CASE REPORTS

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Synchronous malignant multicentric cerebral glioma with atypical neuroradiological presentation and comparatively long survival: Case report and literature review

Sinhroni maligni multicentrični gliom mozga sa atipičnom neuroradiološkom prezentacijom i komparativno dugim preživljavanjem: prikaz bolesnika i pregled literature

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Abstract

Introduction. Synchronous multicentric cerebral gliomas are uncommon brain tumors, mostly malignant, with unknown pathogenesis, unfavorable prognosis and still controversial management. Preoperative differentiation from other multiple brain pathologies by conventional magnetic resonance imaging (MRI) is often difficult, but supplemental use of advanced magnetic resonance techniques should allow the tumor biology to be predicted and an appropriate treatment strategy planned. **Case report.** We reported a 59-year-old man with double synchronous multicentric cerebral lesions, which had initial MRI and diffusion-weighted imaging presentation as left parietal metastasis and ipsilateral amygdalo-hippocampal low-grade glioma. However, magnetic resonance spectroscopy (MRS) of both lesions showed different metabolite profiles of malignant glioma. *En bloc* resection of the easily accessible parietal lesion revealed glioblastoma with methylated O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter. Subsequently, the patient was treated with temozolomide (TMZ)-based chemoradiation according to Stupp's protocol, with continuous standard (5/28) adjuvant TMZ in 12 courses. Despite prolonged stabilization of the disease with good life-quality during treatment, the patient died 19 months after diagnosis. The time to tumor progression estimated by MRI was 17 months. **Conclusion.** MRS significantly improved the differential diagnostic accuracy of conventional MRI in our patient. In accordance with reviewed literature data, the younger age, good initial performance status and methylated MGMT gene promoter were all favorable predictors of longer survival in the reported case. Resection of at least one easily accessible tumor lesion, followed by TMZ-based chemoradiation, with continuous adjuvant TMZ in more than 6 standard courses, seems currently to be the most beneficial therapeutic option for such cases.

Key words:
glioma; glioblastoma; diagnosis; magnetic resonance imaging; magnetic resonance spectroscopy; mgmt protein, human; temozolomide; prognosis; treatment outcome.

Apstrakt

Uvod. Sinhroni multicentrični maligni gliomi mozga su retki moždani tumori koji su uglavnom maligni, sa nepoznatom patogenezom, nepovoljnom prognozom i još uvek spornim dijagnostičko-terapijskim pristupom. Preoperativna diferencijacija u odnosu na druge multiple moždane lezije uz pomoć konvencionalne magnetne rezonance (MR) je često teška, tako da bi dodatna primena naprednih MR tehnika trebala da omogući predikciju biologije tumora i planiranje odgovarajuće strategije lečenja. **Prikaz bolesnika.** Prikazali smo muškarca starosti 59 godine, sa dve sinhrone multicentrične moždane lezije, koje su na inicijalnoj MR mozga sa difuzionom sekvencom izgledale kao parijetalna cerebralna metastaza sa leve strane i ipsilsteralni amigdalo-hipokampalni niskogradusni gliom. Medjutim, magnetno-rezonantna spektroskopija (MRS) obe lezije pokazala je prisustvo metaboličkih profila malignog glioma. Lako

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dostupna parijetalna lezija koja je resecirana u potpunosti, potvrdjena je kao glioblastom, sa metilisanim promotorskim genom za O^6-metilguanin-DNK-metiltransferazu (MGMT). Postoperativno, bolesnik je lečen hemioradioterapijom baziranoj na temozolomidu (TMZ) prema *Stupp*-ovom protokolu, uz kontinuiranu standardnu (5/28) adjuvantnu monohemioterapiju TMZ u 12 ciklusa. Uprkos prolongiranoj stabilizaciji bolesti sa dobrim kvalitetom života tokom lečenja, bolesnik je preminuo 19 meseci nakon dijagnostikovanja bolesti. Vreme do progresije bolesti koje je procenjivano MR pregledom iznosilo je 17 meseci. **Zaključak.** Tehnika MRS je značajno poboljšala diferencijalno-dijagnostičku preciznost konvencionalne MR kod našeg bolesnika. U odnosu na prikazane literaturne podatke, mlado životno doba, inicijalno dobro opšte stanje i metilisani promotorski gen za MGMT bili su povoljni prediktori dužeg preživljavanja kod prikazanog bolesnika. Resekcija bar jedne lako dostupne tumorske lezije, uz postoperativnu hemioradioterapiju baziranu na TMZ i kontinuiranu adjuvantnu hemioterapiju TMZ sa više od 6 standardnih ciklusa, čini se kao trenutno najpovoljnija terapijska opcija kod ovakvih bolesnika.

Ključne reči:
gliom; glioblastom; dijagnoza; magnetna rezonanca snimanje; magnetna rezonanca, spektroskopija; mgmt protein, humani; temozolomid; prognoza; lečenje, ishod.

Introduction

Multicentric glioma (McG) is a well-recognized but uncommon clinical entity, with reported incidence ranging from 0.4–16.2% of all gliomas [1–6]. Glioblastoma (GB) is the most frequent histological pattern of McG [4–6], but extremely rarely multicentric low-grade glioma (LGG) may also be present, though only in 0.4–1.4% of all gliomas diagnosed [3]. Depending on the timing of initial presentation, McG may be synchronous or metachronous, whereby synchronous multicentricity is more frequent one [3–6]. According to Batzdorf and Malamud's [7] widely accepted criteria, McG is characterized by distant, widely separated tumor *foci* localized in different lobes or hemispheres, with no continuity between them and with no apparent dissemination route. Their simultaneous presence at the time of disease detection, or metachronous appearance during disease progression, cannot be attributed to any of the established spreading pathways. In contrast, multifocal glioma (MfG) grows and disseminates along established routes, including white matter tracts, cerebrospinal-fluid channels, blood or local extension by satellite formations [7].

The pathogenesis of McGs is unknown, prognosis is unfavorable and management still remains controversial [4–6, 8]. Due to the limited capacity of conventional (structural) magnetic resonance imaging (MRI) to differentiate McG from others multiple brain pathologies, supplemental use of advanced magnetic resonance techniques such as diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and magnetic resonance spectroscopy (MRS), should allow more accurate preoperative diagnosis and more precise planning of an appropriate treatment strategy [9]. Here, we reported on a patient with ipsilateral, double, synchronous, multicentric cerebral lesions, who had initial MRI and DWI presentation as parietal metastasis and ipsilateral amygdalo-hippocampal LGG. However, MRS of both lesions showed different metabolite profiles of malignant, high-grade glioma (HGG). This was confirmed by the histopathology of the resected parietal lesion, which proved to be GB with methylated O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter. We discussed the diagnostic and therapeutic modalities for patients with malignant McGs, with regard to those used with the reported patient who experienced a comparatively long survival of 19 months, with time to progression (TTP) of 17 months.

Case report

A 59-year-old right-handed Caucasian man presented with an episode of generalized convulsive seizure. On initial neurological examination the patient was disoriented with transient right hemiparesis and sensomotor dysphasia. Physical examination revealed no abnormal findings. Past medical history was unremarkable. A contrast-enhanced brain 3T MRI revealed two different and independent supratentorial ipsilateral cerebral lesions: a solid, nonenhancing left amygdalo-hippocampal lesion with no surrounding edema or mass effect and without restriction of diffusion (Figure 1 A-D), and a parietal, subcortical, regular ring-enhancing necrotic lesion, with recent hemorrhage into the tumor core surrounded by mild peritumoral edema, with a slight mass effect and only marginal restriction of diffusion (Figure 2 A-D). The amygdalo-hippocampal lesion had the MRI- and DWI-characteristics of LGG, while the parietal lesion had the appearance of solitary hemorrhagic metastasis. DWI quantification by calculating the apparent diffusion coefficient and PWI was not performed for technical reasons. However, a single-voxel MRS of both lesions showed metabolite characteristics highly suggestive of HGG: absence of N-acetylaspartate (NAA) with a high myo-inositol (mI) to creatine (Cr) ratio (mI/Cr = 1.8) in the amygdalo-hippocampal lesion (Figure 1 E, F); an increased choline (Cho) to NAA ratio (Cho/NAA = 2.36) and decreased NAA/Cr (NAA/Cr = 0.67) ratio with low mI and the presence of lipids (Lip) in the peritumoral area of the parietal lesion on T2-weighted (T2W) image (Figure 2 E, F). Consequently, the parietal lesion was totally resected through a left parietal craniotomy. The histopathology revealed GB (Figure 3), with a cellular proliferation Ki67 (MIB-1) labeling index of 20%. Nested methylation-specific polymerase chain reaction analysis showed that the tumor contained methylated MGMT gene promoter (Figure 4). In view of these findings, as well as the result of MRS of the amygdalo-hippocampal lesion, no attempt was made to

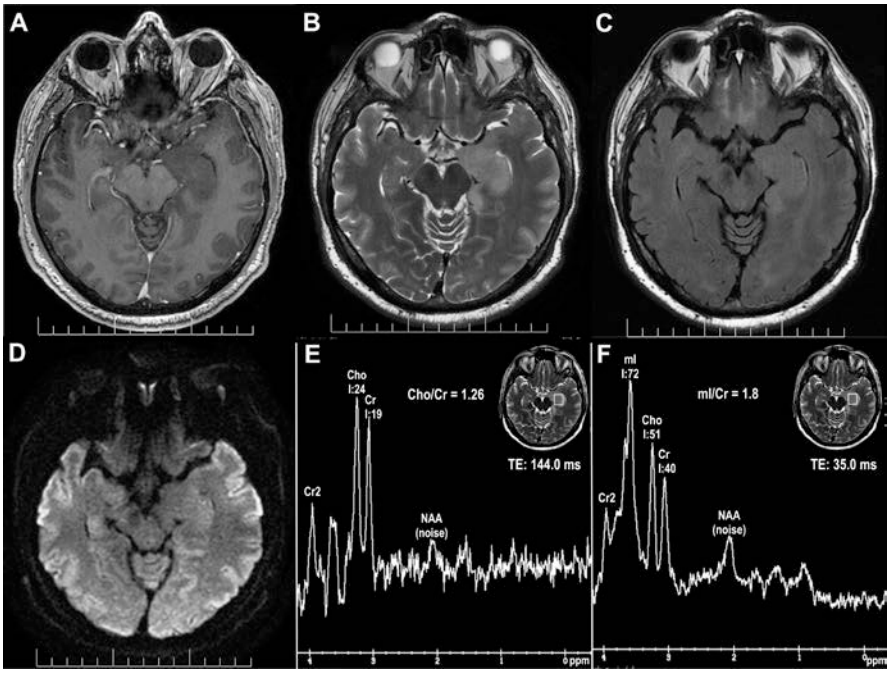


Fig. 1 – Post-contrast axial 3T magnetic resonance imaging: (A) a nonenhancing, isointense left amygdalo-hippocampal lesion compared to cortex in T1-weighted; (B) T2-weighted and (C) fluid attenuated inversion recovery sequences, with no surrounding edema, and (D) with no restriction of diffusion on diffusion-weighted imaging. Single voxel magnetic resonance spectroscopy with the voxel located within the lesion (inserts in E and F): tumor spectra (E) at long echo-time TE (TE = 144 ms) and (F) at short TE (TE = 35 ms) sequences shows absence of N-acetylaspartate (NAA) on both TEs, with (E) normal choline (Cho) to creatine (Cr) ratio (Cho/Cr = 1.26) at long TE, and with (F) high myo-inositol (mI) to Cr ratio (mI/Cr = 1.8) at short TE. Cr2 is the second creatine peak at 3.9 ppm, integral (I) with numbers indicates the relative signal intensity of the corresponding metabolite.

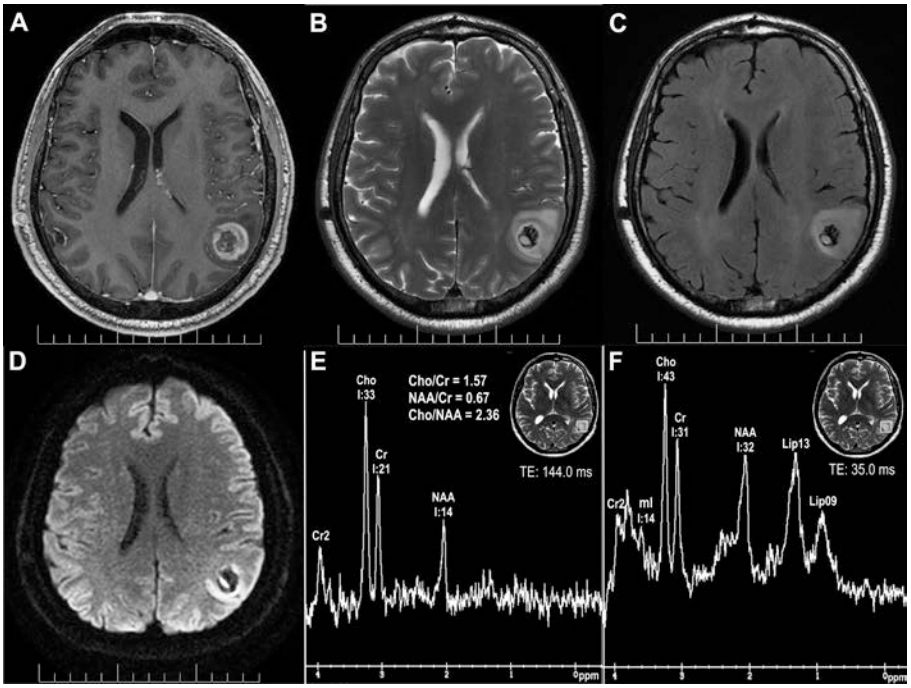


Fig. 2 – Post-contrast axial 3T magnetic resonance imaging: (A) a left parietal, subcortical, necrotic, ring-enhancing lesion, with recent hemorrhage into the tumor core in T1-weighted sequence, surrounded by mild peritumoral edema in (B) T2-weighted and (C) fluid attenuated inversion recovery sequences, and (D) with only marginal restriction of diffusion on diffusion-weighted imaging. Single voxel magnetic resonance spectroscopy with the voxel located within the lower part of the peritumoral vasogenic edema (inserts in E and F), positioned so as to avoid the cystic-hemorrhagic core of the lesion and thus partial volume effect: tumor spectra (E) at long echo-time TE (TE = 144 ms) and (F) at short TE (TE = 35 ms) sequences shows (E) increased choline (Cho) to N-acetylaspartate (NAA) and Cho to creatine (Cr) ratios (Cho/NAA = 2.36, Cho/Cr = 1.57, respectively) and decreased NAA/Cr ratio (NAA/Cr = 0.67) at long TE, and (F) low myo-inositol (mI) with presence of lipid (Lip) peaks at 1.3 and 0.9 ppm at short TE. Cr2 is the second creatine peak at 3.9 ppm, integral (I) with numbers indicates the relative signal intensity of the corresponding metabolite.

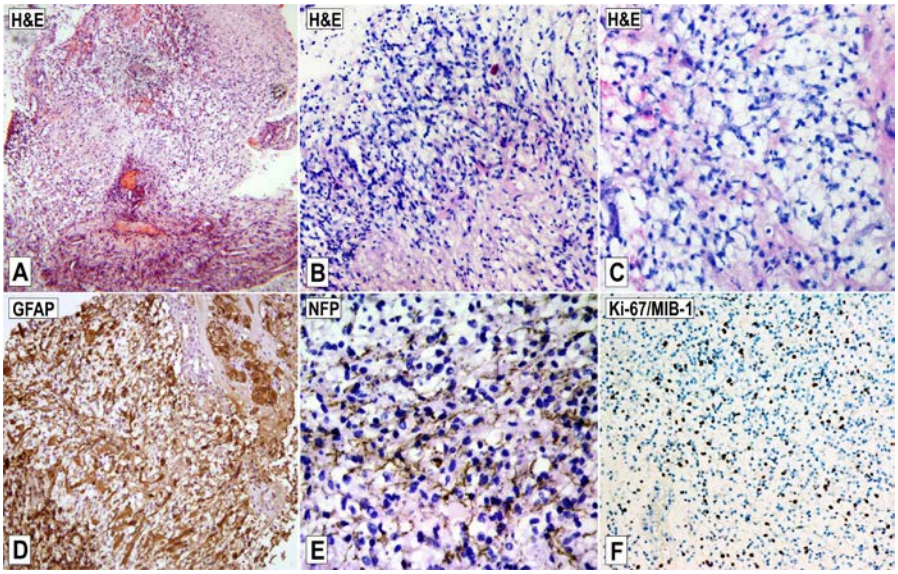
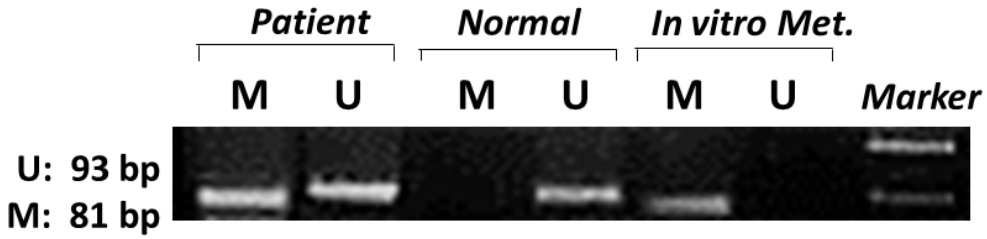


Fig. 3 – Photomicrographs of the surgical specimen from the left subcortical, parietal, ring-like tumor lesion reveals the typical features of glioblastoma: (A) endothelial proliferation with microvascular bleeding into the tumor tissue, (B) pseudopalisading necrosis and (C) hypercellularity with marked cellular atypia and frequent atypical mitosis. (D) Glial fibrillary acidic protein (GFAP) immunoreactivity is strongly and diffusely present in neoplastic glial cells, with only weak (E) neuronal neurofilament protein (NFP) immunoreactivity between them. (F) The Ki-67(MIB-1) nuclear immunoreactivity with labeling index of 20%. Hematoxylin and eosin (H&E) staining, (GFAP, NFP, Ki-67) immunohistochemical staining with DAB as a chromogen contrasted with hematoxylin. Original magnification (A) × 40, (B, D, F) × 100, (C) × 200, (E) × 400.



remove it or performe biopsy. The postoperative course was uneventful. Four weeks after surgery, the patient was well recovered, and his performance status (PS) according to the World Health Organization (WHO) scoring system was 1. He started the standard Stupp's et al. [10] chemoradiation protocol: conformal radiotherapy (CRT) delivered to both lesions, daily fractions of 2 Gy for a total of 60 Gy, with concomitant temozolomide (TMZ) at a dose of 75 mg/m^2 per day over 42 days, followed by 6 standard cycles of adjuvant TMZ 150 – 200 mg/m^2 per day, 5 consecutive days every 28 days (5/28). Since the patient's tolerance to the applied therapy was good, and periodic MRI follow-ups confirmed stabilization of the disease, TMZ was continued with the same dosing schedule up to tumor progression or development of unacceptable toxicity. The patient received a total of 12 standard adjuvant TMZ courses. Despite prolonged stabilization of the disease with good life-quality during extended TMZ treatment, the patient died 19 months after the diagnosis. The TTP estimated by MRI was 17 months: tumor progression was observed 2 months before death as a centrifugal bilateral GB spreading along the white matter tracts. The patient rapidly deteriorated during the final 2 weeks before death, due to a massive parietal intratumoral hemorrhage. In accordance with the wishes of the patient's family an autopsy was not performed.

Discusion

Even though the concept of McG was proposed more than 50 years ago [7], the true origin and nature of this pathology are still moot. Is it a separate nosological entity, a biologically different subtype of glioma with as yet unknown genomic specifics, or just an unpredictable variation in the development of "ordinary" gliomas, mostly malignant, with specific molecular pathways, which we discover in the multicentric phase of their expansion? Several theories have been proposed to explain the synchronous coexistence or metachronous development of glioma multicentricity, such as tumorogenesis at multiple sites or active glioma cell migration invisible to MRI [5, 8, 11–13], but still without conclusive answers. Akimoto et al. [14] recently reported a case of radiologically multicentric, but genetically identical synchronous GB in opposite cerebral hemispheres, which indicates a common monoclonal origin. Schroeder et al. [15] also reported a case of multicentric GB in which all 4 tumor foci shared a common genetic origin, although each had its

own unique set of genetic aberrations. Liu et al. [16] identified overexpression of the *CYB5R2* gene in multicentric and multifocal GB, suggesting that the methylation status of its promoter may serve as a new epigenetic biomarker of multiple GB.

Malignant McGs are mostly localized supratentorially [4–6], but combined supra- and infratentorial localization [4–6, 17–20], and cerebral GB multicentricity with metachronous spinal seeding have also been reported [5, 20, 21]. Ipsilateral multicentricity is more frequent in synchronous than in metachronous malignant gliomas [5]. The number of distant tumor foci may range from 2 to 5 or more, but in most cases there are 2 or 3 [4-6, 18, 22]. Usually, they are of the same histological appearance, but different histotypes or grades of the same histotype are also possible [6, 12, 17, 18, 22]. In three recent clinical studies [1, 2, 23], the frequency of synchronous multicentric GBs among all newly diagnosed multiple (multicentric and multifocal) GBs was between 13% and 24.2%, and in a subanalysis, multicentric GBs ranged from 1.9% to 5% in regard to all newly diagnosed GBs.

Despite the undoubted advantages of conventional contrast-enhanced MRI in diagnosing McGs, their differentiation from other multiple cerebral pathologies such as metastases, lymphoma, infections and vascular or demyelinating diseases may prove difficult or even impossible [8, 9, 24]. Conventional MRI has a limited capacity to differentiate McGs from multiple brain metastases, because their neuroimaging appearance is often similar, equivocal, or indistinguishable [8, 24, 25], as was the case with the parietal lesion in our patient. An additional difficulty in distinguishing these intracerebral lesions is posed by the possibility of the simultaneous presence of brain metastasis in patients affected by glioma, even multicentric [6, 18]. All these facts indicate the need for the use of the advanced MRI techniques such as DWI, PWI and MRS, in order to increase the diagnostic accuracy of conventional MRI, even though none of them are lesion-specific [9].

In contrast to most solid or necrotic metastases, HGGs infiltrate diffusely into the peritumoral area and form neoplastic neovascularization. Consequently, there is a different degree of hyperperfusion on PWI, a restriction of diffusion on DWI and pathologic metabolite ratios of elevated Cho, reduced NAA and mI as well as the appearance of Lip on MRS in the region of the vasogenic edema that surrounds the contrast-enhancing part of HGG on T2W images [9, 26]. Therefore, a metabolic profile consisting of increased Cho/NAA and decreased NAA/Cr ratios at long echo-time (TE = 144 ms), together with low mI and the presence of Lip peaks at short TE (TE = 35 ms), as in the perienhancing region of the parietal lesion in our patient (subsequently confirmed as GB by histopathology), indicated HGG rather than metastasis [9, 27]. Elevated Cho was reported in the peritumoral region of gliomas but not in metastases [26]. The mI signal is absent in metastases, and decreased, but nonetheless present in HGGs [28]. The Lip peaks as a hallmark of necrosis, even if microscopic, in both cases confirm malignancy, whereas in contrast to GB, the prominent Lip signals of metastases are often still seen at long TE [9].

Unlike the parietal lesion, the synchronously present amygdalo-hippocampal lesion in our patient had the MRI- and DWI-characteristics of LGG. Myo-inositol has been shown to be the MRS marker of the astrogliosis and glioma invasion [9, 27, 29]. A high level of mI is present mainly in LGGs, even with no elevation of the Cho/Cr ratio [30]. However, their aggressive continuous infiltrative growth and invasion along the white matter tracts and basement membrane-like structures, leads to further displacement, deviation, and destruction of both neurons and their axons [29]. Consequently, along with a mI increase, NAA as a marker of neuronal density and viability will decline markedly, indicating the more aggressive growth of LGG and its early transformation to a higher grade of malignancy [26, 29]. Therefore, we interpreted the amygdalo-hippocampal lesion in our patient as an "early" or secondary HGG, rather than LGG, given that the high mI/Cr ratio at short TE and absence of NAA on both TEs, were the key characteristics of its spectra. Since the mentioned lesion with “early” malignant glioma characteristics on MRS was not confirmed by histopathology, but was synchronously present with the histopathologically proven parietal GB and the criteria for multicentricity were clear, it was reasonable for us to qualify the reported case as a synchronous malignant McG.

Treatment of patients with malignant McGs is still controversial, and the prognosis remains unfavorable. Reported treatment options range from a biopsy alone, to resection of one or all tumor lesions followed by TMZ chemoradiation [4–6, 8, 17–24, 31]. On one hand, extensive resection increases the risk of hemorrhage and further neurological deterioration. On the other hand, adjuvant chemoradiation will be more effective when the tumor bulk has already been reduced [8, 11]. With regard to these endpoints, it remains debatable how aggressively patients with synchronous or metachronous multicentric disease should be treated [4].

Reportedly, the median survival time (MST) of patients with malignant McGs, regardless of treatment, was between 7.6 and 11 months [4, 6]. Hefti et al. [5] reported that patients with synchronous malignant McG showed a similar MST (110 days) to patients with metachronous disease (72 days), once they developed multicentricity. All the patients in their synchronous cohort underwent surgical resection (gross total or partial), but only 17% of them completed radiotherapy and one third received TMZ chemotherapy with a mean duration of 3.9 cycles [5]. Regarding the treatment applied by Salvati et al. [6] in the pre-TMZ era (before 2005) and di Russo et al. [4] during the TMZ era, longer MST was observed in patients who underwent surgical resection of at least one tumor focus followed by adjuvant therapy, than in those who were treated with a stereotactic biopsy followed by radio- and/or chemotherapy: 9.5 and 12 months *vs* 2.8 and 4 months, respectively. Di Russo et al. [4] stated that MST results similar to theirs were also obtained from a literature review. Median progression free survival (PFS) after surgical resection in their study was 8.5 months with no differences between patients who underwent single or multiple resections. The authors concluded that surgical resection of at least one

easily accessible lesion seems to have a beneficial effect on the survival of selected patients with malignant McGs [4]. We applied the same surgical strategy with our patient by resecting only the easily accessible parietal lesion. However, a recent report by Hassaneen et al. [31] suggests that aggressive resection of all tumor lesions via two separate craniotomies in the same session, in selected patients with synchronous multicentric GB, resulted in a survival duration comparable to that of patients undergoing single-lesion surgery (12.9 *vs* 14.6 months, respectively), without a significant increase in postoperative morbidity. In the cases where surgical resection is not feasible, mainly due to older age and/or poor PS, stereotactic biopsy is recommended as the solution of choice for obtaining the histopathology and planning palliative treatment [8, 31].

In the study by Thomas et al. [1], patients with multicentric GB had worse MST of 3 months compared to those with multifocal and single (unifocal) GBs (10 and 18 months, respectively). However, differences in survival between single and multifocal or multicentric GBs ceased to be significant when taking into consideration independent predictors of outcome such as age, initial PS score, extent of resection, and MGMT gene promoter methylation status. The authors concluded that neither multifocal nor multicentric GB independently predicted worse outcome for patients, but rather were associated with a lower PS score at the time of diagnosis, and the impossibility of performing a gross total resection. Therefore, according to Thomas et al. [1], these findings suggest that unifocal, multifocal and multicentric GB are in fact a spectrum of presentation of a single disease. Paulsson et al. [23] showed that PS remains a dominant prognostic factor in the GB patients, which is particularly relevant in multifocal and multicentric GBs. The authors concluded that response to the standard therapies and overall survival do not differ significantly between multiple GBs and their single focus counterparts, while the worse PFS in multiple GB may be due to increased likelihood of gross total resection in unifocal GB [23].

Since 2005, Stupp's chemoradiation protocol [10] consisting of concurrent CRT with TMZ followed by 6 adjuvant 5/28 cycles of TMZ chemotherapy became a standard of care for patients with newly diagnosed solitary GB after maximal safe tumor resection [32–34]. The reported MST for such patients with methylated MGMT gene promoter was 21.7 months [35]. However, in multicentric disease considerable variations in postoperative treatment protocols were reported [1, 2, 4–6, 8, 16, 17, 19, 20, 22, 23].

Regarding radiotherapy (RT) in patients with synchronous multicentric and multifocal GBs, Showalter et al. [36] found no significant differences in the median TTP or MST between CRT and the whole-brain RT (WBRT), while clinical PS was a consistent and independent predictor of both TTP and MST. On the basis of the progression pattern, but with no clear evidence of its superiority, CRT was recommended as a preferable RT approach, while WBRT should be reserved mainly for patients with poor PS who are unable to complete a prolonged course of CRT [36, 37]. Our patient was treated in accordance with this recommendation, with the addition of concomitant TMZ to CRT according to Stupp's chemoradiation protocol [10] and with good tolerance to the applied therapy. However, significant worsening of PS during postoperative RT in malignant McG patients was reported relatively often in relevant literature as a reason for refusal or termination of further treatment [4, 5, 20].

The exact impact of concomitant and adjuvant TMZ chemotherapy on the MST of patients with malignant McGs is still unknown, mainly due to the rarity of the disease and thus the lack of controlled clinical trials. In a recent report by Paulsson et al. [23], on 8 patients with multicentric GB, various degrees of surgical resection and CRT were followed by TMZ chemotherapy in 6 patients, but without data on their MST or PFS. Moreover, the impact of TMZ chemotherapy cannot be estimated even from the major published studies of Salvati et al. [6] and Hefti et al. [5], because they included patients treated in the pre-TMZ era when TMZ did not become the standard of care in the GB treatment [32, 33]. Only in di Russo et al. [4] study, in all patients except one (17/18), there was resection followed by TMZ chemotherapy and by radiotherapy in 7 of the 18 patients, which might explain, at least in part, the longest MST reported in their study. Moreover, methylation of MGMT gene promoter was recently identified as an independent favorable predictor of outcome in patients with newly diagnosed multicentric and multifocal GBs [1]. Accordingly, as in methylated patients with solitary GB [35, 38], a longer MST could be expected irrespective of a treatment, as well as better response to TMZ in the multicentric GB patients with methylated MGMT gene promoter. Furthermore, this is also a basic argument for continuing adjuvant TMZ beyond 6 standard cycles [39]. Longer adjuvant TMZ in the methylated GB patients should additionally improve tumor control due to their higher sensitivity to the therapeutic TMZ cytotoxicity [34, 39–41]. Keeping this in mind, we extended adjuvant TMZ treatment in our methylated patient to 12 standard cycles while maintaining stable disease and good life-quality all the time during adjuvant therapy and without the appearance of significant additional toxicity. However, in unmethylated patients who are much less responsive to TMZ, there is the option of time- and dose-intensified TMZ regimens which theoretically could reduce the level of MGMT through the enzyme depletion/consumption mechanism. This should lead to the increased and protracted MGMT inactivation, and thus more effective triggering of therapeutic TMZ cytotoxicity [34, 41]. Although, time- and/or dose-modified TMZ regimens have not been shown to be superior to the standard TMZ regimen for newly diagnosed solitary GBs so far [34], their potential role (including the standard one) for malignant McGs still needs to be determined.

Taking all aspects of the applied therapy into account, we believe that our patient received clear benefits from the applied treatment, accomplishing comparatively long survival period of 19 months with a TTP of 17 months. This is considerably longer compared to the reported data for such pathology [1, 2, 4–6, 19, 20, 23], and closer to the MST for newly diagnosed methylated solitary GBs [33, 35]. The main parameters that guided us in choosing the therapeutic

approach were the patient's age and PS and MGMT methylation status, with the basic goal of increasing survival while maintaining good life-quality for as long as possible during the therapy. In addition to the applied therapy, an important factor which probably contributed to longer survival and therefore certainly cannot be ignored, was an "early" malignant glioma lesion synchronously present with a methylated GB lesion, which remained morphologically stabile all through the treatment.

Conclusion

Despite significant improvements in the diagnosis and treatment of malignant gliomas during the last decade, management of synchronous multicentric disease still remains controversial. MRS significantly improved the differential diagnostic accuracy of conventional MRI in our patient and should be included in the initial evaluation of such cases. In accordance with reviewed literature, the younger age, good initial performance status and methylated MGMT gene promoter were all favorable predictors of longer survival in the reported case. Resection of at least one easily accessible tumor lesion, followed by TMZ-based chemoradiation, with continuous adjuvant TMZ in more than 6 standard courses, seems to be currently the most beneficial therapeutic option for such cases. As with all gliomas, an individualized approach based on the structural and metabolic MRI characteristics of the tumor lesions and their particular genomic features, should form the base for the future treatment strategy of synchronous malignant McGs.

REFERENCES

1. *Thomas RP, Xu LW, Lober RM, Li G, Nagpal S*. The incidence and significance of multiple lesions in glioblastoma. J Neurooncol 2013; 112(1): 91–7.
2. *Patil CG, Yi A, Elramsisy A, Hu J, Mukherjee D, Irvin DK*, et al. Prognosis of patients with multifocal glioblastoma: A case-control study. J. Neurosurg 2012; 117(4): 705–11.
3. *Terakawa Y, Yordanova YN, Tate MC, Duffau H*. Surgical management of multicentric diffuse low-grade gliomas: Functional and oncological outcomes: Clinical article. J. Neurosurg 2013; 118(6): 1169–75.
4. *di Russo P, Perrini P, Pasqualetti F, Meola A, Vannozzi R*. Management and outcome of high-grade multicentric gliomas: A contemporary single-institution series and review of the literature. Acta Neurochir (Wien) 2013; 155(12): 2245–51.
5. *Hefti M, von Campe G, Schneider C, Roelcke U, Landolt H*. Multicentric tumor manifestations of high grade gliomas: Independent proliferation or hallmark of extensive disease? Cent Eur Neurosurg 2010; 71(1): 20–5.
6. *Salvati M, Caroli E, Orlando ER, Frati A, Artizzu S, Ferrante L*. Multicentric glioma: Our experience in 25 patients and critical review of the literature. Neurosurg Rev 2003; 26(4): 275–9.
7. *Batzdorf U, Malamud N*. The problem of multicentric gliomas. J Neurosurg 1963; 20: 122–36.
8. *Li Z, Tian Y, Hu G, Yu X*. Multiple gliomas. Chin J Clin Oncol 2007; 4(6): 379–83.
9. *Faehndrich J, Weidauer S, Pilatus U, Oszvald A, Zanella FE, Hattingen E*. Neuroradiological viewpoint on the diagnostics of space-occupying brain lesions. Clin Neuroradiol 2011; 21(3): 123–39.
10. *Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ*, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352(10): 987–96.
11. *Zamponi N, Rychlicki F, Ducati A, Regnicolo L, Salvolini U, Ricciuti RA*. Multicentric glioma with unusual clinical presentation. Childs Nerv Syst 2001; 17(1–2): 101–5.
12. *Wan KR, King NK, Low SY, Sitoh YY, Lee HY, Wong CF*, et al. Synchronous multicentric glioblastoma with PNET and O subtypes: Possible pathogenesis. Surg Neurol Int 2014; 5: 31.
13. *Cage TA, Pekmezci M, Prados M, Berger MS*. Subependymal spread of recurrent glioblastoma detected with the intraoperative use of 5-aminolevulinic acid: Case report. J Neurosurg 2013; 118(6): 1220–3.
14. *Akimoto J, Sasaki H, Haraoka R, Nakajima N, Fukami S, Kohno M*. Case of radiologically multicentric but genetically identical multiple glioblastomas. Brain Tumor Pathol 2014; 31(2): 113–7.
15. *Schroeder B, Shah N, Rostad S, Mccullough B, Aguedan B, Foltz G*, et al. Genetic investigation of multicentric glioblastoma multiforme: case report. J Neurosurg 2016; 124(5): 1353–8.
16. *Liu Q, Liu Y, Li W, Wang X, Sawaya R, Lang FF*, et al. Genetic, epigenetic, and molecular landscapes of multifocal and multicentric glioblastoma. Acta Neuropathol 2015; 130(4): 587–97.
17. *Salunke P, Badhe P, Sharma* A. Cerebellar glioblastoma multiforme with non-contiguous grade 2 astrocytoma of the temporal lobe in the same individual. Neurol India 2010; 58(4): 651–3.
18. *Pejsa V, Grgurevic I, Pazanin L, Lang N, Grgurevic L, Jaksic O*. Multicentric glial brain tumors of a varying degree of differentiation in patient with chronic lymphocytic leukemia. Am J Hematol 2005; 79(1): 50–9.
19. *Arcos A, Romero L, Serramito R, Santín JM, Prieto A, Gelabert M*, et al. Multicentric glioblastoma multiforme. Report of 3 cases, clinical and pathological study and literature review. Neurocirugia (Astur) 2012; 23(5): 211–5.
20. *Shakur SF, Bit-Ivan E, Watkin WG, Merrell RT, Farhat HI*. Multifocal and multicentric glioblastoma with leptomeningeal gliomatosis: A case report and review of the literature. Case Rep Med 2013; 2013: 132679.
21. *Tinchon A, Oberndorfer S, Marosi C, Rudà R, Sax C, Calabek B*, et al. Malignant spinal cord compression in cerebral glioblastoma multiforme: A multicenter case series and review of the literature. J Neurooncol 2012; 110(2): 221–6.
22. *Nakhl F, Chang EM, Shiau JS, Alastra A, Wrzolek M, Odaimi M*, et al. A patient with multiple synchronous gliomas of distinctly different grades and correlative radiographic findings. Surg Neurol Int 2010; 1 48.
23. *Paulsson AK, Holmes JA, Peiffer AM, Miller LD, Liu W, Xu J*, et al. Comparison of clinical outcomes and genomic characteristics of single focus and multifocal glioblastoma. J Neurooncol 2014; 119(2): 429–35.
24. *Wang P, Wu M, Chen Y, Zhao G*. Multicentric gliomas misdiagnosed as metastatic tumors: one case report and literature review. Clin Oncol Cancer Res 2010; 7: 317–21.
25. *Server A, Josefsen R, Kulle B, Maehlen J, Schellhorn T, Gadmar Ø*, et al. Proton magnetic resonance spectroscopy in the distinction of high-grade cerebral gliomas from single metastatic brain tumors. Acta Radiol 2010; 51(3): 316–25.
26. *Bulakbasi N, Kocaoglu M, Ors F, Tayfun C, Uçöz T*. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. AJNR Am J Neuroradiol 2003; 24(2): 225–33.

27. *Cianfoni A, Law M, Re TJ, Dubowitz DJ, Rumboldt Z, Imbesi SG*. Clinical pitfalls related to short and long echo times in cerebral MR spectroscopy. J Neuroradiol 2011; 38(2): 69–75.
28. *Castillo M, Kwock L*. Proton MR spectroscopy of common brain tumors. Neuroimaging Clin N Am 1998; 8(4): 733–52.
29. *Bulik M, Jancalek R, Vanicek J, Skoch A, Mechl M*. Potential of MR spectroscopy for assessment of glioma grading. Clin Neurol Neurosurg 2013; 115(2): 146–53.
30. *Bowen BC*. Glial neoplasms without elevated choline-creatine ratios. AJNR Am J Neuroradiol 2003; 24(5): 782–4.
31. *Hassaneen W, Levine NB, Suki D, Salaskar AL, de Lima MA, McCutcheon IE*, et al. Multiple craniotomies in the management of multifocal and multicentric glioblastoma. Clinical article. J Neurosurg 2011; 114(3): 576–84.
32. *See SJ, Gilbert MR*. Chemotherapy in adults with gliomas. Ann Acad Med Singapore 2007; 36(5): 364–6.
33. *Wilson TA, Karajannis MA, Harter DH*. Glioblastoma multiforme: State of the art and future therapeutics. Surg Neurol Int 2014; 5: 64.
34. *Dresemann G*. Temozolomide in malignant glioma. Onco Targets Ther 2010; 3: 139–46.
35. *Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M,* et al. . MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005; 352(10): 997 –1003.
36. *Showalter TN, Andrel J, Andrews DW, Curran WJ, Daskalakis C, Werner-Wasik M*. Multifocal glioblastoma multiforme: Prognostic factors and patterns of progression. Int J Radiat Oncol Biol Phys 2007; 69(3): 820–4.
37. *Ampil F, Burton GV, Gonzalez-Toledo E, Nanda A*. Do we need whole brain irradiation in multifocal or multicentric high-grade cerebral gliomas?, Review of cases and the literature. J Neurooncol 2007; 85(3): 353–5.
38. *Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC*, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10(5): 459–66.
39. *Franceschi E, Tosoni A, Brandes AA*. Adjuvant temozolomide: How long and how much? Expert Rev Anticancer Ther 2008; 8(5): 663–5.
40. *Hau P, Stupp R, Hegi ME*. MGMT methylation status:The advent of stratified therapy in glioblastoma?. Dis Markers 2007; 23(1–2): 97–104.
41. *Thon N, Kreth S, Kreth FW*. Personalized treatment strategies in glioblastoma: MGMT promoter methylation status. Onco Targets Ther 2013; 6: 1363–72.

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