Case Report
Intraneural malignant perineurioma: a case report and review of literature

Yong Huang1, Hongwei Li1, Zhengwen Xiong1, Rui Chen2

1Department of Pathology, 251 Hospital of PLA, Zhangjiakou, China; 2Department of Pathology, Chongqing Cancer Institute, Chongqing, China

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Abstract: The great majority of malignant peripheral nerve sheath tumors (MPNSTs) exhibit Schwann differentiation. Few MPNSTs with perineurial differentiation are also named malignant perineuriomas. Benign perineuriomas were classified as intraneural, extraneural (soft tissue), sclerosing, and reticular variant. Histopathological features of intraneural perineurioma are individual nerve axons surrounded by whorls of spindle-shaped cells arranged in an onion bulb-like pattern. However, intraneural malignant perineurioma is uncommon, its characteristic histological features were not clearly described yet. Positive for epithelial membrane antigen (EMA), glut-1 and claudin-1, is characteristic of malignant perineurioma. Herein, we report an intraneural malignant perineurioma in median nerve of a 13-year-old girl. The clinicopathological features were summarized and the related literatures were reviewed.

Keywords: Malignant perineurioma, median nerve

Introduction
Peripheral nerve sheath tumors include schwannomas, which arise from Schwann cells; neurofibromas comprising Schwann cells, fibroblasts and endoneurial cells and perineuriomas that display perineural differentiation. Immunohistochemically, schwannomas are diffusely S100 positive, neurofibromas show variable S100 and CD34 positivity and perineuriomas are diffusely epithelial membrane antigen (EMA) positive. Whereas malignant peripheral nerve sheath tumors (MPNST) display variable schwannian differentiation, few MPNSTs with perineurial differentiation, also named malignant perineurioma (MP) or perineurial MPNST, have been documented [1]. MP mostly occurs at soft tissue, and rarely involved the nerve. Herein we encountered a specific case arising in median nerve, and no perineural tissue involved. After initial operation, the tumor recurred twice. Further pathological characteristics of this disease are discussed.

Case report
A 13-year-old girl was referred to our hospital for pain and anesthesia of the left hand for 4 months. Physical examination revealed slightly swelling in her left arm of middle part. Touching revealed an approximately 4 cm mass beneath the dermis. The mass was solid, firm. On operation, a fusiform expansion, 4 cm in length was located in the left median nerve. The epineurium was thickening. The mass was tofukasu-like appearance on cross-resection. Median nerve which was involved by the mass was resected, and neuroanastomosis was carried. The mass associated with part of median nerve was excised and was submitted for the pathologic examination. Through routine examination, no other abnormal was found. After initial operation, the tumor recurred twice in two years.

Pathological findings
Microscopically, a mass was well-circumscribed, unencapsulated, multi-nodules located in median nerve (Figure 1A). At low power the tumor was comprised spindle and epithelioid cells in a lamellar, whorling pattern around the nerve fascicles (Figure 1B). High power magnification showed that tumor composed of sheets of cells with epithelioid features, pale-staining, and mostly inconspicuous nucleoli, ensheathing nerve bundles (Figure 1C).
Frequent mitoses and necrosis were present, and atypical forms of mitosis were also found. The tumor cells were extensively pleomorphic at some areas. Uniform spindle cells in lamellar arrangement were seen at some foci (Figure 1D). The recurrent tumor consisted of ovoid, fusiform and markedly elongate cells with pale, acidophilic cytoplasm disposed in sheets and perivascular pseudorosette-like or pseudo-papilla structures, and necrosis and significant pleomorphism were noted (Figure 3A, 3B). Immunohistochemical staining, the primary tumor cells were positive for cytokeratin (Figure 2A), epithelial membrane antigen (Figure 2B) and claudin-1 (Figure 2C). S-100 was positive in remnant nerve bundles (Figure 2D). The recurrent tumor was also positive for epithelial membrane antigen (Figure 3C), cytokeratin, CD34 was also positive in neoplastic cells (Figure 3D).

**Discussion**

Nerve fibers are each wrapped in a protective sheath known as the endoneurium. These are bundled together into groups known as fascicles, each surrounded by a protective sheath known as the perineurium. The perineurium is composed of connective tissue, which has a distinctly lamellar arrangement consisting of roughly 7-8 concentric layers. Perineurioma is a soft tissue tumor composed of cells resembling normal perineurium, which was first described in 1978 by Lazarus and Trombetta [2] on the
basis of ultrastructural findings. There are several forms of perineurioma: intraneural, extraneural (soft tissue), sclerosing, and reticular. Intraneural perineurioma is a rare condition that has recently been shown to be an intraneural clonal proliferation of perineurial cells. Lesions usually develop in a nerve in the upper extremity of a young individual. On cross-section intraneural perineurioma is consisted of concentric layers of perineurial cells ensheathing a central axon and Schwann cell. But malignant counterpart has different pattern, which has not been clearly described.

By the definition of Enzinger [3], malignant tumors arising from or displaying differentiation along the lines of the various elements of the nerve sheath are referred to as malignant peripheral nerve sheath tumors (MPNSTs). MPNSTs with perineurial differentiation have also been reported [1, 4-11], initial reports suggested that the neoplastic cells in such lesions was incompletely differentiated Schwann cells, but not perineurial cells, or the authors thought only focal perineurial cell component participants in the constitute of such tumor [12, 13]. We know that MPNSTs always focally or weakly express EMA, which are more or less positive for S-100. But our case expressed strong EMA and cytokeratin, and was negative for S-100, and also located in the major nerve, it might be originated from perineurium. In the series of Hirose et al [14], only one nerve-based tumor was encountered. In the current case, immunohistochemical staining of cytokeratin was strong positive. Reviewing the literatures, only Graadt van Roggen et al [15] reported that reticular perineurioma weakly stains cytokeratin. EMA and claudin-1 positive indicated that current tumor was perineurial phenotype. However, cytokeratin positive was rarely reported in perineurioma or MP. Our case was cytokeratin posi-
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tive, associated with CD34 positive. CD34 antigen has been shown to be expressed by the majority of perineurioma [16]. CD34 is expressed in some MPNSTs and is likely a reflection of perineurial differentiation.

Perineurium, the covering of nerves, is very closely related to contiguous meningotheium, the layer covering the brain and spinal cord. Meningiomas are therefore related to perineurioma and indeed, in one study, meningiomas showed extensive expression of the ‘perineurial’ markers glut-1, claudin-1 and EMA [9]. After twice occurrence, the morphology of our case was similar to papillary meningioma. Reviewing the literature, malignant meningioma could express cytokeratin [17]. In particular, the presence of epithelial differentiation of our case, is greater than that normally recognized and accepted in perineurial tumors. This case has the features of epithelial differentiation, suggested that the tumor is MP with prominent epithelial differentiation. The morphology and immunophenotype of our case are similar to the features of epithelioid sarcoma. Given this, we consider that perhaps the tumor is consistent with epithelioid sarcoma; maybe we just confirm a rare case of epithelioid sarcoma arising in the nerve, which suggests that epithelioid sarcoma may be a form of malignant perineurioma with a range of differentiation [18].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yong Huang, Department of Pathology, 251 Hospital of PLA, 13 Jianguo Road, Zhang Jia Kou, Hebei, 075000, PR China. Tel: +86-313-8785267; Fax: +86-313-8785267; E-mail: pathxhy@163.com

Figure 3. Histological and immunohistochemical changes of recurrent malignant perineurioma. A, B: The tumor consisted of ovoid, fusiform and markedly elongate cells with pale, acidophilic cytoplasm disposed in sheets and perivascular pseudorosette-like or pseudo-papilla structures. C: The tumor cells were positive for epithelial membrane antigen. D: CD34 was positive in tumor cells, associated with vessels.
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References


