Original article

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Coexistence of meningioma and schwannoma in the same cerebellopontine angle in a patients with NF2

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Abstract

The coexistence of schwannoma and meningioma in the same cerebellopontine angle (CPA) is uncommon. Especially, the presence of a single mixed tumour composed of demarcated or intermingled components of schwannoma and meningioma tissue is extremely rare. Such a phenomenon is mainly reported in a patient with NF2 or with history of previous irradiation.

We present two cases of simultaneous occurrence of schwannoma and meningioma in the same cerebellopontine angle in young adult patients with clinical manifestation of NF2. The first patient was a 18-year-old young man who presented with bilateral CPA tumours, spinal mass lesion and multiple, small, schwannoma-like lesions of the cauda equina. Both CPA tumours was initially diagnosed as schwannomas based on preoperative MR imagings, however right CPA tumour appeared to be composed of a well-circumscribed transitional meningioma located inside schwannoma of Antoni A and B type. The second patient, a young 16-year-old boy, presented bilaterall CPA tumours as well as many meningeal tumours supratentorially and infratentorially. Two adjacent tumours in the left CPA proved to be schwannoma and meningioma. In both cases, the different neoplastic components were confirmed by histopathological and immunohistochemical studies.

The possible mechanism underlying the occurrence of such coexisting tumors of different histogenesis remains unclear.

Key words: *coexistence, collision tumours, schwannoma and meningioma, NF2, CPA tumours.*

Introduction

The simultaneous occurrence of primary brain tumours of different histology in the same anatomical site is rarely observed. In particular, the coexistence of schwannoma and meningioma in the same cerebellopontine angle (CPA) is uncommon. Various definitions and possible pathomechanisms of such conditions have been proposed. Such tumours of different origin might be considered as collision, concomitant or contiguous tumours [10]. The majority of reported cases usually appear as distinctly separated lesions that can be detected on preoperative MRI imaging [27]. The occurrence of a single mixed tumour composed of distinctly de-

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marcated or intermingled components of schwannoma and meningioma tissue is extremely uncommon. Such cases have been mainly reported in patients with neurofibromatosis type 2 (NF2) [5,6,15], less often in cases without clinical signs of NF2 [1,4,10,12,19].

We present two cases of histologically various tumours that developed in the same CPA in young adult patients with clinical signs of NF2: one case with a well-circumscribed meningioma located inside schwannoma and the second one with two adjacent tumours of schwannoma and meningioma morphology.

Material and methods

The material consisted of surgical samples from the right-sided CPA tumour in Case 1 and from two left CPA tumours in Case 2. The material was routinely fixed in 10% formalin, embedded in paraffin blocks and stained with haematoxylin-eosin (H&E) and Gomori's method. Immunohistochemistry according to the labelled avidin-biotin-peroxidase complex (ABC) method was performed with DAB as chromogen using antibodies against epithelial membrane antigen (EMA), vimentin, S-100 protein and Ki67 (all antibodies from Dako, Glostrup, Denmark).

Case 1

A 18-year-old man presented with a 2-year history of hearing loss and with progressive headache associated with vertigo, vomiting and gait instability for 2 months. Neurological examination on admission to the Neurosurgical Department revealed hearing loss, bilateral facial nerve paresis of grade II according to House Brackmann grading system (HB), mild left-sided paresis and moderate left-sided cerebellar ataxia.

The magnetic resonance imaging (MRI) of the brain revealed bilateral well-defined cerebellopontine angle (CPA) tumours with severe brainstem compression and non-communicating hydrocephalus. The tumours enhanced vividly on T1-weighted images. The size of the tumour was 33 × 39 × 21 mm on the right and 38 × 27 × 30 mm on the left side. The left-sided tumour was accompanied by extratumoral arachnoid cysts (Fig. 1A). A marked widening of the internal acoustic canal was visible on both sides. Moreover, an intradural, extramedullary meningioma-like mass at the level of C2-C3 (Fig. 1B) and multiple, small, schwannoma-like lesions of the cauda equina were detected. Neurofibromatosis type 2 was diagnosed based on the clinical and neuroimaging features.

The management included multi-staged surgery: 1) At the first step, the patient had undergone surgery for the tumour located anteriorly in the cervical spinal canal. The intradural, extramedullary tumour was totally removed via laminectomy at C2-C3 on the left side. Histopathological examination revealed *transitional*, *in part psammomatous*, *meningioma* (WHO grade I) *with infiltration of dorsal root ganglion and spinal nerves*. 2) After 10 days, the patient was operated on for CPA tumour on the left side using the retrosigmoid approach. The histopathological study established the diagnosis of *schwannoma with Antoni type A and B patterns*. Gradual withdrawal of left-sided paresis and also regression of hydrocephalus were observed after the second surgery. However, impairment of the facial nerve function on the left side up to HB grade III was noted postoperatively. 3) The third surgery was performed after an interval of 4 months. The right-sided CPA tumour was removed via retrosigmoid approach and was followed by placement of auditory brainstem implant over the cochlear nuclei. Intraoperatively, macroscopic appearance of this solitary tumour was typical of schwannoma, however histopathological diagnosis was *schwannoma type Antoni A and B enclosing meningothelial meningioma*. At the end of the procedure, an increasing oedema of the cerebellar hemisphere was noted, thus computed tomography scan was performed immediately after the surgery. CT scan showed an acute supratentorial epidural hematoma on the right side in place of fixation of the auditory implant to the temporal bone (Fig. 1C), which required urgent evacuation. As a consequence of this unique complication, a transient exacerbation of the left-sided paresis was observed. Afterwards, the hospital stay was prolonged for rehabilitation. Follow-up CT confirmed the complete removal of CPA tumours (Fig. 1D). At discharge, the patient was in fair condition with deafness, bilateral facial nerve paresis of grade III, left-sided paresis and ataxia, but able to walk with minimal assistance.

Histopathological findings

Histopathological examination of the surgically excised right-sided CPA tumour revealed schwannoma that contained a quite well-demarcated, transitional meningioma (Fig. 2). Schwannoma exhibited a biphasic pattern composed of compact, fascicular Antoni A tissue and loose-textured, hypocellular Antoni B areas with microcystic and degenerative

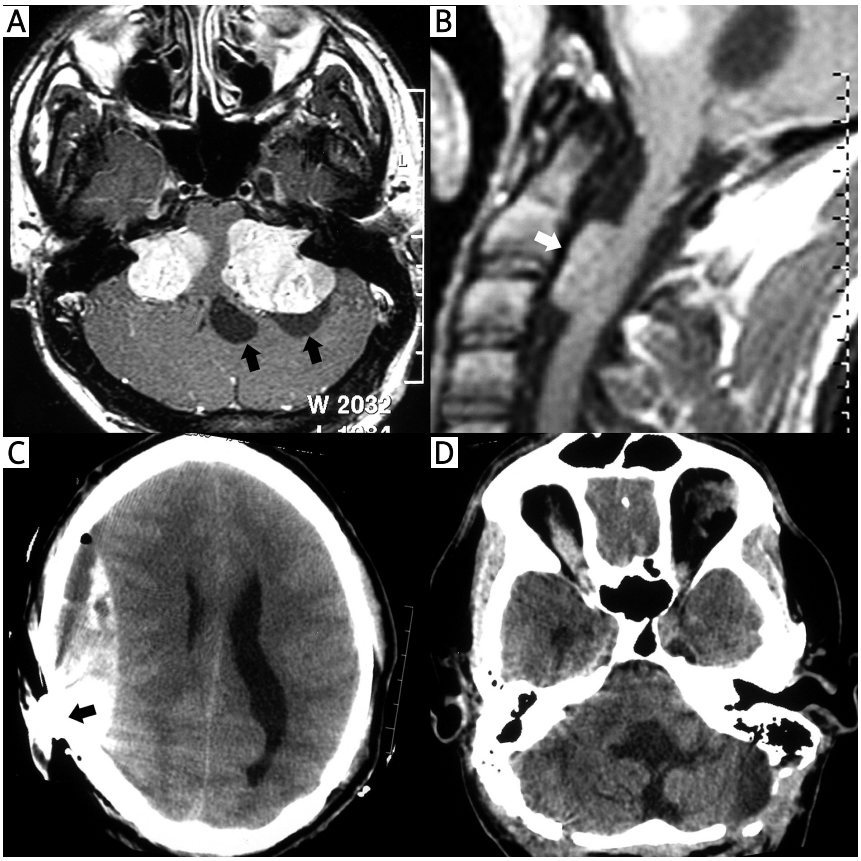

Fig. 1. Case 1. Neuroradiological findings. **A)** T1-weighted MRI image. Bilateral, well-defined CPA tumours with severe brainstem compression and non-communicating hydrocephalus. The left-sided tumour was accompanied by extratumoral arachnoid cysts (arrows); **B)** MRI of the spine. Extramedullary meningioma-like mass at the level of C2-C3; **C)** CT scan revealing an acute supratentorial epidural hematoma on the right side; **D)** CT scan confirming the complete removal of CPA tumours.

changes (Figs. 3A, B). Focal proliferation of microvessels was seen (Fig. 3C). The proliferative labelling index measured by Ki67 expression was low (Fig. 3D). Transitional meningioma revealed typical concentric, whorl-like formations (Figs. 4A, B). Discrete meningothelial foci intermingled with schwannoma neoplastic tissue were occasionally identified at the border of meningioma (Fig. 4C). The Ki67 labelling index was low (Fig. 4D). Schwannoma tissue revealed a pericellular network of reticulin fibres, whereas meningioma cells lack it. These two different neoplastic components were confirmed by immunohistochemical studies. Schwannoma tissue showed strong immunoreactivity for S-100 protein but was negative for EMA, whereas meningioma cells were strongly positive for EMA (Figs. 5A-D).

Case 2

A 16-year-old boy was admitted to the Department of Neurosurgery with previously diagnosed neurofibromatosis type 2. He underwent a surgery for two meningiomas of thoracic spine at the level of Th4-Th5 and Th7 in the Department of Paediatric Neurosurgery 1.5 years before. On admission, the patient presented with progressive bilateral hypoacusis. Neurological examination did not reveal any other abnormalities.

An MR imaging study disclosed tumours of CPA bilaterally as well as many meningeal tumours, both supratentorial and infratentorial (Fig. 6). As compared to MRI performed 9 months before admission, a slight progression of both CPA tumours was noted. CT scans of the temporal bones showed a widening of internal auditory canals on both sides.

The patient was qualified for staged surgical treatment, beginning with the better hearing ear in an attempt to preserve the hearing. The patient underwent a left retrosigmoid craniotomy. Two separate tumours were encountered in the left CPA. They were located very close to each other. The former tumour, arising from the internal auditory canal, was macroscopically considered to be a vestibular schwannoma and was totally resected with anatomical preservation of the facial and cochlear nerves. However, despite the surgery was temporarily interrupted

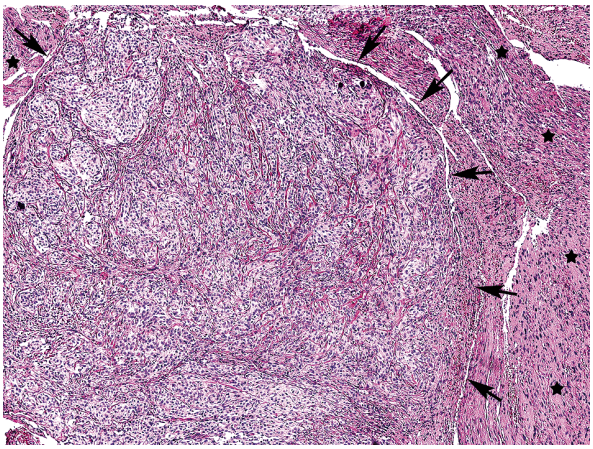

Fig. 2. CPA tumour exhibiting a quite well-demarcated, transitional meningioma (arrows) surrounded by schwannoma tissue (asterisk). H&E. Original magnification ×40.

because of decrease in amplitude of the recorded auditory evoked potentials, cochlear nerve function was lost at the end of dissection. The latter tumour with a broad dural attachment was located just above the porus acusticus internus and was thought to be meningioma. The tumour was totally removed as well, along with dural attachment and endostosis (Simpson grade I). The patient's postoperative course was complicated by cerebrospinal fluid leak, which was successfully treated with external lumbar drainage. On discharge, the patient's condition was good, he was fully independent without facial nerve weakness, but with hearing loss on the left side.

Histopathological findings

The first tumour was found to be a conventional schwannoma with predominant compact, cellu-

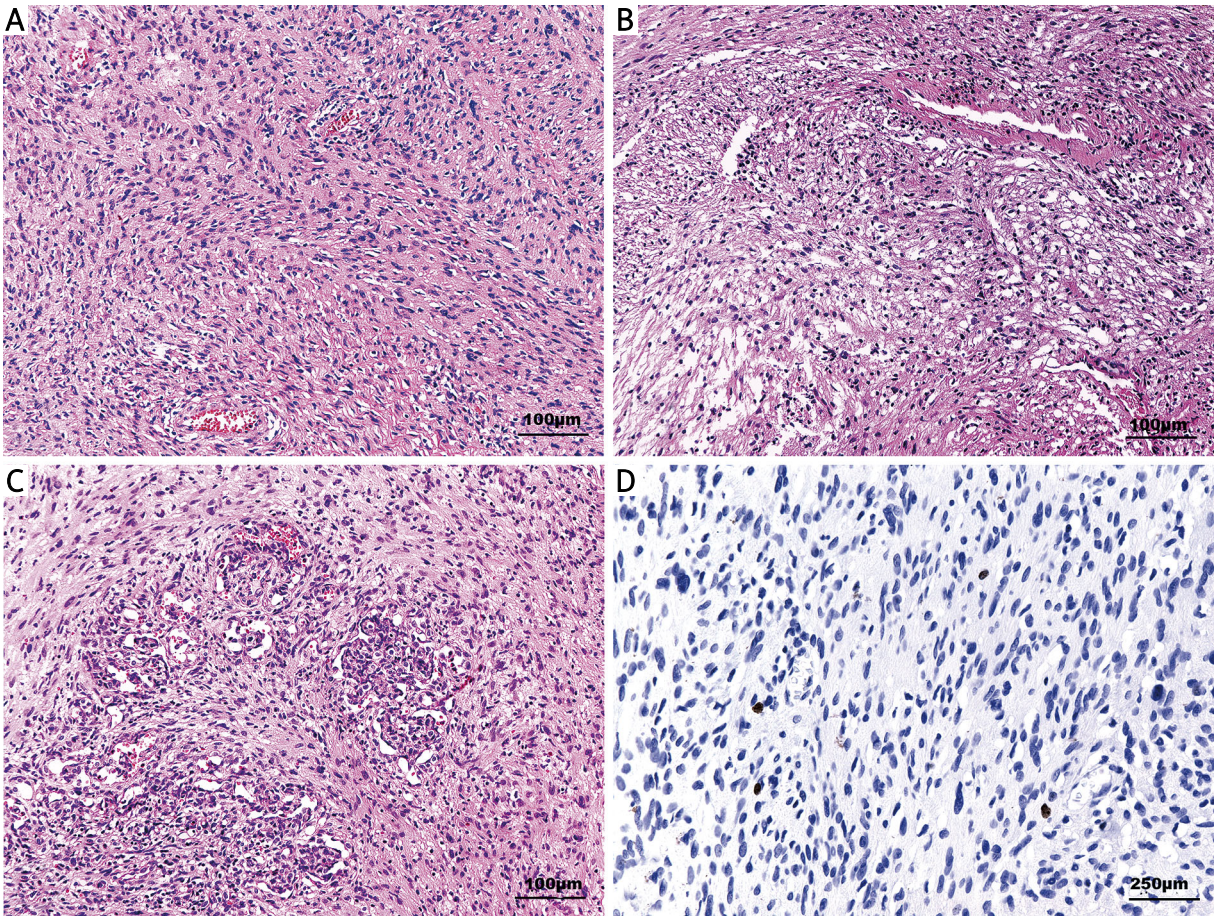

Fig. 3. Histopathology of schwannoma. **A)** Compact Antoni A tissue, H&E. **B)** Loose-textured, hypocellular Antoni B areas, H&E. **C)** Focal proliferation of microvessels, H&E. **D)** Low Ki67 expression. Bars: A, B, C – 100 µm, D – 250 µm.

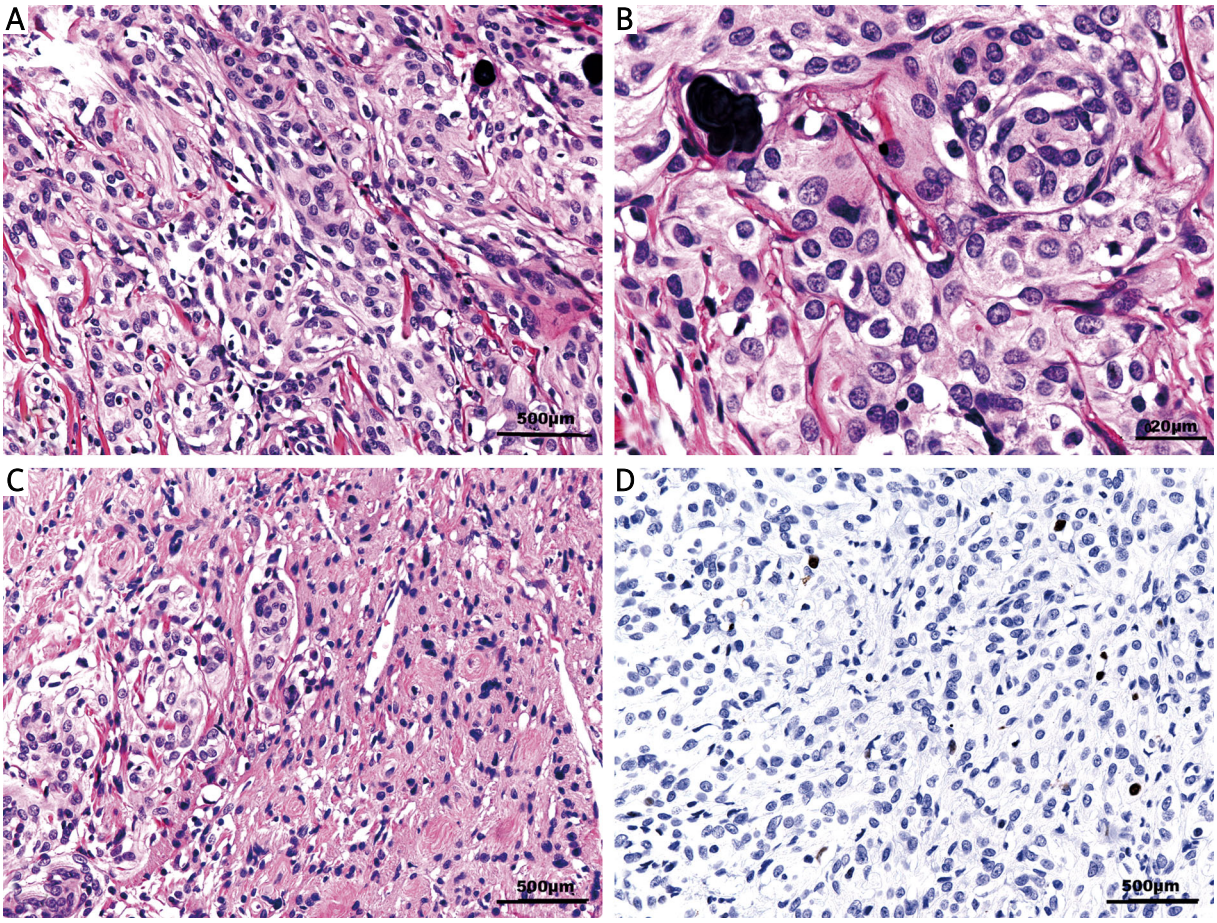

Fig. 4. Histopathology of meningioma. **A, B)** Transitional meningioma with concentric, whorl-like formations and psammoma body, H&E. **C)** Discrete meningothelial foci intermingled with schwannoma neoplastic tissue, H&E. **D)** Low Ki67 labelling index. Bars: A, C, D – 500 µm, B – 20 µm.

lar Antoni A pattern composed of interlacing bundles of elongated, spindle cells (Fig. 7A). The neoplastic cells exhibited focal nuclear pleomorphism. Numerous ganglion cells were visible at the periphery of neoplastic tissue (Fig. 7B). Abundant pericellular reticulin fibres corresponded to pericellular basement membrane. Immunohistochemically, the tumour cells exhibited strong, diffuse immunoreactivity for S-100 protein (Fig. 7C) but were completely negative for EMA (Fig. 7D). The adjacent CPA tumour appeared to be a fibroblastic variant of meningioma (Fig. 8A) with a few psammoma bodies (Fig. 8B). The tumour cells exhibited distinct immunoreactivity for EMA (Fig. 8C), whereas S-100 protein was only slightly positive (Fig. 8D). The Ki67 proliferative index was low in both tumours.

Discussion

The simultaneous occurrence of histologically different brain tumours in the same CPA region is rare and usually develops in a patient with neurofibromatosis type 2 or with a history of previous irradiation. Especially growth of intracranial meningioma in various sites might be induced by radiation therapy [16,20]. The most common type of CPA tumours is vestibular schwannomas, which constitute 62-80% of all CPA lesions, followed by meningiomas which reach 5-12% [14,21]. Schwannomas located in CPA may appear in association with meningiomas. For such coexisting tumours, different terms might be used. They have been called "collision" tumours [22], "coexisting or concurrent" tumours [3,12,17] or they have been referred to as coincidental lesions [13]. Frassinito *et al.* [10] proposed

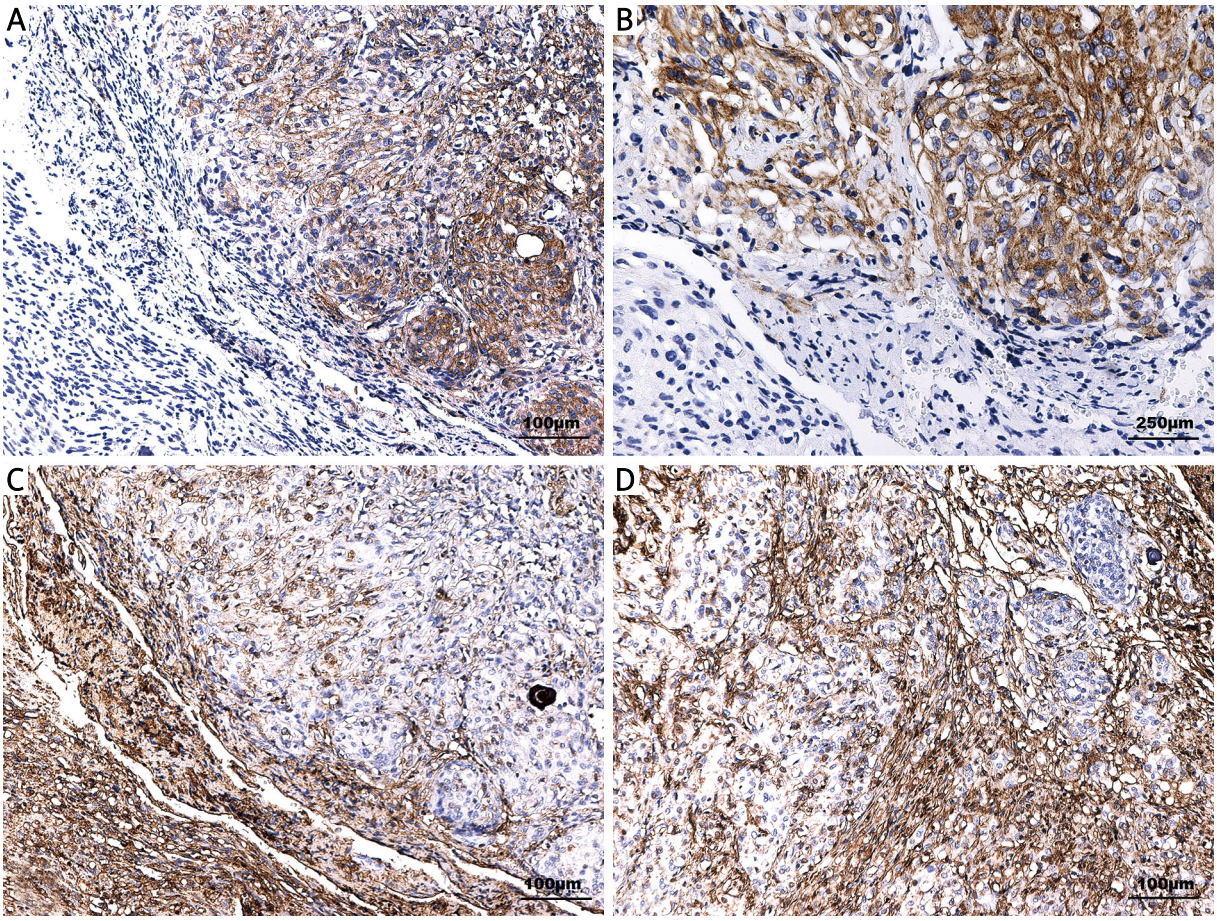

Fig. 5. Immunohistochemistry of neoplastic components. **A, B)** Strong immunoreactivity for EMA in meningioma (right) whereas schwannoma tissue is negative (left), **C)** Schwannoma tissue exhibiting strong immunoreactivity for S-100 protein (left) whereas meningioma was only slightly positive. **D)** Strong S-100 positivity in schwannoma with immunonegative foci of intermingled meningothelial cells. Bars: A, C, D – 100 µm, B – 250 µm.

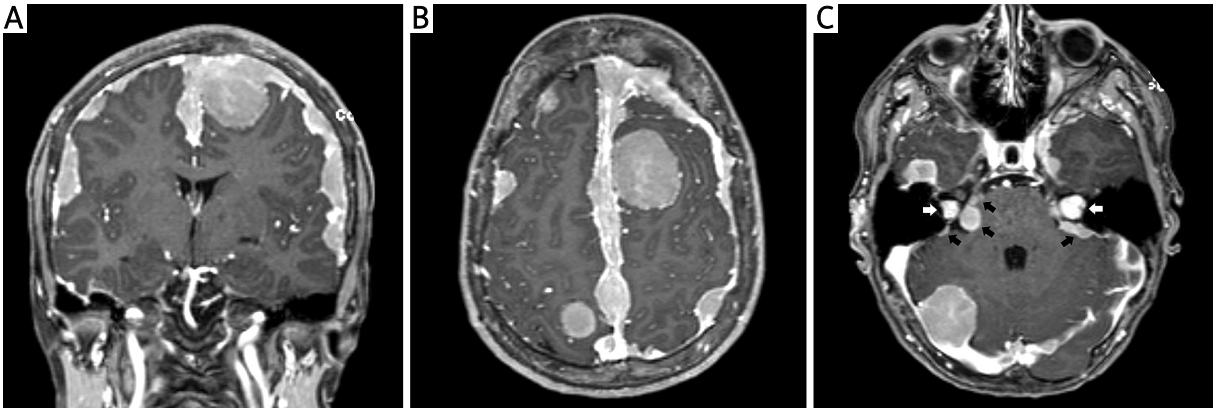

Fig. 6. Case 2. T1-weighted MR images: coronal **(A)** and axial **(B, C)**. Multiple supra- and infratentorial meningeal tumours and bilateral CPA tumours. **(C)** Vestibular schwannomas (white arrows) and coexisting meningiomas (black arrows) are visible in cerebellopontine angles on both sides.

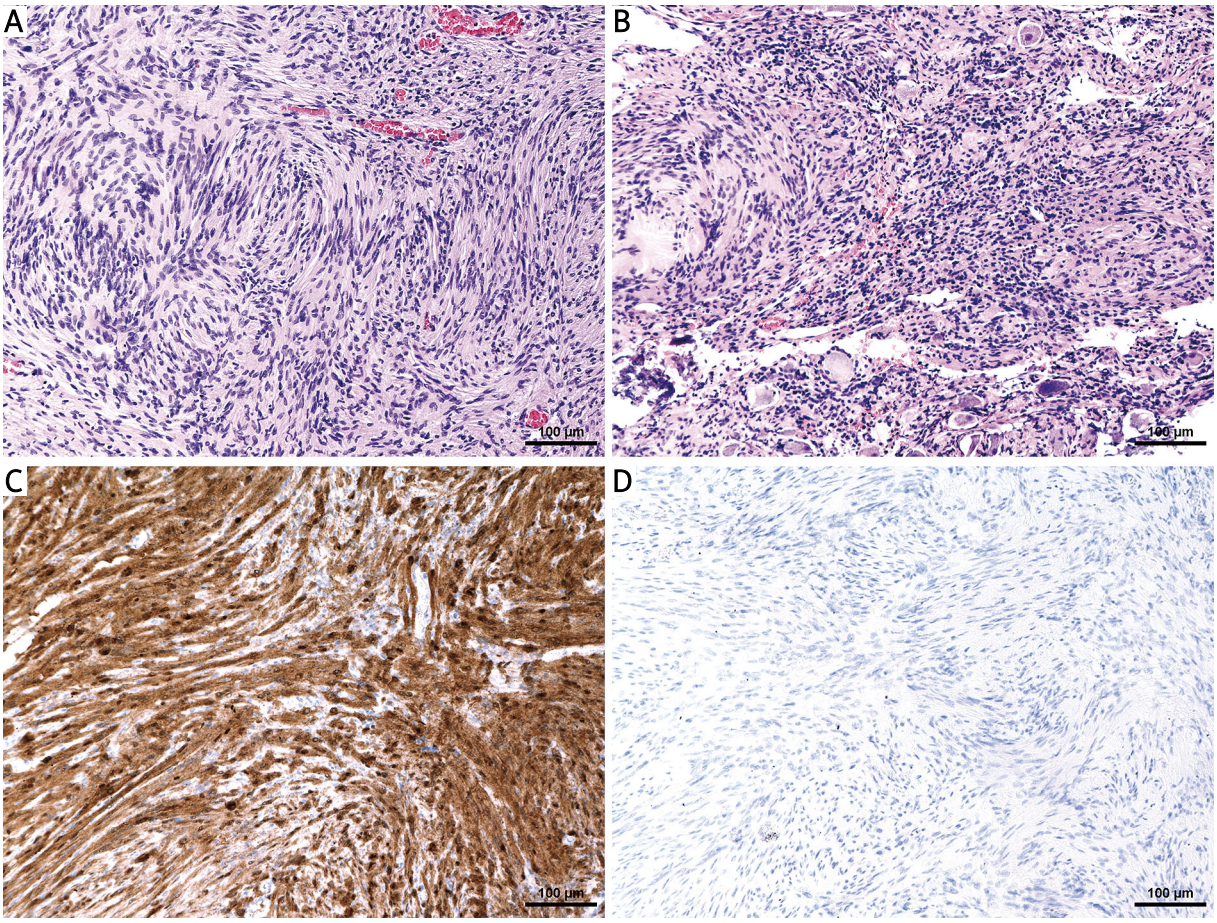

Fig. 7. Histopathology of schwannoma. **A)** Conventional schwannoma with the predominant cellular Antoni A pattern with focal nuclear palisading, H&E. **B)** Numerous ganglion cells within neoplastic tissue, H&E. **C)** Strong, diffuse immunoreactivity for S-100 protein. **D)** Lack of immunoreactivity for EMA. Bars: A, B, C, D – 100 µm.

a more precise classification of tumours occurring at the same localization in order to better determine their pathogenesis and treatment. He suggested that two lesions arising separately but in close contact ought to be considered as an intermediate condition between concomitant and collision tumour and might be named "contiguous tumour". Thus, the concomitant, contiguous and collision tumours most likely represent the subsequent steps of the same continuum.

The presence of a mixed tumour composed of schwannoma and meningioma that manifest themselves as a single CPA tumour is unique. Two distinct components within the same tumour were particularly often reported in patients with neurofibromatosis type 2 [5,6,15]. Such coexistence was also observed in cases without clinical signs of NF2 [1,4,10,12,19] but it can be assumed that current diagnostic criteria for NF2 are too restrictive [4].

NF2 is an autosomal dominant syndrome affecting primarily the central nervous system. It is characterized by hamartomatous and/or neoplastic proliferation of Schwann, meningothelial and glial cells [18]. The diagnosis might be made by clinical and neuroimaging studies but presymptomatic genetic tests are important in the management of NF2 family members [8]. The somatic gene therapy is hoped to be introduced for the treatment of this disease. Typical clinical symptoms of NF2 include bilateral vestibular schwannomas or family history of NF2 accompanied by either unilateral vestibular schwannoma or two of other tumours such as meningioma, glioma, neurofibroma or schwannoma of other cranial and spinal

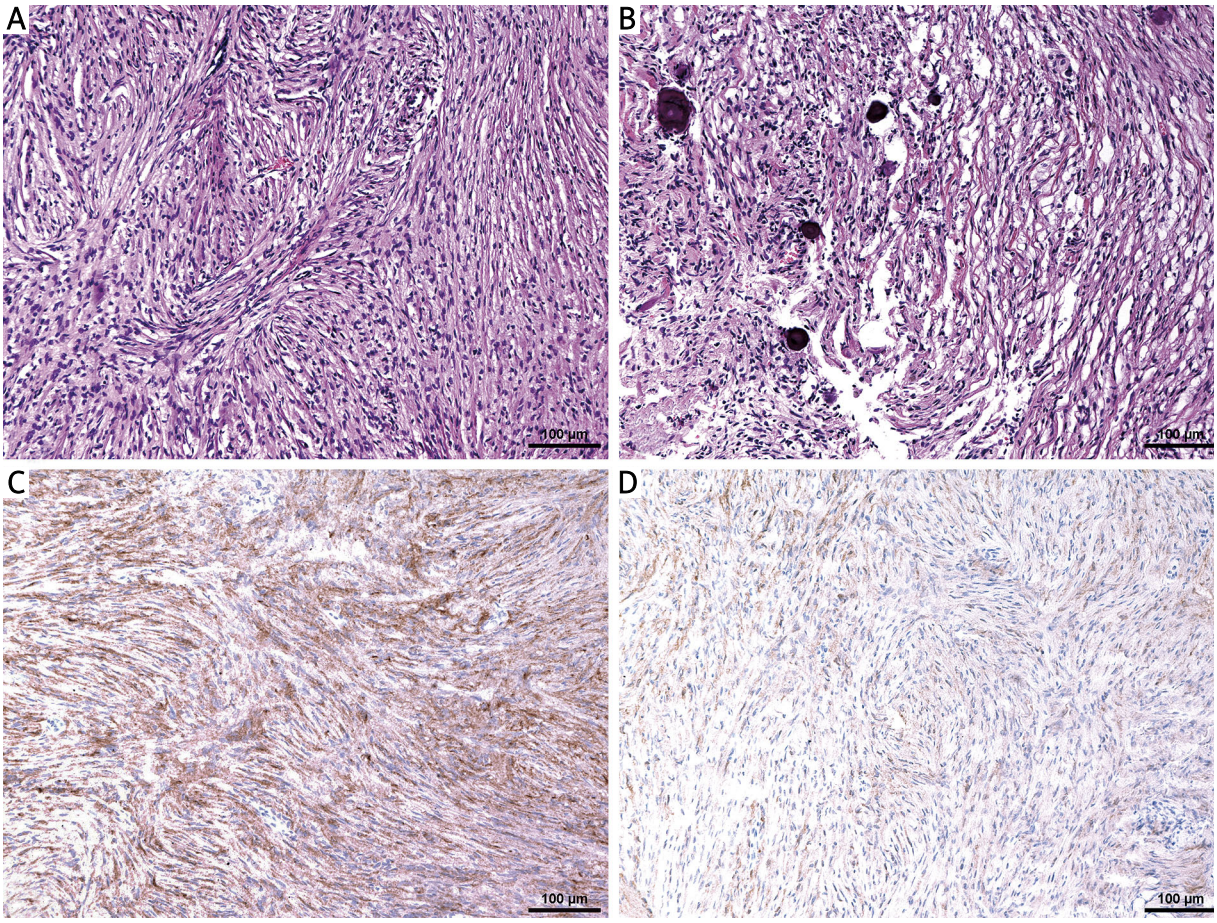

Fig. 8. Histopathology of meningioma. **A)** Fibroblastic variant of meningioma, H&E. **B)** Meningioma tissue with a few psammoma bodies, H&E. **C)** Distinct immunoreactivity for EMA. **D)** Tumour cell slightly positive for S-100 protein. Bars: A, B, C, D – 100 µm.

nerves in other sites [7,24]. The most common tumours in NF2 patients are multiple schwannomas and meningiomas and most of the NF2-associated tumours of Schwann or meningothelial cell origin are WHO grade I. They are usually present at an earlier age, most commonly in the third decade of life. The disorder is caused by mutation of the *NF2* gene, a classic tumour suppressor gene, located on chromosome 22q12.2 [8,9].

In both presented cases, the clinical symptoms, including bilateral vestibular schwannomas, are consistent with the diagnosis of NF2, according to current diagnostic criteria [2]. Bilateral vestibular schwannomas are the basic hallmarks of NF2, whereas meningiomas are the second most common type of tumour occurring in NF2. Our 18-year-old male patient presented with bilateral CPA tumours, spinal mass lesion and multiple schwannoma-like lesions of the cauda equina. Both CPA tumours were initially diagnosed as schwannomas, based on preoperative MR imaging findings, but definitively it occurred that the right CPA tumour was composed of two elements of varying histogenesis. It is usually difficult to establish a diagnosis of the mixed tumour based on preoperative MRI but retrospectively a meningiomatous area can be noticed inside the acoustic neurinoma on magnetic resonance images [15]. In the second case, the patient with NF2 had two distinctly separated tumours of different origin in the same CPA. This represents a more common phenomenon of coincidental meningioma and schwannoma. In most of such reported cases, two neoplastic components might be recognized on preoperative MRI imaging [27].

In both our cases, two different neoplastic components were confirmed by immunohistochemical studies for EMA and S-100 protein. Schwannomas are typically diffusely positive for S-100 protein and display

abundant pericellular reticulin or collagen IV, corresponding to the basement membrane. Schwannomas are generally EMA negative but focal EMA reactivity might be encountered. The majority of meningiomas show EMA positivity, at least focally. They are typically S-100 negative, however the fibrous type might display slight or patchy immunoreactivity for S-100 protein as it was demonstrated in our case 2. The fibroblastic and transitional meningiomas are more commonly reported in CPA but the fibroblastic variant might be misdiagnosed with schwannoma Antoni type A.

The possible mechanism underlying the occurrence of distinctly demarcated or intermingled components of schwannoma and meningioma tissue remains unclear. The simultaneous occurrence of various tumour types in the same location might result from the collision of two separate tumours, metaplasia in the original tumour or differentiation of the same cell line into various neoplastic elements. The development of the mixed tumour might be related to independent development of two components or bidirectional differentiation from common progenitor cells [15]. However, there is no evidence for the existence of common progenitor of both Schwann or meningothelial cells. The reactive meningothelial hyperplasia adjacent to the main tumour mass could be responsible for the occurrence of meningothelial component within schwannoma [11]. It has been reported that up to 21% of schwannomas in a patient with NF2 might develop focal meningothelial cell proliferation [26]. Moreover, the meningothelial-like nodules with a whorls pattern might be found in cellular schwannomas [25]. In such cases, diffuse and strong S-100 protein positivity is important for warranted diagnosis. It is hypothesized that the meningotheliomatous cells infiltrating the schwannoma triggered an autocrine/paracrine growth-stimulatory mechanism that involved an EGF-like action factor [23].

Considering our two cases, the most likely cause of formation of tumour composed of two neoplastic elements seems to be related with focal proliferation of meningothelial cell within or close to schwannoma tissue in patients with NF2.

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Original article

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Differential expression of MMP-9 and AQP4 in human glioma samples

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Abstract

Background: *Metalloproteinase-9 (MMP-9) and aquaporin-4 (AQP4) have been individually reported in glioma development. Here, we co-analyzed their expression in multiple forms of human glioma tissues graded from II to IV.*
Material and methods: *Levels of MMP-9 and AQP4 were evaluated on 50 resected human glioma tissues using immunohistochemistry. Protein levels of both molecules were evaluated by a staining score system based on the percentage of positive cells/staining degree in each dot section. The transwell method was also used to discriminate fast migrating cells and slow migrating cells, in which expression of both MMP-9 and AQP4 was investigated by using immunofluorescence.*
Results: *The staining score of MMP-9 displayed a positively tumor grade dependent manner, whereas AQP4 expression showed a negatively tumor grade dependent manner. The nuclear translocation of both molecules was observed in astrocytomas with glioblastoma transition, or glioblastoma tissues. Fast migrating cells contain more AQP4, whereas more MMP-9 was localized in slow migrating cells.*
Conclusions: *Our findings suggest differential expression patterns of MMP-9 and AQP4 in different grades of gliomas. Nuclear translocation of MMP-9 and AQP4 may exert more functions in glioblastoma transition or deterioration. Co-analysis of MMP-9 and AQP4 may help to identify tumor type and their progression stages.*

Key words: *metalloproteinase-9 (MMP-9), aquaporin-4 (AQP4), human glioma.*

Introduction

Glioma is a kind of frequently occurring behaviorally malignant tumor in the nervous system (NS), accounting for 40-50% of all NS related tumors. It is characterized by invasive growth, high mortality, high recurrence, poor clinical prognosis and low survival time of less than 18 months [4]. Despite intense effort, we still fall back on surgery and radiation therapy for treatment options. A major reason for this status is that glioma development is molecularly a multiple-factor induced pathological condition. Recently, accumulated evidence has pointed to metalloproteinases and aquaporins (AQPs) as key molecules that play an important role in glioma development, especially in tumor related brain edema and metastasis [20].

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