Primary disseminated leptomeningeal oligodendroglioma with 1p deletion

Case report

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The authors report the case of a 2-year-old boy with a primary, diffuse leptomeningeal oligodendroglioma in which the deletion of chromosome arm 1p was identified by performing a fluorescence in situ hybridization (FISH) analysis. This previously healthy child initially presented with malaise, anorexia, nausea, vomiting, and macrocephaly. Imaging studies confirmed the presence of hydrocephalus, and a ventriculoperitoneal shunt was placed. The postoperative course was complicated by emesis, continued weight loss, and numerous seizurelike episodes. A contrast-enhanced magnetic resonance imaging study performed approximately 10 weeks postoperatively showed diffuse leptomeningeal thickening and enhancement without evidence of an intraparenchymal mass lesion. A right frontal lobe brain biopsy revealed a hypercellular proliferation of small oligodendroglioma-like cells, which occupied the leptomeninges diffusely and spared the underlying cortical gray matter. The tumor cells displayed prominent perinuclear clearing and had evenly spaced, uniformly round nuclei. Occasional mitotic figures were observed. Background vessels were thin and delicate, and there was no evidence of necrosis. The tumor cells showed strong immunoreactivity for S100 protein; the results of immunohistochemical staining were negative for glial fibrillary acidic protein, vimentin, epithelial membrane antigen, NeuN, and synaptophysin. The deletion of 1p was demonstrated by FISH analysis; 1q, 19p, and 19q were intact. This appears to be the first reported case of a primary diffuse leptomeningeal oligodendroglioma in which a 1p deletion was identified.

KEY WORDS • leptomeningeal glioma • oligodendroglioma • chromosome arm 1p deletion • pediatric neurosurgery

We report the case of a 2-year-old previously healthy male infant who was found to have a primary disseminated leptomeningeal oligodendroglioma; FISH analysis showed deletion of the short arm of chromosome 1. To our knowledge, this is the first reported case of a 1p deletion in this rare tumor.

Case Report

History. This previously healthy 2-year-old boy initially presented to his primary care physician with a 6-week history of ataxia, weight loss, and irritability. He was found to be macrocephalic, and the initial leading differential diagnosis was leukodystrophy. He was referred for genetics evaluation and MR imaging. The MR imaging study revealed communicating hydrocephalus.

Initial Hospitalization, Examination, and Treatment. Ten days later the patient presented to the emergency department with a 3-day history of increased irritability, vomiting, and dehydration. A computed tomography study was performed. A comparison of the scans and the earlier MR images revealed increased hydrocephalus. The child underwent urgent placement of a ventriculoperitoneal shunt, but experienced a generalized tonic–clonic seizure before the shunt placement. After the procedure, the child experienced additional seizures. An electroencephalographic study showed mild slowing of background activity, but no evidence of seizure. The child had a normal prenatal history and no family history of neurological illness, including neoplasia.

Pertinent physical examination findings at presentation to the emergency department included macrocephaly, irritability, and somnolence. Otherwise, the results of the neurological examination were nondiagnostic.

The initial analysis of the clear and colorless CSF obtained at shunt placement revealed two white blood cells/
mm³, 31 red blood/per mm³, a glucose measurement of 76 mg/dl (reference interval 60–80 mg/dl), and an elevated total protein value of 195 mg/dl (reference interval 12–40 mg/dl). No tumor cells were identified. Cultures grown to determine the presence of aerobic, anaerobic, and acid-fast bacteria were negative. The results of an India ink stain for Cryptococcus sp. and all fungal cultures were negative. Polymerase chain reaction analysis for Mycobacterium tuberculosis also yielded negative findings. The results of all subsequent CSF Gram stains and cultures were negative for microorganisms; CSF was not sent for flow cytometric analysis.

Later Examination and Biopsy. A second MR imaging study (Fig. 1) was performed with administration of a contrast agent approximately 10 weeks after the initial imaging study, and it revealed prominent leptomeningeal thickening and enhancement throughout the basal cisterns, bilateral anterior sylvian cisterns, and along the floor of the anterior cranial fossa. There was diffuse leptomeningeal thickening and enhancement encasing the infundibulum, the optic nerves, and the optic chiasm as well as within the internal auditory canals. There was also thick enhancement of the tentorium and abnormal enhancement along the brainstem surface. No intraparenchymal abnormality was identified.

An MR imaging study of the child’s spine obtained after placement of the ventriculoperitoneal shunt revealed enlargement of the patient’s cervical cord from the C-6 to the T-1 level, enhancement of the ventral thoracic cord, and thickening and enhancement of the lumbar spinal nerve roots. These findings were believed to be consistent with leptomeningeal spread of tumor or inflammation.

Because of the leptomeningeal enhancement, a biopsy procedure was considered warranted. An opaque region was identified on neuroimaging in the arachnoid mater around the gyrus rectus, and biopsy specimens were obtained from this region through a right subfrontal approach.

Histopathological Findings. Examination of sections of the biopsy specimens showed a hypercellular proliferation of small oligodendroglial-like cells that diffusely occupied the leptomeninges and spared the underlying cortical gray matter. No breach of the underlying pia mater was identified in the sampled tissue. The tumor cells showed prominent perinuclear clearing and had evenly spaced, uniformly round nuclei. Occasional mitotic figures were observed. Background vessels were thin and delicate and there was no evidence of necrosis.

The tumor cells displayed strong immunoreactivity for S100 protein (dilution 1:2000; Dako North America, Inc., Carpinteria, CA) and no immunoreactivity for glial fibrillary acidic protein (1:5600; Dako North America, Inc.), vimentin (1:200; BioGenex, Inc., San Ramon, CA), epithelial membrane antigen (1:50; Dako North America, Inc.), NeuN (1:250; Millipore Corp., Billerica, MA), and synaptophysin (1:40; Dako North America, Inc.) (Fig. 2).

Dual-color FISH assays were performed on formalin-fixed, paraffin-embedded tissues for an analysis of chromosomes 1 and 19. Commercial human probes were applied to localize 1p36 (Vysis, Inc., Downers Grove, IL), 1q25 (Vysis, Inc.), 19p13 (Vysis, Inc.), and 19q13 (Vysis, Inc.); DAPI (Insitus Biotechnologies, Albuquerque, NM) was used as a nuclear counterstain. The FISH analysis revealed deletion of 1p but showed that 19q was intact (Fig. 3).

Postoperative Course. Postoperatively the child experienced mild left hemiparesis and remained irritable. Because he continued to have difficulty obtaining adequate nutrition, a percutaneous endoscopic gastrostomy tube was placed. He was initially treated with an induction chemotherapy regimen of cisplatin, vincristine, cyclophosphamide, and etoposide, and continued to be treated with carboplatin and thiopeta until 6 months after surgery, when maintenance chemotherapy was initiated. As of this writing, the maintenance regimen, which consisted of sequential treatment with etoposide, cyclophosphamide, temozolomide, and isotretinoin, was to be continued for a total of 2 years. At the last follow-up examination, the child’s clinical condition was stable, but he had neurological deficits, including a mild left hemiparesis with 4/5 motor strength. The most recent available neuroimaging study, performed 10 months after initiation of chemotherapy, revealed a significant improvement in his intracranial disease (Fig. 4).

Discussion

The dissemination of parenchymal glial tumors into the
Leptomeningeal oligodendroglioma

Fig. 2. Photomicrographs of tumor sections. The tumor tissue (A) is clearly demarcated from underlying brain parenchyma. Monomorphic tumor cells (B) show uniform nuclei, prominent perinuclear clearing, and delicate vessels. H & E (A and B). The staining of tumor cells was negative for glial fibrillary acidic protein (C), vimentin (D), CD68 (E), epithelial membrane antigen (F), NeuN (G), and synaptophysin (H). Original magnifications × 40 (A), × 100 (G and H), and × 200 (B–F).

Fig. 3. Analysis of chromosomes 1 and 19 using dual-color FISH assays of formalin-fixed, paraffin-embedded tissues. Left: Results of FISH analysis for chromosome 1 showing 1p deletion (arrow showing one signal, rhodamine) and 1q intact (arrowhead showing two signals, fluorescein isothiocyanate). Right: Results of FISH analysis for chromosome 19 showing 19p (arrowheads showing two signals, fluorescein isothiocyanate) and 19q (arrow showing two signals, rhodamine) both intact.
leptomeninges has been recognized since the early twentieth century.2 There are also well-recognized cases, designated as either leptomeningeal gliomatosis or PLG, in which authors have reported either solitary or diffuse involvement of the leptomeninges by a glial neoplasm in the absence of a clinically detectable primary parenchymal tumor.1,6,13,15,18–20 In most reported cases of PLG, the tumors displayed astrocytic differentiation, although some tumors have exhibited the morphological characteristics of oligodendroglioma (Table 1).13,15 Perilongo and associates14 have reported a small number of pediatric spinal tumors with extensive dissemination into the leptomeninges that defy classification according to the current World Health Organization scheme.10 These tumors have been given the descriptive designation “spinal low-grade neoplasms with extensive leptomeningeal dissemination.”14,15

It is not surprising that the criteria for the diagnosis of PLG are not firmly established. This situation is due in large part to the necessity of excluding the more common diagnosis of leptomeningeal dissemination of a known parenchymal glioma. As reported by Corsten and colleagues,7 Cooper and Kernohan proposed that three criteria be met before a diagnosis of PLG could be established: 1) absence of attachment of the extramedullary tumor to the underlying parenchyma; 2) no evidence of a primary tumor within the neuraxis; and 3) the existence of a capsule around the tumor. In contrast, Chen and associates8 argue that a diagnosis can only be established after a complete neuroanatomical examination, which includes postmortem examination of the brain and spinal cord, a gross inspection of representative thin sections from the entire neuraxis, and a microscopic examination of all areas that raise the suspicion of pial disruption during gross examination. Although the authors of the majority of studies have contended that these tumors arise from heterotopic nests of glial tissue, a more recent report by Stödberg and coauthors19 raises the possibility that an infectious agent, namely the human herpes virus (subtype 6), may play a role in tumor development.

Despite the uncertainties surrounding classification and pathogenesis, there is little doubt that PLG represents a neoplastic entity. This view is supported in the present case by our finding of a 1p deletion by FISH analysis. To our knowledge, this is the first reported case in which this abnormality has been identified in a primary leptomeningeal oligodendroglioma. Although not specific for oligodendroglioma, the association of loss of 1p—especially in combination with the loss of 19q—with an oligodendroglioma phenotype and a more favorable response to therapy has been well documented in the literature.3,5,9,12,16 Recent work by Pollack and colleagues,16 however, suggests that the survival advantage within the pediatric population may not be as robust as in adults. Additional study is required to answer this question.

TABLE 1

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References


![Fig. 4. Midsagittal (left) and coronal (right) T1-weighted contrast-enhanced MR images obtained 10 months after the initiation of chemotherapy showing significant improvement in leptomeningeal enhancement (arrows).](image-url)
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