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Corticosteroid sensitivity in gliomatosis cerebri delays diagnosis

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Abstract

Purpose—To describe a patient whose diagnosis of gliomatosis cerebri was delayed for one year due mostly to dexamethasone.

Patients and Methods—A 78-year-old woman was followed in clinic for a year with a brain lesion suspicious but not definitive for glioma, whose clinical course and neuroimaging varied with use of dexamethasone. A first biopsy and MR spectroscopy did not find evidence of malignancy.

Results—A second biopsy demonstrated the correct diagnosis when the patient was on a very low dexamethasone dose. Hypercellularity and a positive KI-67 immunostaining confirmed a grade II astrocytoma, although the rapid and aggressive course without dexamethasone suggested a higher grade tumor.

Conclusion—As in primary CNS lymphoma, the diagnosis of gliomatosis cerebri can be unnecessarily delayed with dexamethasone use. Every effort should be made to biopsy these lesions before or shortly after the addition of dexamethasone.

Keywords

Gliomatosis cerebri; glioma; steroids; dexamethasone; viral encephalitis

Introduction

Gliomatosis cerebri (GC) is a rare malignant tumor that originates from the glial cells of the brain. Most experts currently view GC as a pattern of extensive glioma infiltration encompassing at least three cerebral lobes.¹ It may occur at any age with a peak incidence between 40 and 50 years and it is slightly more common in men.² On magnetic resonance imaging (MRI), GC has no or minimal contrast enhancement; however, it has a diffuse hyperintense infiltrative process on T₂-weighted-fluid-attenuated inversion recovery

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(FLAIR) sequence. Diagnosis of GC is most times possible after an open or a stereotactic biopsy. Despite treatment, the median survival of GC varies from 6 to 39 months.³ We report here an unusual presentation of GC, underscoring the difficulty in pinpointing the correct diagnosis after corticosteroids modified the disease course.

Case report

One year before final diagnosis, a 78-year-old woman had an episode of acute onset slurred speech and confusion. An initial brain computed tomography (CT) scan showed diffuse left hemispheric white matter hypodensity with sulcal effacement and minimal midline shift to the right. She was hospitalized locally. A lumbar puncture (LP) was suggestive of viral encephalitis for which she was treated empirically with IV dexamethasone, acyclovir, and oral levetiracetam 500 mg twice daily. After initial improvement she rapidly worsened with corticosteroid tapering. A repeat CT scan of her head showed no change. The patient took dexamethasone 4 mg twice daily before undergoing a brain biopsy, which showed mild hypercellularity suspicious but not definitive for glioma.

Two weeks later, the patient came to our center for a second opinion. The MRI of the brain showed diffuse periventricular and deep white matter hyperintensity signals with no gadolinium enhancement (Fig 1A,B). She was still taking dexamethasone, 4 mg three times daily. The decision was to observe, to gradually taper dexamethasone, and to repeat the MRI in 3 months. This follow-up MRI had more hyperintense signals in the subcortical white matter of the left hemisphere extending to the parietooccipital lobes with no enhancement (Fig 1C,D). A multi-voxel MR spectroscopy did not show evidence of malignancy. It was performed utilizing echo time of 144 ms. Sample voxels placed over left peritrial signal abnormalities showed normal spectrum. Choline/creatine and choline/N-acetylaspartate (NAA) ratios were approximately 1.1 and 0.5, respectively. No lipid or lactate peak was seen. There was no elevation of myoinositol.

Our neurosurgeons agreed to a brain biopsy that was cancelled because a repeat MRI scan for surgical planning showed remarkable improvement with decrease of the scattered area of T2/FLAIR hyperintensity within bilateral cerebral white matter without associated enhancement (Fig 1E,F). The patient during that time was on dexamethasone 2 mg twice daily. After another taper attempt, she worsened with visual hallucinations, fatigue, and multiple falls. She had marked parkinsonism features on physical examination (rigidity with mild cogwheeling, postural instability and positive propulsion). Repeat lumbar puncture was not remarkable. The patient finally was admitted and had an open brain biopsy. The preoperative MRI showed significant progression of the left frontal, temporal and parietal T₂-FLAIR hyperintensities (Fig 1G) with no associated enhancement on T1-weighted sequence (Fig 1H). The biopsy showed mild increase in the white matter cellularity with scattered atypical nuclei and foci of perivascular and perineuronal satellitosis without mitotic activity suggestive of infiltrating astrocytoma (WHO grade II). Immunohistochemistry for Ki-67 (MIB-1) showed scattered strongly positive nuclei (Fig 2A–C). The patient was restarted on intravenous dexamethasone and levetiracetam with symptomatic improvement. Twelve months after her initial presentation the final diagnosis

was GC with a WHO grade II astrocytoma at least. . In view of her condition, her spouse opted for hospice care at home.

Discussion

Gliomatosis cerebri was first described as a diffuse overgrowth of neoplastic cells throughout wide areas of the cerebral hemispheres.⁴ The clinical manifestations of GC in the literature are variable and nonspecific, including seizures, focal signs, headaches, cognitive changes and rapidly progressive hemiparesis.⁵ GC has been divided into two types; Type 1 is the classical form of GC, with diffuse infiltration of neoplastic glial cells with no dominant tumor mass, and type 2, characterized by diffuse brain infiltration with a tumor mass.⁶ The triad of fever, headache and altered level of consciousness are well-known manifestations of acute viral encephalitis.⁷ In fact, reports suggest that gliomatosis cerebri type 2 can mimic acute viral encephalitis.^{8,9} The initial brain biopsy was indicated by the recurrence of symptoms and the persistence of lesion on the CT scan.

The identification of tumor cells in GC can be challenging; immunohistochemistry is useful by showing a proliferating population with elevated Ki-67.² In our patient, the initial MRI was nonspecific and the first biopsy was negative for Ki-67, justifying surveillance with the serial neuroimaging studies.

Corticosteroids have historically played an important role in the management of brain tumors by reducing the peritumoral edema and improving associated neurological deficits.^{10,11} Dexamethasone may decrease vascular permeability by reducing endothelial responsiveness to tumor-derived permeability factors including the vascular endothelial growth factor (VEGF), and by downregulating their expression.¹² Interestingly, experimental studies showed that corticosteroids have also antitumor effects on *in vitro* cell growth of human glioma interfering with DNA synthesis and preventing the cells from reaching the mitotic phase.¹³ In addition, dexamethasone inhibits glioma cells growth in a concentration-dependent manner; this effect was noticed on glioma cells with no toxicity on primary astrocytes towards various dexamethasone levels.¹⁴ In primary CNS lymphoma, steroids may cause rapid resolution of lesions and obscure the histological diagnosis after a biopsy.¹⁵ Steroids have also been used especially in the terminal phase of GC to improve symptoms of glioma.¹⁶

We believe that dexamethasone delayed diagnosis in this patient. True, it was necessary to relieve symptoms and it did, but it also improved the appearance of MRI scans to the point of postponing final tissue diagnosis and confusing the initial biopsy. We recommend that patients with neuroimaging suggestive of GC be biopsied as soon as possible before or soon after they begin steroids for symptom management.

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Figure 1.

(A–H) Axial MRI after initial presentation: Diffuse periventricular and deep white matter hyperintensity signals on fluid-attenuated inversion recovery (FLAIR) images (A) with no gadolinium enhancement on T1-weighted MRI; (B) Follow up MRI 3 months later: Increase in T2/FLAIR hyperintense signals in the subcortical white matter of the left hemisphere extending to the parietooccipital lobes (C) with no gadolinium enhancement on T1-weighted MRI (D). Follow-up MRI for surgical planning (E): Decrease in areas of hyperintensity within bilateral cerebral white matter on FLAIR compared with Fig. 1C, with no gadolinium enhancement on T1-weighted MRI (F). Axial preoperative MRI, FLAIR: Progression of the left frontal, temporal and parietal hyperintensity signals (G) with no gadolinium enhancement on T1-weighted MRI (H).

Figure 2.

(A–C) Left frontal lobe biopsy. Microscopy of the white-gray matter junction shows mild white matter hypercellularity (right lower corner) with scattered mildly atypical nuclei and foci of perineuronal satellitosis (left upper corner) suggestive of infiltrating glioma (A, **H&E; 200X**). Two foci of perivascular tumor cell satellitosis and two foci of perineuronal satellitosis (inset) are morphological features known as secondary structures of Scherer, which support tumor infiltration (B, **H&E; 400X**). Immunohistochemistry for Ki-67 (MIB-1) highlights several strongly positive atypical nuclei (inset – Ki-67;400X) suggestive of tumor cell proliferation (C, **Ki-67; 100X**).