The WHO Grade I Collagen-forming Meningioma Produces Angiogenic Substances. A New Meningioma Entity

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Abstract. *Background: Meningiomas arise from arachnoid cap cells, the so-called meningiothelial cells. They account for 20-36% of all primary intracranial tumours, and arise with an annual incidence of 1.8-13 per 100,000 individuals/year. According to their histopathological features meningiomas are classified either as grade I (meningiothelial, fibrous/fibroblastic, transitional/mixed, psammomatous, angiomatous, microcystic, secretory and the lympholasmacyterich sub-type), grade II (atypical and clear-cell sub-type) or grade III (malignant or anaplastic phenotype). Case Report: A 62-year-old female patient presented to the hospital because of progressive obliviousness and concentration difficulties. In the magnetic resonance imaging (MRI) of the brain, an occipital convexity-meningioma was found in the left hemisphere, which was subsequently resected. Within the tumour tissue there were multiple spheroid precipitates, i.e. secretion products that turned out to consist of collagen. Part of the tumour cells displayed positive reactions for vasogenic substances, namely for vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Correspondingly, the diagnosis "WHO Grade I collagen-forming meningioma" seems to be most appropriate. Conclusion: The "WHO Grade I collagen-forming meningioma" reported herein produces collagen and angiogenic substances. To the best of our knowledge, no such entity has been reported on in previous literature. We propose this collagen-producing meningioma as a novel WHO grade I meningioma sub-type.*

Meningiomas arise from arachnoid cap cells, the so-called meningiothelial cells (1-5). They account for 20-36% of all primary intracranial tumours, and arise with an annual incidence of 1.8-13 per 100,000 individuals/year (1-5). Meningiomas are the second most common central nervous system neoplasms in adults (6-9). The incidence of meningiomas is increasing, which may be due to more sensitive diagnostic modalities (1, 10). The peak incidence of meningiomas is in the middle-aged population, with a female-to-male ratio of approximately 2:1 (11-14).

Benign or low-grade meningiomas tend to occur in a higher frequency in females, compared to males. This may be explained by a progesterone-dependent tumour growth (14-18). The so-called Clemmesen's hook is a phenomenon describing two peaks in the age-grouped distribution among female tumour patients. It is also observed for meningiomas, meaning that cancers with early onset reflect a strong hereditary pathogenesis whilst the acquired phenotypes tend to occur at a later age (13, 19, 20).

Meningiomas mostly feature a benign behavioral course and grow slowly. The majority of meningiomas are localized and non-invasive. However, meningiomas may also feature a more aggressive behavior with tendencies towards invasion of adjacent structures, a high recurrence rate and extracranial metastases (6, 21). A high histological grade, sub-total resection, young age, aggressive tumour sub-type, brain infiltration and a high proliferation rate predispose for recurrence (16, 22-25).

Meningiomas are a heterogeneous group of tumours, with variable clinical presentation, a broad spectrum of histological patterns and an inherent trend to recur (26, 27). Meningiomas may be located anywhere in the central

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Abbreviations: CNS: Central nervous system; DAL-1: protein 4.1B; ECM: extracellular matrix; EGFR: epidermal growth factor receptor; MRI: magnetic resonance imaging; PDGFRB: platelet derived growth factor receptor beta; VEGF: vascular endothelial growth factor; WHO: World Health Organization; YAP: yes-associated protein.

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Key Words: Meningioma, collagen-forming, angiogenic substances, entity.

nervous system (4). Notably, it has been observed that World Health Organization (WHO) grade I meningiomas are more frequently located at the skull-base than other meningioma subtypes (18, 28, 29).

Vascular invasion is commonly observed in meningiomas, however, metastasis only occurs in 0.1% of cases and only in grade III tumours (30). The lungs and pleura are the most common sites of metastasis, followed by the musculoskeletal system, liver, reticuloendothelial system and kidneys (31). The occurrence of several meningioma variants is probably related to the progenitor cells' various functions, for example, meningothelial cap cells may exhibit diverse morphological features and functions that overlap with both epithelial and mesenchymal cells. This is probably due to the complex ontogenesis of the meninges that have their ontogenetic roots in both mesodermal cells and cells of the neural crest (32-34).

Histopathology. In clinical practice, light microscopy of hematoxylin-eosin stained sections, analyzed based on the WHO guidelines, is used for diagnosis of meningiomas (4). According to their histopathological features meningiomas are classified either as grade I (the meningiothelial, fibrous/fibroblastic, transitional/mixed, psammomatous, angiomatous, microcystic, secretory and the lympholasmacyterich subtype), grade II (the atypical and the clear-cell subtype) or grade III (malignant or anaplastic phenotype) (21). The grade I secretory subtype can be differentiated from other subtypes by the occurrence of eosinophilic, non-fibrillary cytoplasm with eosinophilic refractile hyaline globules, according to a recent study (35). The prevalence is highest for the benign category (78-81%), followed by the atypical variant (15-20%), whilst only 1-4% of meningiomas are of the anaplastic phenotype (6). The recurrence rates of grade I, II and III meningiomas range from 7-25%, 29-52% and 50-94%, respectively (4).

In the WHO classification of 2007, a lack of anaplastic features characterizes grade I meningiomas. Grade I meningiomas comprise: the meningiothelial, fibrous/fibroblastic, transitional/mixed, psammomatous, angiomatous, microcystic, secretory and the lympholasmacyterich subtype (26). Grade II meningiomas (atypical meningiomas; including the atypical and the clear-cell subtype) feature at least one of the following criteria: 1) choroid or clear cell histology, 2) 4 to 19 mitotic figures per ten high-power fields, 3) infiltration of the brain, and 4) three or more of the following five histological characteristics: small cell change, increased cellularity, prominent nucleoli, sheet-like growth, or necrosis (4). Atypical or grade II meningiomas grow faster than the benign grade I phenotype and feature more mitoses (26, 36). Grade III meningiomas (anaplastic/malignant meningiomas) usually feature a rhabdoid or papillary sub-type, a histological picture of malignant tumour growth, resembling carcinomas, melanomas or high-grade sarcomas, or 20 or more mitoses per ten high-power fields (4).

Outcome. According to a study by Lim *et al.* on the outcome of patients with malignant meningiomas, the median time to recurrence was 35 months (range=12-61), and the 5-year progression-free survival rate was 53.6% (37). Goldsmith *et al.* reported a 5-year progression-free survival of 48% (38) and Hug *et al.* reported 52% for malignant meningiomas (37, 39). Since surgical removal is the primary treatment for malignant meningiomas, the surgical status becomes an important variable for prediction of recurrence (40-43). Incomplete tumour mass removal has a negative effect on tumour recurrence (39, 44-46). However, malignant meningiomas may even recur after complete surgical removal and after radiation therapy (25, 28, 40, 47). Since it is difficult to completely resect the tumour by surgery, there is sometimes need of adjuvant treatment after surgery, such as radiation therapy or radiosurgery (40, 48-51). Many authors emphasize that adjuvant radiotherapy after surgery should always be performed for the treatment of malignant meningiomas, because mortality rates and morbidity is generally high (25, 26, 28, 52, 53). Stereotactic radiosurgery is also an important treatment option, with lower complication rates compared to fractionated radiation therapy (46, 54-56). Stereotactic radiosurgery has been found to control tumour recurrence and to improve patients' survival rates (38, 46).

Case Report

A 62-year-old female patient presented to hospital because of progressive obliviousness and concentration difficulties. In the magnetic resonance imaging (MRI) of the brain, an occipital convexity-meningioma was seen in the left hemisphere.

Histopathological features. The meningioma was resected in a piecemeal-fashion. Together, the pieces measured 3×3×2.8 cm. The tumour tissue was highly vascularized. The mitotic activity of the tumour cells was low. Tumour cells showed syncytial formations with a rosette-like appearance. There was only mild anisokaryosis, and some parts of the tumour featured angioma-like characteristics.

Within the tumour tissue there were multiple spheroid precipitates, *i.e.* secretion products that turned out to consist of collagen. The immunohistochemical reaction with collagen 1 and 3 was positive. Part of the tumour cells displayed positive reactions for vasogenic substances, namely for vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Reaction with alpha- and beta-amyloid and cytokeratin-expression was negative in the spheroid precipitations. Vimentin and PAS-staining also remained negative. Correspondingly, the diagnosis "WHO Grade I collagen-forming meningioma" seemed to be most appropriate.

To the best of our knowledge, a collagen-producing meningioma entity has not been described in the literature. Therefore, we propose that this new, collagen forming and angiogenic substance-producing meningioma is a novel WHO grade I entity. Figures 1 and 2 illustrate the histopathological appearance in the reported case.

Discussion

Histopathological classification of atypical/grade II and malignant/grade III meningiomas. High-grade meningiomas were first recognized by Cushing and Eisenhardt in 1938 (57). The histopathological features of malignant meningiomas are highly variable (30). Sixteen subtypes have been outlined, but certain tumours also contain a histopathological mixture of these subtypes (58). In 1993, the WHO introduced the atypical meningioma as an intermediate category between the benign, and the malignant meningioma (59). Seven years later the WHO revised the classification criteria to more precise ones, implementing proliferation index, mitotic activity and brain invasion as diagnostic variables (31, 60). According to the classification of 2007, brain-invasive meningiomas have been designated as grade II (31). With the latest standards in classification, it has been shown that grade and outcome correlate better than before (61-63).

Notably, malignant transformation of a histologically benign meningioma is possible (64). As reported by Wang and colleagues, a histologically benign meningioma of a 51-year-old woman was resected, and after multiple resections and radiotherapy the tumour demonstrated malignant transformation (64).

An important histopathological feature in high-grade tumours is the immunohistochemical marker mouse intestinal bacteria 1 (MIB-1; Ki-67). A high MIB-1 index is indicative of increasing malignancy and a poorer prognosis, especially when evaluating tumours with borderline atypia (65).

In the near future, the histopathological classification might also be supported by the presence or absence of genetic alterations and telomerase activation on chromosomes 1p, 10q, 14q and 9p (66).

Molecular genetics of meningiomas. Compared to the knowledge on the molecular genetics of gliomas, relatively little is known on meningiomas to date (6-9).

In WHO grade I meningiomas, mutations of the *NF2* gene on chromosome 22 are observed in the majority of cases (50-60%) (58, 67-69). *NF2* mutations cause neurofibromatosis type II, leading to a proliferation of benign tumours throughout the central nervous system (CNS) (21). The protein Merlin is encoded by the *NF2* gene, and acts as a tumour suppressor for different cell types. Various meningioma entities feature different levels of Merlin loss (70). *NF2* gene mutations lead to impairment of merlin production, which in turn increases Yes-associated protein (YAP) levels in the CNS leading to meningioma proliferation. The Merlin protein regulates YAP levels, which control cell proliferation and the unintentional entry into the S-phase of the cell cycle (71). Loss of the protein 4.1B (DAL-1) is also observed in grade I meningiomas. In 50% of benign meningiomas, both *DAL-1* and Merlin have been found to be mutated (71). In 30-85% of sporadic meningiomas loss of the *TSLC-1* gene (tumour suppressor gene for lung cancer-1), a gene which produces a protein that interacts with DAL-1, has been found (72). Epidermal growth factor receptor (EGFR) tends to be overexpressed in grade I meningiomas, and so is the platelet-derived growth factor receptor beta (*PDGFRB*) gene (73).

In atypical grade II meningiomas, about 60% of the cases show point mutations in various chromosomes (74). Similar point mutations are observed in 75-90% of anaplastic, or grade III, meningiomas (74). In particular chromosome 1 alterations contribute to the aggressiveness and worse prognosis of grade III meningiomas, and are hardly observed in grade I meningiomas (75). There are two target regions on chromosome 1, namely 1p33-34 and 1p36, that are primarily mutated in grade III meningiomas. *PTEN* is a tumour suppressor gene which is located near the p23.3 region on chromosome 10. *PTEN* encodes for a protein that is named phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphate (76, 77). This protein is a negative regulator of the AKT/PKB pathway, which promotes tumorigenesis of meningiomas, but also various other tumour entities (78, 79). Especially in high-grade tumours *PTEN* has been found to promote proliferation and tumour progression. Mutations of genes located on chromosomes 10 and 14 have also been shown to occur in high-grade meningiomas. Deletions on chromosomes 10 and 14 lead to a functional loss of these chromosomes, resulting in an overexpression of genes of the Wnt pathway (*CTNNB1, CDK5R1, ENC1, CCND1*) and of insulin-like growth factor (*IGF2, IGFBP3, AKT3*) (69, 80, 81). The SUFU gene on chromosome 10 has also been found to promote tumorigenesis in grade II and III meningiomas, due to heterozygous germline mutations (69, 80-82). In meningioma cell lines that had no genetic aberrations of the *NF2* gene, the Glu17Lys mutation of the *AKT1* gene on chromosome 14 was observed. This mutation results in over-activation of the Akt kinase (protein kinase B), phosphorylating factors of the AKT/PKB pathway when in fact the pathway should be switched off (69, 80-82). In turn, YAP levels are increased, which leads to a decrease of the expression of pro-apoptotic genes that are usually activated after cellular DNA damage (69, 80, 81). Mainly for WHO grade III meningiomas mutations of genes located on chromosome 9 have been linked to excessive proliferation. Loss of 9p has been observed in 5% of benign meningiomas, 18% of atypical/grade II meningiomas and 38% of

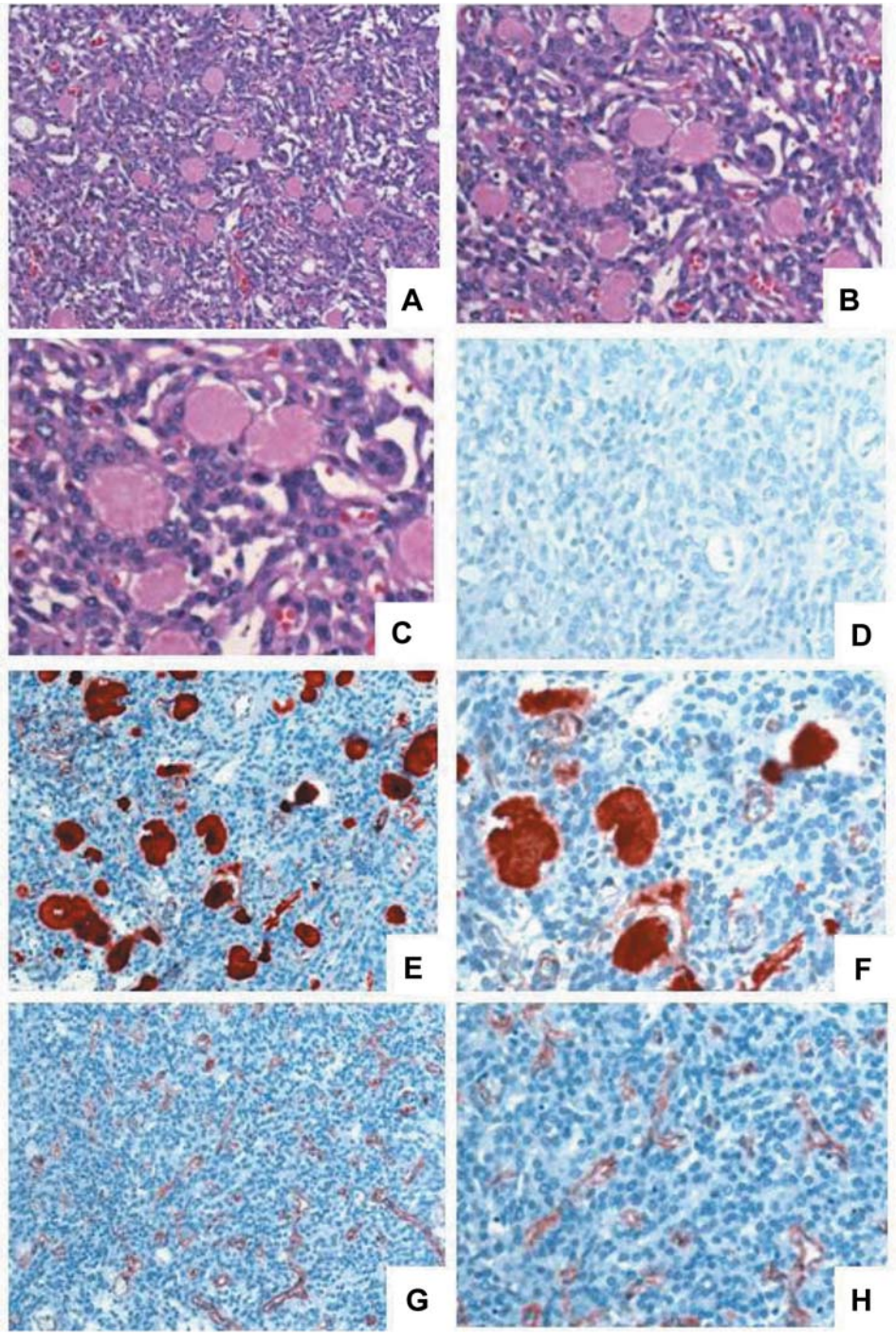

Figure 1. *A, B, C: H&E staining of sections. Magnification ×20 (A), ×40 (B), ×60 (C). D: KI-67 stain. Magnification ×40. E, F: The collagen 1 stain features distinct positivity at some areas. Magnification ×20 (E), ×40 (F). G, H: Positivity also exists for the collagen 4 stain. Magnification ×20 (G), ×40 (H).*

anaplastic/grade III meningiomas (7, 83, 84). Loss of *CDKN2A* (*p16*), p14 and *CDKN2B* (*p15*) are mutations linked to chromosome 9 which are especially observed in anaplastic meningiomas. p15, p14 and p16 are tumour suppressor genes that regulate cellular apoptosis (85). In both benign meningiomas and in grade II and III meningiomas, losses in the *TSLC-1* gene, *DAL-1* and Merlin, have been observed (36). Interestingly, the grade of aggressiveness of meningiomas

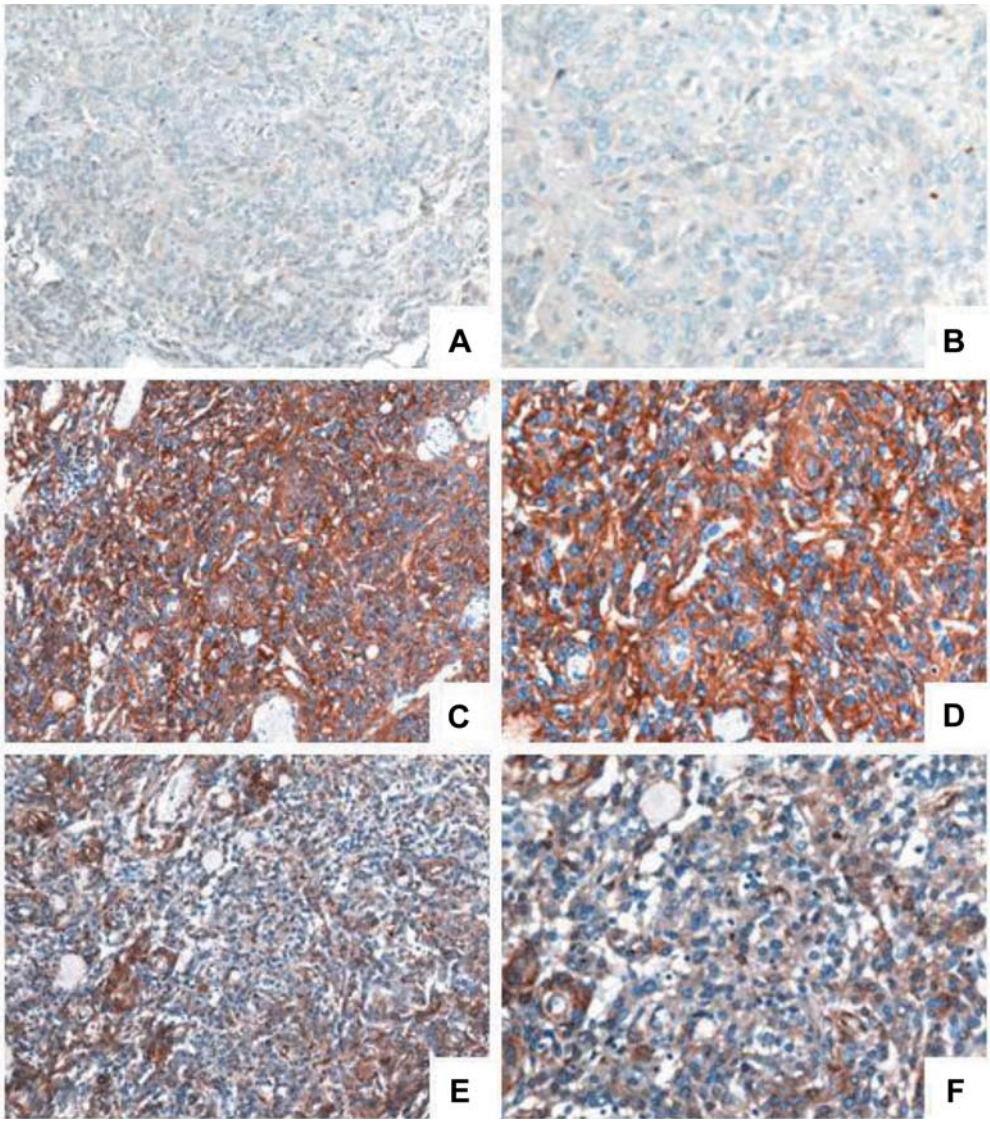

Figure 2. *A, B: The VEGF stain shows weak positivity. Magnification ×20 (A), ×40 (B). C, D: The EGFR stain is strikingly positive. Magnification ×20 (C), ×40 (D). E, F: There is weak positivity for the vimentin stain. Magnification ×20 (E), ×40 (F).*

increases along with the absence of merlin and (86-89). Losses in 6q and 18q as well as gains in 1q, 9q, 12q, 15q, 17q and 20q are other genetic abnormalities that lead to tumorigenesis of high-grade meningiomas have been determined (10, 90).

The extracellular matrix, collagen and cancer. The extracellular matrix (ECM) is a non-cellular three-dimensional macromolecular network composed of collagens, proteoglycans and glycosaminoglycans, elastin, fibronectin, laminins and other glycoproteins (91). The components of the ECM bind each other, and contain cell adhesion receptors forming a complex network in which cells reside. The ECM is part of every tissue type. It is known that cell surface receptors transduce signals into cells from the ECM, thereby regulating cellular functions such as growth, migration and differentiation or survival (91). Deregulation of the ECM is associated with the development and progression of several pathological conditions, including cancer. Indeed, it was found that the collagen alpha-1 (III) (*COL3A1*) gene, encoding an ECM protein, is upregulated in human cancers (92). For example, it has been demonstrated by Wang *et al*. that the COL3A1 protein was upregulated in colon cancer cells, as observed by immunohistochemistry (92). Interestingly, upregulated COL3A1 protein also predicted poor overall and disease-free survival, and silencing of *COL3A1*

suppressed colon cancer cell proliferation *in vitro* as well as in a xenograft model (92). The collagen triple helix repeat containing-1 (CTHRC1) protein was found to be over-expressed in injured arteries, suggesting its role in tissue repair and in vascular remodeling, and in cell migration (90, 93-96). Thus, it has been proposed that CTHRC1 contributes to abnormal angiogenesis, which is a hallmark of cancer (94, 97). Indeed, mutation of the *CTHRC1* gene has been reported to be associated with oral squamous cell carcinoma and hepatocellular carcinoma (98, 99). An elevated *CTHRC1* expression has been observed in various types of human solid cancers such as lung, thyroid, breast, ovarian, cervix, liver and pancreatic cancer (96). It is suggested that an aberrant expression of this gene contributes to cell migration, adhesiveness, cell invasion and metastasis (100, 101). Over-expression of the CTHRC1 protein was also found to be an independent predictive marker for lymph node metastasis in oral squamous cell carcinoma (90). Taken together, ECM deregulation and aberrant expression of collagen-associated genes and proteins may lead to carcinogenesis. We assume that collagen-formation in the meningioma case we report on might be the result of ECM dysfunction and deregulated ECM-to-tumour-cell signaling. It remains to be elucidated what the exact underlying pathophysiological mechanisms of collagen formation in meningiomas are, though.

Conclusion

The "WHO Grade I collagen-forming meningioma" reported herein on produces collagen and angiogenic substances. To the best of our knowledge, no such entity has been reported on in previous literature. We propose this collagen producing meningioma as a novel WHO grade I meningioma sub-type.

Conflicts of Interest

There are no conflicts of interest to be disclosed.

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Received December 13, 2015
Revised January 18, 2016
Accepted January 25, 2016