

Case Report

Glioblastoma with leptomeningeal dissemination

Peter Houston, Adrian Olar, David Cachia

Abstract

Here we report a case of glioblastoma (GB) with leptomeningeal dissemination (LMD) in a 21 year old female presenting with generalized tonic-clonic seizures. After a brain MRI confirmed a non-enhancing left frontal lobe mass, histopathological examination and molecular analysis showed a glioblastoma with features of gliosarcoma that was an IDH wild type, MGMT unmethylated, TERT amplified tumor. She received standard care with combined chemoradiation with temozolomide and targeted radiation. MRI showing disease progression prompted the addition of bevacizumab after which the patient quickly deteriorated and died eight months after initial presentation. Incidence of LMD is an uncommon occurrence and associated with a significant decrease in overall survival when diagnosed at initial presentation. More research is needed to determine what role histopathologic variants and molecular profile plays in prognosis and treatment.

Keywords

Glioblastoma, leptomeningeal dissemination, gliosarcoma, IDH wild type

Case Report

A 21-year-old lady presented in September 2016 with a generalized tonic-clonic seizure. For a few weeks prior to presentation, the patient had also noticed increasingly worsening headaches. She reported a medical history of attention deficit hyperactivity disorder (ADHD) and anxiety. Her family history included hypertension, diabetes, and asthma. A neurological exam at presentation was normal. Routine bloodwork was unremarkable. MRI brain done at the time of presentation showed a non-enhancing left frontal lobe mass as shown in Figure 1A.

The patient was offered a resection of the mass but failed to attend her follow-up appointment. Four months after initial presentation, a repeat MRI showed change in the radiographic characteristics with significant increase in size, development of necrosis, heterogeneous enhancement and evidence of leptomeningeal spread (Figure 1B, black arrows). Leptomeningeal spread along the spine was not demonstrated with a spinal MRI. The patient had a subtotal resection (Figure 2A) with histology showing this to be glioblastoma (GB) with gliosarcoma features and evidence of subarachnoid involvement (Figure 3). Molecular studies showed an Isocitrate dehydrogenase (IDH) wild type, O⁶-methylguanine DNA methyltransferase (MGMT) unmethylated, Telomerase reverse transcriptase (TERT) amplified tumor. These genetic alterations are associated with poorer prognosis and a more aggressive disease course.

Peter Houston MD

Department Pathology and Laboratory Medicine,
Medical University of South Carolina

Adrian Olar MD

Department Pathology and Laboratory Medicine,
Medical University of South Carolina
Department of Neuro-surgery,
Medical University of South Carolina.

David Cachia MD MRCP (UK)*

Department of Neuro-surgery,
Medical University of South Carolina
cachia@musc.edu

**Corresponding Author*

Case Report

Figure 1: A. Axial T2 sequence showing increased T2 signal abnormality in the left frontal lobe (black arrow) B. Axial T1 post contrast sequence showing a large necrotic, heterogeneously enhancing mass in the left frontal lobe. Black arrows point to areas concerning for leptomeningeal spread of tumor with enhancement seen within the sulci. C. Axial FLAIR sequence shows large T2 hyper-intense mass, significantly increased in size compared to original presentation 4 months earlier (Figure 1 A)

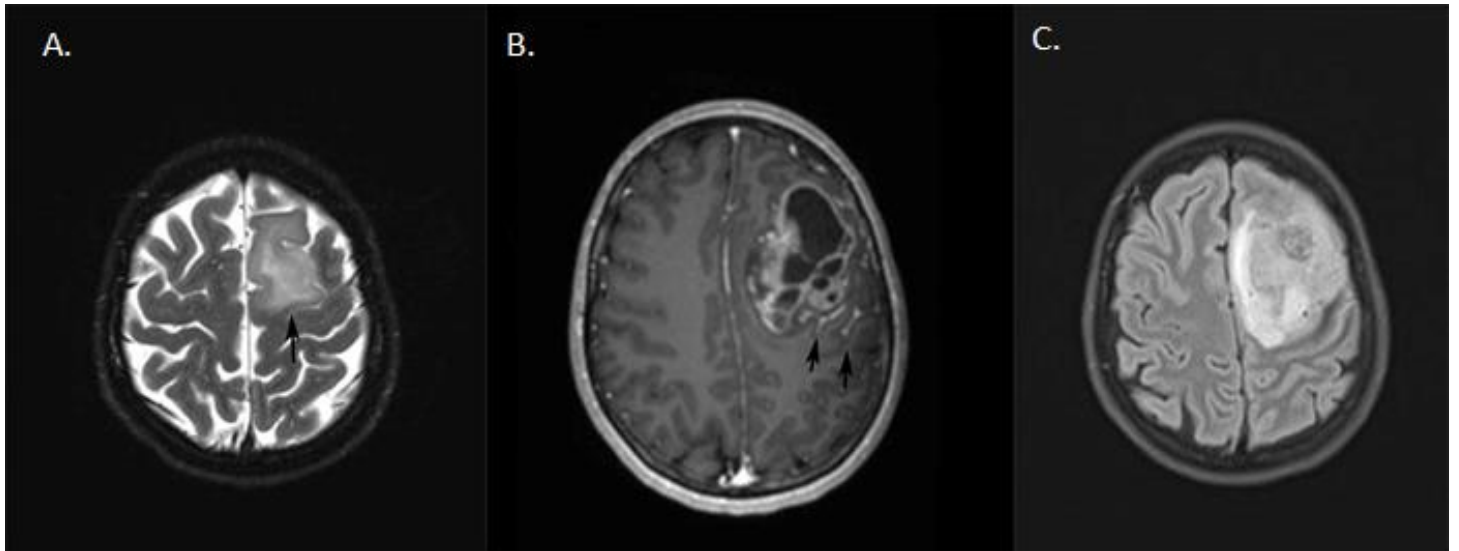
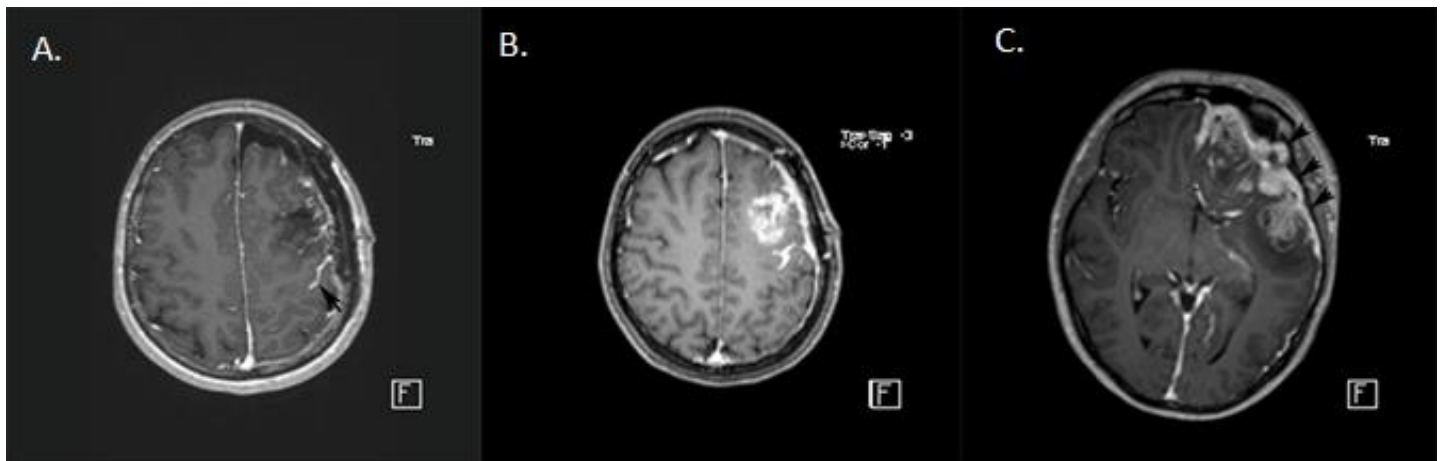
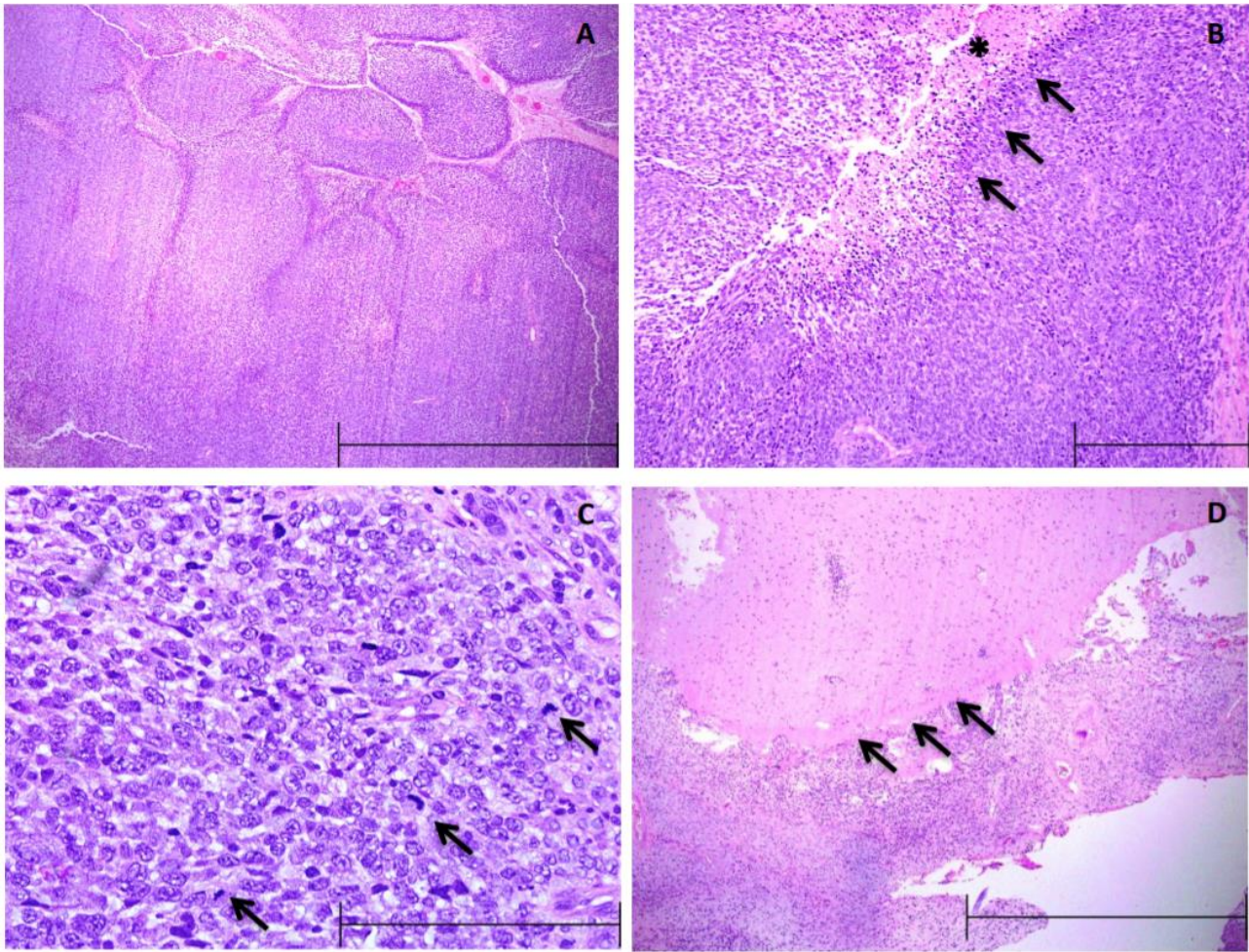


Figure 2: A. Axial T1 post contrast sequence showing post operative scan. Note persistent evidence of leptomeningeal disease (black arrow). B. Axial T1 post contrast sequence prior to initiation of concurrent radiation and chemotherapy shows significant recurrence of disease over a 4 week period from prior scan. C. Axial T1 post contrast sequence post completion of concurrent radiation and chemotherapy shows further progression of disease. Note significant dural involvement of disease (black arrowheads)



Case Report

Figure 3: Histological characteristics of glioblastoma. This low power view demonstrates one of the most recognizable characteristics of GBM showing small foci of necrosis surrounded by centrifugally oriented glial cells creating a pseudopalisading appearance (40x objective) B) A higher magnification shows necrosis (*) and pseudopalisades (arrows, 100x). The rapid proliferation of neoplastic glial cells makes the brain parenchyma appear much more cellular. Additionally, the tumor eventually outgrows its blood supply and cells begin to die, creating foci of necrosis. C) The cell morphology of glioblastoma shows small, pleomorphic cells with clumpy, irregular chromatin and occasional prominent nucleoli. Many mitoses (*) can be seen and correlates with the increased aggressiveness of glioblastoma (400x). D) Subarachnoid spread of the tumor is demonstrated. Normal brain parenchyma appears less cellular in the upper half of the frame. Tumor is adherent of the molecular layer of cerebral cortex (arrows, 40x).



Repeat MRI brain done 3 weeks later prior to initiation of radiation (RT) and chemotherapy showed significant recurrence of disease. (Figure 2B) The patient was treated by standard of care treatment for GB consisting of 6 weeks of intensity modulated radiation therapy (IMRT) with a total dose of 60Gy in 30 fractions and temozolomide, an alkylating chemotherapeutic agent. Post completion of RT and temozolomide, repeat MRI showed further progression. (Figure 2C) She received 1 dose of bevacizumab, a VEGF inhibitor approved for the treatment of recurrent GB but passed away one day after infusion and eight months after initial

presentation. CT scan of the brain done a day prior to her passing away showed increased mass effect and rightward midline shift. (Figure 4) There was also marked effacement of the left lateral ventricle and third ventricle. After the initial seizure at presentation, she was started on prophylactic anti-epileptics (leviteracetam 750mg bid) and steroids. Throughout the disease course she experienced neurological symptoms including headaches, right sided weakness (hemiparesis), and anger outburst that were likely related to frontal lobe involvement of the tumor. Despite treatment, her disease continued to progress.

Case Report

Figure 4: CT head without contrast shows progression of disease with increased size of left inferior frontal and temporal lobe heterogeneous masses. Increased mass effect with effacement of adjacent sulci and increased effacement of the left lateral ventricle. There is rightward midline shift.



GB is the most common primary brain tumor in adults. Despite advances in surgical techniques, radiation treatments and chemotherapy, it continues to have a dismal prognosis with a median overall survival of around 14-16 months.^{1-2,4} Surprisingly, given the location of glioblastoma in the central nervous system and relatively high exposure of the ventricular system during tumor resection, the incidence of leptomeningeal dissemination (LMD) is thought to be uncommon though data on the subject is scarce. In a recent retrospective study of 595 patients with a diagnosis of glioblastoma enrolled in clinical trials, only 4% of these patients developed LMD.³ Patients who were diagnosed with LMD at time of diagnosis of glioblastoma, as was the case in the patient described above, had a worse prognosis compared to those who were diagnosed afterwards (estimated overall survival of 4.7 months compared to 16.0 months). This emphasizes the need to develop better therapies that specifically target tumor cells within the cerebrospinal fluid.

With regard to the histopathology and genetics, one study looking at 20 cases demonstrated that the 85% of cases with LMD were IDH wild type, in keeping with our case.⁵ Of these cases, 50% were of the small cell variant of GB and one was a gliosarcoma variant, all of which were IDH1 wild

type.⁵ This genetic profile carries a well described poorer prognosis than IDH mutants in addition to MGMT unmethylated status and TERT mutations.⁶ There is a paucity of research describing in detail the molecular character of GB with LMD and what role these attributes play in the clinical course. In our case, overall survival was approximately 8 months from the time of diagnosis of GB with LMD. This is a better outcome than the 4.7 months overall survival reported by Mandel et al.³ More research in this area is needed to see if the histopathological variant or molecular profile affect prognosis and therefore have treatment implications.

References

1. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014 February 20;370(8):709-22. doi:10.1056/NEJMoa1308345
2. Gilbert MR, Dignam J, Won M, Blumenthal DT, Vogelbaum MA, Aldape KD, et al. RTOG 0825: Phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM). *J Clin Oncol (Meeting Abstracts)*. 2013; 1-1.

3. Mandel JJ, Yust-Katz S, Cachia D, Wu J, Liu D, de Groot JF, et al. Leptomeningeal dissemination in glioblastoma; an inspection of risk factors, treatment, and outcomes at a single institution. *J Neurooncol*. 2014 December 01;120(3):597-605. doi:10.1007/s11060-014-1592-1.
4. Stupp R, Mason WP, van den Bent, M J, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005 March 10;352(10):987-96. doi:10.1056/NEJMoa043330.
5. Kondo, N., Barth, R. F., Miyatake, S. I., Kawabata, S., Suzuki, M., Ono, K., & Lehman, N. L. Cerebrospinal fluid dissemination of high-grade gliomas following boron neutron capture therapy occurs more frequently in the small cell subtype of IDH1^{R132H} mutation-negative glioblastoma. *Journal of neuro-oncology* 2017 May 22; 133(1): 107–118. doi:10.1007/s11060-017-2408-x.
6. Lieberman F. (2017). Glioblastoma update: molecular biology, diagnosis, treatment, response assessment, and translational clinical trials. *F1000Research*. 2017 October 26; 6: 1892. doi:10.12688/f1000research.11493.1.