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Regression of Choroidal Neovascularization Results in Macular Atrophy in Anti-Vascular Endothelial Growth Factor-Treated Eyes

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Abstract

PURPOSE: To determine the incidence and progression of macular atrophy in patients with neovascular age-related macular degeneration (AMD) treated with vascular endothelial growth factor (VEGF) antagonists.

DESIGN: Retrospective interventional case series.

METHODS: All patients with neovascular AMD treated by the same physician during a 12-month period of ascertainment had all images from their entire follow-up period evaluated, and areas of retina that developed atrophy were compared to the same areas prior to the onset of anti-VEGF treatment. Longitudinal measurements of retinal atrophy were made.

RESULTS: In 39 patients, 52 eyes with neovascular AMD were identified. We excluded 5 eyes from analysis (4 had retinal pigment epithelium tears, and 1 had a laser scar). Fundus photographs of the remaining eyes showed that 18/47 eyes (38%) contained hypopigmented areas suggestive of atrophy within the macula at some time during follow-up. Spectral-domain optical coherence tomography confirmed that these areas had loss of retinal pigmented epithelium and ellipsoids zones, with or without subretinal material suggestive of subretinal fibrosis. Comparison of fundus photographs with fluorescein angiograms showed that in 13/18 eyes (72%), atrophy developed in areas previously occupied by choroidal neovascularization, and the other 5 eyes had atrophy

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prior to the onset of anti-VEGF treatment. The mean (±standard deviation) rate of increase in pure atrophic areas (no subretinal material) was 0.7 ± 0.8 mm^2 per year, with a range of 0.01–2.6 mm^2/year.

CONCLUSION: Treatment of neovascular AMD with a VEGF-neutralizing protein can result in regression of choroidal neovascularization, which is sometimes associated with atrophy of overlying retina.

AGE-RELATED MACULAR DEGENERATION (AMD) IS A common cause of visual loss in residents in developed countries. It is characterized by deposits beneath the retinal pigmented epithelium (RPE) called drusen. The clinical course is quite variable; some patients maintain stable vision for many years while others experience gradual or rapid loss of vision. In some cases, gradual loss of vision occurs in association with the slowly progressive death of the RPE and photoreceptor cells, resulting in areas of retinal atrophy. Atrophy may occur as single or multifocal patches that slowly increase in size, often forming a horseshoe-shaped area of atrophy that surrounds the fovea and can eventually extend into the fovea, causing loss of central vision. This pattern of progression is referred to as geographic atrophy (GA), and the risk of its occurrence is increased in eyes with large soft drusen and pigmentary changes in the macula.[1] In about 10% of patients with AMD, gradual or rapid loss of vision occurs due to the development of choroidal neovascularization (CNV). Eyes that have or have had CNV are classified as having neovascular AMD, while those that have never had CNV are classified as having non-neovascular AMD.

Prior to 2006, neovascular AMD was responsible for the majority of severe vision loss in patients with AMD even though it occurred in a small minority of patients with AMD. However, the realization that vascular endothelial growth factor (VEGF) plays an important part in the pathogenesis of CNV[2,3] and in the development of potent and selective VEGF-neutralizing proteins led to clinical trials demonstrating dramatic improvement in visual acuity (VA) in patients with neovascular AMD after intraocular injections of ranibizumab, an antibody fragment that binds VEGF-A.[4,5] Similar results have been obtained with intravitreous injections of other VEGF-neutralizing proteins, including aflibercept[6] and bevacizumab.[7]

Although there is no doubt that intraocular injections of VEGF-neutralizing proteins have greatly improved the visual outcomes of patients with neovascular AMD over 2 years of treatment,[8] long-term outcomes are uncertain, and the best strategy for long-term treatment is unknown. The outstanding outcomes obtained in early clinical trials occurred with monthly injections of a VEGF-neutralizing protein, but other treatment regimens are commonly used in clinical practice, such as pro re nata (PRN) or treat-and-extend regimens guided by spectral-domain optical coherence tomography (OCT). The Comparison of Age-related Macular Degeneration Treatment trials (CATT) compared outcomes in patients with neovascular AMD who were treated in 4 different ways: monthly ranibizumab, monthly bevacizumab, PRN ranibizumab, or PRN bevacizumab.[7] After 2 years, there was no significant difference in visual outcomes in patients treated with monthly ranibizumab or monthly bevacizumab, whereas patients treated with monthly injections had significantly better visual outcomes than those treated PRN.[8] Analysis of fundus photographs and

fluorescein angiograms (FAs) suggested that a greater percentage of patients treated with monthly injections compared with those treated PRN developed macular atrophy. In a retrospective review of prospectively obtained fundus photographs and/or FAs, an attempt was made to identify risk factors for development of new areas of atrophy.[9] Approximately one fifth of patients developed atrophy that the investigators interpreted as GA within 2 years of baseline, and independent baseline risk factors included poor VA, retinal angiomatous proliferation (RAP), foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. The authors concluded that treatment with anti-VEGF agents may have a role in the development of GA and that although monthly injections may result in slightly better visual outcomes at 2 years than PRN dosing, the increased risk for the development of GA may offset this benefit in the long term. To explore the development of macular atrophy in patients with neovascular AMD being treated with anti-VEGF agents, we reviewed fundus photos, FAs, and spectral-domain OCTs in a cohort of patients with neovascular AMD who were receiving anti-VEGF treatment.

METHODS

ALL PATIENTS WITH NEOVASCULAR AMD RECEIVING treatment with a VEGF-neutralizing protein by a single retina specialist between January 2013 and December 2013 were identified. A retrospective review of the charts and imaging studies was performed in this cohort of patients, which allowed assessments from the onset of anti-VEGF treatment to the most recent follow-up, which often spanned many years. Patients gave informed consent for the treatment of neovascular AMD with anti-VEGF injections. The study was approved by the Johns Hopkins Institutional Review Board. Demographic, VA and treatment data were collected, and fundus photographs were examined to identify areas of atrophy in the macula, defined as single or multiple regions of hypopigmentation with well-defined borders and visible large choroidal vessels. All eyes noted to have atrophy in the macula had had prior fundus photographs and FAs that were examined with careful scrutiny of regions corresponding to the atrophy so as to determine the status of that area at first visit, prior to the onset of anti-VEGF treatment.

In the second part of the analysis, the spectral-domain OCT characteristics of regions that developed atrophy were studied. Starting when Heidelberg Spectralis spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany) equipment became available, all patients had serial infrared (IR) images and raster scans through the entire macula. The IR image and spectral-domain OCT scan characteristics were determined for regions of the macula noted to have atrophy on current or subsequent fundus photographs.

The third part of the analysis involved measuring areas of atrophy over time to determine the rate of atrophy progression. Measurements were performed on the first and last available Spectralis spectral-domain OCT scans. Areas that had complete loss of RPE and ellipsoid zone (EZ) with no subretinal material were included in the measurement of atrophic area. The area of atrophy at its first appearance and at the most recent follow-up visit were used to calculate the rate of progression.

MEASUREMENT OF AREA OF ATROPHY ON SPECTRAL-DOMAIN OCT:

IR images and spectral-domain OCT raster scans were reviewed using the Heidelberg Spectralis software so that locations on the IR image could be correlated with spectral-domain OCT image locations. The same person (RC) obtained all measurements. The pointer tool was used to mark points on the IR image for which spectral-domain OCT scans showed complete loss of RPE and EZ with no subretinal material, except when there were focal areas of abnormal remaining RPE associated with loss of EZ and increased choroidal hyper-reflectivity located within a region of complete loss of RPE and EZ; they were included in the total atrophic area measurement. The free-hand draw tool was used to outline the atrophic area, and the software computed the enclosed area in square millimeters (mm^2). The area measurement tool is illustrated in Figure 1. The IR image (Figure 1, upper left) shows a large hypopigmented area superior-temporal to the fovea, and a scan through this area shows loss of RPE and EZ and no subretinal material (Figure 1, upper right). Figure 1, lower left, shows use of the measurement tool to outline the large hypopigmented area and to measure the area. Areas of atrophy in which there was subretinal material (Figure 1, lower right), which could represent atrophic scars, were not included in atrophy area measurements. In order to assess intra- and intergrader variability of the measuring methodology, 3 masked graders (SB, OA and RC) performed 2 measurements on the same image, for 25 unique images that were randomly selected from a list of patients with GA who had spectral-domain OCT images. Graders were presented with a randomly arranged sequence of the selected 50 (25 unique images × 2) de-identified images without being provided any information related to the patients. Area measurements were analyzed using the mixed-effects model with a random intercept for the graders and a random intercept for the eyes so as to determine intraclass correlation coefficients (ICCs) between the graders and between the 2 measurements from the same grader. The coefficient of repeatability (COR) for each grader was determined using the Bland-Altman analysis technique.

RESULTS

THIRTY-NINE PATIENTS (52 EYES) WITH NEOVASCULAR AMD received treatment with a VEGF-neutralizing protein during the period of ascertainment, January through December 2013. Fundus photographs taken before, during and after the period of ascertainment were examined and showed hypopigmented areas in the macula at some time during follow-up in 23 of 52 eyes (44%). In 18 eyes, the hypopigmentation was due to loss of RPE and EZ on spectral-domain OCT; in 4 eyes, it was due to an RPE tear; and in 1 eye, it was due to laser photocoagulation. Therefore, 18 of 47 eyes (38%) treated with a VEGF-neutralizing protein had an area of atrophy in the macula. Fundus photographs and FAs obtained during a follow-up period that ranged from 0.4 to 7.7 years, with mean ± SD of 3.7± 2.3 years, were examined. Because some patients did not have fundus photographs or FAs during their last few follow-up visits, the total duration of anti-VEGF treatment was slightly longer (mean 4.3 ± 3.2 years; range, 0.4–8.3 years). Of the 18 eyes, 13 (72%) developed atrophy in areas previously occupied by CNV; 5 eyes (28%) had atrophy prior to the development of CNV; and no eyes developed atrophy that was not in an area of prior CNV or adjacent to prior atrophy.

Figure 2 shows images from a patient who developed atrophy throughout a region of the macula previously occupied by a large CNV lesion. The patient is an 84-year-old female with neovascular AMD who presented with distortion and a VA of 20/80 in the left eye due to poorly defined CNV throughout the entire macula (Figure 2, top row). Over a 5-year period, she received 45 injections of a VEGF-neutralizing protein in the left eye, after which VA was stable at 20/32 and fundus photographs showed atrophy that corresponded to the area of prior CNV, except that there was less atrophy in the fovea than in the surrounding areas (Figure 2, bottom row). There was persistent CNV beneath the fovea, as evidenced by periodic appearance of intraretinal fluid in the fovea on spectral-domain OCT scans when the duration between injections was extended beyond 8 weeks. Figure 3 shows another patient who developed atrophy that corresponded to an area of prior ill-defined CNV. The patient is a 94-year-old female with neovascular AMD who presented with a disciform scar in the right eye and more recent gradual reduction of VA to 20/50 in the left eye. Fundus photograph and FA in the left eye showed a large area of occult CNV superior to the fovea that appeared to extend under the fovea to a region of CNV inferior to the fovea (Figure 3, top row). Over a period of 7 years, the patient received 23 injections of a VEGF-neutralizing protein in the left eye. Vision gradually decreased to 20/125, and fundus photography and FA showed atrophy that corresponded to the prior area of CNV (Figure 3, bottom row). Figure 4 shows images from a patient who presented with predominantly classic CNV unlike the ill-defined occult CNV seen in the 2 patients discussed above. At the initiation of anti-VEGF treatment, VA was 20/40, and after 5 years and 24 injections of a VEGF-neutralizing protein, VA had dropped to 20/200 due to macular atrophy. The most profound atrophy as seen by the greatest area of window defect seen on FA (Figure 4, bottom right) was within the boundaries of the classic component of the CNV seen 5 years earlier (Figure 4, top right), but there was also atrophy temporal to the border of the prior classic CNV. On the initial FA, there were subtle abnormalities temporal to the classic CNV that may represent occult CNV (Figure 4, top right).

SPECTRAL-DOMAIN OCT CHARACTERISTICS OF ATROPHIC AREAS:

In the 13 eyes that developed macular atrophy associated with regression of CNV, 4 (31%) had loss of EZ and RPE with no subretinal material and spectral-domain OCT appearances indistinguishable from those of GA (Table 1). In 9 of 13 eyes (69%), there was subretinal material consistent with subretinal fibrosis and/or drusenoid material within a portion of the atrophic area; in 8 of the 9 eyes, subretinal material occupied ≥50% of the atrophic area. The atrophy was extrafoveal in 9/13 eyes (69%) and foveal in 4 eyes. Of the 5 eyes with pre-existent atrophy, 2 developed new atrophy in a region that was initially occupied by CNV; 1 of these eyes had subretinal material in <50% of the atrophic region, and the other had loss of EZ and RPE without any subretinal material. Three eyes appeared to have extension of the prior area of atrophy; 1 of these had pure atrophy without subretinal material, and 2 had subretinal material within the final area of atrophy. Only 1 of the 5 eyes with pre-existent atrophy had foveal atrophy at last follow-up. Thus, foveal atrophy occurred in 5/18 eyes (28%) at last follow–up, regardless of whether there was atrophy prior to the onset of anti-VEGF treatment or not.

REPEATABILITY OF AREA OF ATROPHY MEASUREMENTS USING SPECTRAL-DOMAIN OCT:

The intra- and intergrader repeatability was excellent. ICC and 95% confidence interval (CI) for intragrader repeatability was 0.999 (0.998–0.999) and ICC (95% CI) for intergrader repeatability (SB vs OA) was 0.997 (0.994–0.998). The COR (95% CI) for grader SB was 0.65 (0.57–0.76), which means the difference between 2 measurements for the same patient is expected to be less than 0.65 mm^2 for 95% of observation pairs from grader SB. Grader RC and grader OA had lower COR (95% CI), 0.21 (0.19, 0.25) and 0.16 (0.14, 0.19), respectively.

EVOLUTION OF ATROPHIC AREAS BY SPECTRAL-DOMAIN OCT:

One eye (patient 18) was excluded from measurements due to the presence of severe subretinal fibrosis within the entire area of atrophy, with few or no locations without subretinal material. For 17 eyes, the area of complete RPE and EZ loss devoid of any subretinal material was measured over time (Table 2). The average follow-up time was 1.6 ± 1.1years (range, 0.3–3.8 years). Mean (±SD) increase in area of atrophy was 0.7 ± 0.8 mm^2 and mean increase per year was 0.7 ± 0.6 mm^2 with a range of 0.01–2.6 mm^2. Thirteen eyes had a rate of increase in area over time that was higher than the COR of 0.21 mm^2. The mean number of anti-VEGF injections administered per year during the measurement period was 6.2 ± 3.3, and the type of anti-VEGF administered was either aflibercept or ranibizumab. There was no correlation between the number of anti-VEGF injections administered per year and the rate of atrophy progression (r = 0.03, $P = 0.89$).

VISUAL ACUITY CHANGES OVER TIME:

Snellen VA measurements were obtained for the follow-up period after first identification of atrophy and during which spectral-domain OCT measurements were recorded (the period of atrophy area measurement). Median VA at the first visit atrophy was identified was 20/50 (range, 20/25 to counting fingers) and at the last follow-up visit was 20/80 (range, 20/25 to counting fingers). About half the patients (10/17; 58.8%) had stable vision during the follow-up period: 2 patients gained 1 line, 3 had no change and 5 lost 1 line of VA. One patient lost 4 lines of VA over a period of 2.8 years due to progressive atrophy within an area of the CNV that involved the fovea. The remaining 6 patients lost 2–3 lines of VA. Table 2 summarizes the changes in area of atrophy, VA and anti-VEGF treatments administered to the 17 eyes with atrophic changes.

DISCUSSION

THE PATHOGENESIS OF AMD IS VERY COMPLEX AND NOT well understood. It is a multigenic disease that becomes manifest only late in life. Deposition of material beneath the RPE and/or retina, indicated by the presence of drusen, is one of the early signs. The number and size of drusen tend to increase over time and large and/or confluent drusen are risk factors for development of GA. Focusing on the initial site of GA development and then examining prior fundus photographs for patients enrolled in the Age-Related Eye Disease Study (AREDS), it was found that large drusen were present at the site in 100% of patients.[1] Hyperpigmentation commonly occurred around large drusen, followed by drusen regression,

appearance of hypopigmentation, and then GA. Once noncentral GA develops, there is substantial risk for progression to central GA, one type of advanced AMD.[10] The risk for developing CNV, the other form of advanced AMD, is also increased in eyes with large and/or confluent drusen. A patient who has extensive intermediate drusen, large drusen, or noncentral GA has a 28% chance of developing advanced AMD in 1 eye over 5 years.[11] Because GA and CNV share risk factors, it is not surprising that they sometimes occur in the same eye. Another shared risk factor is drusenoid pigment epithelial detachment (PED), defined as a circumscribed, shallow elevation of the RPE formed by a confluence of soft drusen. An eye with a drusenoid PED has a 19% risk for developing central GA and a 23% risk for developing CNV over a 5-year period.[12] Macular atrophy also occurs after flattening of serous PEDs[13,14] or as a sequela of untreated CNV, particularly in areas of subretinal hemorrhage, after which an atrophic scar occurs 25% of the time.[15] Sarks and associates[16] described development of atrophy around disciform scars that increased in size 2.4–5.1 mm^2 per year in the absence of any treatment. Histopathology studies have shown regions of macular atrophy in 37% of all eyes with AMD, and of these, 30% had atrophy associated with CNV.[17] Thus, there are many sources of atrophy in patients with AMD, and unless the macula is observed at multiple time points during development of atrophy, it is not possible to determine what led to its occurrence.

A secondary exploratory analysis of data from the CATT study concluded that suppression of VEGF by intraocular injections of VEGF-neutralizing proteins may cause GA.[9] This could have significant implications regarding how we treat patients with neovascular AMD; however, our study suggests 2 concerns. The first is related to nomenclature. We propose that the term GA should be reserved for atrophy of RPE and retina that is documented to occur in patients with AMD in the absence of any pre-existent CNV. A second and more substantive concern is how does one determine the cause of atrophy in a disease process in which there are multiple possible causes? As noted above, one strategy is to observe and image the macula throughout the period during which atrophy develops. In the current study, we took this approach by selecting all patients treated by a single physician over a defined period and then evaluating all images available for those patients from initial visit through most recent follow-up. This allowed tracking of the development of atrophy in each of these patients. We observed that the majority of patients (72%) had CNV in the region of the macula that subsequently developed atrophy. Thus, the first important finding of our study is that atrophy is a potential outcome of successfully treating CNV with a VEGF-neutralizing protein.

It is difficult to determine whether the borders of the atrophy corresponded exactly to borders of the CNV because in many cases the borders of the CNV were not well defined (Figure 2 and Figure 3), and even when there was predominantly classic CNV, it was not possible to rule out adjacent occult CNV (Figure 4). However, the substantial overlap between areas of atrophy and prior CNV implicates regression of the CNV in the development of atrophy. In 5 patients (28%), atrophy occurred in areas where there was not identifiable pre-existent CNV, but all of these patients had pre-existent areas of atrophy, which probably represented GA prior to the onset of CNV and prior to treatment with a VEGF-neutralizing protein. Because eyes with noncentral GA tend to have progression of GA including noncontiguous foci, it is possible that this represents normal progression of

GA.[10] Therefore, in this cohort of AMD patients, we did not identify any patients in whom we felt confident that there was new-onset macular atrophy related to treatment with an anti-VEGF neutralizing protein and not associated with regression of CNV or prior GA.

In 31% of eyes with atrophy from regression of CNV, spectral-domain OCT showed loss of RPE and photoreceptors with no evidence of remaining CNV or scarring, suggesting that in these eyes, regression of the CNV was the primary source of atrophy. The spectral-domain OCT in these eyes was indistinguishable from that seen in eyes with GA, indicating that observation of pure atrophy without subretinal material on spectral-domain OCT at 1 point in time does not rule out prior CNV in that area. The other 69% of eyes with atrophy resulting from regression of CNV showed subretinal material consistent with subretinal fibrosis and/or drusenoid material in part of the atrophic region. In these regions it is possible that damage from fibrotic tissue contributed to death of RPE and photoreceptors, but all of these eyes had significant portions of the atrophic area that were devoid of subretinal material. Such areas could easily be interpreted as GA that developed adjacent to an atrophic scar when, in fact, these regions of atrophy occurred in areas of prior CNV that had regressed.

Another important question is this: once atrophy begins from any cause, does treatment with a VEGF-neutralizing protein accelerate its progression? This question cannot be definitively answered without a controlled clinical trial in which patients with atrophy are randomized to treatment with a VEGF-neutralizing protein or no treatment and then compared; such a trial is neither practical nor appropriate. However, it may be possible to determine whether treatment with a VEGF-neutralizing protein markedly accelerates progression of atrophy by comparing rates of progression in treated patients with those previously observed in natural-history studies. In our study, when areas of atrophy were first measured by spectral-domain OCT, they ranged from 0.1 mm^2 to a maximum of 13 mm^2 and the average rate of increase was 0.7 ± 0.6 mm^2/year with a range of 0.01 mm^2–2.6 mm^2/year. The patient with the highest rate of increase in our study falls within the reported rate of increase in area of GA in natural history studies, 0.4–2.6 mm^2/year.[18,19] Therefore, although our sample size is small, our data argue against a rapid rate of atrophy progression in patients with neovascular AMD treated with a VEGF-neutralizing protein, that is substantially greater than the slow spontaneous rate of progression of GA.

In the study evaluating the risk for atrophy (the CATT study), there was no attempt to correlate the area of CNV with the area in which atrophy was later detected.[9] In Figure 1, from the published report of that study, there is overlap between the area of CNV and the region that subsequently developed atrophy and, as discussed above, even with careful scrutiny it would be difficult to determine whether atrophy extends beyond the boundary of the CNV, because adjacent occult CNV can be undetectable. Furthermore, FA provides an assessment of CNV size and location at 1 point in time, and it is possible that growth of CNV occurred despite treatment with a VEGF-neutralizing protein and then later regressed; therefore, any area of atrophy that overlaps with prior CNV could be due to regression of CNV. However, we do not dispute that there may also be causes of atrophy regression other than CNV in patients with neovascular AMD treated with a VEGF-neutralizing protein.

Figure 1A4 in the manuscript cited above[9] may illustrate this, as suggested by the authors, because there is a small region of atrophy that appears remote from the prior CNV.

Limitations of our study include the retrospective design and its relatively small size. The long follow-up for many patients is a strength, but a related disadvantage is that several patients had onset of treatment with a VEGF-neutralizing protein prior to the time when spectral-domain OCT was available, so it was not possible to measure atrophy by spectral-domain OCT during the initial part of their treatment. Despite these shortcomings, our study is valuable because it illustrates that macular atrophy occurs in association with regression of CNV from treatment with a VEGF-neutralizing protein. It is important to distinguish this from atrophy caused by damage to photoreceptors, RPE, and/or choriocapillaris resulting from suppression of VEGF. The main objective of our study was to begin the conversation regarding these 2 possibilities and to stimulate further investigation to distinguish between them.

Even if the majority of the atrophy observed in the CATT study is due to CNV regression and not to direct toxicity of a VEGF-neutralizing protein, it is important to know the impact it has on VA. It is somewhat reassuring that patients who received monthly injections for 2 years had the best visual outcomes despite having the highest incidence of new atrophy. It is possible that subfoveal CNV may be less prone to atrophy resulting from VEGF suppression than extrafoveal CNV, which is suggested by the patient illustrated in Figure 2 and by the determination that only 28% of our patients with macular atrophy had foveal involvement at last follow-up. However, it is possible, as suggested by the CATT investigators, that more aggressive suppression of VEGF, such as that achieved with monthly injections as opposed to PRN treatment, causes more regression of CNV, making regression of subfoveal CNV and foveal atrophy more likely. Additional studies are essential to examine long-term visual outcomes in patients with neovascular AMD treated with VEGF-neutralizing proteins and also to determine the visual impact of atrophy from CNV regression.

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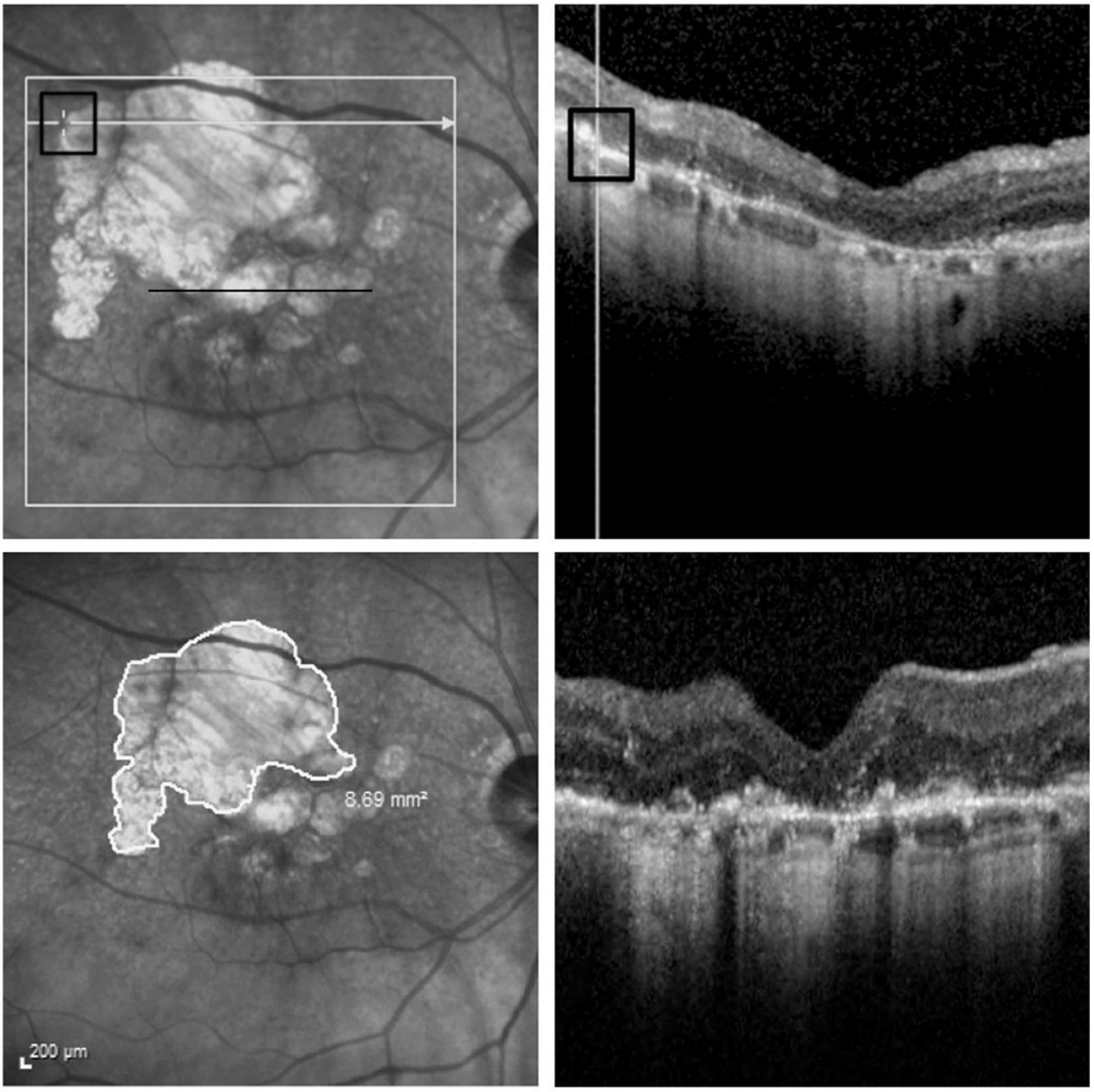

FIGURE 1.

Measurement of the area of atrophy using spectral-domain optical coherence tomography infrared image combined with cross-sections. Left upper panel shows a large area of hypopigmented retina in the superior-temporal part of the macula, with a long gray arrow showing the location of the cross-sectional spectral-domain optical coherence tomography scan shown in the right upper panel and loss of retinal pigmented epithelium (RPE) and ellipsoid zone throughout the area. The black box in the left upper panel shows the edge of the hypopigmented region, which corresponds to the border between normal and atrophic

retina shown in the box on the scan in the right upper panel. Raster scans through the entire large hypopigmented area showed loss of RPE and ellipsoid zone throughout; therefore, the entire area was surrounded by the free-hand tool, and the area was calculated (left lower panel). The lower line in the left upper panel extends through smaller hypopigmented areas that are shown in the scan in the right lower panel. These areas contain subretinal material in regions of RPE and ellipsoid zone loss and were not included in atrophy area measurement. Other hypopigmented areas further inferior lacked subretinal material in areas of RPE and ellipsoid zone loss and were included in area measurements.

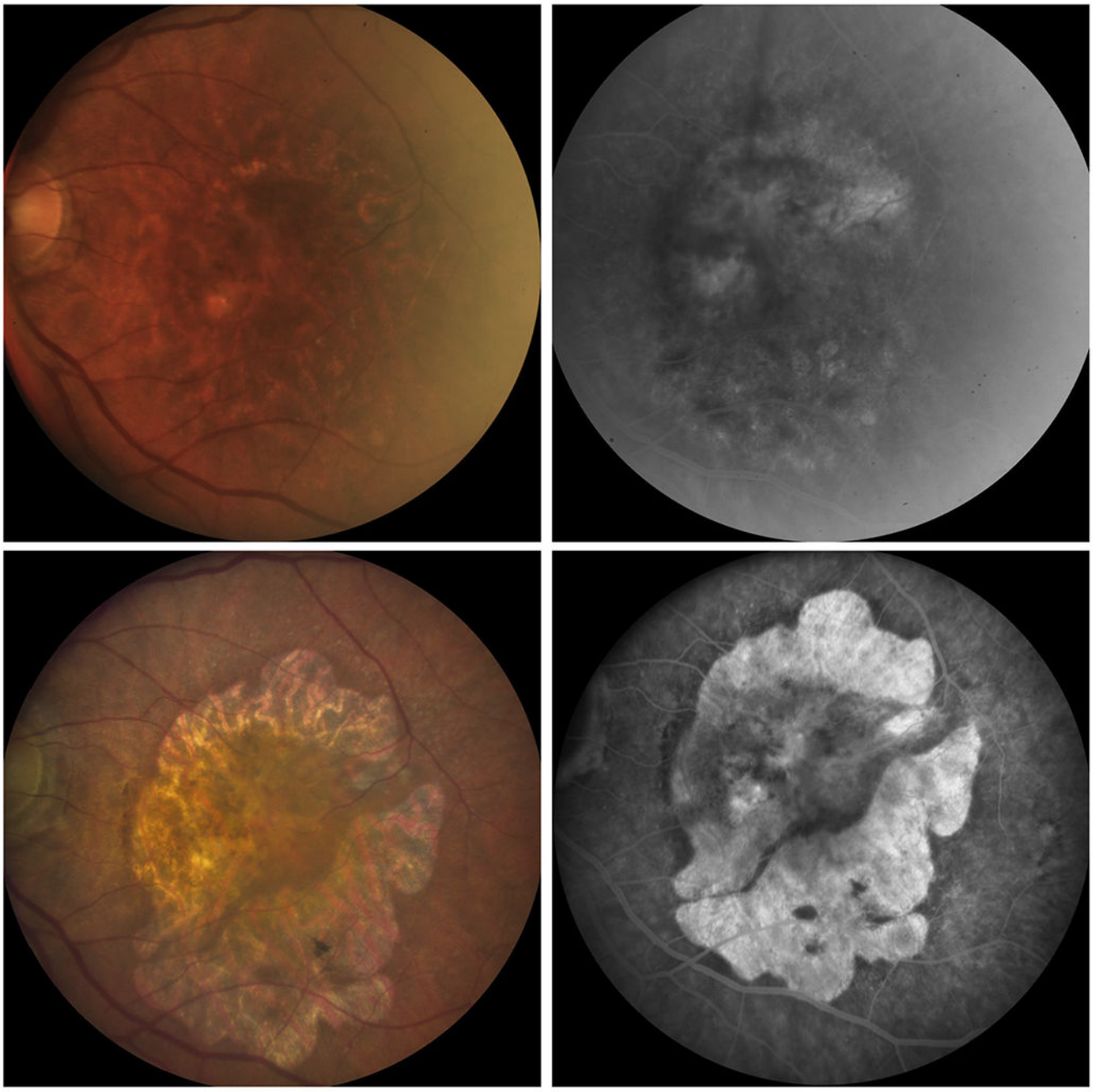

FIGURE 2.

Macular atrophy corresponding to previous area of choroidal neovascularization in a patient with neovascular age-related macular degeneration treated with frequent injections of a vascular endothelial growth factor-neutralizing protein. Top row shows a fundus photograph and late frame of a fluorescein angiogram (FA) at initial visit for patient 1 when visual acuity (VA) was 20/80 and antivascular endothelial growth factor (VEGF) treatment was initiated. Fundus photograph shows hypopigmented areas, and FA shows a large area of minimally classic choroidal neovascularization throughout the entire macula. The bottom

row shows a fundus photograph and a late frame of an FA after 5 years and 45 injections of a VEGF-neutralizing protein. VA was 20/32, and fundus photograph and FA showed atrophy that corresponds to the area of choroidal neovascularization that was present 5 years earlier, except there is less atrophy in the fovea, where there is still active choroidal neovascularization.

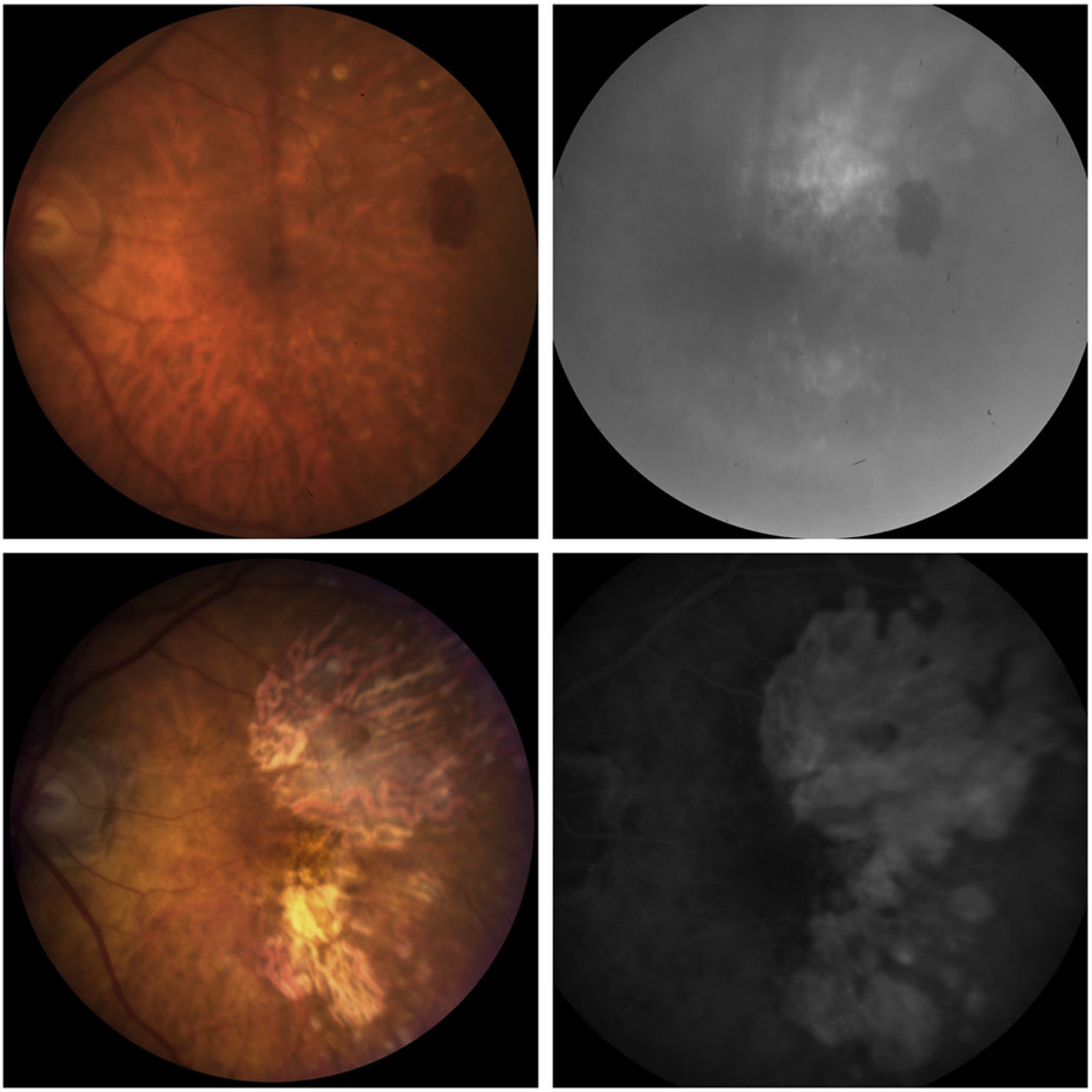

FIGURE 3.

Correspondence of macular atrophy and pre-existent choroidal neovascularization in a patient with neovascular age-related macular degeneration treated with a vascular endothelial growth factor-neutralizing protein. Top row shows a fundus photograph and a late frame of a fluorescein angiogram (FA) from the initial visit of patient 2 at the initiation of antivascular endothelial growth factor (VEGF) treatment when visual acuity (VA) was 20/50. There were subretinal hemorrhage and a few hypopigmented spots, and FA showed poorly defined choroidal neovascularization (CNV) superior-temporal and inferior-temporal

to the fovea. Roughly 7 years after the initial visit, VA was 20/125 and fundus photograph and FA showed atrophy throughout the area previously occupied by CNV (bottom row). During the 7-year follow-up period, the patient received 23 intravitreous injections of a VEGF-neutralizing protein.

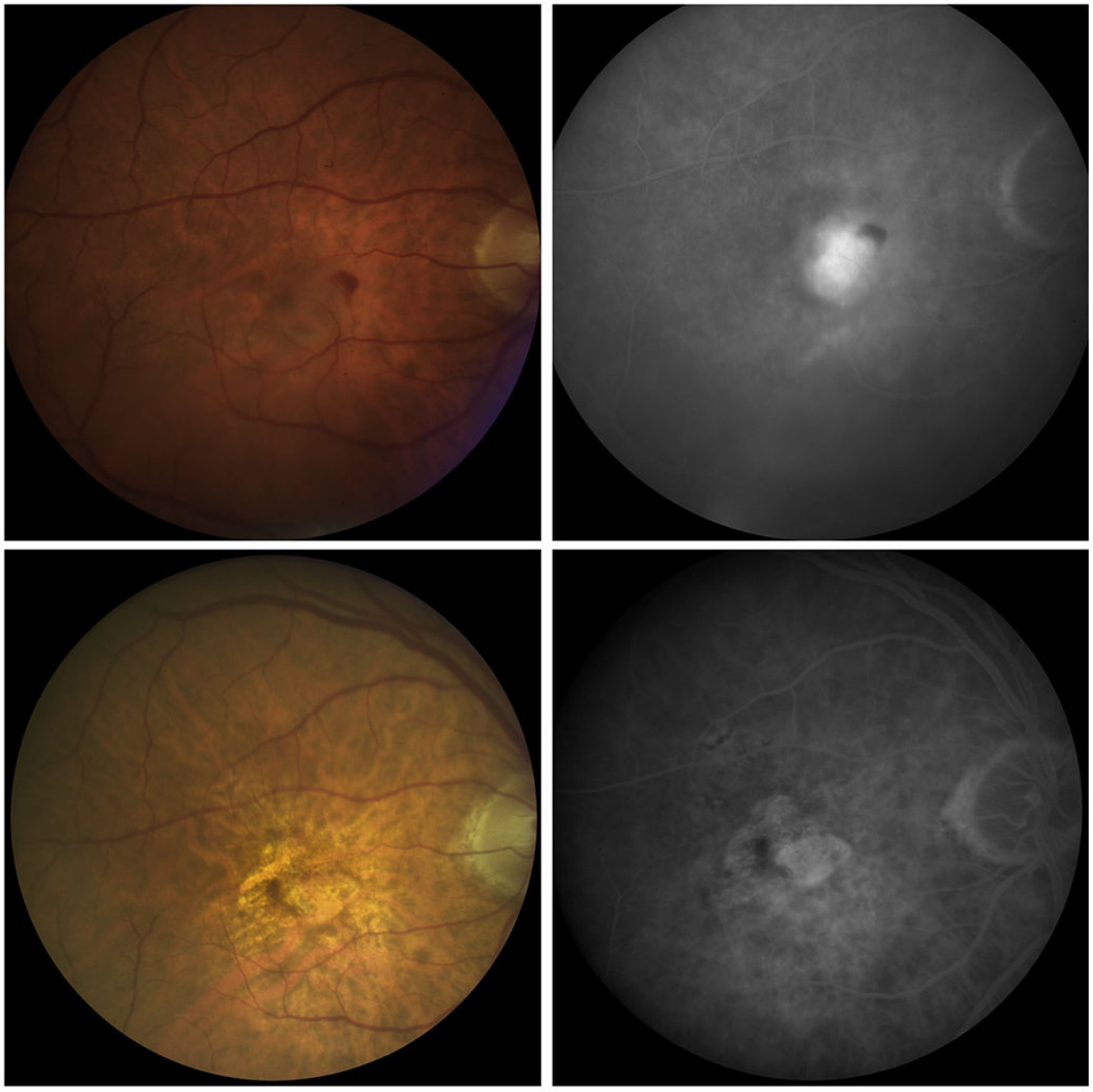

FIGURE 4.

Incomplete correspondence of predominantly classic choroidal neovascularization and subsequent atrophy after treatment with a vascular endothelial growth factor (VEGF)-neutralizing protein in a patient with age-related macular degeneration. Fundus photograph shows subretinal hemorrhage and fluid (top left) overlying predominantly classic choroidal neovascularization (CNV) seen in a late frame of a fluorescein angiogram (FA) (top right) from the initial visit of patient 8, when visual acuity (VA) was 20/40 and antivascular endothelial growth factor treatment was initiated. Five years after the initial visit, during

which time the patient received 24 injections of a VEGF-neutralizing protein, VA was 20/200 and fundus photograph (bottom left) and FA (bottom right) showed an area of atrophy with the greatest window defect on FA within the boundaries of the classic component of the CNV and less profound atrophy beyond the temporal border of the classic CNV. Close inspection of the previous FA (top right) shows subtle abnormalities temporal to the classic CNV that may represent occult CNV.

TABLE 1.

Characteristics of Atrophic Areas on Spectral-Domain Optical Coherence Tomography in Patients With Neovascular Age-Related Macular Degeneration

Patient ID	Atrophy Only or Atrophy and Subretinal Material*	Proportion of Area Involved by Subretinal Material Compared to Atrophy	Did the Atrophic Area Involve the Fovea?	Did the Area of Atrophy Represent an Extension of Pre-Existing Atrophy (Extension) or Regressed Choroidal Neovascularization?†
1	Atrophy and subretinal material	<50%	No	Regressed CNV
2	Atrophy and subretinal material	>50%	No	Regressed CNV
3	Atrophy and subretinal material	<50%	Yes	Extension and regressed CNV
4	Atrophy	0	No	Extension and regressed CNV
5	Atrophy and subretinal material	0	No	Extension
6	Atrophy	0	Yes	Regressed CNV
7	Atrophy	0	Yes	Regressed CNV
8	Atrophy and subretinal material	>50%	Yes	Regressed CNV
9	Atrophy and subretinal material	>50%	No	Regressed CNV
10	Atrophy	0	No	Regressed CNV
11	Atrophy and subretinal material	>50%	No	Extension
12	Atrophy and subretinal material	about 50%	No	Regressed CNV
13	Atrophy and subretinal material	>50%	No	Regressed CNV
14	Atrophy and subretinal material	>50%	No	Regressed CNV
15	Atrophy and subretinal material	>50%	No	Regressed CNV
16	Atrophy	0	No	Extension
17	Atrophy	0	No	Regressed CNV
18	Atrophy and subretinal material	>50%	Yes	Regressed CNV

CNV = choroidal neovascularization.

*Atrophy was defined as complete loss of retinal pigmented epithelium and ellipsoid zone on spectral-domain optical coherence tomography with increased choroidal hyper-reflectivity; atrophy with subretinal material was defined as atrophy with hyper-reflective deposits beneath the retina.

†This column shows whether, on the first available infrared image, atrophy occurred in the same area that previously contained choroidal neovascularization, referred to as regressed CNV, or in an area adjacent to pre-existing atrophy (extension of atrophy). The determination that atrophy was an extension of pre-existent atrophy or resulted from regression of CNV was made after review of all available images for a given patient, including prior fundus photos and fluorescein angiograms and spectral-domain OCT images.

TABLE 2.

Progression of Atrophy Over Time in Neovascular Age-Related Macular Degeneration in Patients Receiving Antivascular Endothelial Growth Factor Agents

Study ID	Area of Atrophy When First Visualized by Spectral-Domain OCT (mm^2)	Area of Atrophy on Final Follow-up Spectral-Domain OCT (mm^2)	Difference in Area (mm^2)	Time Between First and Last Spectral-Domain OCT (Yrs)*	Rate of Increase (mm^2)/Yr	Number of Anti-VEGF Injections for Time Between First and Last Spectral-Domain OCT	Injections/Yr for Time Between First and Last Spectral-Domain OCT	Total Duration of Anti-VEGF Treatment (Yrs)	Snellen VA When Atrophy Was First Visualized by Spectral-Domain OCT	Snellen VA at Final Visit when Spectral-Domain OCT Was Obtained
1	12.6	15.9	3.3	2.8	1.2	20	7	8.3	20/32	20/40
2	1.4	3.0	1.6	2.8	0.6	12	4	7.6	20/50	20/125
3	8.7	9.2	0.5	0.6	0.8	3	5†	0.9	20/100	20/200
4	4.5	5.3	0.8	0.3	2.6	2	7†	0.4	20/160	20/125
5	5.2	5.6	0.4	0.3	1.3	2	7†	0.4	20/100	20/200
6	3.5	4.5	0.9	2.7	0.3	25	9	8.2	20/50	20/63
7	0.3	1.7	1.4	2.7	0.5	7	3	6	20/63	20/125
8	0.2	0.5	0.3	2.2	0.2	9	4	7.7	20/200	20/250
9	0.4	0.8	0.4	1.0	0.4	11	11	2.4	20/40	20/50
10	0.2	0.3	0.1	0.3	0.5	3	12†	1.3	20/80	20/100
11	2.9	3.5	0.6	0.9	0.6	3	3	0.9	CF	CF
12	0.8	1.0	0.2	2.3	0.1	27	12	5.6	20/50	20/80
13	0.1	0.1	0.04	3.8	0.01	8	2	7.8	20/32	20/25
14	0.5	0.7	0.3	1.6	0.2	6	4	7	20/32	20/70
15	0.4	1.0	0.6	1.6	0.4	11	7	7	20/50	20/80
16	1.6	2.3	0.6	0.6	1.1	3	5†	0.5	20/32	20/32
17	0.1	0.3	0.2	0.5	0.5	2	4†	0.7	20/25	20/25

CF = counting fingers at 3 feet; ID = study identification number; OCT = -optical coherence tomography; VA = visual acuity; VEGF = vascular endothelial growth factor; yrs = years.

*Duration of follow-up in this column refers to the duration for which spectral-domain OCT scans were available so that area measurements could be performed.

†Not actual number; extrapolated number appears large due to short follow-up.