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Blood Group Isoantigens in Angioblastic Meningiomas and Hemangioblastomas of the Central Nervous System*

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Summary. The presence of blood group isoantigens in vascular endothelium cells was used in order to identify cells of endothelial origin in CNS tumors. 70 cerebrospinal tumors coded as "angioblastic meningiomas" and 30 cerebellar hemangioblastomas were examined for the detection of BG isoantigens by the specific red cell adherence (SRCA) test by Davidson (1972). In cerebellar and supratentorial hemangioblastomas a positive SRCA reaction in endothelial cells forming the prominent component of this neoplasm was opposed by a negative reaction in the large majority of interstitial (stroma) cells that argues against their endothelial origin. Identical behavior of SCRA test supports the histogenetic identity of hemangioblastomas and angioblastic meningiomas. A consistently negative SRCA reaction in cerebrospinal hemangiopericytomas except for the endothelial cells lining the capillaries supports the concept of a non-endothelial (pericytic) histogenesis of this neoplasm. Richly vascularized meningiomas with positive SRCA reaction restricted to vascular endothelial cells can be separated from angioblastic meningiomas, although transition forms are likely to occur. Angioblastic meningiomas suggested to originate from vasoformative elements (endothelium and pericytes) were found to represent 3.2 percent of a biopsy sample of 660 cases with cerebrospinal meningiomas. Their relationship to primary meningeal neoplasms needs further elucidation.

Key words: Angioblastic Meningioma — Hemangioblastoma — Hemangiopericytoma — Specific Red Cell Adherence — Endothelial Cell — Interstitial cell — Pericyte.

Introduction

Angioblastic meningiomas (Cushing and Eisenhardt, 1938) that constitute about 4 percent of the primary meningeal neoplasms (Pitkethly *et al.*, 1970) include at least three histologically different categories: 1. highly vascularized meningiomas; 2. hemangioblastomas; and 3. hemangiopericytomas (Gullotta and Wüllenweber, 1969; Rubinstein, 1972). Ultrastructural studies support the histogenetic similarity if not identity of the hemangioblastic form of angioblastic meningioma and hemangioblastomas (Castaigne *et al.*, 1968; Cervós-Navarro, 1971), although transitions between hemangioblastic and usual meningiomas showing typical meningiomatous whorls are rather frequent (Pitkethly *et al.*, 1970). Capillary hemangioblastomas (angioreticulomas), most frequently, but not exclusively occurring in the cerebellum, are composed of embryonal vascular channels, proliferating primitive endothelial cells and interstitial (stroma) cells

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which are suggested to originate from vasoformative elements—endothelium and/or pericytes (Cancilla and Zimmerman, 1965; Cervós-Navarro, 1971; Kawamura *et al.*, 1973). Hemangiopericytoma is a vascular tumor in the soft tissues, prominently arising from pericytes (Stout and Murray 1942; Silverberg *et al.*, 1971) although transition forms between pericytes and endothelial cells (Battifora, 1973) or smooth muscle cells have been observed in this neoplasm (Hahn *et al.*, 1973; Popoff and Rosomoff, 1973). The frequent attachment of cerebrospinal hemangiopericytomas to meninges and the finding of meningiomatous whorls in tissue culture lend support for their inclusion with the meningiomas (Muller and Mealey, 1971), although their poorer prognosis (tendency to recur locally and metastatzie extracranially) justifies their differentiation from the general group of angioblastic meningiomas (Pitkethly *et al.*, 1970). Evidence for the ubiquitous presence of blood group isoantigens in endothelial cells of blood vessels and erythrocytes (Davidson, 1972; Denk *et al.*, 1973) was used in order to identify cells of endothelial origin in the course of morphological studies in angioblastic meningiomas and hemangioblastomas.

Material and Methods

From a series of biopsy specimens of 660 cases with meningiomas 70 tumors coded as "angioblastic meningiomas" and 30 cerebellar hemangioblastomas were treated for the detection of blood group isoantigens by the specific red cell adherence test (SRCA), a modification of Coombs' *et al.* (1956) mixed cell agglutination test (for review see Davidson, 1972). As both water and alcohol soluble blood group substances are preserved during formalin fixation and paraffin embedding, specimens fixed in neutral buffered formalin and embedded in paraffin were used. Commercial antisera to blood group substance (BG)—A and B (Ortho) were concentrated to a hemagglutination titre of approximately 1:1000. Only specimens of blood group A and B were used. After completion of the specific red cell adherence reaction the specimens were fixed in 1–5% glutaraldehyde and stained with hematoxylin-eosin. Reagent controls were non-isologous antiserum and isologous indicator erythrocytes and vice versa. The endothelial cells of the blood vessels and the erythrocytes in the normal brain tissue as well as in the tumors were positive with respect to BG-substance in every case thus providing appropriate positive tissue controls. The results in CNS tumors were compared with those in capillary hemangioblastomas and hemangiopericytomas in the orbit and other regions.

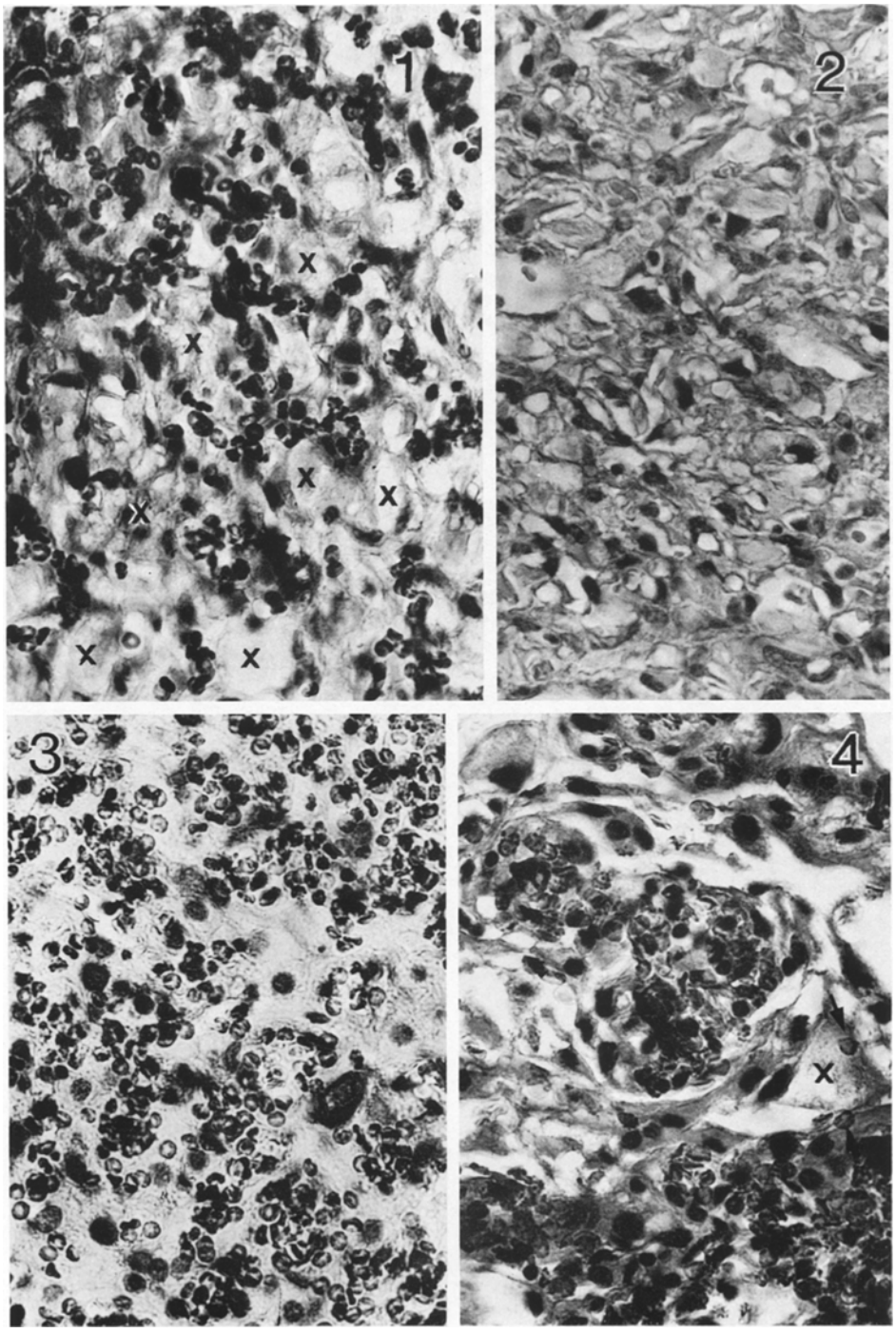
Results

1. In cerebellar hemangioblastomas and histologically similar hemangioblastic type of angioblastic meningiomas in other locations (supratentorial and spinal cord hemangioblastomas) the endothelial cells lining the vascular channels and apposed endothelial cells without visible lumen, as well as red blood cells were positive with respect to BG substances in every case (Figs. 1–6). By contrast, in the large majority of the large, polygonal and often foamy interstitial (stroma)

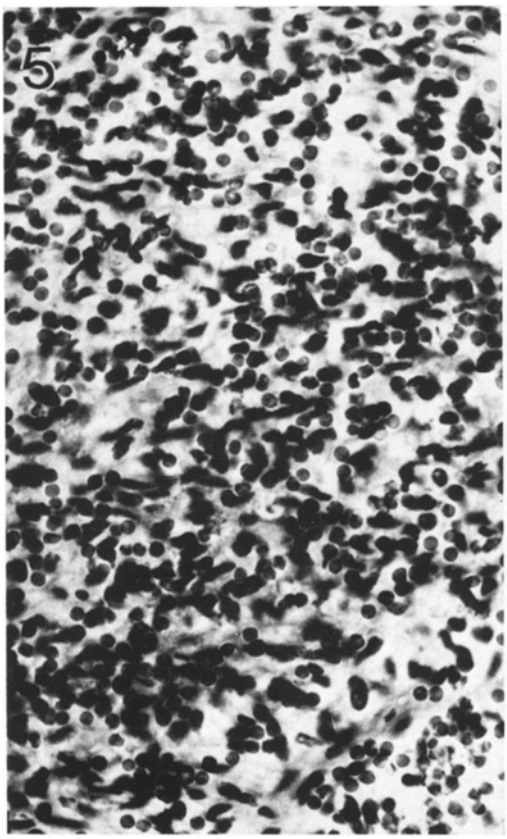
Figs. 1 and 2. Cerebellar hemangioblastoma, female aged 23 years; blood group B (N 79-67). Fig. 1. Positive SCRA reaction in endothelial cells lining vascular branches with negative reaction of stroma cells (*x*). BG B, H &E × 375. Fig. 2. Negative control. BG A—H &E × 375

Fig. 3. Angioblastic meningioma (hemangioblastoma) in parietal region of female aged 65; blood group B (N 184-72). Positive SCRA in many vascular channels. BG B—H &E × 375

Fig. 4. Parietal hemangioblastoma in female aged 64 years; blood group A (N 313-72). Positive SCRA reaction in vascular endothelium, negative in stroma cells except for occasional adherence of erythrocytes to one stroma cell (*x*). BG A—H &E × 375



Figs. 1—4



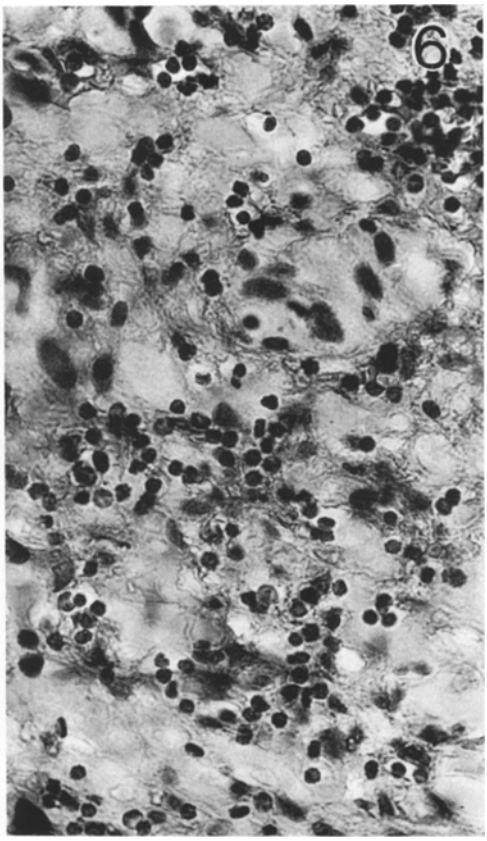


Fig. 5. Spindle cell type of cerebellar hemangioblastoma. (N 416-73). Male aged 60, blood group A. Intensely positive SCRA reaction. BG A—H. & E × 375

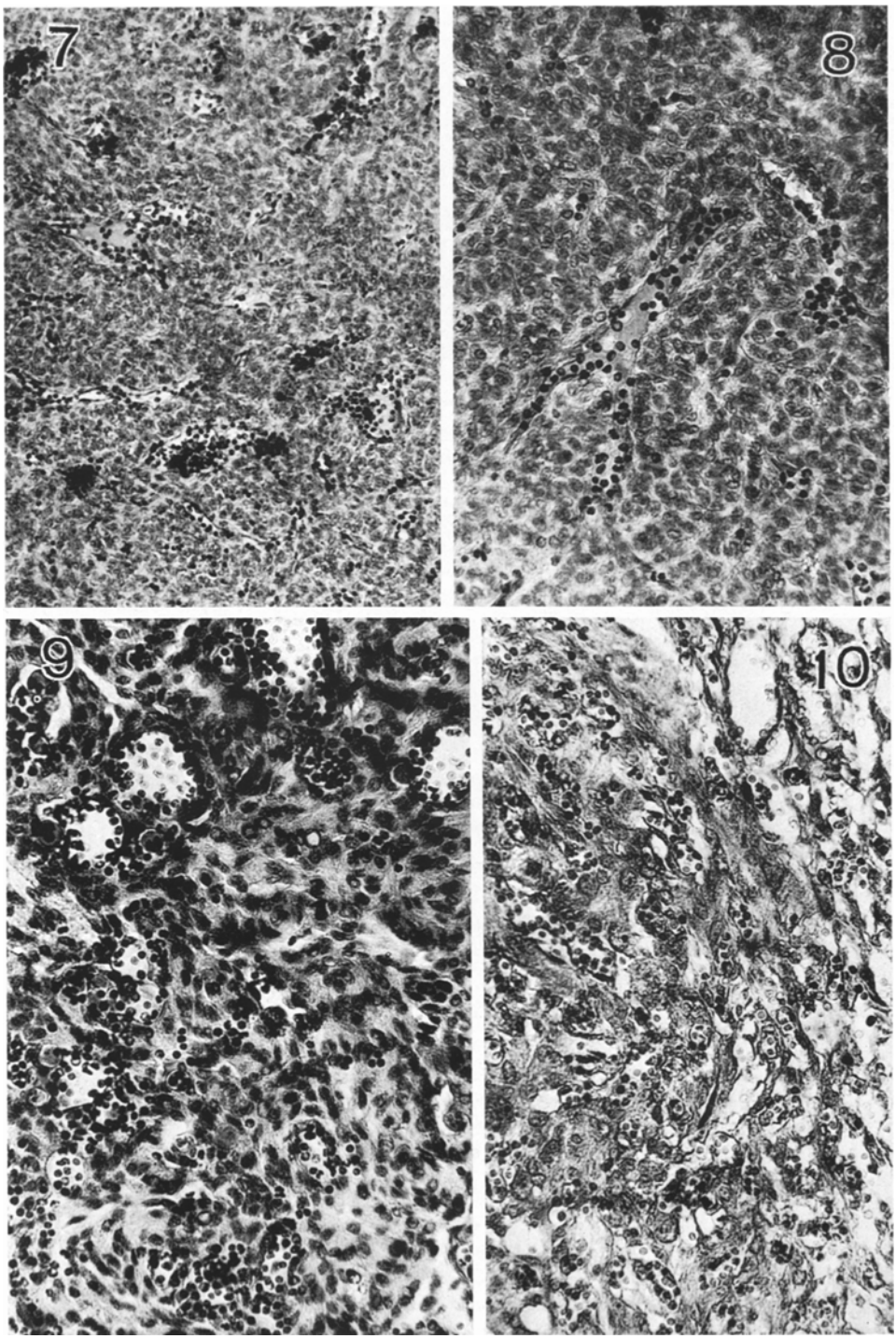
Fig. 6. Clear cell type of cerebellar hemangioblastoma (N 397-72) in male aged 41; blood group A. Positive SCRA in few capillaries and negative reaction in stroma cells. BG A—H & E × 375

Fig. 7. Meningeal hemangiopericytoma in falx region of male aged 28; blood group B. Second recurrence (N 438-73). Positive SCRA reaction only in capillaries, negative in tumor areas. BG B—H & E × 120

Fig. 8. Meningeal hemangiopericytoma in sagittal region of female aged 32; blood group A. Third recurrence (N 472-73). Positive SCRA reaction only in capillaries, negative in tumor areas. BG A—H & E × 250

Fig. 9. Highly vascularized endothelial meningioma in frontal region of female aged 61 years; blood group A (N 204-71). Positive SCRA reaction only in capillaries, negative in meningiomatous tissue. BG A—H & E × 250

Fig. 10. Angioblastic meningioma (transition form) in frontal region of male aged 50; blood group A (N 134-75). Highly vascularized meningothelial area (left) with positive reaction only in capillaries combined with hemangioblastoma areas (right). BG A—H & E × 250



Figs. 7—10

cells *no* BG activities were demonstrable (Figs. 1, 4, 6). Only in a very small number of singular interstitial cells adherence of an occasional indicator erythrocyte was suggestive for the presence of some blood group specific macro-molecules (Fig. 4). From the light microscopic appearance and the intensity of SCRA reaction, two types were distinguished: a) those rich in endothelial cells with small to moderate proportion of large stroma cells with foamy cytoplasm showing no BG activities (Fig. 5). This variety is consistent with the "juvenile type" (Silver and Hennigar, 1952) or "spindle-cell type" (Leu and Rüttner, 1973). b) Other tumors were rich in clear stromal cells, loaden with lipids and occasionally showing giant hyperchromatic nuclei with comparatively few endothelial cells containing BG substances (Fig. 6). They are akin to the "clear-cell type" (Silver and Hennigar, 1952) or "xanthomatous" type (Leu and Rüttner, 1973). Combination and transition forms were rather frequent, but no meningiomatous whorls were seen. There was no valid distinction in the histological appearance and distribution pattern of BG isoantigen activities between cerebellar and supratentorial hemangioblastomas nor between solid and cystic tumors.

2. In hemangiopericytomas of both the central nervous system and extraneural sites presence of BG-activities was limited to erythrocytes and endothelial cells lining the branching slit-like or patent capillaries, while no SCRA activity was demonstrable in the plump intervascular tumor cells (Figs. 7, 8). This distinctive pattern was uniformely observed in 11 such tumors located in the cranial cavity and cauda equina (one case), six of which showed up to 5 local recurrences. None of these tumors showed transition to meningioma-like features. There was no difference between cerebrospinal tumors and those in other locations including uterine angiomatosis or endolymphatic stromal myosis (Denk and Feigl, 1974) which shows close ultrastructural similarities to hemangiopericytoma. Only one recurring orbital hemagiopericytoma in a boy aged 4 years was particularly rich in SCRA-positive endothelial cells with or without lumina thus giving an appearance reminiscent of malignant hemangioendothelioma. Gradual blending of this pattern with areas of fairly typical pericytes without specific BG-activity, however, confirmed the diagnosis of hemangiopericytoma.

4. In examples of highly vascularized meningiomas only the endothelial cells of the blood vessels of the tumor stroma and preexisting erythrocytes showed intense adherence of specific indicator cells thus demonstrating the presence of BG isoantigens (Fig. 9). All areas of meningeal tumor including nests of meningiomatous tissue between the blood vessels and connective tissues were consistently negative.

In a small number of endotheliomatous meningiomas there was local admixture of usual meningothelial tissue showing typical whorls, and loose, reticular, richly vascularized areas with large amounts of BG-positive endothelial cells with variable numbers of SCRA-negative, clear interstitial cells, suggesting combinations or transitions between usual meningioma and hemangioblastoma (Fig. 10).

Discussion

Presence of blood group isoantigens A, B and H has been demonstrated, by means of the SCRA reaction, in erythrocytes, endothelial cells of blood vessels, and normal epithelium in many organs, while negative reactions were seen in connective and lymphatic tissues, leukocytes, basal layers, smooth and striated muscle fibers, nerve cells and glia, and carcinomas and their metastases arising in other-

wise positive tissues (f. rev. Davidson, 1972). The loss of the isoantigens was interpreted as evidence of immunologic dedifferentiation analogous to morphologic dedifferentiation or anaplasia. Ubiquitous positive controls are endothelial cells lining blood vessels.

The results of the SCRA test obtained in hemangioblastomas and angioblastic meningiomas permit the following conclusions:

1. There is identical reaction in infratentorial and supratentorial hemangioblastomas, the latter type often referred to as angioblastic meningioma or hemangioblastic type of angioblastic meningioma.

2. On the basis of our observations it is concluded that the prominent cell type in these neoplasms is formed by or derived from *endothelial cells*. Although the ultrastructure of many endothelial cells in hemangioblastomas makes them different from adult normal endothelium (cf. Kawamura *et al.*, 1973), they show uniformely positive SCRA reaction in both isomorphic and pleomorphic types of capillary hemangioblastoma (angioreticuloma).

3. On the other hand, a negative reaction in the vast majority of the stroma cells in both supratentorial and infratentorial hemangioblastomas argues *against* their general origination from endothelial cells. Whether the demonstration of incomplete SCRA reaction in an occasional interstitial cell may suggest some transitional features noted in the morphology of endothelial and stroma cells (Cancilla and Zimmerman, 1968; Cervós-Navarro, 1971; Kawamura *et al.*, 1973) is still open for discussion.

4. The consistently negative reaction of tumor cells in hemangiopericytomas of the CNS and estraneural sites fails to give evidence favoring their origin from endothelial cells. These findings do not support the close histogenetic relationship between hemangiopericytoma and hemangioblastoma which is suggested by some ultrastructural findings. The positive SCRA reaction in the endothelial cells of hemangiopericytoma cannot answer the question whether these are actively neoplastic (Stout, 1956) or simply a reaction of the host stroma to the proliferation of the tumor cells. On the other hand, rare tumors with features intermediate between hemangiopericytomas and hemangioendotheliomas are suggestive of a common origin for both vasoformative cell components in hemangiopericytoma, i.e. endothelial cell and pericyte (Battifora, 1973). It should be admitted, however, that the histogenesis of pericytes is still a matter of controversy (cf. Cervós-Navarro, 1971). The aggressive growth characteristics of meningeal hemangiopericytomas with their tendency to recur locally is confirmed in the present series. six from 11 patients with such cerebrospinal tumors showed up to 5 recurrences within 10 years as opposed to two among 40 cases of hemangioblastomas of the CNS.

5. The majority of richly vascularized meningiomas can be separated from the "angioblastic" type (hemangioblastomas) on the basis of their light microscopic appearance and the results of SCRA test, although transition or combination forms between common meningiomas and hemangioblastomas are likely to occur.

A preliminary review of 70 CNS tumors previously coded as angioblastic meningiomas revealed 10 hemangioblastomas, 11 hemangiopericytomas, and 49 highly vascularized meningiomas. Angioblastic meningiomas, i.e. tumors attached to cerebrospinal meninges but suggested to originate from vasoformative elements, thus constitute 3.2 percent of primary meningeal neoplasms in the present biopsy material. As the SCRA test obviously does not show different results in

normal, reactive and neoplastic endothelial cells, no distinction between blastomatous and purely reactive proliferation of blood vessels in vasogenic and non-vasogenic tumors can be provided by this reaction. The problems of histogenesis of hemangioblastomas, hemangiopericytomas, and the relationship of both types of vascular tumors to meningeal neoplasms, therefore, remain yet to be clarified.

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