Primary Diffuse Leptomeningeal Gliomatosis in Children: A Clinical Pathologic Correlation

Francesco P. Bernardini, M.D., Juan O. Croxatto, M.D.†‡, Paolo Nozza, M.D.§, Andrea Rossi, M.D.†‡, and Paolo Capris, M.D.**

**Department of Ophthalmology, Ospedale Gaslini, Genova, Italy; †Department of Ocular Pathology, Fundación Oftalmológica Argentina Jorge Malbran, Buenos Aires, Argentina; ‡Department of Neuroradiology, Ospedale Gaslini, Genova, Italy; and §Department of Pathology, Ospedale Gaslini, Genova, Italy*

Purpose: To describe a rare case of primary diffuse leptomeningeal gliomatosis (PDLG) presenting with progressive proptosis and direct involvement of the optic nerve sheath in a child and review of the relevant literature.

Methods: Retrospective review of a single case and systematic literature review of 26 biopsy-proven cases reported in the MEDLINE-indexed English literature. A 10-year-old girl developed proptosis and progressive visual loss associated with thickening of the optic nerve sheaths and dilation of the subarachnoid spaces with multilobulated appearance of the brain meninges and thickened peripheral nerve root sheaths. Biopsy of the optic nerve sheath was diagnostic. The patient underwent chemotherapy combined with oral temozolomide and conformational radiotherapy to the brain and spine. She died 3 years after the onset of the disease. An extensive review of the published literature using the key words "primary diffuse leptomeningeal gliomatosis" and "optic nerve" confirmed the case herein reported to be the first case of primary diffuse leptomeningeal gliomatosis in which direct optic nerve infiltration was demonstrated during the course of the disease.

Results: Immunohistochemistry demonstrated expression of CD56 and glial fibrillary acidic protein, and an elevated level of Ki-67; all the other markers were negative.

Conclusions: According to a comprehensive literature review, we report the first case of PDLG that presented with bilateral proptosis and direct involvement of the optic nerve during the course of the disease. These new findings may explain an alternative mechanism of visual loss and proptosis in PDLG. We emphasize the importance of close collaboration between neurologists and ophthalmologists in all cases of visual symptoms associated with a neurologic condition. In case of optic nerve involvement, ophthalmologists could provide an easier route to achieve tissue specimen early in the course of this rare and fatal disease.

(*Ophthal Plast Reconstr Surg* 2013;29:93–97)

Primary diffuse leptomeningeal gliomatosis (PDLG) is caused by the malignant transformation of heterotopic neuroglial tissue. This disease is characterized by the proliferation of anaplastic glial cells in the meninges of the central nervous system (CNS) without evidence of parenchymal invasion.[1] It has to be differentiated from secondary diffuse gliomatosis, which represents leptomeningeal infiltration from a primary parenchymal glioma. Ophthalmic signs of PDLG at presentation are common and have been reported in at least one third of patients.[2] Ophthalmic manifestations of PDLG include optic disk edema or pallor, bilateral sixth nerve palsy associated with visual loss, and diplopia.[3–5] Neurologic symptoms of PDLG include headache, cranial nerve involvement, meningismus, and decreased mental status.[6] PDLG is a rare disease with only 26 biopsy-proven cases reported in the MEDLINE-indexed English literature, including 10 cases involving children.[2,3] Only 2 patients have been reported in the ophthalmologic literature, despite the frequent and early eye involvement in the disease.[3] The prognosis is very poor, even with treatment; in a significant percentage of cases, the correct diagnosis is established at the time of the autopsy. Differential diagnosis of PDLG includes mainly aspecific viral or tuberculous meningitis. Herein, we report the case of a 10-year-old girl affected by PDLG that presented with bilateral, asymmetric proptosis and marked thickening of the optic nerve sheaths bilaterally and proved to have PDLG. To our knowledge, this is the first case of PDLG presenting with bilateral proptosis in which a direct involvement of the optic nerve sheath is demonstrated as a working diagnosis and not on autopsy.[4–7] This study was conducted according to the principles of the Declaration of Helsinki and Institutional Review Board approval was obtained.

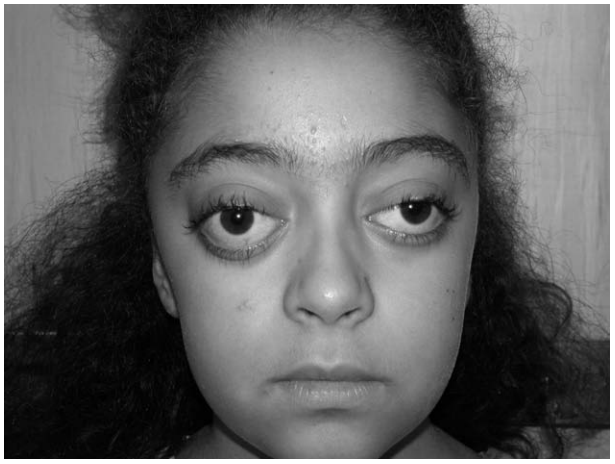

FIG. 1. Clinical appearance of the patient in primary gaze.

Accepted for publication November 2, 2012.
The authors have no financial or conflicts of interests to disclose.
Address correspondence and reprint requests to Francesco P. Bernardini, M.D., Via Cecchi 4\8, 16129 Genova, Italy. E-mail: info@oculoplastica-bernardini.it
DOI: 10.1097/IOP.0b013e318279fe23

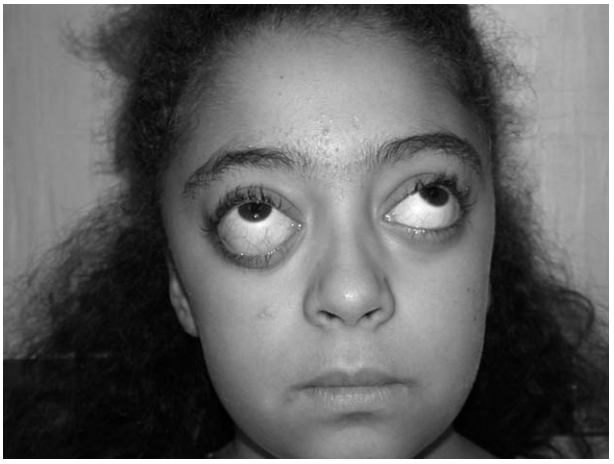

FIG. 2. Proptosis OD greater than OS.

CASE

A 10-year-old girl presented with a recent history of sudden right proptosis accompanied by decreased vision in the OS. Visual acuity was 20/150 on the OS and 20/20 on the OD. Pupil examination revealed a positive left afferent defect. The remainder of the clinical examination revealed asymmetric proptosis, inferior scleral show, and lagophthalmos worse on the right side (Fig. 1 and Fig. 2). Extraocular motility examination showed mild adduction deficit with extreme gaze diplopia on the left. Fundus examination showed normal optic disks bilaterally. Slit lamp examination and intraocular pressure were normal. Ishihara plates were 2/13 in the OS and 13/13 in the OD. A review of family photographs confirmed the presence of recent onset proptosis. Neurologic examination was normal. Medical history and family history were negative. Blood examinations for thyroid disease remained negative through the course of the illness. MRI of the orbits revealed a marked thickening of the optic nerve sheaths bilaterally with gadolinium enhancement (Fig. 3). MRI of the brain showed marked

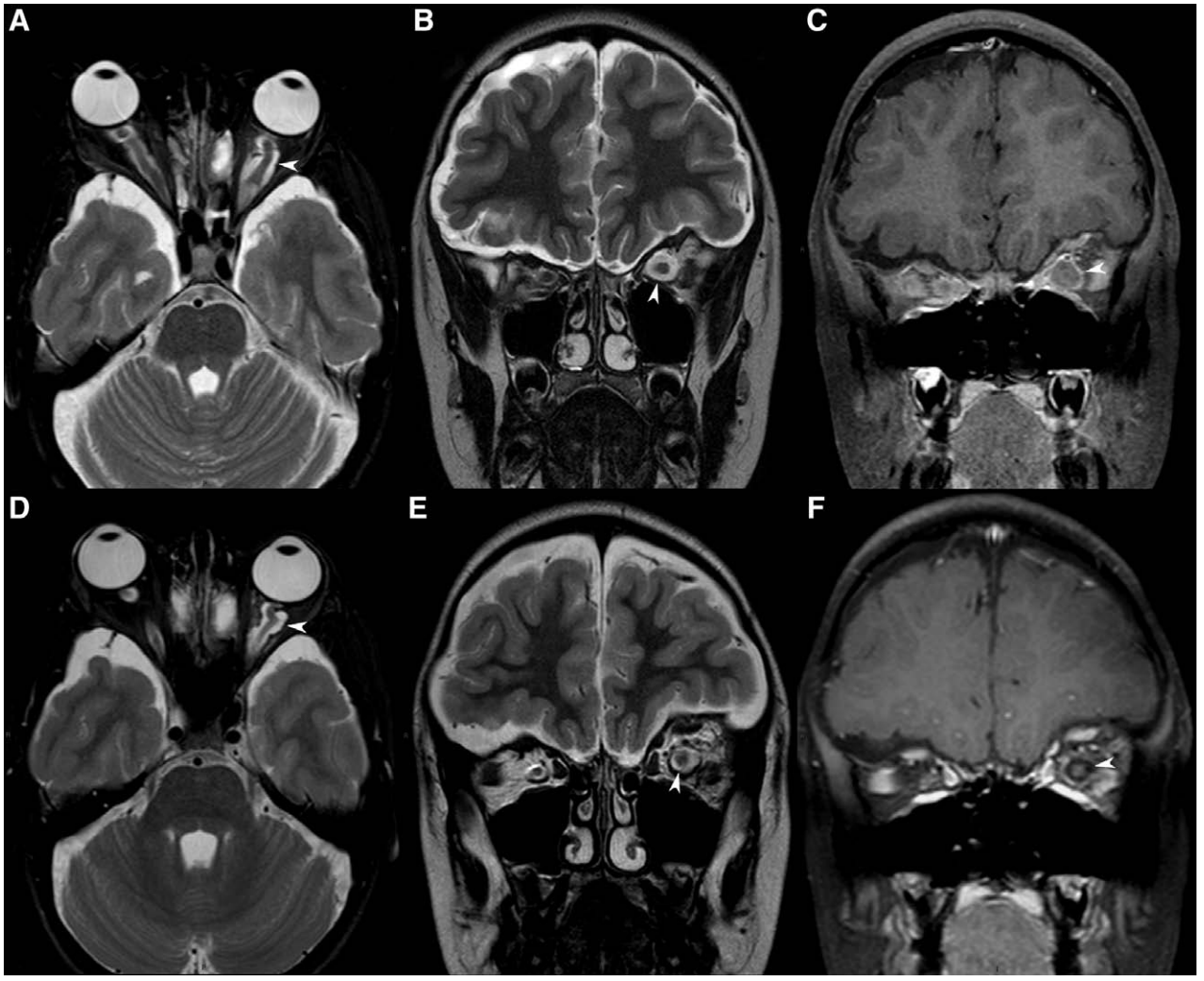

FIG. 3. **A** and **D**, Fat-suppressed axial T2-weighted MRI images show tortuous, Z-shaped left optic nerve with enlarged sheath (*arrowheads*). **B** and **E**, Coronal T2-weighted images confirm marked enlargement of the left optic nerve sheath (*arrowheads*), showing slightly hypointense signal about cerebrospinal fluid. Also notice dilated intracranial subarachnoid spaces with diffuse scalloping of the inner table of the skull. The brain parenchyma is not affected. **C** and **F**, Contrast-enhanced, fat-suppressed coronal T1-weighted images show enhancement of the left optic nerve sheath (*arrowheads*); centrally, the optic nerve fibers do not enhance.

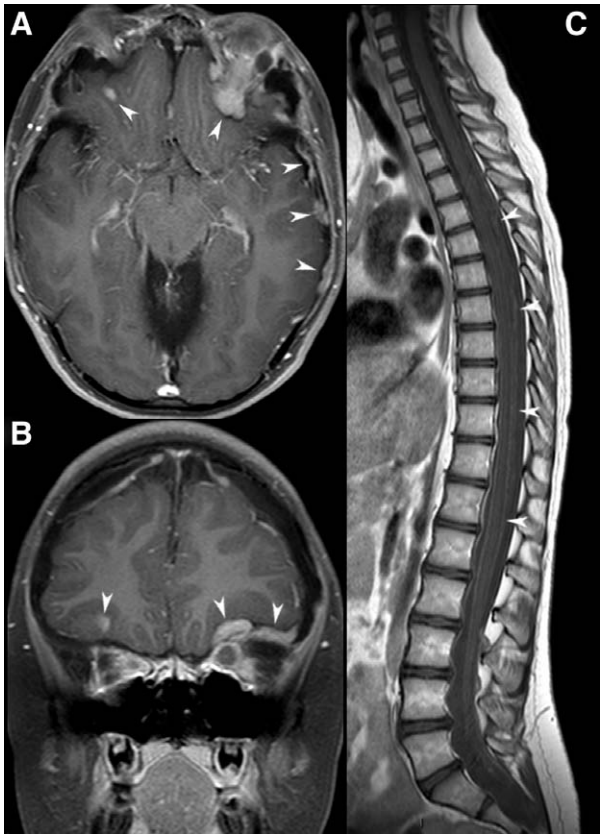

FIG. 4. Axial (**A**) and coronal (**B**) contrast-enhanced fat-suppressed T1-weighted images of the brain show diffuse enhancing pachymeningeal thickenings (*arrowheads*). **C**, Sagittal contrast-enhanced T1-weighted image of the spine shows faint meningeal enhancement (*arrowheads*) over the posterior surface of the spinal cord.

dilation of the subarachnoid spaces with multilobulated appearance in the frontopolar and temporopolar regions bilaterally. The brain parenchyma was spared. Spinal cord studies showed abnormally dilated and thickened peripheral nerve root sheaths, but the spine appeared normal (Fig. 4). Lumbar punctures showed exit pressure between 15 and 20 mm Hg during the course of the disease. Protein content in the liquor was 113 mg/dl. Lymphocytes and monocytes with atypical cells were also found in the liquor. During the following 3 weeks, visual loss on the OS progressed rapidly to count fingers, and pallor of the optic disks became visible bilaterally. Due to the rapid progression of the disease, it was elected to perform a biopsy of the left optic nerve sheath. At the time of the biopsy, the abnormal tissue around the optic nerve was believed hard, thick, and not separable from the optic nerve. No evidence of a subarachnoid space or cerebrospinal fluid was found. Histopathological examination shows connective tissue harboring an infiltrate of small cells, with oval nuclei and scant cytoplasms; no mitosis could be seen. The monoclonal antibody Ki-67-Mib1 stained several nuclei. Immunohistochemistry demonstrated a reliable expression of both CD56 and glial fibrillary acidic protein. The cells expressed neither epithelial membrane antigen nor synaptophysin. S-100 protein stained only small nerve trunks enclosed in the sample. Monoclonal antibodies CD3, CD20, CD34, CD99, cytokeratin, and desmin were negative (Fig. 5). These findings were considered consistent with primary diffuse leptomeningeal gliomatosis. During the first weeks after the biopsy, visual function dropped to NLP in the OS and showed signs of rapid worsening in the OD. The patient underwent systemic chemotherapy with carboplatin and vincristine, combined with oral temozolomide. Conformational radiotherapy to the brain and spine (3,600 Gy) and boost radiotherapy delivered to the frontal lobes of the brain, spine, and optic nerves (total 1,800 Gy), temporarily arrested the progression of the disease. Eventually, the patient died 3 years after the onset of the disease, despite maximal chemotherapy. The family did not authorize an autopsy.

DISCUSSION

While secondary leptomeningeal gliomatosis has been widely reported in the literature, the available data on primary diffuse leptomeningeal gliomatosis have been limited to case reports and 2 case series.[2,3] An extensive review of the published MEDLINE-indexed English literature using the key words "primary diffuse leptomeningeal gliomatosis" and "optic nerve" suggests that this is the first reported case of PDLG with proptosis and direct optic nerve infiltration as the initial manifestations of the disease. The prognosis of PDLG has been very poor because of the combinations of various factors, including the inability to reach the diagnosis, the extensive nature of the lesion in the CNS, and the poor response to conventional chemotherapy or radiotherapy. Mean survival time reported in the literature is less than 1 year regardless of treatment. Time between the first symptoms and death was less than 12 months, and median survival interval is 4 months in adults. The longest survival in a child was 3 years.[8] According to a recent review of 26 patients, visual symptoms or signs are present in 76% of patients at presentation and in 100% later in the course of the disease.[3] Nevertheless, according with previous publications, only 2 patients with PDLG underwent complete eye examination.[3] Exophthalmometry was not performed in any of the published articles, and the presence of proptosis may therefore have been missed or overlooked. Interestingly, the occurrence of all the ophthalmic signs and symptoms during the course of PDLG was considered secondary to cranial hypertension. A direct involvement of the optic nerve in the course of the disease has not been suspected, looked for, or described. Noval et al.[3] mentioned that visual symptoms can occur in the absence of optic nerve edema or in spite of maximal steroid therapy or immediate placement of an external cerebrospinal fluid drainage, suggesting that the optic nerve can be affected by mechanisms other than raised intracranial hypertension. MRI findings in the course of the disease have been described in all the recent articles, but none of the studies where centered on the orbits.[2,3] An analysis of the published MRI images centered on the orbital portion of the optic nerve, available in 1 case only, revealed abnormally enlarged optic nerves, mainly on the left side. The optic nerve findings suggest that the optic nerve may be directly affected more commonly than previously thought. In fact, pallor of the nerve without evidence of disk edema may reflect the direct effect on the nerve fibers in the absence of a high hydraulic pressure within its sheath. The increased size of the optic nerve sheath along its entire orbital tract may also explain the proptosis, especially considering the hardness and rigidity that was believed at the time of the biopsy. It is interesting to note how, in the left side, the optic nerve shows a tight S-shaped turn, almost a Z-shaped turn, and appears "shortened" in the tract proximal to the eye globe. A possible focal contraction of the pathologic tissue on itself may have pulled the optic nerve fibers back along their major axis, causing visual loss and preventing the eye from protruding progressively like the other less affected side. If that were the case, it would make perfect sense that the worse eye is the eye

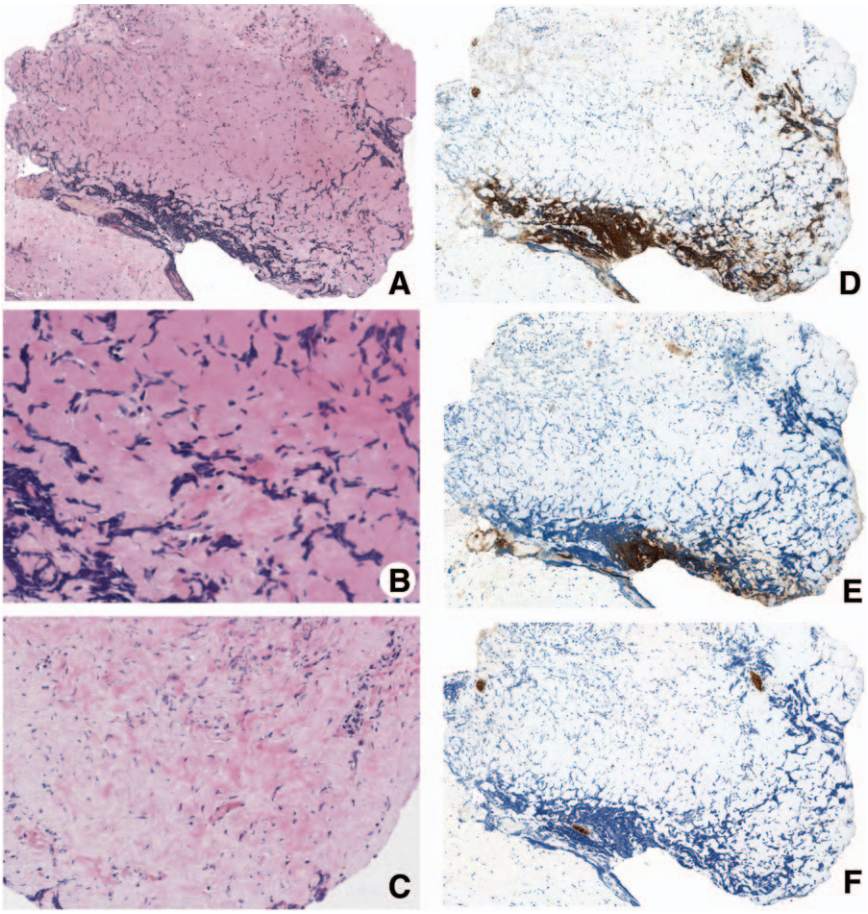

FIG. 5. Biopsy of the optic nerve. **A**, The biopsy consisted in connective tissue infiltrated by tumor cells (hematoxylin-eosin, ×40). **B** and **C**, Spindle cells infiltrate orbital soft tissue (hematoxylin-eosin, ×200). **D**, The neoplastic cells uniformly express CD56 (×40). **E**, No expression of protein S-100 is seen (×40). **F**, The neoplastic cells uniformly express glial fibrillary acidic protein (×40).

with less proptosis. Furthermore, the increased rigidity of the leptomeninges across the entire CNS may explain the elevated intracranial pressure.

Differential diagnosis of PDLG in children includes optic pathway glioma and optic nerve sheath meningioma. Optic nerve glioma is a benign pilocytic astrocytoma of childhood that may arise in any part of the optic pathway.[9] Those involving the orbit present with proptosis, ophthalmoplegia, and painless progressive visual loss. Neuroimaging with MRI scan shows intrinsic enlargement of the optic nerve with enhancing of the mass after gadolinium contrast.[10] Some pilocytic astrocytomas show thickened perineural tissue made up of arachnoidal hyperplasia admixed with neoplastic astrocytes.[9] Such perineural thickening appears to be prominent in tumors associated with neurofibromatosis Type 1.[9] Optic nerve sheath meningioma in children is rare.[11] According to Dutton[12], 4% of the patients were younger than 20 years. The most frequent clinical findings are visual loss, proptosis, chronic disk swelling, and optic atrophy. MRI shows an isointense lesion on T1-weighted images and hyperintense on T2-weighted images, with homogeneous gadolinium enhancement. Images may display a classic "tram tracking" sign. Meningiomas emanating from the orbital part of the optic nerve may cause diffuse, plaque-like thickening of the meninges.

The incidence of PDLG seems to be on the rise due to the more widespread use of contrast-enhanced MRI and an increased awareness of this disease in adults and also in children.[2,3] The presence of rapidly progressive chronic meningitis without any identifiable cause associated with visual symptoms should raise suspicion of PDLG. Diffuse leptomeningeal enhancement with no discernible intra-axial component is a pathognomonic finding on MRI. In light of our findings, it is arguable that ophthalmologists should be involved in the management of these patients from the beginning because ophthalmologists can provide a simple way to reach a diagnosis, avoiding unnecessary delays in the management of this rare disease.

In conclusion, we are aware that, based on a retrospective single case, we can only offer a hypothesis that needs to be proved by larger case series. Finally, because the diagnosis of PDLG is based on a biopsy, the optic nerve sheath may serve, when evidence of optic nerve involvement is proven on MRI, as a more accessible route to provide tissue sampling, with reduced morbidity compared with a neurosurgical approach.[3]

REFERENCES

1. Debono B, Derrey S, Rabehenoina C, et al. Primary diffuse multinodular leptomeningeal gliomatosis: case report and review of the literature. *Surg Neurol* 2006;65:273–82; discussion 282.
2. Jicha GA, Glantz J, Clarke MJ, et al. Primary diffuse leptomeningeal gliomatosis. *Eur Neurol* 2009;62:16–22.
3. Noval S, Ortiz-Pérez S, Sánchez-Dalmau BF, et al. Neuro-ophthalmological features of primary diffuse leptomeningeal gliomatosis. *J Neuroophthalmol* 2011;31:299–305.

4. Baborie A, Dunn EM, Bridges LR, et al. Primary diffuse leptomeningeal gliomatosis predominantly affecting the spinal cord: case report and review of the literature. *J Neurol Neurosurg Psychiatr* 2001;70:256–8.
5. Ruiz-Ares G, Collantes-Bellido E, Rodriguez de Rivera F, et al. Primary diffuse leptomeningeal gliomatosis mimicking meningeal tuberculosis. *Neurologist* 2011;17:160–3.
6. Yomo S, Tada T, Hirayama S, et al. A case report and review of the literature. *J Neurooncol* 2007;81:209–16.
7. Olivera-Leal IR, Gómez-Viera N, Gónzalez-Espinosa L, et al. [Primary diffuse leptomeningeal gliomatosis. Presentation of one case]. *Rev Neurol* 1997;25:1419–21.
8. Paulino AC, Thomas C, Slomiany DJ, et al. Diffuse malignant leptomeningeal gliomatosis in a child: a case report and review of the literature. *Am J Clin Oncol* 1999;22:243–6.
9. Font RL, Croxatto JO, Rao NS. *Tumors of the eye and ocular adnexa.* Washington, DC: American Registry of Pathology, 2006:135–45.
10. Karcioglu ZA. *Orbital tumors*. New York, NY: Springer Science-Business Media Inc, 2004:66–70.
11. Harold Lee HB, Garrity JA, Cameron JD, et al. Primary optic nerve sheath meningioma in children. *Surv Ophthalmol* 2008;53: 543–58.
12. Dutton JJ. Optic nerve sheath meningiomas. *Surv Ophthalmol* 1992;37:167–83.

