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 popsanými 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 kompexní 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 present. 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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