

NERVE SHEATH MYXOMA WITH BIDIRECTIONAL SCHWANNOMATOUS AND PERINEURAL DIFFERENTIATION

Zámečník M., Sedláček T.

Medicyst, s.r.o., laboratory Trenčín, Slovak Republic

Summary

A case of nerve sheath myxoma occurring in occipital region in 70-yr-old woman is presented. The tumor showed typical lobular and myxoid morphology. Immunohistochemically, it showed unusual coexpression of Schwann cell markers S100 protein and GFAP with perineural cell markers EMA and claudin-1. CD34+ fibroblast-like cells were scarce, and nerve axons were not found in the tumor. Clinical pathology and histogenesis of the lesion are discussed.

Key words: nerve sheath myxoma – perineurioma – schwannoma – epithelial membrane antigen – S100 protein

Súhrn

Myxóm nervového púzdra (nerve sheath myxoma) so schwannómovou a perineurálnou diferenciáciou

Prezentovaný je prípad myxómu nervového púzdra u 70-ročnej pacientky v okcipitálnej oblasti. Tumor mal typickú lobulárnu a myxoidnú morfológiu tejto zriedkavej jednotky. Neobvyklá bola difúzna koexpresia markerov Schwannových buniek S100 proteínu a GFAP a perineurálnych markerov EMA a claudin-1. CD34+ fibroblastické bunky boli málo početné a nervové axóny neboli v tumore nájdené. Diskutovaná je klinická patológia a histogenéza lézie.

Kľúčové slová: myxóm nervového púzdra – perineurióm – schwannóm – epitelový membránový antigén – S100 protein

Čes.-slov. Patol., 46, 2010, No. 3, p. 73–76

Nerve sheath myxoma (NSM) (6, 9) is a rare cutaneous/subcutaneous tumor that occurs mostly in middle aged adults on the extremities. Since its original description by Harkin and Reed (9), the lesion was reported under various names, including neurotheceoma (2, 7, 18, 24), cutaneous lobular neuromyxoma (10), myxomatous perineurioma (2, 22), bizarre cutaneous neurofibroma (14), myxoma of nerve sheath (2, 9), and dermal nerve sheath myxoma (19). This variability in nomenclature reflects well the doubts on histogenesis of the tumor. NSM is typically S100 protein positive whereas perineural cell marker EMA is absent or it stains only rare cells. Therefore, most of authors favor close relationship to schwannoma or to neurofibroma (2, 6, 9, 10, 14, 17-19, 21-23). We present an additional case of morphologically typical nerve sheath myxoma that shows, however, an unusual coexpression of Schwann cell and perineural markers. The case indicates that nerve sheath

myxoma can possess bidirectional schwannomatous-perineural differentiation.

MATERIALS AND METHODS

The tissue of the excised tumor was fixed in 4% formalin and processed routinely. The sections were stained with hematoxylin and eosin and Bodian stain for nerve axons. Primary antibodies used for immunohistochemistry are listed in **Table 1**. Immunostaining was performed according to standard protocols using avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Microwave antigen pretreatment was performed prior to applying the primary antibodies. Appropriate positive and negative controls were applied.

Table 1. Antibodies used in the study

Antibody	Clone	Dilution	Source
ASMA	1A4	1:1000	DakoCytomation
CD34	Qbend10	1:800	Novocastra Lab.
claudin-1	poly	1:50	Zymed
cytokeratins	AE1-AE3	1:200	Boehringer
desmin	D33	1:3000	DakoCytomation
EMA	E29	1:700	DakoCytomation
GFAP	poly	1:3000	DakoCytomation
NFP	2F11	1:1000	DakoCytomation
S100 protein	S1/61/69	1:50	Novocastra Lab

ASMA – alpha smooth muscle actin, EMA – epithelial membrane antigen, GFAP – glial fibrillary acidic protein, NFP – neurofilament protein, poly – polyclonal

REPORT OF THE CASE

A 70-yr-old woman presented with superficial tumor in the occipital area. The tumor was excised completely and submitted to histologic examination. No recurrence was observed 24 months after the excision. The patient had no sign of neurofibromatosis.

villus-like structures. The septa between the myxoid lobules were paucicellular and collagenized. The spindle cells were arranged parallelly, sometimes in wavy fascicles. Their nuclei were long, fusiform and bland-appearing and they lacked prominent nucleoli. Rare lymphoplasmocytic aggregates were found in the fibrous septa. **Immunohistochemically (figure 2)**, almost all cells in the myxoid lobules expressed S100 protein (Schwann cell marker), EMA and claudin-1 (perineural cell markers) (8). GFAP stained predominantly the peripheral

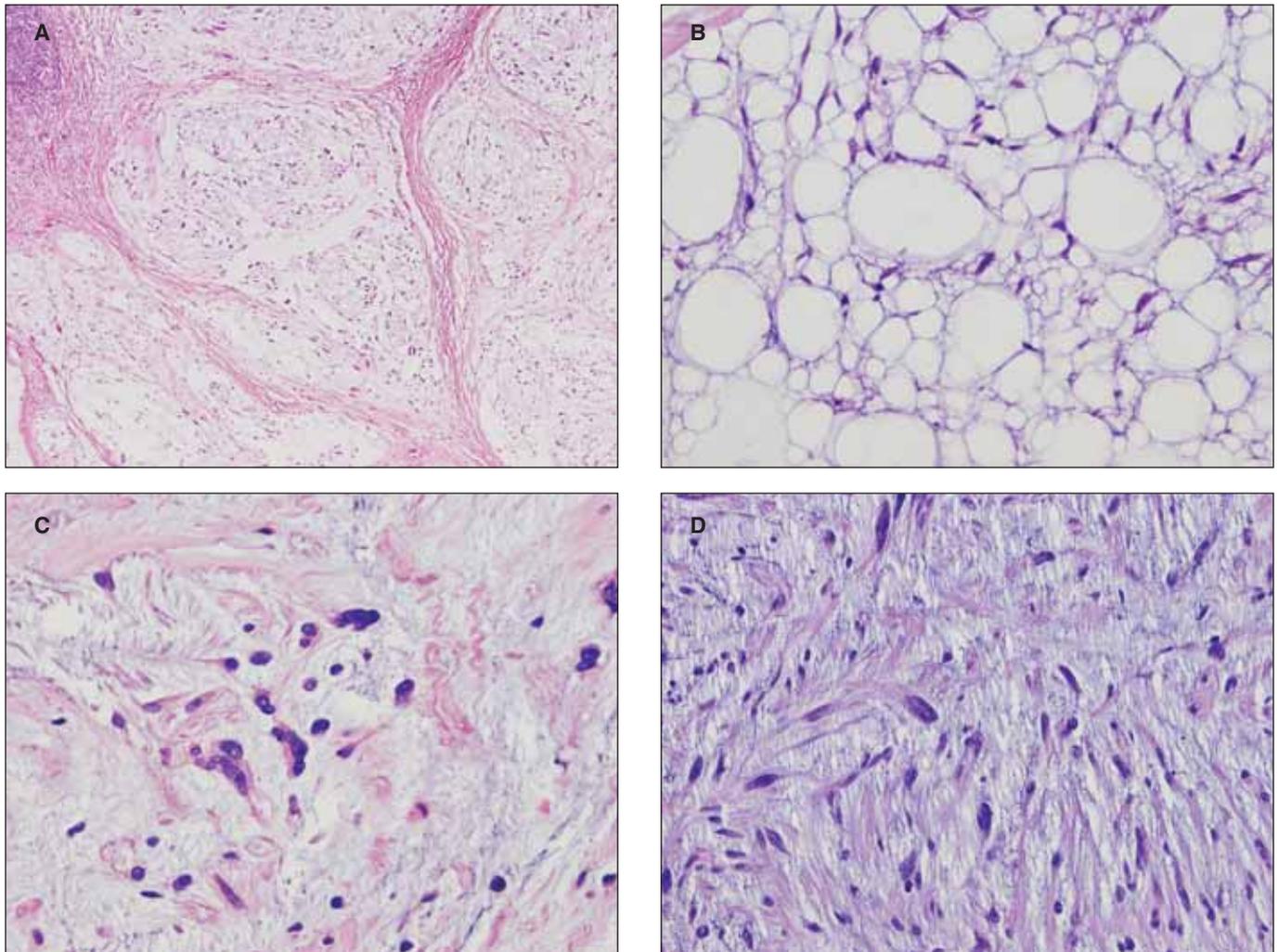


Figure 1. Histologic features of nerve sheath myxoma: (A) nodular myxoid lesion seen at low power; (B) detail of myxoid pattern with vague reticular cell arrangement; (C) plump cells with syncytial-appearing groups of cells; (D) more cellular area with mild nuclear pleomorphism and without mitoses.

Grossly, the 4x3x2cm tumor was well circumscribed, unencapsulated, and its cut surface was lobular myxomatous with fibrous septa. **Histologically (figure 1)**, the tumor was composed of myxoid lobules separated one from another by fibrous appearing septa. The cells of the lobules showed spindle to ovoid morphology. Rarely, some adjacent plump cells were connected and they created syncytial epithelium-like groups or short bands. The nuclei were ovoid, normo- to hyperchromatic, with some intranuclear inclusions and without prominent nucleoli. Rare cells were multinucleated. Mild nuclear pleomorphism with lack of mitotic activity resembled closely pseudoatypia that is commonly seen in ancient schwannomas. In some myxoid areas the interconnected processes of the tumor cells created reticular pattern with empty-appearing vacuoles in the myxoid intercellular matrix. The groups of the cells in some myxoid lobules were disconnected from surrounding tissue, creating ball-like or

zone of the lobules, and only one fifth of the cells in the central zone of the lobules. The septal cells were very rarely positive for S100, GFAP and EMA. CD34 was expressed by rare cells in both myxoid lobules and collagenized septa. Neurofilament protein and Bodian stain showed no nerve axons in the tumor.

DISCUSSION

Nerve sheath myxoma (NSM) (6, 9) is a rare tumor which occurs most often in middle aged adults in the cutaneous/subcutaneous locations. Most frequent locations are extremities followed by trunk, head and neck. Exceedingly rare cases were reported in mucosal locations and in central nervous system (17, 21, 23). In our case, the age (70 years)

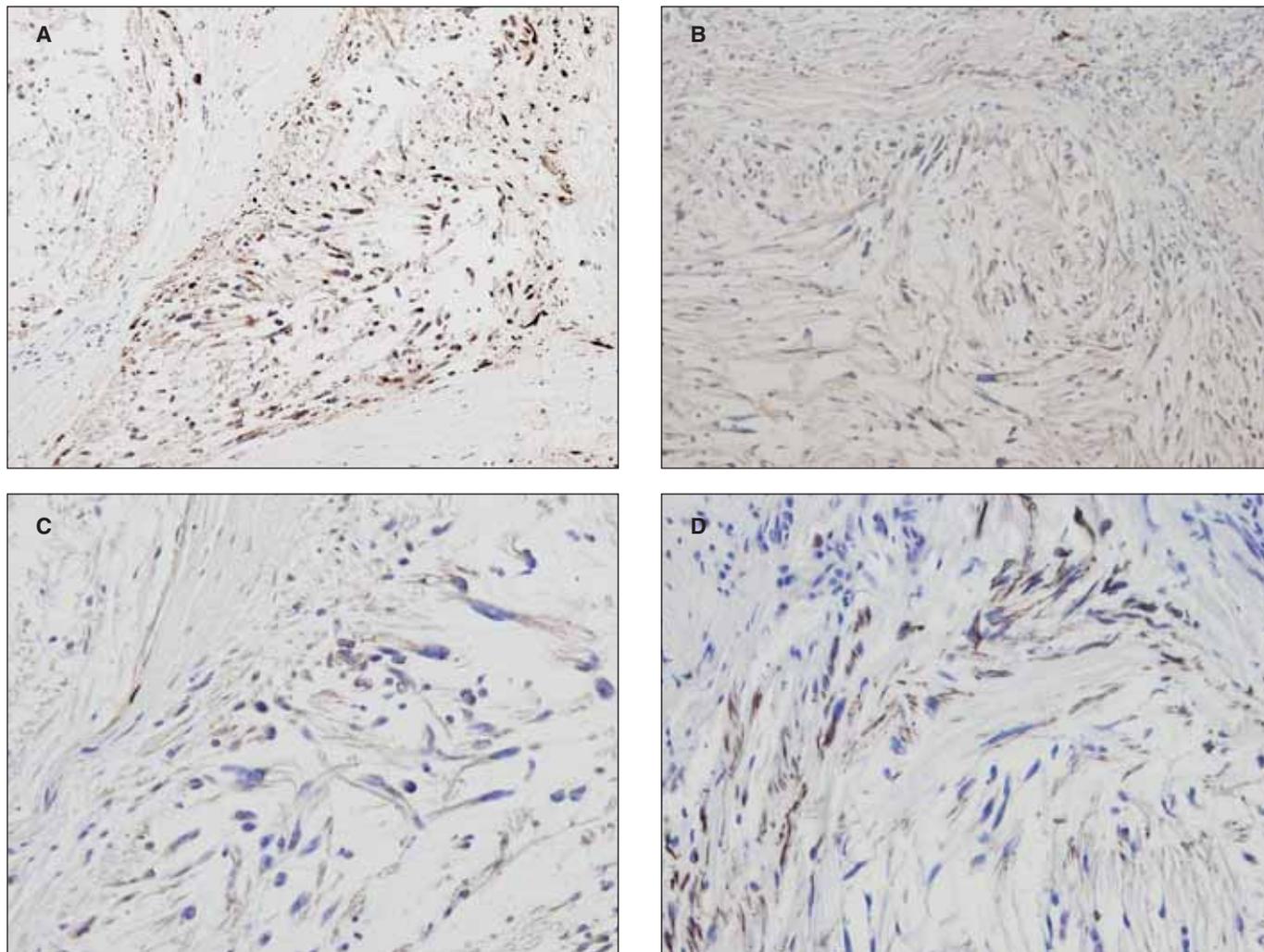


Figure 2. Immunohistochemical features. (A) S100 protein; (B) EMA positivity (includes some plasmocytic cells as an internal control); (C) claudin-1; (D) GFAP is positive in the peripheral zone of the lobule.

and location (occipital area) belong to the less frequent clinical features. However, some lesions in older patients (maximum 84 years) and in head/neck location were reported (2, 6, 17). The behavior of NSM is benign, with higher propensity for local recurrence (6, 24). In the largest published series of 57 cases with sufficient follow-up the recurrence rate was 47% (6). The recurrence occurs often after long time period, reflecting slow growth potential of the tumor. From this point of view, our recurrence free 24 month follow-up appears to be still short.

As mentioned in introduction, the histogenesis of the lesion is still disputable. There is an agreement that the tumor has certainly a phenotype of neurosustentacular cell. However, an exact differentiation and relationship to other nerve sheath lesions (especially to schwannoma and neurofibroma) is not clear. Fetsch et al. (6) in their large study favor close relationship with schwannoma, because in their series following features of schwannoma prevailed over the features of neurofibroma: well-demarcated margin, none or only rare intralesional nerve axons, sometimes vague Verocay body-like arrangement, scarcity of CD34+ fibroblast-like cells as well as of EMA+/claudin+ perineural cells, absence of association with neurofibromatosis. However, rare presence of neurofibroma features such as CD34+ neural fibroblasts, some EMA+/claudin+ perineural cells and nerve axons were observed. Therefore, the authors state that future molecular studies are needed for decision on histogenesis of NSM. In our case, diffuse EMA reactivity synchronous with positivity for S100 protein appears unusual. It indicates that the neoplastic

cells show features of both schwannomatous and perineural differentiation. Such cells are not present in physiologic condition. In neurofibromas, however, such cells were already described in the ultrastructural study by Erlandson (3). This author found in neurofibromas, in addition to typical Schwann cells, perineural cells and fibroblasts, also some "transitional" or "intermediate" forms among these three main cell types, including cells with features of both Schwann cell and perineural cell. It is probable that such hybrid cells are a result of differentiation of a single neoplastic cell. Such view is supported by study of tissue culture that showed similar variable differentiations in the cells originating from neoplastic Schwann cells (13). The line of differentiation is influenced by inherent differentiating property of the neoplastic cells as well as by some environmental factors.

Differential diagnosis in our case included plexiform schwannoma (7), neurofibroma (3, 25), perineurioma (15), mixed neurothekeoma with myxoid change (5), and superficial angiomyxoma (1). In addition, the differential diagnosis includes following recently described variants of nerve sheath tumors which contain Schwann cells, perineural cells and fibroblasts in various proportion: hybrid retiform perineurioma-schwannoma (16), hybrid schwannoma-perineurioma (12, 25), hybrid perineurioma-neurofibroma (12, 20) and hybrid schwannoma-neurofibroma (4).

Plexiform schwannoma (7) can be myxoid, but it shows always, at least focally, a non-myxoid compact-appearing Antoni A pattern. Neurofibroma is occasionally myxoid and it

can contain EMA+ cells in addition to S100+ cells (25). However, it is not so strictly lobular and well-demarcated as NSM. The cells of neurofibroma are more subtle and uniform, with thin wavy nuclei, and the intercellular fibers are more delicate. In addition, nerve axons and numerous CD34+ cells are commonly present in these lesions. Hybrid retiform perineurioma-schwannoma shows very similar and overlapping morphology with our case. This tumor described recently by Michal et al. (16) is composed of myxoid nodules with reticular arrangement of perineural EMA+/S100- cells. In peripheral zone of these nodules is S100+/EMA- non-myxoid spindle cell population of Schwann cells. Thus, the EMA- and S100- expressions show distinct zonal arrangement different from that seen in our case. In addition, all described tumors were restricted to acral sites. Although these mentioned differences exist, they are quite subtle, and therefore we feel that hybrid retiform perineurioma-schwannoma can be closely related to our case of NSM. Other hybrid nerve sheath tumors containing Schwann cells, perineural cells and fibroblasts have their components intermingled and the architecture of the lesions is not so clearly lobular as that of NSM (4, 12, 20, 25).

Superficial angiomyxoma (cutaneous myxoma) (1) is, like NSM, multinodular and myxoid, and it is also composed of spindle cells. However, superficial angiomyxoma lacks peripheral fibrous reaction and shows no expression of nerve sheath markers S100, GFAP and EMA. It can express CD34 and actin. Cellular and mixed neurothekeoma with prominent myxoid change shows nodular architecture similar to NSM. Until recently this entity was classified together with NSM in one group of neurothekeomas. However, immunophenotype of these tumors is according to new studies S100 and GFAP negative, or S100 protein expression is restricted to only a few dendritic cells. The tumors expressed NK1/C3, CD10, microphthalmia transcription factor, and PGP9.5, and sometimes smooth muscle actin and CD68, indicating that they do not represent nerve sheath lesions. They fall in the category (myo)fibrohistiocytic lesions, with close resemblance to low-grade plexiform fibrohistiocytic tumor (11). Fetsch et al. propose for them designation "superficial micronodular (myxo/myo)fibroblastoma" rather than "cellular/mixed neurothekeoma"(5).

In conclusion, we reported morphologically typical NSM with unusual coexpression of Schwann cell markers (S100 protein, GFAP) and perineural markers (EMA, claudin-1) indicating bidirectional schwannomatous and perineural differentiation. The finding can reflect, together with other overlapping features in the group of the nerve sheath tumors, a common origin of these lesions from neoplastic nerve sheath cell that is capable to differentiate toward various lines under the influence of microenvironmental and/or genetic intrinsic factors. Pathologist should be aware of the possible EMA and/or claudin-1 expression in NSM, to render correct diagnosis, as the lesion is clinically different from other nerve sheath tumors especially regarding its high tendency for local recurrence and lack of association with neurofibromatosis.

REFERENCES

- Allen P.W., Dymock R.B., MacCormac L.B.: Superficial angiomyxoma with and without epithelial components. Report of 30 tumors in 28 patients. *Am. J. Surg. Pathol.* 12, 1988, p. 519–30.
- Argenyi Z.B., LeBoit P.E., Santa Cruz D., et al.: Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. *J. Cutan. Pathol.* 20, 1993, p. 294–303.
- Erlandson R.A.: The enigmatic perineurial cell and its participation in tumors and in tumorlike entities. *Ultrastruct. Pathol.* 15, 1991, p. 335–51.
- Feany M.B., Anthony D.C., Fletcher C.D.: Nerve sheath tumours with hybrid features of neurofibroma and schwannoma: a conceptual challenge. *Histopathology* 32, 1998, p. 405–10.
- Fetsch J.F., Laskin W.B., Hallman J.R., et al.: Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. *Am. J. Surg. Pathol.* 31, 2007, p. 1103–14.
- Fetsch J.F., Laskin W.B., Miettinen M.: Nerve sheath myxoma: a clinicopathologic and immunohistochemical analysis of 57 morphologically distinctive, S-100 protein- and GFAP-positive, myxoid peripheral nerve sheath tumors with a predilection for the extremities and a high local recurrence rate. *Am. J. Surg. Pathol.* 29, 2005, p. 1615–24.
- Fletcher C.D., Davies S.E.: Benign plexiform (multinodular) schwannoma: a rare tumour unassociated with neurofibromatosis. *Histopathology* 10, 1986, p. 971–80.
- Folpe A.L., Gown A.M.: Immunohistochemistry for analysis of soft tissue tumors. In: Weiss & Goldblum: *Enzinger and Weiss's Soft Tissue Tumors*, 4th ed., Mosby Inc., St. Louis, USA, 2001, p. 199–246.
- Harkin J.C., Reed R.J.: Solitary benign nerve sheath tumors. In: Firminger HJ, ed. *Atlas of Tumor Pathology, Tumors of the Peripheral Nervous System*, 2nd series. Washington, DC: Armed Forces Institute of Pathology, 1969, p. 60–64.
- Holden C.A., Wilson-Jones E., MacDonald D.M.: Cutaneous lobular neurofibroma. *Br. J. Dermatol.* 106, 1982, p. 211–5.
- Jaffer S., Ambrosini-Spaltro A., Mancini A.M., et al.: Neurothekeoma and plexiform fibrohistiocytic tumor: mere histologic resemblance or histogenetic relationship? *Am. J. Surg. Pathol.* 33, 2009, p. 905–13.
- Kazakov D.V., Pitha J., Sima R., et al.: Hybrid peripheral nerve sheath tumors: Schwannoma-perineurioma and neurofibroma-perineurioma. A report of three cases in extradigital locations. *Ann. Diagn. Pathol.* 9, 2005, p. 16–23.
- Kharbanda K., Dinda A.K., Sarkar C., et al.: Cell culture studies on human nerve sheath tumors. *Pathology* 26, 1994; p. 29–32.
- King D.T., Barr R.J.: Bizarre cutaneous neurofibromas. *J. Cutan. Pathol.* 7, 1980, p. 21–31.
- Lazarus S., Trombetta L.: Ultrastructural identification of a benign perineurial cell tumor. *Cancer* 41, 1978; p. 1823–1829.
- Michal M., Kazakov D.V., Belousova I., et al.: A benign neoplasm with histopathological features of both schwannoma and retiform perineurioma (benign schwannoma-perineurioma): a report of six cases of a distinctive soft tissue tumor with a predilection for the fingers. *Virchows Arch.* 445, 2004, p. 347–53.
- Pal L., Bansal K., Behari S., et al.: Intracranial neurothekeoma: a rare parenchymal nerve sheath myxoma of the middle cranial fossa. *Clin. Neuropathol.* 21, 2002, p. 47–51.
- Papadopoulos E.J., Cohen P.R., Hebert A.A.: Neurothekeoma: report of a case in an infant and review of the literature. *J. Am. Acad. Dermatol.* 50, 2004, p. 129–34.
- Pulitzer D.R., Reed R.J.: Nerve-sheath myxoma (perineurial myxoma). *Am. J. Dermatopathol.* 7, 1985, p. 409–21.
- Shelekhova K.V., Danilova A.B., Michal M., et al.: Hybrid neurofibroma-perineurioma: an additional example of an extradigital tumor. *Ann. Diagn. Pathol.* 12, 2008, p. 233–4.
- Schortinghuis J., Hille J.J., Singh S.: Intraoral myxoid nerve sheath tumour. *Oral. Dis.* 7, 2001, p. 196–9.
- Webb J.N.: The histogenesis of nerve sheath myxoma: report of a case with electron microscopy. *J. Pathol.* 127, 1979, p. 35–7.
- Wong B.Y., Hui Y., Lam K.Y., Wei W.I.: Neurothekeoma of the paranasal sinuses in a 3-year-old boy. *Int. J. Pediatr. Otorhinolaryngol.* 62, 2002, p. 69–73.
- Woo E.K., Lim T.K., Tan S.H.: Neurothekeomas of the upper limb: case series and clinicopathological review. *Hand Surg.* 10, 2005; p. 311–7.
- Zamecnik M., Michal M.: Perineurial cell differentiation in neurofibromas. Report of eight cases including a case with composite perineurioma-neurofibroma features. *Pathol. Res. Pract.* 197, 2001, p. 537–44.

Correspondence address:

M. Zamecnik, M.D.

Medicyt, s.r.o.

Legionarska 28

911 71 Trencin

Slovak Republic

E-mail: zamecnikm@seznam.cz

Phone: +421-32-3936956