (PNSTs) via histopathological and immunohistochemical analysis.

Materials and Methods: In this retrospective study, 115 patients formerly diagnosed as either neurofibroma or schwannoma were re-evaluated histopathologically. Among these patients, 32 cases which showed mixed morphology, suspicious for hybrid PNST were included in the study. Immunohistochemically, S100, CD34, EMA and ki67 were performed to these 32 cases, suspicious for hybrid PNST.

Results: Based on histopathology, 32 of 115 (27.8%) cases were suspicious for hybrid PNST. By the addition of immunohistochemical staining results; 22 of 32 cases were definitely diagnosed as hybrid PNST; of which 18 (81.8%) as schwannoma-neurofibroma and, 4 (18.2%) cases as schwannoma-perineurioma.

Conclusion: Hybrid PNSTs are usually benign and have distinct histopathologic and immunohistochemistry findings. In the literature, rare case reports have described local recurrence and malignant transformation in hybrid PNSTs. Therefore, further studies are needed to demonstrate the pathogenetic and prognostic significance of these tumors. Because of the risk of recurrence and malignancy potential, these tumors should be kept in mind in diagnosis of peripheral nerve sheath tumors.

Keywords: Peripheral nerve sheath tumors, hybrid, immunohistochemistry, schwannoma, neurofibroma, perineuroma.

Öz

Amaç: Nörofibrom ve schwannom tanısı alan olgularımızı histopatolojik ve immünohistokimyasal olarak hibrid periferik sinir kılıfı tümörü (PSKT) açısından değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmada, daha önce nörofibrom ve schwannom tanısı almış 115 olgu histopatolojik bulguları ile tekrar değerlendirildi ve mikst morfolojiye sahip, hibrid PSKT şüphelenilen 32 hasta çalışmaya dahil edildi. Hibrid PNST şüphesi olan bu olgulara immünohistokimyasal olarak S100, CD34, EMA ve ki67 uygulandı.

Bulgular: Çalışmaya dahil edilen 115 hastanın histopatolojik olarak tekrar değerlendirmesinde; hibrid PSKT olduğu düşünülen 32(%27.8) hastanın 22 (%19.1)'si immünohistokimyasal veriler ile birlikte; 18 (%81.8)'i Schwannom-nörofibrom, 4'ü (%18.2) schwannom-perinörom olmak üzere "hibrid PSKT" tanısı aldı.

Sonuç: Hibrid PSKT'leri genellikle iyi huylulu olup farklı histopatolojik ve immünohistokimyasal bulgulara sahiplerdir. Literatürde, hibrid PSKT'lerinin lokal rekürrens ve malign transformasyonu nadir olgu sunumları şeklinde bildirilmiştir. Bu tümörlerin patogenetik ve prognostik önemini göstermek için daha ileri çalışmalara ihtiyaç vardır. Bu tümörler, düşük de olsa rekürrens riski ve malignite potansiyelleri taşımaları nedeniyle periferik sinir kılıfı tümörü tanısı verirken mutlaka akılda tutulmalıdır.

Anahtar kelimeler: Periferik sinir kılıfı tümörleri, hibrid; immünohistokimya, schwannom, nörofibrom, perinöroma.

INTRODUCTION

Schwannoma, neurofibroma and perineurioma are the most common types of peripheral nerve sheath tumors (PNSTs) composed of Schwann cells, perineurial cells, and a mixture of endoneurial components, respectively^{1,2}. In recent years, composite tumors of peripheral nerve sheath have been reported to show combined features of more than one histologic type of PNSTs (i.e. neurofibroma, schwannoma, or perineurioma) within a single lesion³⁻⁹. These composite tumors are termed as “hybrid” PNSTs and are considered to be rare or under-recognized, although exist as hybrid schwannoma / neurofibroma, schwannoma /perineurioma, neurofibroma/perineurioma, or cellular schwannoma/perineurioma over a wide range of ages and anatomical sites^{6,7,10,11}.

Although the exact pathogenesis of hybrid differentiation in PNSTs remains unknown, along with the ongoing debate on whether or not hybrid PNSTs are really a distinct entity^{3,6,12}. Accurate recognition and classification of hybrid PNSTs is considered important in terms of potential prognostic and therapeutic implications⁵.

In this study, 22 cases of hybrid PNSTs were presented based on histopathological re-assessment and immunohistochemical staining of lesions in a retrospective cohort of patients formerly diagnosed as PNSTs including schwannoma or neurofibroma.

MATERIALS AND METHODS

Of 115 patients formerly diagnosed as neurofibroma or schwannoma, 32 cases with mixed histomorphological findings accepted as suspicious for hybrid PNST were included in this retrospective study. Immunohistochemically, S100 protein, CD34, epithelial membrane antigen (EMA) and ki67 were performed in 32 suspicious for hybrid PNST cases. Both histopathological re-assessment and the immunohistochemical findings revealed the definite the diagnosis of hybrid PNST in 22 of 32 cases. Clinical data were obtained from the hospital records and/or from contributing clinicians or pathologists.

Histopathological evaluation

Histopathologic re-assessment was performed by two pathology specialists based on biphasic

appearance, cellular structure, presence of pleomorphism-atypia, growth patterns and stromal characteristics of lesions. The lesions containing neurofibroma with plexiform pattern next to schwannoma including hypercellular and hypocellular (Antoni A and B) areas were accepted as hybrid schwannoma / neurofibroma. Schwannoma / perineurioma cases did not include Antoni A and B areas and verocay body. The dominant appearance was storiform pattern or less commonly lamellar and whorled pattern.

Immunohistochemical analysis

Immunohistochemical staining was performed on 5-mm sections of formalin-fixed, paraffin-embedded tissue. We used monoclonal antibody to detect CD34 (Novacastra, QBEnd/10, Newcastle,UK), S100 (Novacastra,policlonal, Newcastle,UK), EMA (Cell Margue,E29, Roclin, CA, USA) and ki67 (Cell Margue,EP5, Roclin, CA, USA). The visualization system used was the BenchMark XT with enzymatic digestion (ISH protease 2; Ventana) and the iView Blue Detection Kit (Ventana). Immunohistochemically, cytoplasmic and membranous staining for CD34, cytoplasmic and nuclear staining for S100, membranous staining for EMA and nuclear staining for ki-67 were accepted positive.

Statistical analysis

Descriptive statistics were used to summarize data, expressed as n (%).

RESULTS

Final diagnoses of histopathologically suspicious for hybrid PNST (n=32) cases were as follows: 22 (19.1%) definite diagnosis of hybrid PNST, 10 (%8.6) cases as either pure neurofibroma or schwannoma; given the lack of CD34 or EMA positivity.

The former diagnosis was schwannoma in 9/22 (40.9%) cases and neurofibroma in 13/22(59.1%) cases. Final diagnosis was hybrid PNST including schwannoma-neurofibroma and schwannoma-perineurioma in 18 (81.8%) and four (18.2%) patients, respectively. Overall, 12 females (54.5%) and 10 males (45.5%) were diagnosed as hybrid PNST. Localizations of hybrid PNSTs were head/neck in seven (31.8%), lower extremity in six

(27.3%), upper extremity in four (18.2%), trunk in four (18.2%), and intraabdominal in one (4.5%) (Table 1).

Histopathological immunohistochemical features of hybrid nerve sheath tumors in our series (n=22) are presented in Table 2.

Table 1. Overall demographic and clinical characteristics of cases with hybrid PNST (n=22)

Age, mean(min-max)	37.8(9.0-66.0)
Gender, n (%)	
Female	12(54.5)
Male	10(45.5)
Former diagnosis, n (%)	
Schwannoma	9 (40.9)
Neurofibroma	13(59.1)
Final diagnose, n (%)	
Schwannoma-neurofibroma	18 (81.8)
Schwannoma-perineurioma	4 (18.2)
Localization of hybrid PNST, n (%)	
Head/neck	7 (31.8)
Lower extremity	6(27.3)
Upper extremity	4(18.2)
Trunk	4(18.2)
Intraabdominal	1(4.5)

PNST: peripheral nerve sheath tumor

Table 2. Clinical and pathological features of hybrid peripheral nerve sheath tumors (PNSTs) in our series (n = 22)

Former diagnosis	Age (year)	Gender	Tumor Site	Immunohistochemistry findings			Hybrid PNST type
				S100	EMA	CD34	
Neurofibroma	51	F	Intraabdominal	+	-	+	Schwannoma / neurofibroma
	37	F	Trunk	+	-	+	
	51	F	Upper Extremity	+	-	+	
	30	F	Lower Extremity	+	-	+	
	22	F	Head/Neck	+	-	+	
	46	F	Lower Extremity	+	-	+	
	29	M	Trunk	+	-	+	
	28	M	Head/Neck	+	-	+	
	49	F	Head/Neck	+	-	+	
	26	F	Head/Neck	+	+	+	
	50	M	Head/Neck	+	+	+	Schwannoma / perineurioma
	22	F	Trunk	+	+	+	
	41	M	Lower Extremity	+	+	+	
Schwannoma	24	F	Head/Neck	+	-	+	Schwannoma / neurofibroma
	32	F	Upper Extremity	+	-	+	
	26	M	Lower Extremity	+	-	+	
	43	M	Lower Extremity	+	-	+	
	61	M	Upper Extremity	+	-	+	
	51	M	Lower Extremity	+	-	+	
	31	M	Upper Extremity	+	-	+	
	17	M	Head/Neck	+	-	+	
66	F	Trunk	+	-	+		

Of 13 patients formerly diagnosed as neurofibroma, nine patients were diagnosed as schwannoma-

neurofibroma type of hybrid PNST, and four patients as schwannoma-perineurioma type of

hybrid PNST, whereas all patients with former diagnosis of schwannoma (n=9) were diagnosed as schwannoma-neurofibroma type of hybrid PNST.

Our cases with definite diagnosis of hybrid PNST demonstrated the classic immunohistochemical staining profile of “diffuse S100 positivity/CD34 and EMA negativity” in schwannomatous areas and, “S100 negativity /CD34 and EMA positivity” in perineuromatous areas. Ki-67 was in the range of 1% to 2% in all cases.

Histopathological assessment of tumors with schwannoma morphology revealed predominantly biphasic pattern with identification of hypercellular schwannoma areas alongside loose myxoid areas in majority of cases. S100 positivity was identified in both myxoid and cellular schwannoma areas, whereas CD34 positivity was evident in loose myxoid stromal areas but not in cellular areas (Fig 1).

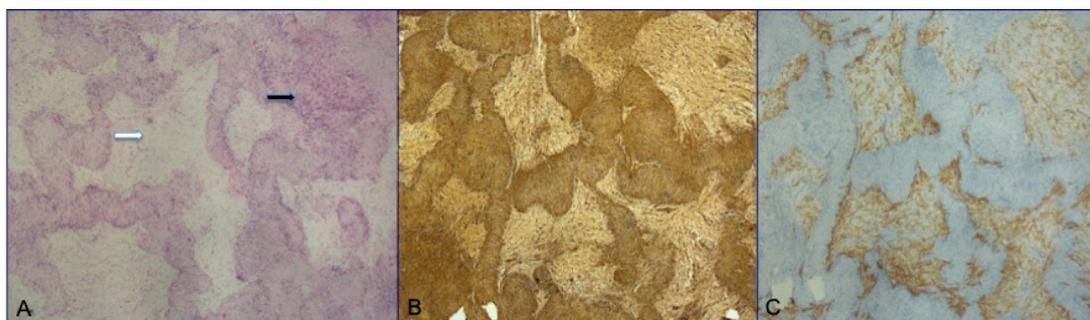


Figure 1. Hybrid neurofibroma – schwannoma. **A:** Neurofibroma areas composed of uniform spindle cells in myxoid appearance (white arrow) beside marked cellular schwannoma areas (black arrow) are observed (H&E, x40). Immunohistochemically; **B:** Schwannoma areas with strong S100 positivity while variable S100 positivity in neurofibroma areas (IHC, x40). **C:** CD34 was negative in schwannoma areas, but some spindle cells in neurofibroma areas were positive (IHC, x100).

Amongst the lesions with diffuse neurofibroma morphology, four cases with predominance of atypia and pleomorphism with no mitosis had diffuse and strong S100 positivity with focal CD34 positivity. Upon detection of focal EMA positivity in stromal cells and perineurium, the diagnosis was considered to be schwannoma-perineurioma hybrid tumor in these four cases (Fig 2).

DISCUSSION

Peripheral nerve sheath tumors are commonly seen as pure lesions. Hybrid PNSTs show combined features of neurofibroma, schwannoma and perineurioma. In our study, we found 19.1% (22 patients) hybrid tumors with histopathological and immunohistochemical findings in patients previously diagnosed as either neurofibroma or schwannoma. Schwannoma-neurofibroma (n=18) was the most common type of hybrid PNST diagnosed in our case series, while the hybrid schwannoma-perineurioma was diagnosed in only four cases. This rarity seems to be correlated with

less common occurrence and relatively later recognition of perineuriomas in terms of microscopically distinctive patterns; when compared to schwannomas and neurofibromas^{1,3,4,13,14}. Indeed, hybrid schwannoma/perineurioma and hybrid neurofibroma/schwannoma are also considered to be more common types of hybrid PNSTs as compared with hybrid neurofibroma/perineurioma^{6,7,12,15,16}.

Although hybrid PNSTs have been reported in all age groups, most of the cases reported to date were composed of young adults with no gender predilection and a wide anatomic distribution^{3,6}. Nonetheless, mean age (37.8 years) and female to male ratio (1.2:1) results of our series are very similar with previous studies which report median 38 years of age at diagnosis and a slight female predilection with a female-to-male ratio of approximately 1.2:1^{3,11}.

Four cases of hybrid schwannoma/perineurioma were located in head/neck, trunk and lower extremity, consistent with the results of a case series

of 42 hybrid schwannoma/perineurioma tumors, which were distributed as lower limb, followed by the upper limb, trunk and head and neck region⁷.

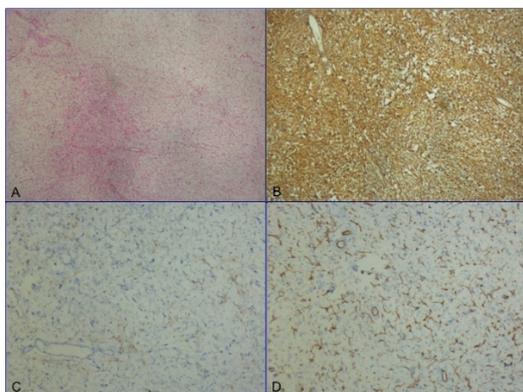


Figure 2. Hybrid schwannoma – perineurioma. A: Schwannoma areas, which do not contain significant areas of Antoni A and B, it can be difficult to identify the perineurial cells in the loose stroma with H&E (H&E, x40). Immunohistochemically, B: diffuse S100 positivity (IHC, x40) in both histological patterns; C: focal EMA positivity (IHC, x40) and D: CD34 (IHC, x40) positivity in perineurial cells.

Additionally, most of lesions in our hybrid PNST case series showed biphasic pattern rather than a monophasic pattern of histopathologically. While, monophasic pattern has frequently been determined only by immunohistochemistry, both patterns have been associated with diagnostic challenges due to hybrid morphology and mixed immunohistochemical staining, particularly in differentiating between a schwannoma and neurofibroma component^{3,5,7,10-12,20}. Besides, intermediate or transitional cells that exist in some PNST cases are considered to differentiate into both cell types²¹.

Hence, schwannoma-neurofibroma and schwannoma-perineurioma types of hybrid PNSTs were identified in a considerable portion of patients formerly diagnosed as neurofibroma or schwannoma in our case series; this seems to emphasize the importance of including immunochemistry staining, given the suggestion that hybrid PNSTs are distinct entities with distinct hybrid morphology^{3,5,6}.

Cells with ultrastructural features compatible with transitional stages such as Schwann cells, perineurial cells, endoneurial fibroblasts and intermediate cells

(Schwann-perineurial cells and Schwann cell-fibroblasts) were demonstrated in neurofibromas^{4,5,21-23}. Later studies also provided immunohistochemical evidence for existence of EMA positive perineurial cells in some neurofibromas^{5,24-26}.

Although no quantitative criteria exist for perineuriomatous areas in a lesion to be qualified as a hybrid one, in a largest series of hybrid schwannomas-perineuriomas, immunohistochemical staining was shown to confirm the morphological presentation of dual cell population with S100 protein staining in Schwannoma cells, EMA and CD34 positivity in perineurial cells^{5,16,19,27}. Accordingly, hybrid schwannoma-perineurioma was diagnosed based on strongly and diffuse S100 positivity in schwann cells and EMA-confirmed perineuriomatous differentiation in four cases with former diagnosis of neurofibroma in our study.

While the exact rates of recurrence and malignant transformation in hybrid PNSTs remain inconclusive, hybrid tumors are considered to show similar biological behavior with benign PNTs with extremely rare occurrence of malignant transformation^{7,30,31}.

Hyper-cellularity, nuclear atypia with hyperchromasia, high mitotic rate and ki67 proliferation index over 20% have been considered to denote malignancy in hybrid PNSTs^{4,10,32}. Notably, while atypia and nuclear pleomorphism were present in 5 cases with hybrid schwannoma-neurofibroma in our series, all hybrid tumors we describe in this report had a low mitotic count and 1-2% ki-67 index. This seems notable given the likelihood of the more cellular and prominent schwannomatous areas in schwannoma-neurofibroma type hybrid PNST to be mistaken for foci of malignant, despite the lack of atypical features such as hyperchromasia, prominent mitotic activity, atypical mitoses and necrosis⁵.

After the identification of the hybrid peripheral nerve sheath tumors by the World Health Organization (WHO), awareness in the diagnosis of these tumors has been increased in PNSTs. As seen in our study, hybrid tumors are not rare tumors and should be kept in mind in diagnosis of PNST. The limitation of our study is low number and absent of follow-up data of the patients. Further studies addressing the pathogenesis and genetic background of hybrid differentiation in PNSTs are needed for

better understanding of hybrid PNSTs as distinct entities as well as for potential prognostic and therapeutic implications.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EB, GG; Veri toplama: EB, AA, MAD; Veri analizi ve yorumlama: EB, AA, MAD; Yazı taslağı: EB; İçeriğin eleştirel incelenmesi: EB, AA; Son onay ve sorumluluk: EB, AA, GG, SZ, MAB; Teknik ve malzeme desteği: Süpervizyon: EB, GG, SZ; Fon sağlama (mevcut ise): yok.

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