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CASE REPORT Open Access

Multifocal glioblastoma multiform with "encephalitis-like presentation" : a case report

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Abstract

Background: Glioblastoma multiform is the most common and aggressive type of primary malignant tumor that affects the central nervous system in adults. It clinically presents with seizures, headache, and/or progressive focal neurological deficits. Radiologically, glioblastoma multiform appears as a single distinguishable, large heterogeneous lesion affecting the cerebrum with characteristic central necrosis, marginal enhancement, and surrounding vasogenic edema. This article describes a patient that exhibited an atypical clinical presentation of multifocal glioblastoma multiform with misleading early radiological features that simulated herpetic encephalitis.

Results: A 66-year-old female that presented with left-sided hemiparesis and left partial motor seizures underwent multi-slice computed tomography (MSCT) and magnetic resonance imaging (MRI) scans. A cerebrospinal fluid (CSF) polymerase chain reaction (PCR) test was also performed to screen for herpes simplex virus 1 (HSV-1).

Conclusions: The early stages of glioblastoma may manifest as symptoms typical to encephalitis, which can delay diagnosis and treatment. Therefore, early diagnosis and identification of atypical glioblastoma multiform presentations, as reported in this article, are essential.

Keywords: Glioblastoma, Glioblastoma multiform, Radiological features, Encephalitis-like

Background

Glioblastoma (astrocytoma WHO grade IV, or previously known as glioblastoma multiform) is the most common and aggressive primary malignant tumor that affects about 15% of adults. It is also the most common type of central nervous system glioma and constitutes at least 50% of these tumors [1]. The peak age for onset of glioblastoma multiform is between 50 and 60 years. Unfortunately, it has a poor prognosis with an average survival of approximately 1.5 years, even with surgical resection and postoperative chemotherapy and radiotherapy. Glioblastoma often presents with headache, seizures, or insidiously progressive focal neurological deficits depending on the site of the tumor. Most glioblastomas appear as single large lesions in the cerebrum, but it is not uncommon for the cerebellum and the spinal to be affected. Glioblastoma multiform predilection sites in the cerebrum include the frontal lobes, deep white matter, thalami, and basal ganglia [2]. Radiologically, glioblastomas are characterized by their large size, apparent irregular outlines, thick and often enhancing margins, and necrosis at the core with or without a hemorrhagic component. They are usually surrounded by vasogenic edema, which contains neoplastic cellular infiltrations [3]. This article describes a case of glioblastoma with atypical clinical presentation and misleading early radiological features that simulated encephalitis.

Case presentation

On November 2017, a 66-year-old woman with left-sided hemiparesis and left motor seizures was admitted to the emergency room (ER). On November 21, 2017, an

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initial multi-slice computed tomography (MSCT) brain scan revealed a right temporal hypodensity and chronic small vessel ischemic changes in the deep white matter that were suggestive of cerebrovascular stroke (Fig. 1).

On November 22, the patient underwent magnetic resonance imaging (MRI) brain scans, which showed a poorly circumscribed T1-hypointense and T2-fluid-attenuated inversion recovery (FLAIR)-hyperintense lesion at the medial aspect of the right temporal lobe with partially restricted MRI apparent diffusion coefficient (ADC) values and surrounding edema. Diffusion-weighted imaging (DWI) determined that diffusion was also partially restricted (Fig. 1, 2).

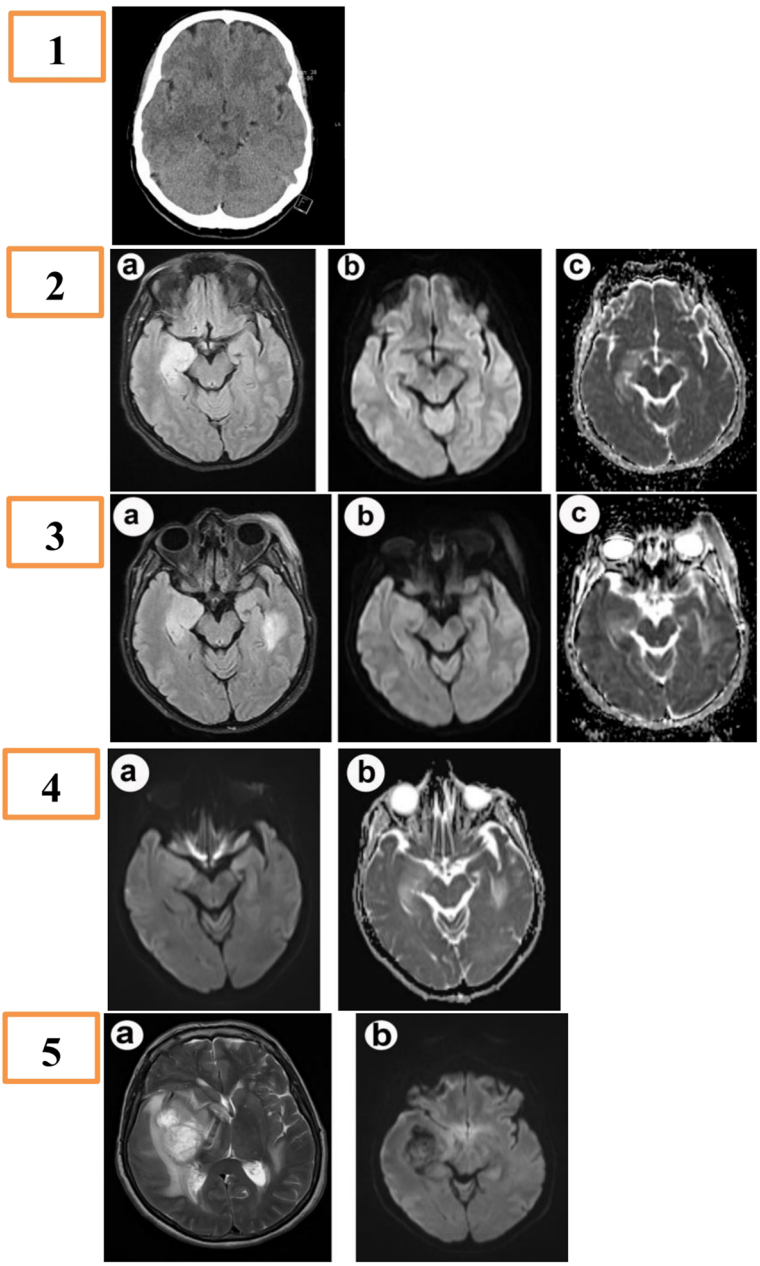

Fig. 1 1—Plain MSCT brain scan showing right temporal hypodensity and deep white matter ischemia. 2—MRI scan of brain and posterior fossa showing (**a**) irregular FLAIR-hyperintense right temporal lesion with (**b**) restricted diffusion on SWI and (**c**) ADC. 3—MRI brain and posterior fossa showing bilateral temporal lobe with ill-defined lesions with a FLAIR hyperintense signal surrounded by (**a**) edema and mild diffusion restriction on (**b**) SWI and (**c**) ADC films. 4—MRI brain scan of bilateral temporal lobe lesions showing faint restriction on (**a**) SWI and evident high signal on (**b**) ADC. 5—MRI brain scan showing (**a**) large right temporal mass lesion with heterogeneous intensity on T2 film with surrounding vasogenic edema and mass effect on the anterior and posterior horns of the lateral ventricle and midline shift. (**b**) The lesion showed restriction of diffusion on SWI. The left hemisphere shows hyperintense signal on the mesial temporal lobe

In clinical correlation with the patient's seizures, this temporal lobe lesion was thought to be a radiological feature of herpetic encephalitis. CSF analysis revealed lymphocytic pleocytosis, normal glucose levels, and increased protein levels. Furthermore, the CSF polymerase chain reaction (PCR) test was positive for herpes simplex virus 1 (HSV-1). Therefore, a herpetic encephalitis diagnosis was recommended and anti-encephalitic measures were initiated. Despite treatment, the patient's clinical condition deteriorated. On November 30, another MSCT brain scan was performed and revealed ill-defined bilateral temporal lobe hypodensities with surrounding edema. On December 2, another MRI brain scan was subsequently recommended and conducted; it confirmed that bilateral T1-hypointense and T2-FLAIR-hyperintense lesions were present in both temporal lobes with surrounding edema and that the lesions were exerting mass effect on the nearby anterior horns of the lateral ventricles (Fig. 1, 2, 3).

Upon follow-up on December 14, an MRI brain scan performed showed a slight progression of the size of the temporal lesions with evident restriction on the ADC map (Fig. 1, 2, 3, 4).

On March 12, 2018, the temporal lobe masses became evident. After the previous MRI brain scan, they had significantly increased in size and developed the classical radiological features of glioblastoma with heterogeneous signals, peripheral vasogenic edema, infiltration into surrounding brain tissue, and high signal intensity on the ADC map (Fig. 1, 2, 3, 4, 5).

On March 22, MRI perfusion was done and revealed high relative cerebral blood volume (r-CBV) and infiltration into surrounding normal-looking brain tissue (Fig. 2). The patient then underwent surgical resection of the right temporal lobe mass due to extensive mass effect and uncal and subfalcine herniation. Histopathology confirmed the glioblastoma multiform diagnosis. Histopathology of the specimen revealed a cellular neoplasm with vascular proliferation and areas of necrosis. The tumor was composed of areas of hypercellularity and areas of hypocellularity, and the individual cells exhibited moderate pleomorphism and abundant eosinophilic cytoplasm. The cells were also actively undergoing mitosis.

Fully informed consent was prospectively obtained from the study participant and can be requested at any time. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Discussion

Glioblastoma multiform is one of the most aggressive primary central nervous system tumors. Glioblastoma multiform diagnosis is usually achieved by combining both clinical features and characteristic radiological findings, and it is confirmed by histopathology. Early diagnosis is important because early aggressive treatment often leads to a better outcome [4]. However, early diagnosis is sometimes challenging because the tumor can cause atypical clinical and radiological presentations during the early stages. Basically, glioblastoma multiform often presents with insidious progressive focal neurological deficits that vary depending on the location of the tumor. Headache and seizures are common initial manifestations and symptoms of increased intracranial tension, such as vomiting, blurring of vision, headache, lethargy, or even coma, may particularly occur with advanced disease. False localizing signs, including sixth nerve palsy, third nerve palsy (with uncal herniation), and perinaud syndrome (with rostral midbrain compression) are not uncommon [5]. The patient described in this article presented with seizures and motor weakness. Although they are common presentations of glioblastomas, they are also common in a wide variety of other neurological conditions, particularly encephalitis. While some studies have simply reported the co-occurrence of herpes simplex encephalitis and glioblastoma multiform, other studies have argued that the two diseases are associated with each other [6–8]. However, the pathophysiology of this potential association remains elusive. Furthermore, levels of HSV-1 antibodies have been found to be significantly high among patients with glioblastoma multiform. Some glioblastoma cases have responded to acyclovir treatment. This may be due to the inhibitory effect of acyclovir on regulatory T helper cells and glioblastoma cell growth [9]. The case reported in this article is another example of the diagnostic dilemma caused by the similar clinical presentations of HSV-1 and early-stage glioblastoma.

Glioblastoma multiform consistently presents distinguishable radiological features that may facilitate radiological-based diagnosis of the tumor at the early stages of the disease. At the time of diagnosis, glioblastomas are typically large lesions with characteristic heterogeneous signal intensities at the cores due to central necrosis and hemorrhagic transformation. On MSCT images, they appear as large, ill-defined hypodense masses with slightly hyperattenuating margins. Hyperdense foci indicating hemorrhages can be observed and heterogenous enhancements are often present. On MRI scans, glioblastomas appear as T1 iso- or hypointense and T2-FLAIR hyperintense lesions in the white matter with irregular margins and abnormal signals at the core. They typically have irregular peripheral marginal enhancement with or without central foci of enhancement around the necrotic core. Moderate to massive vasogenic edema and mass effect can be visualized during advanced stages of the disease. Based on DWI and ADC data, glioblastomas often exhibit high flow restriction, especially when compared to surrounding vasogenic

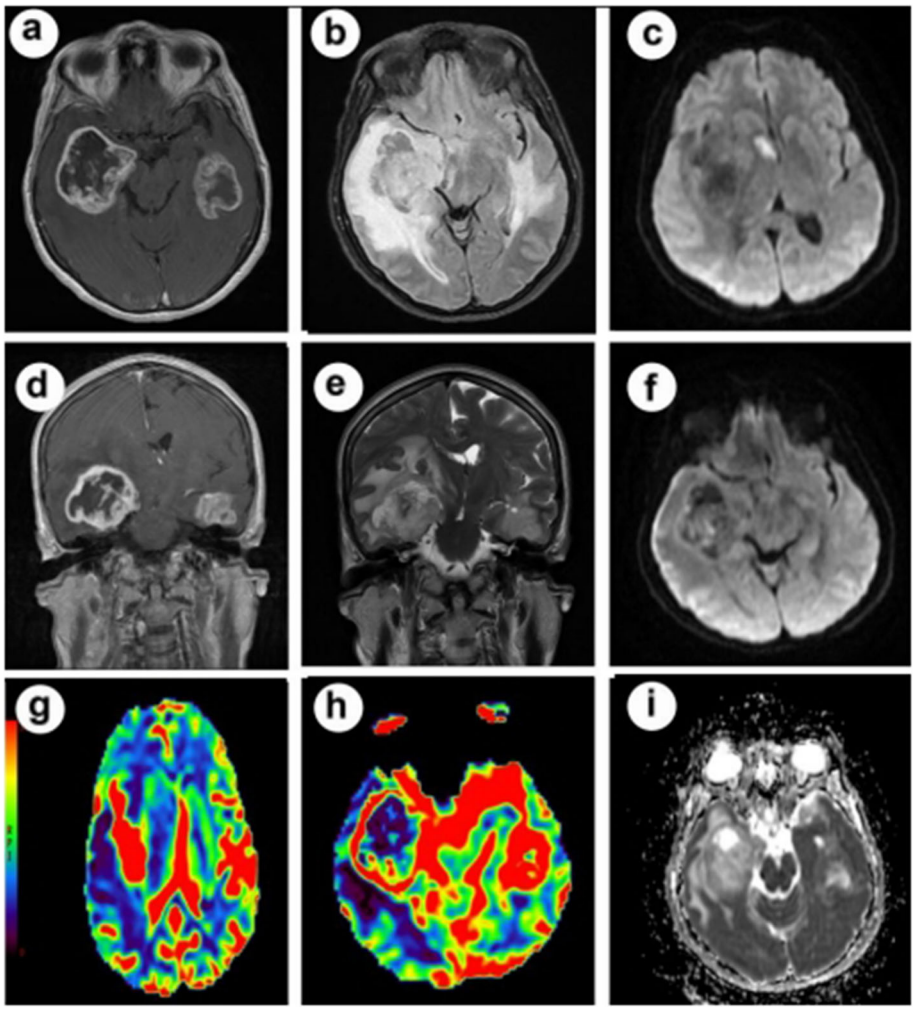

Fig. 2 MRI brain scan with contrast and MR perfusion showing bilateral temporal lobe lesions that are hypointese on T1 with Gad-enhancing irregular margins (**a** indicates "axial" and **d** indicates "coronal"), with heterogeneous signal intensity on T2 (**e** indicates "coronal") and FLAIR (**b** indicates "axial"). The lesions were surrounded with massive vasogenic edema that exerted a mass effect on the ipsilateral ventricle and resulted in midline shift. ADC (**c** and **f**) and SWI (**i**) revealed restricted diffusion. The lesions showed high rCBV on MR perfusion (**g** and **h**) with infiltrations into the surrounding tissue

edema. Because of high cellularity, MR perfusion imaging often shows that tumors are hyperperfused with elevated r-CBV [3, 10, 11]. The patient described in this study was admitted to the ER before the tumor was developed enough to be accurately diagnosed based on radiological features. Therefore, a diagnosis could not be made at the beginning. The tumor appeared as an anteromedial temporal lobe lesion that simulated herpetic viral encephalitis with minimal surrounding edema and no central necrosis. These symptoms were misleading and did not readily prompt the need for a biopsy. When the patient's condition progressed and the radiological features of the glioblastoma became evident, surgical resection was performed and the diagnosis was histopathologically confirmed.

Conclusions

This case report confirms that it is important to consider glioblastoma multiform in the differential diagnosis of patients presenting with encephalitis-like clinical and radiological features; early stages of glioblastoma may have the typical appearance of encephalitis and result in delayed diagnosis and treatment. Additionally, there seems to be an association between glioblastomas and HSV-1 encephalitis. Although the mean survival of patients with glioblastoma is generally short (around 15 months), early diagnosis and aggressive surgical resection of the tumor with a wide safety margin followed by chemotherapy and radiotherapy may provide a better outcome. Hence, early diagnosis and identification of atypical presentations of glioblastoma multiform, as presented in this case report, are essential.

Abbreviations
MSCT: Multi-slice computed tomography; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; PCR: Polymerase chain reaction; HSV-1: Herpes simplex virus 1; ER: Emergency room; ADC: Apparent diffusion coefficient; SWI: Diffusion-weighted imaging; rCBV: Relative cerebral blood volume

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Declarations
1. The work has not been published elsewhere.
2. The work is not currently under consideration for publication in other journals.
3. The work does not infringe on copyright of other parties.
4. All authors (as mentioned below) have read the work and accepted its submission for publication.
5. The manager (managers) of the institution where the work was created accepts (accept) its submission for publication (not applicable to works submitted by independent research fellows).

Authors' contributions
IS conceived and designed the study, conducted the study, collected and organized the data, analyzed the data, and interpreted the results. MS wrote the initial and final drafts of the article. All authors read and approved the final manuscript.

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Availability of data and materials
Yes

Ethics approval and consent to participate
The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and the approval was obtained from the ethical committee of Middle East University-Amman-Jordan. Fully informed written consent was prospectively obtained from the study participant can be requested at any time.

Consent for publication
I understand that the information will be published without my/my child or ward's/my relative's (circle as appropriate) name attached, but that full anonymity cannot be guaranteed. I understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. The pictures, videos, and text may also appear on other websites or in print, may be translated into other languages, or used for commercial purposes. I have been offered the opportunity to read the article. This consent form will be submitted with the article and will be treated confidentially. Signing this consent form does not remove my rights to privacy. Also, the study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and the approval was obtained from the ethical committee of Middle East University-Amman-Jordan.

Competing interests
The authors declare that they have no competing interests.

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