symptom, followed by ipsilateral nasal obstruction (73%) and aural dysfunction (62%).[2] Cranial nerve palsies were found in 20% of patients with NPC.[2] When a cranial nerve palsy is present, the trigeminal nerve (12.5%) or abducens nerve (10.5%) are typically involved, although involvement of each cranial nerve has been reported.[2] Optic nerve involvement, with subsequent decreased VA, is a very rare presentation of NPC. There have been only 6 reports of decreased VA as the initial presenting feature of NPC, in either the primary or recurrent setting, in which only 2 of these cases presented with no light perception vision loss.[3–8] In contrast to the previously published case reports, this patient was from Hungary, an area not generally recognized as having a high incidence of NPC. This case further highlights that ophthalmic signs and symptoms may occasionally be the initial manifestation of NPC.

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Advanced unilateral retinoblastoma: a case of sparing enucleation treatment failure

Over the last few years, intra-arterial chemotherapy (IAC) has become an effective alternative for treatment of intraocular retinoblastomas (RB), allowing improved globe salvage and reducing systemic chemotherapy toxicities.[1–3] IAC may occult extraocular tumour cells and this risk represents the main criticism concerning its use.[4] We report a case of a child with unilateral heavily pretreated RB who developed a relatively small intraocular recurrence with a massive postlaminar optic nerve invasion after IAC.

A 30-month-old male was admitted for left eye (LE) leukocoria. The patient was examined under anaesthesia with clinical evaluation, indirect ophthalmoscopy, fundus photography, ultrasonography, and fluorescein angiography. The right eye was normal. A large tumour overhanging the optic disc and macula with diffuse vitreous seeding and moderate subretinal seeding was detected in LE and classified as group D (Fig. 1A), according to the International Intraocular Retinoblastoma Classification (IIRC).[5] Magnetic resonance imaging (MRI) confirmed an LE intraocular tumour without extraocular involvement. Cerebrospinal fluid cytology was negative for tumour cells, and family history was also negative. Molecular analysis of *RB1* using Next-Generation Sequencing and Multiple Ligation-dependent Probe Assay (MLPA) combined approach revealed nither point mutation nor intragenic rearrangement on blood sample.

The patient underwent 4 cycles of etoposide (300 mg/m^2) and carboplatin (560 mg/m^2), and 2 carboplatin courses combined with focal treatments (chemothermotherapy and thermotherapy). Partial response at the main posterior pole mass with incomplete remission of vitreous seeding and subretinal fluid was achieved (Fig. 1B). MRI routinely performed after intravenous chemoreduction (IVC) and focal therapies confirmed the absence of tumour involvement in optic nerve, orbit, and brain. The patient received 5 intravitreal injections of melphalan (30 µg/0.1 mL dose) every 7 to 10 days and 3 IAC administrations of melphalan (4 mg) at monthly intervals, achieving a regression of both vitreous seeding and solid tumour. Four months later, a relapse with solid tumour at posterior pole was diagnosed and the patient received 3 further IAC treatments with melphalan (4 mg) and topotecan (1 mg), achieving complete tumour response (Fig. 1C).

After 1 month, recurrent tumour localized in the papillary area was detected (Fig. 1D). MRI showed an enhancement area of 8 mm in length of the optic nerve behind the lamina cribrosa. Enucleation was performed with inclusion of the optic nerve stump as long as possible. Histopathological findings confirmed postlaminar optic nerve invasion involving the surgical cut end (Fig. 2A, B). According to the International Retinoblastoma Staging

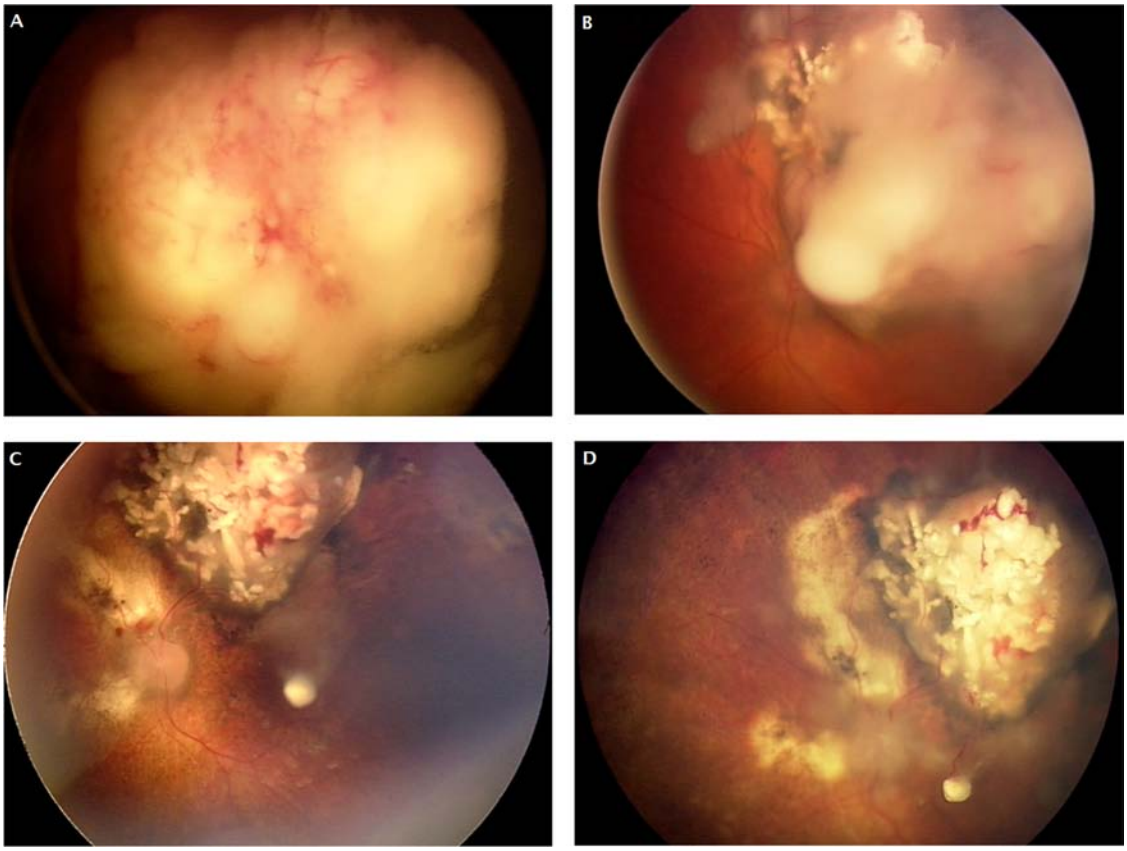

Fig. 1—Fundus appearance of the patient's left eye before and after treatment. (A) Fundus photograph showing large tumour overhanging the optic disc and macula with multiple vitreous seeds and moderate subretinal seeds on presentation. (B) Fundus photograph after 6 monthly cycles of intravenous chemoreduction combined with focal treatments. The tumour and vitreous seeds regressed, showing partial response with residual viable vitreous and subretinal seeds. (C) Fundus photograph after 5 intravitreal melphalan injections and 3 sessions of intra-arterial chemotherapy (IAC) with melphalan, followed by 3 sessions of IAC with melphalan and topotecan. Tumour showed a calcified regression with vitreous and subretinal response. (D) Fundus photograph of the relapse occurred 1 month after IAC, with melphalan and topotecan showing viable tumour in papillary area.

System,[6] the patient was classified to have stage II:N3,C0, S0 and received adjuvant chemotherapy with ifosfamide 9 g/m^2, etoposide 450 mg/m^2, and carboplatin 750 mg/m^2 for 2 courses and 2 high-dose chemotherapy cycles based on thiotepa 900 mg/m^2 followed by autologous peripheral hematopoietic stem cell rescue; local orbital radiotherapy was then performed. The patient is alive without evidence of disease 11 months from relapse.

For over a decade, IVC has been used as first-line treatment for retinoblastoma, improving ocular prognosis. Nevertheless, IVC systemic toxicities are well known as the limited efficacy in patients with advanced retinoblastoma and in cases of vitreous seeds recurrence.[2] IAC seems to be useful as primary treatment in both advanced and less advanced (groups C and D) disease, and it can also be indicated in cases of failure of standard treatments.[2,7] Melphalan is the most widely used drug, even with its combination with other agents such as topotecan, mainly in cases of extensive vitreous seeding and advanced tumour stage and as secondary treatment in case of systemic chemotherapy failure.[8] Shields et al. reported that IAC as primary therapy achieved globe salvage in 100% of group C, 100% of group D, and 33% of group E RB, whereas, when employed as secondary treatment, globe salvage was achieved in 50% of cases.[9] In case of advanced RB, the recent use of intravitreal chemotherapy combined with IAC can increase the rate of ocular salvage, providing control of vitreous seeding in up to 100% of cases.[10]

Despite excellent results in terms of globe salvage rate, IAC has some limitations. The low systemic drug exposure could potentially lead to inadequate control of micrometastases with an increased risk of dissemination.[4,11] Gobin et al. reported a 2.5% incidence of metastatic disease after IAC.[8] Eagle et al. analyzed 8 enucleated eyes after IAC and observed optic nerve invasion in 3 eyes, laminar invasion in 1 eye, and choroidal invasion in 1 eye.[12]

We report a case of advanced, unilateral RB with partial response after IVC, treated with intravitreous chemotherapy and IAC with excellent control of vitreous seeding. We decided to treat this advanced pretreated unilateral RB with IAC on the basis of reported results of up to 50% of

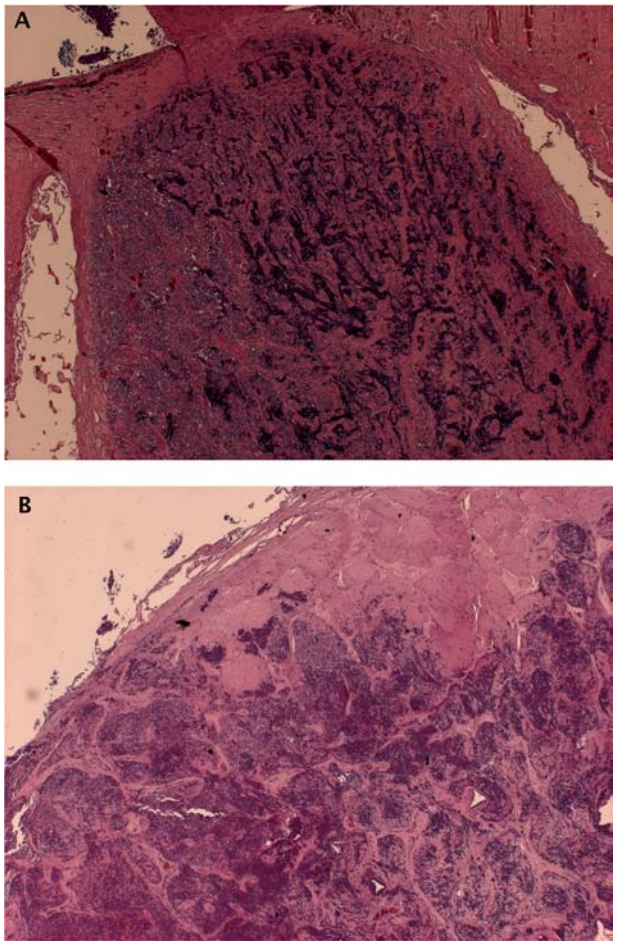

Fig. 2—Retinoblastoma of the left eye with postlaminar optic nerve invasion. (A) The histopathological specimen demonstrates postlaminar optic nerve invasion by retinoblastoma cells (haematoxylin–eosin, original magnification ×5). (B) The histopathological specimen showing invasion of the cut section of optic nerve (haematoxylin–eosin, original magnification ×5).

globe salvage in refractory/relapse RB receiving secondary IAC.[9,13] Finally, the patient showed a solid tumour recurrence after combined melphalan and topotecan IAC. The intraocular recurrence in papillary zone was not extensive but was associated with massive postlaminar optic nerve tumour involvement. The MRI, routinely performed during the follow-up, allowed us to detect the postlaminar optic nerve tumour growth, with the consequent decision to submit the patient to enucleation. It is conceivable that IAC drug concentration within the optic nerve should be lower than that in the retina and in the choroid, resulting in a less effective control of extraocular tumour cells.

According to our experience, the enucleation-sparing strategy did not represent the best choice in unilateral and advanced/relapsed retinoblastoma as in this case. Reasonably, an early enucleation treatment would have been the optimal option avoiding systemic chemotherapy and its toxicities and reducing metastatic spread risk. Furthermore, as reported by Levin et al., chemotherapy strategy masks histopathologic features and promotes extraocular dissemination by resistant cells.[14] On the basis of histopathologic findings, the patient received adjuvant systemic chemotherapy to reduce metastatic risk and increase survival chances. To avoid both tumour extent underestimation and surgery delay, we preferred to promptly perform enucleation without neoadjuvant chemotherapy. Moreover, in cases with postlaminar optic nerve involvement at MRI, enucleation, by means of a combined anterior (ophthalmological) and subfrontal (neurosurgical) approach, is recommended to minimize the risk of residual tumour at the surgical margin of the optic nerve.[15] According to our experience, in children with advanced and resistant unilateral RB, we suggest performing IAC with caution, always considering enucleation as the best strategy to prevent metastatic disease. A strict follow-up with MRI every 3 to 4 months during IAC treatment is then recommended for early detection of both local and metastatic spread.

Advanced and refractory RB management still represents a challenge. IAC is an effective therapy in terms of tumour control and globe salvage rate. However, in patients with advanced or recurrent RB, IAC needs to be used cautiously for its possible lack of metastatic disease control.

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Bilateral neovascular glaucoma in idiopathic retinal vasculitis, aneurysms, and neuroretinitis syndrome

The association of bilateral retinal macroaneurysms with retinal vasculitis and neuroretinitis was first described by Kincaid and Schatz.[1] The condition later was renamed as idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN).[2] The retinal vasculitis may result in capillary occlusion and capillary nonperfusion. This causes retinal ischemia, leading to release of vascular endothelial growth factors, and subsequently results in anterior segment neovascularization causing neovascular glaucoma (NVG). We report a case of a young girl with IRVAN who presented with neovascular sequelae of the disease. She was treated with pan-retinal photocoagulation for posterior segment ischemia and was given intracameral bevacizumab injection, which was followed by mitomycin-C-augmented trabeculectomy for NVG in both eyes.

Case Report

A 17-year-old female presented to our tertiary eye care centre with complaints of gradually progressive diminution of vision in her left eye (LE) for >3 months. She had no systemic complaints. Her best corrected visual acuity (BCVA) was 6/9 right eye (RE) and 6/60 LE. On examination, her intraocular pressure (IOP) was 18 and 40 mm Hg in RE and LE, respectively. Slit lamp biomicroscopy revealed florid neovascularization of iris (NVI) in the LE with keratic precipitates, whereas NVI was absent in the RE. On gonioscopy, fine-angle neovascularization along with presence of goniosynechiae was seen in the RE. In the LE she had total synechial angle closure (Fig. 1). Stereoscopic fundus examination with 90D lens showed temporal disc pallor in both eyes along with mild blurring of disc margins (Fig. 2). The vertical cup/disc ratio was 0.4:1 RE and approximately 0.8:1 LE. On indirect ophthalmoscopy, both eyes had multiple aneurysmal dilatations of arterioles, vascular sheathing, sclerosis of peripheral arterioles, and exudation over macula (Fig. 3a). Fluorescein angiography of both eyes confirmed the presence of aneurysms and capillary nonperfusion (CNP) areas (Fig. 3b). The arm–retinal circulation time was 8 seconds, thus ruling out circulation delay in the patient.

Systemic investigations were done. Her hemoglobin level was 11.5 mg/dL and total leucocyte count was 8500, with polymorphonuclear leucocytes being 64%, lymphocytes 34%, monocytes 2%, and eosinophils 2%. Erythrocyte segmentation rate was found to be 14 mm at 1st

Fig. 1—Goniophotograph of the left eye showing total synechial closure with keratic precipitates.

Fig. 2—Left eye disc photograph showing neuroretinitis.