

19-YEAR-OLD MALE WITH HEADACHES AND A POSSIBLE SEIZURE

MacLean P. Nasrallah MD, PhD¹; Ilya M. Nasrallah MD, PhD²; Marisa S. Prelack MD³; Margaret O. Johnson MD, MPH³; Travis B. Lewis MD, PhD³; Michael Rubenstein MD³; Jane E. Minturn MD, PhD⁴; Arati Desai MD⁵; Paul Marcotte MD⁶; Mariarita Santi MD, PhD⁷; Maria Martinez-Lage MD¹

¹ Departments of Pathology and Laboratory Medicine; ²Radiology; ³Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA.

⁴ Division of Oncology/Neuro-Oncology, Children's Hospital of Philadelphia, Philadelphia, PA.

⁵ Departments of Medical Oncology; ⁶Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, PA.

⁷ Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.

CLINICAL HISTORY AND NEUROIMAGING

A 19-year-old male with history of narcolepsy, but otherwise healthy with normal development and cognition, presented in April 2015 with 1 month of daily headache and a single unprovoked transient confusional episode consistent with a seizure. During the episode, the patient experienced right upper extremity incoordination, orolingual automatisms and aphasia. Physical examination was notable only for macrocephaly. MRI of the brain revealed multiple heterogeneously enhancing dural-based masses and dural nodularity with mild parenchymal volume loss, thinning and remodeling of the calvarium, remodeling of the skull base and sagging appearance of brainstem (Figure 1A,B). There was no lesion in the spinal canal. Cerebrospinal fluid analysis was normal except for elevated protein content. Electroencephalography showed left temporal focal slowing with sharp transients. Extensive serologic testing was within normal limits, notable for normal ANA, ANCA, RF, RPR, Quantiferon Gold, FSH, LH, prolactin, TSH, SPEP, antigliadin antibody and IgG4, as well as negative HIV. CT scans of the chest, abdomen, and pelvis did not identify any visceral lesions and ophthalmologic and dermatologic examinations were essentially normal. A biopsy of the left parietal dural-based nodule was performed, but did not yield a definitive diagnosis. The patient was treated with levetiracetam and corticosteroid therapy and discharged home with planned outpatient follow up. Approximately 4 weeks later, he presented with

recurrence of severe retro-orbital headache and emesis. A second biopsy, this time of a left frontal dural-based nodule was performed.

GROSS AND MICROSCOPIC PATHOLOGY

Grossly, the left parietal biopsy (first biopsy) consisted of a firm spherical nodule of tan soft tissue attached to a portion of thickened, white dura. Microscopically, the biopsy was remarkable for a florid meningotheial proliferation (Figure 1C) with granulomatous changes, including multinucleated giant cells with refractile crystalline inclusions (Figure 1D) and vessel wall abnormalities. The meningotheial proliferation had cystic areas and infiltrating cells with clear and foamy cytoplasm and was adherent to thickened dura, which was infiltrated by cords and nests of atypical cells with clear cytoplasm. EMA was positive in the meningotheial proliferation. The histiocytic foamy and clear cells were positive for CD68 (Figure 1E) and the infiltrating clear cells were positive for S100 (Figure 1F,G) and synaptophysin; CD1a, HMB45 and melanA showed no staining. The second biopsy of the frontal nodule showed infiltrating cords and nests of cells with clear cytoplasm on a continuum with sheets of cells with a higher nuclear/cytoplasmic ratio, involving the meninges and dura (Figure 1H,I). At higher magnification, up to 8 mitoses per 10 high power fields as well as numerous apoptotic bodies were seen (Figure 1J). The clear and round cells were positive for S100, synaptophysin and Olig2 (Figure 1K). **What is your diagnosis?**

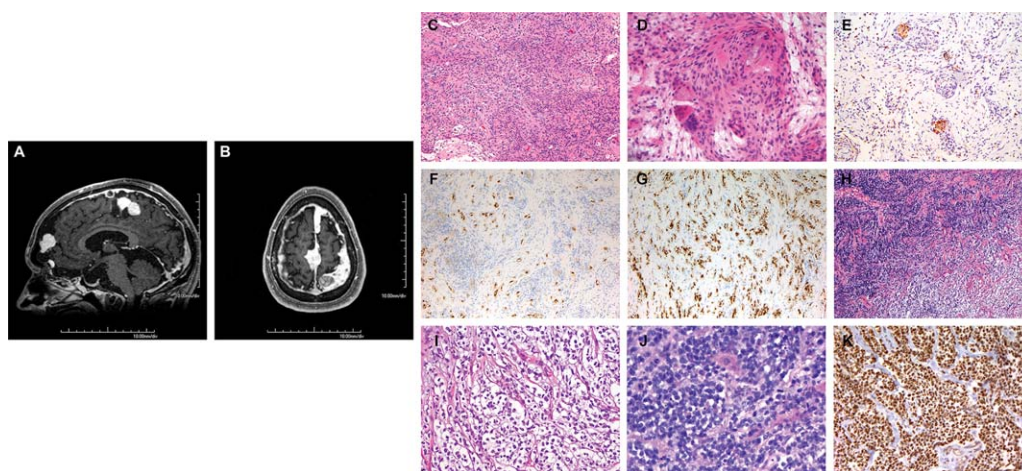


Figure 1.

DIAGNOSIS

Disseminated oligodendroglial-like leptomeningeal tumor with malignant (anaplastic) transformation.

DISCUSSION

Disseminated oligodendroglial-like leptomeningeal tumor of childhood is a rare neoplasm that was first described in 1942, but has only recently been better characterized in a report describing 36 patients (4). The current literature suggests that the tumor cells are of glial, neuronal or glioneuronal origin, and may originate from rests of cells commonly present in the meninges (1, 2, 4). Although intraparenchymal lesions are seen in a number of cases, these foci are generally considered to be secondary involvement of a primary meningeal neoplasm. Most cases are low-grade, but approximately a fifth show anaplastic features, such as seen in our patient's tumor. The oligodendroglial origin of the tumor cells is suggested by histology, which shows clear cells containing round nuclei, but also supported by Olig2 immunohistochemical expression and occasional 1p/19q co-deletion, 1p deletion and/or polysomy. A high rate of concurrent *BRAF-KIAA1549* gene fusion and 1p deletion has been seen (5). All cases have S100, synaptophysin and Olig2 positivity, as our case does. In addition, FISH in our case demonstrated 1p/19q co-deletion and polysomy in tumor cells, as seen in 20% of cases, and further molecular testing revealed 1p19 loss and a TERT promoter point mutation, but no mutations in IDH1 or IDH2, and no fusions.

The imaging appearance in our case indicated heterogeneity of the dural lesions, with some areas having features suggesting more aggressive findings of higher cellularity and leptomeningeal involvement. Radiological evaluation favored a chronic process due to the associated calvarial and skull base remodeling, with the differential primarily consisting of meningiomatosis and neurofibromatosis type 2. Inflammatory diseases, particularly neurosarcoidosis, along with lymphoma, histiocytosis and dural metastases, all of which could cause dural masses, were considered less likely both because they would not account for the chronic osseous changes and because of the lack of additional systemic findings.

The differential diagnosis of this tumor may be broad due to the associated reactive changes, and the pathologist must be aware of the disseminated oligodendroglial-like leptomeningeal tumor to consider it upon encountering infiltrating atypical clear cells in the leptomeninges and dura in the context of imaging that shows diffuse dural nodularity with no intraparenchymal lesion. The exuberant meningotheelial reaction is virtually indistinguishable from meningioma, and if it is the main entity sampled on a biopsy, may lead to misdiagnosis of meningiomatosis. However, as on our patient's initial biopsy, some infiltrating clear cells are present that are not macrophages (Figure 1C). A densely histiocytic reaction may lead to consideration of a histiocytic neoplasm, such as

Langerhans cell histiocytosis (LCH), which can present as discrete nodules attached to the dura. However, CD1a staining will be positive in LCH, unlike in our case. In addition, Rosai–Dorman Disease (RDD) may rarely involve the CNS, and very rarely may be isolated to the CNS. In RDD, tumor cells are defined by their positivity for CD68 and S100, and emperipolesis is usually present. Although we do not see emperipolesis, staining for CD68 and S100 in our case highlights infiltrating cells, and it is difficult to determine whether the two antibodies are staining the same population of cells. Finally, the granulomatous inflammation and vascular changes could suggest a granulomatosis with polyangiitis (ie, a Wegener's granulomatosis-like process). Indeed, ANCA-negative cases with florid dural-based lesions that were diagnosed according to the clinical criteria of 1990 and 1992 have been reported, and these patients respond to cyclophosphamide and prednisone therapy (3).

If areas of the characteristic clear cells are sampled on biopsy, the diagnosis becomes a question of identifying the tumor, and the possibilities of disseminated carcinoma, melanoma and a glioneuronal neoplasm may be entertained. In our case, the areas of small anaplastic blue cells raised additional concerns for lymphoma, undifferentiated sarcoma, Ewing's sarcoma, and poorly differentiated myoepithelial carcinoma. Immunostains and FISH for these entities were negative.

Our patient was initiated on daily temozolamide 90mg/m²/dose, with excellent radiographic and clinical response as early as 4 weeks into treatment. After 11 weeks, MRI revealed marked decrease of the extra-axial masses and he was transitioned to monthly temozolamide monotherapy at 200mg/m²/dose, 5 days per month, and underwent craniospinal radiation with boost to areas of residual tumor burden with excellent response.

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