Section Editors: Robert Avery, DO
Karl C. Golnik, MD
Caroline Froment, MD, PhD
An-Guor Wang, MD

Diffuse Leptomeningeal Glioneuronal Tumor Presenting With Progressive Cranial Neuropathies

Mohammad Z. Siddiqui, MD, Abdelrahman M. Elhusseiny, MD, Paul H. Phillips, MD, Raghu H. Ramakrishnaiah, MD, Murat Gokden, MD, Luis F. Carrillo, MD, Joseph G. Chacko, MD

An 18-year-old Caucasian man with hereditary osteochondromas and recent SARS2-COVID-19 disease was admitted for evaluation of altered mental status, hemiparesis, areflexia, seizures, headaches, and multiple cranial neuropathies. Cerebral vasculitis was a diagnostic consideration. Computed tomography angiography of the head and neck, Magnetic Resonance Imaging (MRI) with gadolinium, and MR angiography (MRA) of the head and neck showed mild vasospasm of the right internal carotid artery (ICA) but was otherwise unremarkable with no sign of stroke (Fig. 1A). Lumbar puncture showed an opening pressure of 31 cm H_2O, with elevated protein (299 mg/dL) and white blood cells (9 leukocytes/mm); however, cytology showed no malignant cells in the cerebrospinal fluid (CSF). Laboratory investigations were negative for antiacetylcholine receptor antibodies, antinuclear antibodies, antinuclear cytoplasmic antibody, T-spot tuberculosis test, toxoplasma antibodies, syphilis serology, CSF SARS-CoV-2 polymerase chain reaction, complement (C3 and C4), multiple sclerosis panel, Myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and anti-Gq1b. C-reactive protein (11.2 mg/dL) and erythrocyte sedimentation rate (21 mm/hour) were elevated. He was diagnosed with transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) syndrome and treated with intravenous methylprednisolone 125 mg every 6 hours, followed by a short course of oral prednisone.

At initial presentation, his best-corrected visual acuity (BCVA) was 20/20 in each eye. Pupils were equal, reactive, and with no relative afferent pupillary defect. Extraocular motility showed −3 limited abduction of both eyes. The patient had ptosis with a margin reflex distance (MRD) of 1 mm in the right eye and left eye. Fundus examination revealed mild pallor of both optic discs.

In 2 weeks, his symptoms progressed. His BCVA decreased to 20/100 in the right eye and 20/70 in the left eye with bilateral dilated fixed pupils. His ocular motility deficits progressed to −4 limitation of ductions in all fields of gazes, and he had complete ptosis with MRD −4 in both eyes. Fundus examination showed mild pallor of both optic discs with no disc edema. The patient had an acute decline in mental status, precluding formal optic nerve and visual field testing in the clinic. Repeat MRI brain and orbit with gadolinium showed acute infarcts in the corpus callosum and left cerebral hemisphere, hydrocephalus, diffuse basal cistern enhancement, leptomeningeal enhancement of the brain and spine, marrow space enhancement of the spine, and bilateral postseptal soft-tissue infiltration of extraocular muscles (Fig. 1B–D). Lumbar puncture showed opening pressure at 36 cm of H_2O, leukocytosis (24 leukocytes/μm), normal glucose (72 mg/dL), elevated protein (400 mg/dL), and normal cytology. Complete blood counts were significant for leukocytosis (16.62 K/μL). Biopsies were performed of the dura, leptomeninges, and brain cortex. Meningeal biopsies showed neoplastic cells infiltrating leptomeninges with immunohistochemical positivity for glial markers *OLIG2* and *SOX10* and the neural marker *CD56/NCAM* (Fig. 2A–C), confirming the diagnosis of diffuse leptomeningeal glioneuronal tumor (DLGT). Ki-67 proliferation index was high, which suggested an aggressive course. No IDH-1 (R132H) and BRAF V600E mutations were identified by immunohistochemistry.

The patient was referred to the oncology service and started on chemoradiation. He received temozolomide followed by radiotherapy. He developed pancytopenia suggestive of aplastic anemia secondary to radiotherapy vs a myelodysplastic process. His treatment was changed to weekly carboplatin and vincristine. Bone marrow biopsy was devoid of hematopoietic cells and revealed groups of neoplastic cells and areas of fibrosis. These cells were positive immunohistochemically for *OLIG2*, *SOX10*, and glial fibrillary acidic protein (*GFAP*), indicating DLGT bone marrow infiltration (Fig. 2D). A ventriculoperitoneal shunt was placed to treat the hydrocephalus. At the 5-month follow-

Department of Ophthalmology (MZS, AME, PHP, JGC), Harvey and Bernice Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Department of Radiology (RR), Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and Department of Pathology (MG, LC), University of Arkansas for Medical Sciences, Little Rock, Arkansas.

The authors report no conflicts of interest.

Address correspondence to Mohammad Z. Siddiqui, MD, Jones Eye Institute, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Little Rock, AR 72207; E-mail: msiddiqui@uams.edu

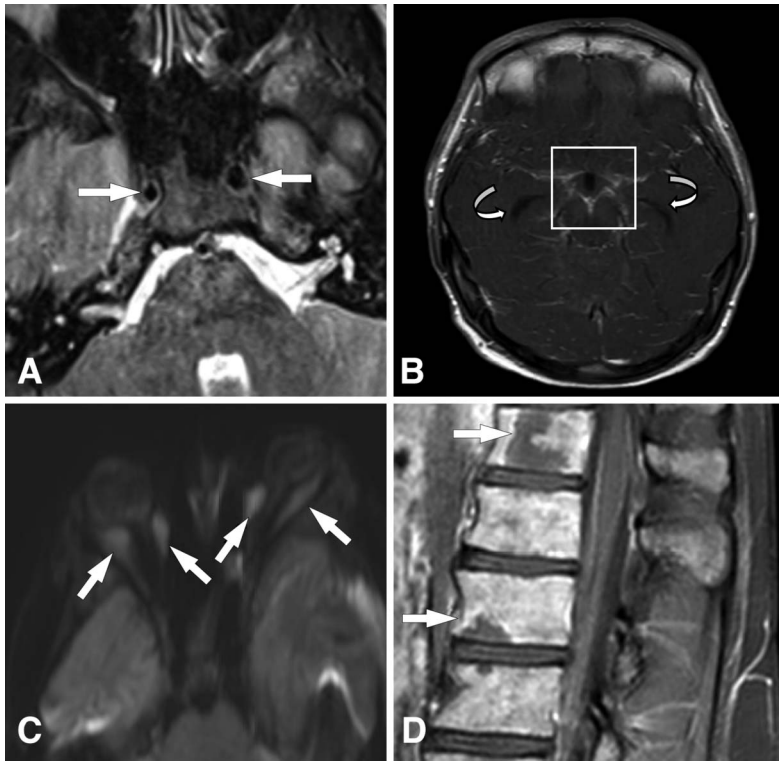

FIG. 1. Axial T2-weighted image (**A**) from the initial MRI show mild vasospasm of the right internal carotid artery. Notice the caliber difference between the right and left ICA (*arrows*). Postcontrast T1-weighted image (**B**) follow-up MRI study shows diffuse postcontrast enhancement of the basal cisterns (box) with mild interval development of the ventricles (*curved arrows*). Diffusion-weighted image (**C**) from the follow-up MRI shows bilateral postseptal soft-tissue tumor infiltration of the extraocular muscles (*arrows*). The sagittal postcontrast T1-weighted image of the spine (**D**) shows diffuse marrow space heterogeneous enhancement (*arrows*), suggesting tumor infiltration.

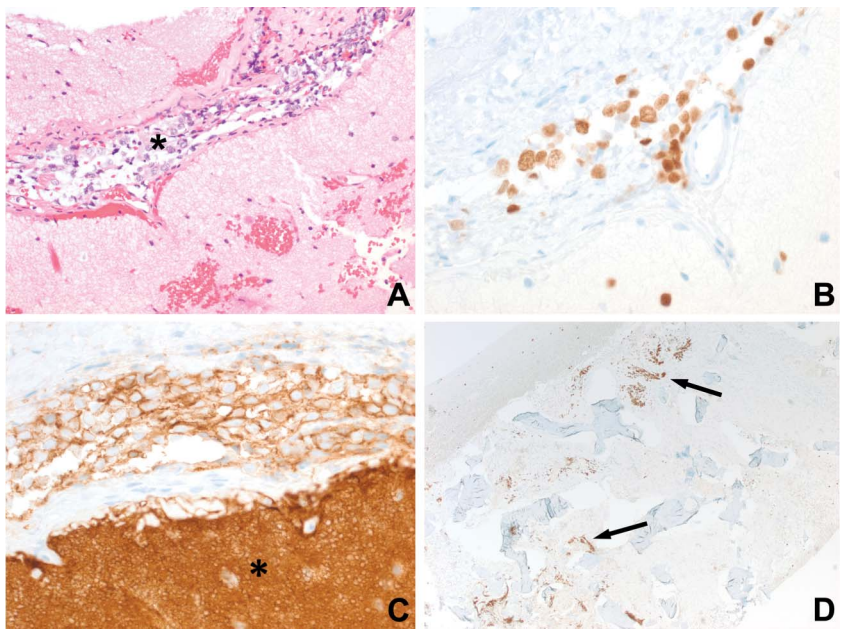

FIG. 2. Histologic findings in the brain biopsy tissue: (**A**) The neoplastic cells infiltrate the leptomeninges (*) but are not present within the neuroglial parenchyma. Immunohistochemically, they are positive for glial markers olig2 (**B**) and neural marker CD56/NCAM (**C**). The latter also normally highlights the brain parenchyma (*). Many groups of similar cells (*arrows*) are present throughout the bone marrow (**D**) and are highlighted by olig2 (Original magnifications: (**A**) ×200; (**B** and **C**) ×400; (**D**) ×40).

up, his BCVA was 20/30 in the right eye and counting fingers in the left eye. Both pupils were dilated. Fundus examination showed optic atrophy in both eyes, worse in the left eye. Visual improvement of the right eye was attributed to improvement in mentation. Visual decline in the left eye was attributable to optic atrophy from carcinomatous meningitis. He was scheduled to receive optical coherence tomography of his nerve and visual fields in 3 months; however, his disease progressed, and he passed away shortly after.

DLGT has been classified as a distinct clinical entity under neuronal and mixed neuronal–glial tumors (1). DLGT predominantly affects men with a median age of presentation of 4 years; however, adult cases have been reported (2). The growth of these tumors is usually slow. The characteristic imaging finding of DGLT is diffuse thickening and enhancement of the leptomeninges with or without cystic-like lesions in both the brain and spinal cord. These lesions may be associated with a spinal cord mass (2). The radiologic characteristics of DGLT are nonspecific. Therefore, most cases are misdiagnosed initially, leading to delayed diagnosis and management. In Europe and Asia-Pacific regions, it is not uncommon for DGLT to be misdiagnosed as chronic tuberculous meningitis (3).

There is limited literature on DGLT with ophthalmic manifestations. Casey and colleagues (4) reported an otherwise healthy 13-year-old boy who presented with bilateral rapidly progressive painless diminution of vision. Examination revealed papilledema with macular exudates and peripheral perivascular hemorrhages. MRI showed chronic hydrocephalus with diffuse leptomeningeal enhancement. The diagnosis of DGLT was established by histopathological findings on ventricular biopsy. Although the patient underwent craniospinal irradiation, there was no visual improvement (4). Xiao et al (5) described a 16-year-old woman who presented with headache, nausea, vomiting, and painless vision loss. She was initially misdiagnosed with neuromyelitis disease, for which she received intravenous immunoglobulin and intravenous methylprednisolone with no improvement before the diagnosis of DGLT was established by biopsy.

Our case is unique in that he presented with progressive ocular motor deficits in addition to vision loss from optic neuropathy. The ocular motor deficits were partially due to orbital infiltration of extraocular muscles. In addition, the presence of optic atrophy, ptosis, and pupil involvement implicates CN II and III dysfunction. This is also the first case to show DLGT infiltration of the bone marrow. Our patient was found to have extracentral nervous system metastasis to the bone marrow, resulting in hematologic findings as well as metastatic deposits in the head and neck region, suggesting the possibility of perineural spread.

In summary, this case highlights the importance of repeating the neuroimaging and CSF analysis when ocular involvement is progressing. DGLT should be considered as a possible diagnosis when characteristic MRI findings are found without evidence of infection.

STATEMENT OF AUTHORSHIP

Conception and design: M. Z. Siddiqui, J. Chacko, P. Phillips, A. Elhusseiny; Acquisition of data: M. Z. Siddiqui, A. M. Elhusseiny, P. H. Phillips, R. Ramakrishnaiah, M. Gokden, J. G. Chacko; Analysis and interpretation of data: M. Z. Siddiqui, A. M. Elhusseiny, P. H. Phillips, R. Ramakrishnaiah, M. Gokden, L. Carrillo, J. G. Chacko. Drafting the manuscript: M. Z. Siddiqui, A. M. Elhusseiny, P. H. Phillips, R. Ramakrishnaiah, M. Gokden, J. G. Chacko; Revising the manuscript for intellectual content: M. Z. Siddiqui, A. M. Elhusseiny, P. H. Phillips, R. Ramakrishnaiah, M. Gokden, L. Carrillo, J. G. Chacko. Final approval of the completed manuscript: M. Z. Siddiqui, A. M. Elhusseiny, P. H. Phillips, R. Ramakrishnaiah, M. Gokden, L. Carrillo, J. G. Chacko.

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