CLINICAL CASE

Primary cerebral gliosarcoma: a case presentation with review of the literature

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Summary

In this presentation we describe a rare case of a 42-year-old female with a large right frontal gliosarcoma (GS) treated with gross total resection of the tumor and postoperative external radiotherapy. The patient did not respond to treatment and she died 3 months after the end of radiotherapy. We also present a review of the literature on epidemiology, pathogenesis, clinical presentation, diagnosis and treatment of this uncommon clinical entity.

Key words: brain tumor, gliosarcoma, review

Introduction

Gliosarcoma is a rare primary malignant neoplasm of the central nervous system that accounts for approximately 2% of glioblastomas [1,2]. The main characteristic is its biphasic tissue pattern displaying gliomatous and sarcomatous differentiation. Since 1895 when Strobe firstly described this uncommon clinical entity [3], several cases have been reported. Its pathogenesis remains unclear and the most recent hypothesis suggests that both components derive from a single precursor cell clone, which progresses into subclones with distinct morphological features during tumor evolution. It usually arises in the cerebral hemispheres of adult people, with preferential manifestation between the fourth and seventh decade of life. The clinical presentation reflects the tumor location and size, and the severity depends on the extent of elevation of intracranial pressure. Diagnosis is established with histological examination of the surgical specimen and supported by computed tomography (CT) and magnetic resonance imaging (MRI). Surgery and adjuvant postoperative radiotherapy are considered the main treatment approach. Alternative treatment options are under investigation. However, prognosis remains poor, since patients with GS usually fail to live more than one year, probably due to the high aggressiveness of the tumor.

In the present study we describe a case of a cerebral GS treated with postoperative external radiotherapy.

Case presentation

The patient was a 45-year-old female admitted to our hospital, reporting a 4-month history of right headache, inattention and left-sided weakness. She had visited her personal doctor who attributed the symptoms to overwork and suggested resting. However, her condition gradually aggravated and she developed right weakness with unsteady gait and she had several episodes of urinary incontinence. CT scan of the brain revealed a large right frontal mass. She was operated on with a right frontal craniotomy and gross total removal of the tumor. The histological examination showed increased cellularity with extensive necrotic areas and a biphasic tissue pattern in the remaining cells comprising of gliomatous and mesenchymal differentiation (Figure 1). Both glial and
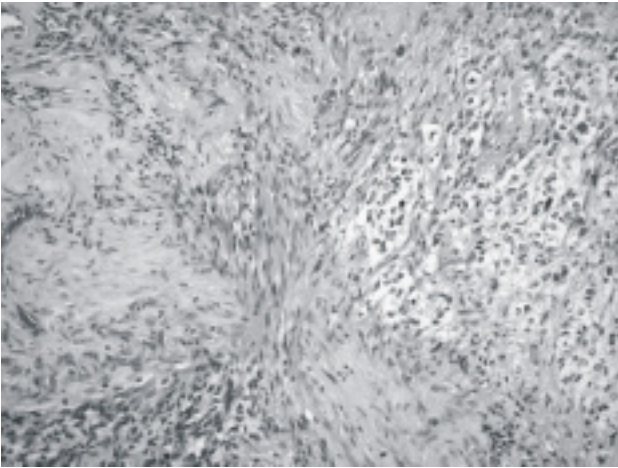
Figure 1. Gliosarcoma. The gliomatous component is separated by the sarcomatous tumor cells (H&E X200).

mesenchymal components displayed varying degrees of anaplasia and mitotic activity. The sarcomatous part of the tumor was composed of atypical spindle cells that were positive for vimentin. In addition, scattered spindle cells were positive for desmin. The glial component was positive for glial fibrillary acidic protein (GFAP). Staining for reticulin showed that in some areas the sarcomatous component was well demarcated from the glial one (Figure 2). The final diagnosis was gliosarcoma.

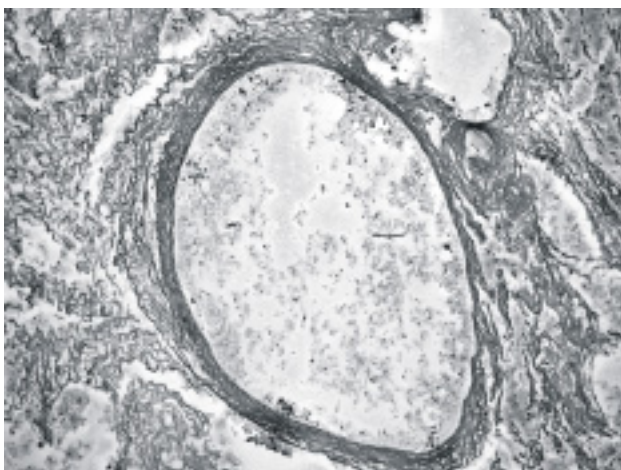One month after her operation she started postoperative external radiation therapy with two parallel-opposed fields (anterior and posterior). The tumor region with a 3 cm margin was treated. Radiotherapy was given in 30 fractions with linear accelerator (6MV). The daily dose was 2.0 Gy and the total dose was 60 Gy. The fields were reduced after 40 Gy (shrinkage technique). She tolerated her treatment well, without interruption due to side effects. The patient didn't respond to her programmed visit 3 months after the end of radiotherapy. Her family was contacted by phone and we were told that she experienced a rapid clinical deterioration and died.

Discussion

Gliosarcomas are rare biphasic central nervous system malignancies composed of distinct sarcomatous and glial neoplastic cell populations. According to the WHO classification of tumors of the nervous system, they are considered highly malignant tumors, histologically corresponding to grade IV [4]. They are most commonly encountered in adults between the fourth to seventh decade of life, concerning mainly the brain. The most common localization is at the frontal, temporal, and parietal lobes and few cases of cerebellar GS have also been described [5]. There is a slight male preponderance, similar to that seen in malignant astrocytomas [1,6,7].

The pathogenesis of the sarcomatous component of GS has been a matter of controversy and remains unclear despite different theories over time. Until recently the biclonal model of histogenesis was the dominant theory. According to this model, the sarcomatous component arises from neoplastic transformation of proliferating hyperplastic vascular stroma within glial tumors and not from the glial component [8]. This hypothesis is supported by the reactivity of some of the spindle cells to factor VIII/ von Willebrand factor [9]. Pluripotent mesenchymal cells, histiocytes, fibroblasts, and vascular smooth muscle cells have also been considered potential cells of origin of the sarcomatous component in this model [10]. However, the monoclonal model has challenged these assumptions recently. Accumulating data have attributed the origin of GS to a sarcomatous evolution via aberrant mesenchymal differentiation of a highly malignant glioma or from a common precursor cell [11,12]. Genetic studies have identified similar cytogenetic abnormalities in both GSs and glioblastomas. Actor et al. [13] analyzed both gliomatous and sarcomatous components by comparative genomic hybridization after histological microdissection in order to address the question whether they are of mono-or

Figure 2. Areas with a reticulin network are characteristic of the sarcomatous region and are well demarcated from the glial portion (H&E X200).

polyclonal origin and whether there are genomic aberrations that specifically associate with either component. They revealed that both components shared 57% of the chromosomal imbalances detected and provided further support for the hypothesis that the gliomatous and sarcomatous components are derived from a single precursor cell clone, which progressed into subclones with distinct morphological features during tumor evolution. According to their data, gain/amplification of genes on proximal 12q may facilitate the development of a sarcomatous phenotype. Moreover, they found that the genomic changes in GSs closely resemble those found in glioblastomas.

The relationship between radiation therapy and the development of GSs is under investigation. GSs are known to arise *de novo*, whereas others may appear after radiotherapy of malignant gliomas [14]. In either case, there are no apparent morphological differences in the sarcomatous components that might indicate a specific etiology, that is, malignant progression *versus* radiation induction. The most common radiation-induced injuries in the central nervous system are necrosis, white matter changes, mineralizing microangiopathy, cerebral atrophy, vasculopathy, carcinogenesis and others. Several criteria have been suggested for the establishment of a relationship between radiation therapy and occurrence of a neoplasm [15]. These are: a) a sufficiently long latent period between the irradiation and the development of the second tumor; b) the latter tumor must be in the irradiated field; c) the histology of the second tumor must be different from that of the initial one; d) a family history of tumor diathesis must be excluded.

The clinical presentation reflects location and tumor size and the severity depends on the extent of elevation of intracranial pressure. The most common symptoms are focal neurological deficits, tonic or clonic seizures and other symptoms reflecting the location and elevation of intracranial pressure such as weakness, headache, confusion, nausea, vomiting, blurring of vision, lethargy, ataxia, altered mental status and others. Diagnosis is established with the histological examination of the surgical specimen and supported by CT and MRI. CT scan and MRI usually reveal large and irregular lesions with indistinct margins followed mostly by surrounding edema and mass effect, an image similar to that of glioblastoma multiforme. Sometimes GSs mimic meningiomas, particularly when the tumour is superficial and cortical and receives blood supply from the meningeal vessels [16]. At CT scan the tumor is iso- or hypodense or slightly hyperdense, with usually marked heterogeneous enhancement. Foci of hemorrhage may be seen, while calcification is rare. On MRI T1W images the tumor is usually hypointense, with a large amount of surrounding edema and mass effect, whereas on T2W images hyperintensity with marked heterogeneous enhancement are seen. Intratumoral hemorrhage, necrosis and cyst formation are common. Adjacent white matter tracks usually demonstrate extensive high signal, reflecting a combination of an infiltrating tumor and peritumoral edema. Clinical modalities that should be considered in the differential diagnosis of GS are glioblastoma multiforme, brain metastases, malignant meningioma and lymphoma of the central nervous system.

However, despite the advances in imaging techniques for brain tumors, definite diagnosis is given by the histopathological examination of the tumor. Histologically, GS consists of both anaplastic glial and mesenchymal areas. The glial component is most commonly astrocytic and resembles glioblastoma. Other glial components such as oligodendroglioma and ependymoma are rarely seen. Characteristic lesions have a periphery of glioma surrounding a sarcomatous center. GFAP immunoreactivity can demonstrate the gliomatous areas. The sarcomatous areas in most cases show the typical herringbone pattern of fibrosarcoma, with densely packed bundles of spindle cells. In others, a pleomorphic lesion is apparent, similar of a malignant fibrous histiocytoma. Other reported lines of differentiation include smooth muscle, striated muscle, bone and cartilage.

The occurrence of spindle cells within a glioblastoma does not always permit the diagnosis of a GS. In some cases of glioblastomas, there is a regional fascicular pattern of spindle cells resembling sarcoma. In other cases, glioblastomas actually undergo mesenchymal metaplasia. Moreover, sometimes, trapped reactive and non-neoplastic glial cells may be seen in sarcomas primarily arising in the nervous system. The demonstration of GFAP-positive areas, as well as a dense reticulin network in the sarcomatous malignant component surrounded by the GFAP gliomatous areas is an important tool for the diagnosis of a GS.

Gross total or subtotal resection of the tumor – according to tumor features and intraoperative findings- followed by postoperative external radiotherapy remains the main treatment option. The total dose ranges from 40 to 80 Gy in reported series [1,6,7]. Radiotherapy could be delivered either as whole brain therapy alone or as whole brain radiotherapy for the first 40 Gy followed by a boost to the tumor region for the final 20-25 Gy (shrinkage technique) [7]. The role of chemotherapy in the treatment of GS is under investi-

gation [6]. Additional treatment options include radio-surgery [17] and brachytherapy [18]. New treatment modalities such as gene therapy and use of angiogenesis inhibitors remain in experimental levels [19].

Current treatment protocols in patients with GS have very limited success. Prognosis remains poor with a median survival ranging from 4 to 11.5 months in the reported studies [3,6,7]. The variability in survival times is probably attributed to differences among studies in calculating times from different time-points. In rare cases prolonged survival has been reported, attributed to the peripheral location of the tumor as well as to the extent of the surgical resection [20]. Local recurrences and extracranial metastases are common in GSs including lung, liver, lymph nodes, cervical cord and abdominal metastases [7].

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