

The transformation of pediatric gliomatosis cerebri to cerebellar glioblastoma multiforme presenting as supra- and infratentorial acute disseminated encephalomyelitis

Case report

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✓ Cerebellar glioblastoma multiforme (GBM) is a rare entity in adults and an extremely rare entity in children. Approximately 30 cases have been reported in the literature. The authors report the case of a histologically confirmed cerebellar GBM presenting initially as supra- and infratentorial gliomatosis cerebri. Acute disseminated encephalomyelitis had been diagnosed in the patient and that diagnosis remained until near the end of his treatment. This case underscores the need for recognizing the clinical presentation of gliomatosis cerebri and multifocal GBM in the pediatric subpopulation thought to harbor demyelinating disease.

KEY WORDS • cerebellar glioblastoma multiforme • gliomatosis cerebri • acute disseminated encephalomyelitis • pediatric neurosurgery

WE present the case of a 5-year-old boy who presented with the history, signs, and symptoms of acute disseminated encephalomyelitis. The initial neuroimaging studies seemed to support this diagnosis and the child was treated accordingly. Later a large enhancing lesion was found on intracranial Gd-enhanced MR imaging and following biopsy the diagnosis was changed to GBM.

Case Report

History. This previously healthy 5-year-old boy was admitted to the hospital with a medical history of mild reactive airway disease and chronic constipation. For 4 days preceding his admission he had displayed decreasing appetite and lethargy. The patient had not suffered any recent febrile illness. He had experienced upper respiratory infections without sequelae during the previous month, and his mother noted a rash on his right thigh, which was diag-

nosed as nummular eczema. The patient's father had been ill with a headachelike illness 2 weeks prior to the child's admission.

Two days before admission, the patient vomited twice and became increasingly lethargic. The patient's primary care physician diagnosed strep throat and placed the boy on an amoxicillin regimen. The day before admission, the patient refused to walk downstairs, vomited twice, and experienced a fever of 101°F. The morning of admission the patient was again febrile and vomited twice; his mother observed left facial weakness. He was taken to his primary care physician who noted ataxia, left facial droop, and dizziness when lying down.

Examination, Initial Diagnosis, and Treatment. The patient was brought to the hospital and was observed to be suffering from a fever of 101°F. He was somnolent but arousable and presented with a left facial droop, nystagmus, and ataxic gait. Magnetic resonance imaging of the brain revealed cerebral edema associated with abnormal deep white matter signal changes that extended through the cerebral peduncles, more so on the left side, with pontine and cerebellar involvement.

The patient was admitted to the hospital, and ADEM

Abbreviations used in this paper: ADEM = acute disseminated encephalomyelitis; FLAIR = fluid-attenuated inversion-recovery; GBM = glioblastoma multiforme; Ig = immunoglobulin; MR = magnetic resonance.

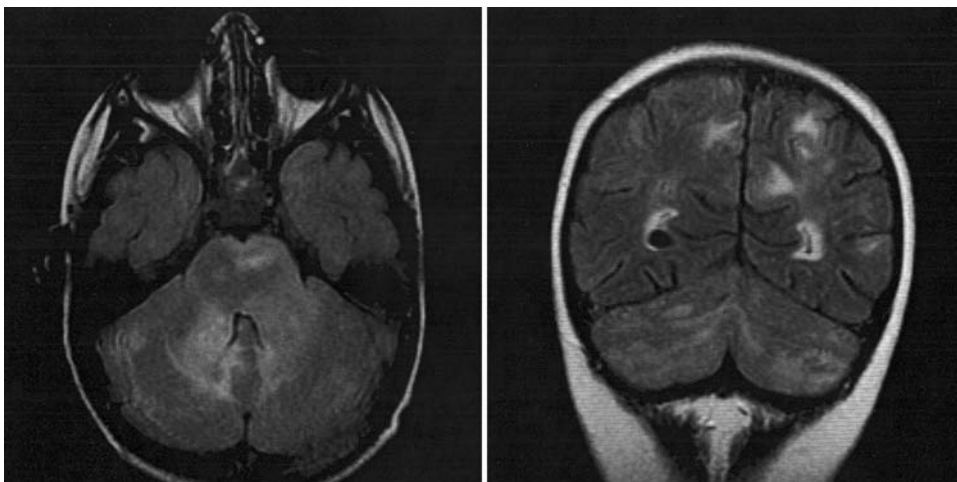


FIG. 1. Magnetic resonance FLAIR images obtained at the time of the ADEM diagnosis. *Left:* Axial image demonstrating the enlargement and masslike appearance of the left cerebellar peduncle with an abnormal signal anteriorly in the pons and in the white matter (dentate nucleus) of the cerebellum. *Right:* Coronal image revealing bilateral abnormal hyperintensities in the subcortical and periventricular white matter as well as bilateral cerebellar hyperintensities. The findings in each image are consistent with white matter leukoencephalopathy and ADEM.

was diagnosed. He was started on a regimen of ceftriaxone, acyclovir, and a 10-day course of intravenous dexamethasone (25 mg daily). Cerebrospinal fluid and blood serological findings were normal. Repeated MR imaging studies performed 5 days after admission demonstrated no change (Fig. 1). The patient was discharged 12 days after admission, the dosage of steroid medications was slowly tapered, and he demonstrated modestly improved neurological status.

Repeated Presentations, Examinations, and Final Diagnosis. One month later, the patient was readmitted with a 3-week history of intermittent left-sided hearing loss, numbness and tremor of the left arm, and the inability to look to the left side. The patient responded well to a short course of intravenous steroid agents and was discharged on a regimen of oral prednisone therapy. No MR imaging studies were performed during that hospital stay.

Three weeks later, the patient suffered a second exacerbation of his symptoms, including dysarthria, left-sided ataxia, diplopia, left-sided hearing loss, and dysphagia. He was admitted for a course of 2 g/kg intravenous Ig after which he improved modestly and was discharged. Once again, MR images were not obtained.

One week later, he developed seizurelike symptoms consisting of multiple episodes of left arm jerking associated with a loss of consciousness, head turning to the left side, and a right hemiparesis. Computerized tomography scans of the head obtained at admission and subsequent MR imaging studies demonstrated cerebellar patchy enhancement and abnormally enhancing foci bilaterally in the frontal and parietal subcortical white matter. Single-voxel MR spectroscopy was performed but the findings were nonspecific. Electroencephalography demonstrated brief electrographic seizures with left temporal origin and spread to the neighboring cortex. The patient was treated with Cerebyx, Cellcept, and steroid agents, which resulted in resolution of seizure activity but no improvement in the encephalopathy, facial nerve palsy, or right hemiparesis. He became increas-

ingly lethargic and paretic despite continued therapy and eventually required transfer to the intensive care unit.

Gadolinium-enhanced MR imaging performed 1 month later revealed a large enhancing lesion in the left cerebellar peduncle, vermis, and medulla oblongata. Effacement of the fourth ventricle and obstructive hydrocephalus without evidence of supratentorial enhancement were also demonstrated (Fig. 2C and D). Axial FLAIR imaging documented persistent, stable patches of supratentorial hyperintensity (data not shown). There was no evidence of abnormal leptomeningeal enhancement, either linear or nodular, to indicate a spread of disease in this manner. A neurosurgical consultation was requested and biopsy was recommended. Subsequent suboccipital craniectomy for biopsy and concurrent endoscopic third ventriculostomy were performed. Frozen and permanent tissue samples confirmed the diagnosis of GBM (Fig. 3). A conversation among the physicians and family concluded with the decision not to pursue aggressive measures. The patient died shortly thereafter.

Discussion

This patient suffered from an aggressive subacute disease process that evolved inexorably in a period of 3 months. During that time, the patient exhibited signs and symptoms resembling those associated with supra- and infratentorial lesions, including decreased mental status, seizures, ataxia, and cranial nerve palsies. Neuroimaging revealed a diffuse, widespread white matter disease process involving the cerebral hemispheres, brainstem, and cerebellum. Such findings indicate a broad differential diagnosis that includes demyelinating processes such as ADEM and multiple sclerosis, infectious processes such as viral encephalitis, vasculitic processes such as connective tissue disease vasculitis, leukodystrophies, and neoplastic processes such as lymphoma and gliomatosis cerebri.

Based on the initial clinical presentation and imaging results, a working diagnosis of ADEM was ascribed. A well-

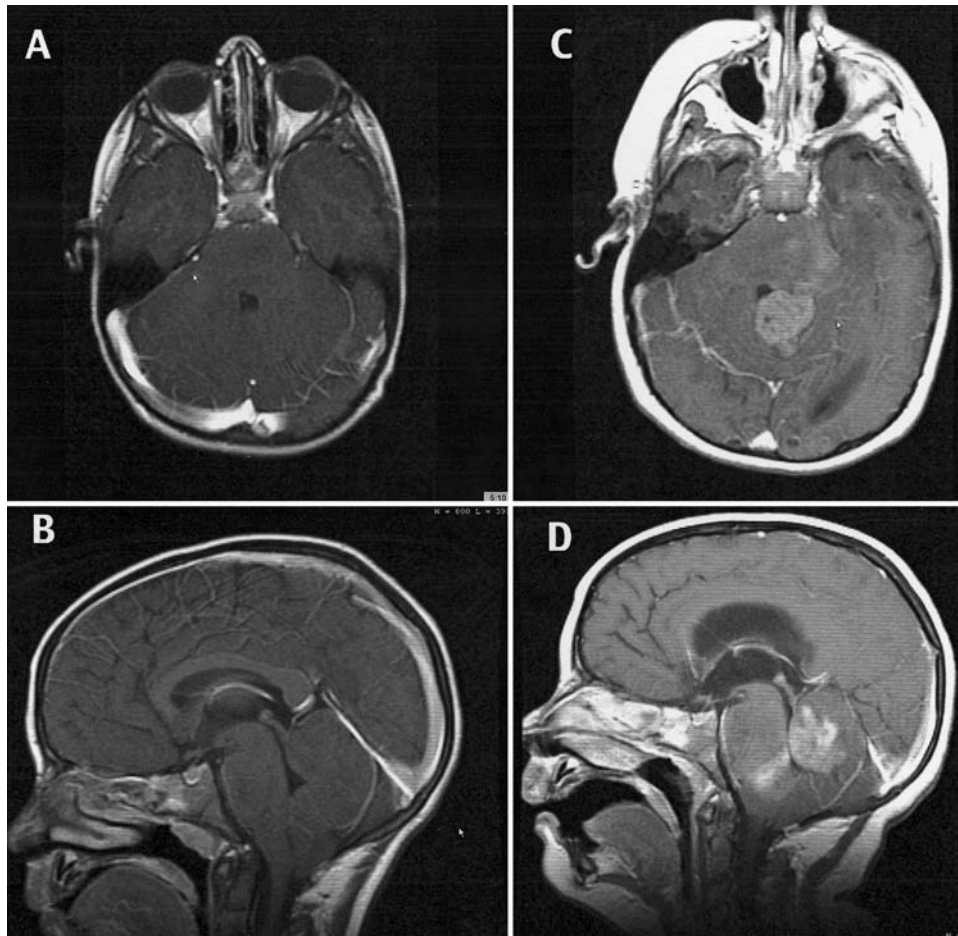


FIG. 2. Gadolinium-enhanced T₁-weighted MR images obtained at admission (A and B) and 1 month after diagnosis (C and D). The initial axial (A) and sagittal (B) images reveal a mass effect in the left cerebellar peduncle without evidence of abnormal enhancement. Later axial (C) and sagittal (D) images demonstrate a persisting mass effect appearing as a bulky enhancing mass arising from the left cerebellar peduncle into the fourth ventricle. Note the additional enhancement in the anterior pons.

characterized condition, ADEM usually presents abruptly in children and young adults, causing multifocal neurological disturbances that are accompanied by generalized complaints of headache, fever, nausea, vomiting, and changes in mental status ranging from somnolence to coma.^{2,3,8,18,22} It usually follows a viral prodrome or vaccination, typically 5 to 14 days after the initial exposure.^{2,3,22} At London Hospital, its prevalence in the pediatric population accounted for approximately one third of all cases of encephalitis between 1963 and 1978.¹³ The most common presenting feature is ataxia, although less common presentations such as nausea and vomiting or acute psychosis have been documented.^{4,18} Although gray matter can be involved, MR imaging generally demonstrates white matter lesions. The ADEM lesions as demonstrated on MR images include the following characteristics: 1) few in number; 2) localized to the brainstem and posterior fossa; 3) asymmetrical; 4) non-hemorrhagic; and 5) easily correlated to clinical symptoms.² Lesions involving the corpus callosum and periventricular region are less common than those seen in multiple sclerosis.⁸ In addition to targeting suspected offending infective agents, the most widely employed therapies for

ADEM are corticosteroid agents, intravenous Ig, and Cellcept.^{1,19,20}

In this case, the patient presented with history, signs, symptoms, and neuroimaging findings consistent with ADEM. During the month before his first admission the patient was noted to have had upper respiratory infections, a rash on his thigh, and exposure to viral illness no more than 12 days prior to becoming symptomatic. In the days immediately preceding admission the patient was febrile, and exhibited nausea, vomiting, lethargy, and asymmetric neurological findings that correlated anatomically with the neuroimaging findings. The finding of infratentorial as well as supratentorial white matter changes is particularly consistent with ADEM as opposed to tumor. For the aforementioned reasons, the presumptive diagnosis of ADEM was therefore justified. Steroid therapy, intravenous Ig, and treatment with Cellcept were instituted with only modest success. Ultimately these therapies failed to arrest progression of the disease process, as the clinical and neuroimaging examinations demonstrated. The boy was ultimately found to harbor a cerebellar GBM and died of this disease.

In view of the histological diagnosis of cerebellar GBM,

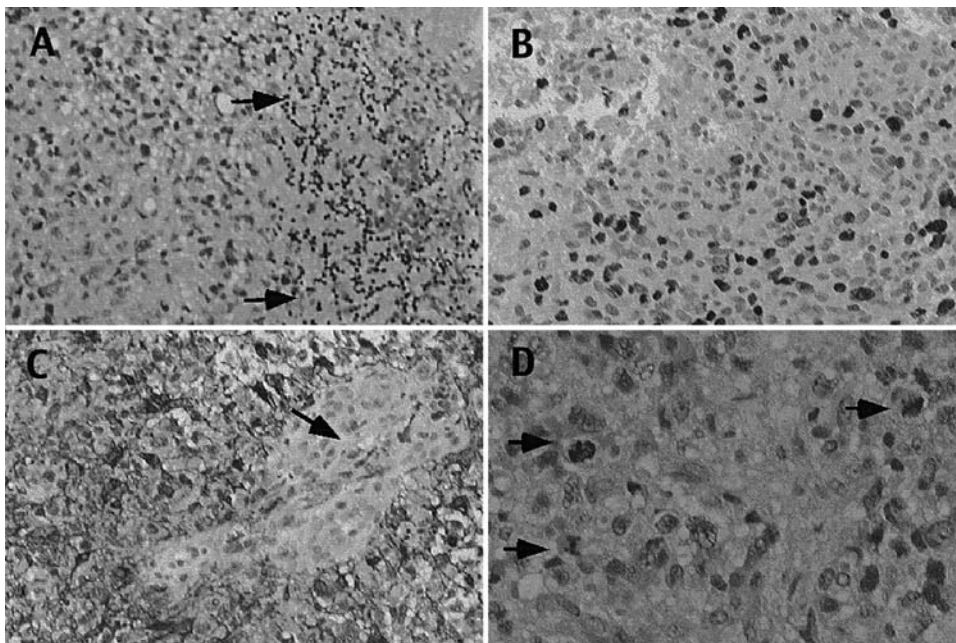


FIG. 3. Photomicrographs showing frozen and permanent sections. A: The tumor consists of tightly packed pleomorphic cells arranged in sheets that are invading into the granular layer of the cerebellar cortex (arrows). B: The immunohistochemical staining for MIB-1 shows a high proliferation rate of the tumor. C: The immunohistochemical staining for glial fibrillary acidic protein reveals a coarse, fibrillar network of the tumor cell processes surrounding a “glomeruloid” vessel (arrow). D: Individual neoplastic cells have polygonal, pleomorphic nuclei. Frequent mitoses are identified in the field (arrows). Original magnifications $\times 10$ (A, B, and C); $\times 40$ (D).

it is more likely that the widespread supra- and infratentorial white matter involvement represented gliomatosis cerebri that rapidly progressed to GBM of the cerebellum.

Gliomatosis cerebri, described by Nevin in 1938, is a rare primary brain tumor, neuroepithelial in origin, typified by diffuse infiltration of glioma cells into at least two lobes of the brain. The lesion frequently extends into the corpus callosum, the basal ganglia, the thalamus, the brainstem, or the cerebellum.^{5,17} Preservation of central nervous system structures and the underlying cytoarchitecture is characteristic of this disease process.^{5,17} Diagnosis is usually made in the late stages of the disease and it is frequently misdiagnosed early in its course. Patients frequently present with headache or seizures, but can present with findings such as hemiparesis, nausea, vomiting, ataxia, and changes in personality or mental status.^{7,14} The characteristic features of gliomatosis cerebri are best appreciated on long repetition time and echo time images such as T₂-weighted or FLAIR MR sequences.¹²

Gliomatosis cerebri is classified into two types by some pathologists: Type I consists of diffuse overgrowth with neoplastic elements without focal mass and Type II (which may derive from Type I) is characterized by diffuse invasion and manifests a focal mass, usually a high-grade glioma.^{10,24}

In this case, the patient presented with gliomatosis cerebri with both supra- and infratentorial involvement that rapidly progressed to a focal left cerebellar GBM. At the time of writing this manuscript the authors are unaware of a previous report of histologically confirmed cerebellar GBM in the pediatric population that presented simultaneously as supra- and infratentorial glial transformation. Our report is

in keeping with a recent study of gliomatosis cerebri of the entire neuraxis in a 7-year-old girl in whom anaplastic astrocytoma of the optic nerve was discovered.²⁴

We would like to underscore the rarity of cerebellar GBM in the pediatric population. Despite the observation that congenital GBM commonly occurs in the cerebellum when it presents, only approximately 30 cases of cerebellar GBM have been reported in the literature. The twofold rarity of supra- and infratentorial transformation and cerebellar GBM make this case unique.

Based on the MR images (Figs. 1 and 2) and on evaluation of the entire series of MR imaging studies in this patient, we do not think leptomeningeal spread of disease is a serious possibility in this case because on several contrast-enhanced images no abnormal leptomeningeal enhancement, linear or nodular, was apparent. Intraventricular spread of disease is also unlikely due to the lack of ependymal or subependymal enhancement on the neuroimaging studies. Initial MR images obtained in the patient after administration of contrast agents reveal no abnormal parenchymal or leptomeningeal enhancement (Fig. 2A and B).

One may question our confidence that the early manifestations of this child's disease process were due to gliomatosis cerebri rather than multifocal GBM, particularly given that the final histologically confirmed diagnosis was cerebellar GBM and that the incidence of multifocal GBM is significantly greater than that of gliomatosis cerebri.^{5,23} Although both multifocal GBM and gliomatosis cerebri involve multiple brain areas and are associated with poor survival, a significant pathophysiological difference exists between the two processes. Unlike gliomatosis cerebri,

multifocal GBM typically does not preserve central nervous system structures or spare the underlying cytoarchitecture. An initial presentation resulting from multifocal GBM would have most likely revealed moderate edema and a mass effect on MR images as well as strong and heterogeneous enhancement;¹⁵ such findings were not consistent with neuroimaging studies from the early stages of this patient's disease (Fig. 1).

Furthermore, from a clinical standpoint, the early stages of this patient's symptomatology, which mimicked ADEM, are much more consistent with gliomatosis cerebri than multifocal GBM; previously reported cases have demonstrated the ability of gliomatosis cerebri to mimic infectious lesions such as acute diffuse encephalomyelitis, tuberculosis, Creutzfeldt–Jakob disease, and herpes encephalitis.^{6,9,23} Although multifocal GBM can theoretically present as an infective lesion, it is far less likely than gliomatosis cerebri to present in this fashion.

Given that transformation of gliomatosis cerebri to GBM is rare, one might speculate that the patient initially presented with multifocal GBM; however, this is not supported by the literature. Although gliomatosis cerebri is rare, multiple cases of the transformation of initial gliomatosis cerebri to GBM have been reported.^{7,11,16,21} Moreover, we propose that this case represents an example of gliomatosis cerebri Type II in which a focal high-grade mass lesion of the cerebellum evolved in the context of a diffuse glial neoplastic process.¹⁰ Given the progressive nature of this child's disease process and its documentation on clinical and neuroimaging examinations, it is reasonable to infer that the cause of the patient's symptoms was gliomatosis cerebri rather than multifocal GBM.

It would also have been reasonable to consider less likely alternatives than ADEM, gliomatosis cerebri, and multifocal GBM within the differential diagnosis at the initial presentation. Multiple sclerosis was a possible diagnosis because, like ADEM, it can mimic the early symptoms and neuroimaging findings described earlier. That multiple sclerosis is exceedingly rare in young children, that the patient's symptoms persisted despite the use of steroid medications and intravenous Ig, that no oligoclonal bands were identified in the cerebrospinal fluid, and that early lesions did not enhance or reduce the likelihood of this diagnosis. Lymphoma, although similar in its clinical presentation, was considered unlikely because of the absence of enhancement on imaging studies and this patient's poor response to steroid medications. Various types of angitis might have mimicked the appearance of the presenting lesions on neuroimaging studies, but without clinical evidence of sickle cell disease, connective tissue diseases (that is, Marfan syndrome, Ehler–Danlos syndrome), homocystinuria, or moyamoya, these causes would be unlikely. The absence of neuroimaging findings such as basal ganglia flow voids, significant gray matter involvement, cerebral atrophy, and a positive diffusion-weighted MR imaging signal strengthen the argument against angitis. The existence of a viral prodrome raises the specter of viral encephalitis. The atypical anatomic distribution, however, combined with the absence of personality changes or hemorrhagic lesions in this patient make viral encephalitis unlikely. Although adrenoleukodystrophy and metachromatic leukodystrophy occur in children within the correct age range (3–10 years of age), they are unlikely to have

caused this patient's symptoms because evidence of liver, spleen, kidney damage, adrenal failure, or psychomotor deterioration was lacking.

Conclusions

The diagnosis of ADEM remained with our patient for 3 months as his disease progressed. Early consideration of gliomatosis cerebri would have likely prompted the performance of a brain biopsy at an earlier period in the patient's treatment. Such intervention would have excluded the diagnosis of ADEM and given the family a better understanding of the diagnosis, management, and prognosis in this child. This report underscores the importance of the consideration of gliomatosis cerebri in the differential diagnosis of children presenting with signs and symptoms of ADEM who fail to respond to conventional steroid and immunotherapy.

References

1. Apak RA, Anlar B, Saatci I: A case of relapsing acute disseminated encephalomyelitis with high dose corticosteroid treatment. **Brain Dev** 21:279–282, 1999
2. Atlas SW, Grossman RI, Goldberg HI, Hackney DB, Bilaniuk LT, Zimmerman RA: MR diagnosis of acute disseminated encephalomyelitis. **J Comput Assist Tomogr** 10:798–801, 1986
3. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG: Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. **Brain** 123:2407–2422, 2000
4. David P, Baleriaux D, Bank WO, Amrom D, De Temmerman D, Babusiaux C, et al: MRI of acute disseminated encephalomyelitis after coxsackie B infection. **J Neuroradiol** 20:258–265, 1993
5. Elshaikh MA, Stevens GH, Peereboom DM, Cohen BH, Prayson RA, Lee SY, et al: Gliomatosis cerebri: treatment results with radiotherapy alone. **Cancer** 95:2027–2031, 2002
6. Fallentin E, Skriver E, Herning M, Broholm H: Gliomatosis cerebri—an appropriate diagnosis? Case reports. **Acta Radiol** 38:381–390, 1997
7. Hirose Y, Hayashi T, Sagoh M, Murakami H: Secondary glioblastoma remarkably reduced by steroid administration after anaplastic transformation from gliomatosis cerebri—case report. **Neurol Med Chir** 38:865–870, 1998
8. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ: Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. **Neurology** 56:1308–1312, 2001
9. Jayawant S, Neale J, Stoodley N, Wallace S: Gliomatosis cerebri in a 10-year-old girl masquerading as diffuse encephalomyelitis and spinal cord tumour. **Dev Med Child Neurol** 43:124–126, 2001
10. Jennings MT, Frenchman M, Shehab T, Johnson MD, Creasy J, LaPorte K, et al: Gliomatosis cerebri presenting as intractable epilepsy during early childhood. **J Child Neurol** 10:37–45, 1995
11. Kannuki S, Hirose T, Horiguchi H, Kageji T, Nagahiro S: Gliomatosis cerebri with secondary glioblastoma formation: report of two cases. **Brain Tumor Pathol** 15:111–116, 1998
12. Keene DL, Jimenez C, Hsu E: MRI diagnosis of gliomatosis cerebri. **Pediatr Neurol** 20:148–151, 1999
13. Kennard C, Swash M: Acute viral encephalitis: its diagnosis and outcome. **Brain** 104:129–148, 1981
14. Kim DG, Yang HJ, Park IA, Chi JG, Jung HW, Han DH, et al: Gliomatosis cerebri: clinical features, treatment, and prognosis. **Acta Neurochir** 140:755–762, 1998

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15. Lafitte F, Morel-Precetti S, Martin-Duverneuil N, Guermazi A, Brunet E, Heran F, et al: Multiple glioblastomas: CT and MR features. **Eur Radiol** **11**:131–136, 2001
16. Martinez-Mata AM, Martinez-Pardavila R, deArriba-Villamor C, Espinosa-Mogro H: [Cerebral gliomatosis with development of multifocal glioblastoma.] **Rev Neurol** **28**:781–783, 1999 (Sp)
17. Meligoni G, Sur M, Ouma J, Grayson W, Farrell VJ: Gliomatosis of the brain and spinal cord masquerading as infective lesions. **Surg Neurol** **57**:399–404, 2002
18. Nasr JT, Andriola MR, Coyle PK: ADEM: literature review and case report of acute psychosis presentation. **Pediatr Neurol** **22**:8–18, 2000
19. Nishikawa M, Ichiyama T, Hayashi T, Ouchi K, Furukawa S: Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. **Pediatr Neurol** **21**:583–586, 1999
20. Pradhan S, Gupta RP, Shashank S, Pandey N: Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. **J Neurol Sci** **165**:56–61, 1999
21. Romero FJ, Ortega A, Titus F, Ibarra B, Navarro C, Rovira M: Gliomatosis cerebri with formation of a glioblastoma multi-form. Study and follow-up by magnetic resonance and computed tomography. **J Comput Tomogr** **12**:253–257, 1988
22. Rust RS: Multiple sclerosis, acute disseminated encephalomyelitis, and related conditions. **Semin Pediatr Neurol** **7**:66–90, 2000
23. Shimura T, Hirano A, Nakasu S, Llena JF, Leeds NE: [Multifocal glioma of the brain—an autopsy case.] **No Shinkei Geka** **14**:97–101, 1986 (Jpn)
24. Yip M, Fisch C, Lamarche JB: AFIP archives: gliomatosis cerebri affecting the entire neuraxis. **Radiographics** **23**:247–253, 2003

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