Case Report

Meningioangiomatosis Occurring in a Young Male Without Neurofibromatosis

With Special Reference to Its Histogenesis and Loss of Heterozygosity in the NF2 Gene Region


A 16-year-old young male experienced persistent headache, and brain computed tomography and magnetic resonance imaging showed an abnormal mass with calcification in the right temporal lobe of the cerebrum. The tumor was located in the leptomeninges and cerebral cortex. In the leptomeninges, multiple calcified–fibrous nodules were noted. In this area spindle-shaped cells were arranged in a fascicular or storiform pattern. A few meningioma-like nodules were also present. With continuity of this leptomeningeal lesion, a diffuse infiltrative lesion composed of proliferating perivascular cells and hyalinized small vessels was also present in the cerebral cortex. The proliferating vessels were small and narrowed by proliferation of surrounding spindle-shaped cells. Immunohistochemically, the spindle-shaped cells had strong to moderate positivity for vimentin and CD34 and weak positivity for epithelial membrane antigen and S-100 protein. The maximum Ki67 labeling index was 0.3%. The spindle-shaped cells showed loss of heterozygosity on D17S929 and D17S282 microsatellite markers flanking the NF2 gene. These histopathologic and genetic findings are consistent with meningioangiomatosis, and meningioangiomatosis has been thought to be a neoplastic lesion of meningothelial cells. This is the first report of a genetic alteration in a case of meningioangiomatosis.

Key Words: Meningioangiomatosis—Neurofibromatosis—CD34—NF2—LCM.


Meningioangiomatosis (MA), first described in 1915 by Bassoe and Nuzum1 and named in 1937,25 is a rare condition that usually occurs in children and young adults with presentation of seizures and/or headache. The histogenesis and pathogenesis remain controversial, but its histology is unique. To our knowledge, about 60 cases have been so far reported in the English medical literature.6–10,15,17,19,23 There are two types of MA: that with type II neurofibromatosis (NF) and that without.23 However, there have been few reports of genetic changes in MA until now.19

We encountered a case of MA without stigmata of NF in a 16-year-old male patient. The clinical, histopathologic, and immunohistochemical findings and findings of microsatellite instability of two microsatellite markers flanking the NF2 gene in this case are presented. The possible histogenesis of this unique tumor is also discussed. To our knowledge, this is the first report in the English medical literature of genetic alterations in MA.

MATERIALS AND METHODS

A sample obtained from brain surgery was fixed in 10% buffered formalin overnight. Sections cut from the tissue embedded in paraffin were stained with hematoxylin and eosin and Gordon & Sweets reticulin stainings. Immunoperoxidase staining was carried out by the avidin-biotin peroxidase complex methods. The treatment for retrieval of antigen was done in citrate buffer (pH 5.5) with microwave incubation for 10 minutes. The primary antibodies used are listed in Results.

Genetic analyses were performed using formalin-fixed, paraffin-embedded tissues. Microdissection was performed using laser capture microdissection (LM200,
ARCTURUS Engineering, Santa Clara, CA, USA). In brief, a dewaxed dehydrated tissue section was stained with hematoxylin and eosin and overlaid with a thermoplastic membrane mounted on optically transparent caps. The proliferating spindle-shaped cells and non-neoplastic brain parenchyma were only captured by focal melting of the membrane through laser activation. Approximately 100 spindle-shaped cells and 100 non-neoplastic cells were necessary for PCR. After visual control of the completeness of dissection, the captured tissue was immersed in digestion solution containing proteinase K. After extracting DNA using the previously described method, polymerase chain reaction-based microsatellite analysis was performed with two microsatellite markers flanking the NF2 gene: D22S929 (intragenic microsatellite marker of the NF2 gene) and D22S282 (telomeric microsatellite marker of the NF2 gene). Loss of heterozygosity (LOH) in an informative case is considered to have occurred if the intensity of the autoradiographic signal of a given allele from the tumor DNA is reduced by at least 50% compared with that of the corresponding normal allele.

**CASE REPORT**

A 16-year-old male experienced headache for a period of 4 months. No neurologic abnormalities were detected by physical examinations. Brain computed tomography (CT) (Fig. 1) and magnetic resonance imaging (MRI) showed an abnormal mass with calcification in the right temporal lobe of his cerebrum. Carotid angiography also showed the presence of abnormal vessels. Clinically, either hemangioma or arteriovenous malformation was suspected, and resection of the tumor was performed in January 1999. At the operation the tumor was found to be located in the right middle temporal gyrus, and thickening of arachnoid mater and dilatation of arachnoidal vessels were noted. The tumor margin was clearly distinguishable from surrounding normal cerebral tissue. The patient’s postoperative course was uneventful, and he was discharged in February 1999. No signs of recurrence or clinical symptoms were detected for 30 months after the operation. Valproic acid, an anti-epileptic drug, was prescribed as a prophylaxis against seizures. Cafe-au-lait spots, neurofibroma, or acoustic schwannoma has not been observed so far, and there is no family history of NF.

**Pathologic Findings**

**Gross and Microscopic Findings**

The tumor was located in the leptomeninges and the cerebral cortex. In the lesion of the leptomeninges, multiple “tophi-like” calcified-fibrous nodules and spindle-shaped cells arranged in a fascicular or storiform pattern were noted. A few meningioma-like nodules were also present (Fig. 2A). Numerous small and large proliferating blood vessels with scattered small lymphocytes and hemosiderin-laden macrophages were also noted. The inner border of this leptomeningeal lesion had diffusely infiltrated into the underlying cerebral cortex (Fig. 2B). The main histopathologic features in the cerebral cortex were proliferation of spindle-shaped cells and small blood vessels. In some areas spindle-shaped cells were palisading around hyalinized fibrous nodules. The spindle-shaped cells were proliferating mainly in a small perivascular area and were arranged in a fascicular or storiform pattern (Fig. 2C). The cells possessed small nucleoli without pleomorphism through all areas, and no mitotic figures were observed. Multiple foci of psammoma bodies were noted. Reticulin was abundant in the areas of spindle-shaped cell proliferation (Fig. 2D). No necrotic foci were present. The proliferating vessels were small and narrowed by the proliferation of spindle-shaped cells. The basic cortical architectures were obscured. No neurofibrillary tangles in neurons and Rosenthal fibers were noted; however, neurons incorporated by this tumor showed abnormal shapes and degenerative changes.

**Immunohistochemical Findings**

Immunohistochemical analysis using microwave antigen retrieval showed the cytoplasm of the spindle-shaped cells to have positivity for vimentin (DAKO Japan, Kyoto, Japan) and CD34 (Novocastra, Newcastle upon Tyne, UK) and weak positivity for epithelial membrane
antigen (EMA) (DAKO). These spindle-shaped cells did not show positivity for alpha-smooth muscle actin (DAKO) or S-100 protein (DAKO), but positive staining for proliferating blood vessel walls was observed. Glial fibrillary acidic protein (GFAP) was not present in the spindle-shaped cells, but the background non-neoplastic cerebral cortex was strongly positive for GFAP. Only vascular endothelium showed positivity for CD31 (DAKO). Results of tests for cytokeratins (AE1/AE3, DAKO; and CAM5.2, Becton-Dickinson, Bedford, MA, USA) and p53 (DO-7, Novocastra) were negative. The maximum Ki67 (MIB1, Immunotech, Marseilles, France) labeling index was 0.3% (1000 tumor cells being counted).

Genetic Analysis
The spindle-shaped cells (T) showed LOH on both D22S282 (telomeric microsatellite marker of the NF2
MA is a rare, benign, focal lesion of leptomeninges and the underlying cerebral cortex, characterized by leptomeningeal and meningovascular proliferation. In a comprehensive analysis by Wiebe et al., MA was found to have occurred sporadically in 75% of patients and in association with NF in 25% of patients. The age distribution of patients ranges from 9 months to 70 years (average age, 28 and 21 years with and without NF, respectively). Clinical presentation includes seizure, headache, facial pain, or lower cranial nerve palsies. It has been reported that 70% of MAs are located in the frontotemporal region of the cerebrum and that the right hemisphere is affected twice as frequently as the left hemisphere. Multiple MA lesions have been reported in some patients with MA in association with NF.

Differential diagnosis includes invasive or atypical meningioma, desmoplastic infantile astrocytoma, intracranial schwannoma, vascular malformation, and some hereditary disorders. Invasive meningioma and atypical meningioma show infiltrative growth into the brain parenchyma. Infiltration of invasive meningioma into the brain parenchyma is usually associated with destruction of pia mater or the Virchow-Robin space, and invasive meningioma is composed of spindle-shaped or polygonal arachnoid cells, but it lacks the prominent vascular component. Atypical meningioma (WHO grade II) shows increased mitotic activity or three or more of the following features: increased cellularity, small cells with high nucleus/cytoplasm ratio, prominent nucleoli, interrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis. Desmoplastic infantile astrocytoma usually involves the superficial cerebral cortex and leptomeninges, often attached with dura mater, and it consists of a prominent desmoplastic stroma with a neuroepithelial population, mainly restricted neoplastic astrocytes, or astrocytes together with a variable neuronal component. Intracranial schwannoma is usually encapsulated and is composed of differentiated Schwann cells arranged in a nuclear palisading pattern (Antoni A) or in a pattern of less cellular, loosely textured, often lipidized tumor areas (Antoni B), and the tumor cells show strong positivity for S-100 protein and Leu-7. Arteriovenous malformation is composed of a jumble of abnormal vessels with varying degrees of muscularrization, and small luminal protrusions or cushions are typical. In contrast to cavernous hemangioma, there is considerable brain parenchyma between the abnormal vessels. All of the tumors and tumor-like lesions mentioned above are different from the histologic and immunohistochemical features of the present case.

MA is considered to be a hamartomatous or maldevelopmental lesion, a reactive condition, or an entity of neoplastic origin. However, the histogenesis or etiology of MA has been debated for a long time. One possibility is that MA is a primary meningothelial cell proliferation and a variant of meningioma and meningioma-en-plaque. Giangaspero et al. reported two cases of meningioma with MA and suggested that MA is primarily a meningothelial lesion. Mut et al. and Blumenthal et al. also described similar cases. Kunishio et al. reported the ultrastructural findings of proliferating cells in MA and negative S-100 protein by immunohistochemistry, and they suggested that MA originated from meningothelial cells. Wiebe et al. reported various staining patterns for EMA, S-100, Leu-7, GFAP, lectin, and CAM5 in their six cases and other cases reviewed in the literature (total of 24 cases), and their results indicate that pluripotent cells may differentiate into the various cell types found in MA. Others have suggested a fibroblastic (probably perivascular) origin on the basis of association with procollagen I and III, lack of collagen IV, and vimentin positivity. Izycka-Swieszewska et al. suspected a myofibroblast or possibly smooth muscle cell as an original cell. They also speculated that the abundant vascular network within the lesion may be physiologic, developmental, reproductive, and reactive processes regulated by many growth factors and inhibitors, including basic fibroblastic growth factor, vascular endothelial growth factor, and transforming growth factors. Chakrabartty and Franks reported a case of MA showing negative immunoreactivity for GFAP and EMA, and they suspected a primitive perivascular mesenchymal cell.
association of MA with arteriovenous malformations suggests that the primary abnormal vascular proliferation induces the diffuse proliferation of perivascular meningothalial cells.

In the present case the presence of meningioma-like nodules in leptomeninges and the immunohistochemical results, including vimentin, CD34, and EMA positivity, indicate that the origin of this tumor is from meningothalial cells. CD34 positivity does not conflict with a meningothalial origin because a subset of meningiomas was reported to be positive for CD34. Stemmer-Rachamimov et al. reported the absence of somatic mutations of the NF2 gene region in meningiomas.

Further study, including sequencing analysis of the NF2 gene, is necessary.

Regarding treatment, partial or complete resection of the MA lesion has been recommended. Seizures persist to one focus. Thus, anti-epileptic agents are required even after the removal of MA. The present patient has not shown any clinical symptoms after the operation; however, careful follow-up is necessary.

REFERENCES

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