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Glioblastoma Multiforme developed in site of Motor Cortex Stimulation

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Introduction

Motor cortex stimulation (MCS) is a potential treatment option for patients with severe, chronic neuropathic and medically refractory pain. According to the literature, MCS is safe and effective treatment [1, 2]. Only one case where glioblastoma multiforme (GBM) developed during chronic deep brain stimulation (DBS) in subthalamic nuclei (STN) for Parkinson's disease was reported [3]. Gliomas arising after gamma knife surgery and radiation therapy have been previously reported [4, 5].

Clinical Case

A 55-year-old male patient presented with an intracerebral hemorrhage of right basal ganglia with left side hemiparesis. Consequently, patient developed left-sided medically refractory pain. After evaluation, patient became a candidate for the MCS, and four years later, underwent surgery. A burr hole was drilled on the right parietal bone and two epidural electrodes were implanted on the motor cortex (*3587A, Medtronic*); the extensions were placed subcutaneously towards right pectoral region where they were connected with pulse generator (*Prime advanced, Medtronic*). Surgery went without any complications and patient recovered uneventfully. The stimulation started on second postoperative day, with following parameters: (0-,1-,2-,3-,4+,5+,6+,7+) 2.7 V, 20 Hz, 270 μs. Significant decrease of pain level was reported. Since the implantation, the patient underwent regular neurological controls during which the stimulation was set up between 2.5 and 2.8 V, respectively. Pain level was decreased after every control.

Five years later, the patient presented with partial motor seizures and previously described left-sided hemiparesis. Initial computerized tomography (CT) revealed a hemorrhagic venous infarction in the right frontoparietal region of brain. Radiologists were not confident about the etiology of lesion, although assuming a tumor with hemorrhagic component. Therefore, magnetic resonance imaging (MRI) was recommended. In order to perform MRI, MCS system had to be removed. Antiedematous therapy was applied and the patient clinically improved. Due to differential diagnosis, that included both venous infarctions, as well as a tumor lesion, we decided to remove the MCS system to enable the possibility of performing MRI. MCS was removed, alongside with both epidural electrodes and pulse generator. Initial MRI revealed a heterogeneous lesion in the right frontoparietal brain region, with multilocular hyperintense signals inside the lesion, indicating subacute intralesional hemorrhage. Expansive nature of the lesion, as well as prominent adjacent perilesional edema caused left-side midline shift (Fig. 1). Control MRI, six weeks later, showed large inhomogeneous zone with partial hemorrhage areas in the right frontoparietal brain region and surrounding edema causing left side midline shift (Fig. 2). Additionally, MRI spectroscopic analysis revealed increased metabolism of choline in regard to N-acetylaspartate and increased activity of lactate, which primarily pointed out to an infiltrative tumor process. In order to confirm the diagnosis and to obtain representative tissue samples for the pathohistological diagnosis, patient underwent frameless biopsy. Tissue samples from multiple sites of tumor were taken. According to World Health Organization classification it corresponded to the glioblastoma multiforme, grade IV. Postoperative CT showed no signs of bleeding in the trajectory line nor in the site of the biopsy. According to the tumor size, the location and the pathohistological diagnosis, gross total resection was not indicated. An oncologist was consulted. Patient underwent fractionated external beam radiation therapy of the whole brain. The dosage of 60 Gy was administrated in 2 Gy fractions delivered during the period of six weeks. The patients did not received concomitant chemotherapy during radiotherapy. Furthermore, two months after applied radiotherapy, the patient was treated with chemotherapy. The temzolomide was administered, 150 to 200 mg/m^2 for five days every 25-28 days for six maintenance cycles. Unfortunately, four months after oncological treatment, the patient died.

Comments

GBM is one of the most common primary parenchymal brain tumors with median survival of less than one year [6, 7]. Multiple predisposing genetic and environmental factors in GBM formation have already been vastly discussed. Several cases of glioblastoma masqueraded as intracerebral hemorrhage (ICH), traumatic ICH, intraventricular hemorrhage or arteriovenous malformation has been reported previously [8-11]. Although the exact connection between previous hemorrhage and the glioblastoma development is yet unknown, according to literature, two possible mechanisms can be considered. First one is tumor bleeding during the development of hypervascular tumors. In addition, there is a possibility that trauma participated in the hemorrhage; tumor vessels and microcysts may have been damaged during the impact, causing both vessels and cyst thin walls to rupture [9-11]. Other one is abnormal repair

mechanism within white matter injured previously which in turn could facilitate the malignant transformation of the glial cells [9].

In addition, there is a suggestion that malignant astrocytic tumors can arise from neoplastic transformation of damaged astrocytes, based on case reports of glioblastomas occurring at the site of traumatic brain injuries [7]. Several reported cases of high-grade gliomas arising at sites of encephalomalacia from prior vascular brain injury suggest a potentional etiological association between glioblastoma development and vascular brain injury. Ischemic brain injury results in activation of astrocytes and induction of expression of transcriptional factors, as well as proinflammatory cytokines. They support cellular migration and astrocytic proliferation, factors linked to gliomagenesis. Post ischemic inflammatory microenvironment, as well as new studies that include stem cells and cell migration, explain possible connection between injury and gliomagenesis [12]. On contraire, recent studies found no association between structural brain injury and malignant astrocytic tumors [6]. We consider that these potential etiological associations are worth mentioning since the lesion in our patient was primarily neuroradiologically described as an ischemic brain injury.

However, beside possible vascular injury as one of precipitating factors for GBM development, we must consider the MCS implanted epidurally on motor cortex on the same site where the GBM has developed and, according to neuroradiological images, was on top and in center of developed lesion that spread both frontally and parietally. Therefore, we contemplated whether continuous electrical stimulation during MCS treatment that lasted for more than five years could have induced the development of GBM under the area of stimulation. Also, could the electromagnetic field induced around the electrodes participate in the formation of glioma? According to the literature and several conducted epidemiological studies, there is no evidence that exposure to electrical or magnetic fields is a risk factor for the glioma formation [13, 14]. In Yamamoto et al., where a unique case of a patient who developed GBM after DBS in STN is described, this possibility is also being excluded. Also, authors suggest a very slight possibility that continuous electrical brain stimulation itself induced the formation of GBM [3]. Of course, we cannot exclude the possibility that this GBM occurred spontaneously without any connection to MCS. Still, interesting point of view, when considering existing potential etiological correlations, is reflecting the possibility that continuous electrical stimulation, with possible thermal effect, could activate the cells in encephalomalatic region and induce neoplastic transformation of damaged astrocytes resulting in high grade gliomas. Cases of glioma arising after interaction of several different factors suggest that further studies are necessary in order to get new insights into the neurobiology of glioblastoma development. We emphasize the importance of reporting individual cases like this one, as MCS is common procedure. More studies should be implemented in order to confirm possible correlation between the MCS and neoplastic transformation. Furthermore, should it once be scientifically proven, we believe that the patients must be honestly informed about possible downsides of a long-term electrical stimulation.

Disclosure of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

Figure 1. Initial brain MRI reveling extensive heterogeneous lesion in the right frontal and parietal lobes, with prominent adjacent perilesional edema on axial plain, T2 weighted image, without contrast (A); multilocular hyperintense signals inside the lesion indicating subacute intralesional hemorrhage on axial plain, T1 weighted image, without contrast (B); irregular, predominantly peripheral enhancement of the lesion, indicating blood-brain barrier breakdown on axial plain, contrast enhanced T1 weighted image (C), while control brain MRI revealed large inhomogeneous zone with partial hemorrhage areas in the same region and surrounding edema causing left-sided midline shift presented on axial plain, susceptibility weighted image (D); and zones of diffusion restriction in the right frontal and parietal lobe, with prominent perilesional edema, diffusion-weighted images (E) (scale bar, 5 cm).

Figure 2. Merged patients CT images with epidural electrodes and MRI reveling extensive right frontal and parietal lesion; (A) merge shows more CT characteristic, (C) merge shows more MRI characteristic; still, electrode artefact is clearly visible. 3D reconstruction of merged CT and MRI presenting more clearly the position of electrode (marked with black arrows) above the lesion site (B). Note: The medial part of electrode is not clearly visible due to artefact. Both image merge and 3D reconstruction were performed on Medtronic Stealth Station software.