



Identification of Retinal Vascular Lesions Using Ultra-Widefield Angiography in Hereditary Hemorrhagic Telangiectasia Patients

Samrat Sindhar, BS,¹ Bliss E. O'Bryhim, MD, PhD,² Jordan Licata, DO,¹ Jay F. Piccirillo, MD,¹ Rajendra S. Apte, MD, PhD^{2,3,4}

Purpose: To determine the presence and to characterize location of retinal vascular lesions in patients with hereditary hemorrhagic telangiectasia (HHT).

Design: Prospective cross-sectional pilot descriptive study.

Participants: Eighteen patients (age range, 22–65 years) with a clinical diagnosis of HHT.

Methods: Patients completed the 25-item National Eye Institute Visual Function Questionnaire and underwent a single study visit with dilated ophthalmic examination, OCT angiography (OCTA), and fluorescein angiography (FA) with widefield imaging.

Main Outcome Measures: Presence of retinal vascular abnormalities in 1 or more quadrants identified on widefield FA, Visual Function Questionnaire scores, retinal vessel architecture on FA and OCTA, and dilated ophthalmic examination findings.

Results: Of the 18 patients recruited, fine telangiectatic vessels with capillary dilation and tortuosity were identified in 78% by FA imaging.

Conclusions: In the first FA and OCTA analysis of the retina of unrelated HHT patients, we found a high rate of temporal and nasal telangiectasias. These telangiectasias were more apparent in older patients, suggesting that they may appear in later stages of HHT development. No abnormalities of the macular vasculature and architecture were identified, explaining the generally well-preserved visual acuity. Temporal and nasal telangiectasias may have clinical significance in a patient's risk for retinal hemorrhage and likely warrant periodic surveillance by annual FA imaging. *Ophthalmology Retina* 2019;3:510-515 © 2019 by the American Academy of Ophthalmology

Hereditary hemorrhagic telangiectasia (HHT) is a genetic vasculopathic syndrome with an incidence rate of 1 in 10 000 patients per year. Most cases are caused by an autosomal dominant mutation in 1 of 4 genes that are critical for regulating blood vessel development and response to transforming growth factor β signaling.¹ Clinically, HHT is diagnosed according to the Curacao criteria: (1) mucocutaneous telangiectasias; (2) recurrent epistaxis; (3) vascular telangiectasias in the gastrointestinal tract or arteriovenous malformations in the lungs, brain, liver, or spine; and (4) a family history of affected first-degree relatives.² Because of recurrent and persistent bleeding in 1 or more organs and associated comorbidities, patients often benefit from care by a multidisciplinary team of providers.

Ocular manifestations among HHT patients, although not a criterion for diagnosis, have been described in as many as 45% to 65% of patients.^{3–5} Hemorrhagic epiphora resulting from conjunctival telangiectasias is the most common ophthalmologic symptom, with a prevalence of

approximately 35% to 42%.^{3–5} A variety of retinal lesions also have been described in HHT patients, including dilation and tortuosity of veins, neovascularization, and parafoveal telangiectasias.^{6,7} Loss of vision secondary to retinal and vitreous hemorrhage in HHT patients with prior known retinal vascular abnormalities additionally has been reported,^{8,9} suggesting that retinal vascular lesions among these patients may predispose them to vision-threatening hemorrhage.

Several prior studies have investigated the prevalence of intraocular lesions among HHT patients. Vase and Vase⁵ identified retinal telangiectasias in 1 of 47 patients (2%), and a second study by Brant et al³ identified retinal lesions in 2 of 20 HHT patients (10%). However, these studies evaluated patients on routine ophthalmologic examination with slit-lamp examination and dilated funduscopic evaluation. Only 1 of 47 patients with a suspicious finding during routine examination underwent fluorescein angiography (FA) imaging in the study by Vase and Vase,⁵

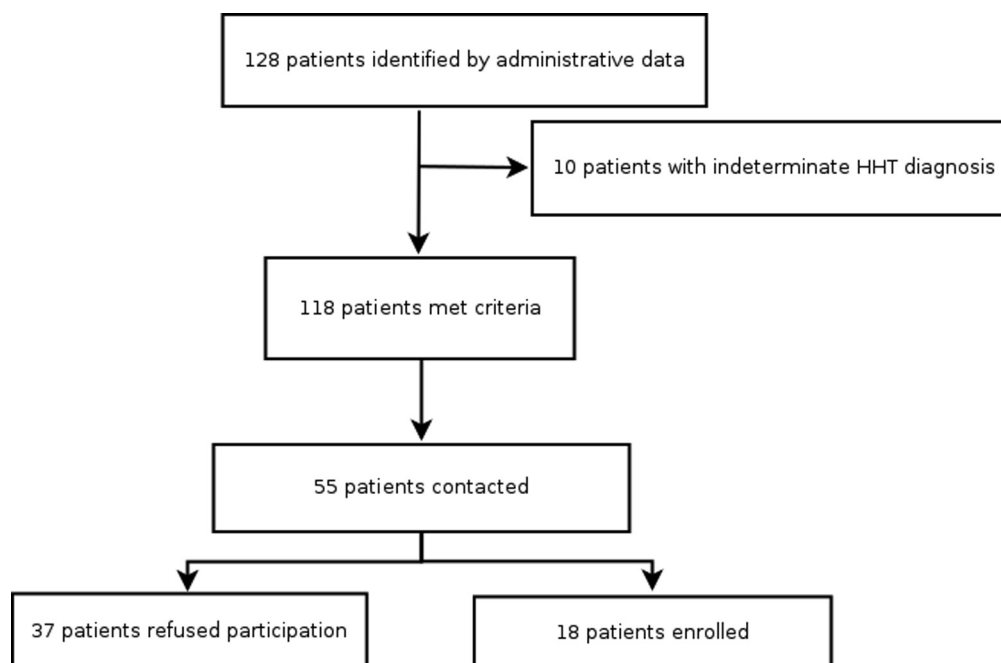


Figure 1. Flow chart showing participant recruitment and enrollment. HHT = hereditary hemorrhagic telangiectasia.

and none underwent FA in the Brant et al³ study, precluding identification of subtle vascular alterations imperceptible on funduscopy.

Fluorescein angiography is used routinely to detect subtle vascular abnormalities of the retina and choroid, such as in diabetic retinopathy and age-related macular degeneration.¹⁰ A prior study by Rinaldi et al¹¹ used routine FA in the evaluation of retinal abnormalities among 8 related family members with HHT with a single mutation in the *ALK1* gene and identified choriocapillaris atrophy in as many as 3 of 8 patients (38%).

In this cross-sectional study, we sought to determine the prevalence retinal abnormalities detected by widefield FA in HHT patients and to describe the distinct pattern and anatomic location of FA- and OCT-detected retinal abnormalities, as well as to correlate these abnormalities with functional visual disturbances. Our study is unique because of the combined approach of widefield FA to examine the far peripheral retina and OCT angiography (OCTA) to examine the central macula. In addition, our cohort represents participants with active HHT who have many systemic lesions requiring therapy.

Methods

Participants

Individuals 18 to 65 years of age who previously had been diagnosed with HHT by the Curacao criteria² were recruited from the practices of 2 Washington University physicians (JFP, Murali Chakinala) specializing in treatment of HHT patients and the Cure HHT Foundation. Of 128 patients identified by administrative data, 18 patients enrolled in the study (see Fig 1) between February 2017 and May 2018. Exclusion criteria

included (1) active conjunctival hemorrhage or bloody epiphora; (2) contraindications to fluorescein dye, including allergic hypersensitivity to fluorescein, pregnancy, history of severe reaction to any allergen, renal failure or undergoing dialysis, severe asthma, or significant cardiac disease; and (3) any ophthalmic pathologic feature precluding retinal imaging (e.g., dense cataract, corneal disease). Because this study was designed to be a descriptive evaluation of retinal lesions in HHT patients, no control participants were recruited because it was deemed unethical to subject individuals without known disease or pathologic features to FA without an indication.

Procedures

All participants were evaluated at the Washington University Eye Center. The study visit included completion of the 25-item National Eye Institute Visual Function Questionnaire,^{12,13} an HHT severity questionnaire, and a dilated eye examination. The OCTA images were collected with the Optovue Avanti RTVue XR machine (Optovue, Fremont, CA). Fluorescein angiography images were collected on an OPTOS Ultra Wideview California AF P200DTX device (Optos, Marlborough, MA).

Assessment of Images

The OCTA measurements were automated using the Optovue software from 6 OCT images per eye (right and left), which were treated separately rather than averaged, and thus collected in an objective manner. Each data point was reviewed to evaluate for potential confounding pathologic features (e.g., epiretinal membrane) or data collection error (e.g., motion artifact). Data outcomes collected included measurement of foveal and parafoveal thickness; macular, foveal, and parafoveal vascular density; and foveal avascular zone. Fluorescein angiography images were reviewed by 2 authors (BEO, RSA) who have significant experience with Optos imaging. Subjective information was collected on vascular changes found in HHT patients beyond normal peripheral, age-appropriate changes.

Table 1. Patient Characteristics (n = 18)

Characteristic	Data
Age (yrs), mean (SD)	52.3 (9.7)
Years since diagnosis, mean (SD)	23.2 (16.7)
Telangiectasias, no. (%)	
Lips or oral cavity	16 (89)
Eyelid	4 (22)
Other skin	14 (78)
Intranasal	16 (89)
Gastrointestinal	5 (28)
Arteriovenous malformations, no. (%)	
Pulmonary	10 (56)
Hepatic	7 (39)
Cerebral	4 (22)
Spinal	0 (0)
Family history, no. (%)	
>1 first-degree relative	11 (61)
1 first-degree relative	6 (33)
No family history	1 (6)
Chronic bleeding, no. (%)	
Epistaxis	16 (89)
Gastrointestinal bleeding	1 (6)
Patients meeting ≥ 3 Curacao criteria, no. (%)	17 (94)

SD = standard deviation.

Statistical Analysis

Basic descriptive statistical analyses were conducted using IBM SPSS Statistics for Windows version 24.0 (IBM Corp, Armonk, NY). OCT angiography data were compared with normative values available from Optovue for foveal and parafoveal thickness and with prior research for foveal and parafoveal vessel density.^{14,15} A 2-sided α with threshold of 0.05 was used for a 1-sample *t* test.

Institutional Review Board Approval

This study received institutional review board approval at Washington University School of Medicine in St. Louis on February 15, 2017 (identifier, 201612105) and adhered to the tenets of the Declaration of Helsinki and the provisions of the Health Insurance Portability and Accountability Act. All participants provided written informed consent.

Results

Eighteen patients were enrolled in the study. The mean age of patients was 52.3 years (range, 22–65 years). Of the 18 patients, 12 (67%) were women, 1 (6%) showed type 2 diabetes mellitus, and 5 (28%) showed hypertension. All patients met Curacao criteria for HHT diagnosis (Table 1): 16 (88%) showed recurrent epistaxis; 13 (72%) showed visceral arteriovenous malformations; 18 (100%) showed telangiectasias on the lips, eyes, face, gastrointestinal tract, or other skin; and 17 (94%) showed a family history of the disease. This study included 1 mother-and-son pair and 1 set of siblings, representing 16 total families.

All patients reported symptomatic bleeding, with 11 patients (61%) receiving oral or intravenous iron treatment, 3 (17%) requiring blood transfusions, and 10 (56%) undergoing sclerosing therapy for epistaxis. Prior complications of HHT requiring

Table 2. Visual Health among Patients

Characteristic	Mean (SD)
Best-corrected visual acuity (logMAR)	
Left eye	0.107 (0.139)
Right eye	0.103 (0.171)
Mean intraocular pressure (mmHg)	
Left eye	15.9 (2.7)
Right eye	16.3 (3.4)
25-Item Visual Function Questionnaire score	
Driving	91.7 (9.9)
Color	98.6 (5.9)
Peripheral	91.7 (19.1)
Composite	88.9 (6.8)
Ophthalmic examination findings, no. (%)	
Cataracts (both eyes)	5 (28)
Drusen (left eye/right eye/both eyes)	5 (28)
Vitreous syneresis	11 (61)

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

hospitalization in our study population included anemia or blood transfusion (n = 10), hemoptysis or hemothorax (n = 3), stroke or intracranial hemorrhage (n = 1), seizure (n = 1), and brain abscess (n = 1). All patients demonstrated a history of recurrent epistaxis, with 9 patients (56%) experiencing active bleeds at least daily, 8 patients (50%) experiencing bleeds of longer than 5 minutes, and 7 patients (41%) experiencing gushing epistaxis. At the time of the study, 7 patients (39%) self-reported anemia.

Ophthalmic Examination

Mean best-corrected visual acuity was 0.033 logarithm of the minimum angle of resolution in the right eye and 0.056 logarithm of the minimum angle of resolution in the left eye. Two of the 18 patients reported subjective deterioration of vision over the previous few years. The average composite Visual Function Questionnaire score was 88.9 (standard deviation, 6.8). No vascular abnormalities were noted on dilated ophthalmoscopy. Other findings of the ophthalmic examination are detailed in Table 2.

OCT Angiography Findings

OCT angiography data were collected from 29 eyes of 18 patients; data from 5 eyes were omitted because of significant motion artifact interfering with accurate analysis. Mean \pm standard deviation foveal avascular area was 0.253 ± 0.11 mm² (mean difference, -0.013 mm²; 95% confidence interval [CI], -0.06 to 0.03 mm²). Mean foveal vessel density was $31.96 \pm 5.21\%$ (mean difference, 2.06%; 95% CI, 0.15%–3.97%); mean parafoveal density was $53.73 \pm 3.09\%$ (mean difference, -0.47% ; 95% CI, -1.6% to 0.67%). Mean foveal thickness was 258.84 ± 24.46 μ m (mean difference, 3.64 μ m; 95% CI, -5.33 to 12.6 μ m); mean parafoveal thickness was 319.26 ± 12.25 μ m (mean difference, -0.34 μ m; 95% CI, -4.84 to 4.15 μ m).

Fluorescein Angiography Findings

Thirty of 36 eyes (83%) from 14 of 18 study participants (78%) were found to have peripheral areas of fine telangiectasias, with capillary dilation and tortuosity on review of FA imaging (Fig 2).

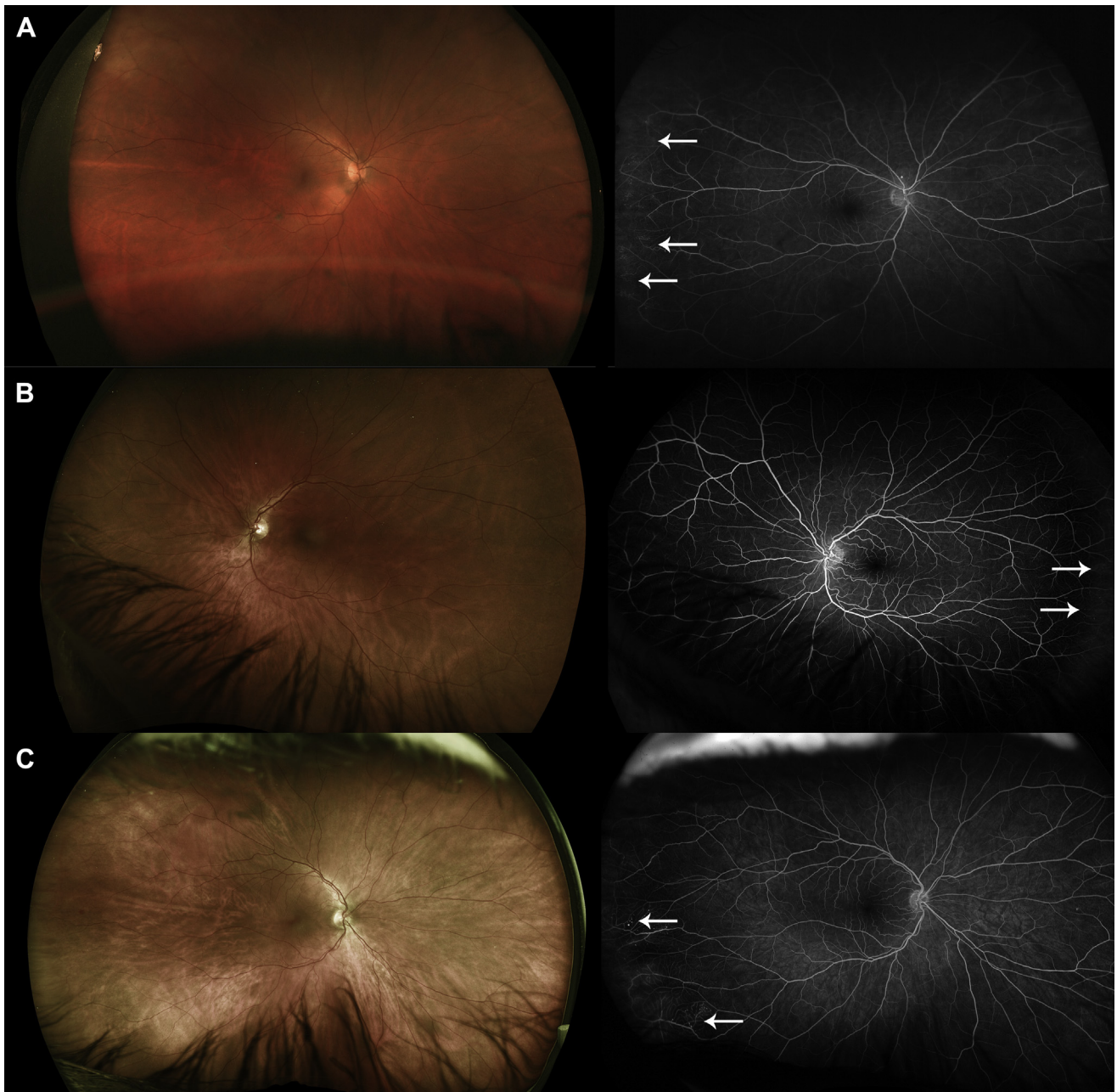


Figure 2. Example widefield color fundus photographs and corresponding angiograms from study participants with hereditary hemorrhagic telangiectasia. **A**, Right eye from a 52-year-old man showing temporal telangiectasias (arrows). **B**, Left eye from a 54-year-old man showing fine telangiectasias temporally (arrows). **C**, Right eye from a 43-year-old man demonstrating peripheral telangiectasias temporally (arrows).

Data from 6 eyes were omitted because of poor quality of images. Most patients showed telangiectasias in either the temporal or nasal retina; however, 3 participants demonstrated lesions in more than 1 quadrant. These findings were not readily apparent on color fundus photography (Fig 2).

Discussion

Ocular involvement is not included in the clinical diagnostic criteria of HHT. However, common ocular symptoms

include bloody epiphora and conjunctival telangiectasias. Previously reported retinal abnormalities include dilation and tortuosity of retinal vessels, parafoveal telangiectasias, and neovascularization, although reporting of intraocular lesions in HHT patients is highly variable and is not accompanied with information regarding the systemic burden of HHT on patients.^{6,7}

This was an in-depth vascular analysis of the peripheral retina of HHT patients using FA and OCTA. Most patients in our cohort (78%) were found to have peripheral telangiectasias in either the temporal or nasal retina. OCT

angiography analysis revealed no vascular or architectural alterations within the macula, and no patient demonstrated clinically actionable lesions, which may explain the relatively well-preserved visual acuity in this cohort of study participants. Only 2 patients reported subjective deterioration of visual acuity, and notably, both patients showed peripheral telangiectasias temporally.

Notably, the only 2 participants with no findings in either eye were younger than the mean age. It is plausible that these participants may demonstrate telangiectasias later in life, because nearly all patients older than the mean age showed peripheral telangiectasias; however, this study was not designed to follow up participants longitudinally. For example, although epistaxis emerges as an early clinical finding at an average of 12 years of age among HHT patients,¹⁶ telangiectasias commonly appear 10 to 30 years after the onset of epistaxis, and symptomatic gastrointestinal bleeding does not present until the fifth or sixth decade of life.¹⁷ This suggests that retinal telangiectasias may develop as a late complication of HHT. However, the natural history of vascular malformations across the lifespan of HHT patients is not well understood.¹⁸

Prior studies have shown that rates of retinal lesions vary from 0% to 10% in all patients,^{3–5} with no consistent topographic location of these lesions. Two prior case series of patients with HHT also reported fine telangiectic capillaries and tortuous arteriovenous malformations,^{19,20} although these were found in a minority of study participants. The authors in one of these studies³ acknowledged that subtle retinal vascular alterations may have been overlooked in the remaining participants that did not show fundoscopic abnormalities and consequently did not undergo FA examination.³ Certainly, the lack of obvious findings on clinical examination in all of our study participants would support this acknowledgement. The novel use of FA with widefield imaging likely explains the disparity in reported incidence of retinal findings in our cohort compared with those previously published. The clinical significance of these lesions may relate to the increased risk of patients with known retinal vessel malformations demonstrating vision-threatening hemorrhages.^{8,9} Our study showed that patients with HHT have a much higher proportion of vascular anomalies as compared with other patients with retinal vascular diseases, such as diabetes and age-related macular degeneration. However, intraocular lesions in HHT patients predominately affect the peripheral vasculature, whereas retinal vascular diseases typically affect the more metabolically active central vasculature of the retina.

Strengths of our study include enrollment of nonrelated patients, increasing generalizability to a larger spectrum of HHT patients compared with prior studies.¹¹ Additionally, we assessed patients undergoing active treatment for HHT-related multisystem pathologic features, whereas prior studies have not assessed disease severity among patients.^{3,5} However, our study has its limitations. Of 118 individuals, we were able to contact only 55 individuals and recruit only 18 participants, which may be a reflection of the

tertiary care setting. The lack of genetic testing of all our study participants limits our ability to determine if these findings are associated with specific genotypes.

Based on these results, we recommend that HHT patients follow up with an ophthalmologist or retinal specialist to obtain baseline FA with widefield imaging to document subtle, peripheral retinal vascular alterations, in addition to annual dilated examinations with repeated FA to monitor for progression of disease or presence of any lesions that warrant more frequent monitoring. In addition to providing improved surveillance of any lesions that may put patients at increased risk of vision-threatening hemorrhage, increased monitoring with FA would improve our understanding of the natural history of the retinal involvement in HHT and would provide longitudinal assessment of the evolution of these lesions.

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¹ Department of Otolaryngology-Head and Neck Surgery, Washington University in St. Louis, St. Louis, Missouri.

² Department of Ophthalmology and Vision Science, Washington University in St. Louis, St. Louis, Missouri.

³ Department of Medicine, Washington University in St. Louis, St. Louis, Missouri.

⁴ Department of Developmental Biology, Washington University in St. Louis, St. Louis, Missouri.

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Sindhar, O'Bryhim, Licata, Piccirillo, Apte

Analysis and interpretation: Sindhar, O'Bryhim, Licata, Piccirillo, Apte

Data collection: Sindhar, O'Bryhim, Licata, Apte

Obtained funding: Sindhar, Piccirillo, Apte

Overall responsibility: Sindhar, O'Bryhim, Piccirillo, Apte

Abbreviations and Acronyms:

CI = confidence interval; **FA** = fluorescein angiography;

HHT = hereditary hemorrhagic telangiectasia; **OCTA** = optical coherence tomography angiography.

Correspondence:

Rajendra S. Apte, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, Washington University in St. Louis, 660 South Euclid Avenue, Box 8096, St. Louis, MO 63110. E-mail: apte@wustl.edu.