EVALUATION OF THE EFFECTIVENESS OF COMBINATION TREATMENT FOR COATS' RETINITIS

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RESUME

The aim of this study *is to evaluate the efficacy of a combined treatment modality for Coats' disease, integrating anti-angiogenic therapy with retinal laser photocoagulation.*
The presented clinical case illustrates the advantages of a combined, staged treatment approach for Coats' disease. A marked increase in exudative manifestations within the macular region and along the inferior-temporal vascular arcade, observed following the initial session of retinal laser photocoagulation (which included barrier and delimiting applications to the macula), would have precluded subsequent laser intervention without a significant risk of complications. Consequently, the administration of anti-VEGF agents as adjuvant therapy proved optimal for establishing favorable conditions for the next stage of laser photocoagulation. Given that the clinical course of Coats' disease in adult patients is frequently associated with hypercholesterolemia, performing a lipid profile and initiating appropriate corrective measures for any identified dyslipidemia is essential. This management also contributes to the reduction of cholesterol exudation. Thus, the implemented combined, staged treatment regimen in this patient resulted in the stabilization of the pathological process and the preservation of high visual acuity.
Conclusion. *Laser photocoagulation remains the primary treatment for Coats' disease. However, the use of anti-VEGF agents, either as neoadjuvant or adjuvant therapy, facilitates the stabilization of the pathological process and aids in the preservation of the patient's maximum potential visual function.*

Key words: *Coats' disease, retinal arterial macroaneurysm, retinal edema, retinal laser coagulation, angiogenesis inhibitors.*

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ОЦЕНКА ЭФФЕКТИВНОСТИ КОМБИНИРОВАННОГО ЛЕЧЕНИЯ РЕТИНИТА КОАТСА

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РЕЗЮМЕ

Целью данной работы *является оценка эффективности комбинированного лечения ретинита Коатса с применением антиангиогенной терапии и лазеркоагуляции сетчатки.*
На примере клинического случая показаны преимущества комбинированного поэтапного лечения ретинита Коатса. Выраженное усиление экссудативных проявлений в макулярной области и по ходу нижне-височной сосудистой аркады после лазеркоагуляции сетчатки (отграничительная, барраж макулы) не позволило бы провести следующий этап лазерного лечения без серьёзных осложнений. Поэтому применение анти-VEGF препаратов в качестве адъювантной терапии оптимально для создания благоприятных условий для следующего этапа лазеркоагуляции. Учитывая, что течение ретинита Коатса у взрослых пациентов часто ассоциировано с гиперхолестеринемией, необходимо проведение липидограммы и назначение адекватной коррекции выявленных нарушений, что также способствует снижению экссудации холестерина. Таким образом, комбинированное поэтапное лечение ретинита Коатса у данной пациентки позволило стабилизировать патологический процесс и сохранить высокую остроту зрения.
Заключение*. Основным методом лечения ретинита Коатса остаётся лазеркоагуляция. Однако применение анти-VEGF препаратов в качестве неоадъювантной либо адъювантной терапии способствует стабилизации патологического процесса и сохранению максимально возможного зрения у пациента.*

Ключевые слова: *ретинит Коатса, ретинальная артериальная макроаневризма, отёк сетчатки, лазеркоагуляция сетчатки, ингибиторы ангиогенеза*

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Exudative retinitis, also known as Coats' disease, is a rare idiopathic eye disease characterized by telangiectasia, micro- and macroaneurysms of the retinal vessels, and the deposition of hard exudates (intra- and subretinal).

The disease was first described in 1908 by ophthalmologist G. Coats. Coats' retinitis is most often diagnosed in the first or second decade of life, with the majority of cases occurring between the ages of 3 and 9. In 90 % of cases, Coats' retinitis is unilateral, with only 10 % of patients experiencing bilateral involvement. Men are more commonly affected by Coats' retinitis, although no differences in clinical presentation have been identified between men and women [1, 2]. No racial or ethnic predisposition to Coats' retinitis has been identified. In adults, the disease may be associated with hypercholesterolemia [3].

The etiology and pathogenesis of Coats' disease are unknown. Initial theories suggested an infectious origin for the disease. Toxoplasmosis has also been hypothesized as a possible cause. A.C. Woods and J.R. Duke proposed an inflammatory theory based on the presence of atrophic lesions in the chorioretina of patients with Coats' disease. However, failure of anti-inflammatory and hormone therapy has not supported these theories [3].

In previous studies (P. Genkova, 1986, G.L. Skuta, 1987), genetic defects have not been identified. However, there is currently literature on a potential genetic predisposition for the development of Coats' retinitis. A cytogenetic examination of children with Coats' disease revealed a pericentric inversion of chromosome 3 in one case and a partial deletion of chromosome 13 in another [3]. Furthermore, it has been suggested that the vascular changes associated with Coats' disease may be similar to those caused by mutations in the NDP gene, which is located on the X chromosome and encodes norrin. This may explain why Coats' retinitis predominantly affects men, as estrogen inhibits the expression of NDP in women [2].

Currently, the leading theory for the pathogenesis of Coats' disease is vascular. This condition is thought to be caused by a primary lesion to the retinal vasculature, which disrupts the blood-retina barrier, leading to lipid exudation, retinal ischemia, and VEGF activation [1, 2, 4].

There is no universally accepted classification system for Coats' retinitis. However, the most commonly used classification is that proposed by Shields J.L. et al. (2000), which divides the disease into five stages: stage 1 – retinal telangiectasia, stage 2 – telangiectasia and exudation, stage 3A – subtotal exudative retinal detachment, stage 3B – total retinal detachment, stage 4 – total retinal detachment and glaucoma, stage 5 – terminal stage [5].

Russian ophthalmologists use I.M. Mosin's classification system in their clinical practice:

I. Initial stage

A. Vascular malformations (micro- and macroaneurysms, arteriovenous shunts, telangiectasia), foci of solid exudates in the central and peripheral retina;

B. Vascular malformations and protruding foci of solid exudates in the macula and periphery.

II. Advanced stage

A. Localized protruding deposits of solid exudate at the posterior pole. Limited exudative retinal detachment (less than 2 squares in extent).

B. Extensive, tumor-like solid exudative deposits. Subtotal exudative retinal detachment (2-3 squares in extent). Posterior vitreous detachment.

III. Far-advanced stage

A. Total retinal detachment. Subretinal membranes.

B. Uveitis, cataracts, and rubeosis iridis

IV. Terminal stage

A. Neovascular glaucoma.

B. Subatrophy of the eyeball (phthisis) [6].

According to I.M. Mosin, 96 % of children who do not receive treatment for Coats' disease develop total retinal detachment, uveitis, and complicated cataracts within several years. Additionally, 57–75 % of these patients develop secondary glaucoma [6]. Without timely and appropriate treatment, the prognosis for visual outcomes is unfavorable [7].

Currently, the treatment of Coats' retinitis presents significant challenges due to the absence of a unified therapeutic approach. In the early stages of the disease (stages 1A, B and 2A), the primary treatment method remains laser coagulation of the retina to shut off areas of non-perfusion and obliterate vascular abnormalities in order to reduce or prevent further exudation. However, the use of laser coagulation as the sole treatment, even in the initial stages of the disease, does not always lead to stabilization of the process or improved visual acuity. Consequently, research into new methods or combination therapies for Coats' retinitis treatment continues.

THE AIM OF THE STUDY

To evaluate the efficacy of a combined treatment modality for Coats' disease, integrating anti-angiogenic therapy with retinal laser photocoagulation.

A CLINICAL CASE

Patient P., born in 1989, visited the Irkutsk Branch of S.N. Fyodorov Eye Microsurgery Federal State Institution due to complaints of blurred distance and near vision in the right eye. When working at close range, the patient noted letter loss and visual distortion. These symptoms had been present for the past three weeks. The patient reported that she was in good physical health and had given birth to a healthy child two years prior without complications.

The visual acuity for the right eye when turning is 0.6 cyl (-) 0.5 D ax 87° = 1.0, and the left eye is 1.0.

Upon examination of both eyes, the anterior segments were found to be unremarkable. In the fundus of the right eye, the optic disc was observed to be pale pink with clear borders and a central deep excavation measuring 0.5 DD. In the macular region, deposits of solid exudate, calcifications, and edema were noted. Along the temporal vascular arcades, particularly the inferior temporal arcade, retinal edema, multiple fusiform retinal arterial macroaneurysms and deposits of solid exudate were present. The venules in the inferior temporal quadrant were tortuous and their course was not always traceable. An atrophic lesion was also noted at the extreme periphery of the retina at 7 o'clock (Fig. 1A). In the fundus of the left eye, the optic disc was similarly pale pink with clear margins and a central, deep excavation measuring 0.5 DD, with preserved reflexes in the macular region. The retinal periphery was considered quiet, and the a:b ratio was 2:3.

The results of the additional examinations

Optical coherence tomography (OCT) OD: foveal profile distortion. A juxtafoveal intraretinal hyperreflective lesion was blocking the underlying retina. In addition, there were macroaneurysms present above the lesion and along the inferotemporal vascular arcade, as well as intraretinal edema and deposits of solid exudates (Fig. 1B and 1C).

Fluorescein angiography (FA) OU – the time taken for the dye to transit was unchanged and the vascular bed was completely filled. OD – choroidal filling appeared to be uneven. The caliber of the arterial vessels was also uneven, with narrowing followed by dilation in the superior and inferior temporal and inferior nasal branches of the central retinal artery, and multiple saccular and fusiform aneurysmal dilatations were present. These were more pronounced in the inferior temporal branch of the central retinal artery system. Perifoveal capillary perfusion in the inferotemporal segment was decreased. Dye extravasation around the aneurysms was moderate, and the dye impregnated the retina and accumulated in intraretinal cysts (Fig. 2A and 2B).

Lipidogram: cholesterol – 6.68 mmol/l, high-density lipoprotein cholesterol (HDL) – 1.38 mmol/l, low-density lipoprotein cholesterol (LDL) – 5.13 mmol/l, triglycerides – 0.93 mmol/l. A lipid profile correction has been prescribed by the therapist due to dyslipidemia – rosuvastatin (Crestor), 5 mg, once daily.

A follow-up examination has revealed a significantly negative trend in the pathological changes. Within 2 weeks, the best-corrected visual acuity of the right eye has decreased to 0.65, due to increased retinal edema in the macular region and along the inferior temporal vascular arcade. Based on these findings, it has been decided to proceed with the initial stage of laser retinal coagulation on the right eye in order to establish an artificial barrier and prevent further progression of the observed changes. Laser coagulation was performed using an ELLEX laser system

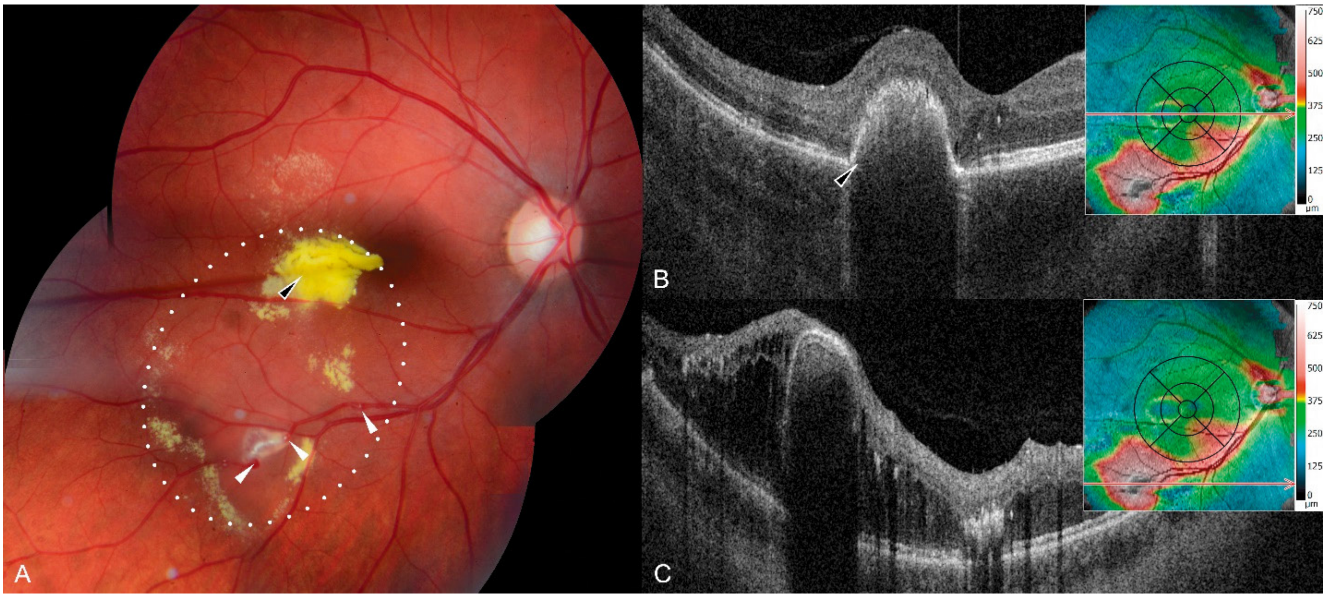

FIG. 1.
A. *Fundus image: white arrows indicate retinal arterial macroaneurysms, black arrow with white outline indicates hard exudate deposits in the macular area, retinal edema is indicated by a dotted elliptical line.* ***B.*** *OCT. Horizontal B-scan through the center with a retinal thickness map. Foveal profile deformation. Juxtafoveal intraretinal hyperreflective lesion blocking the underlying retina is indicated by a black arrow with white outline.* ***C.*** *Horizontal B-scan along the inferotemporal vascular arcade through a retinal arterial macroaneurysm with a retinal thickness map*

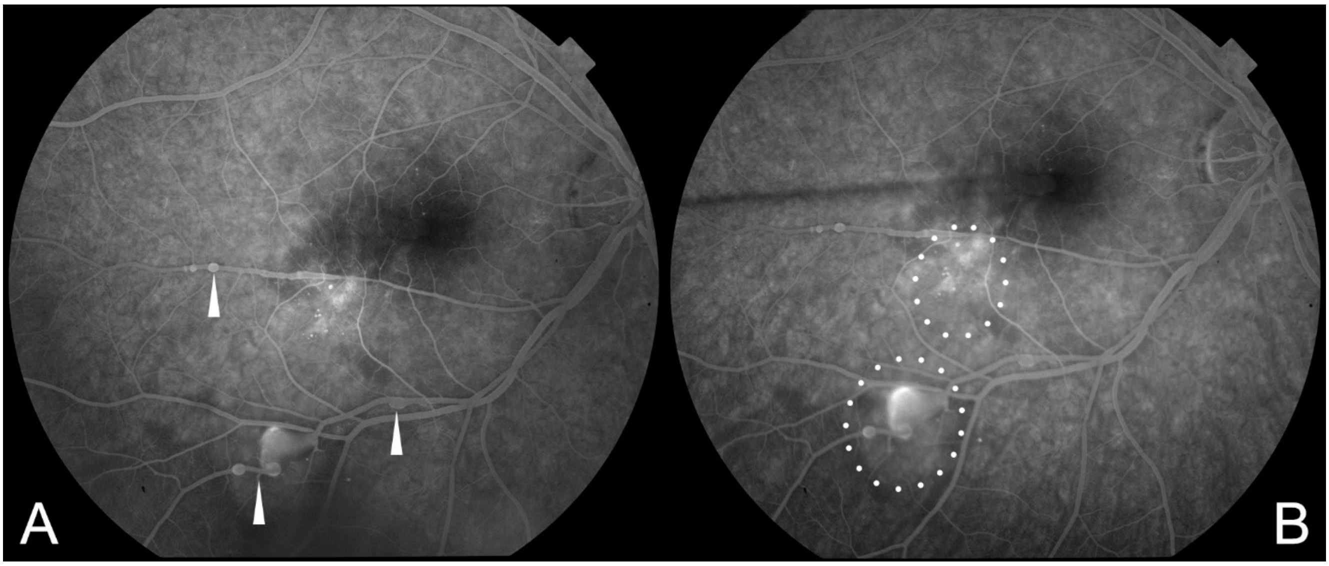

FIG. 2.
A. FAG *– white arrows point to multiple saccular and fusiform aneurysmal dilatations (macroaneurysms), most prominent in the inferior temporal branch of the central retinal artery.* ***B*** *– elliptical dots indicate moderate dye extravasation in the projection of the aneurysms*

with a wavelength of 561 nm. The following coagulation parameters were used: a power between 110 and 150 mW, an exposure time of 0.02 sec, a spot diameter between 100 and 200 μm, and a total of 502 coagulates. During the initial stage, the coagulates were applied along the inferior temporal vascular arcade and within the macular region in a horseshoe-shaped pattern that opened towards the fovea.

At the one-month follow-up visit, the patient reported a continued decline in visual acuity in the right eye, which had decreased to 0.3. Ophthalmoscopic examination revealed an increase in retinal edema in the macular region and along the inferior temporal vascular arcade. In the macular area, pigmented coagulates were observed in a horseshoe-shaped pattern, extending to the foveal area, and along the inferior temporal arcade. Multiple retinal arterial macroaneurysms were identified along the vascular arcades (primarily the inferior temporal arcades), along with the presence of solid exudates and vessels of uneven caliber (Fig. 3).

Given the increasing retinal edema and decreasing visual acuity, it was recommended to use anti-VEGF therapy to improve the resorption of subretinal fluid and solid exudates, followed by laser coagulation of retinal arterial macroaneurysms. The decision to administer intravitreal angiogenesis inhibitors was taken after consultation and approval from the local ethics committee. Written informed consent for the surgical intervention was obtained from the patient. Five monthly intravitreal injections of aflibercept (Eylea) were administered. Anti-VEGF therapy led to complete resorption of subretinal fluid and partial resorption of solid exudates. The visual acuity in the right eye improved to 0.8. Blood tests showed a reduction in total cholesterol levels to 3.4 mmol/l, with no abnormal fractions.

Three months later, the patient experienced a recurrence of increased retinal edema and solid exudate deposits in the inferior temporal arcade and macular region. The visual acuity in the right eye had decreased to 0.3. Blood tests revealed an elevation in total cholesterol levels to 6.8 mmol/l. The patient had discontinued rosuvastatin therapy (Crestor) without consulting her healthcare provider. Her physician recommended rosuvastatin (Roxera) 5 mg daily in order to manage dyslipidemia.

Laser coagulation of macroaneurysms was performed using an ELLEX laser system with a wavelength of 561 nm and coagulation parameters: a power of 130 mW, an exposure time of 0.2 sec, a spot diameter of 200 μm (the spot diameter overlaps the diameter of the macroaneurysm), and a total of 12 coagulates. The coagulates were applied to projections of two macroaneurysms located along the inferotemporal vascular arcade.

After 3 weeks of examination following laser coagulation of the patient's macroaneurysms, she reported an improvement in her vision. The visual acuity in the right eye had increased to 0.95. Upon ophthalmoscopic examination of the fundus in the right eye, a pale pink, centrally deepened optic disc was observed, measuring 0.5 DD, with no retinal edema in the macular region. Dyspigmentation, solid exudates, and pigmentary coagulates were also noted. Along the inferior temporal vascular arcade, retinal arterial macroaneurysms were present, as well as minor

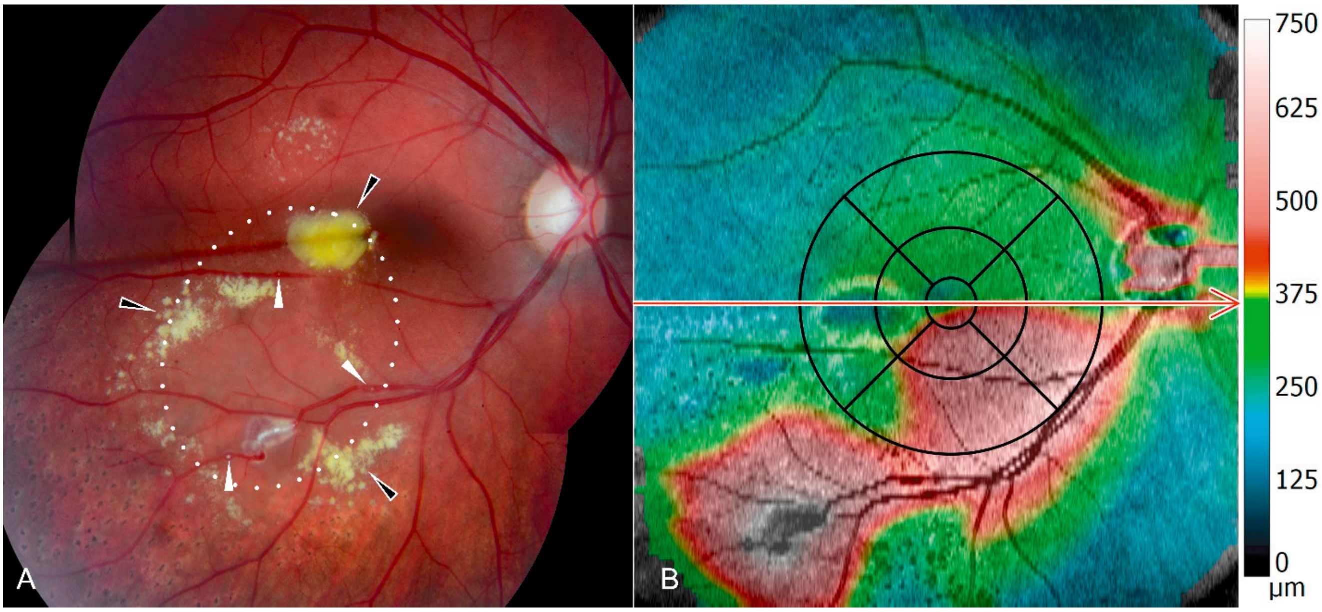

FIG. 3.
A. *– fundus image: white arrows indicate retinal arterial macroaneurysms, black arrows with a white outline indicate hard exudate deposits in the macular area, retinal edema is indicated by a dotted elliptical line.* ***B.*** *OCT – retinal thickness map*

retinal edema and deposits of solid exudates and pigmentary coagulates. At the site of the macroaneurysm coagulation, subretinal hemorrhage was observed during ophthalmoscopy, which may have resulted from a rupture in the macroaneurysm's wall following laser treatment. Additionally, an atrophic focus was noted at the extreme peripheral edge of the retina, at 7 o'clock position (Fig. 4).

Consecutive restrictive (barrier) laser coagulation, five injections of aflibercept, and laser coagulation of macroaneurysms allowed us to stabilize the pathological process and achieve resorption of macular edema and solid exudates (Fig. 5).

According to the fluoroscopic examination, dye extravasation in the aneurysm projections is moderate, approaching a mild level. The dye has penetrated the retina and there is no evidence of accumulation in intraretinal cyst formations. Transient fluorescence can be observed in the projection of the coagulates (Fig. 6).

Given the minor extravasation of the dye, it is recommended to continue dynamic observation. When the patient returned 6 months after fluorescein angiography, the visual acuity in the right left eyes was 1.0. Ophthalmoscopic examination of the fundus in the right eye showed that the optic disc had a pale pink color with a deep central excavation of 0.5 DD. There was no retinal edema in the macular region, dyspigmentation or pigmentary coagulates. Minor retinal edema, solid exudate deposits, retinal arterial macroaneurysms, and pigmentary coagulates persisted along the inferior temporal vascular arcade. An atrophic lesion was observed at the periphery of the retina at 7 o'clock. In the fundus of the left eye, the optic disc appeared to be pale pink with well-defined borders and a deep central excavation measuring 0.5 DD. Reflexes within the macular region were retained. The peripheral retina appeared to be calm. The a:b ratio was 2:3. Further observation is recommended. If there is an increase in exudation from retinal arterial microaneurysms, further treatment options should be considered (Fig. 7).

DISCUSSION

Currently, there is no standardized approach to the management of Coats' retinitis. The choice of therapy is at the discretion of the physician and depends on the severity of the disease. Different treatment modalities are employed at various stages of Coats' retinitis: laser photocoagulation, cryotherapy of the retina and retinal vessels, intravitreal administration of angiogenesis inhibitors, corticosteroids, and in advanced cases, vitreoretinal surgery. For neovascular glaucoma, transscleral cyclophotocoagulation with a diode laser is performed, and in certain cases (painful subatrophy), the eye may be enucleated [3, 7, 8]. Efforts at conservative therapy (corticosteroids, antibiotics) have been unsuccessful. In the initial stages of Coats' retinitis treatment, the aim is to obliterate vascular changes (micro- and macroaneurysms, telangiectasia), shut off areas of non-perfusion, in order

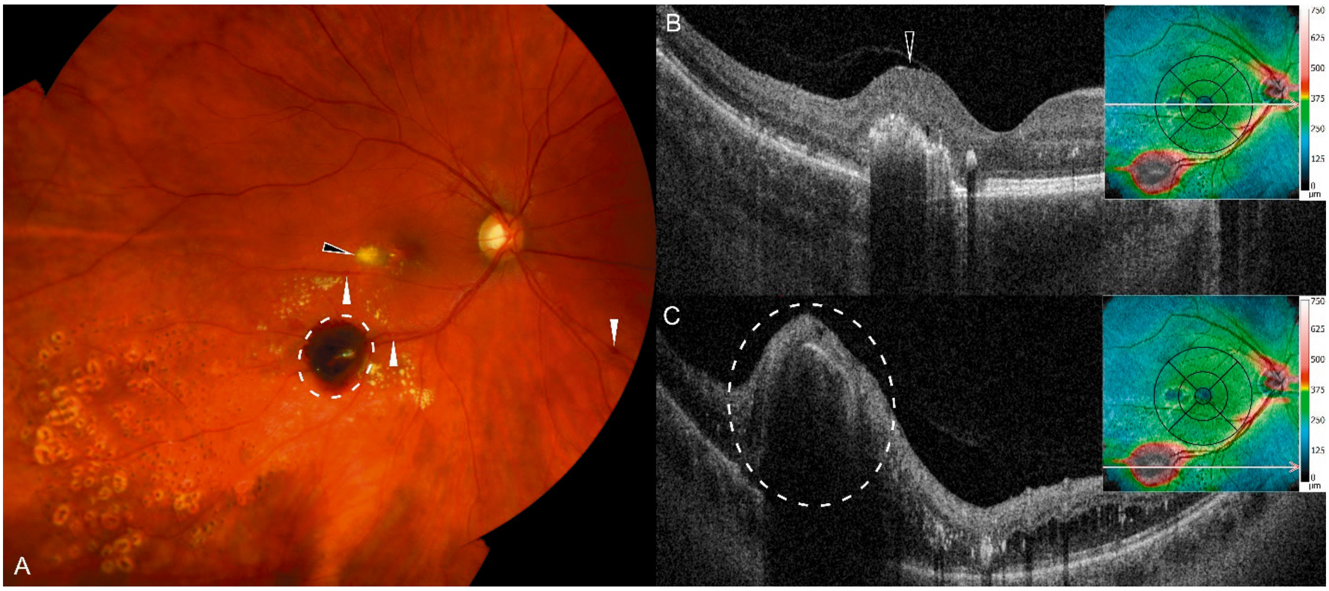

FIG. 4.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits in the macular area, subretinal hemorrhage is indicated by the dotted line in the form of an ellipse.* ***B.*** *OCT. Horizontal B-scan through the center with a retinal thickness map. Deformation of the fovealar profile. Juxtafoveolar intraretinal hyperreflective lesion (hard exudates) blocking the underlying retina is indicated by a black arrow with a white outline.* ***C.*** *OCT. Horizontal B-scan along the inferotemporal vascular arcade through the retinal arterial macroaneurysm with a retinal thickness map. The hyperreflective protruding lesion (blood) blocking the underlying tissues is indicated by the dotted line in the form of an ellipse*

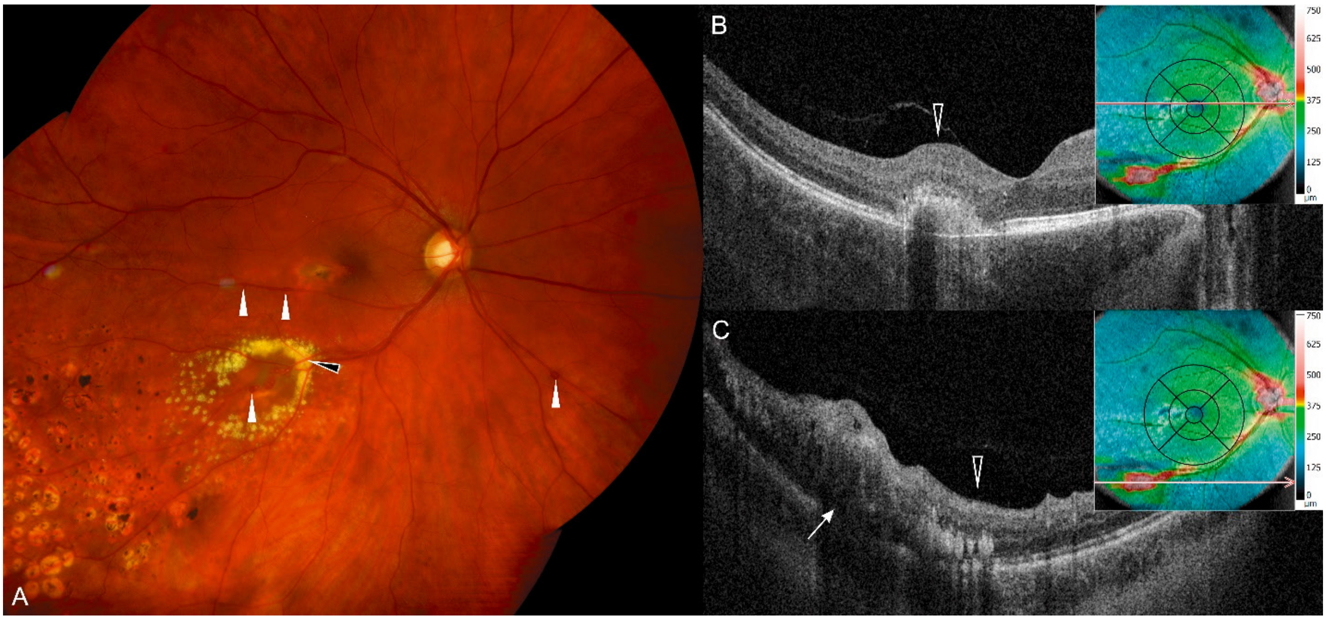

FIG. 5.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits along the inferotemporal arcade.* ***B.*** *OCT. Horizontal B-scan through the center with retinal thickness map. Deformation of the fovealar profile. Juxtafovealar intraretinal hyperreflective lesion blocking the underlying retina is indicated by a black arrow with white outline.* ***C.*** *OCT. Horizontal B-scan along the inferotemporal vascular arcade through the retinal arterial macroaneurysm with retinal thickness map. The white arrow points to destruction of the outer retinal layers*

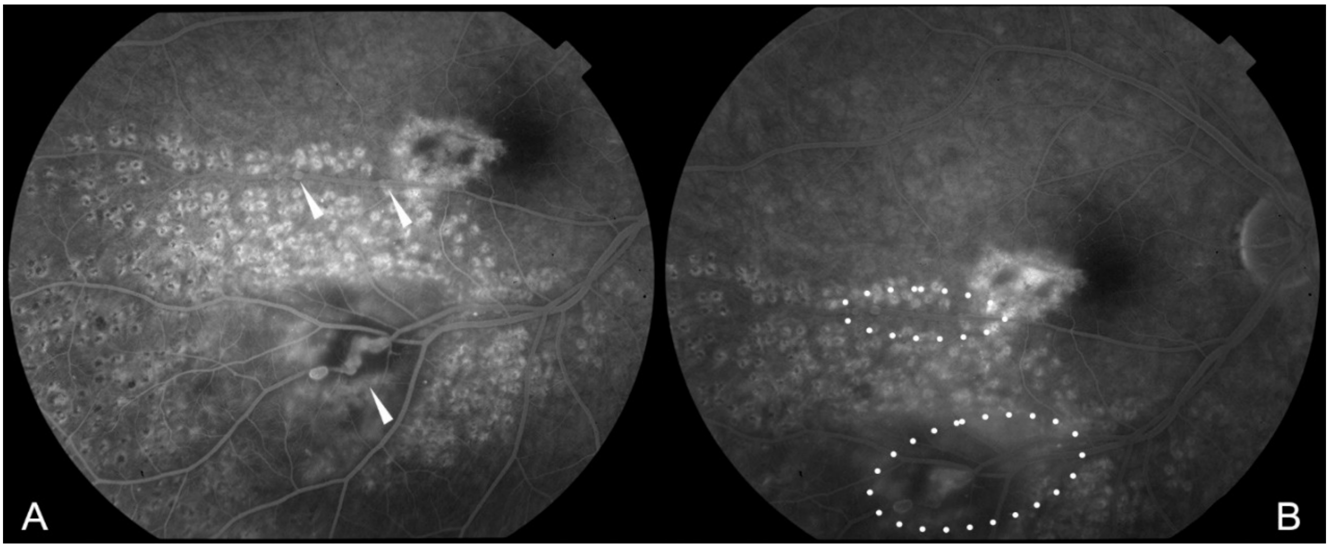

FIG. 6.
A – *FAG: white arrows point to multiple saccular and fusiform aneurysmal dilatations (macroaneurysms) in the inferior temporal branch of the central retinal artery.* ***B.*** *The dotted elliptical line indicates moderate dye extravasation in the projection of the macroaneurysms*

to prevent the development and progression of exudative retinal detachment, as well as secondary neovascular glaucoma and eyeball subatrophy [2, 3, 5].

Today, there are several treatment options available for this disease, but laser coagulation of the retina (zones of nonperfusion) and treatment for vascular changes remains the preferred method. G. Meyer-Schwickerath and K.J. Pesch were the first to propose the use of laser coagulation as a treatment for this pathology in 1960 [3, 4, 9, 10]. The number of laser coagulation stages depends on the severity of the disease and ranges from two to six on average. Recently, there has been a shift in approaches to laser coagulation for Coats' retinitis. Yellow-wavelength lasers (577 nm) are considered to be the most effective as they exhibit maximum absorption by blood hemoglobin and oxyhemoglobin, facilitating direct laser coagulation of vascular malformations [11]. Additionally, due to their low absorption by macular xanthophylls and their central location, yellow-wavelength laser use is preferred, reducing the risk of retinal damage to the central part of the fundus. However, the use of monotherapy with laser coagulation at various wavelengths for Coats' retinitis is restricted to the early stages of the disease (1A, 1B, and 2A, according to the classification system used by I.M. Mosin) and, in most cases, its peripheral location [2, 3, 7, 8]. When there is significant retinal exudation and exudative retinal detachment in the central part, the efficacy of this method is greatly reduced.

In case of central localization of vascular malformations, it is not always feasible to perform laser coagulation to the full extent, as complications after treatment

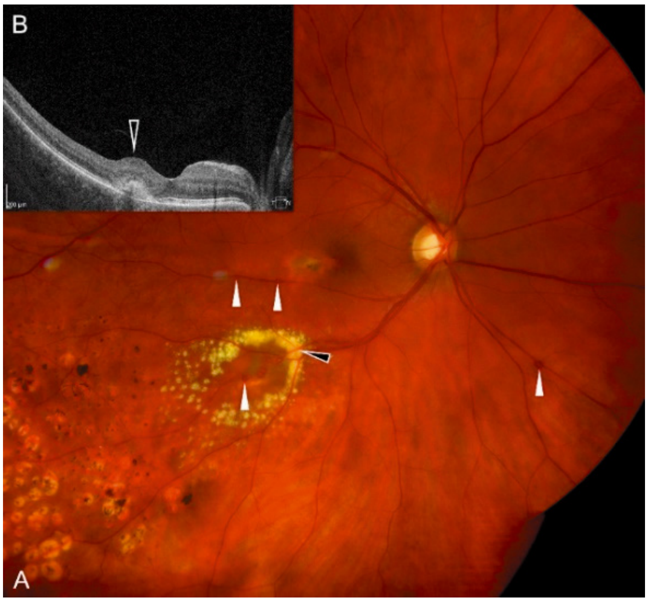

FIG. 7.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits along the inferotemporal arcade.* ***B.*** *OCT. Horizontal B-scan. Fovealar profile deformation. Juxtafovealar intraretinal lesion of medium reflectivity blocking the underlying retina is indicated by a black arrow with white outline*

may lead to a significant reduction or even loss of visual acuity. Therefore, the efforts to find alternative treatment modalities in order to preserve the patient's visual function as much as possible continue. To date, vascular theory is considered the predominant theory of Coats' disease pathogenesis. Thickening and hyalinization of blood vessels, as well as loss of endothelial cells from the vascular walls due to the action of "certain" factors, lead to impairment of the blood-retinal barrier and the development of vascular malformations (telangiectasia, micro- and macroaneurysms). These vascular disorders contribute to lipid exudation, retinal ischemia and activation of VEGF [1, 8, 9, 12]. Previous research has demonstrated that intravitreal administration of anti-VEGF drugs is effective for the treatment of retinal arterial macroaneurysms and macular edema of various origins [13].

According to foreign researchers, elevated levels of VEGF have been found in the anterior chamber fluid and vitreous body of patients with Coats' retinitis [10, 12]. Elevated VEGF levels have been associated with retinal ischemia, although the exact role of VEGF in the pathogenesis of Coats' retinitis is still unclear. Considering this data, there has been discussion about the potential use of anti-VEGF medications as a supplementary treatment option (neoadjuvant or adjuvant) in combination with laser therapy [14-17].

On the one hand, analysis of data from foreign and domestic literature has shown the efficacy of anti-VEGF drugs in treating patients with Coats' retinitis [14-18]. However, there is also conflicting data. A group of researchers conducted a retrospective study of cases based on treatment outcomes for Coats' disease (initial stages 1-3A according to Shields' classification), assessing the efficacy by visual acuity and fundus changes. The study analyzed treatment with anti-VEGF monotherapy in 69 eyes and standard laser coagulation treatment in 96 eyes. The results were conflicting. While the use of anti-VEGF as monotherapy (1–5 injections) resulted in subretinal fluid resorption and solid exudate reduction in 33.3 % of cases, active vascular lesions required laser treatment. According to the authors, the use of laser coagulation as monotherapy resulted in an improvement or stabilization of Coats' retinitis in 39 % of early-stage cases, although this was not always accompanied by an increase in visual acuity [19]. Therefore, anti-VEGF therapy can improve the prognosis of the disease, even in the most severe cases of Coats' retinitis. However, it does not lead to a long-term remission or cure for the patient [18, 19]. Laser coagulation of the retina remains the primary treatment method for early-stage Coats' retinitis [2, 16, 19].

Our clinical case demonstrates the benefits of a combined, staged approach to the treatment of Coats' retinitis. A significant increase in exudative activity in the macular region and along the inferior temporal arcade following retinal laser photocoagulation (restricting, macular band) would have prevented the need for further laser treatment without significant complications. Therefore, the use of anti-VEGF drugs as adjuvant therapy is optimal to create favorable conditions for subsequent laser photocoagulation stages. The combined, staged treatment of Coats' retinitis in this patient has stabilized the pathological process and preserved high visual acuity. Therefore, combined treatment with retinal laser photocoagulation and anti-VEGF therapy for Coats' retinitis has shown promising results. Anti-VEGF drugs may be used as adjuvant therapy depending on individual patient presentation. It should also be noted that the course of Coats' retinitis in adult patients is often associated with hypercholesterolemia. Therefore, it is necessary to perform a lipidogram and prescribe appropriate treatment for the identified disorders, which helps to reduce cholesterol excretion [3, 10].

CONCLUSION

Coats' retinitis is a condition that requires constant monitoring and, if necessary, appropriate treatment. The treatment depends on the stage of the disease and is at the discretion of an ophthalmologist. Currently, there is no standardized treatment protocol, and laser photocoagulation is the primary treatment option for Coats' disease. Laser photocoagulation, as a monotherapy, is only feasible for peripheral lesions in the initial stages of Coats' retinitis. Therefore, anti-VEGF drugs can be used as adjuvant therapy for retinal laser photocoagulation.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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