# Anti-VEGF as Adjunctive Therapy for Coats Disease

In this case report, anti-VEGF therapy obviated the need for subretinal drainage, improving outcomes.

BY KARL WAITE, MD; EUGENE NG, MD, MBA; AND MICHAEL D. BENNETT, MD

Coats disease is an idiopathic exudative retinopathy characterized by abnormal retinal vascular development (telangiectasia) that results in massive intraretinal and subretinal lipid accumulation. This disease entity was first described by a Scottish ophthalmologist, George Coats, in 1908.[1] Coats disease is classically a unilateral process (80% of cases) affecting young males with a peak age of diagnosis at 6 to 8 years of age, without racial predominance. Males are affected three times as often as females. An adult variant of the disease is less commonly seen and is frequently associated with hypercholesterolemia.

## PATHOPHYSIOLOGY OF COATS DISEASE

The clinical picture of Coats disease is that of localized, lipid-rich, subretinal exudation and abnormal vasculature, including aneurysmal dilitations, telangiectasias, areas of capillary nonperfusion, and neovascularization. Shields et al[2] defined the stages of Coats disease as following Stage 1 is limited to retinal telangiectasia. Stage 2 includes telangiectasia with exudation (2A is extrafoveal and 2B is foveal exudation). Stage 3 occurs with development of an exudative retinal detachment (3A subtotal and 3B total retinal detachment). Stage 4 has total retinal detachment with glaucoma, and Stage 5 is advanced, end-stage disease. The natural history of Coats disease is generally progressive, but in a variably relapsing-remitting fashion. Spontaneous remissions have rarely been reported.[3]

The clinical picture of Coats disease is that of localized, lipid-rich, subretinal exudation and abnormal vasculature.

In 1971, Tripathi and Ashton[4] described in detail the pathologic features of Coats disease, comprised of a host of retinal abnormalities, in particular the absence of endothelium and pericytes in aberrant retinal blood vessels. They proposed presciently that abnormal endothelial permeability, ie, breakdown of the inner blood-retinal barrier, was the primary pathology. Whether this breakdown was structural or functional, it would secondarily result in telangiectasis and leakage. Three decades later, Black et al,[5] through genetic analysis, proposed that a somatic mutation in the NDP gene, which results in a deficiency of the protein norrin, is a causal factor in Coats disease. The NDP gene is responsible for Norrie disease, and researchers believe that norrin is important in normal retinal vasculogenesis.

## TREATMENT OF COATS DISEASE

Early therapeutic intervention is necessary to halt the progression of Coats disease. Laser photocoagulation or

Figure 1. Subretinal exudation extending into the fovea.

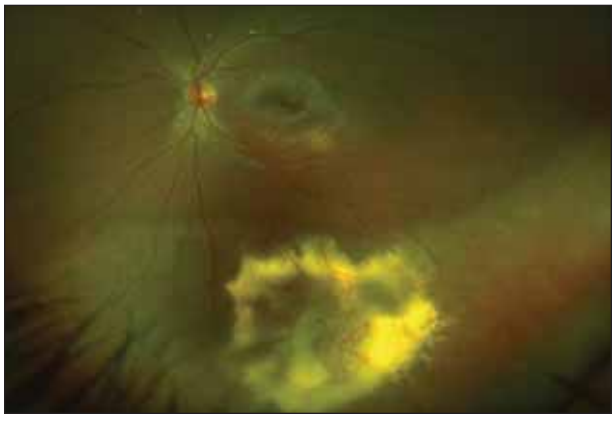

Figure 2. Subretinal exudation inferior to the macula.

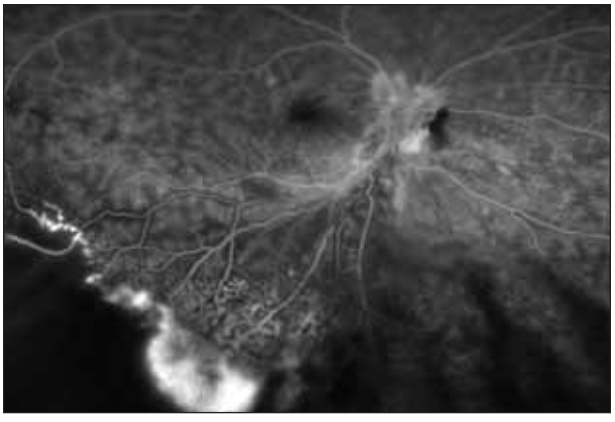

Figure 3. Fluorescein angiography of the right eye shows abnormal inferotemporal vessels with aneurysmal dilatation and telangiectasia with profuse leakage.

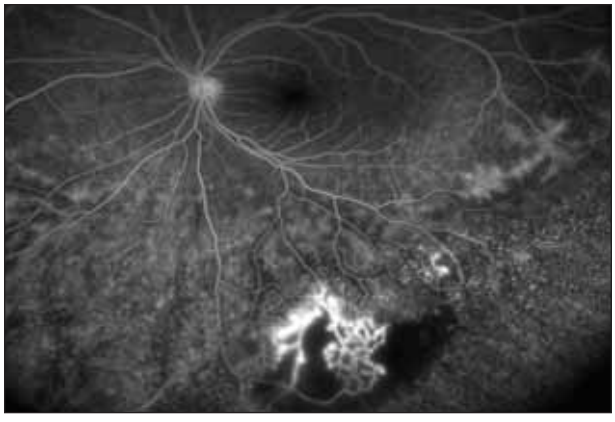

Figure 4. Fluorescein angiography of the left eye shows similar changes as in Figure 3, but less severe.

Figure 5. Photo of the right eye 7 months after treatment. The patient's vision improved to 20/20 in both eyes.

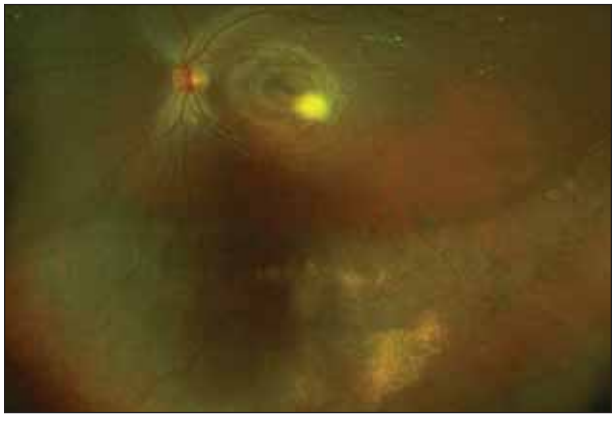

Figure 6. Photo of the left eye 7 months after treatment.

cryotherapy are traditionally employed to destroy abnormal retinal vessels in the early stages of the disease. More advanced stages typically require surgical interventions, such as vitrectomy, scleral buckling, subretinal fluid drainage, and vitreous replacement with air, gas, or silicone oil for retinal reattachment. These traditional approaches, however, in particular cryoablation, can incite further inflammation and breakdown of the blood-retinal barrier,

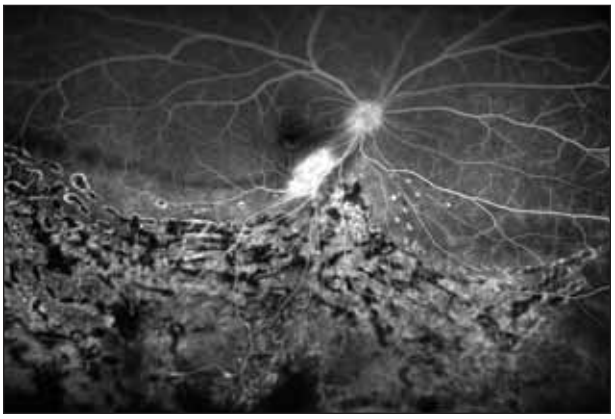

**Figure 7. Fluorescein angiography of the right eye 5 months after treatment demonstrated obliteration of abnormal vessels with cessation of peripheral leakage in both eyes.**

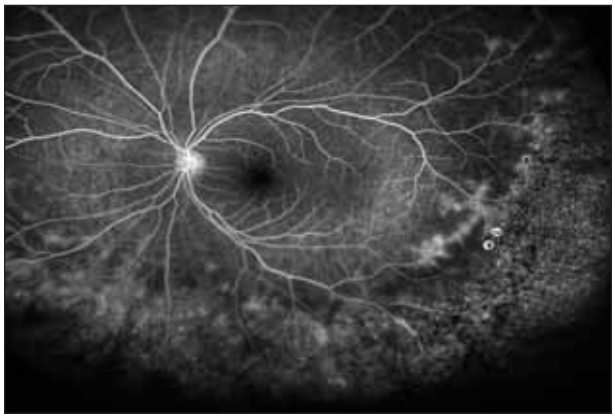

**Figure 8. Fluorescein angiography of the left eye 5 months after treatment.**

which compromise the visual outcome. Recently, anti-vascular endothelial growth factor (anti-VEGF) agents (bevacizumab [Avastin, Genentech, Inc.], ranibizumab [Lucentis, Genentech, Inc.], and pegaptanib sodium [Macugen, Eyetech]) have been used adjunctively. Intraocular corticosteroids have also been employed.

Multiple case reports and case series document beneficial responses to anti-VEGF agents in Coats' disease.[6-13] Intraocular VEGF is noted to be elevated in Coats disease.[13] Typically, anti-VEGF agents are used to stabilize the blood-retina barrier and reduce the amount of subretinal exudation prior to laser photocoagulation. These reports often document substantial improvement of visual acuity, rather than mere stabilization of the disease process or preservation of the globe, as is expected with more traditional approaches.

## CASE REPORT

One exemplary case from our institution is that of a 15 year-old boy who presented with bilateral Coats disease. The patient presented with decreased visual acuity (20/50) in his right eye secondary to subretinal exudation extending into the fovea (Figure 1) and peripheral visual field changes in his left eye (visual acuity 20/20) secondary to subretinal exudation inferior to the macula (Figure 2). Fluorescein angiography of the right eye (Figure 3) revealed abnormal inferotemporal vessels with aneurysmal dilatation and telangiectasia, which leaked profusely. Peripheral to the abnormal vasculature was an area of capillary nonperfusion. Fluorescein angiography of the left eye (Figure 4) demonstrated similar vascular changes, but of less severity. The patient was treated with intravitreal bevacizumab and laser photocoagulation, followed by vitrectomy with fluid-air exchange in his right eye. His left eye was treated with laser photocoagulation only, as the amount of subretinal exudation did not necessitate treatment with intravitreal bevacizumab.

Seven months after treatment, the patient regained vision to 20/20 in both eyes (Figures 5 and 6). Fluorescein angiography 5 months after treatment demonstrated obliteration of abnormal vessels with cessation of peripheral leakage in both eyes (Figures 7 and 8). The peripheral retina completely flattened in both eyes and now has an epiretinal membrane that developed over the course of treatment in the right eye.

## DISCUSSION

Given the rarity of Coats disease and its variable course, therapeutic strategies have to be tailored to each individual patient. As with other diseases, a search for approaches that improve outcomes with fewer side effects is warranted. A promising new addition to our retinal tool kit is perioperative intravitreal anti-VEGF agents. With reduction of vascular permeability, there have been reports of reduction in subretinal lipid exudation, exudative retinal detachment, and macular edema in patients with Coats. This enables more effective laser photocoagulation, as the retina is better apposed to the retinal pigment epithelium following anti-VEGF treatment. In our case, we believe that the use of intravitreal bevacizumab obviated the need for subretinal fluid drainage, and we support its use as an adjunct prior to laser photocoagulation. The promising efficacy signals observed with anti-VEGF agents suggest that VEGF plays a role in the pathophysiology of Coats disease. Areas of retinal ischemia are present in the disease, and anti-VEGF therapies presumably act by reducing vascular permeability secondary to VEGF blockade.

In summary, a multimodality and stepwise approach to the treatment of Coats disease, including the use of

tools that target the pathophysiology of the disease, appears to provide encouraging results. ■



*Karl Waite, MD, is a vitreoretinal fellow at the Retina Institute of Hawaii in Honolulu.*

*Eugene Ng, MD, MBA, is a vitreoretinal surgeon at the Retina Institute of Hawaii.*

*Michael D. Bennett, MD, is a vitreoretinal surgeon at the Retina Institute of Hawaii and an Associate Professor in the Department of Surgery at the University of Hawaii, John A. Burns School of Medicine. He states that he is a paid consultant to Alcon Laboratories, Inc., Allergan, Inc., Genentech, Inc., Optimedica, Optos, Optovue, (OSI) Eyetech, Heidelberg Engineering, and Neovista. Dr. Bennett is a* Retina Today *Editorial Board member. He can be reached at +1 808 955 0255.*

1. Coats G. Forms of retinal disease with massive exudation. *Royal London Ophthalmic Hospital Reports*.1908;17(3):440-525.
2. Shields JA, Shields CL, Honavar SG, Demirci H, Cater J. Classification and management of Coats disease: the 2000 Proctor Lecture. *Am J Ophthalmol*. 2001;131:572-583.
3. Jones JH, Kroll AJ, Lou PL, Ryan EA. Coats' disease. *Int Ophthalmol Clin*. 2001;41(4):189-198.
4. Tripathi R, Ashton N. Electron microscopical study of Coat's disease. *Br J Ophthalmol*. 1971;55(5):289-301.
5. Black GC, Perveen R, Bonshek R, et al. Coats disease of the retina (unilateral retinal telangiectasis) caused by somatic mutation in the NDP gene: a role for norrin in retinal angiogenesis. *Hum Mol Genet*. 1999;8(1):2031-2035.
6. Chiu SL, Chen SN, Chen YT, Chen PJ. Coats' Disease and neovascular glaucoma in a child with neurofibromatosis. *J Pediatr Ophthalmol Strabismus*. 2010 Feb 26:1-3. [Epub ahead of print]
7. Entezari M, Ramezani A, Safavizadeh L, Bassirnia N. Resolution of macular edema in Coats' disease with intravitreal bevacizumab. *Indian J Ophthalmol*. 2010;58(1):80-82.
8. Kaul S, Uparkar M, Mody K, Walinjkar J, Kothari M, Natarajan S. Intravitreal anti-vascular endothelial growth factor agents as an adjunct in the management of Coats' disease in children. *Indian J Ophthalmol*. 2010;58(1):76-78.
9. Lin CJ, Hwang JF, Chen YT, Chen SN. The effect of intravitreal bevacizumab in the treatment of Coats disease in children. *Retina*. 2009 Dec 4. [Epub ahead of print]
10. Lin KL, Hirose T, Kroll AJ, Lou PL, Ryan EA. Prospects for treatment of pediatric vitreoretinal diseases with vascular endothelial growth factor inhibition. *Semin Ophthalmol*. 2009;24(2):70-76. Review.
11. Jun JH, Kim YC, Kim KS. Resolution of severe macular edema in adult Coats' disease with intravitreal triamcinolone and bevacizumab injection. *Korean J Ophthalmol*. 2008;22(3):190-193.
12. Cakir M, Cekiç O, Yilmaz OF. Combined intravitreal bevacizumab and triamcinolone injection in a child with Coats disease. *J AAPOS*. 2008;12(3):309-311.
13. Sun Y, Jain A, Moshfeghi DM. Elevated vascular endothelial growth factor levels in Coats disease: rapid response to pegaptanib sodium. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(9):1387-1388.

**SHARE YOUR FEEDBACK**

Would you like to comment on an author's article?
Do you have an article topic to suggest?
Do you wish to tell us how valuable
*Retina Today* is to your practice?
We would like to hear from you. Please e-mail us at letters@bmctoday.com with any thoughts or questions you have regarding this publication.