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REVIEW

Recent advances in the diagnosis and treatment of Coats' disease

Xinyue Yang · Chenguang Wang · Guanfang Su

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Abstract

Purpose To review and summarize the recent progress in the diagnosis and treatment of Coats' disease.

Methods Literature was collected from Web of Science, Medline and Pubmed, through searching of these keywords: "Coats' disease", "diagnosis" and "treatment".

Results Coats' disease is characterized by idiopathic leaky retinal vascular telangiectasia and microvascular abnormalities often accompanied by intraretinal or subretinal exudation and retinal detachment. Neovascular glaucoma and phthisis bulbi often occur in advanced cases. Coats' disease has significant diversity in terms of its clinical presentation and morphology. Anti-VEGF therapy combined with laser photocoagulation for early Coats' disease and anti-VEGF therapy combined with minimally invasive vitrectomy for advanced Coats' disease can achieve good efficacy.

Conclusion Early diagnosis and timely treatment based on clinical stage are critical to retaining the patient's visual function. Patients should be aware that close long-term follow-up is necessary.

X. Yang · C. Wang · G. Su (✉)
Department of Ophthalmology, The Second Hospital of Jilin University, 218 Ziqiang Street, Changchun 130041, Jilin, China
e-mail: sugf2012@163.com

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Introduction

Coats' disease was first proposed by George Coats, a Scottish ophthalmologist, in 1908 and was defined as retinal telangiectasia and aneurysm with retinal exudation in unilateral eyes of young males. For a century, research on the natural history, morphology, incidence and clinical manifestations of Coats' disease has considerably progressed [1, 2]. Coats' disease is characterized by retinal telangiectasia and intraretinal or subretinal exudation. Vascular abnormalities are more common in the peripheral retina, and exudation occurs mostly in the macular area. Based on a prospective study conducted in the UK, the incidence of Coats' disease is 0.09 per 100,000 population [3]. Coats' disease can occur in both children and adults. Peng et al. [4] reported a case of early-onset Coats' disease in a preterm boy born at $31^{5/7}$ weeks of gestational age who was initially diagnosed with retinopathy of prematurity (ROP) affecting only one eye at 39 weeks postmenstrual age (PMA). Charles et al. [5] reported a case of a 3-week-old boy who presented with atypical rapidly progressing Coats' disease. This disease is an occasional, perhaps congenital but non-familial disease and is usually not

associated with systemic disease. There are no ethnic differences, but there are significant gender differences with a strong male predominance (3:1). Previous studies have reported that this disease usually occurs unilaterally, and 0% to 10% of patients with Coats' disease have bilateral disease [6]. For the first time, Stanga et al. [7] reported microvascular changes in the fellow eyes of patients with Coats' disease, demonstrating the bilaterality of this disease using optical coherence tomography angiography (OCTA). Recent research has shown that bilateral vascular abnormalities are more common than previously reported in Coats' disease, so that surveillance of both eyes over the lifetime of the patient is warranted due to the potential progression to exudative disease requiring treatment [8, 9]. Using OCTA and ultra-widefield imaging, Rabiolo et al. [10] demonstrated that Coats' disease should be regarded as an asymmetric bilateral disease rather than a unilateral disease connected with poor vascular development. The natural history of Coats' disease often progresses to blindness and even atrophy, and the younger the age of onset is, the faster the disease progresses, and the worse the visual outcome is; thus, treatment should be performed immediately [11].

Clinical manifestations and staging

Clinical manifestations

Children with Coats' disease have no symptoms during the early stages until poor visual acuity (VA), eye pain, glaucoma, leukocoria and squinting are found, and 60% to 70% of symptoms occur within 10 years after birth. Adult Coats' disease has two manifestations: One manifestation is consistent with the findings of Coats' disease in children and the other manifestation is characterized by retinal capillary abnormalities.

Ophthalmoscopy examination: Generally, there are no abnormalities in the anterior chamber. With the development of the disease, the conjunctiva is congested, the cornea is hazy, the anterior chamber has a glint associated with cholesterolosis and rubeosis iridis, and total white cataracts and posterior subcapsular cataracts can be observed. The vitreous is generally clear; after losing retinal function, the posterior segment can sustain disorganization with the development of vitreous hemorrhage, vitreoretinal traction, vitreous fibrosis and proliferative vitreoretinopathy [12, 13]. Fundus examination shows telangiectatic vessels mostly located in the superotemporal retina. "Bulb-like" aneurysm changes and dilated follicular expansion of the macula are less common. Subretinal and intraretinal exudates are usually involved in the macular region, with macular edema and exudative macular detachment, and an epiretinal membrane is common. Dense macular exudation can be visualized as a nodular fibrotic lesion commonly described as a "subfoveal nodule" that progresses to macular scarring and fibrosis within a few months or as late as the third decade. Coats' disease has infrequent involvement of the choroid and sclera [14].

Staging

The disease is staged according to Shields' criteria (Table 1). Stage 1 involves only retinal telangiectasia; stage 2 involves telangiectasia and exudation with 2A representing extrafoveal exudation and stage 2B representing exudation involving the macular fovea; furthermore, Daruich et al. suggested an updated classification system introducing two subcategories within stage 2B, namely stage 2B1 (without subfoveal nodules) and stage 2B2 (with subfoveal nodules) [15]; stage 3 involves exudative retinal detachment, in which stage 3A1 does not involve the fovea, stage 3A2 involves the fovea, and stage 3B involves total retinal

Table 1 Classification of Coats' disease [15]

Stage 1	Retinal telangiectasia only
Stage 2	Telangiectasia and exudation
	A. extrafoveal exudation
	B. foveal exudation
	1. without subfoveal nodule
	2. with subfoveal nodule
Stage 3	Exudative retinal detachment
	A. subtotal detachment
	1. extrafoveal
	2. foveal
	B. total retinal detachment
Stage 4	Total retinal detachment and glaucoma
Stage 5	Advanced end-stage disease

detachment; stage 4 involves total retinal detachment with glaucoma; and stage 5 involves severe end-stage disease [16].

Histopathology and pathogenesis

The typical histopathology of Coats' disease involves subretinal exudation, mononuclear cellular infiltration and prominent cholesterol crystals. Foam or "ghost cells" and glial proliferation are often present in the inner retinal layers. The main components of subretinal fibrin exudate are lipids and pigment-laden macrophages. The retinal pigment epithelial layer exhibits fibroid metaplasia, especially after retinal laser photocoagulation. Electron microscopy examinations reveal the loss of the vascular endothelium and pericytes and diffuse thickening of the retinal capillary adventitia in the region. Advanced disease can lead to diffuse retinal structural disorders and calcification caused by osseous metaplasia [17].

For over a decade, significant efforts have been made to investigate the pathogenesis of Coats' disease; however, the cause is still largely unknown. The core pathological changes in Coats' disease are abnormalities of the microvasculature. On the one hand, the destruction of the blood–retinal barrier at the endothelial level causes plasma leakage into the vessel wall, causing it to become disorganized and necrotic. The abnormal pericytes and endothelial cells subsequently degenerate, causing aneurysms, and the closure of the vessels leads to ischemia and leakage of lipid-rich exudates into the retina, which can cause changes in the retina, including thickening, cyst formation or retinal detachment. The exudate stains positive with periodic acid–Schiff (PAS) due to plenty of lipids, foamy macrophages and cholesterol clefts [18]. The retrobulbar blood vessels show decreased hemodynamic parameters in the affected eyes in patients with Coats' disease compared to the contralateral unaffected eyes, particularly during the advanced stages of the disease [19]. Lim et al. [20] demonstrated that perivascular T cell and macrophage infiltration was present in the retina of an enucleated eye with Coats' disease. Satoru et al. demonstrated that chronic inflammation occurs in both the retina and the choroid in eyes with Coats' disease. They demonstrated that CD3-positive T cells, but not B cells, infiltrate the proliferative vitreoretinopathy membrane in addition to the cholesterol cleft, suggesting that cellular immunity plays a significant role in the pathogenesis of proliferative vitreoretinopathy in Coats' disease [21]. Ghassemi et al. investigated the serum hypercoagulability state and protozoan and viral infections in 22 consecutive patients. These authors did not find any association between the above factors and Coats' disease, but did find that the serum beta globulin levels were increased in children with Coats' disease [22]. Studies have shown that nitric oxide and vascular endothelial growth factor (VEGF) are significantly elevated in aqueous humor samples from patients with increasingly advanced Coats' disease [23, 24]. Yang et al. used iTRAQ to conduct comparative proteomic profiling of aqueous humor samples among patients with three different stages of Coats' disease to identify disease-specific proteins and found that several crystalline-related proteins, including CRYBB1, CRYBB2, CRYGS and CRYGD, were decreased; furthermore, vitamin A-related proteins and tropomyosin skeleton proteins were decreased in aqueous humor samples from patients with Coats' disease. Apolipoprotein C-1 (APOC1) and fibrinopeptide B (FGB) were elevated in the aqueous humor samples from the patients. These findings may provide additional insight into the mechanism of Coats' disease and provide potential biomarkers for identifying individuals with Coats' disease [25].

Some phenotypic similarities in the family increase the likelihood of genetic factors in Coats' disease. Using single-strand conformation polymorphism (SSCP)/heteroduplex analysis and PCR, Black et al. analyzed the genes of a woman with unilateral Coats' disease and her son suffering from Norrie disease and found that both had a missense mutation of the Norrie disease protein gene (*NDP*); *NDP* showed a third explicit mutation of base C at position 704 to G, resulting in a missense mutation in C96W, and a missense mutation in the *NDP* gene found in the eyeball of the Coats' disease patient was found in the affected retinal tissue, suggesting that *NDP* mutations may be associated with Coats' disease [26]. Peene et al. [27] reported that the exudative retinopathy observed in Coats'-like disease can be caused by mutations in a telomere-capping gene (*TERC*). Saatci et al. [28] reported ABCA4 gene mutations in a 12-year-old girl with bilateral stage 2B Coats' disease, and *NDP* gene mutations were not present. In recent years, researchers have studied other potentially

related genes but have not yet obtained definitive evidence to support the genetic basis of this disease. Other scholars have also studied some candidate genes, such as the frizzled homolog 4 basis, *RCBTB1*, *PANK2* and the crumb homolog 1 gene (*CRB1*). However, there are still not enough samples to confirm that Coats' disease has a clear relationship with a specific gene [29–32]. Given the non-familial, congenital and unilateral features of Coats' disease, the presence of a somatic mutation is a compelling hypothesis [26]. The genetics underlying Coats' disease require further investigation for genetic testing to be clinically useful.

Diagnosis and differential diagnosis

Diagnosis

The diagnosis can be confirmed based on the patient's medical history, clinical manifestations, ophthalmologic examination and auxiliary examination. As the auxiliary inspection equipment is continuously updated, these examinations for Coats' disease are gradually improved.

B-scan ultrasonography: Typical manifestations can be visualized, including hyper-reflective masses of exudates, a clear subretinal space without significant choroidal thickening or vitreoretinal traction that is relatively immobile, and serous retinal detachment contiguous with the optic nerve head can be visualized. Color Doppler ultrasound: When secondary retinal detachment occurs, blood flow signals that are continuous with the central retinal veins can be detected at the detached retinal tract echoes, and weak echoes without blood flow signals can be detected under the retinal tract echoes. When the retinal detachment position is high, self-motion of the weak echoes can be observed, and an abnormal blood flow signal can be generated, but there is no characteristic blood flow spectrum. This "sand-like" change is unique to Coats' disease [16].

Spectral-domain optical coherence tomography (SD-OCT) & OCTA: SD-OCT, an updated imaging modality, confers the additional advantage of providing cross-sectional imaging in vivo to quantify the type and extent of macular involvement and to identify intraretinal edema, intraretinal/subretinal exudates, epiretinal membranes, macular holes, macular fibrosis, ellipsoid zone disruption, external limiting membrane disruption, subfoveal nodules, subretinal fluid (SRF), intraretinal cystoid spaces, subretinal hyper-reflective nodules and macular atrophy and can be utilized to describe structural and visual responses to therapy [15, 33]. A compact hyper-reflective structure (fibrotic nodules/macular fibrosis) and outer retinal atrophy persist after treatment, and the presence of these structures at baseline and at the final visit is associated with poor final VA; however, untreated SRF, foveal subretinal thickness and bright hyper-reflectivity (retinal exudation) are correlated with poorer VA prior to the initial treatment, but these changes can resolve and are associated with an improvement in VA post-therapy [34]. The vascular pathologies in Coats' disease involve both the deep and superficial retinal plexuses. OCTA scans allow detailed assessment of both of these plexuses, whereas fluorescein angiography fails to visualize the deep vascular plexus. Hautz et al. evaluated the usefulness of OCT and OCTA for monitoring 9 pediatric patients with Coats' disease and demonstrated that OCTA in combination with fluorescein angiography and OCT can be useful in diagnosing and monitoring Coats' disease. The OCTA results were in good agreement with the results of fluorescein angiography, but OCTA failed to be a valid substitute for conventional angiography as a sole diagnostic method (the "gold standard"). The use of multimodal imaging including these three techniques and color photography of the fundus affords a comprehensive picture of Coats' disease pathologies [35].

Computed tomography (CT) and magnetic resonance imaging (MRI): These modalities can help to differentiate malignant lesions with similar clinical signs to those of Coats' disease because calcification can be visualized. The CT features of Coats' disease are thickening in the ipsilateral eye wall, and crescent-shaped and "V"-shaped high-density areas behind the vitreous, usually without calcifications, and enhanced CT can show a lack of enhancement with exudate. In advanced Coats' disease cases, CT shows lipid exudates as hyperdense areas within the orbit and retinal detachment. MRI demonstrates high-intensity T1- and T2-weighted signals converging on the optic nerve head corresponding to exudative retinal detachment [36].

Fluorescein angiography: Fluorescein angiography has the advantage of allowing visualization of even

slight vascular pathologies of the posterior pole and retinal periphery, and this modality can aid in the early detection of stage 1 Coats' patients. The characteristics of Coats' disease on fluorescein angiography are as follows: areas of non-perfusion, telangiectasia causing early hyperfluorescence and exudation hyperfluorescence. Aneurysms can be clearly visualized, characteristically demonstrated as "light bulb dilations." Additional angiographic findings include vascular leakage, tortuosity and blockage from overlying exudate [37]. With the application of wide-angle fluorescein imaging and a wide-angle digital retinal imaging system, the detection rate of lesions associated with Coats' disease can be improved, which is helpful for early diagnosis [38]. Blaire et al. performed wide-angle fluorescein angiography and imaging examinations of 32 patients with Coats' disease, and 22 of them had clinical manifestations of binocular imbalance. Indocyanine green angiography is less commonly reported, but this technique contributes to identifying tumor or choroidal neovascular disease [8]. In recent years, Sigler et al. conducted a prospective study of 21 Coats' disease patients using multimodal imaging systems, such as color fundus photography, wide-angle fluorescein angiography and OCT, and found that 24% of patients had retinal hemangioma proliferation and choroidal retina vascular anastomosis. It is believed that some of the previously described submacular fibrosis and submacular nodules are retinal hemangioma proliferation and chorioretinal anastomosis. These authors demonstrated that choroidal neovascularization and choroidal retinal vascular anastomosis are common in children with Coats' disease. Ultra-widefield angiography, which captures $> 30°$ to $< 200°$ of the fundus in a single image, allows far peripheral retinal pathology to be imaged, is the newest technology in the evolution of fundus fluorescein angiography and has been successfully used without sedation for evaluation of children with Coats' disease [10]. Ultra-widefield fluorescein angiography captures more peripheral retinal pathology than standard fluorescein angiography. Tsui et al. [39] reported the outpatient use of ultra-widefield fluorescein angiography without sedation in younger children (aged 6–7) with Coats' disease. Rabiolo et al. [10] reported that five children and teenagers (aged 8–15) underwent ultra-widefield fluorescein angiography in an outpatient setting and determined that 77.8% of asymptomatic fellow eyes had far peripheral non-perfusion and capillary telangiectasias. Patients with Coats' disease should undergo careful examination of the fellow eye with fluorescein angiography to detect vascular abnormalities that might not be visible clinically [40]. Suzani et al. [41] studied a series of children with early Coats' disease and demonstrated that wide-angle fluorescein angiography-guided treatment resulted in outstanding anatomical and visual outcomes.

Differential diagnosis

The list of differential diagnoses includes cysticercosis, retinoblastoma, Norrie disease, choroidal melanoma, capillary hemangioma, cavernous hemangioma, familial exudative vitreoretinopathy, persistent fetal vasculature, toxocariasis, retinitis pigmentosa, uveitis, retinal vasculitis and macular telangiectasia [42–46]. Insufficient understanding and the lack of specificity of the clinical manifestations of Coats' disease lead to misdiagnosis, which often causes serious consequences, such as delayed treatment and even enucleation.

Treatment

The management of Coats' disease varies depending on the stage of the disease. In stage 1 cases of retinal telangiectasia alone or telangiectasia with exudation (stage 2) that are not vision-threatening, patients should be periodically observed; in patients with stage 2 to 3A Coats' disease, cryotherapy or laser photocoagulation is commonly performed and seems to be effective. If retinal detachment occurs (stage 3A or higher), surgery is preferred, and relatively successful surgical outcomes have been reported. For patients with stage 4 Coats' disease and severe eye pain, enucleation may be considered. For patients with stage 5 Coats' disease who are asymptomatic, blind and hopeless, they can be observed and left untreated. Eyes with stage 2A or more advanced-stage disease can be treated appropriately to prevent disease progression and worsening in VA. Stage 2A and 2B eyes that were treated with ablation to full resolution of exudates showed good visual outcomes when macular scarring did not develop. The advancement of disease research and the application of new drugs in recent years have

provided new avenues for the treatment of Coats' disease [1, 47–50].

Cryotherapy

Cryotherapy is mainly utilized in patients with peripheral telangiectasia accompanied by extensive exudation and retinal detachment. Cryotherapy is more frequently used in severe cases because it is more effective in producing closure even in the detached retina. Cryotherapy may be performed two or three times during the same session under indirect ophthalmoscopy (double or triple freeze–thaw technique). Severe destruction of the blood–retinal barrier after cryotherapy can also increase the retinal fluid in the short term after surgery. There is some evidence that confirms that cryotherapy increases the incidence of retinal anterior membrane and vitreoretinal traction. However, cryotherapy remains an effective treatment to eliminate subretinal exudation and microvascular dilatation [51].

Laser photocoagulation

Laser photocoagulation for Coats' disease was first described by Meyer-Schwickerath et al. in the 1960s [52]. Laser photocoagulation is aimed at obliterating abnormal vasculature and aneurysmal dilations and minimizing exudation. A conventional green or yellow laser with a relatively long duration (0.1–0.5 s) is preferred to produce effective closure of the vessels [53].

Traditional treatment with laser photocoagulation is effective for patients with simple exudation. For those who have retinal detachment, treatments such as cryotherapy and surgery are needed. Nucc et al. [54] first demonstrated selective photocoagulation, and young Coats' patients responded quickly to laser photocoagulation. However, Shapiro et al. believe that patients with exudative retinal detachment treated with laser photocoagulation can still achieve improved results. These authors applied green diode laser ablation therapy in 14 eyes with advanced Coats' disease. After a median follow-up of 39.5 months, 13 (93%) of the treated eyes had no active exudation [55]. Levinson et al. described the outcomes of 17 eyes (8 with retinal detachment) with Coats' disease treated with a 577-nm yellow laser. After a mean follow-up period of 21 months, the eyes with retinal detachment required a mean of 2.9 treatment sessions. Sixteen of the eyes (94%) achieved complete ablation of all visible telangiectasias and resolution of SRF [56]. Xuan et al. first performed minimally invasive two-port pars plana endolaser photocoagulation in 24 patients (25 eyes) with stage 3 Coats' disease. Some patients were also treated with SRF drainage, intravitreal triamcinolone or anti-VEGF injection. The results showed that 96% of patients had retina reattached and 29.41% of patients had improved vision, indicating that endolaser photocoagulation by two-port pars plana non-vitrectomy was a safe and effective approach for treating advanced Coats' disease with serous retinal detachment [57]. These authors believe that the advantages of this technology are that the laser directly destroys the dilated capillaries rather than causing thermal damage to the retinal pigment epithelial layer; thus, this treatment is less invasive than three-channel vitrectomy and more thorough, accurate and effective.

Surgical treatment

Surgical management of advanced Coats' disease has always been a challenge for surgeons. External and internal drainage of SRF has been performed for several decades [58, 59]. Vitrectomy is considered to be the ultimate means of resolving refractory retinal detachment in Coats' disease. The disadvantages of vitrectomy include a higher risk of complications and technical difficulty. The most serious complication is the creation of an iatrogenic retinal break. If such a break is created in a retina without surrounding exudate in an eye with minimal disease, the retinal break can be sealed and the retina reattached without much difficulty. However, if a break is created in a retina with a large amount of surrounding exudates in an eye with a high disease burden, retinal reattachment can be very challenging. With the application of anti-VEGF drugs, the incidence of refractory retinal detachment has been reduced. Relatively good anatomical outcomes have been reported; however, postoperative functional results, particularly in young patients and/or severe cases, seem to be limited [60]. Li et al. demonstrated that in patients with stage 3B Coats' disease, ablative therapy with a combination of pars plana vitrectomy (PPV), SRF (XD) or scleral buckling (SB) was effective in preventing progression to neovascular glaucoma or phthisis [61]. Desai et al.

demonstrated a technique involving external transscleral fluid drainage, initially via passive drainage and then via active aspiration with an aspiration cannula on a vitrectomy machine. After attaching the retina, cryotherapy was applied to ablate any abnormal vessels. Avastin was injected at the end of the procedure. This technique is less invasive/traumatic and helps to provide early recovery with good postoperative outcome. Imaizumi et al. performed external SRF and lens-sparing vitrectomy, and 0.5 mg of bevacizumab was injected in a patient with advanced Coats' disease. A reduction in SRF and exudate was observed after 3 months, and during the 11 months of follow-up, the condition of the eye remained unchanged [62]. Suesskind et al. performed a retrospective analysis of 13 patients (13 eyes) with Coats' disease who underwent vitrectomy. 77% of the patients had abnormal vascular and exudative retinal detachments that increasingly regressed over time following surgery, 27% of the patients had improved VA, 36% of the patients had sustained vision, 36% of the patients had VA deteriorated, and in two eyes, VA could not be evaluated because of young age. As a result of long-term inflammatory responses, patients with Coats' disease often have an epiretinal membrane, and sustained vitreous macular traction can also aggravate retinal exudation. Studies have shown that stripping the epiretinal membrane during surgery can help improve visual function [63]. Karacorlu et al. evaluated 23 patients with advanced Coats' disease with a follow-up of at least 1 year and demonstrated that 23-gauge PPV combined with cryotherapy, laser photocoagulation and intraocular tamponade could be an effective treatment option for advanced Coats' disease, achieving high anatomical success and stable or even improved VA, and minimizing the need for retreatment [59]. Mino et al. reported a case of adult-onset Coats' disease with a proliferative epiretinal membrane without prior treatment that was successfully treated with 25-gauge PPV combined with epiretinal membrane peeling, laser photocoagulation and cryotherapy [64]. In addition, vitrectomy can remove a large number of cytokines from the vitreous and prevent the disease from worsening.

Intravitreal adjuvant therapy

Anti-VEGF treatment

The pathogenesis of Coats' disease is being researched, and VEGF may play a major role. The level of VEGF in the eyes of Coats' disease patients was significantly higher than that in those in a control group [65, 66]. He et al. [67] reported the levels of VEGF in four eyes with Coats' disease (mean 2394.5 pg/ml) and VEGF levels in five eyes with rhegmatogenous retinal detachment (mean 15.3 pg/ml). They noted a reduction in VEGF from 1247 to 20.4 pg/ml in one eye treated with a single injection of bevacizumab. Intravitreal bevacizumab was recommended after 2008 and was used in eyes with stage 2B disease and advanced-stage disease. Zhao et al. [23] observed that the aqueous VEGF concentrations significantly increased from 91 ± 32 pg/ml in Coats' disease patients with stage 2 to 100 ± 37 pg/ml in patients with stage 3A1, 185 ± 56 pg/ml in patients with stage 3A2, and 256 ± 93 pg/ml in patients with stage 3B, indicating that the increasing severity of Coats' disease is greatly associated with intraocular VEGF concentrations. Several studies have confirmed that intravitreal injection of anti-VEGF agents (bevacizumab and ranibizumab) can significantly reduce macular edema and exudates in the retina, and the incidence of exudative retinal detachment can be reduced by a single administration [68].

Giannakopoulo et al. evaluated the effectiveness of intravitreal ranibizumab in combination with laser photocoagulation in the management of a 13-year-old boy with Coats' disease. They demonstrated that anti-VEGF drugs contributed to decreases in the vascular permeability of capillary endothelial cells, thus increasing the efficacy of laser application [69]. As adjuvant therapy, anti-VEGF drugs combined with retinal laser photocoagulation, cryotherapy and vitreoretinal surgery for advanced Coats' disease can significantly improve the best-corrected VA and greatly prevent the serious consequences of Coats' disease, such as neovascular glaucoma and ocular atrophy. There are also different opinions on the application of VEGF drugs. The use of intravitreal bevacizumab and ranibizumab in Coats' disease is considered to possibly be associated with the development of vitreoretinal fibrosis and subsequent traction retinal detachment. Kam et al. demonstrated a

potential adverse effect—rapid development of an "epiretinal membrane" following a single injection of intravitreal bevacizumab in a patient with stage 2 juvenile Coats' disease [70]. Ramasubramanian et al. performed conventional treatment combined with bevacizumab (Avastin; Genentech, San Francisco, California, USA) intravitreal injection in 8 eyes with stage 2–3B Coats' disease, and following the observation period, vitreous fibrosis developed (4 eyes, 50%) at a mean of 5 months post-treatment after a mean of 1.75 bevacizumab injections; three eyes (38%) evolved into traction retinal detachment; therefore, the authors believe that bevacizumab should be used with caution [65]. However, Villegas et al. performed a retrospective analysis of 24 patients who presented with exudative retinal detachments associated with advanced Coats' disease, and all the patients were treated with laser photocoagulation combined with intravitreal bevacizumab injection. During follow-up, no patient developed progressive retinal detachment, neovascular glaucoma or ocular atrophy. All eyes had good retinal reattachment [71]. Li et al. studied seventeen stage 3 Coats' disease patients treated with vitreal injection of ranibizumab as the initial treatment and subsequent treatment, including cryotherapy and laser photocoagulation. The results showed that all patients had different degrees of SRF absorption and some of the new blood vessels subsided. No ocular or systemic complications were observed during follow-up [72]. Lin et al. evaluated three eyes with Coats' disease treated with intravitreal bevacizumab as a primary treatment. Laser photocoagulation and cryotherapy were performed after resolution of the SRF at 1–3 months. No ocular or systemic complications related to bevacizumab were observed during the 1-year follow-up in all three cases, indicating that intravitreal bevacizumab injection is an effective and safe treatment for Coats' disease [73]. Lin et al. evaluated anti-VEGF drug therapy combined with laser photocoagulation and cryotherapy in 10 eyes of 9 patients with Coats' disease. Only 1 eye treated with bevacizumab combined with cryotherapy showed vitreoretinal proliferation and traction retinal detachment. The authors believe that the natural course of Coats' disease develops rapidly. Vitreoretinal proliferation and traction retinal detachment that occurs after a very small number of drug treatments may not be caused by drugs but by the development of the disease [74]. Fiorentzis et al. treated a 14-year-old patient with intravitreal bevacizumab after cryotherapy treatment. The retinal exudate was not relieved. After another session of cryotherapy and laser treatment, three intravitreal bevacizumab injections were performed. At 22 months of follow-up, the exudative retinal detachment gradually disappeared, the patient's symptoms disappeared, and the patient's VA was 0.8 [75]. Park et al. [76] studied 13 eyes of 13 patients with adult-onset Coats' disease and demonstrated that intravitreal bevacizumab injection combined with laser treatment may be an effective option for adult-onset Coats' disease. Kodama et al. demonstrated that after laser photocoagulation treatment in a 15-year-old patient with monocular stage 3A Coats' disease, recurrence occurred after 5 months. The changes in exudate were resistant to laser therapy, so intravitreal bevacizumab was added as an adjuvant before photocoagulation. Fourteen days after intravitreal bevacizumab injection, phased laser photocoagulation was administered, and a good prognosis was obtained with decreased exudation and improved VA. For another 11-year-old patient with monocular stage 3A disease, multiple laser photocoagulation treatments were performed; however, the exudative changes were resistant. Laser photocoagulation was performed 7 days after intravitreal bevacizumab injection. After 1-year follow-up, the best-corrected VA was improved to 0.7, the subfoveal hard exudates were reduced, and the OCT images showed interruptions in the subfoveal external limiting membrane (ELM) and inner segment/outer segment (IS/OS) were repaired. Ranibizumab has a shorter half-life and a lower serum concentration after injection than bevacizumab [77]. Gaillard et al. used ranibizumab combined with laser photocoagulation and cryotherapy in patients with stage 3B and 4 Coats' disease. After 4 years of follow-up, 8 of 9 eyes achieved anatomical success, 5 had fibrotic vitreoretinopathy, and 1 had retinal detachment and final atrophy. In the past, only 22% of patients with stage 4 Coats' disease have achieved globe preservation, but with this treatment, 4 patients with stage 4 disease retained the eyeball, 3 eyes had anatomical success, and 4 eyes had an improved visual function [78]. Although several studies have highlighted the efficacy of adjunctive bevacizumab injections combined with laser photocoagulation, Shieh et al. presented a case of Coats' disease in which treatment with aflibercept was effective in a patient with refractory macular edema

Table 2 A summary of the published experience to date with intravitreal anti-VEGF treatment in Coats' disease

First author	Year	Patients (*n*)/ age (a)	Follow-up (months)	Additional treatment	Comments
Lin [73]	2010	3 (0.5–12)	12	Cryotherapy, laser	Resolution of subretinal fluid without adverse reaction
Ramasubramanian [65]	2012	8 (0.6–20)	8.5	Cryotherapy, laser, sub-Tenon's fascia triamcinolone	Vitreous fibrosis developed (50%) evolving into traction retinal detachment (38%), bevacizumab should be used with caution
Lin [74]	2013	9 (0.5–12)	40.50 ± 20.52	Laser	90% anatomical improvement, 70% visual improvement, 20% visual stabilization, 10% visual deterioration
Kodama [77]	2014	2 (11–15)	3	Laser	IVB is effective for Coats' disease with exudative change resistant to laser therapy
Gaillard [78]	2014	8 (0.92–3.2)	50	Cryotherapy, laser	Ranibizumab plays an important role in advanced disease by transient restoration of the hemato–retinal barrier and suppression of neovascularization to facilitate classic treatment
Villegas [71]	2014	24 (0.75–13.3)	22.4	Laser	Repetitive intravitreal bevacizumab combined with laser ablation may be utilized effectively for advanced Coats' disease presenting with exudative retinal detachment
Fiorentzis [75]	2015	1 (14)	22	Cryotherapy, laser	The exudative retinal detachment disappeared, improved vision
Park [76]	2015	13 (23–54)	24.8	Laser	IVB combined with laser may be an effective treatment option for adult-onset Coats' disease. Poor initial BCVA and the occurrence of subfoveal hard exudates at baseline were associated with poor prognosis
Yang [80]	2016	17 (2–15)	9.7 ± 3.3	Cryotherapy, laser	Intravitreal ranibizumab combined with cryotherapy/laser as an initial treatment is an effective and safe treatment approach for Coats' disease
Giannakopoulo [69]	2017	1/13	72	Laser	The retina was flat with no signs of macular edema or exudates, improved vision
Li [72]	2017	17 (2–11)	24.12 ± 5.99	Cryotherapy, laser	All patients had different degrees of subretinal fluid absorption and new blood vessels subsided during follow-up, improved vision
Kam [70]	2018	1/7	4	Laser 25 + PPV	IVB may induce rapidly progressive "epiretinal membrane" in patients with juvenile Coats' disease

IVB Intravitreal bevacizumab injection; *BCVA* baseline best-corrected visual acuity

unresponsive to bevacizumab and laser photocoagulation [79]. Yang et al. studied seventeen Coats' disease patients with stage 3A and 3B disease and demonstrated that intravitreal ranibizumab combined with laser photocoagulation or cryotherapy as an initial treatment was an effective and safe treatment for Coats' disease that may improve VA and reduce SRF, exudates and telangiectasia [80]. A summary of the published experiences to date with intravitreal anti-VEGF treatment in Coats' disease patients is presented in Table 2. Further studies are necessary to establish the efficacy and safety of anti-VEGF therapy in Coats' disease.

Intravitreal corticosteroid therapy

Intravitreal corticosteroids are known to attenuate vascular leakage and leukostasis and suppress inflammation [81]. The efficacy of intravitreal dexamethasone implants for the initial management of Coats' disease has been reported recently [82]. Bergstrom et al. performed retinal cryotherapy in 5 eyes of 5 patients with stage 3B Coats' disease who had already received intravitreal injections of triamcinolone acetonide, and 75% of the patients developed severe vitreous hyperplasia and traction retinal detachment [83]. Othman et al. demonstrated that the application of triamcinolone acetonide combined with laser or cryotherapy improved the patients' VA, but treatment with triamcinolone acetonide was complicated by cataract formation and high intraocular pressure. These complications limit the application of triamcinolone acetonide [84]. Intravitreal dexamethasone implantation is another alternative but has a better safety profile than triamcinolone acetonide injection. Saatciao et al. achieved good results in 2 eyes of 2 patients with Coats' disease who underwent intravitreal injection of dexamethasone and laser photocoagulation. They believed that dexamethasone had fewer side effects than triamcinolone acetonide and was a viable drug for the treatment of Coats' disease [85]. Latest in the management of Coats' disease is the use of intravitreal dexamethasone implants. Kumar et al. used dexamethasone implants as the primary treatment for a 41-year-old female patient with massive exudation; when the SRF was absorbed, laser photocoagulation was performed to obliterate the abnormal vasculature and hyperpermeable aneurysmal dilatations. Combined therapy with intravitreal steroids and laser photocoagulation/cryotherapy can have sustained and long-term effects for keeping the disease under control [86].

Conclusions and perspectives

At present, experts do not completely agree on the treatment plans for Coats' disease. It is generally accepted that children should be examined under general anesthesia. Wide-angle fluorescein imaging and OCT should be routinely performed. Laser photocoagulation should be performed in patients with stage 1 Coats' disease or patients with mild symptoms. When the risk of macular involvement is present, early laser photocoagulation can help retain the patient's vision. For patients with macular edema, anti-VEGF therapy alone should be effective; for patients with stage 2 or 3 Coats' disease, adult patients with macular follicular telangiectasia and less exudation may be treated with laser photocoagulation to prevent exudative retinal detachment. Patients who are treated with anti-VEGF therapy at an outpatient clinic should be followed up once a month. For patients with significant macular edema, retinal effusion and exudative retinal detachment, laser photocoagulation should be performed after anti-VEGF therapy; patients with stage 3 and 4 Coats' disease should undergo invasive vitrectomy or SRF drainage and appropriate laser photocoagulation or cryotherapy for peripherally abnormal capillaries. Patients with stage 5 Coats' disease with persistently painful, blind eyes should undergo enucleation, while patients with no light perception and a comfortable, cosmetically acceptable globe may be observed.

The use of wide-angle fluorescein imaging has made the early diagnosis of many cases of asymptomatic Coats' disease possible. Early diagnosis and timely treatment based on clinical stage are critical to retaining the patient's visual function. At present, Coats' disease treatment is still controversial, but many studies have confirmed that anti-VEGF therapy combined with laser photocoagulation for early Coats' disease and anti-VEGF therapy combined with minimally invasive vitrectomy for advanced Coats' disease can achieve good efficacy. Coats' disease is considered a chronic disease, so patients should be aware that close long-term follow-up is necessary. In addition, advances in the study of the pathogenesis of Coats' disease with the development of technology may provide new targets for the treatment of Coats' disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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