Case Report

Journal Of Clinical & Medical Images Case Reports

Open Access, Volume - 1

Therapeutic management of gliosarcoma in the stupp protocol and temozolomide era

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Received Date : Nov 22, 2021
Accepted Date : Dec 23, 2021
Published Date : Dec 30, 2021
Archived : www.jcmimagescasereports.org

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Abstract

Background: The clinical management of primary gliosarcoma grade IV with curative intent is not entirely defined and the available data are limited, so the therapeutic management may be a challenge The application of the Stupp protocol may be the only effective treatment option.

Case report: We report the case of a 57-year-old woman with a gliosarcoma of the left frontal lobe treated in a curative intent. She underwent craniotomy, followed by adjuvant radioterapy and 6 cycles of temozolomide, according to the Stupp protocol, resulting in complete response after 3.5 years from diagnosis.

Conclusions: Gliosarcoma and glioblastoma are different histopathological entities and the use of the Stupp protocol, specifically studied for glioblastoma, is an off label application of the treatment protocol. Efforts should be focused in order to assess the efficacy of this treatment modality and then on the prognosis carried by gliosarcoma tumor type.

Keywords: Gliosarcoma; chemotherapy; radiotherapy.

Introduction

Gliosarcoma (GSM) is a rare malignant brain tumor which accounts for 1-8% of all malignant glioma [4]. GSM is a type of glioma grade IV with a biphasic tissue pattern, alternating areas displaying glial and mesenchymal differentiation Even if GSM and glioblastoma (GBM) share some common features, they are different histological entities and should be considered separately also from a therapeutical and prognostic point of view. The therapeutic management of GSM patients remains a real challenge even in the Stupp protocol and temozolomide era, since there are no prospective randomized trials supporting the efficacy of any standardized treatment [1]. The lack of a standardized treatment derive from its well known rarity that makes a standard treatment for these patients difficult to define. Our current knowledge of GSM relies on retrospective studies, the majority of which precedes the diffusion of the Stupp protocol and its multimodality therapy [1].

Case Description

In March 2018, A 53-year-old woman working as a lifeguard, affected by sinus bradycardia and obsessive compulsive disorder, with a history of second thoracic vertebra fracture on a polytrauma with residual right facial nerve paresis, was admitted to the emergency department due to right arm and right hand palsy, moderate headache and short term memory loss.

A computed tomography (CT) of the brain was performed. The exam showed a left frontal intra-axial lesion between the middle frontal gyrus and precentral gyrus (3x3x3 cm), associated with left frontal vasogenic edema of the white matter. A cranial magnetic resonance imaging (MRI) was also performed in order to better characterize the lesion (**Figure 1**, 1st column). The MRI confirmed the CT results and showed cystic/necrotic alterations of the lesion with nodular pattern on the T2 weighted images. The diagnostic work-up was completed with a whole body CT scan which resulted to be negative for

Citation: Claudio Cammalleri, Gianfranco Angelo Pesce, Paolo Spina, Francesco Marchi, Mariacarla Valli1, Francesco Martucci, et al. Therapeutic management of gliosarcoma in the stupp protocol and temozolomide era. J Clin Med Img Case Rep. 2021; 1(1): 1054.

other suspected lesions.

The patient was transferred to the Neurosurgery department, where a left frontal craniotomy was performed. The lesion was removed under intraoperative neuromonitoring, with the help of ultrasonography and neuronavigation. Postoperatively, in the Intensive Care Unit, no new neurological deficits were observed with the persistence of the previous known fine motor deficit of the right arm, as well as the mild short-term amnesia. The postoperative MRI (Figure 1, column b) showed alterations associated with cytotoxic edema on the superior and posterior surgical margin, sites of possible future postsurgical enhancement on subsequent MRIs follow-up. The electroencephalogram showed low grade slow anomalies of the left fronto-central parietal region, compatible with the post-surgical context and no epileptic anomalies.

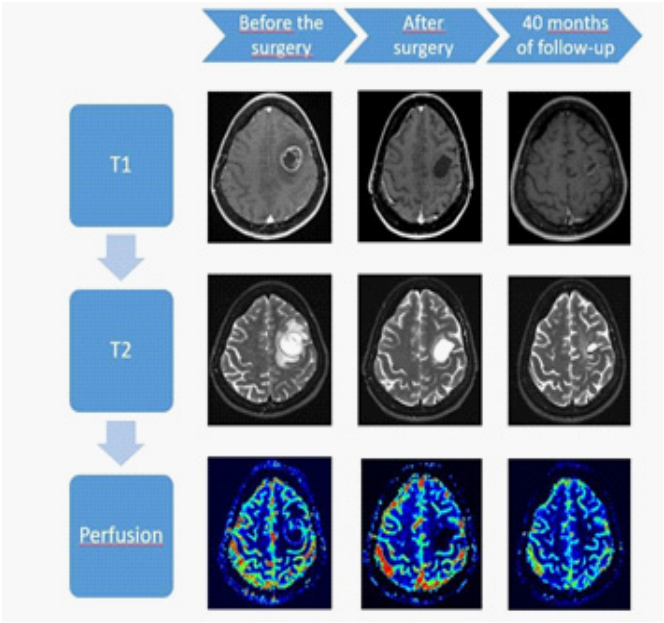

Figure 1: *This figure shows the comparison of T1, T2 and perfusion MRIs before surgery, after surgery and after 40 months of FU.The first column shows the left frontal intra-axial lesioin between precentral gyrus, and middle frontal gyrus with a maximum diameter of 3 cm before the tumor excision. The second column shows the surgical bed after surgical resection. The last column shows the surgical cavity after 40 monthss of FU.*

Histologically, the specimen showed a biphasic tissue pattern [1]: a glial portion showing the typical features of a glioblastoma (with necrosis and vascular proliferation), and a sarcomatous component, with densely packed long bundles of atypical spindle cells, compatible with the diagnosis of gliosarcoma, grade 4. FISH results did not display EFGR amplification, neither 1p/19q co-deletion. No IDH1 or IDH2 mutations was detected. The tumor showed methylation of O6MGMT promoter.

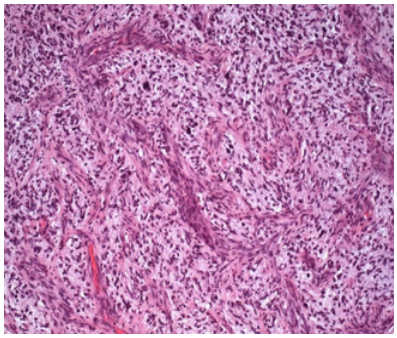

Figure 2: *Biphasic tumor consisting of malignant gliomatous areas admixed with sarcomatous areas showing a spindle cell pattern (hematoxylin and eosin, x100).*

After the observation in the Intensive Care Unit, the patient was transferred to the neurosurgical ward in which the postoperative exams were performed and the physiotherapy with ergotherapy started. The patient was then discharged and transferred to the rehabilitation clinic in order to improve the right arm and right hand motricity before starting the oncological treatment. A safe wide surgical excision definetely improves the prognosis [5] although further studies are needed in order to asses the impact on the overall survival.

The median survival of patients with GSM without treatment is incredibly poor (approximately 4 months) [6] Many retrospective studies have shown an improved overall survival associated with adjuvant radiotherapy [6, 7, 8, 9]. On the other hand many retrospective studied failed to prove the therapeutic efficacy of combined TMZ- based chemoradiotherapy over radiation therapy alone [11].

According to our internal policy, the case of this patient was discussed during the weekly multi-disciplinary meeting dedicated to neurological neoplasms and a multimodal treatment according to Stupp protocol [2] was advised. At the beginning of April 2018 the concomitant chemo-radiotherapy treatment started according to the Stupp protocol [2]. In line with the ESTRO-ACROP guidelines, RT treatment schedule included 30 fractions of 2 Gy, with a total dose of 60 Gy. The patient was treated with V-MAT (RapidArc®) technique (**Figure 3**). At the end of the treatment the patient was neurologically and clinically stable, without focal deficits of new onset. Chemotherapy consisted of concomitant TMZ 75mg/m2/day, followed by 6 consecutive cycles of TMZ 150-200 mg/m2/day, every 28 days. Chemotherapy was also well tolerated, without relevant toxicities and with no need of unplanned interruptions.

After the end of the treatment as well as during the follow-up period, a brain MRI was performed every 3 months and the case was re-discussed during the neuro-oncology multidisciplinary meeting in order to monitor the lesion in time and to find an eventual relapse or a new lesion. After 3.5 years from diagnosis the patient is in complete response (**Figure 1**, 3rd column) according to response assessment in neurooncology criteria (RANO) criteria [4].

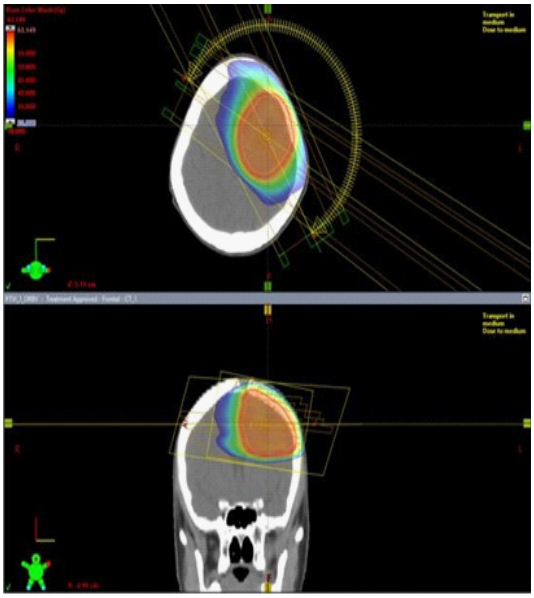

Figure 3: *Dose distribution using V-MAT (RapidArc®) technique with 2 opposing arcs 150°-300°.*

Conclusions

The management of GSM patients is more challenging, compared to the more common glioblastoma cases, due to its rarity that makes hard to identify a standardized treatment protocol. Considering that the GSM and GBM are different histological entities, even if they both arise from glial cells, the use of the Stupp protocol [2] for GSM patients is still off label. The analysis of the prognosis of GSM is even harder:because the lack of common guidelines makes every patient different from each other and so difficult to compare. In our experience the combination of surgical excision and RT improves the outcome and the overall survival of these patients; we cannot state the same for TMZ, as its use in GSM patients should be further analyzed. We still decided to follow the Stupp protocol for our patient, with the support of the MDM, considering the young age of the patient and her high performance status.

The median survival of GSM patients without treatment is around 4 months, and 10-14 months for treated patients [1]. On the other hand our patient survived over 40 months from the diagnosis, over 30 from the end of the treatment and she is still alive, without any metastatic location or focal neurological deficit. The multimodality treatment according to the Stupp protocol in our case resulted effective and well tolerated. Nevertheless further studies are needed in order to confirm the efficacy of such a protocol in patients affected by GSM.

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