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Metastatic unilateral retinoblastoma to the contralateral orbital optic nerve presenting with optic disc edema

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ABSTRACT

Retinoblastoma (Rb) is a malignant eye tumor that poses a significant risk of mortality once metastasized. We present the case of a 30-month-old girl with left-sided Rb who underwent primary enucleation with pathology-confirmed diagnosis without high-risk pathologic features. Therefore she did not receive adjuvant chemotherapy. Six months later, the patient developed skull bone and bone marrow metastasis, which were treated with systemic chemotherapy, excision of bone metastasis, focal radiation treatment to the site of osseous metastasis, and bone marrow transplantation. Follow-up for two years was unremarkable until she presented with vision loss in the remaining contralateral eye. Ophthalmic examination revealed severe optic disc edema without intraocular masses, initially thought to be optic neuritis. However, the patient did not respond to steroids, and the initial cerebrospinal fluid (CSF) analysis was negative. This was repeated based on high clinical suspicion of metastasis, revealing only a few malignant cells. The presentation and appearance of the optic nerve were considered metastasis-related and treated with radiation therapy, which resulted in dramatic clinical and radiological improvement. Unfortunately, a few weeks later, the patient developed lower limb weakness, and imaging showed diffuse leptomeningeal metastasis, confirmed by CSF findings. This case represents the first documented isolated contralateral optic nerve metastasis in Rb.

KEY WORDS: metastasis; optic nerve; optic neuritis; retinoblastoma

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INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular malignancy in children worldwide and the most common intraocular malignancy across all ages in Jordan. Timely diagnosis and prompt management are critical for cure in these patients [1, 2]. The primary goal of Rb treatment is to cure the patient and secondarily to preserve the globe and vision when possible, ensuring this is safe. Rb is a complicated disease treated by different management modalities, including systemic chemotherapy, intra-arterial chemotherapy, intra-vitreal chemotherapy, and focal consolidation therapy [3–10]. Previous

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studies have shown that the cause of mortality in patients with Rb is related to metastatic disease [mainly to the central nervous system (CNS) or bone marrow], subsequent malignancies (seen especially in hereditary Rb survivors who received radiotherapy), and other non-tumor cause-specific mortality, including infections, endocrine and metabolic diseases, neurological diseases, circulatory diseases, and others [11–15].

Rb represents less than 4 % of all childhood malignancies. Rb incidence ranges from 1 in 18,000 to 30,000 live births [16]. Rb is most commonly diagnosed in the first two years of life, with the average age at diagnosis being around 18 months old [17].

Most patients present with leukocoria noticed by the caregiver. Other less common presentations include reduced vision, red uveitis like eye, buphthalmos, or proptosis.

Rb can be unilateral or bilateral, with bilateral disease most likely being hereditary.

In developed countries, Rb survival rates reach up to around 95% [18].

It is advised that patients with retinoblastoma be treated in a specialized center with general agreement that patients should be evaluated routinely, with 6 monthly ophthalmology exams, orbit, brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and bone marrow biopsies [18]. Further relevant investigations according to the clinical presentation are recommended as well.

Herein, we present an unusual metastatic retinoblastoma to the intra-orbital optic nerve of the contralateral normal eye in a patient with unilateral retinoblastoma.

CASE PRESENTATION

A 30-month-old female child presented in April 2016 with left leukocoria. The patient and her family were residing outside Jordan at that time, where she underwent examination under anesthesia showing total exudative retinal detachment, with a brain orbit MRI study showing a large left-sided intraocular mass, showing a hypointense signal on T2 weighted sequence with intermediate T1 signal intensity, mild post-contrast enhancement with retinal detachment (Fig. 1A) correlating with retinoblastoma, group D according to the International intraocular retinoblastoma classification (IIRC) [19].

Brain and orbit magnetic resonance imaging (MRI) was free of any extraocular tumor extension or brain metastasis at diagnosis. She underwent primary enucleation outside Jordan. The pathology report of the enucleated eye confirmed the clinical diagnosis of Rb with no high-risk pathological fea-

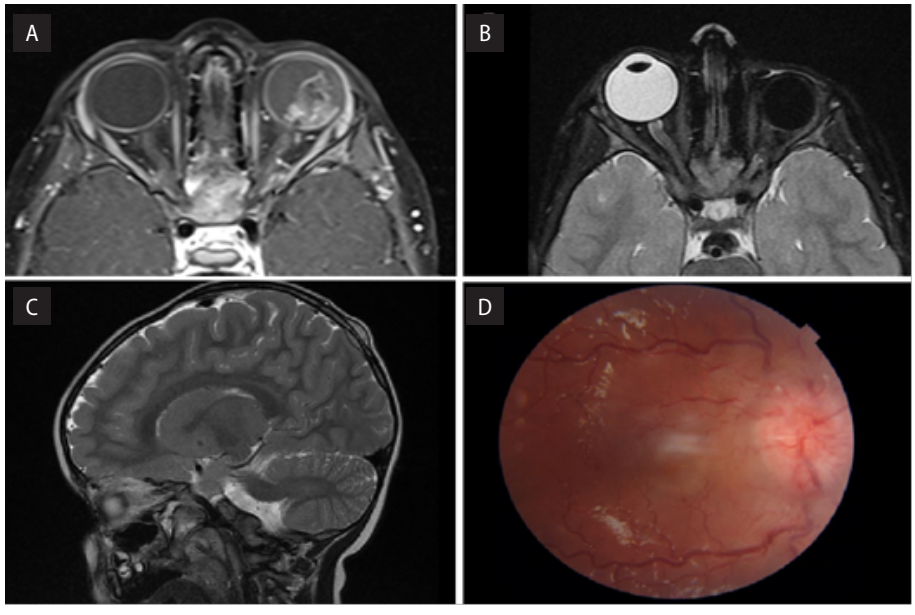

FIGURE 1. A. Axial orbit magnetic resonance imaging (MRI) fat saturated post intravenous (*i.v.*) contrast image. Contrast enhancing left intraocular mass, in keeping with known retinoblastoma. The left optic nerve appears normal; **B.** Axial orbit MRI STIR sequence post enucleation and implant insertion. The stump of the left optic nerve appears normal, and the right orbit and right optic nerve are normal; **C.** Sagittal brain MRI T2 weighted image shows a calvarial osseous lesion with extraosseous accompanying soft tissue; **D.** Right fundoscopy image shows right optic disc swelling

tures i.e., there was no evidence of choroid invasion, optic nerve invasion, ciliary body invasion, or extra scleral extension. A month after enucleation, the patient and her family returned to Jordan, and her parents opted to consult the ocular oncology team at King Hussein cancer center (KHCC).

At KHCC, the patient underwent examination under anesthesia for the contralateral right orbit, which was normal. Paraffin blocks were not available for review by the pathologists at KHCC.

Orbit and brain MRI was repeated, with no evidence of left orbital tumor, CNS disease, and a normal right eye. Prosthesis fitting was provided (Fig. 1B). No adjuvant chemotherapy was offered. Six months later, the patient presented to KHCC with a lesion in the right contralateral parietal bone (Fig. 1C). MRI confirmed the presence of a right parietal osseous mass with accompanying soft tissue. No orbital recurrence, no contralateral orbital masses, or brain metastasis was seen. The osseous lesion was excised at KHCC, and pathology confirmed Rb metastasis.

The CSF biopsy was negative at that time; however, bilateral bone marrow biopsy showed metastatic disease, with 80–90% of tumor cells positive for synaptophysin and chromogranin. Subsequently, the slides and paraffin blocks of the left enucleated eye became available. A pathology review at KHCC

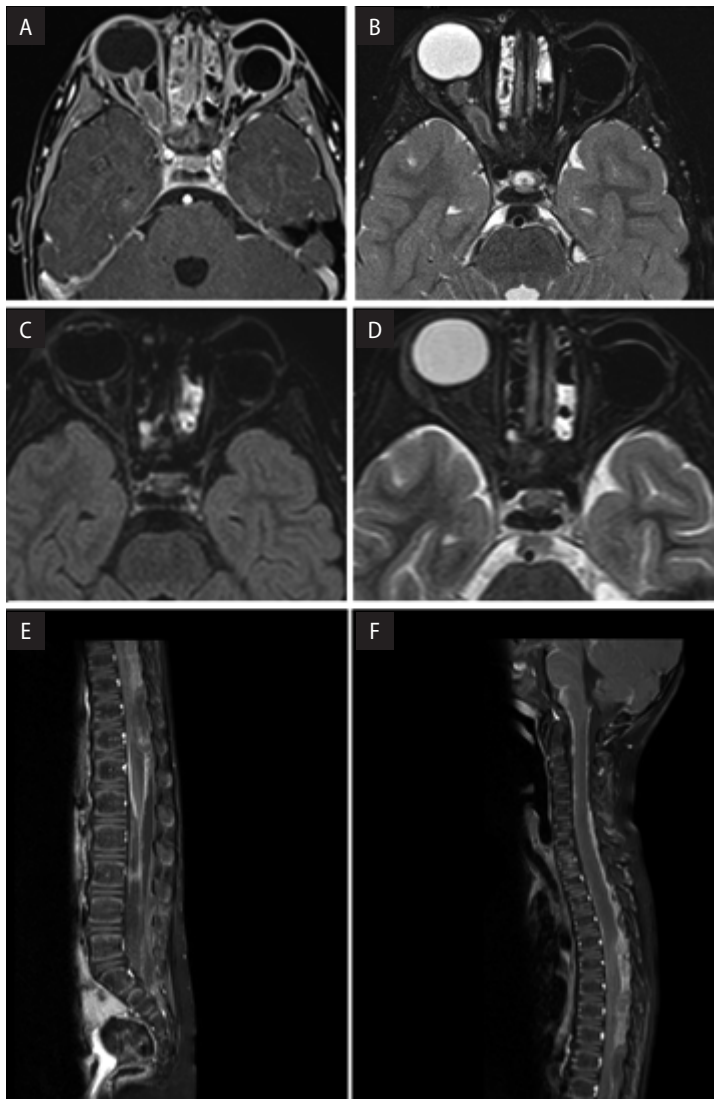

FIGURE 2. A. Axial orbit magnetic resonance imaging (MRI) T1-weighted fat saturated post intravenous (*i.v.*) contrast; **B.** Axial orbit MRI STIR sequence showing thickening and contrast enhancement of the right intraorbital optic nerve; **C.** Axial FLAIR sequence showing both orbits; **D.** Axial STIR of both orbits showing resolution in the previously seen thickening and contrast enhancement of the right intraorbital optic nerve; **E.F.** Sagittal fat saturated TI-weighted post *i.v.* contrast images of the spine, showing diffuse leptomeningeal contrast enhancement, in keeping with leptomeningeal metastasis

confirmed the diagnosis. The focal choroidal invasion was identified, with a single focus less than 3 mm, without any other pathological high-risk features.

The patient received 4 cycles of systemic chemotherapy (cisplatin, cyclophosphamide, etoposide), as per extra-ocular Rb protocol, which was completed in Jan 2017. She underwent an autologous bone marrow transplant (BMT) almost 10 months after enucleation in March 2017. This was followed by external beam radiation therapy (EBRT) to skull metastasis (EBRT as 25 Gy/10 fx to the pre-surgical volume) in May 2017.

The patient was kept on follow-up with routine clinical, ophthalmology examination under anesthesia, brain/orbit MRI and CSF and bone marrow biopsies every 6 months.

The patient was free of metastatic disease for almost 2 years. In April 2019, a month after the last free orbit and brain MRI, nearly one year after the BMT, three years after the initial diagnosis, the patient complained of a vision drop in the right eye from 20/20 to 20/50. Clinical examination showed right optic disk swelling (Fig. 1D) with no intraocular tumors. MRI showed diffuse thickening and contrast enhancement of the right intraorbital optic nerve in the previously normal eye (Fig. 2A, B). CSF biopsy did not show evidence of metastasis. The provisional clinical diagnosis was optic neuritis, given MRI findings and rapid vision loss. The patient was treated by intravenous pulse steroids for 3 days, 30 mg/kg. The visual acuity improved from 20/50 to 20/20. The patient was shifted to oral steroids. Unfortunately, 3 days after the oral steroids, her visual acuity dropped to counting fingers at 1 meter, without improvement in the severity of the optic disc edema.

The repeated MRI was stable as well.

The multidisciplinary ocular oncology team decided to consider the optic nerve enlargement as metastatic disease to the optic nerve. A repeat CSF biopsy was performed and showed only a few malignant cells. Chemoreduction with vincristine, carboplatin, and etoposide was initiated, but etoposide was unfortunately stopped due to an allergic reaction. This was followed by EBRT to the eye globe to save vision (EBRT as 20 Gy/10 fx). She showed a marked radiological response (Fig. 2CD), complete resolution of the optic disc edema, and improved visual acuity to 20/100.

Unfortunately, a few weeks later, she presented with lower limb weakness, as she could not walk. A whole spine MRI showed extensive diffuse leptomeningeal enhancement correlating with diffuse leptomeningeal metastasis (Fig. 2EF), and the CSF examination confirmed the diagnosis of CNS metastatic Rb. The patient passed away a few weeks later, and no autopsy was performed.

DISCUSSION

Metastasis and extraocular spread are seen in up to 5% of Rb cases in the developed world.

Jubran et al. [20] suggested four patterns of extraocular disease, including metastasis to the central nervous, regional metastasis, and distant metastasis, in addition to trilateral retinoblastoma. The central nervous system is the most common site of metastasis [21].

Bone marrow metastasis is also common. Extraocular or metastatic retinoblastoma has a poor prognosis [17].

A few reported cases of retinoblastoma metastasizing to unusual sites such as the parotid gland [17] or long bone [18]. Mohan et al. reported a case of retinoblastoma metastasizing to the contralateral bony orbit involving the maxillary sinus with orbital floor involvement [22].

To the best of our knowledge, no prior case of Rb with isolated metastasis to the contralateral optic nerve has been reported in the literature.

In the adult population, optic nerve metastasis can be seen in breast and lung cancer [23].

In pediatrics, optic nerve metastasis is rare, with only a few reported cases.

Kim et al. reported isolated optic nerve infiltration in a girl with prior history of non-Hodgkin's lymphoma [24].

Garrity et al., reported a case of posterior fossa medulloblastoma with biopsy-proven metastasis to the optic nerve 28 months after surgery, chemotherapy, and craniospinal irradiation [25]. Hurtle et al., reported a pineoblastoma metastasizing to the optic nerve in a 10-year-old girl two years after primary cancer treatment [26].

Tumors arising from the optic nerve itself are uncommon. Optic nerve glioma, which causes fusiform thickening of the optic nerve, is the most common primary tumor of the optic nerve, which may or may not show contrast enchantment and is commonly associated with neurofibromatosis type 1 (optic pathway gliomas) [27]. Optic nerve meningioma usually extends from intracranial meningioma through the optic canal [27]. Optic nerve sheath meningioma is a different entity, with only

2–4% reported in pediatric patients [28]. Both conditions, optic nerve glioma and meningioma, have indolent clinical course.

Patients with hematolymphoid malignancies, including lymphoma and leukemia, may have orbital and/or optic nerve infiltration. The confirmed diagnosis, proper lab investigations, CSF, and bone marrow biopsies are important clues to the diagnosis. MRI offers helpful diagnostic features showing hypointense T2 signal and diffusion restriction with the hypointense signal on the apparent diffusion coefficient map (ADC map).

Non-tumoural lesions of the optic nerve include inflammatory causes such as optic neuritis.

The appearance of the right optic nerve in our patient was presumed to be inflammatory, representing optic neuritis, given rapid vision loss and MRI appearance.

Optic neuritis is uncommon in pediatrics, usually linked to viral illness or vaccination [29].

It presents with rapid vision loss, which tends to be more severe than in adulthood, pain during eye movement, and the appearance of the optic nerve head on ophthalmoscopy.

Treatment is usually indicated in bilateral cases with severe loss of visual acuity. Unilateral cases and less severe cases can be observed and followed up [30]. Brain MRI in patients with optic neuritis is advised in the first 2 weeks to assess for the possible manifestation of multiple sclerosis [29]. Re-assessment of any atypical or irresponsive cases is mandatory [31].

Optic neuritis is expected to respond to steroid treatment, with faster recovery in patients undergoing IV steroids; however, no such studies in the pediatric population are available [32].

Our patient's lack of response to treatment was worrisome, and the metastatic process was considered based on clinical suspicion. A repeat CSF analysis is recommended to increase sensitivity [33]. In our patient's case, the repeat CSF showed only a few malignant cells. Recent data from China shows that retinoblastoma with CNS metastasis carries a poor prognosis with a median survival of 6 months [33]. Although advances in the management of retinoblastoma treatment have improved the overall prognosis in children with the disease, metastatic disease is still seen, particularly in developing countries. A high index of suspicion for metastasis, especially in developing countries, should be kept in mind. Patients presenting with a new complaint should be thoroughly investigated.

CONCLUSION

Retinoblastoma metastasis to the contralateral optic nerve has not been previously reported. Patients with retinoblastoma presenting with new symptoms should be investigated thoroughly. Unusual metastasis of retinoblastoma can be seen with increased patient survival. A negative CSF analysis does not rule out CNS metastasis; repeat CSF is advised if high clinical suspicion exists.

Conflict of interest

None declared.

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REFERENCES

1. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. Nat Rev Dis Primers. 2015; 1: 15021, doi: 10.1038/nrdp.2015.21, indexed in Pubmed: 27189421.
2. Yousef YA, Mohammad M, Al-Nawaiseh I, et al. Retinoblastoma and uveal melanoma in Jordan: incidence, demographics, and survival (2011-2020). Ophthalmic Genet. 2023; 44(2): 119–126, doi: 10.1080/13816810.2022.2090008, indexed in Pubmed: 35848346.
3. Dimaras H, Kimani K, Dimba EAO, et al. Retinoblastoma. Lancet. 2012; 379(9824): 1436–1446, doi: 10.1016/S0140-6736(11)61137-9, indexed in Pubmed: 22414599.
4. Friedman DL, Himelstein B, Shields CL, et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol. 2000; 18(1): 12–17, doi: 10.1200/JCO.2000.18.1.12, indexed in Pubmed: 10623688.
5. Yousef YA, Al-Nawaiseh I, Mehyar M, et al. How Telemedicine and Centralized Care Changed the Natural History of Retinoblastoma in a Developing Country: Analysis of 478 Patients. Ophthalmology. 2021; 128(1): 130–137, doi: 10.1016/j.ophtha.2020.07.026, indexed in Pubmed: 32682835.
6. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020; 68(11): 2356–2365, doi: 10.4103/ijo.IJO_721_20, indexed in Pubmed: 33120616.
7. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol. 2002; 133(5): 657–664, doi: 10.1016/s0002-9394(02)-01348-x, indexed in Pubmed: 11992863.
8. Yousef YA, Noureldin AM, Sultan I, et al. Intravitreal Melphalan Chemotherapy for Vitreous Seeds in Retinoblastoma. J Ophthalmol. 2020; 2020: 8628525, doi: 10.1155/2020/8628525, indexed in Pubmed: 32047663.
9. Hamel P, Heon E, Gallie BL, et al. Focal therapy in the management of retinoblastoma: when to start and when to stop. J AAPOS. 2000; 4(6): 334–337, doi: 10.1067/mpa.2000.107902, indexed in Pubmed: 11124666.
10. Abramson DH, Marr BP, Francis JH. Intra-arterial Chemotherapy for Retinoblastoma. JAMA Ophthalmol. 2016; 134(10): 1202, doi: 10.1001/jamaophthalmol.2016.2714, indexed in Pubmed: 27533893.
11. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. J Natl Cancer Inst. 2009; 101(8): 581–591, doi: 10.1093/jnci/djp046, indexed in Pubmed: 19351917.
12. Wong JR, Morton LM, Tucker MA, et al. Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. J Clin Oncol. 2014;

32(29): 3284–3290, doi: 10.1200/JCO.2013.54.7844, indexed in Pubmed: 25185089.
13. Kleinerman RA, Tucker B, Sigel BS, et al. Patterns of cause-specific mortality among 2053 survivors of retinoblastoma, 1914–2016, J National Cancer Inst. 2019; 111(9): 961–969.
14. Abramson DH, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. Ophthalmology. 1998; 105(4): 573–9; discussion 579, doi: 10.1016/S0161-6420(98)94006-4, indexed in Pubmed: 9544627.
15. Moll AC, Imhof SM, Schouten-Van Meeteren AY, et al. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945-1997: is there an age effect on radiation-related risk? Ophthalmology. 2001; 108(6): 1109–1114, doi: 10.1016/s0161-6420(01)00562-0, indexed in Pubmed: 11382638.
16. Wang P, Li YJ, Zhang SB, et al. Metastatic retinoblastoma of the parotid and submandibular glands: a rare case report. BMC Ophthalmol. 2017; 17(1): 229, doi: 10.1186/s12886-017-0627-8, indexed in Pubmed: 29197363.
17. Purkayastha A, Sharma N, Pathak A, et al. An extremely rare case of metastatic retinoblastoma of parotids presenting as a massive swelling in a child. Transl Pediatr. 2016; 5(2): 90–94, doi: 10.21037/tp.2016.02.01, indexed in Pubmed: 27186527.
18. Sheth J, Soman M, Iqbal S, et al. A rare case of bilateral retinoblastoma metastasizing into the forearm. Ind J Ophthalmol. 2022; 2(1): 170, doi: 10.4103/ijo.ijo_658_21.
19. Fabian ID, Reddy A, Sagoo MS. Classification and staging of retinoblastoma. Community Eye Health. 2018; 31(101): 11–13, indexed in Pubmed: 29915461.
20. Jubran RF, Erdreich-Epstein A, Butturini A, et al. Approaches to treatment for extraocular retinoblastoma: Children's Hospital Los Angeles experience. J Pediatr Hematol Oncol. 2004; 26(1): 31–34, doi: 10.1097/00043426-200401000-00011, indexed in Pubmed: 14707710.
21. Leal-Leal CA, Rivera-Luna R, Flores-Rojo M, et al. Survival in extra-orbital metastatic retinoblastoma:treatment results. Clin Transl Oncol. 2006; 8(1): 39–44, doi: 10.1007/s12094-006-0093-x, indexed in Pubmed: 16632438.
22. Mohan K, Gupta A, Saini JS, et al. Retinoblastoma metastatic to the contralateral orbit. Br J Ophthalmol. 1990; 74(5): 311–312, doi: 10.1136/bjo.74.5.311, indexed in Pubmed: 2354141.
23. Goldberg RA, Rootman J, Cline RA. Tumors metastatic to the orbit: a changing picture. Surv Ophthalmol. 1990; 35(1): 1–24, doi: 10.1016/0039-6257(90)90045-w, indexed in Pubmed: 2204127.
24. Kim UR, Shah AD, Arora V, et al. Isolated optic nerve infiltration in systemic lymphoma--a case report and review of literature. Ophthalmic Plast Reconstr Surg. 2010; 26(4): 291–293, doi: 10.1097/IOP.0b013e3181bd436f, indexed in Pubmed: 20523257.
25. Garrity JA, Herman DC, Dinapoli RP, et al. Isolated metastasis to optic nerve from medulloblastoma. Ophthalmology. 1989; 96(2): 207–210, doi: 10.1016/s0161-6420(89)32912-5, indexed in Pubmed: 2704540.
26. Hertle RW, Robb RM. Pinealoblastoma metastatic to the optic nerve. J Clin Neuroophthalmol. 1990; 10(2): 95–99, indexed in Pubmed: 2141866.
27. Joseph AK, Guerin JB, Eckel LJ, et al. Imaging Findings of Pediatric Orbital Masses and Tumor Mimics. Radiographics. 2022; 42(3): 880–897, doi: 10.1148/rg.210116, indexed in Pubmed: 35245105.
28. Parker RT, Ovens CA, Fraser CL, et al. Optic nerve sheath meningiomas: prevalence, impact, and management strategies. Eye Brain. 2018; 10: 85–99, doi: 10.2147/EB.S144345, indexed in Pubmed: 30498385.
29. Pérez-Cambrodí RJ, Gómez-Hurtado Cubillana A, Merino-Suárez ML, et al. Optic neuritis in pediatric population: a review in current tendencies of diagnosis and management. J Optom. 2014; 7(3): 125–130, doi: 10.1016/j.optom.2013.12.008, indexed in Pubmed: 25000867.
30. Bonhomme GR, Mitchell EB. Treatment of pediatric optic neuritis. Curr Treat Options Neurol. 2012; 14(1): 93–102, doi: 10.1007/s11940-011-0159-0, indexed in Pubmed: 22190178.
31. Hirst LW, Miller NR, Kumar AJ, et al. Medulloblastoma causing a corticosteroid-responsive optic neuropathy. Am J Ophthalmol. 1980; 89(3): 437–442, doi: 10.1016/0002-9394(80)90017-3, indexed in Pubmed: 7369303.
32. Dooley MC, Foroozan R. Optic neuritis. J Ophthalmic Vis Re. 2010; 5(3): 182–187, indexed in Pubmed: 22737354.
33. Hu H, Zhang W, Wang Y, et al. Characterization, treatment and prognosis of retinoblastoma with central nervous system metastasis. BMC Ophthalmol. 2018; 18(1): 107, doi: 10.1186/s12886-018-0772-8, indexed in Pubmed: 29685116.