Mediastinal ganglioneuroma with perineural cell differentiation. Report of a case

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SUMMARY
An unusual case of ganglioneuroma with perineural cell differentiation is presented. The tumor was removed from the mediastinum in a 34-year-old male patient. Histologically, it contained neuroid bundles of bland spindle cells, scattered ganglion cells, and some foci of adipocytic metaplasia. Immunohistochemically, the tumor showed expected expressions of S100 protein, neurofilament protein and calretinin. In addition, many spindle cells were positive for perineural cell markers EMA, claudin-1, and GLUT-1. These cells were often arranged in an organoid fashion around the schwannoid bundles. This case indicates that the cells of ganglioneuroma can mature simultaneously towards both Schwann cell and perineural cell phenotypes.

Keywords: ganglioneuroma – perineurioma – EMA – claudin-1 – GLUT-1

Ganglioneuróm s perineurálnou diferenciáciou. Kazuistika

SÚHRN
Prezentovaný je prípad ganglioneurómu s neobvyklou perineurálnou diferenciáciou. Jednalo sa o tumor mediastína u 34-ročného muža. Histologicky obsahoval neuroidné zväzky blandných vretenovitých buniek, zrelé gangliové bunky a ložiskovú adipocytárnu metapláziu. Imunohistochemicky vykazoval tumor očakávané expresie S100 proteinu, kalretinínu a neurofilament proteinu. Prekvapujúcou bola pozitivita početných buniek na perineurálne markery EMA, klaudín-1 a GLUT-1. Jednalo sa často o bunky v organoidnom usporiadaní okolo S100-pozitívnych schwannoidných zväzkov. Prezentovaný prípad ukazuje, že elementy ganglioneurómu sa môžu diferencovať do fenotypu bunky Schwannovej i perineurálnej.

Kľúčové slová: ganglioneuróm – perineurióm – EMA – claudin-1 – GLUT-1

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Ganglioneuroma is a benign neoplasm composed of ganglion cells and neuroid spindle cells, occurring usually in adults, and most often located in the posterior mediastinum and retroperitoneum (1). It arises through maturation of neuroblastoma (2,3) or de novo (1). Ultrastructurally, the spindle cell component contains mostly Schwann cells (1). Rare ultrastructural studies have found, in addition to a Schwann cell population, some cells with the features of the perineural cell type (4,5). However, immunohistochemical expression of perineural cell markers such as epithelial membrane antigen (EMA), claudin-1 and GLUT-1 has not yet been described in this type of tumor to our knowledge and according to our literature search. Here, we would like to present a case of ganglioneuroma, in which a well-developed perineural cell component with the expression of perineural cell markers EMA, claudin-1 and GLUT-1 was found (6–8).

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MATERIAL AND METHODS

The tissue of the tumor was fixed in 10% formalin and processed routinely. The sections were stained with hematoxylin and eosin. For immunohistochemistry, the following primary antibodies were used: S100 (polyclonal, 1:400), alpha-smooth muscle actin (clone 1A4, 1:1000), desmin (clone D33, 1:3000), neurofilament protein (clone 2F11, 1:1000), GLUT-1 (polyclonal, 1:200), GFAP (polyclonal, 1:3000), EMA (clone E29, 1:700) (all from DAKO, Glostrup, Denmark), calretinin (clone 5A5, 1:100, Novocastra Lab., Newcastle upon Tyne, UK), claudin-1 (polyclonal, 1:50, Zymed, San Francisco, USA), CD34 (clone Qbend/10, 1:800, Novocastra Lab., Newcastle upon Tyne, UK).

Immunostaining was performed according to standard protocols using an avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Appropriate positive and negative controls were applied.

CASE REPORT

In a 34-year-old male patient, a tumor of the posterior mediastinum detected on CT was removed surgically.

Grossly, the tumor tissue was obtained in four fragments which measured together 7.5x5x4cm. The fragments from the marginal

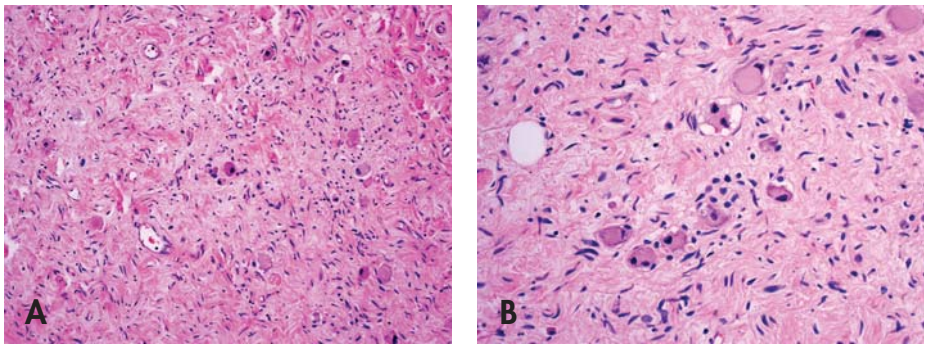

Fig. 1. Ganglioneuroma with perineural cell differentiation. The tumor shows typical neuroid stroma and ganglion cells (HE, original magnifications x60 (**A**) and x160 (**B**)).

zone of the tumor showed a thin capsule. The cut surface of the tissue was grayish-white and fibrous in appearance.

Histologically (Fig. 1), the tumor was composed of irregular neuroid bundles of bland spindle cells with elongated or wavy nuclei and without visible nucleoli. Throughout this neuromatous background, easily visible ganglion cells were scattered. They were seen as isolated cells or in small cell clusters. Some of the ganglion cells were binucleated, and some of them showed degenerative vacuolization or calcification. A few larger interstitial dystrophic calcifications were seen in the tumor. In addition the lesion contained some areas of adipocytic metaplasia that comprised 10 % of the tumor volume. Melanin pigment was not observed in the tumor cells.

Immunohistochemically (Fig. 2), ganglion cells expressed strongly neurofilament protein, calretinin and S100 protein (Figs. 2A and 2B). The spindle cells were positive for S100 protein and GFAP. Neurofilament protein and calretinin immunoreactions highlighted also numerous axons in the neuroid stroma. In addition to these expected expressions, numerous spindle cells were positive for perineural cell markers EMA, claudin-1 and GLUT-1 (Figs. 2C–E). These cells were often arranged in organoid fashion around the schwannoid bundles. CD34 stained a few spindle cells. Myoid markers actin and desmin were negative.

DISCUSSION

The morphology and immunophenotype of the present tumor is typical of ganglioneuroma, mature subtype (1). In addition, our immunohistochemical finding of an expression of perineural cell markers indicates the unquestionable presence of perineural cells in the tumor.

The histogenesis of these cells is unclear. For stromal cells in ganglioneuroma, the following three possible origins are considered (5): 1) neuroblastoma cells are capable of differentiating along neuronal and stromal lines; 2) stromal cells are formed by differentiation of ubiquitous (non-neoplastic) mesenchymal cells in response to the formation of neuritic processes; 3) nerve sheath cells in the surrounding tissues are induced to proliferate and migrate into the tumor. We believe that stromal cells of ganglioneuroma can arise from an immature neuroblastoma cell that is capable of differentiating terminally toward various lines, including the perineural cell line seen in the present case. This appears to be analogical with cells of "mixed" nerve sheath tumors in which such various lines of differentiation have already been described, for example neurofibroma-schwannoma (9), schwannoma-perineurioma, neurofibroma-perineurioma (10), nerve sheath myxoma (11), and neurofibroma with perineural cells (12,13).

In summary, our case indicates that ganglioneuroma can show also perineural cell differentiation with immunohistochemical expressions of corresponding markers. These expressions (especially of EMA) can be unexpected in ganglioneuroma, but they should not alter the diagnosis. The positivity for perineural cell markers indicates that neuroid stroma of ganglioneuroma is more similar to neurofibroma than to schwannoma.

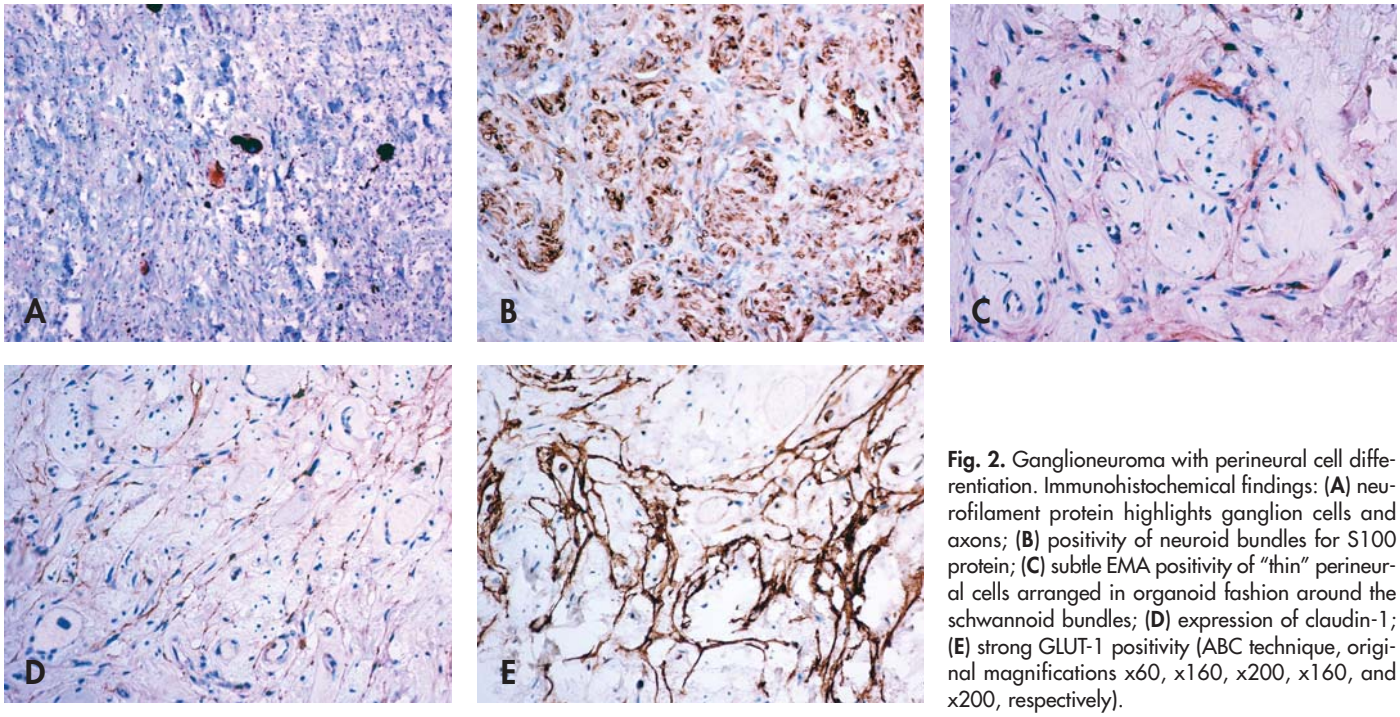

Fig. 2. Ganglioneuroma with perineural cell differentiation. Immunohistochemical findings: (**A**) neurofilament protein highlights ganglion cells and axons; (**B**) positivity of neuroid bundles for S100 protein; (**C**) subtle EMA positivity of "thin" perineural cells arranged in organoid fashion around the schwannoid bundles; (**D**) expression of claudin-1; (**E**) strong GLUT-1 positivity (ABC technique, original magnifications x60, x160, x200, x160, and x200, respectively).

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■ HEMATOPATOLOGIE

... lymfoproliferatívne ochorenia GIT – pragmatický návod ako na ne

Gastrointestinálny trakt (GIT) je najčastejším miestom výskytu extranodálnych lymfómov, pričom ich spektrum je pomerne široké a zahŕňa lymfómy B- aj T- pôvodu. Najčastejším typom je difúzny veľkobunkový B-lymfóm (DLBCL), nasledovaný extranodálnym lymfómom z buniek marginálnej zóny typu MALT, ktorý je však najčastejší v žalúdku.

S rozvojom endoskopických metód a rozšírením najmä H. p. pozitívnych gastritíd, ktoré sú často prekurzorom tohto typu nádorovej lymfoproliferácie, je vyšetrovanie endoskopických biopsií GIT-u denným chlebíkom väčšiny rutínnych patológov. Hoci kritériá pre odlíšenie reaktívnej lymfoidnej hyperplázie a nádorovej lymfoproliferácie boli spolu s koncepciou lymfatického tkaniva asociovaného so sliznicou (MALT) vypracované a akceptované už 80-tych rokoch minulého storočia, najmä endoskopické biopsie nás stále nútia kráčať po tenkom ľade medzi nenádorovou a nádorovou lymfoproliferáciou, ktorej určenie je aj za pomoci najnovších metód vrátane prietokovej cytometrie a molekulárnej genetiky niekedy viac než obtiažne.

Preto ma osobne veľmi potešil nižšie uvedený článok, ktorý svojim rozsahom neumožňuje krátku recenziu v našom Monitore, ale je voľne dostupný v pdf formáte so skvelými obrázkami (www.archivesofpathology.org/doi/abs/10.5858/arpa.2011-0145-RA), a preto ho vrele doporučujem do Vašej pozornosti ako užitočnú pomôcku v našom každodennom „trápení".

Zdroj:
Burke JS. Lymphoproliferative disorders of the gastrointestinal tract. A review and pragmatic guide to diagnosis. ***Arch Pathol Lab Med*** 2011; 135: 1283–1297.

– P. Szépe –

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