

Skull base secretory meningioma. Value of histological and immunohistochemical findings for peritumoral brain edema formation

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Abstract

Meningiomas are very common neurosurgical problem. Their histological appearance, different size and localization, adherence to vital neural and vascular structures or extensive peritumoral brain edema (PTBE), especially in deep seated tumors, may lead to severe, life-threatening complications. We report a case of tuberculum sellae meningioma (TSM). A 48-year old female presented with 7-month history of blurred vision and progressive visual impairment. Intracranial tumor was confirmed by magnetic resonance imaging (MRI). After ophthalmological and endocrinological evaluation, the patient underwent surgical removal of the tumor. She immediately recovered from her visual disturbances and no tumor recurrences were seen during follow-up. Pathological diagnosis showed a meningioma of the secretory subtype (MS). We discuss the role of immunohistochemical staining in the diagnosis and the role of different factors in the PTBE formation. Selection of surgical route to the TSM is discussed, as well. Review of the literature is presented.

INTRODUCTION

The term “secretory meningioma” has been proposed by Alguacil-Garcia in 1986 (Alguacil-Garcia 1986). Formerly, Eisenhardt and Cushing had described a subtype of meningiomas with unique formation of glandular structures containing secretory globules (hyaline bodies) (Colakoğlu 2003). Afterwards, Kepes called these hyaline bodies as pseudopsammoma bodies (PPB) (Kepes 1961). MS is histologically benign entity but is more often surrounded by extensive PTBE than other meningiomas of similar size and location (Tiratokai 2006). Additionally, PTBE might lead to severe, life-threatening complications, especially

in postoperative course (Gurkanlar 2005; Pereira-Filho 2010; Regelsberger 2008). Authors present a case of deep-seated skull base MS without evident PTBE. Review of the literature is also discussed.

CASE REPORT

48-year old female with 7-month history of blurred vision and progressive visual impairment was admitted to our institution. She experienced also progressive headache for last 4 years. On admission her body weight was 72 kg and was unchanged per last three years and her height was 163 cm. Calculated body mass index (BMI) was 27 kg/m². Observed central obesity was not typically

cushingoid without moon face and buffalo hump. There were no acromegalic features, as well. The patient had no symptoms of neurofibromatosis. Neuroophthalmological examination revealed a decrease of visual acuity to 0.2 in right eye and to 0.8 in left eye and a sharply-demarcated right temporal visual field loss without macular sparing. The optic discs were normal. Apart from the visual impairment, neurological examination was normal without symptoms of raised intracranial pressure. On preoperative laboratory investigation, a slightly elevated serum level of prolactin (PRL) was seen (39 ng/ml; normal range to 25 ng/ml) with normal circadian rhythm of PRL secretion. The serum level of remaining pituitary hormones were within normal limits. There were no fluid-electrolyte disturbances before admission. Preoperative MRI demonstrated large, sessile lesion (28×26×21 mm) extending in the suprasellar cistern and the anterior cranial fossa, compressing optic nerves and chiasm, displacing laterally both carotid arteries (Figure 1A and 1B). There was a clumpy sclerosis (enostosis) of the bone along limbus sphenoidale. The body of the pituitary gland was com-

pressed within the pituitary fossa. There was no peritumoral edema in the surrounding brain, optic nerves, chiasm and optic tracts (Figure 1C and 1D). The patient was operated on. The tumor was exposed and totally removed (Simpson Grade I) via unilateral right small subfrontal approach. Pathological examination revealed moderately cellular neoplasm composed of nests and sheets of epithelioid cells, some of which contained oval spaces filled with homogenous, hyaline, round corpuscles. These structures stained strongly purple with PAS, and showed no evidence of mucins. Some tumor cells contained characteristic intranuclear inclusions, observed in other types of meningiomas. The mitotic activity of the neoplasm was very low and neither signs of anaplasia nor tumor necrosis were found (Figure 2). Immunohistochemically tumor cells showed diffuse expression of epithelial membrane antigen (EMA) and vimentin (VM). The latter was absent in cells surrounding oval secretory spaces and PPBs. (Figure 3) These cells showed distinct epithelial differentiation confirmed by presence of cytokeratins (CK) in their cytoplasm. Moreover, cells surrounding pseudopsammoma

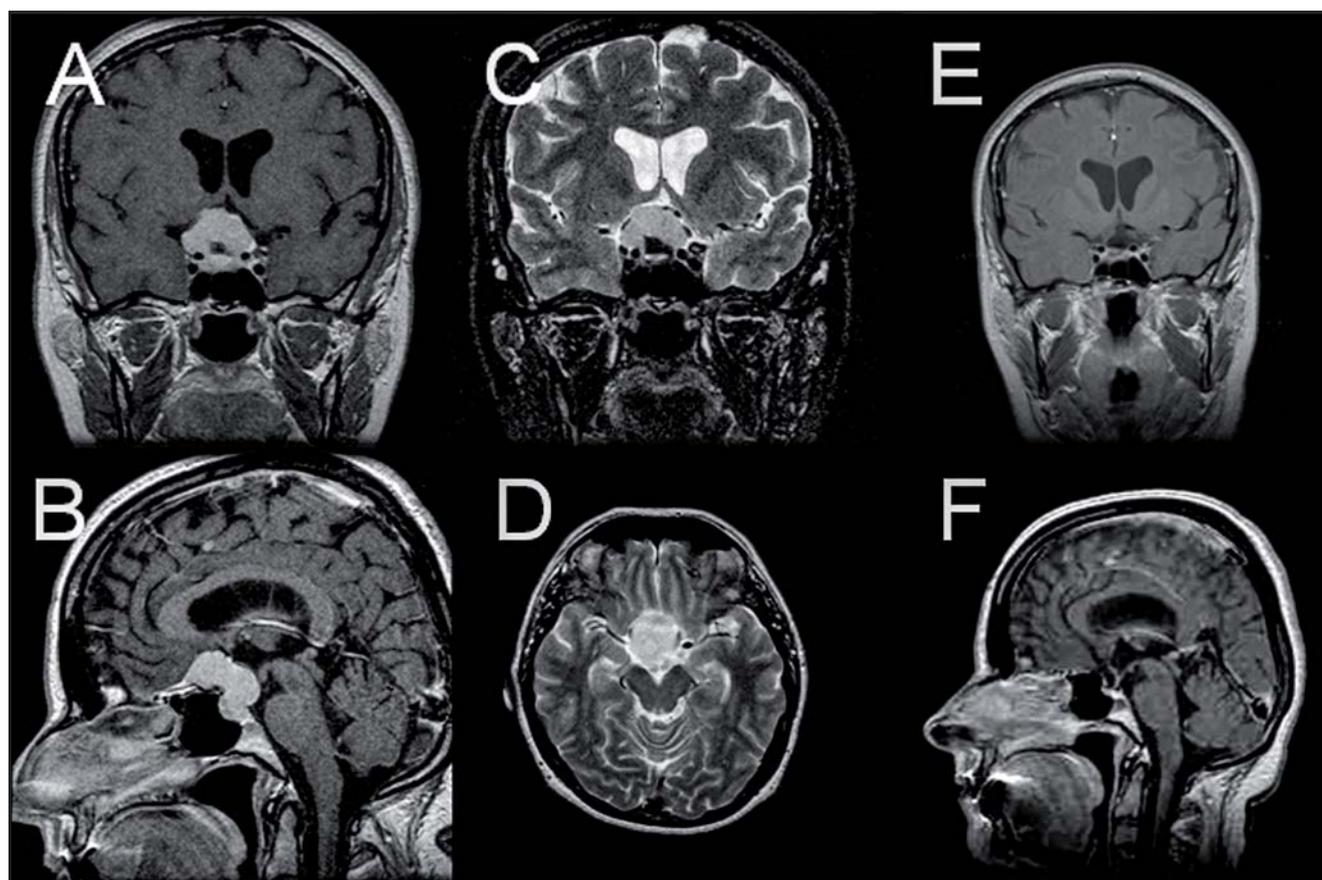


Fig. 1. **A** and **B** - MR imaging (coronal and sagittal T1-weighted after Gd-DTPA administration) demonstrated large, sessile lesion extending into the suprasellar cistern and the anterior cranial fossa, compressing optic chiasm and optic nerves, displacing laterally both carotid arteries, **C** and **D** - coronal and axial T2-weighted MR scans showed no peritumoral oedema in the surrounding brain, optic nerves and optic chiasm. **E** and **F** - postoperative MR scans (coronal and sagittal T1-weighted after Gd-DTPA administration) revealed total tumor removal.

bodies, as well as PPBs themselves, reacted strongly with anti-CEA antibody (CEA – carcinoembryonal antigen). PPBs also showed weak expression of S-100 protein. The labeling index with use of anti-Ki-67 antibody (clone MIB-1) was below 0.5%. (Figure 4) The diagnosis of secretory meningioma was established. Postoperative course was uneventful. Complete recovery of the visual acuity and visual field was observed. An endocrinological reassessment carried out 3 months later confirmed normal pituitary function. During the follow-up period the patient's pituitary function has been normal and we have not observed meningioma regrowth on the MRI for 5 years (Figure 1E and 1F).

DISCUSSION AND REVIEW OF THE LITERATURE

Meningiomas are slow growing, benign, usually non-metastasising neoplasms deriving from meningoblasts and/or arachnoid cap cells which are located at sites of arachnoid granulations along the dura (Commins 2007). They account for approx. 20% of primary intra-

cranial tumors. Only 4% of all meningiomas arise from the limbus sphenoidale, chiasmatic sulcus and tuberculum sellae, and are called the TSM (Couldwell 2004).

The most common initial sign of TSM is progressive visual disturbance. Occasionally endocrine dysfunction with mildly elevated PRL level is observed (Marosi *et al.* 2008). When the tumor gains large size, a frontal lobe syndrome can be diagnosed. It might be contributed to the improper regional cerebral blood flow caused by the tumor mass or extensive PTBE (Gurkanlar 2005; Pereira-Filho 2010; Commins 2007). Edema might be seen along optic tract, as well (Sklar 2000). In reported case the diameter of the tumor was quite large but either PTBE or optic tract edema was not observed.

In CT and MR scans, meningiomas show typical features that allow their accurate diagnosis (Regelsberger 2008). Because of radiological advancements, especially MR spectroscopy, perfusion and diffusion studies, MRI has become a first line imaging modality which even gives clues to the histological differentiation of the tumors (Dorenbeck 2005). Apart from the characteristic appearance of the meningioma and its anchoring to

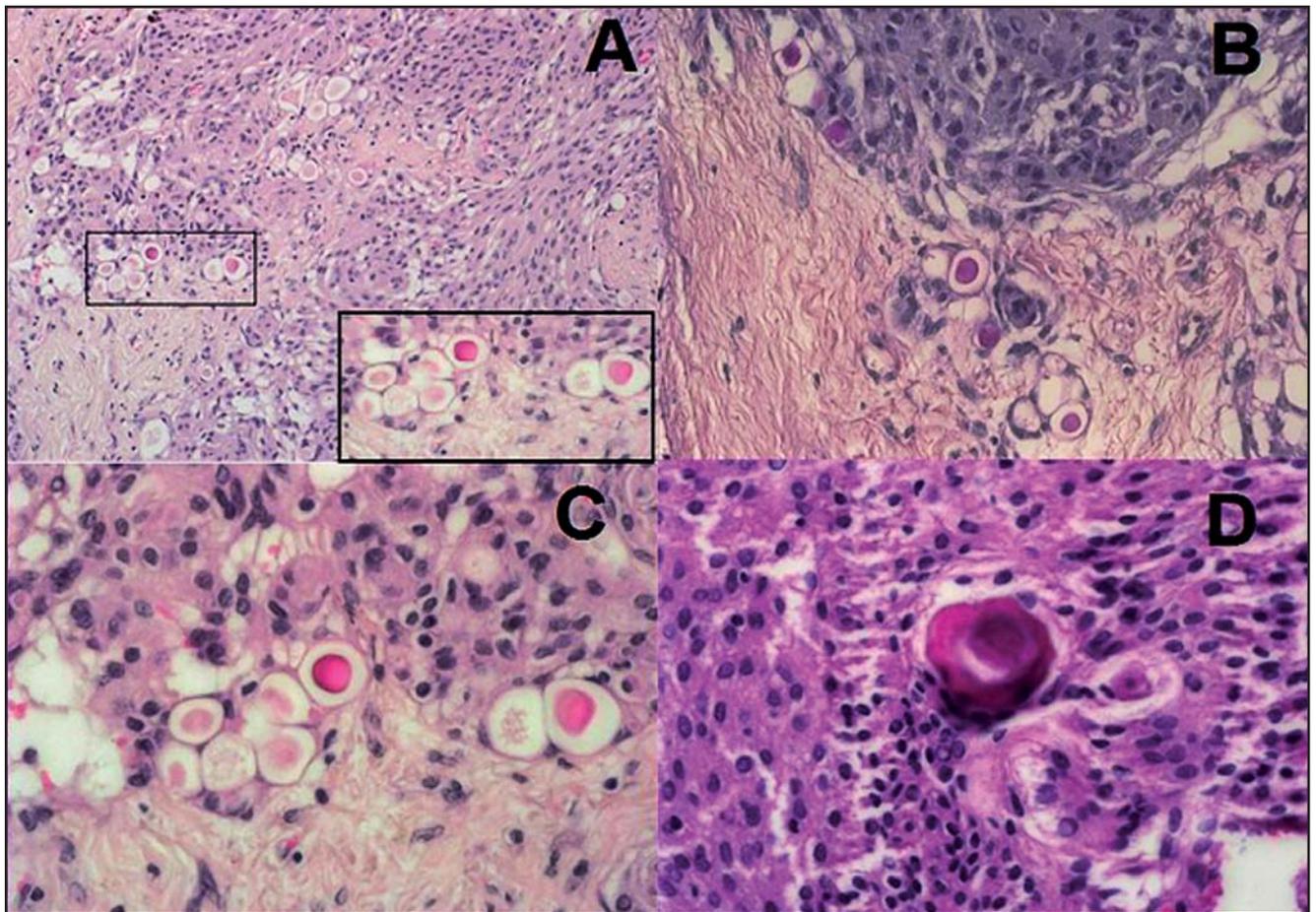


Fig. 2. **A** – Histologic appearance of secretory meningioma. The box highlights presence of hyaline pseudopsammoma bodies. The pseudopsammoma bodies stained intense purple in paS method. **(B)** Below - comparison of homogenous pseudopsammoma bodies **(C)** and larger, calcified psammoma body with visible laminated structure **(D)**.

the dura matter (“dural tail sign”) radiological examination inform about vascularization and peritumoral edema (Rennert & Doerfler 2007). PTBE is a significant factor in the occurrence of clinical signs and symptoms (Gurkanlar 2005; Pereira-Filho 2010). Some extra-axial tumors are associated with considerable underlying cerebral edema and high vascularity (Kamp 2011). The differential diagnosis includes metastases, haemangiopericitomas, lymphomas, malignant meningiomas and meningeal sarcomas (Rennert & Doerfler 2007). All of them are distinct lesions with high rate of local recurrence and late extracranial metastasing (Marosi *et al.* 2008).

Only few larger series concerning MS have been published. Regelsberger *et al.* have recently presented correlation between the clinical and histopathological features in the largest single-center series of 44 cases of MS (Regelsberger 2008). Probst-Cousin *et al.* selected 31 cases and characterized this type of tumor (Probst-Cousin 1997). The clinicopathological studies of several cases were also published by Tiratokai *et al.* (14 cases), Colakoglu *et al.* (12 cases) and Buhl *et al.* (11 cases) (Buhl 2001; Colakoglu 2003; Tiratokai 2006). Apart from these publications only few case reports were pre-

sented in recent years (Jeong & Lee 1996; Louis 1991; Nishio 2001).

It is well known that the MS are more often than other meningiomas of similar size and location surrounded by extensive PTBE causing signs and symptoms of increased intracranial pressure (Tiratokai 2006). The cerebral edema around the lesion is variable and ultrastructurally similar with vasogenic brain edema (Pereira-Filho 2010). Its formation might be also induced by cortical penetration of the tumor because it produces disruption of the tumor-brain barrier (Regelsberger 2008). Although PTBE is well controlled with the use of steroids it plays an important role in life-threatening postoperative complications, especially if the tumor is located in the skull base (Marosi 2008; Regelsberger 2008). The exact pathogenesis of this phenomenon is probably multifactorial and not completely understood (Sklar 2000).

There were some speculations that overexpression of CEA in meningiomas might cause severe PTBE (Louis 1991). Alguacil-Garcia found positive staining for CEA in MS (Alguacil-Garcia 1986). Louis confirmed expression of CEA in meningioma cells and reported elevated

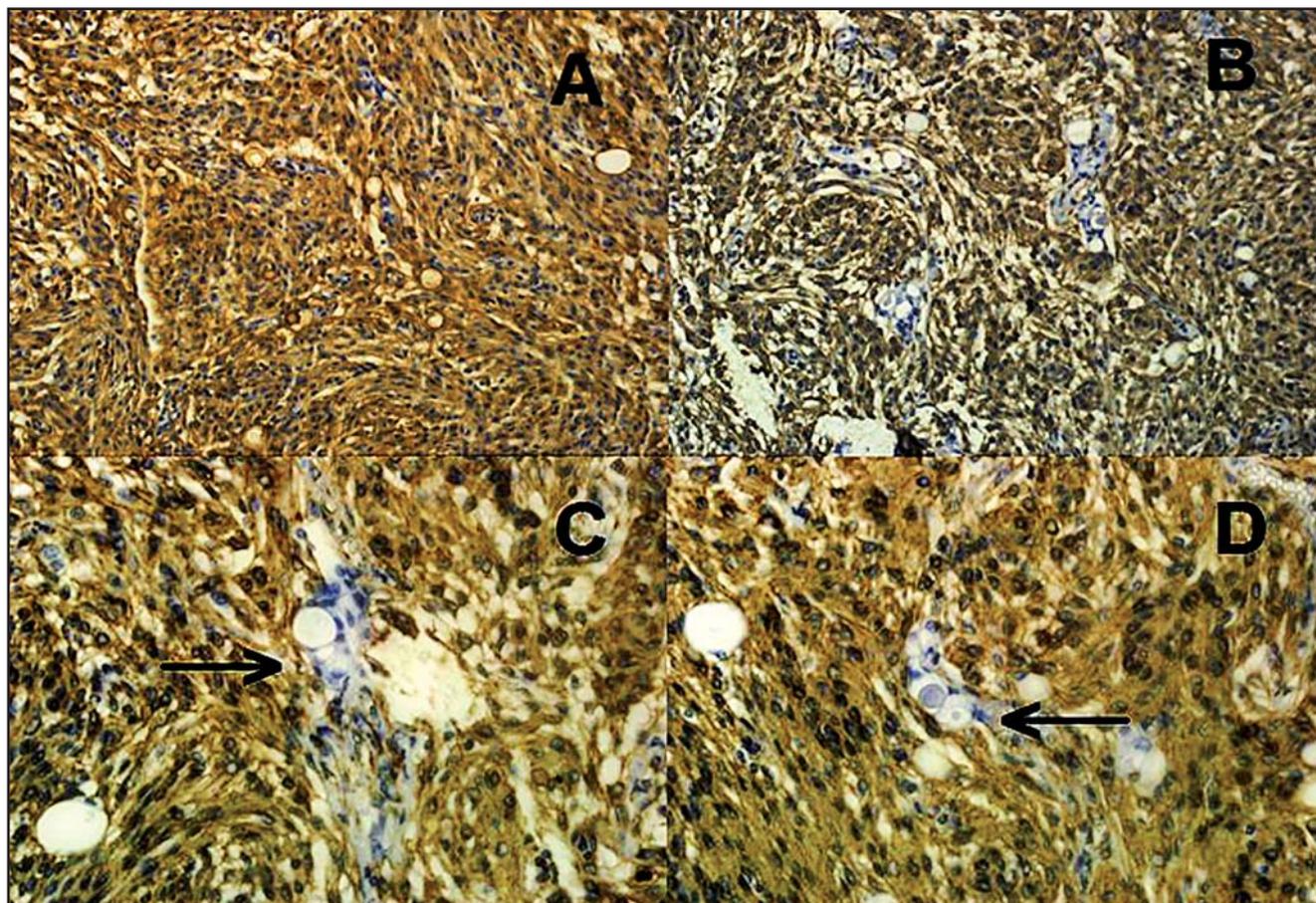


Fig. 3. Tumour showed diffuse expression of epithelial membrane antigen (EMA) (A). The presence of vimentin was detected in majority of tumor cells (B). The exception was tumor cells containing pseudopsammoma bodies and oval secretory spaces. (C and D, arrows).

serum CEA levels, which returned to normal values after successful surgery (Louis 1991). Regelsberger *et al.* also postulated the role of CK (cytokeratin) in PTBE formation (Regelsberger 2008). Their research group revealed a highly significant correlation between expression of CK and grade of edema, as well as a correlation between PAS and PTBE (Regelsberger 2008).

In presented case, there is no edema in adjacent brain although tumor cells surrounding PPBs, as well as PPBs themselves, reacted strongly with anti-CEA antibody and neoplastic cells showed presence of CK in their cytoplasm.

There is well known relationship between the tumor size and the degree of PTBE (Kamp 2011). Growing neoplasms reduce and exacerbate cerebral blood flow (Fahlbusch & Schott 2002). Perfusion and diffusion MR studies have revealed diminished regional blood flow in brain areas adjacent to the meningioma and might play an important role as a initial step inducing focal edema (Bitzer *et al.* 2002). According to the venous compression theory, meningiomas located at the sites of large veins orifices to venous sinuses might have influence on PTBE (Regelsberger 2008).

The other discussed mechanism of PTBE formation might be compound with complicated cytophysiological mechanism (Sklar 2000). It is very interesting that the higher number of mast cells is found in MS than in other subtypes of meningiomas (Tirakotai 2006). It is well known the mast cells are a source of a great many cell mediators (histamine, serotonin, heparin, prostaglandin, vascular endothelial growth factor (VEGF), MMP9, HIF-1 α , tenascin, interleukin-6, etc.) (Probst-Cousin 1997). They are associated with vasodilation and local vascular permeability disturbance (Sklar 2000). Possible etiologic role of mast cells in PTBE might be defined (Tirakotai 2006). We didn't observed mast cells in our tumor specimens, so it might be a cause of PTBE absence in reported case.

Surgery is mainstay of treatment for TSMs and alone cures the vast majority of patients (Fahlbusch & Schott 2002). The operation is a challenge because of close proximity to the surrounding vital structures, infiltration of the dura matter and invasion of the central skull base (Couldwell 2004). Additionally, described earlier PTBE is crucial in postoperative life-threatening complications (Pereira-Filho 2010; Regelsberger 2008).

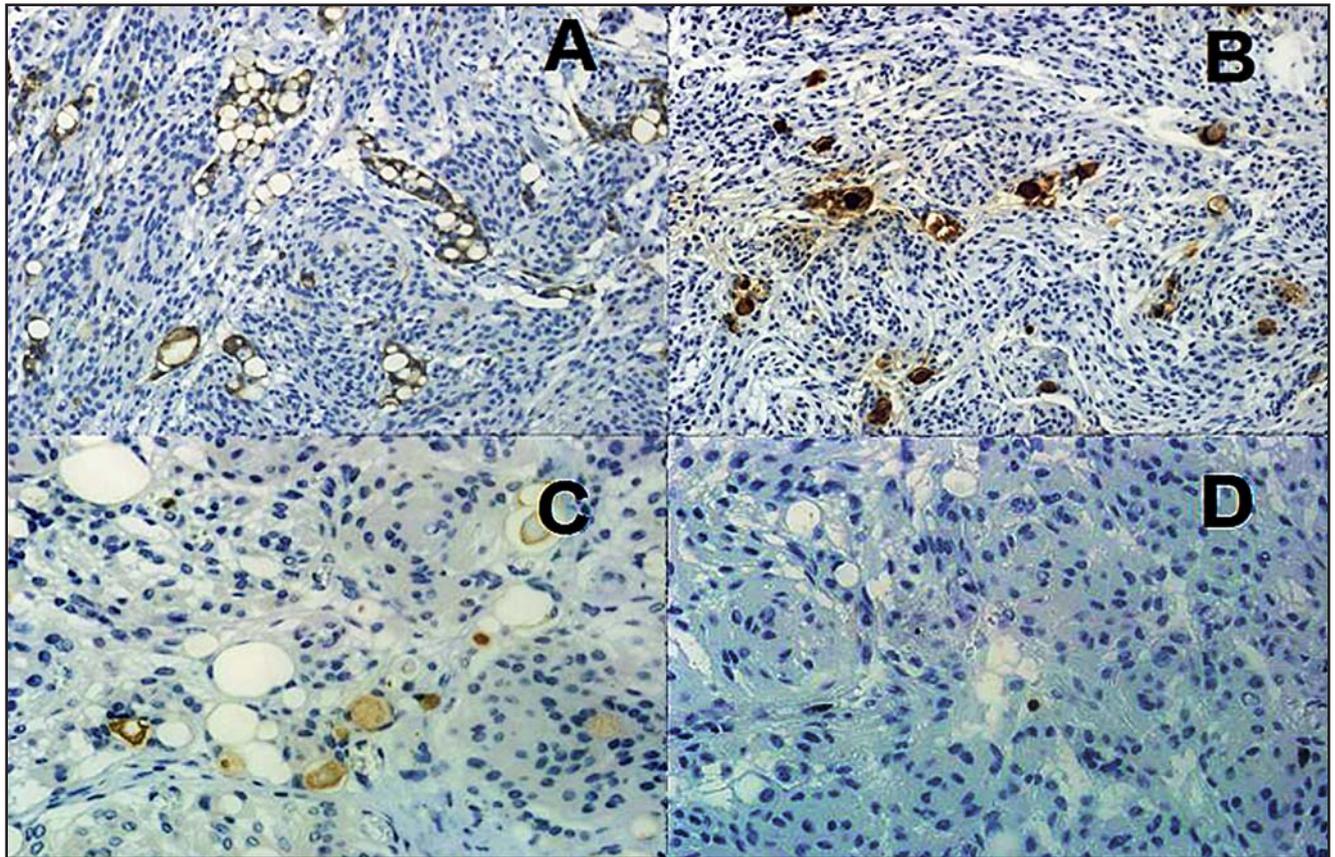


Fig. 4. **A** – Meningioma cells surrounding pseudopsammoma bodies and secretory spaces showed expression of cytokeratin (CKAE1/AE3). The same tumor cells, as well as pseudopsammoma bodies, reacted strongly with anti-CEA antibody (**B**). The meningioma cells were negative for S-100 protein, but weak expression was seen in pseudopsammoma bodies (**C**). The mitotic activity of neoplasm was very low. Only few cells reacted with antibody against Ki-67 antigen (clone MIB-1) (**D**).

Several approaches may be suitable for resection of a variety of tumor size and attachments in this region (Fahlbusch & Schott 2002). Samii group presented recently their experience in TSM, in which the bifrontal, then pterional and then – frontolateral approach were used (Nakamura 2006). They achieved total tumor resection in 92%. The similar results and the evolution of the surgical technique from larger to less invasive craniotomies have been published by Fahlbusch and Mathiessen, as well (Fahlbusch & Schott 2002; Mathiessen & Kihlström 2006). Development of the operating endoscope by Jho, and then by Couldwell and de Devitiis allows to remove suprasellar lesions via the transsphenoidal route (Couldwell 2004; de Devitiis 2007). The authors approach all TSMs, including large and giant tumor, via unilateral, subfrontal approach.

The entity appeared in the WHO classification of tumors of the central nervous system in 1993 and is classified as grade I neoplasm (Riemenschneider 2006). According to the literature, MSs constitute a group of 1.1 to 4.4% of all resected meningiomas, characterized by the presence of epithelial differentiation in form of intracellular secretory structures, *i. e.* PPBs (Louis 1991; Nishio 2001; Probst-Cousin 1997). In our Institute only 3 of 615 surgically removed primary meningiomas in years 1997–2009 were MSs, what is below 0.5%. Furthermore, two of them were surrounded by PTBE. In authors knowledge, presented case is the fourth description of the MS located in the sellar region (TSM). Moreover, only one of TSM reported in the literature was encircled by PTBE (Regelsberger 2008).

MS has distinct histological appearance with presence of strongly PAS-positive PPBs (hyaline inclusions) (Kepes 1961). By means of immunohistochemistry the investigations of PPBs showed presence of CEA, IgA, IgG, IgM and α -1 antitripsin (Nishio 2001). Moreover, tumor cells surrounding PPBs expressed CEA and CKs. Some authors noted, that these cells showed diminished or absent reaction with anti-vimentin antibody (Probst-Cousin 1997).

Besides other types of meningiomas, differential diagnosis includes metastatic carcinomas (Pereira-Filho 2010). Despite features of glandular epithelial differentiation, MS lacks signs of malignancy, cellular atypia and prominent mitotic activity (Marosi *et al.* 2008).

Prognosis in this entity is good, similarly to other types of histologically benign meningiomas (Probst-Cousin 1997). The recurrence seems to be strictly related to incomplete resection of the tumor (Couldwell 2004; Fahlbusch & Schott 2002).

CONCLUSIONS

MS is very rare and benign entity. Its treatment of choice is microsurgical excision. Histological features are characteristic but some diagnostic difficulties might occur. The differential diagnosis includes other types of meningioma and extra-axial tumors (e.g.: metasta-

ses, haemangiopericitomas, meningeal sarcomas) and immunohistochemical staining is required. Unique PTBE responsible for life-threatening postoperative complications is typical but unstable sign, especially in perichiasmatic tumors. Different factors are responsible for PTBE but their role is not well known. The dimension of PTBE might correlate with infiltration of the tumor by mast cells.

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