

Hybrid peripheral nerve sheath tumors: A review

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SUMMARY

Hybrid peripheral nerve sheath tumors (HPNST) are relatively recently described tumors. With ongoing research, a considerable amount of important findings have been made, much of which has substantial clinical implications. However, a comprehensive review of the whole topic has not been published in the literature so far. In the presented manuscript, the various hybrid tumors are discussed separately with a special emphasis on the morphological and immunohistochemical findings as well as on their association with tumor syndromes.

Keywords: Hybrid peripheral nerve sheath tumors – schwannoma – perineurioma – neurofibroma – neurofibromatosis – schwannomatosis

Hybridní nádory z obalů periferních nervů: přehledový článek

SOUHRN

Hybridní nádory z obalů periferních nervů jsou poměrně nedávno popsány jednotkami. S postupujícím výzkumem bylo v této oblasti dosaženo značného množství důležitých poznatků, z nichž mnohé jsou významné i z klinického hlediska. V literatuře však dosud chybí komplexní souhrn tohoto tématu. V předkládaném přehledovém článku jsou probrány jednotlivé typy hybridních tumorů se zvláštním zaměřením na jejich morfologické a imunohistochemické vlastnosti, přičemž důraz je rovněž kladen na jejich vztah k nádorovým syndromům.

Klíčová slova: Hybridní nádory z obalů periferních nervů – schwannom – perineuriom – neurofibrom – neurofibromatóza – schwannomatóza

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The issue of hybrid peripheral nerve sheath tumors (HPNST), i.e. tumors containing areas of schwannoma, perineurioma and neurofibroma in various combinations is a relatively new chapter in the pathology of both soft tissue and nervous system. Although the existence of tumors showing hybrid features between neurofibroma and schwannoma has already been mentioned in earlier literature, it was only 18 years ago when the first major work on this topic was published by Feany et al (1). Three years later, the first published case of HPNST showing perineuriomatous differentiation (hybrid perineurioma - schwannoma) was presented by Zamecnik and Michal (2).

Three main cell types constitute the normal connective tissue sheath of a peripheral nerve, namely Schwann cells, perineurial cells, and fibroblasts. Schwannomas are believed to consist of a nearly pure population of cells showing schwannian differentiation which can be confirmed by ultrastructural examination of these tumors (3). Perineuriomas, the rarest lesion of the main triad of peripheral nerve sheath tumors (PNST), are similarly composed exclusively of one cell type: the neoplastic perineurial cell (4). The situation is not so straightforward with respect to neurofibromas in which a more complex cellular mixture is pres-

ent. The ultrastructural studies published previously suggested the presence of Schwann cells, perineurial cells, endoneurial fibroblasts (5), intermediate cells (Schwann cell - fibroblast and Schwann - perineurial cells), scattered axons and mast cells in neurofibromas (6-8). Although this fact had for a long time remained immunohistochemically unsubstantiated, later several studies confirmed the presence of perineurial cells in some neurofibromas (2,9). Eventually, using a highly sensitive detection system, Hirose et al. proved that all neurofibromas contain a small number of EMA positive perineurial cells (5).

Briefly, from the genetic perspective, both neurofibromas and schwannomas originate from either somatic or germline biallelic gene mutations. *NF1* gene (17q11.2) mutations with a functional loss of the protein neurofibromin are found in neurofibromas (10), whereas schwannomas typically harbor biallelic loss of the *NF2* gene (22q12.2) function leading to loss of merlin (schwannomin) protein activity (11). Similarly, perineuriomas have been shown to have a pathogenic relationship to the loss of *NF2* gene function (8,12,13). In tumors that arise in patients with neurofibromatosis type 1 or 2 (*NF1*, *NF2*), one allele contains a germline mutation of *NF1* or *NF2* gene respectively, whereas the second allele becomes mutated later in life (somatic mutation). In sporadic tumors, both mutations are somatic. Schwannomatosis is a disease defined by multiple nondermal schwannomas and a lack of vestibular schwannoma. Schwannomatosis-associated schwannomas exhibit four genetic events: non-germline biallelic inactivation of the *NF2* gene and mutations of the SWI/SNF chromatin remodeling subunit SMARCB1/INI1 (22q11.23) on both alleles (8,14).

In general, our experience and that of others shows that the various types of biphasic lesions may manifest either abrupt transition of the 2 components or the two cellular components

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are closely intermingled (15). In the latter situation, it is frequently possible to determine the biphasic composition only by immunohistochemistry (IHC). In fact, the routine use of IHC has been suggested to increase the frequency of HPNST detection (16). Interestingly, in cases in which the biphasic composition is evident on H&E-stained slides, the individual areas may occasionally display patterns encountered in the less usual subtypes of "monophasic" PNST such as retiform (reticular) perineurioma (2,17,18) or epithelioid schwannoma (19,20).

When approaching HPNST it is always essential to combine morphology with immunohistochemical results. Due to the available antibodies for perineurial differentiation (epithelial membrane antigen (EMA)/Claudin-1/Glut-1), which may be considered quite specific in the context of HPNST, the detection of this line of differentiation is usually not a problem. The most challenging task is to differentiate between a schwannoma and neurofibroma component, especially because hybrid schwannomas - perineuriomas do not exhibit other classical features of schwannomas (hyalinized vessels, Antoni A and B zonation etc.) (21). Although both are S100 protein positive, the Schwann cells in schwannomas are large spindle cells with plump nuclei. In contrast, the Schwann cells in neurofibromas are much smaller (21) and the nuclei have a more elongated, curved (8) or wavy appearance. Moreover, S100 protein positivity in schwannomas is much more diffuse and is present in practically 100% of tumor cells, while in neurofibromas the expression is more limited (approximately 50% of tumor cells). Schwannomas usually contain only focal intratumoral axons, whereas these are often readily identifiable by IHC or by histochemical stain in neurofibromas (3). Although CD34 labels a fibroblastic population in neurofibromas, it may, in up to 50% of cases, also highlight the perineurial cells of perineuriomas (22). Thus again, careful attention must be paid to the morphology of the stained cells. While fibroblasts in neurofibromas have a bland round to oval nuclei, featuring long multipolar cytoplasmic processes (23), the perineurial cells are composed of very thin spindle cells with wavy nuclei and delicate, elongated bipolar or multipolar cytoplasmic processes (22). Most reported examples of hybrid neurofibroma - perineurioma are not morphologically much different from plexiform neurofibroma (15). This architectural trait was encountered in only one sporadic case of hybrid schwannoma - perineurioma (21). Also, based on the published data, the hybrid neurofibroma - perineurioma variant seems to be the by far least frequently encountered. The remaining two groups occur with comparable frequency. Nevertheless, as will be further discussed, in some cases, a clear distinction cannot be made with certainty.

Although the whole topic of HPNST may appear of mere academic interest, significant progress in this field has been accomplished since the initial reports, yielding important clinical implications. Hence, the ability to accurately recognize and classify HPNST proves to be substantial with respect to the management of the patient, and in some cases, to the management of the patients' whole family.

To our knowledge, this is the first comprehensive review of this topic in the literature. For this purpose, the various combinations of HPNST consisting of schwannomas, neurofibromas and perineuriomas will be addressed separately, focusing mainly on the morphology and their association with tumor syndromes. Since most of the hybrid tumors occur in a superficial (dermal or subcutaneous) soft tissue over a wide anatomic distribution, we will specify the tumor location only in cases which show deviation from this scheme.

NEUROFIBROMA - SCHWANNOMA

Due to the morphological similarities between schwannomas and neurofibromas, the only arrangement of hybrid schwanno-

mas - neurofibromas reported so far and also probably the only one histologically recognizable, is in the form of two clearly separated tumor populations. They exhibit the typical features of ordinary neurofibroma enclosing distinct, small (usually less than 1 cm in size), often multiple areas with larger cells containing more ample and eosinophilic cytoplasm, significantly higher cellularity and palisading nuclei corresponding to the Antoni A regions of schwannomas (1,11) (Figure 1A and B). Alternatively, some authors categorize these tumors as neurofibromas with Schwann cell nodules (8). Only a minority of some larger nodules may additionally contain Antoni B regions (11). The Antoni A areas frequently feature hyalinized vessels, which is in contrast to the surrounding neurofibromatous regions, where such vessels are not found. Both Antoni A and B regions are strongly and diffusely positive for S100 protein. While an increased proliferation index (Ki-67) reaching as much as 18% is not uncommon in the schwannomatous area (1,11), the mitotic activity is either very focal or absent. In the less dense neurofibromatous parts, the tumor cells show the characteristic elongated and wavy appearance, with abundant collagen fibers and there is frequent myxoid change in the surrounding stroma. These neurofibromatous parts show virtually no mitoses, stain strongly with CD34 antibody and also react with S100 protein, but the expression is not as diffuse when compared to the schwannomatous areas (11).

There are two reasons why it is crucial to be familiar with this type of HPNST. The first lies in the fact that the more cellular and prominent schwannomatous areas could be mistaken for foci of malignant degeneration in a neurofibroma. Although more cellular, often with an increased proliferation index and occasional mitoses, the Schwann cell component in these tumors does not show other atypical features such as hyperchromasia, prominent mitotic activity, atypical mitoses, necrosis en mass etc. Moreover, early malignant PNSTs (MPNSTs) normally do not grow in a nodular arrangement, as these hybrid tumors in question do (8).

Putting together the data of the two largest studies on this topic, in almost 30% (20/69) of these hybrid tumors, the neurofibroma was of the plexiform type. Knowing that this kind of neurofibroma is almost pathognomonic for NF1 (24) it is not surprising to learn that such hybrid tumors arising in this setting may also be associated with this syndrome. Much more surprising are the facts recently reported by Harder et al (11) who found that NF1 is the least frequently encountered among the three inheritable genetic syndromes causing the development of PNST, namely NF1, NF2 and schwannomatosis. The authors reviewed PNSTs from 14 schwannomatosis patients and found that 71% (10/14) of them had either single or multiple hybrid neurofibromas - schwannomas. Separately, they also studied 23 patients with hybrid neurofibromas - schwannomas whose clinical information were initially unknown. After review of their clinical data, the most common genetic syndrome recorded was NF2 (6/23) followed by schwannomatosis (4/23), whereas only 2 patients showed the stigmata of NF 1. Additionally, the remaining 11 patients showed either signs of an inherited syndrome which could not be accurately specified (2/11) or no clinical data were available for review, thus precluding further classification. Hence, based on this study, a clear conclusion can be drawn that hybrid neurofibromas - schwannomas are very frequently, if not always, associated with a hereditary tumor syndrome.

Very recently, using molecular genetic methods, Stahn et al analyzed 22 cases of hybrid neurofibromas - schwannomas and among other molecular events, one of the most prominent findings was the uncovered monosomy of the chromosome 22 identified in almost half of the tumors tested (14). Biallelic but not germline inactivation of this gene is found in all schwannomas, including those diagnosed in patients with schwannoma-

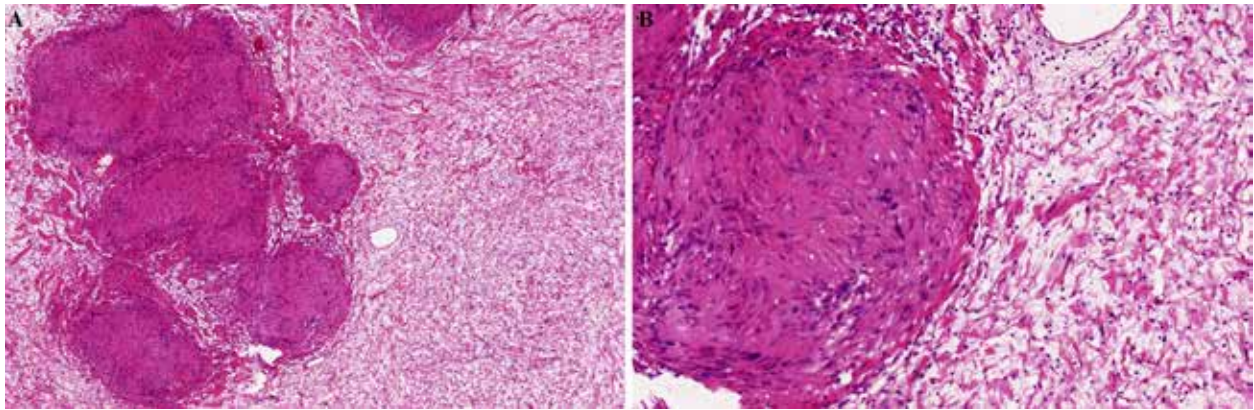


Figure 1. Hybrid neurofibroma – schwannoma. **A, B:** These tumors exhibit the typical features of ordinary neurofibroma enclosing small often multiple areas with larger cells containing more ample and eosinophilic cytoplasm, significantly higher cellularity and palisading nuclei corresponding to the Antoni A regions of schwannomas. In the less dense neurofibromatous parts, the tumor cells show the characteristic elongated and wavy appearance, with abundant collagen fibers and there is frequent myxoid change in the surrounding stroma.

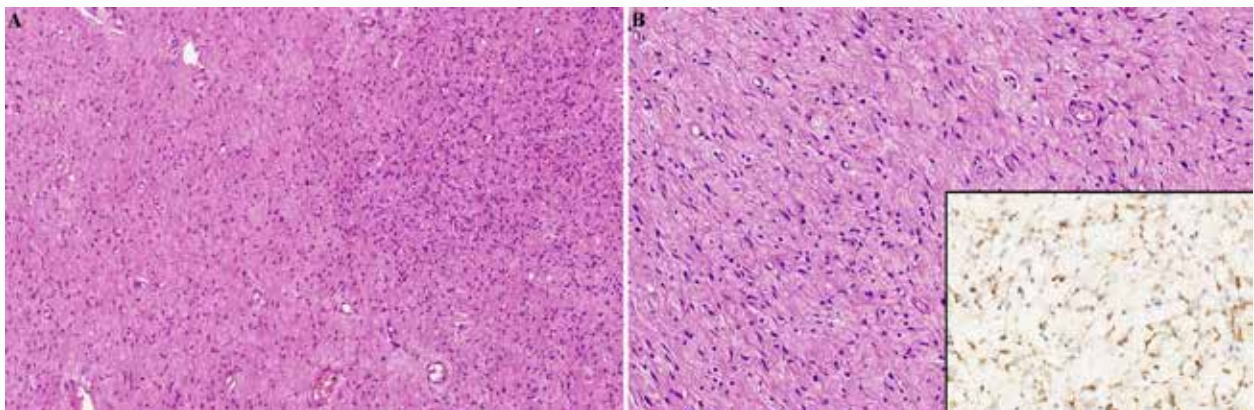


Figure 2. Hybrid neurofibroma – perineurioma with retiform arrangement. **A:** Lesion with a biphasic pattern produced by areas with a retiform perineurioma appearance (on the left - mosaic-like arrangement of interconnected spindle-shaped cells with bipolar or stellate nuclei) which gradually merge into areas which look like an ordinary neurofibroma (on the right - Schwann cells with spindled wavy nuclei). **B:** Higher power view of the retiform perineurioma area with a strong claudin-1 staining (inset).

tosis. On the contrary, patients with NF2 have germline mutations found in this gene (8,25).

NEUROFIBROMA – PERINEURIOMA

As mentioned above, the ultrastructural studies have for a long time indicated the presence of perineurial cell subpopulation in neurofibromas. Nevertheless, this had remained immunohistochemically unproven until 2001, when Zamecnik and Michal analyzed 99 neurofibromas and demonstrated EMA positive perineurial cells being present in 7 of these lesions in a sparse, but quite diffuse manner (2). However, although no exact criteria exist, the amount of perineuriomatous tissue in these neurofibromas was not significant enough as to warrant the designation of HPNST.

The first two cases of hybrid neurofibroma – perineurioma were presented four years later by Kazakov et al (18). Both tumors had a unique appearance but differed from one another. The first was a lesion with a biphasic pattern produced by areas with a retiform perineurioma appearance (Figure 2B; mosaic-like arrangement of interconnected spindle-shaped cells with bipolar or stellate nuclei) which gradually merged into areas which looked like an ordinary neurofibroma (Figure 2A; Schwann cells with spindled wavy nuclei). Immunohistochemically, the tumor showed abundant S-100 protein positive wavy Schwann cells and CD34 positive fibroblasts in the neurofibromatous areas. EMA was nega-

tive in these parts. Conversely, antibodies to EMA and claudin-1 stained the perineuriomatous areas strongly (Figure 2B - inset) and reacted negatively with the spindled wavy Schwann cells. No CD34-positive fibroblasts and very scarce S-100 protein positive wavy cells were present in the perineuriomatous compartments.

The second tumor showed a different arrangement of the two components that mostly merged together imperceptibly within a lesion: individual spindled cells with wavy nuclei identical to those found in neurofibroma were closely intermingled with spindled cells with bipolar or stellate nuclei corresponding to the perineurial cell differentiation. Thus the biphasic pattern was poorly discernable on HE-stained slides but was appreciable on immunohistochemical slides, with the spindled cells having wavy nuclei manifesting S-100 protein+/EMA-/claudin-1- phenotype surrounded by EMA+/claudin-1+/S-100 protein- stellate cells. CD34 labeled plentiful fibroblasts distributed evenly within the lesion (18). Notably, this case was shown to contain a point mutation in the *NF2* gene (18). This group of authors later reported an additional and virtually identical case (26). A similar example is depicted in Figure 3.

In 2013, Kacerovska et al published a series of 5 patients with NF1 who presented with hybrid neurofibromas – perineuriomas. In four cases, the tumors at first glance represented ordinary plexiform neurofibromas. The perineuriomatous component was admixed in a very discreet, intermingled fashion and was not apparent on H&E-stained slides (Figure 4A-C). In the last

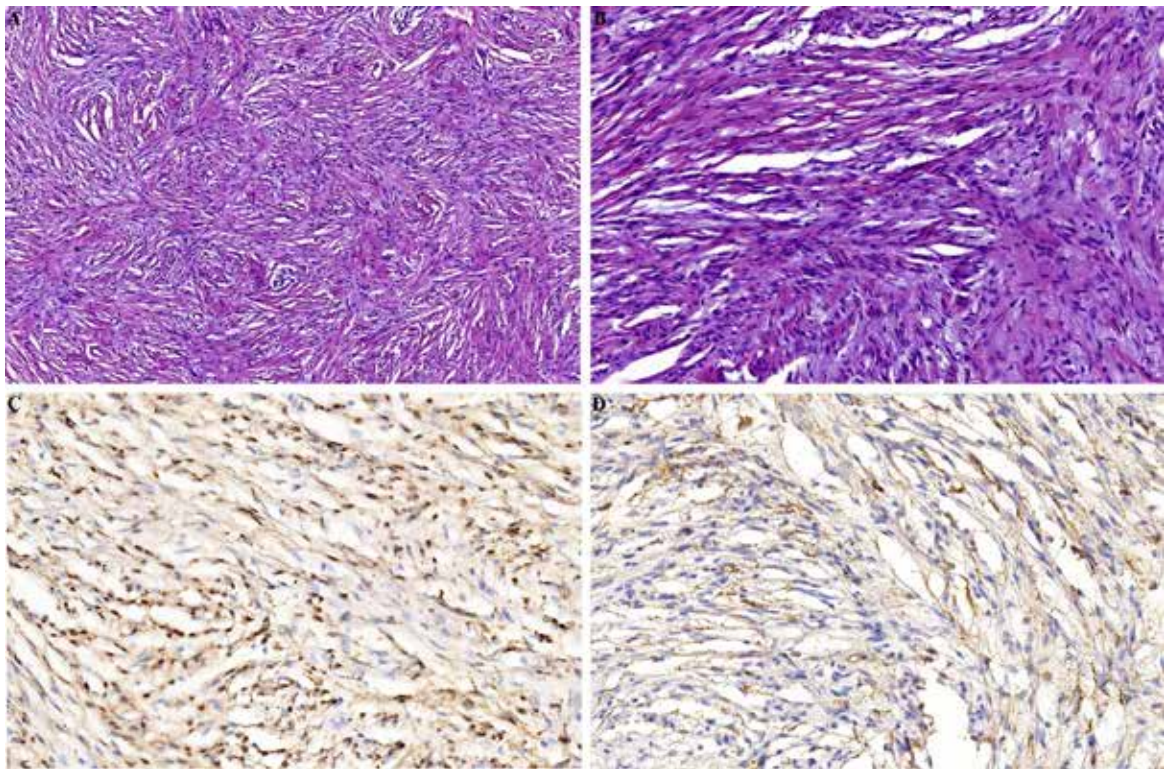


Figure 3. Hybrid neurofibroma – perineurioma. **A, B:** Different arrangement of the two components that mostly merge together imperceptibly within a lesion: individual spindled cells with wavy nuclei identical to those found in neurofibroma are closely intermingled with spindled cells with bipolar or stellate nuclei corresponding to the perineurial cell differentiation. **C:** The biphasic pattern is poorly discernible on HE-stained slides but is appreciable on immunohistochemical slides, with the spindled cells having wavy nuclei manifesting S-100 protein positivity. **D:** They are surrounded by EMA positive bipolar or stellate cells.

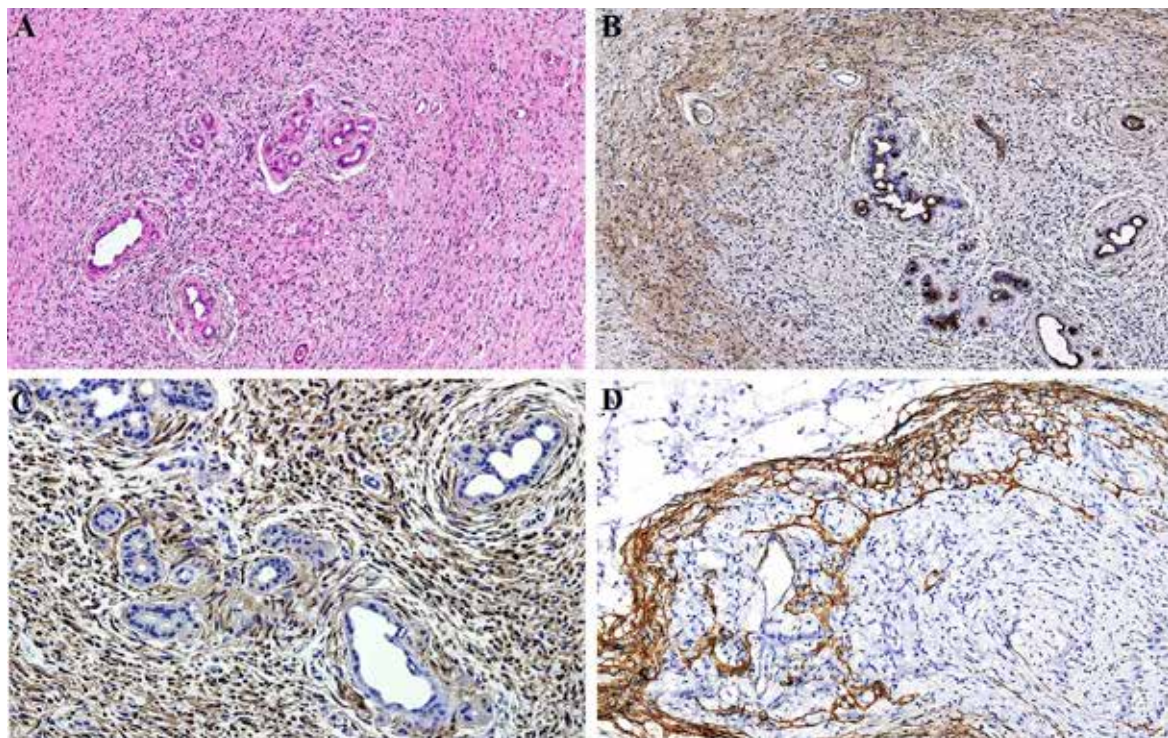


Figure 4. Hybrid neurofibroma – perineurioma in a patient with NF1. **A:** The tumors at first glance represent ordinary neurofibromas. The perineuriomatous component is admixed in a very discreet, intermingled fashion and is not apparent on H&E-stained slides. **B:** However, it is easily discernible on immunohistochemical staining with EMA. **C:** EMA negative parts are usually S100 protein positive. **D:** Several nerve fibers in the vicinity show prominent reticular networks of GLUT-1-positive perineurial cells. Among PNSTs, these intraneural lesions are restricted only to cases harboring hybrid neurofibroma - perineurioma. This finding supports the role of these intraneural lesions as precursors of hybrid neurofibroma – perineurioma.

case, areas with perineuriomatous differentiation were clearly visible on H&E-stained slides as spindled cells with bipolar or stellate nuclei arranged in short fascicles or whorls. The neurofibromatous element resembled diffuse neurofibroma and the 2 components were segregated from one another. In addition to the bland-looking neurofibromatous and perineuriomatous areas, there were multifocal hypercellular areas showing numerous mitotic figures and closely packed epithelioid and spindled pleomorphic cells arranged in nests and fascicles which were classified as features of MPNST. The neoplastic cells in the malignant areas stained for S-100 protein and were negative for EMA, GLUT-1, and Claudin-1 (15). Although neurofibroma can on rare occasion be a benign precursor to MPNST and several tumors classified as MPNST with perineurial differentiation have also been described (27-29), this was the first and so far the only case of MPNST reported in any type of HPNST.

Interesting observations regarding the relationship between hybrid neurofibromas – perineuriomas and NF1 have recently been reported by Agaimy (30). Employing immunohistochemical antibodies for perineurial differentiation (EMA, Claudin-1, GLUT-1) he analyzed histologically normal-looking nerve fibers in resections specimens harboring PNSTs from NF1 patients. Of these, several nerve fibers showed prominent reticular networks of EMA/claudin-1/GLUT-1-positive perineurial cells. These intraneural lesions were restricted practically only to cases harboring hybrid neurofibroma – perineurioma and were not present in other PNSTs. This finding supports the role of these intraneural lesions as precursors of hybrid neurofibroma - perineurioma (30). Identical intraneural proliferations of perineurial cells were also present in our series of NF1 associated hybrid neurofibromas – perineuriomas (15) (Figure 4D).

Perineuriomas have shown a pathogenic relationship to loss of NF2 gene function (8,12,13) and are generally not considered

a part of the NF1-associated spectrum of tumors. However, two case reports of perineuriomas arising in the setting of NF1 are on record (31,32). While knowing that a large proportion of HPNST is overlooked in routine practice, the findings reported by Kacerovska et al and by Agaimy suggest that tumors exhibiting perineurial cell differentiation in the setting of underlying NF1 may not be as uncommon as previously thought. Nevertheless, this by no means excludes the possibility that similarly to normal soft tissue perineuriomas, some HPNST with perineurial differentiation may still contain mutations of the NF2 gene as exemplified in the aforementioned study by Kazakov et al (18).

SCHWANNOMA – PERINEURIOMA

Quite similarly to the described examples of neurofibroma – perineurioma, the two populations found in schwannomas – perineuriomas can be either closely intermingled or occur in a segregated manner. The cells in the perineuriomatous component in the latter cases often also resemble retiform (reticular) perineurioma. As was mentioned previously, rare cases of non-hybrid PNST exist, where it is extremely difficult to precisely classify the tumor as either schwannoma or neurofibroma, an opinion shared by others as well (3,33). Accordingly, the non-perineuriomatous component in hybrid tumors can also have ambivalent features of both schwannoma and neurofibroma (18). Hence, admittedly, the final classification of HPNST as hybrid neurofibroma - perineurioma or hybrid schwannoma - perineurioma may be quite subjective in certain cases. This fact was best illustrated in the aforementioned study by Zamecnik and Michal (2). In addition to the examples of neurofibroma with focal perineuriomatous differentiation, one unique case where the latter moiety was much more prominent was identified by the authors who described this tumor as having features

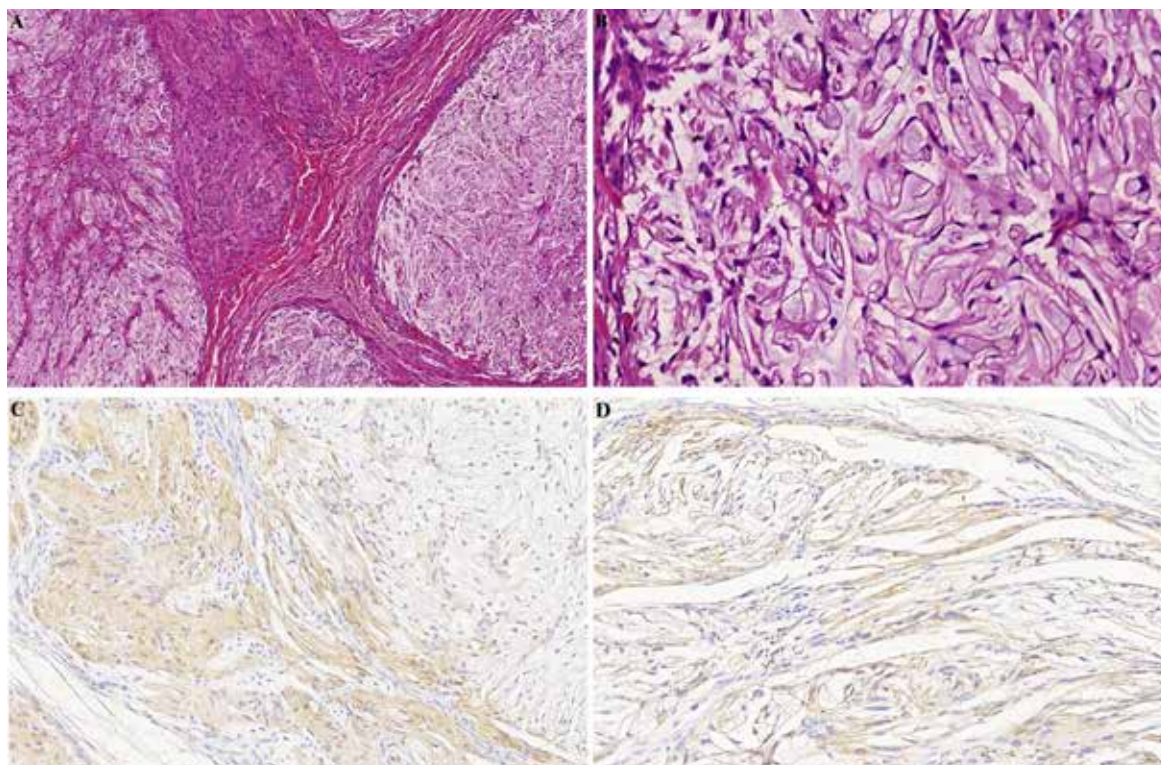


Figure 5. Hybrid schwannoma – retiform perineurioma. **A:** The lesions feature a multilobular architecture. The variably sized and shaped lobules are separated by variably thick collagenous septae. The schwannomatous component (central part) consists of elongated cells with tapered, spindled nuclei, mostly arranged in a compact Antoni A pattern and the cells, in contrast to the perineurial cells, have deeply eosinophilic cytoplasm. **B:** The perineuriomatous component has the appearance of retiform perineurioma and is EMA positive. **C:** S100 protein is positive in the schwannomatous areas and negative in the perineuriomatous parts. **D:** EMA staining of the perineuriomatous area.

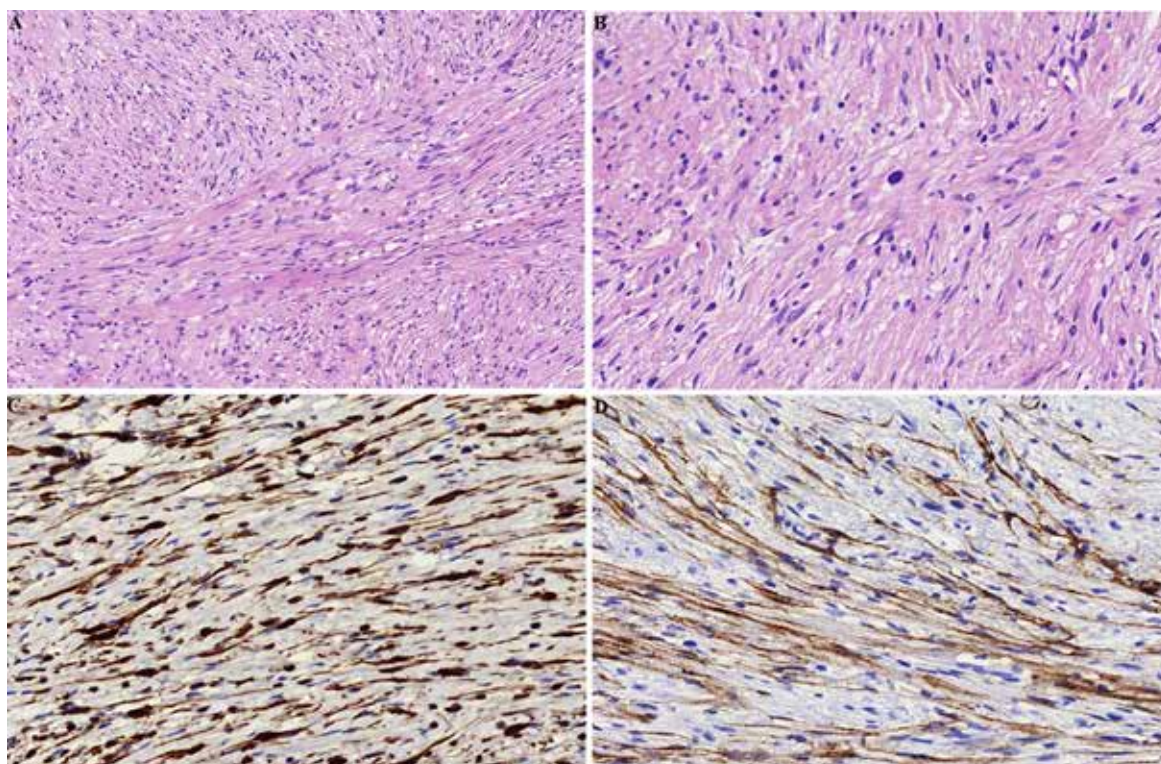


Figure 6. Hybrid schwannoma – perineurioma. **A:** On low magnification, the first impression of these tumors is rather that of a perineurioma, mainly due to the prominent storiform, lamellar and whorled growth patterns. **B:** However, on higher magnification, the dominant cytology is schwannian, with the slender, elongated perineurial cells being obscured by the more numerous and large Schwann cells. Notably, nuclear atypia in the form of scattered pleomorphic cells with hyperchromatic, smudged nuclei is often present and does not herald malignant behavior in such cases. **C:** By IHC, the dual cell population is again readily appreciable with positive staining for S100 protein in the larger cells. **D:** Conversely, the more slender and elongated perineurial cells stain with EMA.

of both neurofibroma and retiform perineurioma. In 2004, while preparing another study on hybrid schwannomas - retiform perineuriomas, this case was re-reviewed by the authors and together with five other similar cases, it was immunohistochemically studied for the presence of neurofilament protein and CD34 expression, which label axons and fibroblasts in neurofibromas respectively (5). The nonperineuriomatous parts of all tested tumors were found to be devoid of axons, and only a few CD34-positive cells were detected. Based upon these findings the tumor was reclassified as hybrid schwannoma – perineurioma (34), thus representing the first published example of this kind. Overall, this tumor as well as all other 5 lesions included in the study occurred on the hands, with a predilection for the fingers. Importantly, no association with any syndrome was noted. Microscopically, the lesions featured a multilobular architecture. The variably sized and shaped lobules were separated by variably thick collagenous septae (Figure 5A). The schwannomatous component (Figure 5C; S-100 protein +/EMA and CD34 -) consisted of elongated cells with tapered, spindled nuclei, mostly arranged in a compact Antoni A pattern and the cells, in contrast to the perineurial cells, had deeply eosinophilic cytoplasm (Figure 5A). The perineuriomatous component had the appearance of retiform perineurioma (Figure 5B) and was S-100 protein/CD34 negative and EMA positive (Figure 5D). These two components either formed separate nodules or the schwannomatous tissue surrounded the perineurial parts located in the centers of the lobules (Figure 5A) (34).

The largest series of hybrid schwannomas – perineuriomas was published by Hornick et al, first in an abstract form at the annual USCAP meeting in 2004 (35), and then, several years later, as a full article (21). Unlike the previous studies on this topic, the authors presented tumors composed purely of an intimate

admixture of the two cell types. The tumors showed a wide anatomic distribution, and no association with NF1 was recorded, both findings being confirmed later in an additional study on this topic by different authors (36). Microscopically, on low magnification, the first impression of these tumors was that of perineurioma, mainly due to the prominent storiform, lamellar and whorled growth patterns (Figure 6A). However, on higher magnification, the dominant cytology was schwannian, with the slender, elongated perineurial cells being obscured by the more numerous and large Schwann cells. Notably, degenerative nuclear atypia in the form of scattered pleomorphic cells with hyperchromatic, smudged nuclei was present in one quarter of the cases (Figure 6B) (21). By IHC, the dual cell population was again readily appreciable. Using the elegant method of double immunostaining, the authors clearly illustrated that these tumors are composed of two separate populations of cells arranged in parallel arrays. Usually constituting 60-70% of the lesion, the larger cells were stained with S100 protein (Figure 6C), whereas the second type of cell expressed the EMA antibody (Figure 6D). Although practically all the cases were diffusely labeled with CD34, the authors did not interpret this feature as fibroblastic staining. Instead, they concluded, that this staining was present in the perineurial cells, a feature that may occur in more than 50% of perineuriomas (22).

Included in this series and also reported earlier in a separated case report (37) was hybrid schwannoma – perineurioma occurring in the colon, the first ever reported HPNST of the GI tract. Later, additional GI cases were reported in other parts of the GI tract (36,38). All lesions were morphologically analogous to the schwannoma – perineurioma of soft tissue as described by Hornick et al (21), thus having features very different from conventional GI schwannomas. The differentiating traits include dif-

ferent growth patterns, an absence of peripheral lymphoid cuff, more prominent and diffuse CD34 expression and the presence of alternating fascicles of schwannian and perineurial cells, as again confirmed by double immunostaining (38).

Finally, very recently, Kacerovska et al. reported a case where the schwannomatous moiety showed prominent epithelioid features and was thus classified as hybrid epithelioid schwannoma – perineurioma. These epithelioid cells were arranged singly or in small aggregates or short cords and although closely admixed, due to the larger size of the Schwann cells in this case, the biphasic composition was well apparent already on the H&E-stained slides (20).

SCHWANNOMA - NEUROFIBROMA - PERINEURIOMA

As repeatedly discussed in this review, some tumors are remarkably difficult to fit not only into one specific category of schwannoma, neurofibroma or perineurioma, but even into the various categories of hybrid tumors. One tumor, arising on a sporadic basis and classified as a hybrid tumor containing all three PNST types was reported in the nasopharyngeal area by Kuroda et al (39). Another such lesion was encountered in a patient with NF1 and is illustrated in the Figure 8 in the review by Rodriguez et al (40). Furthermore, as mentioned in one of our publications (15), due to the quite pronounced and illustrated presence of perineurial cells in some cases reported by Harder et al (11), some of them might in fact represent HPNST containing neurofibromatous, schwannomatous, and perineuriomatous differentiation. However, admittedly, at present no quantitative criteria for such a classification exists.

CONCLUSION

The research of HPNST has yielded several important findings, especially with respect to the clinical management of the patients and their kindred. Hybrid neurofibromas – schwannomas show a very strong association with NF2 and schwannomatosis and, to a lesser degree, with NF1. It is important not to confuse these tumors with a malignant transformation in neurofibroma. NF1 may further provide the genetic background for the development of neurofibromas – perineuriomas. Attention must be paid to accurately interpret the non-perineuriomatous part of these tumors and not to mistake them for schwannomas – perineuriomas which seem to be non-syndromic tumors. However, occasionally, the distinction may be extremely difficult and there seem to be rare cases, where all three components can coexist in one specimen. Further research, especially with respect to the genetic background of these tumors is needed, as the exact molecular events occurring in these tumors remain largely unknown.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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