CASE REPORT

Four cases of multifocal glioblastoma managed at a tertiary university hospital in Nairobi, Kenya

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Abstract

Glioblastomas are malignant, poorly differentiated tumours of glial origin. They are the most common primary brain tumours, occurring in 2 to 3 per 100 000 adults. Published data on glioblastomas in Africa are scarce; however, the incidence has been found to be lower in people of African origin. In 0.5% to 15% of all cases, glioblastomas manifest as multiple lesions. In this report, we describe 4 patients with multifocal glioblastoma managed at our institution.

There were 47 patients diagnosed with glioblastoma between 1 January and 31 December 2019, among whom we identified 4 (3 men and 1 woman) with multifocal glioblastoma and analysed their data. The median age at diagnosis was 50.5 years (range, 31-55 years). The median overall survival in our series was 8 months (range, 2-13 months). Two of our patients underwent excision of a single lesion, and the other 2 underwent biopsy only. One patient in our series received chemotherapy and radiotherapy after surgery. We found that multifocal glioblastoma is a rare presentation associated with poor outcomes.

Keywords: glioblastoma, multifocal glioblastoma, management, survival, Kenya

Introduction

Glioblastomas are malignant, poorly differentiated tumours of glial origin.[1] They are the most common primary brain tumours, occurring in 2 to 3 per 100 000 adults in the West. Published data on glioblastomas in Africa are scarce; however, the incidence has been found to be lower in people of African origin.[2]

Malignant lesions of glial origin can be solitary lesions, multicentric, or multifocal. Multicentric gliomas have no microscopic or macroscopic connections between the multiple tumours. In multifocal gliomas, there is evidence of microscopic connections and spread of the tumours.[3] The distinction between multifocal and multicentric glioblastomas, which together account for 0.5% to 15% of all glioblastomas,[4],[5] has little clinical value, and they are often collectively referred to as multifocal glioblastomas.

Multifocal glioblastomas have a poorer prognosis than solitary glioblastomas, and they are associated with overall survival durations of about 10±1.5 months, compared with 18.0±2.1 months for solitary glioblastomas.[4]

This article describes 4 cases of multifocal glioblastoma managed at our institution.

Ethical approval was obtained from the Institutional Ethics Review Committee (Ref: 2019/IERC-105 v2) of the Aga Khan University Hospital Nairobi, a tertiary facility that offers specialized medical and surgical care, including specialist neurosurgical, radio-oncological, and neuro-oncological services.

There were 47 patients diagnosed with glioblastoma between 1 January and 31 December 2019, among whom we identified 4 patients with multifocal glioblastoma and analysed their data.

Case presentations

Patient 1

A 55-year-old man presented with a 3-week history of headache and seizures. Magnetic resonance imaging (MRI) of the brain revealed 6 lesions in left posterior temporal lobe and left parietal lobe. He underwent an excisional biopsy of the lesion in the left parietal lobe, which histopathologic examination identified as glioblastoma (not otherwise specified [NOS]), World Health Organization (WHO) grade IV, glial fibrillary acidic protein (GFAP) and S100 positive. His Karnofsky performance status (KPS) at diagnosis was 70%. He died 7 months after diagnosis.

Patient 2

A 46-year-old man presented with a 2-week history of memory loss, dysarthria, dysgraphia, and dyscalculia. Brain MRI

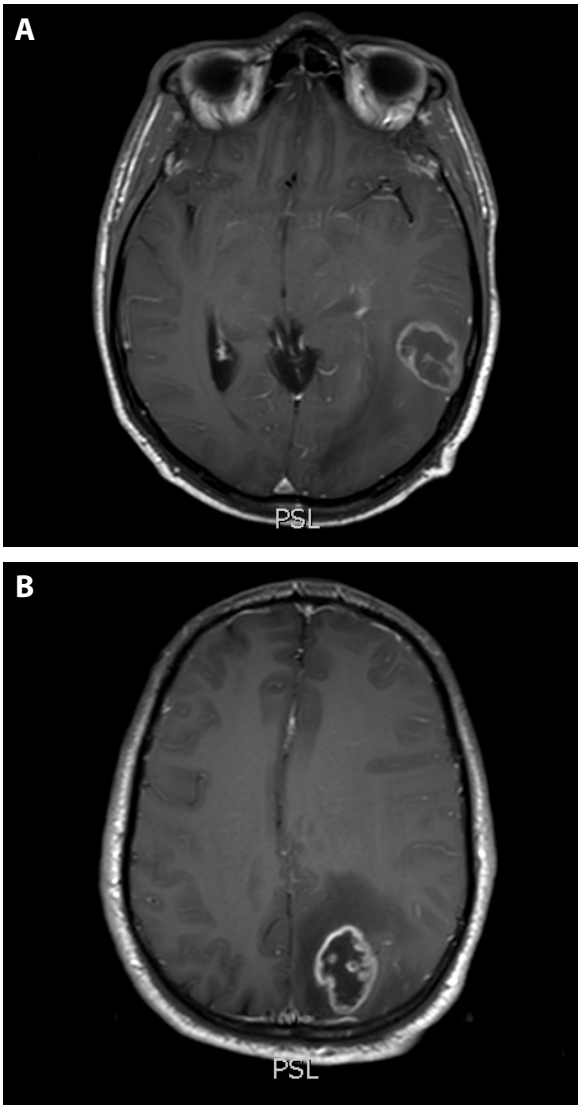

Figure 1. Magnetic resonance images of the brain, T1 with contrast, axial view showing multiple irregular, thick-walled, ring-enhancing lesions in the (A) left posterior temporal lobe (diameter, 3.0 cm) and (B) left posterior parietal lobe (diameter, 3.4 cm)

revealed a lesion in the left inferior frontal lobe and another in the right anterior temporal lobe. He underwent excision of the left frontal tumour, which was histopathologically identified as glioblastoma (NOS) WHO grade IV, GFAP and S100 positive. He received radiotherapy of 6000 cGy in 30 fractions to both sites. He also received 140 mg of oral temozolomide concomitantly with the radiotherapy. This was followed by 1 cycle of chemotherapy with 280 mg of temozolomide once daily for 5 days. His KPS at diagnosis was 70%. He died 13 months after diagnosis.

Patient 3

A 55-year-old woman presented with a history of seizures and visual disturbance. Brain MRI revealed lesions in the left parietal lobe and left peritrigonal region. She underwent a biopsy of the lesions but declined further treatment. The

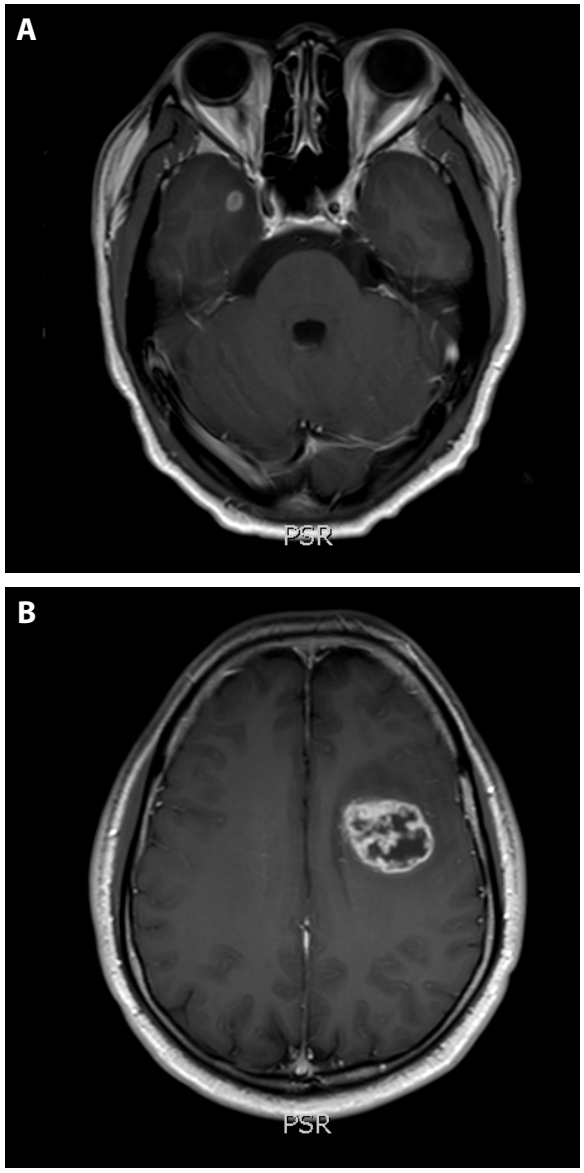

Figure 2. Magnetic resonance images of the brain, T1 with contrast, axial view showing multiple irregular, thick-walled, ring-enhancing lesions in the (A) right temporal lobe (diameter, 0.7 cm) and (B) left inferior frontal lobe (diameter, 3.8 cm) with surrounding vasogenic oedema

histopathologic diagnosis was glioblastoma (NOS), WHO Grade IV, GFAP positive, CD34 and p53 negative. Her KPS at diagnosis was 50%. She died 9 months after diagnosis.

Patient 4

A 31-year-old man presented with loss of consciousness and aphasia. MRI of the brain revealed lesions in the genu of the corpus callosum, right superior frontal lobe, and left inferior frontal lobe. He underwent a stereotactic brain biopsy. The histopathology report identified the lesions as glioblastoma (NOS), WHO Grade IV, GFAP positive, and CD 45 and CD 68 negative. His KPS at diagnosis was 30%. He died 2 months after diagnosis.

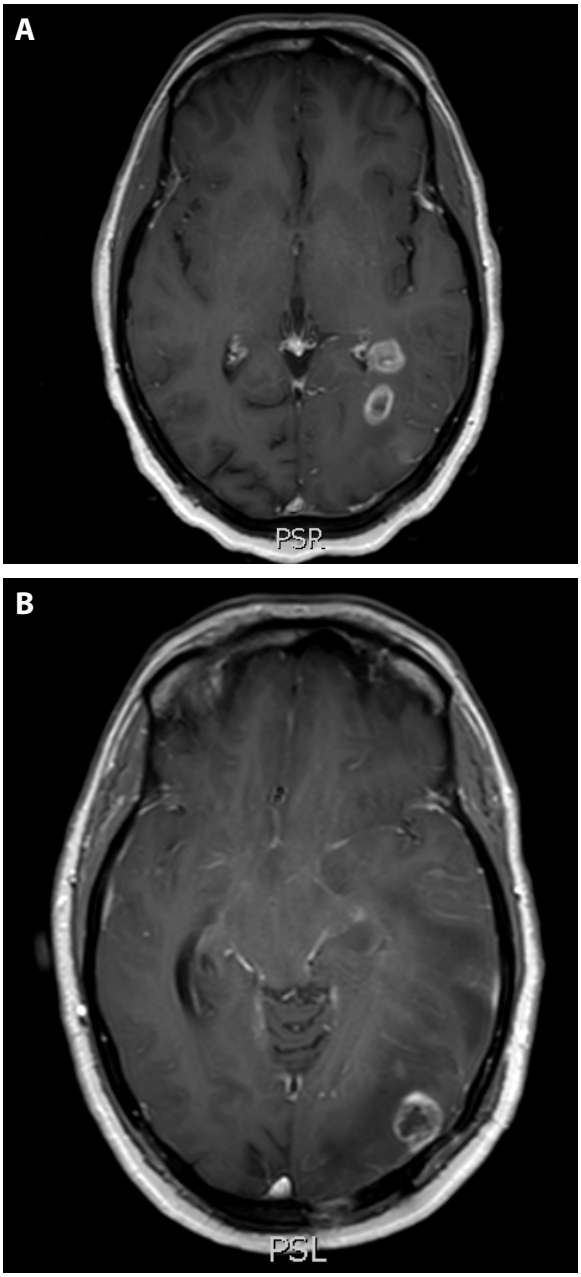

Figure 3. Magnetic resonance images of the brain, T1 with contrast, axial view showing multiple irregular, thick-walled, ring-enhancing lesions in the (A) left parietal lobe (diameter, 1.2 cm) abutting the ipsilateral ventricular trigone and (B) left posterior parietal lobe (diameter, 1.5 cm)

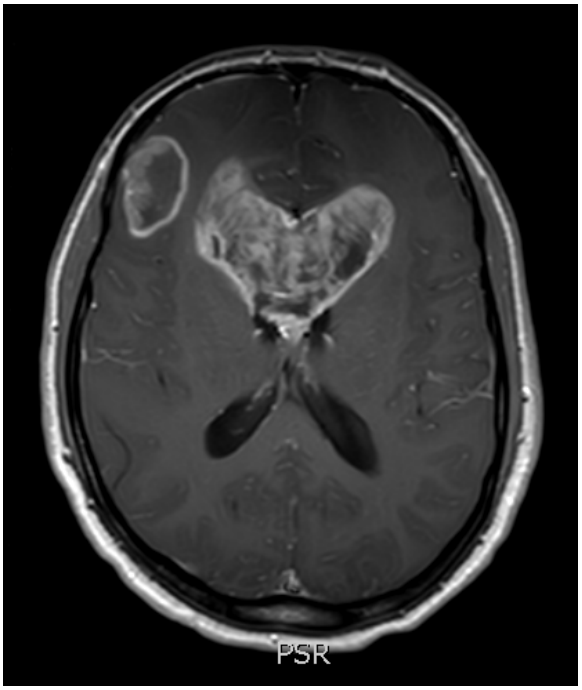

Figure 4. Magnetic resonance image of the brain, T1 with contrast, axial view showing a heterogeneous mass centred in the genu of the corpus callosum with (widest diameter, 6.3 cm) and a smaller mass in the right superior frontal lobe (diameter, 3 cm)

Discussion

At our centre, glioblastoma with multiple lesions accounted for 8.5% of the patients diagnosed with glioblastoma in 2019. Three of the 4 patients were male. This aligns with published demographic data indicating the proclivity of glioblastoma to affect men more than women, with a reported male-to-female ratio of 1.26:1.[2] The median age at diagnosis of the patients in our series was 50.5 years (range, 31-55 years). Glioblastoma epidemiological studies have indicated a peak age at diagnosis between 50 and 60 years and a wide age range at diagnosis—from 28 to 86 years.[2],[8]

Most patients with glioblastoma have no identifiable risk factors. The established risk factors for glioblastoma development are prior therapeutic radiation and genetic factors. Patients undergoing radiotherapy for head and neck tumours have been found to have a higher risk of glioblastoma, with an average latency period of 15 years.[9] Germline genetic abnormalities in genes that regulate DNA repair or apoptosis, such as the NF1, p53, and MM1 genes, predispose individuals to glioma formation; associated diseases include neurofibromatosis 1, Li–Fraumeni syndrome, and Turcot's syndrome.[10]

Glioblastomas commonly present with a short history of less than 3 months.[11] All of our patients presented with less than 1 month of symptoms. A systematic review and metanalysis by DiCarlo et al.,[8] including 23 case–control studies and case reports, found that the most common presenting complaint, accounting for 44.1% of glioblastoma cases, was focal neurological deficits. In our series, 3 of 4 of patients presented with neurological deficits.

Two of our 4 patients had frontal lobe tumours. Three patients had bilateral tumours, and 1 had unilateral left-sided lesions. The systematic review by Di Carlo et al.[8] did not find a predilection for either hemisphere; 45% of patients had bilateral tumours, and 83.6% of patients had frontal lobe tumours.

The majority of glioblastomas (90%) develop de novo from normal glial tissues, and 10% develop from preexisting lower-grade astrocytomas.[12] Glioblastomas are composed

of poorly differentiated pleomorphic cells with necrosis and vascular endothelial proliferation.[1] The 2016 WHO Classification of Tumours of the Central Nervous System divides glioblastomas into 3 types: (1) isocitrate dehydrogenase (IDH) mutants, IDH wild type and NOS. The IDH–wild type molecular glioblastoma subtype lacks IDH1 and IDH2 mutations; these are de novo glioblastomas. The IDH mutant molecular subtype is associated with IDH1 and IDH2 mutations, and patients with this subtype have a better prognosis. When molecular testing is unavailable, as was the case for all patients in this series, the tumours are classified as NOS.[13]

The reported expected overall survival duration for multicentric and multifocal gliomas is about 10±1.5 months, compared with 18.0±2.1 months for solitary glioblastomas.[3] The median survival after diagnosis in our series was 8 months (range, 2-13 months).

On imaging it is important to differentiate multiple gliomas from metastases to the brain. Irregular borders, cortical involvement, and evidence of meningeal, intraventricular, and subependymal spread favour the diagnosis of multiple gliomas over metastatic lesions.[14] However, histopathologic examination is required for definitive diagnoses.

Treatment of multiple gliomas begins with a biopsy to establish the diagnosis. Two of our patients underwent excision of a single lesion, and the other 2 only had biopsies. Total resection is attempted if all tumours are accessible.[6] Resection of more than 98% of the tumour has been shown to significantly improve survival.[15] Subtotal resection can also be performed to relieve the mass effect and preserve neurological function. Surgery is followed by focal or whole-brain radiotherapy. Focal radiotherapy is preferred to avoid toxicity. However, in some cases of multifocal glioblastoma, it is impossible to design local radiotherapy to target multiple lesions without overlapping fields and, therefore, whole-brain radiotherapy is given. The standard target dose for glioblastoma is 60 Gy delivered over 6 weeks in 2-Gy fractions.[16] Adjuvant chemotherapy with temozolamide is also given orally at 75 mg/m^2 daily during the course of radiotherapy. Subsequently, temozolomide is given 4 weeks after the completion of radiation therapy at a dose of 150 mg/m^2 daily for 5 days out of a 28-day cycle. Subsequent cycles are dosed at 200 mg/m^2 if blood counts are acceptable.[17] Only 1 patient in our series received postoperative chemotherapy and radiotherapy. He survivived for 13 months after diagnosis, which was the longest survival interval in our series. Treatment with radiotherapy plus temozolamide has been associated with improved survival compared with radiotherapy alone.[6] Molecular targeted agents and biological therapy, such as immunotherapy, are currently being investigated in clinical trials for patients with newly diagnosed glioblastomas.

Limitations

The management of these cases was limited by a lack of access to molecular diagnostic and staging tools.

Conclusions

Multifocal glioblastoma is a rare diagnosis in our setting. Glioblastomas mostly affect young men, and their management is limited by the unavailability of molecular diagnostic and staging tools. The diagnosis is associated with poor outcomes, and further research is needed to understand the determinants of poor prognoses.

The objective of this report is to create awareness of the existence of multifocal glioblastoma. With the prevalence of HIV in this region, multifocal intracerebral lesions are almost always attributed to opportunistic infections. Neurosurgeons, neurologists, and other stakeholders who care for patients with intracranial lesions need to keep an open mind about the diagnosis. It is prudent to obtain a histolopathologic diagnosis via stereotactic biopsy or open excision before subjecting patients to therapy.

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