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Case Report

Dexamethasone-associated regression of glioblastoma

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ABSTRACT

Background: Dexamethasone-induced regression of an intracranial space-occupying lesion is commonly characteristic of primary central nervous system lymphoma (PCNSL). However, dexamethasone does not have an established chemotherapeutic role in glioblastoma multiforme (GBM). This is a report on dexamethasone-induced regression in GBM with the aim of exploring the mechanisms behind the phenomenon.

Case Description: We present the case of a 63-year-old male presenting with status epilepticus. Initial imaging showed a high-grade glioma with significant vasogenic edema. Following 23 days of dexamethasone therapy, magnetic resonance imaging demonstrated notable tumor regression, raising differential diagnoses, including lymphoma or a nonneoplastic inflammatory process. After discontinuation of dexamethasone, the tumor rapidly regrew. A biopsy confirmed the diagnosis of high-grade glioma. Immunohistochemistry revealed the following: glial fibrillary acidic protein positive, isocitrate dehydrogenase-1 (IDH-1) R132H negative, ATP-dependent helicase ATRX (ATRX) positive, p53 with 30% nuclear labeling index, and Ki-67 with maximal labeling index of 25%. The patient underwent an image-guided awake craniotomy for tumor resection.

Conclusion: This case demonstrates substantial dexamethasone-induced GBM regression in our patient, serving as a diagnostic confounder with PCNSL. The decision to wean steroids with the aim of increasing diagnostic yield for PCNSL resulted in a missed opportunity for early surgery for GBM, with the development of neurological symptoms, higher surgical risk and possibly shorter survival. Healthcare professionals caring for patients with suspected GBM must be aware of this potential pitfall in rare cases, planning for timely surgical intervention to optimize the outcome for such patients. This case introduces the second case of a GBM behaving in such a manner, along with molecular characterization.

Keywords: Dexamethasone, Glioblastoma multiforme, Molecular profile, Regression

INTRODUCTION

Glioblastoma multiforme (GBM) in the CNS World Health Organization (WHO) classification from 2021 reclassified as "glioblastoma, IDH-wildtype" (GBM) is the most common form of glial cell tumor as well as one of the most aggressive malignancies. GBM is a WHO grade 4 tumor thought to arise from astrocytes, presenting with neurological deficit, headaches, visual disturbances and seizures.[12] Despite the combination of therapies such as surgery, chemo- and radiotherapy, the prognosis of GBM remains abysmal, with a median overall survival rate of 15 months, posing a public health crisis.[7] Given the inevitably poor prognosis of GBM, the aim of medical management encapsulates the prolongation and maintenance of the patient's quality of life.[5,7] Novel agents such as temozolomide have resulted in increased overall survival in GBMs

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with methylation of the deoxyribonucleic acid (DNA)-repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) when combined with radiotherapy.[13]

However, cerebral edema represents a leading cause of morbidity and mortality in GBM due to the increased risk of brain herniation. Dexamethasone, a synthetic glucocorticoid, is a popular choice in brain tumor treatment owing to its strong anti-inflammatory action against GBM-induced cerebral edema through the modulation of gene expression and function of claudins, occludins, and vascular endothelial-cadherin that regulate endothelial permeability and therefore the blood–brain barrier. Various studies have hypothesized that dexamethasone also plays a role in GBM cell proliferation and migration.[3]

Dexamethasone-induced regression of an intracranial space-occupying lesion (SOL) is commonly associated with primary central nervous system lymphoma (PCNSL), whereby the administration of steroids induces cell cycle arrest and cell death.[11] However, glucocorticoids must be withheld before obtaining a pathological diagnosis through biopsy as these agents can cause significant radiographical changes, which can lead to misdiagnosis or nondiagnostic biopsy results.[8]

This phenomenon was previously thought to be characteristic of PCNSL. Dexamethasone does not have an established chemotherapeutic role in GBM. However, a literature search by Cuoco *et al*. described 6 cases of corticosteroid-induced regression of GBM since the phenomenon was first reported in 1997.[4] To our knowledge, this is the second case to report molecular data and immunohistochemistry for inflammatory markers in corticosteroid-regressed GBM and the first case reported following the introduction of the 5th edition of WHO classification of CNS tumors, emphasizing molecular markers. The following case describes the impact of corticosteroid-induced regression on the diagnostic process in patients with GBM.

ILLUSTRATIVE CASE

A 63-year-old male presented to the Emergency Department (ED) with the first onset of seizures and status epilepticus following a period of bizarre behavior. A tonic seizure was witnessed by the family, followed by a period of unconsciousness with a Glasgow Coma Scale of 3 on arrival of emergency services. A further tonic seizure was witnessed. On arrival at the ED, the patient was posturing, hypertonic, with a lateral gaze palsy. He had a past medical history of gout and hypertension but was otherwise well and independent in his daily activities. A computed tomography head was performed, which demonstrated a small ovoid hypodensity identified within the left temporal lobe, measuring approximately 16 mm with moderate surrounding vasogenic edema indicative of a possible SOL [Figure 1]. This was thought to be responsible for the presenting seizures.

The patient was intubated and ventilated for airway protection and admitted to the intensive care unit under the care of the Neurology team, initially being commenced on antibiotics for suspected intracranial infection, high-dose dexamethasone, levetiracetam, and sodium valproate.

Following his admission, a magnetic resonance imaging (MRI) head with contrast showed a left temporal lobe irregular peripherally enhancing lesion measuring 34 × 33 mm, suggestive of a high-grade glioma [Figure 2]. The lesion was associated with focal edema and mass effect on adjacent sulci, extending into the inferior aspect of the insular cortex, external capsule, and putamen. The patient had a prolonged 19-day stay in intensive care due to treatment for status epilepticus and prolonged ventilatory wean, requiring a percutaneous tracheostomy, which was removed before intensive care discharge. As his neurological status could not be reliably assessed during intensive care admission, he was maintained on high-dose dexamethasone (6.6 mg 3 times a day) during this period. When initially assessed in the inpatient ward, the patient experienced mild expressive dysphasia and object-naming difficulty, but he was able to obey commands and move all four limbs with normal power.

Due to the interval between initial admission and discharge from intensive care, an updated MRI head with contrast was performed, demonstrating a reduction in the size of the previously identified left temporal lobe presumed high-grade tumor, now approximately 24 × 22 mm. This created an element of diagnostic uncertainty, introducing lymphoma or a nonneoplastic process as possible differential diagnoses [Figure 2]. Moreover, the patient demonstrated a

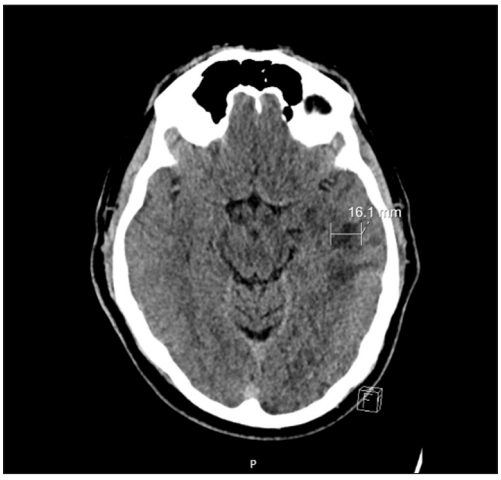

Figure 1: Computed tomography head on day 1 of admission showing a small ovoid hypodensity within the left temporal lobe suspicious of an underlying space-occupying lesion.

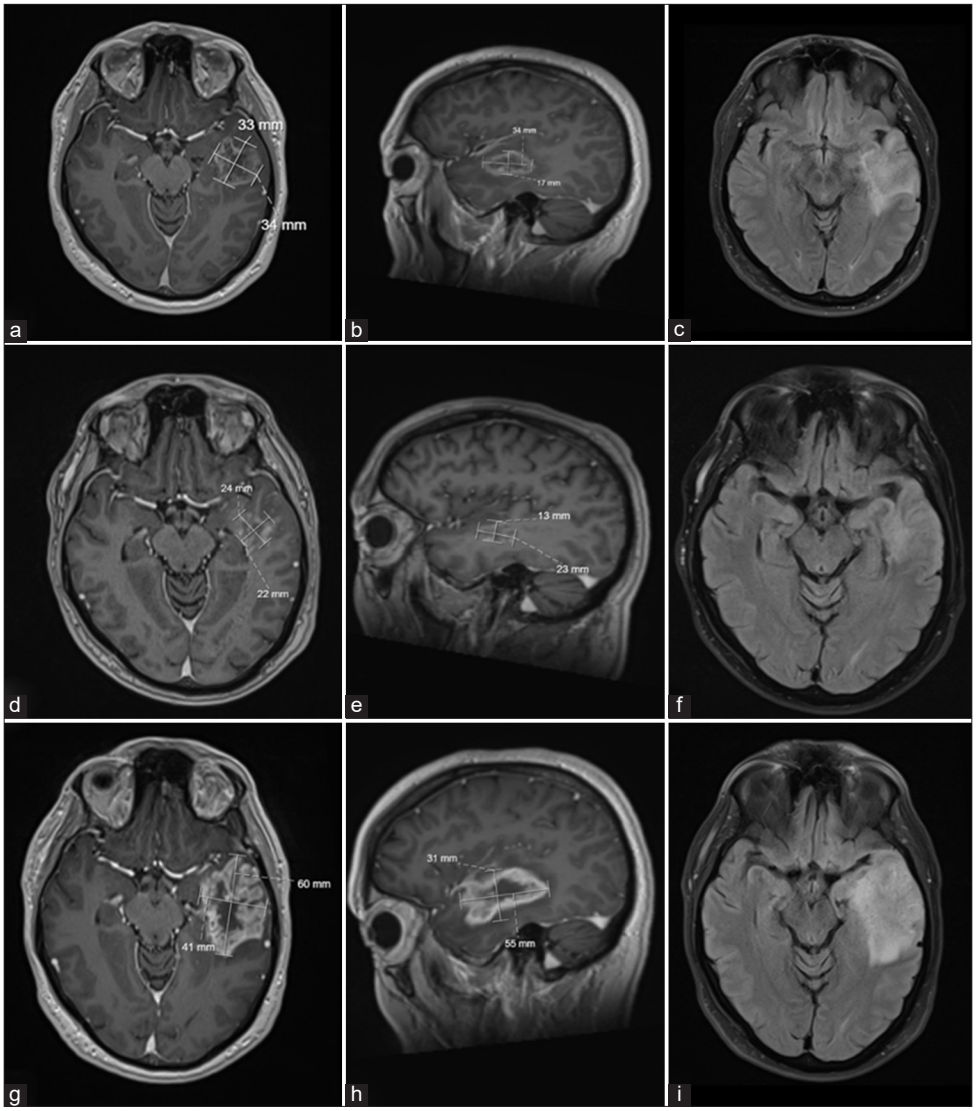

Figure 2: The size of the space-occupying lesion (SOL) was estimated using bidimensional measurements of an axial image. The diameter was measured using electronic callipers on each plane in two orthogonal directions. The plane with the greatest diameter was chosen. Sagittal images have been included for completion. (a) Axial and sagittal (b) postcontrast magnetic resonance imaging (MRI) brain T1 stealth on day 2 of admission demonstrating a SOL approximately 34 × 33 × 17 mm in size. (c) Postcontrast MRI brain T2-fluid-attenuated inversion recovery (FLAIR) on day 2 of admission showed a left temporal lobe lesion associated with focal edema and associated mass effect on adjacent sulci. (d) Axial and sagittal (e) postcontrast MRI brain T1 stealth on day 23 of dexamethasone regimen demonstrating a decrease in size of the left temporal lobe temporal lesion, measuring approximately 24 × 22 × 13 mm in size. (f) Postcontrast MRI brain T2-FLAIR on day 23 of dexamethasone regime. (g) Axial and sagittal (h) postcontrast MRI brain T1 stealth on day 64 of admission, 3 weeks following the cessation of dexamethasone. Now measuring 41 × 60 × 31 mm, a large enhancing lesion with the appearance of a necrotic core in the left anterosuperior temporal lobe extending into the left basal ganglia. (i) Postcontrast MRI brain T2-FLAIR on day 64 of admission demonstrating high T2-signal vasogenic edema and local swelling.

symptomatic improvement with no word finding difficulties, although limited vocabulary. The patient's case was discussed in the neuro-oncology multidisciplinary team meeting, with a decision made to wean to stop dexamethasone and perform further interval imaging 3 weeks later to investigate whether there was a further change in the appearance of the lesion. However, the initial regression of the lesion on imaging delayed biopsy.

The patient was started on a steroid weaning regimen, whereby his dexamethasone was stopped a month after its initiation (8 mg twice a day for 4 days, 8 mg once a day for 4 days, 4 mg once a day for 5 days, 2 mg once a day for 5 days [Figure 3]). The interval MRI head with contrast demonstrated an increase in the left temporal lesion than upon initial presentation, measuring 41 × 60 mm. The lesion was enhanced with high T2-signal vasogenic edema and with the appearance of a necrotic core centered in the left anterosuperior temporal lobe and extending to the left basal ganglia [Figure 2]. At this time point, the patient experienced a deterioration in neurocognitive symptoms, including volatility in mood and difficulty with word finding.

Given the atypical steroid response of the lesion, a biopsy was performed, revealing a cellular high-grade glioma with moderately pleomorphic nuclei and ill-defined eosinophilic cytoplasm consistent with GBM. Immunohistochemical studies of the tumor cells revealed the following: GFAP positive, IDH-1 R132H negative, ATRX positive (expression retained), p53 expression suggestive of *p53* gene mutation, Ki-67 labeling index of 25%, admixed with rare CD3/CD8-positive T-lymphocytes, and a moderate, diffuse infiltrate of CD68-positive histiocytes/macrophages [Figures 4a-d]. Genetic testing revealed that the MGMT promoter was unmethylated (1.5%), with methylation defined as >10% methylation rate.

Four weeks following the initial biopsy, the patient underwent an image-guided awake craniotomy for resection of the left temporo-insular tumor with intraoperative monitoring, in line with evidence demonstrating a positive correlation between the extent of resection in GBM and survival.[10] Histology of the resection specimen [Figures 4e-h] showed essentially similar morphological and immunohistochemical appearances as the biopsy, with features typical of glioblastoma with mitoses, microvascular proliferation, and necrosis. Immunohistochemistry for inflammatory cells was almost identical with low numbers of T-lymphocytes and a diffuse infiltrate of histiocytes.

Notably, while carrying out the postresection ultrasound sweep, the patient developed right-sided weakness and speech arrest. Postoperatively, the patient had severe expressive aphasia; however, he was able to name high-frequency images. He was unable to follow one-stage commands even with a visual prompt. The patient developed dense right-sided weakness, suggestive of intra-operative vasospasm resulting in a thalamic stroke, which was demonstrated on the postoperative MRI scan. The patient's condition improved, but the dense right-sided hemiplegia persisted. Follow-up imaging 1 month later showed recurrence of the lesion, and the patient underwent palliative radiotherapy with no adjuvant chemotherapy; he died 11 months following his initial presentation.

DISCUSSION

Observations

This offers the opportunity to compare the clinical characteristics of our case with previously published cases reporting corticosteroid-induced regression of GBM.

In previously published reports, the parietal lobe was involved in 5 out of 6 cases, and the longest survival time was 4 months in 4 of the 6 cases with documented outcomes. One case described the tumor's molecular profile: [4] Wildtype IDH1/2, methylated MGMT, nonamplified epidermal growth factor receptor (EGFR), and poor p53 expression. Our case is the second, to our knowledge, to report molecular data and immunohistochemistry for inflammatory markers of corticosteroid-regressed GBM, and of note, is in a different anatomical location to the previously published cases.

The first specimen was taken 33 days following the cessation of dexamethasone, while the second specimen was taken following dexamethasone therapy. However, both specimens showed similar morphological and immunohistochemical features, revealing low numbers of

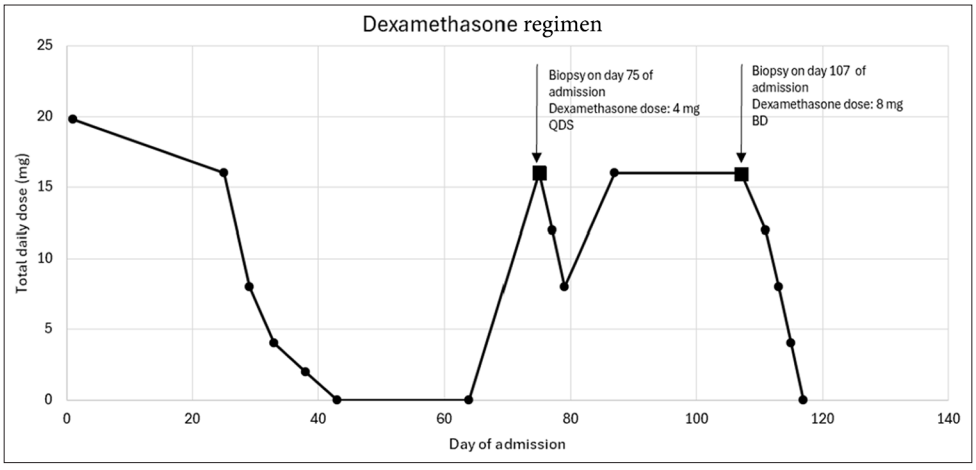

Figure 3: Summary of dexamethasone regimen throughout admission.

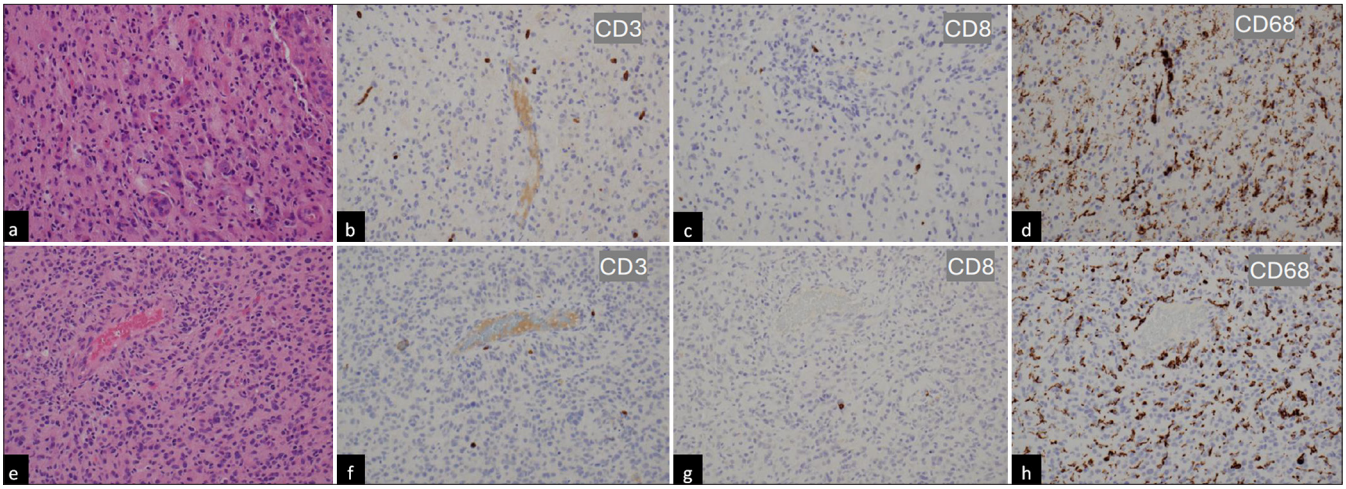

Figure 4: Histology (histochemistry and immunohistochemistry) of subsequent specimens, taken 1 month apart, with (a-d) initial biopsy and (e-h) subsequent resection specimen, both showing essentially similar morphological and immunohistochemical features (hematoxylin and eosin staining; a and e) of mitotically active, high-grade glioma including microvascular proliferation, with scant infiltrates of CD3/CD8-immunopositive T-cells (b and c, f and g), no CD20-immunopositive B-cells (not illustrated), and a moderate, diffuse infiltrate of CD68-immunopositive histiocytic cells with dendritic morphology (d and h). All images were taken at 200-fold magnification.

T-lymphocytes and a diffuse infiltrate of histiocytes. Reports in the literature describe that dexamethasone decreases the number of macrophages and T-lymphocytes in the GBM microenvironment. Corticosteroids negatively affect salient cellular and molecular immune mediators, which in turn may affect the effectiveness of checkpoint inhibitor immunotherapy in glioblastoma models and patients.[14]

Moreover, our patient had a longer period of dexamethasone use compared to the other reported cases (4 weeks vs. 2.9 weeks). This is partially explained by his prolonged intensive care admission in his index admission, where he was kept on high-dose dexamethasone as his neurological function was not assessable. Indeed, the prolonged intensive care admission and subsequent administration of high-dose steroids resulted in a delay in re-imaging, biopsy, and, therefore, resection. In addition, the extended 4-week interval between biopsy and resection resulted from a lack of surgeon or theater capacity; we acknowledge that this may have impacted his prognosis.

Corticosteroids have a cytolytic effect on lymphoma cells and, therefore, can increase the risk of a nondiagnostic biopsy. Therefore, there was a further delay in the biopsy following re-imaging because the steroids had to be weaned before the biopsy. Although this is common practice, there is some evidence arguing against this routine practice of withholding corticosteroid therapy, proposing that corticosteroids do not substantially increase the risk of nondiagnostic biopsy. Additional high-quality, evidence-based recommendations are essential to enhance consensus and improve patient care.[1]

There is little understanding regarding the antineoplastic effects of dexamethasone in GBM. The majority of studies exploring this phenomenon are *in vitro,* with a few *in vivo* murine xenograft models. The effects of dexamethasone on GBM cell proliferation are dependent on the cell type, drug concentration, and experimental conditions.[3,9] There are various hypotheses for this, suggesting the involvement of the extracellular signal-regulated kinases (ERK) and mitogen-activated protein kinase (MAPK) pathways; however, the exact mechanism is still unclear. With new evidence contradicting previous findings where dexamethasone has a pro-proliferative effect on GBM cells, controversy is stark and research still necessary.[3]

The most common dose of dexamethasone used in cases where corticosteroid-induced regression of a GBM has been shown is 16 mg/day.[4] The patient, in our case, was on 6.6 mg 3 times a day (total of 19.8 mg daily) for 23 days, followed by 8 mg twice a day (16 mg daily) for 4 days, followed by 8 mg daily for another 4 days, followed by 4 mg daily for 5 days and 2 mg daily for a final 5 days. It has been shown that patients treated with doses higher than 4.1 mg daily have a significantly shorter lifespan than those treated with lower doses and a higher incidence of adverse effects.[3,6,15] The most prevalent systematic side effects of dexamethasone are cushingoid appearance, hyperglycemia, and psychiatric symptoms.[15]

This case report demonstrates that corticosteroid-induced regression of a GBM could be mistaken for potential PCNSL, the management of which would involve stopping the corticosteroids for 2–3 weeks and performing a biopsy after confirmation of persistent presence of the lesion. In our case, the lesion had progressed dramatically after stopping corticosteroids. The biopsy confirmed a GBM, which was managed with an awake craniotomy with an aim to achieve maximal safe resection, with literature supporting

the superiority of gross total resection in patients with GBM.[2] This case highlighted the potential pitfall for delayed treatment for a GBM, which had led to the deterioration of his neurological function, thereby, a higher surgical risk of neurological deficit and potentially a shortened survival.

CONCLUSION

Our case demonstrates dexamethasone-induced, substantial GBM regression in our patient, serving as a diagnostic confounder with PCNSL as a differential diagnosis. The decision to wean steroids with the aim of increasing diagnostic yield for PCNSL resulted in a missed opportunity for early surgery for GBM, with the development of neurological symptoms, higher surgical risk, and possibly shorter survival. Hence, healthcare professionals caring for patients with suspected GBM must be aware of this potential pitfall in rare cases, planning for timely surgical intervention to optimize the outcome for such patients.

Moreover, our case represents the second report of a partially molecularly characterized GBM behaving in such a manner. Pharmacogenetics may allow for the optimization of dexamethasone therapy, perhaps harnessing this phenomenon, ensuring maximum efficiency, and minimizing morbidity and mortality. This calls for further investigation of the molecular profile of GBM tumors that demonstrate corticosteroid-induced regression and the optimization of dexamethasone dosing schedules.

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