

# Leptomeningeal dissemination of a pediatric neoplasm with 1p19q deletion showing mixed immunohistochemical features of an oligodendroglioma and neurocytoma

Richard B. Rhiew · Sunil Manjila · Andrew Lozen ·  
Murali Guthikonda · Sandeep Sood · William J. Kupsky

Received: 24 February 2010 / Accepted: 21 April 2010  
© Springer-Verlag 2010

**Abstract** Leptomeningeal dissemination of an oligodendroglioma is rarely reported in the neurosurgical literature, especially in cases with a classical 1p19q deletion. The authors describe a case wherein a 1p19q deletion in a disseminated tumor with mixed immunohistochemical features of oligodendroglioma and neurocytoma was encountered and treated. Stereotactic right frontal craniotomy was undertaken for obtaining definitive histological diagnosis. The results revealed a neuroectodermal neoplasm with histologic and immunohistochemical features of oligodendroglioma and neurocytoma. FISH analysis confirmed classical 1p19q deletion. The patient was treated postoperatively with chemotherapy and radiation therapy. He showed good clinical response and remains alive 16 months after diagnosis.

**Keywords** Leptomeningeal dissemination · Oligodendroglioma · Neurocytoma · Mixed tumor

## Introduction

Apart from the diagnostic dilemma of distinguishing between neurocytomas and oligodendrogliomas, the recognition of rare mixed glial and neurocytic tumors presents an obstacle in tumor classification. Reports of leptomeningeal dissemination of tumors in this category are extremely rare, particularly those harboring the classic 1p19q co-deletion. The authors present such a histological variant of oligodendroglioma with evidence of extensive craniospinal leptomeningeal dissemination (LMD). The present case report highlights the importance of recognizing this discrete subtype of low-grade craniospinal neoplasms, which carry features of both tumors and therefore are not classified using the existing WHO system for CNS tumors.

## Case report

An 11-year old boy was admitted with a 1-week history of mid-thoracic back pain and a 1-day history of right leg weakness with inability to walk. His past medical history was remarkable for an occurrence of sterile meningitis 4 years prior to admission. At that time, a neuroradiologist reported no abnormal contrast enhancement on magnetic resonance imaging (MRI) of the brain (Fig. 1a). Cerebrospinal fluid (CSF) analysis revealed elevated protein to 153 while glucose was within normal range. CSF culture was negative and no cytology was sent as no tumor was suspected. Three years later, the patient underwent placement of a ventriculo-

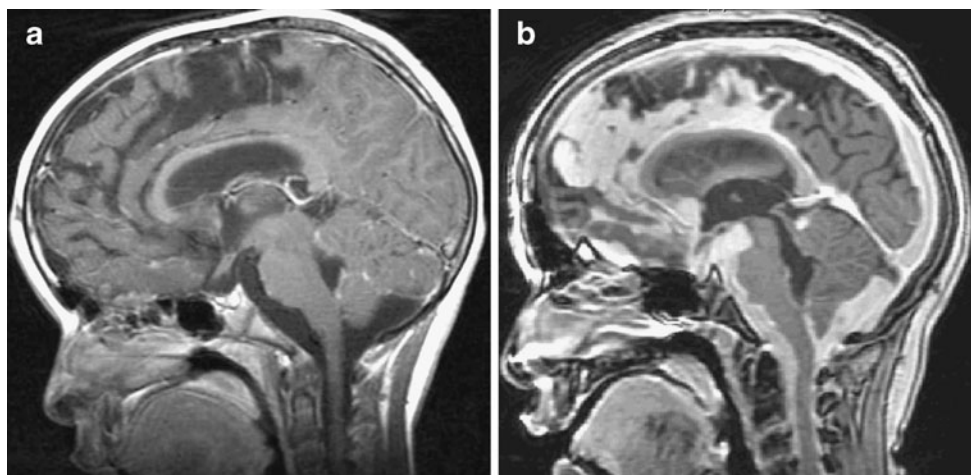
---

R. B. Rhiew · S. Manjila · M. Guthikonda  
Department of Neurosurgery,  
Wayne State University School of Medicine,  
Detroit, MI 48201, USA

A. Lozen (✉)  
Department of Neurosurgery,  
Medical College of Wisconsin & Froedtert Hospital,  
9200 W. Wisconsin Avenue,  
Milwaukee, WI 53226, USA  
e-mail: alozen@mcw.edu

S. Sood  
Department of Pediatric Neurosurgery,  
Children's Hospital of Michigan,  
Detroit, MI 48201, USA

W. J. Kupsky  
Department of Pathology,  
Wayne State University School of Medicine,  
Detroit, MI 48201, USA



**Fig. 1** **a** T1-weighted sagittal MRI of the brain with contrast 4 years prior to admission, at the time of presentation with suspected sterile meningitis. **b** T1 sagittal MRI scan of the brain with contrast revealing

extensive intense leptomeningeal thickening and nodular enhancement along the convexities of the frontal, temporal, parietal, and occipital lobes

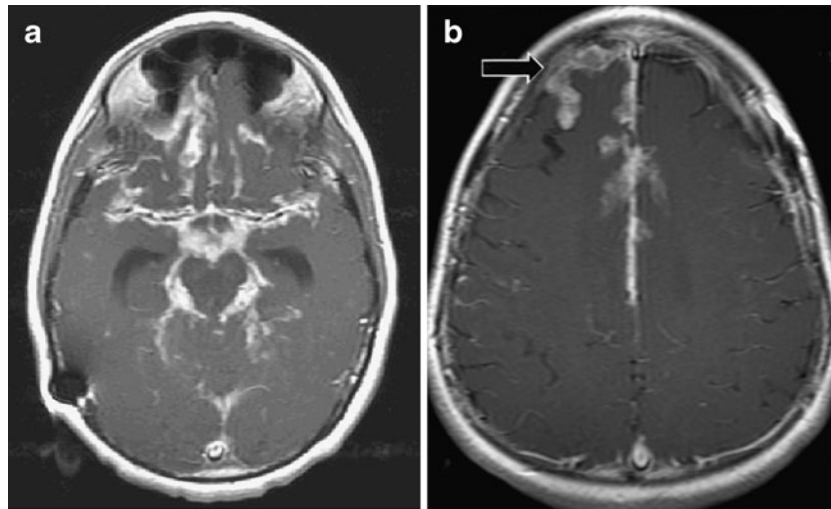
peritoneal shunt for presumed postmeningitic hydrocephalus. Additionally, the patient was known by our department for an episode of closed head trauma with evacuation of a subdural hematoma 11 months prior.

MRI of the head with contrast administration revealed extensive craniospinal leptomeningeal enhancement with evidence of intense thickening and nodularity of leptomeninges, especially over convexities in the frontal, temporal, parietal, and occipital lobes (Fig. 1b). Similar enhancement patterns were also seen along the lateral, third, and fourth ventricles, the basal cisterns, suprasellar cistern, prepontine cisterns, and encasing the circle of Willis (Fig. 2a). A well-defined lesion within the middle frontal gyrus was appreciated. The lesion was thought to represent posttraumatic encephalomalacia; however, a cystic glial tumor could not be excluded. A spinal MRI revealed intense leptomeningeal enhancement involving the posterior fossa, cervical-thoracic-lumbar spine, and showed an anterior intradural extramedullary fluid collection extending from C7 to T3. Likewise, a cystic fluid collection effacing the thoracic cord was observed at the T6 to T9 levels with an enhancing expansile intramedullary lesion at T11. Increased T2 signal was demonstrated from the T3 level through the conus medullaris, and a loculated fluid collection was appreciated within the spinal canal just posterior to the sacral vertebral bodies.

The patient underwent a T6–7 laminotomy for biopsy of the intradural–intramedullary lesion. Pathological examination of the resected specimen demonstrated leptomeningeal tissue with fibrosis and mild meningotheial hyperplasia; no tumor was identified. Three weeks later, the patient underwent a stereotactic right frontal craniotomy for definitive biopsy (Fig. 2b). The results described a mass of mucoid neoplasm filling the subarachnoid space and overlying the cerebral

cortex without evidence of significant brain invasion or infiltration. The final pathologic diagnosis was a tumor of neurocytic differentiation not classified as a recognizable entity. The subarachnoid space was massively expanded by mucoid fluid (Alcian blue-positive) containing loosely cohesive small round tumor cells with relatively uniform round nuclei and sparse cytoplasm. Some tumor cells had visible cytoplasm containing small vacuoles, which extended into short coarse processes, while other cells showed a clear perinuclear halo. Few mitotic figures were seen, and no areas of necrosis, calcification, solid cellular tumor, formed chondroid matrix, or pleomorphism were appreciated.

The tumor cells were found to be immunoreactive for S-100 (Fig. 3a), CD 57 (leu 7) (Fig. 3b), synaptophysin (Fig. 3c), and neuron-specific enolase (Fig. 3d). They were unstained for glial fibrillary acidic protein (GFAP), phosphorylated neurofilament protein, chromogranin, VEGF, EGFR, EMA, vimentin, CD68, CD45, keratin-C, cytokeratins AE1/AE3, myogenin, desmin, CD 99 (Ewing sarcoma antigen), and oil red O. The tumor showed focal microvascular proliferation in subarachnoid vessels but lacked frank anaplastic features such as pleomorphism or evidence of necrosis. Ki-67 labeled only occasional nuclei, estimated at only 1–2%. FISH analysis was performed and sent for outside consultation. The patient was shown to have loss of both 1p (1q25 and 1p36 probes, showing deletion of 1p36) and 19q (19q13 and 19p13 probes showing deletion of 19q13) markers. Postoperatively, the patient remained paraplegic. Chemotherapy was initiated with vincristine and carboplatin along with 20 cycles of radiotherapy. After 10 months, treatment with temozolamide was initiated. He showed good initial clinical response and remains alive 16 months after diagnosis



**Fig. 2** **a** T1-weighted axial MRI scan of the brain with contrast revealing extensive intense leptomeningeal thickening and nodular enhancement along the basal cisterns in the posterior fossa including the suprasellar, prepontine, ambient, and cerebellopontine angle

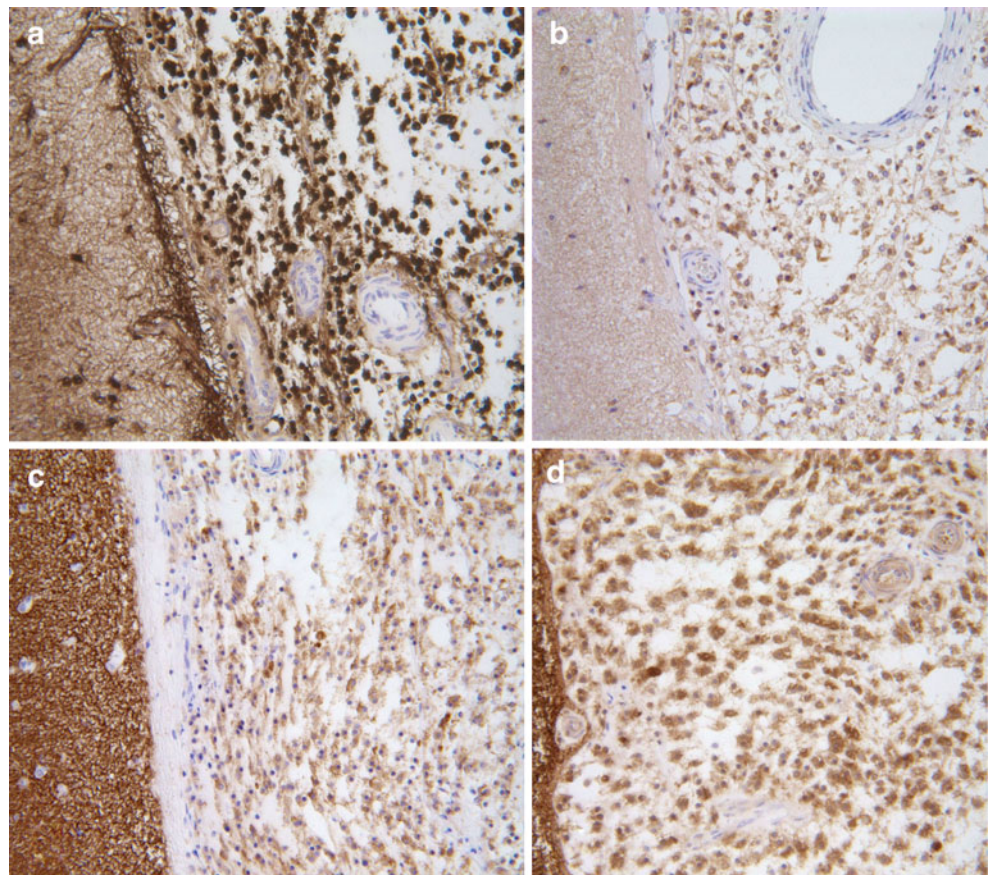
cisterns and encasement of the circle of Willis. **b** T1-weighted axial MRI scan of the brain with contrast revealing leptomeningeal thickening and nodular enhancement along the intrahemispheric fissure and an *arrow* depicting the site of biopsy

### Discussion

The leptomeningeal dissemination of low-grade CNS tumors, such as pilocytic astrocytoma and oligodendro-

glioma, has been recognized for many decades [7, 10, 19]. While the first description of such leptomeningeal carcinomatosis was reported by Eberth et al. in 1870, the spread of such neuroepithelial tumors was not formally recognized

**Fig. 3** The tumor cells were immunoreactive for S100 (**a**) and CD57 (**b**). Additionally, they were found to be immunoreactive for synaptophysin (**c**) and NSE (**d**)





until 1926 when Bailey and Cushing proposed their classification of secondary leptomeningeal spread of medulloblastomas [3, 8]. Since that time, the dissemination of many lesions including oligodendrogliomas, medulloblastomas, glioblastomas, ependymomas, ependymoblastomas, pineal tumors, and choroids plexus tumors has been reported [4].

The natural history of a typical diffuse leptomeningeal oligodendroglial tumor has been described throughout the neurosurgical literature. Polmeteer and Kernohan reported a series of 42 patients with meningeal gliomatosis. In their series, many cases were characterized by such extensive infiltration that the leptomeninges appeared “thickened and opaque, and resembled those which are commonly in the terminal stages of chronic meningitis” [15]. Armaoa et al. reported a case wherein LMD presented with an enhancing nodule in the spinal cord and a noncontributory biopsy of fibrocellular proliferation [2]. This is not surprising, as the diagnostic yield from these biopsies is low because of regional variation in the density of neoplastic cells or focally prominent fibrosis of the leptomeninges.

Tumors that present in the leptomeningeal space without any detectable primary site are described as having primary LMD. In the case described, there was no clear visualization of an intraparenchymal primary tumor. Previous MR imaging of the brain did not show any mass lesion, leptomeningeal enhancement, or even a diffuse meningeal thickening. At presentation, the radiological picture ranged from meningeal enhancement to extensive nodular cisternal involvement. This early imaging was thought to be consistent with both carcinomatous and tuberculous meningitis. However, in this patient, sterile meningitis could have been secondary to the leak of tumor contents into the thecal space. In final assessment, it remains difficult to postulate the likely primary site of this child’s tumor. The hypothalamic and chiasmatic region has frequently been reported to be the epicenter for such tumors, particularly for low-grade astrocytomas with polymixoid characteristics. This may be the case with the tumor reported herein; however, such mixed immunohistochemical features may suggest an alternative origin. A periventricular origin common to other neurocytomas may be likely. In such case, the patient’s remote history of hydrocephalus would be consistent.

Polmeteer and Kernohan suggested that the leptomeningeal spread was affected by the neoplasm’s access to the ventricular system or subarachnoid space, its implantation potential, as well as tumor grade [15]. These factors were said to be influenced by CSF circulation, alterations of CSF flow dynamics, gravity, or trauma. Additionally, soft, friable, and adhesive tumors were thought to be more likely to spread. Bhrany et al. reported a patient with diffuse ventricular and leptomeningeal astrocytoma in whom the mechanism of spread appeared to be direct shedding of neoplastic subependymal glial cells into the ventricles due

to a focal ependymal disruption [5]. Given the proposed risk factors, the patient described above may have been markedly at risk as a result of his history of head trauma, multiple surgical interventions, and sterile meningitis.

Our understanding of dissemination in tumors of neurocytic differentiation is varied [1, 9, 17, 18]. Investigation into the origins of these lesions has shown that both the pathogenesis and cytogenetics of oligodendrogliomas and neurocytomas are likely intertwined. Since these tumors retain glial differentiation potential, they likely harbor an origin from bipotential progenitor cells of the periventricular matrix. In the mammalian brain, such potential persists throughout life and could be responsible for such varied presentation.

In 2004, Mrak et al. reported an atypical extraventricular neurocytoma with oligodendroglioma-like spread and an unusual pattern of chromosome 1p19q deletion [11]. A similar report was published by Perry et al. on four supratentorial infiltrative gliomas with oligodendroglial histology, evidence of neuronal immunophenotype, and demonstration of co-deletion on 1p19q on FISH analysis [14]. These reports, in addition to the case reported herein, support an etiology of bipotent adult neuroectodermal precursors. Such a shared genealogy of cell lines hints that oncological research should be directed at 1p loss sensitivity in non-oligodendroglial tumors as 1p LOH deletion could be a strong predictor of survival in central neurocytomas and mixed tumors.

The main pathological features of neurocytomas include: positivity for synaptophysin, MAP2, neuron-defined epitopes, the finding of elements of neuronal differentiation on electron microscopy, and the presence of neuron-associated adhesion molecules. These tumors react negatively for neurofilament protein and glial fibrillary acid protein in the majority of cases. The finding of nuclei with a slightly ganglionic appearance and clear and dense-core vesicles is, likewise, suggestive of neurocytoma. NeuN (neuronal nuclear antigen), a slightly more specific marker than enolase, can also be helpful in diagnosis. Markers selective for oligodendroglioma include GFAP and Leu-7 (a carbohydrate epitope associated with myelin). More recently, OLIG2 has been identified as a useful marker for identification of oligodendroglioma as absent or focal identification seems to argue against the diagnosis [16]. Despite the great arsenal of cellular markers, however, an appropriate classification to accommodate these ambiguous tumors is yet to be proposed. The mixed or equivocal pattern observed here is consistent with a neurocytic tumor such as central neurocytoma (synaptophysin, NSE) but contains markers (S-100, CD57) and a disseminated presentation which are associated with an oligodendroglial neoplasm.

The allelic loss of chromosome 1p serves as a marker for longer progression-free survival among those receiving radiotherapy and nitroso-urea-based chemotherapy when

compared to other oligodendrial tumors. However, while the role of genetics is well established in the treatment of oligodendrogliomas, it is less so in tumors with neurocytic characteristics [6, 12, 13]. To date, the implications of mixed immunohistological features in addition to the deletion of chromosome 1p remain unknown. Further insight could serve as an important stratification variable in future chemotherapeutic trials for these tumors.

**Acknowledgements** Special thanks to Dr. Peter Burger (Johns Hopkins Univ.) and Dr. Paul McKeever (Univ. of Michigan—Ann Arbor) for serving as neuropathology experts in the review of histologic preparations.

## References

1. Ando K, Ishikura R, Morika T, Nakao N, Matsumoto T, Arita N (2002) Central neurocytoma with craniospinal dissemination. *Magn Reson Med Sci* 1(3):179–182
2. Armaoa DM, Stonea J, Castillo M, Mitchell KM, Bouldina TW, Suzukia K (2000) Diffuse leptomeningeal oligodendrogliomatosis: radiologic/pathologic correlation. *Am J Neuroradiol* 21:1122–1126
3. Bailey P, Cushing H (1926) A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. Lippincott, Philadelphia
4. Beck DJK, Russell DS (1942) Oligodendrogliomatosis of the cerebrospinal fluid pathway. *Brain* 65:352–372
5. Bharny D, Murphy GM, Horenstein S, Silbert SW (1974) Diffuse periventricular and meningeal glioma. *Acta Neuropathol* 30(3):243–249
6. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, Silver JS, Stark PC, Macdonald DR, Ino Y, Ramsay DA, Louis DN (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 7;90(19):1473–1479
7. Cooper IS, Kernohan JW (1951) Heterotopic glial nests in the subarachnoid space; histopathologic characteristics, mode of origin and relation to meningeal gliomas. *J Neuropathol Exp Neurol* 10(1):16–29
8. Eberth CJ (1970) Zur Entwicklung des Epitheliomas dur Pia under der Lung. *Virchow's Arch* 49:51–63
9. Eng DY, DeMonte F, Ginsberg L, Fuller GN, Jaeckle K (1997) Craniospinal dissemination of central neurocytoma. Report of two cases. *J Neurosurg* 86(3):547–552
10. Horoupian DS, Lax F, Suzuki K (1979) Extracerebral leptomeningeal astrocytoma mimicking a meningioma. *Arch Pathol Lab Med* 103(13):676–679
11. Mrak RE, Yasargil MG, Mohapatra G, Earel J Jr, Louis DN (2004) Atypical neurocytoma with oligodendroglioma-like spread and an unusual pattern of chromosome 1p and 19q loss. *Hum Pathol* 35(9):1156–1159
12. Perilongo G, Gardiman M, Bisaglia L, Rigobello L, Calderone M, Battistella A, Burnelli R, Giangaspero F (2002) Spinal low-grade neoplasms with extensive leptomeningeal dissemination in children. *Childs Nerv Syst* 18(9–10):505–512, Epub 2002 Aug 17
13. Perilongo G, Garre ML, Giangaspero F (2003) Low-grade gliomas and leptomeningeal dissemination: a poorly understood phenomenon. *Childs Nerv Syst* 19(4):197–203
14. Perry A, Scheithauer BW, Macaulay RJ, Raffel C, Roth KA, Kros JM (2002) Oligodendrogliomas with neurocytic differentiation. A report of 4 cases with diagnostic and histogenetic implications. *J Neuropathol Exp Neurol* 61(11):947–955
15. Polmeteer FE, Kernohan JW (1947) Meningeal gliomatosis. A study of forty-two cases. *Arch Neurol Psychiatry* 57:593–616
16. Preusser M, Budka H, Rössler K, Hainfellner JA (2007) OLIG2 is a useful immunohistochemical marker in differential diagnosis of clear cell primary CNS neoplasms. *Histopathology* 50(3):365–370
17. Psarros TG, Mulne SD, AF BDK (2005) Neurocytoma-like neoplasm of the thoracic spine in a 15 month-old child presenting with diffuse leptomeningeal dissemination and communicating hydrocephalus. Case report. *J Neurosurg* 103(2 Suppl):184–190
18. Takao H, Nakagawa K, Ohtomo K (2003) Central neurocytoma with craniospinal dissemination. *J Neuro-oncol* 61(3):255–259
19. Wolbach S (1907) Congenital rhabdomyoma of the heart: report of a case associated with multiple nests of neuroglial tissue in the meninges of the spinal cord. *J Med Res* 16:495–519