

# LATE CHOROIDAL NEOVASCULAR COMPLICATIONS IN A PATIENT TREATED FOR RETINOBLASTOMA. A CASE REPORT

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*The authors of the study declare that no conflict of interests exists in the compilation, theme and subsequent publication of this professional communication, and that it is not supported by any pharmaceuticals company. The authors further declare that the study has not been submitted to any other journal or printed elsewhere, with the exception of congress abstracts and recommended procedures.*

Received: 21 September 2022

Accepted: 15 October 2022

Available online: 30 December 2022



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## SUMMARY

**Aim:** Case report of choroidal neovascularization (CNV) detection in patient who was treated for bilateral retinoblastoma in early childhood.

**Material and methods:** Patient at 1.5 years of age treated for endophytic retinoblastoma stage 4 (according to the Reese-Ellsworth classification) bilaterally, with a positive mutation in the Rb1 gene. After undergoing bilateral retinal laser treatment and 6 cycles of systemic chemotherapy, the tumor remained inactive without other complications. At the age of 14, the boy developed visual impairment in his left eye with metamorphosis. Based on a local finding and other auxiliary examinations, he was diagnosed with CNV in the macular area at the interface of the tumor scar and the healthy retina of the left eye.

**Results:** After three applications of anti-VEGF (antibodies blocking vascular endothelial growth factor) substance intravitreally (bevacizumab 1.2 mg), there was a reduction in CNV and also an improvement in visual function.

**Key words:** retinoblastoma, complications, neovascularization

Čes. a slov. Oftal., 78, 2022, No. 6, p. 320–324

## INTRODUCTION

Retinoblastoma is the most common malignant intraocular tumour in children, which is responsible for 1% of infant deaths and 5% of infant blindness [1]. The incidence of the tumour is within the range of 15 000 to 18 000 live born children [2]. It originates from embryonic retinoblasts, and the overwhelming majority of cases are manifested by the time the child reaches the age of 5 years. The most common clinical manifestation is leukocoria in 56% of cases, or strabismus in 20%. We recognise non-hereditary and hereditary form within a ratio of approximately 3:1. Hereditary incidence is present in all bilateral findings and approx. in 15% of unilateral patients, while the non-hereditary

aetiology of retinoblastomas is manifested exclusively unilaterally [1].

Within the framework of differential diagnostics, we may consider persistent hyperplastic primary vitreous (PHPV), morbus Coats, ocular form of toxocariasis, retinopathy of prematurity [3] or other lesions simulating retinoblastoma upon various types of retinal detachment [4,5]. It is manifested clinically in three different forms, namely endophytic form, upon which the tumour grows from the internal nuclear layer, spreading directly into the vitreous body; exophytic form, when the tumour grows from the outer nuclear layer and spreads subretinally; and diffuse form, when the tumour afflicts the entire retina throughout [1]. In the 1960s the Reese-Ellsworth classification was intro-

duced as an aid for determining the state of preservation of the eye in external radiotherapy, which has 5 stages [6]. With the introduction of general chemotherapy in the treatment of retinoblastoma, the International Intraocular Retinoblastoma Classification (IIRC) was adopted. The IIRC schema divides tumours into groups from A to E, depending on their size, location and other characteristics, including the presence of dissemination of retinoblastoma in the vitreous body or retinal detachment [7].

The aim of treatment is to cure the disease, but also to preserve sight. An individual approach is applied in the selection of the therapeutic procedures, with reference to clinical aspects such as the age of the patient at the time of manifestation, the size, localisation and staging of the tumour, uni- or bilateral incidence and heredity (mutation in Rb1 gene). Thanks to general chemotherapy (vincristine, etoposide, carboplatin), transscleral brachytherapy, laser photocoagulation, cryotherapy, thermotherapy and intravitreal chemotherapy, it is possible to cure the majority of patients permanently. We proceed to enucleation in more severe cases, when there is no longer any chance of preserving sight, and there is presence of neovascular glaucoma, intravitreal dissemination or uncontrolled growth of the tumour. At present, external radiotherapy is used less frequently in the treatment of retinoblastoma [2].

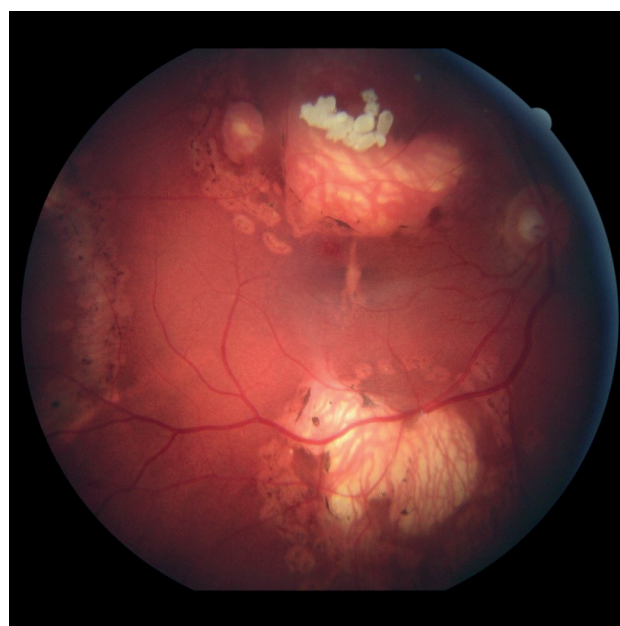
Complications of radiotherapy include secondary malignancies, craniofacial abnormalities, cataract, radiation neuropathy and retinopathy, glaucoma and necrosis of the sclera [8]. Systemic chemotherapy applied in the case of retinoblastoma has been associated with adverse side effects such as myelosuppression, subsequent infection and the need for a blood transfusion [9]. Vitreoretinal complications are not common, appearing in 6.8% of patients treated for retinoblastoma. They occur more frequently in combination of systemic or regional therapy with various local methods of treatment. This group comprises retinal cracks, rhegmatogenous and tractional retinal detachment, pre- and subretinal fibrosis, vitreous tractional streaks and pseudovitreal dissemination [10].

## CASE REPORT

A 14-year-old boy who had been treated for bilateral endophytic retinoblastoma stage 4 in childhood (according to the Reese-Ellsworth classification) was referred to the Department of Pediatric Ophthalmology at the National Institute of Children's Diseases in Bratislava in August 2019 due to acute deterioration of vision in the left eye, with presence of metamorphopsias. At the age of 16 months (March 2006) the patient had been diagnosed with bilateral retinoblastoma with positive mutation in the Rb1 gene. He underwent a cycle of general chemotherapy (vincristine, etoposide, carboplatin), and also underwent local treatment with diode laser three times in both eyes under general anaesthesia. In December 2006 the finding on the retina was without tumour activi-

ty, and monitoring of the patient at the regional hospital continued without complications until August 2019.

In August 2019 best corrected visual acuity (BCVA) in the right eye was 5/30, and in the left eye 5/15. The local fundoscopic finding was dominated by numerous scars and coralliform deposits in both eyes following the healing of tumours. A vertical fibrous streak passed through the centre of the macula in the right eye (Figure 1), and a choroidal neovascular membrane (CNV) with a size of 1/3 x 1 PD had developed on the edge of the scar adjacent to the macula (Figure 2), which we also confirmed with the aid of OCT (optical coherence tomography). We also conducted a fluoroangiographic examination (FAG), in which we recorded infiltration in the later phases in the location of CNV in the left eye (Figure 3). We subsequently decided to apply the vascular endothelial growth factor blocker bevacizumab 1.2 mg to the left eye, administered twice intravitreally at an interval of one month. After the first application there was an improvement of the patient's BCVA in the left eye to 5/7.5. Due to the onset of the COVID-19 pandemic, the patient did not report for the next scheduled follow-up examination until May 2020, after a delay of 6 months, when BCVA in the left eye was unchanged. A follow-up FAG examination was conducted, at which discrete infiltration persisted in the location of CNV. By this time it was possible also to perform OCT-angiography at our clinic (Figure 4), and subsequently bevacizumab 1.2 mg was applied for a third time to the left eye intravitreally. The follow-up FAG examinations in August and December 2020 were without signs of CNV activity (Figure 5), and BCVA in the left eye remained unchanged at 5/7.5. As of today we are continuing to monitor the patient.



**Figure 1.** Fundoscopic finding in right eye. Multiple scars and coralliform deposits following healed tumours and fibrotic streak passing through the macular region (2019)

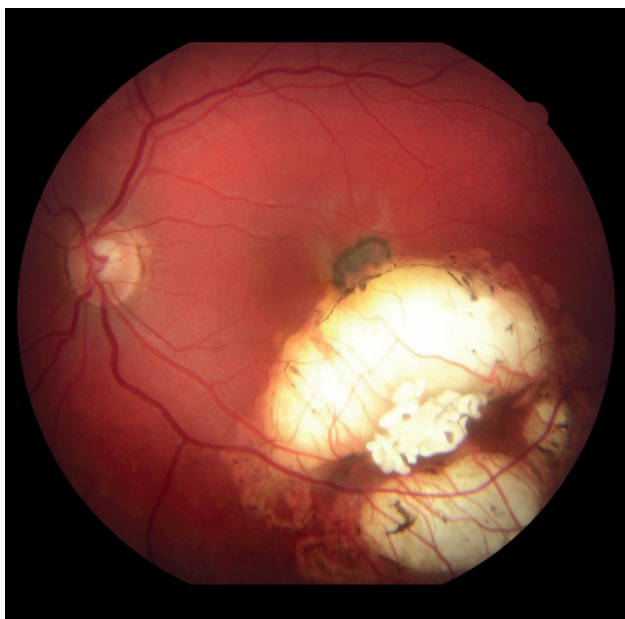
## DISCUSSION

Vitreoretinal complications following the treatment of retinoblastoma are not common, but may occur as a consequence of local and general therapy of the tumour. These include haemorrhage (vitreal, retinal and choroidal), retinal vascular occlusion, preretinal and subretinal fibrovascular proliferation, retinal cracks and folds, as well as rhegmatogenous and tractional retinal detachment [10].

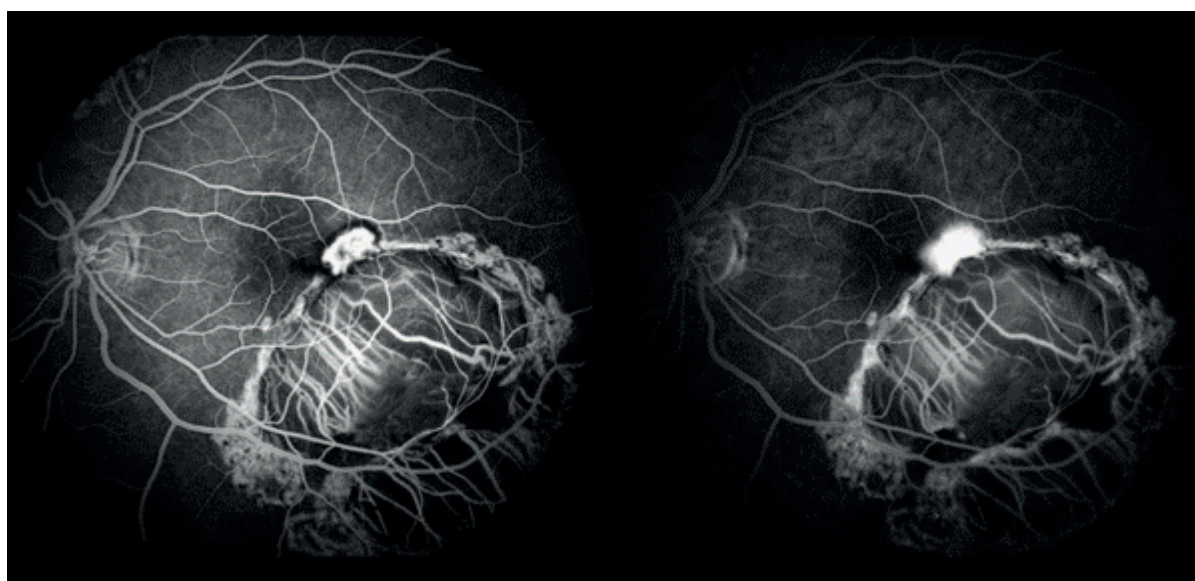
Choroidal neovascularisation (CNV) is a relatively rare condition in children and adolescents. In the majority of

cases it is caused by a different aetiology, such as infection or inflammation, upon anomalies of the optic nerve papilla, retinal dystrophies, high myopia, choroidal tumours and trauma. Often the cause is not determined, and the cases are recorded as idiopathic. Although the prevalence of blindness caused by CNV is lower in children than in adults, the consequences of blindness are more severe. Treatment of CNV incorporates photodynamic therapy (PDT), application of anti-VEGF or submacular membranectomy [11].

With the increasing trend of using anti-VEGF also on younger patients, there still remains the question of the safety and long-term results of this therapy in children and adolescents. VEGF (vascular endothelial growth factor) plays an important role in normal angiogenesis, regulation of vascular permeability and in maintaining the blood-brain and blood-retinal barriers. It is therefore necessary to continue monitoring the long-term effects of inhibition of these functions, in order to ensure that the use of this therapy is completely safe. It appears that stabilisation of CNV in children requires fewer injections of anti-VEGF substances in comparison with adults. The reason may be the better functional condition of the retinal pigment epithelium (RPE) in younger individuals than in older patients. The smaller number of applied injections may potentially reduce the risk of adverse effects of anti-VEGF substances in younger patients [12]. According to Avery et al., the use of ranibizumab instead of bevacizumab in children may reduce systemic exposure thanks to its far shorter serum half-life, as has been determined in several trials on animals [13]. In the paediatric population it is possible to consider PDT with verteporfin. A number of case studies indicate that child patients require fewer repeated therapies in comparison with adult patients in order to stabilise CNV and achieve an improvement in visual



**Figure 2.** Fundoscopic finding in left eye. Subretinal neovascularisation manifested on edge of scar in macula (2019)



**Figure 3.** Fluoroangiographic examination of left eye, early and late phase with infiltration in location of CNV (2019)



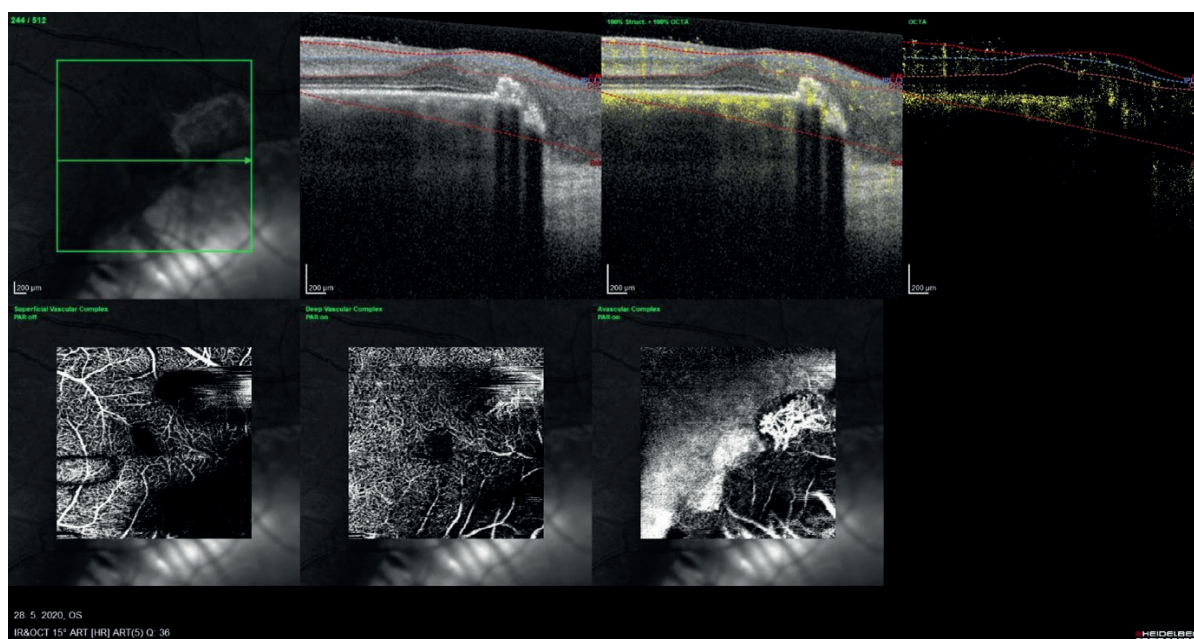
acuity. However, atrophic changes in the RPE may occur [14,15].

In our patient CNV probably developed upon a breach of the Bruch's membrane during the course of healing and therapeutic processes of the retinal tumour. With reference to the close proximity of the localisation to the fovea, in our patients we did not presume an iatrogenic breach of the Bruch's membrane by the laser which was used in local therapy. However, W. Laovirojjanakul et al. describe such a potential aetiology, especially if this concerns treatment up to a distance of 0.5 PD (papillary diameter) from the fovea, or in the case of stronger or repeated applications [16]. Our patient was treated with

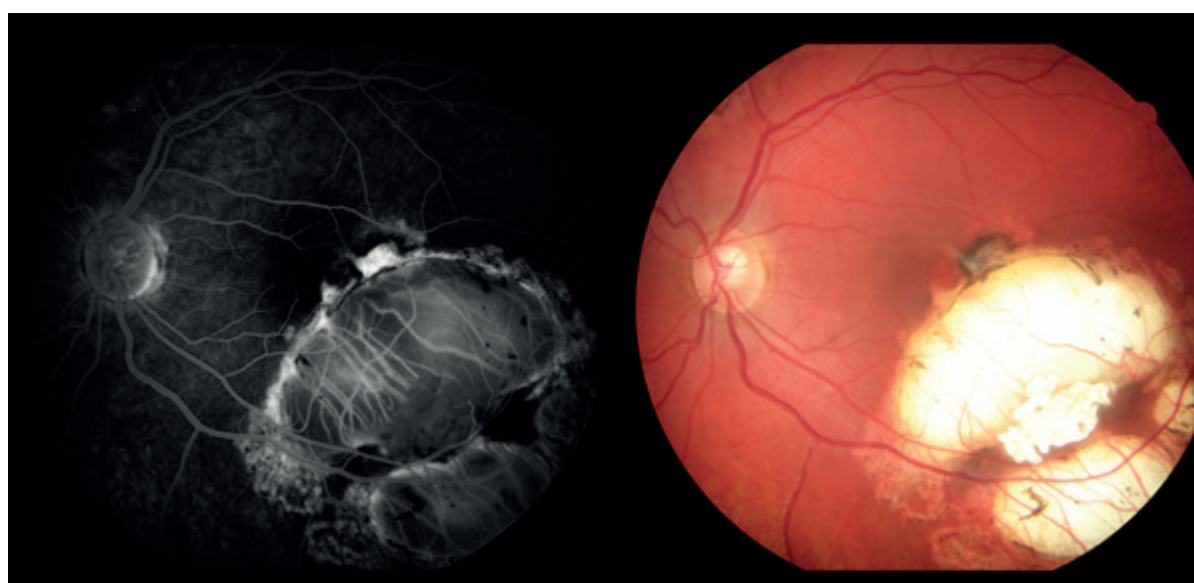
intravitreally applied bevacizumab 1.2 mg three times, without any observed adverse effects and with a good therapeutic result.

## CONCLUSION

In patients treated for retinoblastoma in childhood, several risks remain present also at a higher age, either in the sense of secondary malignancies or other ocular complications. In our case this concerned a rare complication with the development of CNV at a longer time interval following treatment, with a good reaction to intravitreal therapy using anti-VEGF.



**Figure 4.** OCT – angiography with neovascular membrane on edge of macula (2020)



**Figure 5.** Fluoroangiographic follow-up examination and photograph of ocular fundus (2020)

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