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Epidermal Growth Factor Receptor Overexpressed Malignant Fibrous Histiocytoma Associated With Recurrent Meningothelial Meningioma

—Case Report—

Rosario CALTABIANO, Giuseppe PARISI*, Vincenzo ALBANESE*, and Salvatore LANZAFAME

Department G.F. Ingrassia, Section of Anatomic Pathology, and *Department of Neurosurgery, University of Catania, Catania, Italy

Abstract

A 71-year-old woman presented with a rare case of malignant fibrous histiocytoma (MFH) associated with recurrent meningothelial meningioma. The neuroimaging findings were consistent with a diagnosis of recurrent meningioma. Surgical removal was performed. Histological and immunohistochemical examinations detected meningothelial and MFH tumor components. The MFH component showed diffuse 3+ staining for epidermal growth factor receptor protein, predominantly located on the cell membrane and to a lesser extent within the cytoplasm. However, a fluorescein isothiocyanate analysis detected no amplification of epidermal growth factor receptor gene.

Key words: malignant fibrous histiocytoma, meningioma, epidermal growth factor receptor, fluorescein isothiocyanate, case report

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Introduction

The term malignant fibrous histiocytoma (MFH) was first introduced in 1963 to refer to a group of soft tissue tumors consisting of fibroblasts, myofibroblasts, and undifferentiated mesenchymal cells, and characterized by storiform architecture and the presence of pleomorphic giant cells, which were initially believed to be derived from histiocytes. However, immunohistochemistry has shown that the phenotype of this tumor is more closely related to fibroblasts than histiocytes. Now there is general agreement that the term MFH should be used only if the histological and immunohistochemical findings show no definable line of differentiation.⁷⁾ Therefore, pleomorphic MFH is synonymous with undifferentiated pleomorphic sarcoma in the World Health Organization classification. There are several histological subtypes of MFH: storiform-pleomorphic, myxoid, giant cell, and inflammatory types.¹⁰⁾ The most common is the storiform-pleomorphic type consisting of a mixture of storiform and pleomorphic areas.

MFH is a tumor of late adult life, with most cases occurring in patients aged 50 to 70 years. The most common location is the lower extremities, especially the thigh, followed by the upper extremities and retroperitoneum. Primary intracranial MFH is extremely rare, with only reported 28 cases,^{1,4,9,12,14}) as well as one case of MFH associated with meningothelial meningioma.¹¹) The preoperative differential diagnosis between meningioma and intracranial MFH is very difficult, as the neuroimaging findings are very similar.

We describe a rare case of MFH associated with recurrence of meningothelial meningioma, and the immunohistochemical and epidermal growth factor receptor (EGFR) gene amplification findings in both tumors.

Case Report

A 71-year-old woman first underwent surgical treatment for a left temporo-parietal meningothelial meningioma in 2004. Remnants of the tumor were evident on postoperative magnetic resonance (MR) imaging (Fig. 1). She developed hypesthesia of the right hand and the right lower limb, aphasia, reduction of the short-term memory, and alterations of the field of vision in 2007. MR imaging demonstrated a 6-cm long tumor mass in the left parietal region, appearing as inhomogeneously hyperintense with a central hypointense region (Fig. 2).Therefore, she underwent second surgical treatment for recurrence of the left parietal transitional meningioma. She did well after the surgery, but suffered sudden paresis of the right upper limb, aphasia, and right lateral hemianopsia after few weeks.

On admission to our facility, physical examination revealed hyperreflexia of the right arm with Babinski response, and ataxia-spastic gait. Laboratory investigations, chest radiography, and electrocardiography revealed no abnormalities. MR imaging demonstrated a 5-cm long tumor mass in the left parietal region, appearing as inhomogeneously hyperintense with a central hypointense region, corresponding to the location of the tumor



Fig. 1 Coronal (left) and axial (right) T_1 -weighted magnetic resonance images demonstrating remnants of the tumor after surgical treatment in 2004.



Fig. 2 Coronal (left) and axial (right) T_1 -weighted magnetic resonance images demonstrating a 6-cm long tumor mass in the left parietal region, appearing as inhomogeneously hyperintense with a central hypointense region, before surgical treatment in 2007.



Fig. 3 Coronal T_1 -weighted magnetic resonance image demonstrating a 5-cm long tumor mass in the left parietal region, appearing as inhomogeneously hyperintense with a central hypointense focus.



Fig. 4 Photomicrograph showing one tumoral component consisting of meningiomatous cells with indistinct cellular borders aggregated into small sheets and large lobules, and a second tumoral component consisting of proliferating atypical spindle cells with irregular elongated and pleomorphic nuclei and many mitoses. Hematoxylin and eosin stain, \times 50.

(Fig. 3). These findings were consistent with a diagnosis of recurrent meningioma. The patient underwent craniotomy and a large 5-cm tumor mass was removed. MR imaging detected no residual tumor after the surgery. The histological diagnosis was MFH associated with meningothelial meningioma. Therefore, the patient was also treated with radiotherapy. One month after surgery, the patient had aphasia and right hemiplegia. She was still alive 6 months after the surgical treatment.

Histological investigation: All specimens were fixed in 10% neutral-buffered formalin at room temperature, embedded in paraffin wax, and $4 \,\mu m$ serial sections mounted on silane-coated glass slides. Histological examination demonstrated 2 types of tumor cell proliferation. The first component consisted of meningiomatous cells with indistinct cellular borders aggregated into small sheets and large lobules, with rather isomorphic and pale nuclei with some pseudoinclusions and small evident nucleoli. The general aspect was syncytial. Small whorl formations were also evident, but mitoses were absent. The second component was characterized by proliferating atypical spindle cells, with irregular elongated and pleomorphic nuclei and many mitoses. These cell proliferation patterns merged into a dense tumor with elongated and pleomorphic cells, storiform pattern, and focal necrosis. Pleomorphic tumor cells varied from spindle-shaped fibroblast-like cells to more rounded cells with clear, oval-shaped nuclei consistent with histiocytes, containing abundant vacuolated cytoplasm (Fig. 4).

Immunohistochemistry was performed with mouse antibody against vimentin (DAKO, Glostrup, Denmark; trypsin; 1:150), glial fibrillary acidic protein (GFAP) (DAKO; microwave pretreatment; 1:100), epithelial membrane antigen (EMA) (DAKO; no antigen retrieval; 1:200), Ki-67 (DAKO; microwave pretreatment; 1:250), CD34 (DAKO; microwave pretreatment; ready to use), CD68 (BIOGE-NEX, San Ramon, Calif., U.S.A.; microwave pretreatment; ready to use), desmin (DAKO; no antigen retrieval; ready to use), and EGFR pharmDxTM (DAKO; no antigen retrieval; ready to use). All antibodies were applied di-



Fig. 5 Photomicrograph showing positive staining for epithelial membrane antigen (EMA) in the meningioma component and negative staining for EMA in the malignant fibrous histiocytoma component. \times 50.



Fig. 6 Photomicrograph showing diffuse 3+ staining for epidermal growth factor receptor protein predominantly located in the cell membrane and to a lesser extent within the cytoplasm of the malignant fibrous histiocytoma component. \times 100.

rectly to each section and the slides were incubated overnight (4°C). Immunocomplexes were subsequently treated with the secondary antibody and then detected with streptavidin peroxidase, both were incubated for 30 minutes at room temperature (Vectastain ABC kit; Vector Laboratories, Burlingame, Calif., U.S.A.). Immunoreactivity was visualized by development for 2 minutes with 0.1% 3,3'-diaminobenzidine and 0.02% hydrogen peroxide (DAB substrate kit; Vector Laboratories). Sections were counterstained with Mayer-hematoxylin, and mounted with permount. Immunoreactivity was evaluated by two independent observers unaware of the clinical details. Negative controls consisted of sections in which primary antibodies were replaced with either nonimmune murine serum (X 0910; DAKO) or with 1% bovine serum albumin in phosphate buffered saline. The MIB-1 labeling index was defined as the percentage of immunoreactive cells divided by the total number of cells in the evaluated area. Distinct nuclear staining was considered as positive. The first type of cell proliferation was characterized by positive staining for EMA (Fig. 5) and vimentin, negative staining for GFAP, desmin, EGFR protein (EGFr), CD68, and CD34, and low MIB-1 index. The second type of cell proliferation was characterized by positive staining for vimentin, EGFr (Fig. 6), and CD68, negative staining for EMA (Fig. 5), GFAP, desmin, and CD34, and high MIB-1 index.

Gene amplification was determined by fluorescein isothiocyanate (FISH) analysis using fluorescent-labeled deoxyribonucleic acid probe sets (Vysis, Downers Grove, Ill., U.S.A.) containing a spectrum green-labeled EGFRspecific probe and a spectrum orange-labeled chromosome 7 centromere probe to standardize copy number. The sections were counterstained with 4V,6-diamidine-2V-phenylindole dihydrochloride and p-phenylenediamine (Vysis) and examined under a fluorescence microscope (Olympus, Tokyo). The FISH analysis detected no gene amplification of EGFR.

The diagnosis of MFH associated with meningothelial meningioma was based on the morphological and immunohistochemical features. Reexamination of the tumor specimens obtained in 2004 confirmed the diagnosis of meningothelial meningioma, whereas the tumor specimens obtained in 2007 had already revealed the coexistence of meningothelial meningioma with MFH.

Discussion

Intracranial MFH can be classified into meningeal MFH that originates from the dura, and intracerebral MFH that develops in the brain. Only a few cases of intracranial MFH have been reported since the first in 1976.8) These rare tumors are especially important because of the poor prognosis and potential for diagnostic confusion caused by the clinical resemblance to other brain tumors, in particular meningiomas. Such confusion between meningioma and MFH is illustrated by the diagnosis of the present tumor in 2007. Great care is necessary to distinguish MFH from fibrous meningioma and meningeal solitary fibrous tumor because of the wide variability in morphological appearance and lack of distinctive features.⁵⁾ However, fibrous meningioma with fascicular arrangement and solitary meningeal fibrous tumor are not difficult to differentiate because MFH shows pleomorphism, high mitotic activity, and negative CD34 staining. MFH might also be difficult to distinguish from the sarcomatous component associated with glioblastoma (gliosarcoma). Although MFH is an uncommon tumor in neuropathologic practice, criteria for correct diagnosis are important to establish. In our case, negative GFAP staining excluded the possibility of an astroglial tumor. The tumor is consisted of a MFH component with a storiform pattern, many mitoses, and high MIB-1 index, and a meningothelial meningioma component with cells aggregated into small sheets and large lobules, and pale nuclei occasionally with cytoplasmic invaginations (pseudoinclusions).

I. Etiology of MFH

The cellular origin and molecular processes underlying the evolution of MFH are not completely understood. Early studies suggested derivation from histiocytes but pluripotent mesenchymal cells are now generally accepted as the origin, differentiating into fibrocytic and histiocytelike elements.¹³⁾ Some evidence suggests that MFH can be induced by irradiation for tumors of various types, only developing after an interval of several years.²⁾ Our patient had previously undergone surgery for a meningioma at the same site, but did not receive any irradiation prior to the present illness, so that the MFH cannot be considered as secondary to radiotherapy. Traumatic etiology has also been suggested in several studies, so the surgical treatment of the previous meningioma could have been the trigging event in our patient. Intracranial MFH may also occur as metastatic disease secondary to an extracranial primary tumor. In our case, no extracranial primary MFH was identified.

II. Relationship between MFH and meningioma

The present case also raises questions about the relationship between MFH and meningioma. MFH probably arises from pluripotent mesenchymal cells differentiating into fibrocytic and histiocyte-like elements, so our case of MFH may have arisen from the mesenchymal stem cells of the dura, which subsequently infiltrated pre-existing meningioma. However, our case may also have arisen from the mesenchymal stem cells of the interlobular septa of the meningioma or, as for intranervous MFH, from the perivascular mesenchymal cells of the meningioma. The consensus that MFH is synonymous with pleomorphic sarcoma, which shows no definable line of differentiation, suggests that our case of MFH may have differentiated along the meningiomatous line. However, the absence of any transitional cell type between meningioma and MFH, and the sharp border between the two tumors do not support this hypothesis. Another possibility to be considered is the occurrence of sarcomatous foci within meningioma. The present case of MFH could represent transformation of the previous meningioma, but the two lesions were widely separated, both in location and time, and were histologically and immunohistochemically distinct entities.

In the present case, the MR imaging findings were consistent with those of recurrent meningioma. The macroscopic appearance of the tumor was also consistent with that of meningioma during surgery. Only the histological findings established the correct diagnosis of MFH associated with meningioma, resulting in a complete change in the course of postoperative management. Soft tissue sarcomas generally respond to radiotherapy, and the beneficial effects of adjuvant chemotherapy are increasingly reported.³⁾ Previous studies reported EGFR overexpression and gene amplification in MFH.⁶⁾ Our immunohistochemical and FISH analysis found EGFr overexpression without gene amplification only in the MFH and not in the meningioma. These findings underline the difference between the two tumors, and may suggest treatment of this patient with anti-EGFR antibody and small molecule tyrosine kinase inhibitors, aimed at inhibiting or interrupting this signaling pathway.

III. Treatment

Unfortunately, there are no established treatment principles for intracranial MFH. Surgical excision was performed in 16 of 17 previous cases,¹⁴⁾ considering that the tumor has a firm clear boundary with few blood vessels. However, dural attachment may remain, resulting in recurrence. In our case, it was considered that total excision could be performed. Seventeen cases of primary intracranial MFH included 5 local recurrences (29%) and 3 extracranial metastases (18%).¹⁴⁾ Whether the prognosis of MFH involving the extremities or retroperitoneum is the same as that of aggressive primary intracranial MFH remains unclear, but several patients had a rapidly progressive course leading to death within the first year after surgery followed by adjuvant chemoradiotherapy.¹⁾

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- Address reprint requests to: Salvatore Lanzafame, M.D., Department G.F. Ingrassia, Section of Anatomic Pathology, University of Catania, Santa Sofia 87 street, 95123 Catania, Italy. *e-mail*: lanzafas@unict.it