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Gliosarcoma arising from a fibrillary astrocytoma

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ABSTRACT

We report a 67-year-old woman who was diagnosed with a gliosarcoma at a second operation after diagnosis of a fibrillary astrocytoma 5 months previously. Initially, she underwent a CT-guided stereotactic biopsy. Histological examination showed fibrillary astrocytoma (World Health Organization [WHO] grade II). Loss of heterozygosity (LOH) on 1p, 10q, and 19q was not detected. She received chemotherapy, but no radiotherapy. Five months after the biopsy, MRI revealed rapid tumor growth. Tissue obtained from partial removal of the tumor revealed gliosarcoma (WHO grade IV), and LOH on 10q and 19q was detected. The history, histopathology, and genetic alterations of this patient are discussed.

1. Introduction

Gliosarcoma is a rare malignant neoplasm of the central nervous system that accounts for 2% to 8% of all patients with glioblastoma multiforme (GBM).[1,2] Gliosarcoma is defined as a GBM variant with a biphasic tissue pattern of glial and mesenchymal differentiation, with significant clinical and genetic similarities.[1,3] The mechanism of pathogenesis of gliosarcoma is unclear. Most gliosarcomas are diagnosed *de novo* at the time of first resection of a brain tumor, however a small number are diagnosed at subsequent surgery for a previously resected and irradiated GBM.[4–6] The former is termed primary gliosarcoma, and the latter secondary gliosarcoma. However, malignant transformation from diffuse astrocytoma to gliosarcoma has not been previously described. We report a patient with gliosarcoma diagnosed at a second operation after a previous diagnosis of fibrillary astrocytoma.

2. Case report

2.1. History

A 67-year-old woman reported having dizzy episodes. A CT scan showed a high-density mass in her right hemisphere. Neurological examination revealed no deficits. An MRI scan demonstrated a mass in the right corona radiata (Fig. 1A and B). Magnetic resonance (MR) spectroscopy showed no elevation of lactate levels (Fig. 1C). A CT-guided stereotactic biopsy was performed of the slightly enhancing area of the lesion on the MRI, with preoperative fusion of the CT scan and MRI. The histological diagnosis was fibrillary astrocytoma (World Health Organization [WHO] grade II). The patient received 50 mg of ranimustine with interferon-β. She received no radiotherapy. Five months after the biopsy, follow-up MRI revealed rapid tumor growth, with projection into the right lateral ventricle (Fig. 1D and E). MR spectroscopy showed an elevated lactate peak and a decline of the N-acetylaspartate peak (Fig. 1F). The neurological symptoms now included head heaviness and mild right hemiparesis. The patient underwent surgery to partially remove the tumor located in the right lateral ventricle using a transcortical–transventricular approach. The tumor was composed of grayish and reddish, rubbery, firm tissue that was not removable using suction. The histological examination showed gliosarcoma (WHO grade IV). Three months later, the patient died due to tumor progression. No autopsy was performed.

2.2. Histology at the first operation

On hematoxylin and eosin (H&E) staining of the tumor removed at first diagnosis, cellularity was moderately increased, and nuclear atypia was mild. Mitosis, necrosis, and microvascular proliferation

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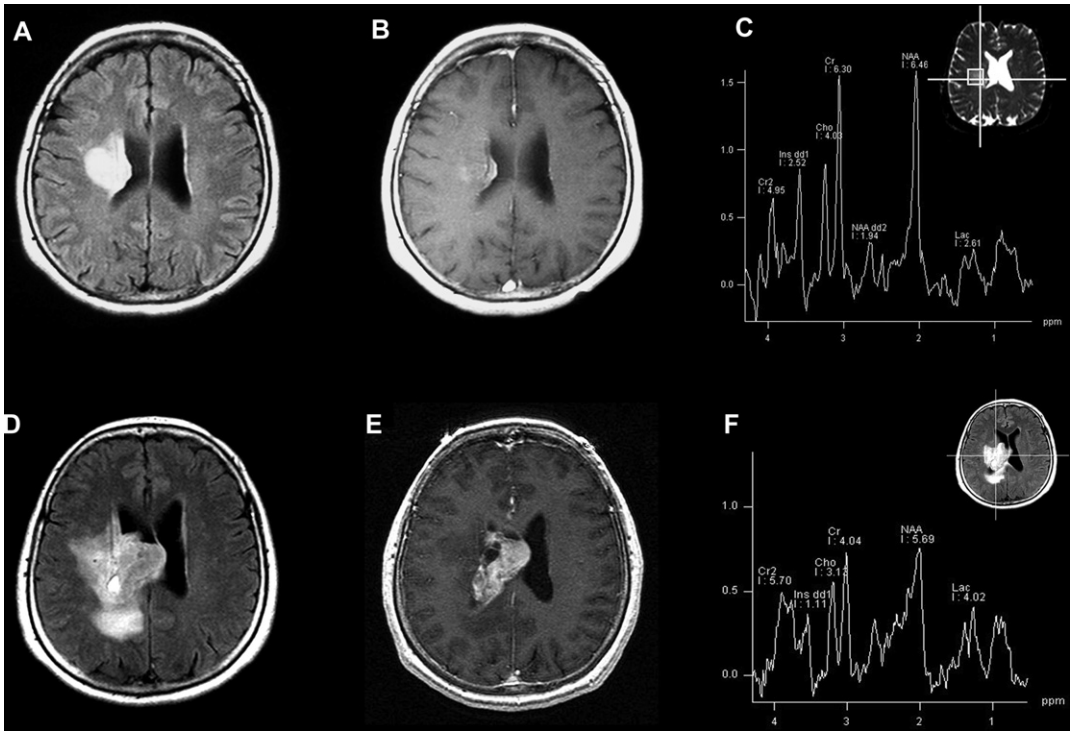

Fig. 1. (A) Axial fluid-attenuated inversion recovery (FLAIR) and (B) axial gadolinium (Gd)-enhanced T1-weighted MRI taken before the first operation showing a mass with mild enhancement in the right corona radiata. (C) Magnetic resonance (MR) spectroscopy showing no elevation of the lactate peak (Lac). (D) Axial FLAIR and (E) axial Gd-enhanced T1-weighted MRI images taken before the second operation showing rapid growth of the tumor with prominent enhancement. (F) MR spectroscopy shows an elevation of Lac levels and a decline of the N-acetylaspartate (NAA) peak.

were absent (Fig. 2A). The tumor contained Rosenthal fibers (Fig. 2B), typical in brain areas with prolonged proliferation of astrocytes. Immunohistochemical (IHC) staining demonstrated many astrocytes, with most cells testing positive for vimentin (Fig. 2E) and glial fibrillary acidic protein (GFAP) (Fig. 2F). The MIB-1 labeling index (LI) was less than 1% (Fig. 2C), and p53 expression was 11% (Fig. 2D). Silver staining showed no positive areas (Fig. 2G).

2.3. Histology at the second operation

Histological examination after resection of the progressing tumor demonstrated a biphasic differentiation pattern with gliomatous and sarcomatous areas (Fig. 2H). In some regions, the gliomatous and sarcomatous components existed in a mosaic pattern. The gliomatous portion showed the typical features of GBM, including nuclear atypia, mitosis, necrosis, and microvascular proliferation. The sarcomatous portion showed spindle cells with nuclear atypia. IHC for vimentin (Fig. 2K) and GFAP (Fig. 2L) stained the tumor cells of the glial component, whereas the sarcomatous component contained a reticulin network visible with silver staining (Fig. 2M). The MIB-1 LI was 16% (Fig. 2I), and p53 expression was 20% (Fig. 2J).

2.4. Analysis of loss of heterozygosity

DNA was extracted from a paraffin-embedded sample of tumor tissue and corresponding peripheral blood. To enrich the tumor cell population, tumor areas were selected from the H&E-stained slides and isolated by microdissection. Both the gliomatous and sarcomatous components were dissected. Loss of heterozygosity (LOH) of 1p, 10q, and 19q was assessed by polymerase chain reaction (PCR)-based microsatellite analysis. The following microsatellite markers were used: D1S468 and D1S1172 on chromosome 1p; D10S520 and D10S521 on chromosome 10q; D19S408, D19S601, and D19S867 on chromosome 19q. LOH on 1p, 10q, and 19q was not detected in the specimen taken at initial diagnosis. LOH on 10q and 19q was detected in the specimen taken from the progressing tumor (Fig. 3).

3. Discussion

Gliosarcoma was first described by Stroebe in 1895[7] and gained general acceptance through the landmark papers of Feigen and Gross[8] and Rubinstein.[9] In the present patient, the tumor from the second operation displayed a biphasic differentiation pattern with glial and sarcomatous components. The sarcomatous area showed a reticulin network on silver staining. IHC for GFAP stained the tumor cells of the glial component, and silver staining was absent in glial areas. These features are diagnostic of gliosarcoma. However, the initial diagnosis of the tumor was of fibrillary astrocytoma. Astrocytomas frequently demonstrate considerable histopathological heterogeneity, with focal areas of more malignant features spread among regions with a more benign appearance.[10,11] Because of the heterogeneous organization of gliosarcoma tumors, the first biopsy may have been malignant glioma with sampling error. However, we performed the CT-guided stereotactic biopsy of enhancing region of the tumor accurately with preoperative fusion of CT scans and MRI. Moreover, the tumor from the first operation showed Rosenthal fibers, which indicated that the tumor had grown slowly over a significant period of time. Follow-up MR spectroscopy indicated malignant change in the progressing tumor. In the present patient, the tumor appears to have transformed from fibrillary astrocytoma into gliosarcoma. To our knowledge, there have been no prior reports of such a rapid malignant transformation from diffuse astrocytoma to gliosarcoma.

GBM develop *de novo* (primary GBM) or through progression from low-grade or anaplastic astrocytomas (secondary GBM).