

CASE REPORT

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Eight-year follow-up of a patient with glioblastoma multiforme who completed radical treatment

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ABSTRACT

The aim of the study is the presentation of an unexpectedly long, eight year survival of a female patient, suffering from glioblastoma multiforme (GBM), who completed radical treatment, which was composed of neurosurgery followed by radiochemotherapy with temozolomide. The condition of the patient was regularly examined and brain computed tomography was performed to exclude recurrence of the disease. During eight years of follow-up, no relapse was observed. After radical treatment, the neurological condition of the patient systematically improved. At present, as a result of rehabilitation, neurological symptoms are not observed. Currently, the patient does not require any drugs, including anticonvulsants. In conclusion, despite extremely unfavorable prognosis, every patient who is fit enough should receive radiochemotherapy with temozolomide after neurosurgery, because long-term survival in GBM is achievable. In case of technical difficulties (unavailable radiotherapy or chemotherapy in smaller hospitals) patients should be referred to oncology centers for combined treatment.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common subtype accounting for 70% of gliomas and typically occurs in patients 45–70 years old. It has extremely unfavorable prognosis. Expected survival is only 12–15 months after primary diagnosis [1]. Survival longer than the above-mentioned is rarely observed [2–7].

CASE REPORT

A 65-year-old woman without comorbidities was admitted to the emergency department in 2012 due to sudden, strong pain of the head and neck, associated with vision disturbances on the right side. Physical examination revealed Gerstman syndrome with typical symptoms (dysgraphia, dyscalculia, finger agnosia, and left-right disorientation). Vital signs together with other laboratory parameters, such as complete blood count, kidney and liver function, d-dimers, thyroid-stimulating hormone

were within normal limits. Brain computed tomography (CT) in the parieto-occipital area presented visible ring enhancement. The lesion was accompanied by edema, causing complete tightening of the occipital posterior horn of lateral ventricle and the stem of left lateral ventricle. Moreover, a slight dislocation of the cerebral falx to the right was visible. Computed tomography scan suggested presence of brain tumor, with differentiating diagnosis of abscess (Figure 1).

The chest X-ray and abdominal ultrasound were normal. In order to lower intracranial pressure the patient was treated with dexamethasone 3 mg per day and furosemide. Then she was transferred to the neurosurgery department and a resection of the tumor was performed. On histopathological examination the tumor showed typical features of high-grade astrocytic glioma with striking polymorphism (Figure 2), extensive necroses and with palisade formations (Figure 2A–C) which was glial fibrillary acidic protein (GFAP)-positive. The tumor was additionally characterized by proliferation of endothelia, frequent mitoses (12/10 high power fields: HPF) of tumor cells and high Ki-67 index, measured as percentage of nuclear Ki-67 positivity (approx. 25%) (Figure 2B). Moreover, strong expression of p53 was observed (Figure 2C). Only in minority of areas, there were morphologic microscopic patterns with extreme pleomorphism and also with some delicate reticulin network, which might suggest pleomorphic xanthoastrocytoma (PXA) (Figure 2D). Based on the above-mentioned microscopic picture, anaplastic WHO grade III variant could have been considered. However, domination of glioblastoma-like morphology and p53 expression, which is typical for glioblastoma (GBL WHO grade IV) and not for PXA, spoke in favor of the former. Finally, the diagnosis of glioblastoma G IV was established. After the surgery the patient was in a good condition (performance status [PS] 1 according to Eastern Cooperative Oncology Group criteria), but she experienced partial seizures in the following days. A diagnosis of epilepsy was made and valproic acid (500 mg two times daily) was added to the treatment. After a multidisciplinary consultation, the patient was qualified for radiation therapy together with temozolomide (75 mg/m², 120 mg daily for 42 days). Radiation therapy was performed using intensity-modulated radiation therapy (IMRT) technique. The gross tumor volume (GTV) was defined as primary tumor and edema on preoperative CT plus resection cavity on postoperative CT. Additional margin of 2 cm was added to GTV, for clinical target volume (CTV), to account for sub-clinical tumor infiltration. To account for daily setup errors, a margin of 5 mm was added to the CTV for planning target volume (PTV). A dose of 60 Grays (Gy) in 2.0 Gy daily fractions was given to the PTV using 6 MV photons. The following adverse effects were observed: anemia G1, hepatic toxicity G3 with no skin abnormalities (stage of toxicity in accordance to Common Terminology Criteria for Adverse Events [CTCAE] version 4.0), elevation of liver enzymes, which was probably caused by valproic

acid, which was therefore replaced with levetiracetam. After radiation therapy, faint skin erythema and alopecia were observed. Upon completing radiochemotherapy, in April 2013, the woman was in good condition (PS1) with stable vision disturbances and central facial palsy. Since April 2013, she has been receiving temozolomide: during the first cycle, at the daily dose 260 mg (150 mg/m²), for 5 consecutive days, and subsequently at the daily dose 340 mg (200 mg/m²), for 5 consecutive days per cycle. Control brain CT was performed in 2013 and revealed ring enhancement, which was still visible in the tumor bed, but was weaker than in preliminary examination. The edema surrounding the lesion was similar to the previous CT from 2012. Mass effect has not been found. Medial structures were not dislocated. Later on, the patient was regularly monitored neurologically. Computed tomography of the brain was performed at least once a year and no recurrence of the disease during the eight-year mining period had been found till now (Figure 1B and C).

At her most recent follow-up, visit in July 2020, the woman did not report any major complains or neurological abnormalities (PS 1). In summary, the patient has finished treatment in 2013 and is still being monitored regularly, without any sign of recurrence.

DISCUSSION

In the presented case, the patient has been alive for over eight years, without any signs of recurrence after completion of the treatment. In the literature, there are a few cases reporting long-term survival of the patients with GBM. Factors which are considered to be associated with better clinical outcome are: tumor size and location, treatment, age at presentation, PS at presentation, histologic findings, and molecular genetic factors [5]. Cervoni et al. [6] reported a case of a 13-year-old girl with supratentorial GBM located in right frontal lobe. She survived 14 years after complete excision and radiochemotherapy. Deb et al. [7] presented six cases of

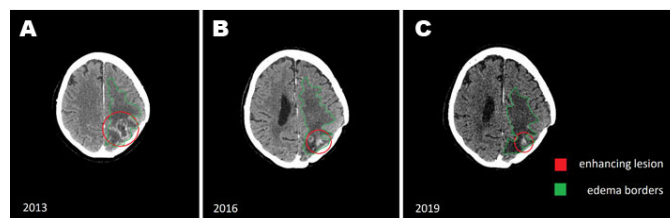


Figure 1: Brain contrast enhanced CT. (A) From year 2013—ring enhancement focus in occipital lobe of left hemisphere accompanied by 2nd degree edema. (B) From year 2016—significant regression of ring enhancement, only weak enhancement was visible in the tumor bed, accompanied by edema similar to previous examinations, ring enhancement, which had been visible before was not found at present CT, mass effect was not found. (C) From year 2019—both the level of enhancement and edema extent are consistent with 2016 CT.

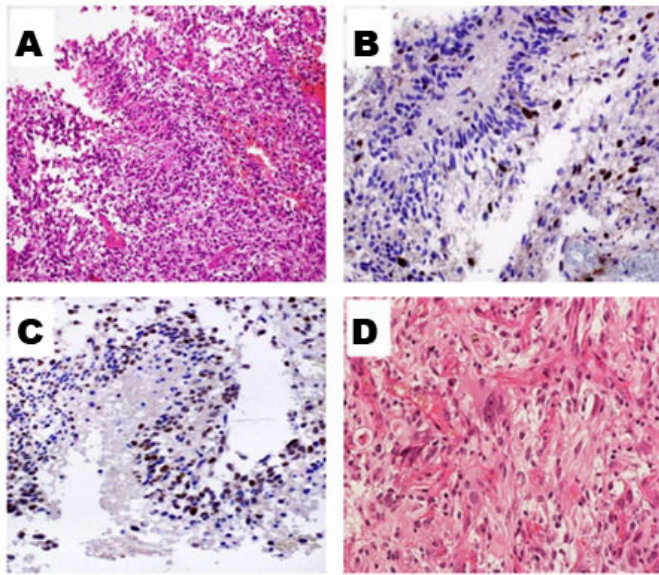


Figure 2: Microscopic picture of GBM: (A) Striking nuclear pleomorphism and cellularity of the tumor. Areas of necroses surrounded by palisading alignment of tumor cells are visible (also seen in (B) and (C)). (Hematoxylin-eosin staining, obj. magn. 10×); (B) Very high proliferation activity reflected by nuclear expression of Ki67 (immunohistochemical staining for Ki-67, obj. magn. 20×); (C) Strong expression of p53 (immunohistochemical staining for p53, obj. magn. 20×); (D) Region of extreme pleomorphism, which could have justified diagnosis of GBM (WHO IV).

GBM with an average survival of nine years (range 5–15 years). Interestingly, all were young patients with mean age of 27 years (range 8–45 years). Supratentorial and cerebellar gliomas are more feasible to surgical treatment thus carry better clinical outcome. Additionally, patients younger than 40 years old are in the group with better prognosis [8]. Krex et al. [9] have analyzed 55 patients of GBM with longer survival than three years. They have found, methylguanine-DNA methyltransferase (MGMT) methylated in 74% cases, but 1p 19q deletion was not an indicator for good prognosis (as in oligodendroglioma) in this group. In the case report presented by Sperduto et al. [10], the patient with triple-positive GBM patients (MGMT methylated, phosphatase and tensin homolog gene [PTEN] and p53 positive) survived 20 years. Various molecular alterations have been examined in terms of prognostic value in GBM. In the study of Korshunov et al. [8], epidermal growth factor receptor (EGFR) amplification, loss of 9p21, and gain of chromosome 9 were associated with unfavorable clinical outcome in all patients, whereas gain of chromosome 7 and loss of 10q23/PTEN worsen the prognosis only in patients >40 years-old. However, the prognostic value of EGFR amplification was not confirmed by Burton et al. [11]. On the other hand, methylation of the MGMT promoter, which results in gene silencing, prolongs the survival in patients with GBM, who receive alkylating agents [12]. Additionally, tumors of the patients with survival longer

than three years have p53 and MDM2 overexpression and a lower proliferation rate (than levels of 15–20%, which is recommended by World Health Organization for conventional GBM) [11, 13]. The histologic features related to better outcome in GBM include: presence of giant cells, focal oligodendroglial differentiation, absence of small anaplastic cells, and evidence of better differentiation with more GFAP positivity [14, 15].

When it comes to management of patients suffering from brain tumors imaging examinations play vital role. Recent development of imaging modalities and improvement of existing techniques, such as magnetic resonance imaging (MRI) or CT have influenced detection, and consequently identification and characterization of different forms of brain tumors. New possibilities enable excluding other diseases, which could be mistakenly diagnosed as brain tumors. Modern imaging modalities ensure detailed preoperative assessment pertaining to determining tumor stage and its relation to surrounding tissues and structures. Correct assessment prevents unnecessary risk during surgery and allows to choose the best treatment options [16, 17]. In the above-presented case, CT examination played a key role, enabling tumor detection and diagnosis, as well as treatment monitoring. Contemporary standard treatment of GBM includes neurosurgery followed by radiochemotherapy and chemotherapy with temozolomide. Such approach is more effective than neurosurgery, followed by radiation therapy alone, and results in a clinically meaningful and statistically significant survival benefit, with minimal additional toxicity (two-year survival rate of 26.5% with radiation therapy plus temozolomide and 10.4% with radiotherapy alone) [18]. The benefit from radiochemotherapy is even greater in case of methylation of the MGMT promoter [12]. In the presented case status of MGMT promoter is unfortunately unknown; however, considering achieved long-term survival we could assume that it was probably methylated. Treatment was generally well tolerated, with minor hematologic toxicity and no long lasting side effects. Due to the good tolerability of the therapy, the patient received all planned treatment (continuation of temozolomide after the end of radiochemotherapy). According to the literature [18–20], the final effect of temozolomide after radiochemotherapy has not been proven, due to the fact that some patients did not receive all the planned therapy. Very often treatments have to be terminated because of unacceptable toxicity. Radiochemotherapy with temozolomide is associated with up to 14% grades 3–4, according to criteria CTCAE hematological toxicity and is more effective than radiotherapy alone [18–20]. In the future research, a detailed analysis of the patient's germline and somatic (analysis of tumor tissue) genetic profile is planned. Perhaps the specific biological features, yet unknown, are associated with such a good effect and tolerance of the therapy. The identification of possible predictive factors of response to the treatment is of major importance to improve the effects of the treatment in the GBM.

CONCLUSION

In conclusion, described case revealed that, despite extremely unfavorable prognosis, every patient who is fit enough should receive radiochemotherapy with temozolomide after neurosurgery, because long-term survival in GBM is achievable. In case of technical difficulties (unavailable radiotherapy or chemotherapy in smaller hospitals) patients should be referred to oncology centers for combined treatment. Complete, combined radical treatment gives a chance for long-term survival of patients diagnosed with GBM.

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Aleksandra Grela-Wojewoda – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Maksymilian Kruczała – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Elżbieta Łuczyńska – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content,

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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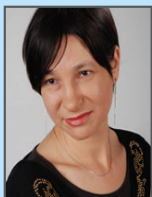
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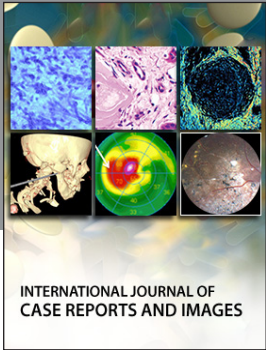
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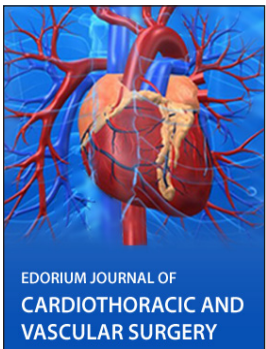
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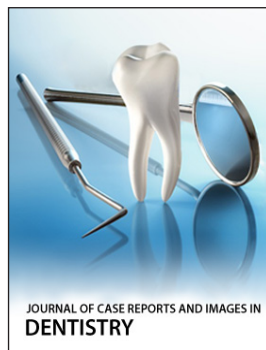
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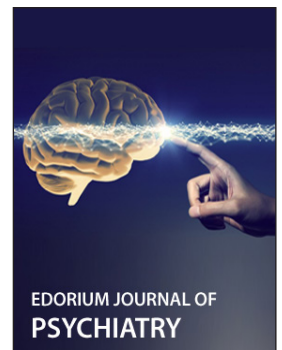
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