

Gliosarcoma with Chondroblastic Osteosarcomatous Differentiation: Report of Two Case with Clinicopathologic and Immunohistochemical Features

Kondroblastik Osteosarkomatöz Farklılaşmayla Beraber Olan Gliosarkom: Klinikpatolojik ve İmmünohistokimyasal Özellikleri ile İki Olgu Sunumu

ABSTRACT

Gliosarcoma is a rare tumor of the central nervous system characterized by a biphasic histological pattern. Our objective is to describe clinical, morphological and immunohistochemical features of two cases of gliosarcoma with chondroblastic osteosarcomatous differentiation and to discuss its pathogenetic mechanisms. Case 1: A 52-year-old male patient underwent parietal craniotomy due to anaplastic ependymoma. The case had radiotherapy and chemotherapy postoperatively. After the first operation, additional resections were performed for tumor because of recurrences at the fourth, seventh and tenth months. The patient died after the last tumor resection. Histopathologic examination of the postmortem biopsy revealed neoplasm displaying a biphasic morphologic pattern including both gliomatous and sarcomatous components. Case 2: The case was a 69-year-old male patient with a right frontal lobe mass histologically diagnosed as gliosarcoma displaying sarcomatous and glial components. Immunohistochemical features were similar to those of the first case in general, but diffuse nuclear reaction with p53 protein was detected in both components. We report two cases with an extremely rare histopathologic aldiagnosis of "gliosarcoma with features of chondroblastic osteosarcoma".

KEYWORDS: Gliosarcoma, Osteosarcomatous differentiation, Radiation, p53 protein

ÖZ

Gliosarkom, bifazik histolojik patern ile karakterize santral sinir sisteminin nadir tümörüdür. Amacımız, kondroblastik osteosarkomatöz farklılaşmayla birlikte olan iki gliosarkom olgusunun klinik, morfolojik ve immünohistokimyasal özelliklerini tanımlamak ve onların patogenetik mekanizmalarını tartışmaktır. Olgu 1: Anaplastik ependimom nedeniyle parietal kraniyotomiye gitmiş 52 yaşında erkek hastadır. Olguya postoperatif radyoterapi ve kemoterapi verildi. İlk operasyondan sonra, dördüncü, yedinci ve onuncu aylarda rekürrensden dolayı tümör için ilave rezeksiyonlar yapıldı. Sonuncu tümör rezeksiyonundan sonra hasta exitus oldu. Postmortem biyopsinin histopatolojik incelemesinde, hem gliomatöz hem de sarkomatöz komponentler içeren bifazik morfolojik patern sergileyen neoplazi gözlemlendi. Olgu 2: Histolojik olarak, sarkomatöz ve glial komponent sergileyen gliosarkom tanısı alan sağ frontal lob kitlesi olan 69 yaşında erkek hastadır. İmmünohistokimyasal özellikleri genelde ilk olgununkine benzemektedir, fakat p53 protein ile diffüz nükleer reaksiyon her iki komponentte saptandı. "Kondroblastik osteosarkom özellikleri ile beraber olan gliosarkom" olarak oldukça nadir histopatolojik tanı iki olgu rapor ettik.

ANAHTAR SÖZCÜKLER: Gliosarkom, Osteosarkomatöz farklılaşma, Radyasyon, p53 protein

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INTRODUCTION

Gliosarcomas represent a rare but well-established entity in the classification of central nervous system neoplasms (3,8-11,19-22). They are classified as a variant of glioblastoma in the revised 2007 World Health Organization (WHO) tumor classification (15,16). They constitute approximately 2% of all malignant glial neoplasms with a similar age and gender distribution as glioblastomas (7,19-22,24). They were first described in 1895 by Heinrich Stroebe (3-5,13,14,21-30), a pathologist who worked at Freiburg University Hospital (17), and have long been recognized as novel hybrid central nervous system tumors (1,3,4,26). In 1955, Feigin et al. defined gliosarcomas as glioblastoma multiforme that acquired the features of a sarcoma with the proliferating vessels (5). Hence, gliosarcoma is sometimes referred to as "Feigin's tumor" (1).

Gliosarcoma consists of gliomatous and sarcomatous elements (17-19,26-30). Malignant astrocytoma constitutes the majority of malignant glial component in gliosarcomas, but oligodendrogliomas have also been described. Gliosarcomas arising in association with ependymomas are extremely rare (3,4,11,13,27). Typically, sarcomatous components resemble fibrosarcoma or malignant fibrous histiocytoma, and contain neoplastic smooth muscle elements, occasionally endothelial cells, and even rarely chondroid or osseous elements. Osteosarcomatous differentiation in gliosarcoma has rarely been reported (4,7,9,10). To our knowledge, only a few cases of gliosarcoma containing areas of osteosarcomatous differentiation have been reported (3,9). Gliosarcomas with osteosarcomatous differentiation tend to appear after cerebral radiation therapy (11,28).

The etiology of gliosarcoma remains to be clarified. Multiple mechanisms have been proposed to describe the origin of the mesenchymal component of gliosarcoma. Our objective is to describe the clinical, morphological and immunohistochemical features of two cases of gliosarcoma with chondroblastic osteosarcomatous differentiation and to discuss its pathogenetic mechanisms. One of these two cases was a secondary gliosarcoma arising from a previously irradiated anaplastic ependymoma and the other was a primary gliosarcoma.

CASE REPORTS

Case 1: The patient was a 52-year-old Caucasian male who first applied to the hospital with a history of intractable headaches. His cranial computed tomography revealed a 4.5x2.5x2 cm mass at the right parietal lobe (Figure 1A). The patient underwent right parietal craniotomy with tumor excision, and the tumor was designated as anaplastic ependymoma (grade III, World Health Organization scale). The histopathologic findings from tumor resection displayed a well-circumscribed ependymal neoplasm with abundant perivascular pseudorosettes and ependymal rosettes (Figure 1B). However, there were also regions of increased anaplasia, abundant endothelial proliferation, geographic necrosis, and high mitotic activity, all consistent with anaplastic transformation. Tumor cells expressed vimentin, epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), and S-100 protein. Postoperatively the patient had external brain radiotherapy and chemotherapy (CCNU and Cisplatin). Additional resections were performed for tumor because of recurrences at the fourth, seventh and tenth months after the first operation. Areas of high-grade glial tumor were encountered in all of the following tumor resections. The patient died after the last operation. Histopathologic examination of postmortem biopsy revealed neoplasm showing a biphasic morphologic pattern. The dominant pattern consisted of areas of sarcomatous tumor (Figure 1C), with lobules of malignant-appearing cartilage surrounded by atypical spindle cells associated with osteoid production and the second type pattern consisted of focal residual areas of high-grade glial tumor. These sarcomatous areas were reticulin rich, with individual sarcoma cells invested in reticulin (Figure 1D). In contrast, reticulin staining was absent in glial areas. Moreover, immunohistochemistry for GFAP (Figure 1E) reacted with only the glial component of the tumor cells. The tumor cells expressed EMA and vimentin, but not S-100 protein. Focal nuclear reaction was detected in sarcomatous regions by p53 protein (Figure 1F). Histopathologic diagnosis was "gliosarcoma with features of chondroblastic osteosarcoma".

Case 2: The case was a 69-year-old male patient, with a history of weakness lasting at least 10 days, urinary incontinence, gait imbalance and slurred speech. Magnetic resonance images revealed a mass 5x5x4 cm in dimension at the right frontal lobe (Figure

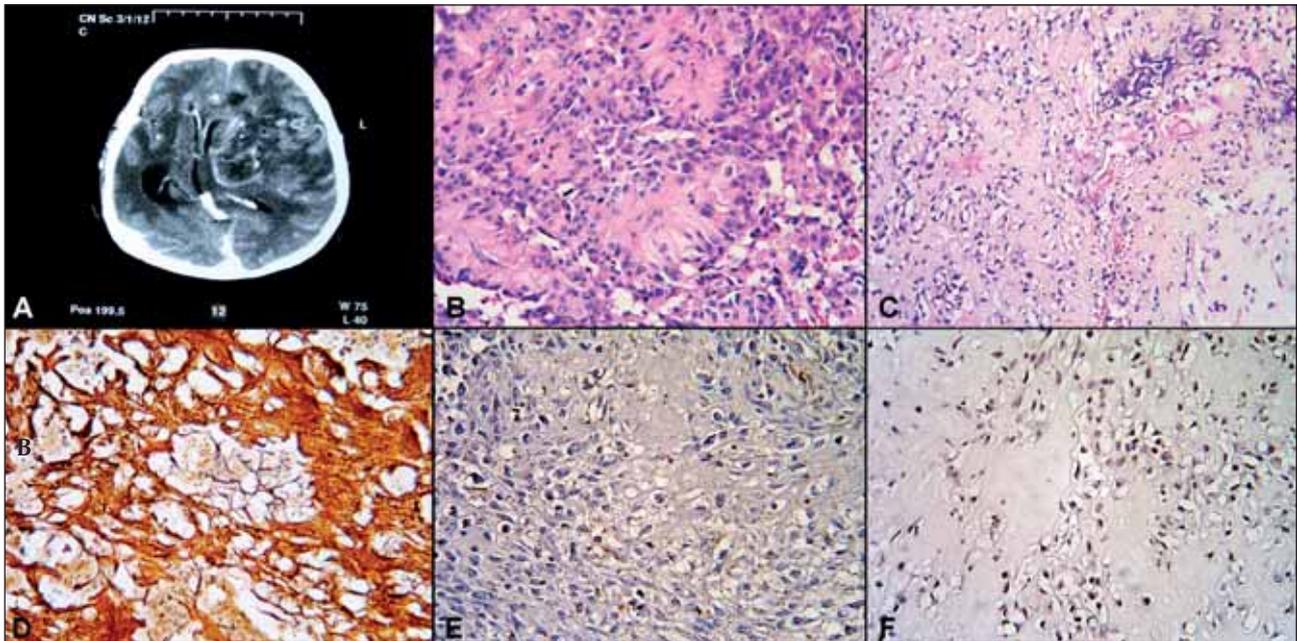


Figure 1: Secondary gliosarcoma arising from anaplastic ependymoma **A)** A contrast-enhanced computerized tomography scan demonstrates a deeply located mass lesion in left hemisphere showing irregular enhancement with prominent right-sided displacement of the midline structures. **B)** Anaplastic ependymoma with abundant perivascular pseudorosettes (HE, X400). **C)** Atypical spindle cells associated extracellular osteoid material and lobules of malignant-appearing cartilage (HE, X200). **D)** Histochemical staining of silver impregnation for reticulum in osteosarcoma areas. **E)** Immunohistochemical staining of GFAP in sarcomatous component (B-SA, DAB, X400). **F)** Focal p53 expression in glial and sarcomatous areas (B-SA, DAB, X400).

2A). Histological examination of the right frontal lobe mass with hematoxylin-eosin staining displayed sarcomatous and glial components. The glial component was remarkably similar to glioblastoma, with nuclear pleomorphism, high mitotic index, marked vascular proliferation and foci of necrosis (Figure 2B). The sarcomatous component was composed of spindle cell proliferation with herringbone architecture, and sometimes storiform areas arranged in a dense, pink, amorphous extracellular material and malignant-appearing cartilage resembling chondroblastic osteosarcoma (Figure 2C). Reticulin histochemical (Figure 2D) and immunohistochemical features (Figure 2E) of the second case resembled the first one in general, but included diffuse nuclear reaction in glial components and sarcomatous regions by p53 protein (Figure 2F). The patient with a diagnosis of “gliosarcoma with features of chondroblastic osteosarcoma” died postoperatively 19 days after the second operation performed two months later for recurrence.

DISCUSSION

Gliosarcoma is a rare glioblastoma variant, characterized by biphasic tissue pattern with

alternating areas of glial and mesenchymal differentiation (1,7,11,26,30). According to most authors, gliosarcoma is clinically inseparable from glioblastoma (17). Gliosarcoma behaves in a similar manner to glioblastoma (1). The tumor characteristics of gliosarcoma are almost identical to glioblastomas with regards to age, gender, tumor location, size and median survival. Most gliosarcoma cases are encountered between the ages of 40 and 60, with a mean of 53 years. The male to female ratio is 1.8:1 (17,18,22,23,31). The ages of our two cases were 52 and 69, and both of them were male. The most common symptoms are seizures, focal neurological deficits, headaches and other symptoms related with increased intra-cranial pressure (22), as in our two cases.

Most studies have demonstrated that gliosarcoma shows temporal lobe preponderance, with the tumor being found less commonly, in decreasing order of frequency in frontal, parietal and occipital lobes, and corpus callosum (11,17,23,24). They are mainly located in the temporal lobe and correspond to WHO grade IV tumors (1,11,24,28). In our cases the tumors were located in the parietal and frontal lobes. In the presented cases, clinical features, neuroradiological

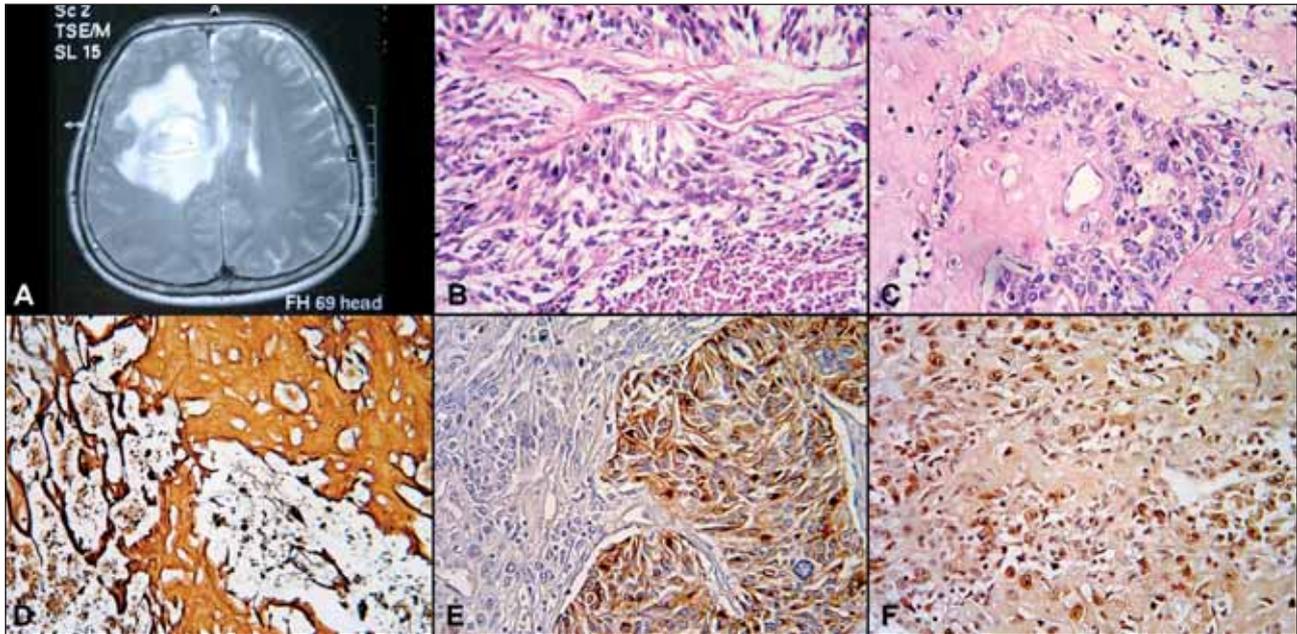


Figure 2: Primary gliosarcoma **A)** Axial T2-W1 demonstrating a heterogeneous intraaxial lesion with solid and cystic components located in the right frontal lobe. The surrounding vasogenic edema is remarkable. The lesion exerts mass effect with compression of the right lateral ventricle. **B)** Malignant glial tumor with nuclear pleomorphism, high mitotic index, marked vascular proliferation and foci of necrosis (HE, X400). **C)** Chondroblastic osteosarcoma with atypical spindle cells and amorphous extracellular osteoid material and malignant-appearing cartilage (HE, X400). **D)** Histochemical staining of silver impregnation for reticulum in gliosarcoma. **E)** Immunohistochemical staining of GFAP in sarcomatous component (B-SA, DAB, X400). **F)** Diffuse p53 expression in glioblastoma and sarcomatous areas (B-SA, DAB, X400).

findings, and macroscopic appearances at operation were all consistent with gliosarcoma, and the mesenchymal component of the neoplasm exhibited histopathologic and immunohistochemical characteristics similar to those of chondroblastic osteosarcoma arising in soft tissue. GFAP immunostaining is very important in distinguishing gliosarcoma from glioblastoma, with strong GFAP expression in glial regions, but only very low quantities in sarcomatous regions (21,31), as in our cases.

Gliosarcoma is a rare tumor with a poor prognosis (11,17,19,23,24). The prognosis of gliosarcoma is similar to that of glioblastoma since the sarcomatous component is prognostically insignificant (31). In some publications, the tendency of gliosarcomas to metastasize was found to be higher than that of glioblastoma. The treatment of gliosarcoma is almost identical to glioblastoma, involving surgery, radiotherapy and chemotherapy (23,24,31). It should always be considered as a diagnostic possibility whenever a differential diagnosis of glioblastoma has been made. Gliosarcoma shares many features with glioblastoma and should be treated in a similar

manner, but treatment protocols may vary in the future as novel therapies become available (1,17,21). Among the most promising of these newer treatment modalities is immunotherapy, where therapeutic agents are directed against specific antigens (1).

The histogenesis of the sarcomatous portion of gliosarcoma has been a matter of controversy since its initial description (4,24,29,31). This neoplasm is thought to arise secondarily from the neoplastic transformation of stromal cells, which proliferate as a response of the host against the infiltration of malignant glioma cells (4,6,18,26-30). Endothelial cells, histiocytes, fibroblasts, and vascular smooth muscle cells have all been considered potential cells of origin of the sarcomatous component in this model (6-11,26-30). Whereas morphological studies suggested an evolution of sarcomatous component from microvascular proliferations within a highly malignant glial tumor, recent genetic studies revealed the presence of identical p53 and PTEN mutations and similar chromosomal imbalances and cytogenetic alterations in both components of gliosarcomas, suggesting a monoclonal origin (17,18,26-29). In accordance with this finding, it is most likely that

sarcomatous and gliomatous cells are derived from a common stem cell, with both cell types demonstrating high immunoreactivity for the p53 tumor suppressor gene (1,2,18). Numerous genetic studies of gliosarcomas support this monoclonal hypothesis (4). The glial dedifferentiation theory proposes that the sarcomatous component of gliosarcoma is derived from the dedifferentiation of malignant glial cells (1,3,17,29).

The role and significance of p53 protein in the development of gliosarcoma is still to be clarified (11). In our second case, single p53 expressing tumor cells were detected in all tumor portions, supporting the concept of a monoclonal origin of gliosarcomas (2,26,28). A few p53 positive tumor cells do not justify the assumption that genetic aberrations in the evolution of these tumors might appear after differentiation into glial and sarcomatous components (26,28) as noted in our first case. Non-uniform distribution of p53 expression in these cases may be a result of radiation, chemotherapy, or both.

Gliosarcomas are known to arise de-novo, whereas others appear after radiation therapy of malignant gliomas (13,20,22-25,31). It is well known that irradiation of the central nervous system may cause eventual development of various types of malignant cerebral and meningeal tumors, predominantly sarcomas, a subject recently reviewed by Kaschten et al. (12). A gliosarcoma arising from an irradiated ependymoma was first described by Kepes et al. in 1996 (13). The authors speculated that differentiation of osteosarcomatous elements could arise secondarily as a radiation-induced modification in a neoplasm that was primarily a glioblastoma in some cases (3,13,14,30). Being aware of post-irradiation gliosarcoma as in our first case is important because of potential differences in histogenesis, natural history, treatment options and prognosis, and because of the widespread use of radiotherapy in the treatment of glioblastoma and gliosarcoma (12-14).

We reported two extremely rare cases. We thought that radiotherapy had a significant role in the development the first secondary gliosarcoma arising from anaplastic ependymoma, and that although still speculative in the second case p53 expression might have played an important role in the pathogenesis of primary gliosarcoma. Gliosarcoma might actually be not a single pathological entity with one pathogenetic mechanism but a heterogeneous group of brain

neoplasms with divergent pathogenesis. Understanding the pathogenesis of these tumors seems critical to develop novel treatment modalities.

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