Choroidal Neovascularization

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The realization that highly myopic eyes were prone to develop choroidal neovascularization (CNV) occurred relatively recently. Fuchs' spots [1], also known as Foster-Fuchs spots, were described as pigmentary changes in the posterior pole of myopes. These spots, sometimes associated with hemorrhage, were first described by Forster in 1862 and Fuchs in 1901. The reason for the hemorrhage was not known at the time. In 1953 Lloyd [2] wrote that Fuchs' spots were often preceded by a cystic appearance of the macula and attributed the Fuchs' spot to stretching of the choriocapillaris. In 1973, Focosi and coworkers [3] described a group of myopic eyes that developed serous and serosanguineous detachments of the macula. The authors found these patients had fluorescein angiographic evidence of leakage, sometimes from multiple lesions. Close inspection of the published angiograms shows the eyes had findings suggestive of multifocal choroiditis and panuveitis (MCP, a condition described much later) complicated by neovascularization. The authors thought the patients had serous pigment epithelial detachments with no neovascularization, and the blood present originated from the constituent vessels of the choroid. In 1977 fluorescein angiographic evidence was presented to show Fuchs' spots were actually caused by choroidal neovascularization [4]. In this paper Levy and coauthors hypothesized laser photocoagulation may prove to be a useful treatment. Since then the importance of CNV as a major cause of vision loss in highly myopic eyes has been more fully appreciated, and several successive treatment modalities have been developed.

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15.1 Clinical Characteristics

The principle symptoms from CNV in myopia are loss of acuity, scotomata, and distortion of vision. Some patients with advanced myopic degeneration have prior impairments to their vision, and the addition of CNV may not cause enough incremental change in their vision for them to notice any early irregularity. The presenting abnormalities of myopic CNV differ by degrees from that seen in AMD. The CNV in myopic eyes is less likely to have sub- or intraretinal fluid or lipid and seems to be associated with less proliferation in the subretinal space than CNV in AMD. Myopic CNV almost never has associated serous pigment epithelial detachments. CNV in myopia is generally fairly small in contrast to that seen in AMD. The size of the CNV seems to vary inversely with the amount of myopia.

Growth of neovascularization occurs in eyes showing other signs of abnormalities related to high myopia. Mechanical dehiscence of Bruch's membrane occurs in eyes with high myopia to produce thin branching lines in the posterior pole called lacquer cracks. These ruptures affect the full thickness of Bruch's membrane and as a consequence involve the choriocapillaris as well. Thus it is common to see subretinal hemorrhage in eyes with high myopia that are overlying lacquer cracks or clear to show new lacquer cracks (Fig. 15.1) [5–8]. Eyes with high myopia have concurrent reduction in the thickness of the choroid [9–12], and with advanced amounts of myopia, particularly in older patients, the choroid may shrink to have nearly no thickness. These eyes appear to develop areas of full thickness loss of the choroid and overlying retinal pigment epithelium. Lacquer cracks and full thickness atrophy both appear to be risk factors for development of CNV [5, 8, 13, 14]. While preexisting lacquer cracks provide an easy avenue for the ingrowth of new vessels, neovascularization can erode directly through intact Bruch's membrane [15]. In most cases the CNV appears to originate from a lacquer crack, however [14]. Once the neovascular process begins, the vessel ingrowth can be partially or completely engulfed by proliferating

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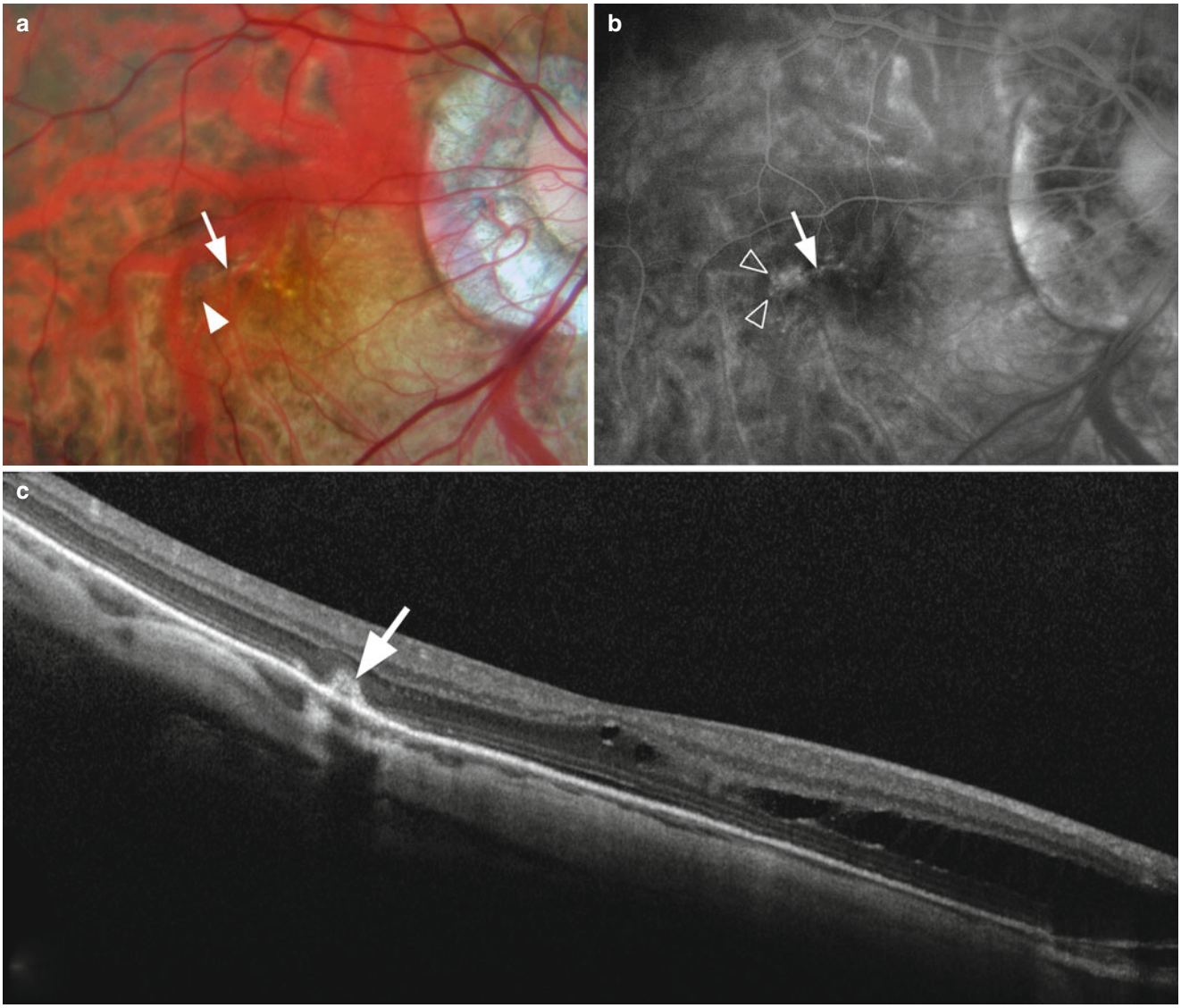

Fig. 15.1 (**a**) This −16 diopter myope developed a small scotoma near the center of the visual field. There were lacquer cracks, one of which was highlighted by the *arrow*. There was some associated pigmentary changes (*arrowhead*). (**b**) Fluorescein angiography showed a hyperfluorescent lesion consistent with choroidal neovascularization. A lacquer crack is seen coursing horizontally (*arrow*) and there is a region of late staining (*open arrowheads*) at its temporal extent. (**c**) The optical coherence tomography scan shows a small elevated lesion (*arrow*) and also nonassociated macular schisis

pigment cells, producing a Fuchs' spot. In the past, prior to the availability of treatment for myopic CNV, the visualization of pigmentation around the neovascularization was seen to be a favorable sign suggestive of stabilization of the process. If the neovascularization is not enveloped with RPE cells, it appears a grayish-white thickening under the retina. There may be associated small hemorrhages and sometimes subtle flecks of lipid. The converse, big hemorrhages or large amounts of lipid exudation are almost never seen.

Fluorescein angiography demonstrates the vascular ingrowth as early hyperfluorescence with variable amounts of leakage later in the angiographic sequence (Figs. 15.1 and 15.2). Some eyes show nearly no leakage of fluorescein. Thus the neovascularization seen in highly myopic eyes can show some but not necessarily all of the features required to classify the neovascularization as being "classic." The proportion of cases classified as predominantly classic were approximately 80 % in the Verteporfin in Photodynamic therapy pathologic myopia (VIP-PM) study [16, 17], although some authors consider most [14] or all [18] neovascularization in high myopia to be classic. Optical coherence tomography (OCT) can show signs of exudation such as intra- or subretinal fluid being present in eyes with myopic CNV [19]. Small hemorrhages are usually not easy to visualize with OCT. The infiltration causes a low, flat alteration in the contour of the RPE monolayer. The subtlety of findings seen in the two main

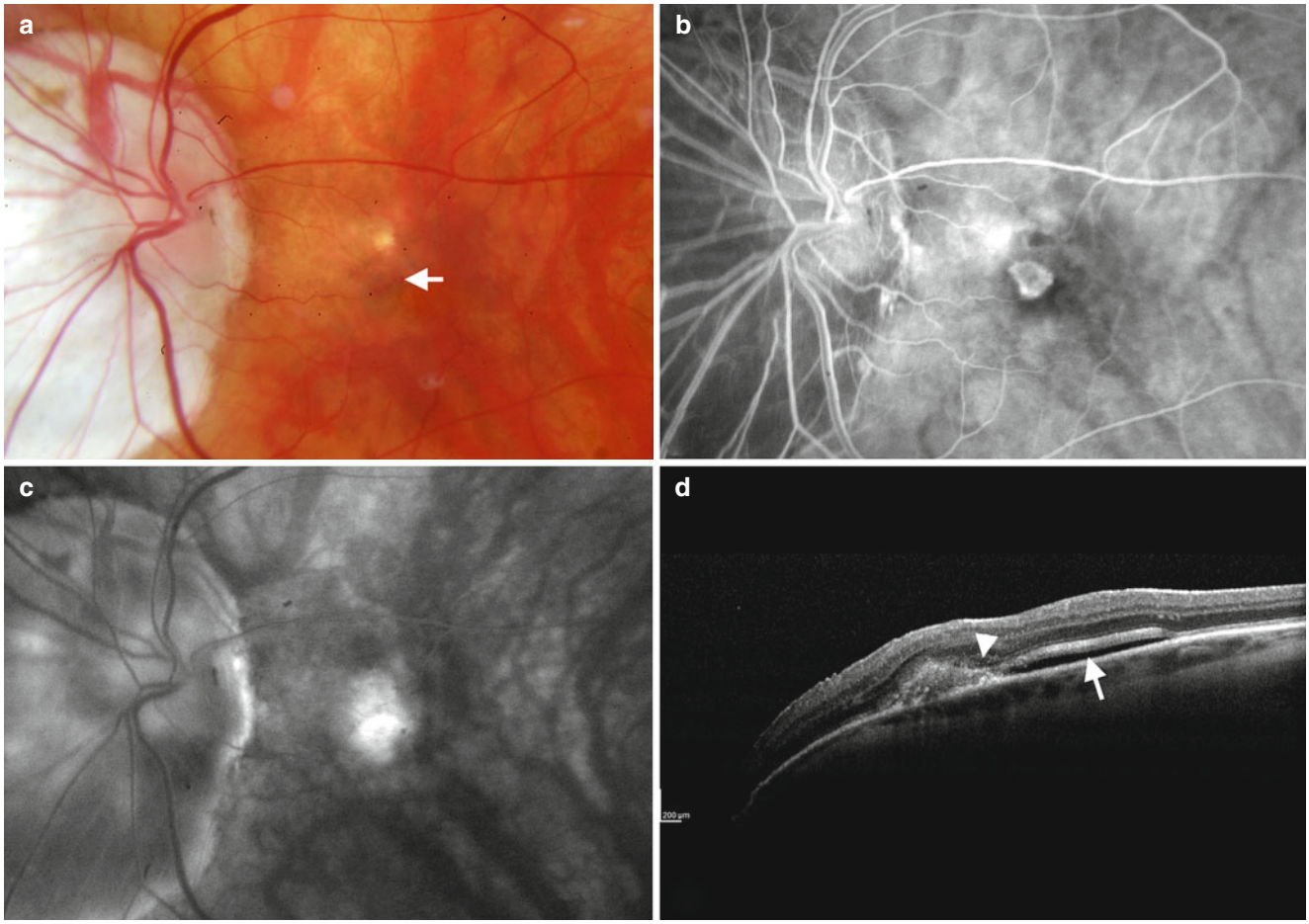

Fig. 15.2 Presentation of choroidal neovascularization in a high myope. (**a**) There is a small area of focal hypopigmentation with an adjacent, but not contiguous area of altered pigmentation and barely visible hemorrhage (*arrow*). (**b**) The early phase of the fluorescein angiogram shows early visualization of the vascular network. Note the separation between the vessels and the hypopigmented area. (**c**) In the later phases of the angiogram, there is leakage from the vessels, which is another angiographic characteristic required to make the diagnosis of classic choroidal neovascularization. (**d**) Optical coherence tomography shows a triangular elevation of the retina with poor delineation between the lesion and the retina. There is granular material in the space above the lesion (*arrowhead*) and subretinal fluid (*arrow*)

testing modalities for CNV, along with the relatively small neovascular lesions, can make diagnosis of CNV difficult in some cases. These same testing modalities are used in treated eyes as a gauge to administer additional treatment and, as will be seen later, highlight a significant underlying weakness that "as needed" treatment strategies have in high myopia.

The differential diagnosis for myopic CNV includes macular hole, small focal areas of chorioretinal atrophy or scarring, and inflammatory conditions such as MCP [20]. Because of the relative depigmentation of the fundus in a high myope, macular holes may not be that obvious. These holes are often associated with decreased acuity and can have associated subretinal fluid. The diagnosis is readily apparent using OCT. High myopes frequently have small areas of altered pigmentation in the posterior pole. Small hyperpigmented spots are usually flat and do not have a surrounding area of atrophy. True CNV causes an elevation at the level of the RPE. Fluorescein angiography shows hyperfluorescence later in the angiographic sequence if new vessels are present. True Fuchs' spots are usually surrounded by varying amounts of depigmentation or frank atrophy. MCP causes grayish-white inflammatory lesions at the level of the RPE that can have associated subretinal fluid during the acute, active phase. OCT shows the inflammatory lesions to be conical elevations of the RPE. During fluorescein angiography these lesions can show early fluorescence with late staining. Clues that the eye harbors MCP are recurrent accumulations of new lesions, multiple lesions in the fundus, clinically evident inflammatory cells, and the characteristic OCT appearance. These same eyes may develop CNV, which is heralded by an increase in exudation and scarring, often with minimal hemorrhage. These eyes may have reactive changes in the RPE, which are hypofluorescent in fluorescein angiography and hyperautofluorescent with autofluorescence imaging [21].

The incidence of CNV in high myopia probably is related to a number of factors, which may in turn influence estimates.

These factors include age, refractive status, gender, and potentially involvement of the fellow eye [22–30]. Curtin and Karlin reported Fuchs' spots were present in 5.2 % of eyes with an axial length of 26.5 mm [22]. Grossniklaus and Green [31] found a similar proportion in what were reported to be myopic eyes coming to histopathologic evaluation, although no axial length or refractive error data for those eyes was presented. There appears to be a female predominance in myopic CNV.

15.2 Potential Pathologic Mechanisms

The actual pathogenic sequence of the early phases of any form of CNV is unclear, and myopic CNV is no exception. A variety of contributing factors have been proposed to explain why CNV occurs, but all of these seem to have shortcomings. What we do know is eyes with myopia have axial lengthening and apparent stretching of the structures in the posterior pole. The choroidal thickness decreases in high myopia [9, 10, 12], but the thickness of the overlying RPE cells and the packing density of the photoreceptors decrease in a manner that initially may be proportionate. With the passage of time, the choroid becomes even thinner, at which point decompensation secondary to outer retina ischemia seems possible. Coincident with, or perhaps in part related to, the choroidal thinning are alterations of Bruch's membrane manifested as lacquer cracks. Eyes with lacquer cracks have RPE alterations in the same general area. Lacquer cracks may offer avenues for the ingrowth of vessels or may indicate a general degeneration of Bruch's membrane such that CNV may be more likely to occur. Other conditions leading to the ingrowth of neovascularization in the context of breaks in Bruch's membrane include choroidal ruptures due to trauma, angioid streaks in pseudoxanthoma elasticum [32], and microbreaks in AMD [33]; however, each of these has other factors at play that may encourage the growth of CNV. Most eyes with high myopia have lacquer cracks [5, 6, 13, 14], but only a minority develops CNV, so other factors may be involved in myopic CNV as well. Grossniklaus and Green proposed the growth of new vessels from the choroid may be a compensatory mechanism for the loss of choroidal blood flow through a degenerating choriocapillaris in AMD [34]. This same pathophysiologic mechanism may be operative in high myopia and offers a tantalizing explanation for CNV growth. However observation of the growth characteristics of myopic CNV argues against simple ischemia. The choroidal thickness decreases with increasing myopia, but neither the size nor the number of CNV lesions increases with increasing myopia. If CNV were a compensatory response, it is difficult to understand why the RPE would envelope and seemingly limit the growth of vessels. Certainly ischemia would continue or increase with time, so one would expect ever-increasing incidence of CNV in highly myopic eyes and multiple new lesions over time if ischemia was the sole cause.

15.3 Disease Characteristics

In 1981 several papers were published that showed many of the salient characteristics of myopic CNV. Hotchkiss and Fine published a case series in which nearly half of the eyes followed deteriorated to legal blindness [24]. The location of the CNV was found to be an important determinant of the final visual acuity. A significant proportion of eyes did not have neovascularization under the fovea, and these eyes appeared to have a lower risk of poor visual outcome. Some of the eyes in the series had laser photocoagulation, which was thought to potentially stabilize the visual acuity. The authors recommended a large prospective study to evaluate laser photocoagulation as a treatment. In the same year Rabb and coauthors reported the clinical findings of a large series of patients with CNV secondary to high myopia [23]. They described choroidal atrophy, the need to recognize lacquer cracks as a potential precursor for choroidal neovascularization, and that eyes with CNV develop scars, atrophy, and even macular holes. They also mentioned laser photocoagulation of CNV could preserve visual acuity. The authors thought the development of atrophy to be the most common reason for eyes to have poor visual acuity. Also in 1981 Fried and coauthors described a series of eyes with Fuchs' spots [25]. These generally occurred with increasing age of the patient but were seen in some as young as 14 years old. These authors described the use of laser photocoagulation. In 1983 Hampton and coworkers published a retrospective study of patients with visual loss secondary to myopic CNV [35]. They reported the visual acuity was related to the size and location of the neovascularization, the age of the patient, and duration of follow-up. At last follow-up 60 % of the eyes in their study were 20/200 or worse. The visual acuity was lost in the eyes in a rapid early phase of disease and more slowly later, with development of atrophy as a common end-stage outcome. Avila and coworkers [36] reported a series of patients with CNV associated with degenerative myopia in 1984 and concluded CNV was a self-limited disorder. There is an old medical school joke that hemorrhage is a self-limited disorder; however, the implication was the pathologic process caused a loss of function early after the development of the neovascularization and did not smolder on. They reported results of laser photocoagulation in 19 eyes, and the mean acuity of treated eyes did not improve. As a consequence of these "disappointing" results, the authors stated they stopped performing laser photocoagulation [36], which is curious given a theme this paper had with other contemporaneous publications was the poor natural history of the disease.

In 1999 Tabandeh and coworkers investigated patients aged 50 years or more in relation to the findings of CNV in high myopia [37]. As is typical for myopic CNV, the lesions were small, but a greater proportion of patients, as compared with historical controls, had a visual acuity of 20/200 or worse. Bottoni and Tilanus [38] showed that for a mean follow-up of 3 years, eyes with nonsubfoveal CNV were more likely to retain good acuity as compared with eyes with subfoveal involvement. Yoshida and coauthors [39] reported 10-year follow-up of a retrospective series of 25 highly myopic eyes with CNV, and nearly all of them had a visual acuity less than 20/200 [39]. In examining the 5-year outcomes, Hayashi and coworkers found patients with a good prognosis for visual acuity preservation in the absence of treatment were more likely to be younger, with smaller areas of CNV and better initial acuity, and the lesions were more likely to be nonsubfoveal [40]. Secretan and coauthors [41] reported a group of 50 eyes with nonsubfoveal disease that were not treated. Over time all of the eyes developed subfoveal extension of neovascularization. Yoshida and coauthors reported, in agreement with previous reports, that older eyes were more likely to have decreased vision from myopic CNV [42]. The untreated group of the VIP-PM group showed a rapid initial loss of acuity, expansion of the CNV, and enlargement of macular scarring over time [16]. The initial phases of neovascularization appear to be the more significant in causing vision loss, but the process continues with a smoldering expansion of neovascularization in many and the late development of atrophy affecting the central macula.

15.4 Treatment of Myopic Choroidal Neovascularization

Successive forms of treatment have been developed for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Most of the major developments were the product of extensive preclinical work, progression to small pilot studies, and then multicentered randomized clinical trials. Fortunately the main multicentered clinical trials were large and well-designed, giving treating physicians enough information to formulate both a reasonable expected outcome and an appropriately narrow confidence interval of the treatment effect. Advances in the treatment of CNV secondary to pathologic myopia have trended those from AMD in both the proposed theoretical basis and practice. Unfortunately the myopia studies uniformly examined smaller numbers of patients and suffered from design defects. As a consequence estimates of treatment effect, and the corresponding confidence intervals, are less precise. For each therapeutic modality the development and multicentered trial results for AMD will be presented. Then the adaptation of the treatment to myopic CNV will be shown through review of applicable studies along with a discussion of their general strengths and weaknesses. The treatment response as it relates to the special characteristics of highly myopic eyes and the complication profiles will be presented. Several of these treatments seem to share a similar late-stage outcome, namely, the development of atrophy, and a set of possible mechanisms for the development of atrophy will be proposed.

15.5 Thermal Laser Photocoagulation

In the 1960s the idea that neovascularization was an important component of exudative AMD was derived from information gleaned from the then newly developed testing modality, fluorescein angiography [43]. The new blood vessels were seen to proliferate into regions not ordinarily containing vessels, and concurrently the eyes were seen to develop signs of exudation and bleeding. The contemporaneous development of laser technology provided a method to deliver high-density photothermal energy to selected areas in the eye [44, 45]. Many small series of laser photocoagulation for AMD-related CNV were published and helped define the clinical response that could be expected [46–48]. The results from these reports formed a base of knowledge to design a randomized clinical trial.

The efficacy of thermal laser photocoagulation was investigated in the late 1970s and early 1980s in the Macular Photocoagulation Study, a series of related multicentered clinical trials. The strategy employed was to photocoagulate neovascular lesions, along with a border of seemingly normal retina, in order to preserve surrounding areas of macula [49]. Refinement of the ideas about the fluorescein angiographic imaging of CNV occurred during this time, and the importance of differentiating classic from occult neovascularization became apparent. CNV located 200–2,500 μm (extrafoveal lesions) and 1–199 μm (juxtafoveal lesions) from the geometric center of the fovea were evaluated in two related studies [49–52]. Thermal laser photocoagulation was found to reduce the incidence of severe visual loss, which was defined as a loss of 6 or more lines of visual acuity using a standardized measurement protocol [53], in both the extrafoveal and juxtafoveal studies. Recurrence of the CNV was a frequent occurrence after photocoagulation. The reappearance of new vessels was much more common on the foveal side of the photocoagulation scar and typically was associated with subfoveal extension of disease [52]. Eyes with no recurrence had much better acuity than eyes with recurrence. The problem with laser photocoagulation for CNV secondary to AMD is that a remarkably small proportion of the eyes do not have subfoveal involvement at presentation [54]. Later studies showed photocoagulation of lesions that was

not classic neovascularization did not result in a treatment benefit and that choice of wavelength was not an important consideration in terms of treatment outcome [55].

15.6 Laser Photocoagulation for Myopic Choroidal Neovascularization

There are several potential reasons that thermal laser photocoagulation of CNV secondary to high myopia would be easier than for AMD. The neovascularization seen in high myopia is usually not masked by blood or lipid to the extent seen in eyes with AMD and as a consequence is readily visualized. They typically are small classic lesions that are frequently nonsubfoveal. The enveloping pigmented cells are an attribute in terms of absorbing laser energy. Early reports of laser therapy for CNV demonstrated what was to be a recurrent theme: treated patients could have stabilization, and even improvement in some cases, but many eyes developed areas of atrophy that expanded over time [23, 24, 36, 56–59]. Some authors of the early papers questioned the value of laser, even though contemporaneous reports of the natural course of myopic CNV to be dismal in the long term [36]. A later study by Pece and coauthors with a larger patient sample showed laser photocoagulation resulted in a mean stabilization of acuity, even with longer-term follow-up [57]. A randomized trial of 70 eyes showed in the early phase after treatment, eyes receiving photocoagulation had a much better mean acuity than did non-treated eyes [58]. The difference at 5 years was no longer significant, the result of expansion of the area of atrophy in the treated eyes. A retrospective study from the same group showed laser-treated patients had less decline in acuity during the first 2 years as compared with historical controls, but the effect was not seen at 5 years [41].

Two main problems complicate thermal laser photocoagulation for myopic CNV. The first is recurrence of the neovascularization, much the same as in AMD. The majority of treated patients have recurrences, and most of these recurrences are at the foveal edge of the laser photocoagulation. The second problem is that an overwhelming majority of eyes develop enlargement of the area of atrophy that eventually involves the fovea with loss of acuity as the result. Mechanical stretching of the posterior pole of the eye appears to influence the expansion characteristics of the atrophic area [60]. The expansion of atrophy is more problematical in treating CNV in myopic eyes as compared with those having AMD. Laser photocoagulation has been studied only in eyes with nonsubfoveal lesions, which are the minority of cases of myopic CNV. Laser photocoagulation of subfoveal CNV would result in loss of central vision. As a consequence laser photocoagulation does not appear to be a good treatment for myopic CNV.

15.7 Surgical Treatment

The surgical treatment for age-related macular degeneration involves three main strategies used independently or in combination: direct surgical removal of neovascularization, removal of hemorrhage, or translocation of the macula to a more favorable location. Early reports of removal of neovascularization, hemorrhage, or both suggested most eyes had visual stabilization in AMD, with some patients showing substantial improvement [61–63]. Patients with neovascularization that was idiopathic or secondary to inflammatory conditions such as presumed ocular histoplasmosis syndrome were purported to have a better outcome [63]. The Subretinal Surgery Trials were organized and this group of multicentered randomized trials examined the role of surgery in visual performance of affected patients [64–67]. In a study of 454 patients with CNV secondary to AMD, surgical removal did not show any benefit as compared with observation alone [65]. The median visual acuity decreased from 20/100 to 20/400 in both arms at 24 months. Cataracts and retinal detachments were more common in the surgical arm. In a group of 336 patients with subretinal hemorrhage secondary to CNV associated with AMD, drainage of the hemorrhage did not increase the chance of stable or improved visual acuity [66]. The surgical arm had a high proportion (16 %) of patients going on to have rhegmatogenous retinal detachment. In a group of 225 patients with CNV lesions that were either idiopathic or associated with presumed ocular histoplasmosis, no treatment benefit was demonstrated for surgical removal as compared with observation [67]. Later the Visual Preference Value Scale findings from these patients showed no quality of life improvements among patients having surgery as compared with observation [68]. Following these reports and coincident with the availability of agents directed against vascular endothelial growth factor, there did not appear to be any compelling reason to undertake surgical extraction approaches to CNV lesions that were idiopathic or associated with AMD or inflammatory disorders.

Macular translocation is an attempt to move the macular region to an area not affected by neovascularization. This modality can be combined with removal of neovascularization and offers the possibility of placing the fovea on a relatively healthy RPE bed. The rotation of the retina causes a correspondingly large alteration of visual perception and can cause severe diplopia. Therefore in practice it was reserved to treat the second eye of a patient with bilateral disease [69–74]. In a series of 61 AMD, patients underwent 360 macular translocation, and the median improvement of visual acuity was 7 letters [71]. There was a significant corresponding improvement in vision-related quality of life scores [72]. One randomized trial of 50 eyes in which translocation was compared with photodynamic therapy (PDT) for predominantly classic subfoveal membranes secondary to AMD

found after 2 years of follow-up the translocation group had a mean change of +0.3 letters while the PDT group lost a mean of 12.6 letters [73]. Quality of life testing showed improved performance in the translocation group in several subsets [74]. The surgery required for macular translocation is difficult and time-consuming and has a high proportion of eyes eventually experiencing complications. A long-term follow-up study showed the development of atrophy was a common occurrence limiting visual potential [75].

Surgical removal of neovascularization in high myopia does not appear to cause visual acuity improvement. Uemura and Thomas reported the visual acuity results of 23 patients with myopic CNV followed for a mean of 24 months and 9 eyes had an improvement of 2 or more lines of Snellen acuity, 6 remained stable, and 8 had decreased acuity [76]. Recurrences were seen in 57 % of the eyes. In a series of 22 eyes with a mean follow-up of nearly 30 months reported by Ruiz-Moreno and de la Vega, no substantive improvement of visual acuity was seen in eyes having surgical removal of CNV, but recurrences were seen in 4 eyes, cataract in three, and retinal detachment in one, and two patients required intraocular pressure-lowering agents [77]. In a series of 17 eyes with subfoveal CNV associated with high myopia, Hera and associates reported 4 had visual acuity improvement, 10 had no change, and 3 had a decrease in acuity [78]. Given the small sample size, lack of standardization of acuity measurement, absence of a control group, and no long-term follow-up information, it is difficult to gauge the magnitude of a benefit with this surgery, if any.

Macular translocation for subfoveal CNV in high myopia has been reported in case series and in one comparative trial. Hamelin and coauthors reported a retrospective study of 32 eyes treated by either limited macular translocation in 14 eyes or surgical extraction in 18 eyes [79]. The mean follow-up in the extraction group was 14 months, and the mean change in acuity was loss of 0.7 lines. The mean follow-up in the translocation group was 11 months, and the mean change in acuity was 3.8 lines. Recurrences were seen in 39 % of the surgical removal and 14 % of the translocation eyes. Retinal detachment occurred as a complication in two eyes of each group. The small sample size, lack of a control group, and any long-term information make analysis of translocation surgery for high myopia difficult.

15.8 Photodynamic Therapy

Photodynamic therapy for subfoveal CNV in AMD using verteporfin was investigated in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study. Verteporfin was injected at a dose of 6 mg per square meter of body surface area, and the neovascular lesion then was irradiated with a nonthermal laser spot (50 J/cm^2) 1,000 μm larger than the greatest linear dimension of the lesion. Patients were retreated every 3 months if they showed leakage by fluorescein angiography [80]. Patients were given 3.4 treatments in the first year and 2.2 treatments in the second year. Patients with predominantly classic CNV had treatment benefit that extended to the second year of the study [81]. Patients with occult with no classic did not have a statistically significant benefit at 1 year, but at 2 years there was a statistically significant treatment benefit [17]. Retrospective analysis of pooled data showed that lesion size was significantly related to the response to PDT with small lesions appearing to show response regardless of lesion composition, while larger lesions only showed treatment benefit if the lesion was predominantly classic [82]. Patients with predominantly classic CNV had a 39 % chance of experiencing a 3-line or more visual acuity loss [80], and the expectation for treated patients was a slower decline in visual acuity than what would occur without treatment. Analysis of cases by the reading center suggested there was a slight undertreatment among patients in the registration trials. In open-label expanded access trial was performed with 4,435 patients and in a clinic setting the number of treatments per year was lower than that seen in the registration trials [83]. There are many possible explanations for this finding, but one was in a real world deployment of an as needed strategy may result in undertreatment.

Eyes with myopic CNV were evaluated in the Verteporfin in Photodynamic (VIP) Therapy Study. In contrast to studies done on AMD, the primary outcome was the proportion of eyes experiencing fewer than 8 letters, which is about 1.5 lines, of visual acuity loss. At 1 year fewer patients treated with photodynamic therapy lost 8 letters as compared with the untreated controls [16]. Contrast sensitivity was better in the treated eyes as well. The mean number of treatments was 3.4 in the treatment arm versus 3.2 in the sham group. The treatment effect began to wane so that by 2 years the advantage in the treated group was no longer significant [84] (see Fig. 15.3.) In the second year the mean number of treatments was 1.7 in the treatment group and 1.4 in the control group. The 3-year results showed stability from the 2-year results [85]. Several studies examining treated patient series reported longer-term follow-up, but it is difficult to put these studies into perspective because all of them lacked a control group [86–103]. Krebs and coauthors [93] reported 3-year results of 20 treated eyes and found the distance acuity and central field threshold sensitivity showed stabilization, but reading acuity declined from year 1 to year 3. Pece and coworkers followed 62 eyes of 62 patients for a mean of 31 months and found 13 % improved by 1 or more lines of Snellen acuity, 32 % deteriorated, and 55 % remained stable [94]. The authors thought younger eyes (≤55 years) did better than older eyes. Lam and colleagues [86] reported a 2-year study of pathologic myopia in Chinese patients comparing PDT to

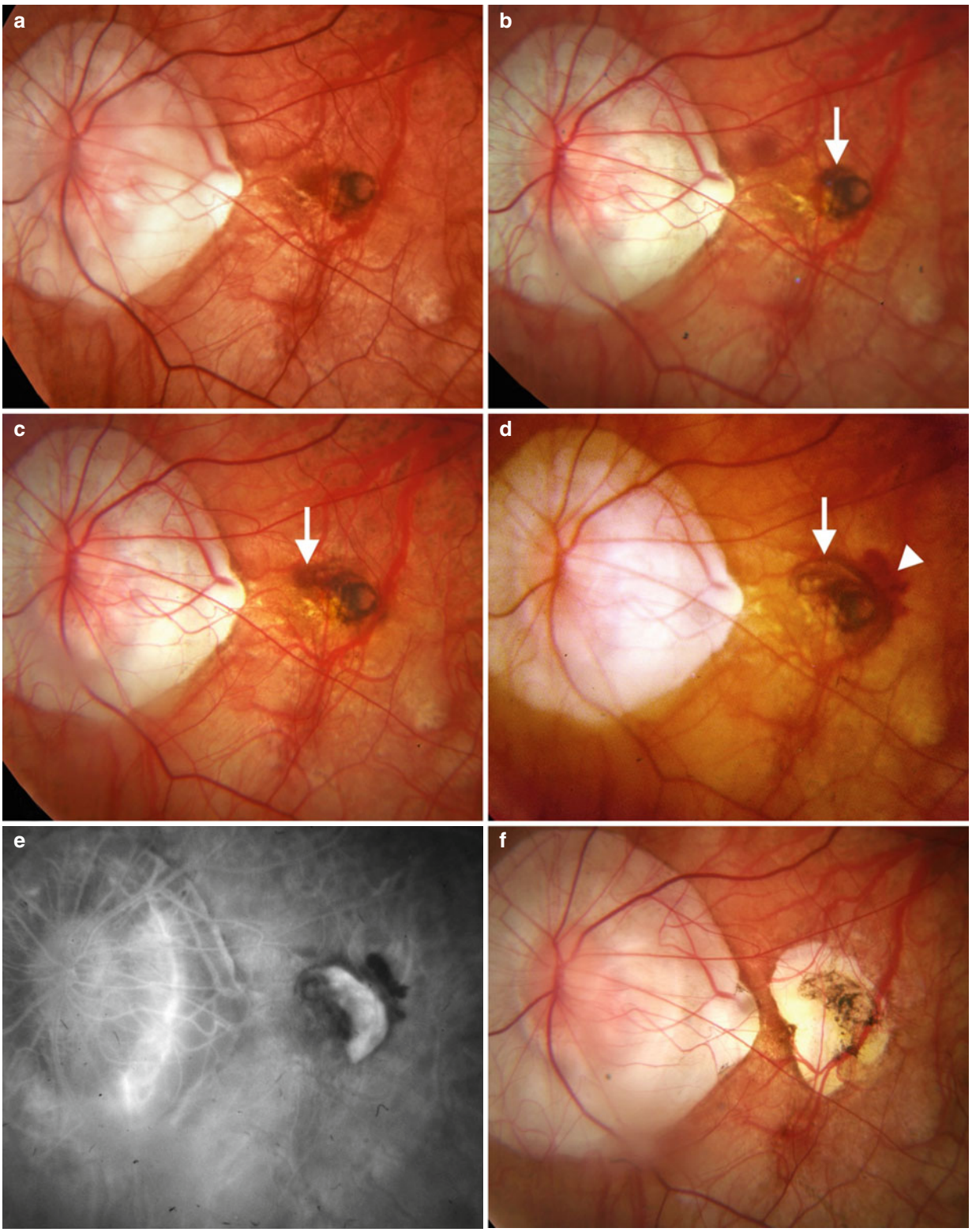

Fig. 15.3 Expansion of choroidal neovascularization with photodynamic therapy and subsequent treatment with bevacizumab. (**a**) This patient was treated with photodynamic therapy for myopic choroidal neovascularization. Note the rings of pigment centrally. Since the patient had leakage, he was treated with photodynamic therapy. (**b**) The patient had expansion of the lesion. Note the pigment (*arrow*). He was treated with photodynamic therapy again which was associated with expansion of the lesion, arrow in (**c**), and with further expansion (*arrow* in **d**) with hemorrhage (*arrowhead*). His visual acuity was 20/80. (**e**) The fluorescein angiographic image shows the extent of the neovascularization. The patient was given an injection of intravitreal bevacizumab 1.25 mg. (**f**) Over time the patient was given 2 additional injections. In this picture 6 years after first being treated with bevacizumab, the patient has some residual hyperpigmentation but also a wide area of pigmentary loss. When last examined nearly 7 years after injection, his visual acuity was 20/60

the results of the VIP-PM study. The authors stated the visual results were similar in the two studies, but Chinese patients seemed to require fewer treatments as compared with the VIP-PM study group. However, the eyes had juxtafoveal CNV exclusively, which may have impacted the treatment frequency. Younger (<55 years) patients had a better final acuity than older patients. Hayashi and coworkers [101] reported the visual results of 48 eyes of 46 patients with subfoveal and nonsubfoveal CNV in Japanese patients with pathologic myopia. The visual acuity did not change in a significant way after PDT. A minority of eyes had follow-up for 4 years or more, but 70 % of these developed chorioretinal atrophy, particularly if the neovascularization was initially subfoveal. Coutinho and coauthors reported the 5-year follow-up of 43 consecutive eyes of 36 patients [102]. There results were amazingly good, as 32.6 % of the eyes had a visual acuity improvement of 3 or more lines and the mean acuity of the group was better at 5 years than at baseline.

Common to all studies was the need for treatment at closer intervals early after the treatment began with fewer needed later. In the controlled study, VIP-PM, the sham group showed visual stability while "requiring" fewer treatments in the second year. This is consistent with the known natural history of the disease; the lesions show fewer signs of disease activity over time, and the decline in vision is not as rapid as in the earlier phases. That is not to say the natural history is good; it appears PDT offers little help in changing the outcome over after the initial phases of neovascularization. Analysis of many of these cases showed a propensity to develop atrophy.

15.9 Agents Directed Against Vascular Endothelial Growth Factor

A requirement for tumor growth to recruit blood vessels for metabolite supply started a multiyear effort that ultimately resulted in the identification and modalities to block the effects of vascular endothelial growth factor (VEGF) [104–106]. The potential of anti-VEGF agents in use against CNV offered a second use for these agents. In parallel development tracks, bevacizumab, a full-length antibody, was developed for use in cancer therapy, and ranibizumab, an antibody fragment, was created for use in the eye. Bevacizumab was found to be effective in the treatment of colon cancer when used in combination with standard chemotherapy and was approved by the Federal Food and Drug Administration in 2004 [107]. Ranibizumab was shown to have remarkable efficacy in the treatment of CNV secondary to AMD in multicentered, randomized Phase III trials [108, 109]. In open-label extension investigation the rate of treatments in clinic settings was much lower than that seen under the registration trials [110]. The visual acuity concurrently decreased, suggesting that real-world implementation of an as needed strategy may have resulted in undertreatment.

The results of the trials were available well before ranibizumab was, due to the FDA approval process. In an attempt to get the same clinical efficacy, bevacizumab was given intravitreally and appeared to have beneficial effect [111–113]. Early studies being published showing bevacizumab had effects mirroring those of ranibizumab. Investigators from around the world examined the potential safety and efficacy of bevacizumab in human and animal studies [114]. No significant ocular toxicity was found. Medicare reimbursement of bevacizumab enabled patients with AMD to have cost coverage early after it began to be used despite the lack of any randomized trial showing efficacy. The cost difference between ranibizumab and bevacizumab is astounding. A dose of ranibizumab is approximately $2,000, while bevacizumab is about 1/50th the cost. The chief competitor for ranibizumab became bevacizumab, although each was made by the same company. In 2007 the company had a press release stating they would stop the sale of bevacizumab to compounding pharmacies [115]. Senator Herb Kohl sent a letter to Kerry Weems, the Acting Administrator of the Centers for Medicare and Medicaid Services expressing concerns about the costs of the proposed ban [116]. In a compromise negotiated by the American Academy of Ophthalmology and the American Society of Retinal Surgeons, the ban was lifted.

Over time studies of bevacizumab for the treatment of CNV secondary to AMD became more refined and sophisticated, ultimately resulting in the Comparison of AMD Treatment Trials, or CATT [117, 118]. This multicentered randomized trial had 4 arms, ranibizumab monthly, bevacizumab monthly, ranibizumab given on an as needed basis, and bevacizumab given as needed. The monthly dosing of ranibizumab was used in the trials used for FDA approval, and the other treatment arms were compared to that in a non-inferiority design. At the end of 1 year, the 4 arms were rerandomized to more examine how alterations in treatment frequency would affect visual acuity outcomes. At 1 year the visual acuity outcomes showed roughly similar outcomes for all arms, although that is not the primary goal of a non-inferiority design [117]. The bevacizumab given as needed did not meet the non-inferiority endpoints as compared with ranibizumab given monthly or bevacizumab given monthly. The authors of the paper stated these results were inconclusive given the 1-year follow-up and the small mean difference in visual acuity seen. The report of the second year results condensed the multiple arms the patients were separated into to determine as needed approaches consistently resulted in lower visual acuity than did monthly dosing [118]. Of interest is the switch from monthly dosing to an as needed strategy was met with a statistically significant loss of visual acuity even if the patients received 12 previous injections on a monthly interval.

Studies for myopic CNV started in a similar manner to that seen for AMD, except the sample sizes were much smaller [119–158]. Early studies showed rapid resolution of exudation along with improvement in mean visual acuity in patients treated with intravitreal bevacizumab independent of if they had previous PDT or not. Later studies reported longer duration of follow-up from the initial studies with only a few months to 1 year and later multiyear follow-up. The sample sizes increased in later studies as well. The visual acuity outcomes from these studies seemed robust, as far as can be discerned, and were associated with cessation of exudation and improvement of acuity. The reported studies for myopic CNV did not show comparable improvement in design or sophistication to the degree that the preceding AMD studies did. No published study administered a gold standard monthly dosing schedule such as that used in Phase III registration studies or in the CATT. Therefore the upper limit of expected visual acuity performance in myopic CNV is not known for either ranibizumab or bevacizumab. Later patient series treated with ranibizumab seemed to have roughly the same results as bevacizumab did, but even this is not known with certainty, due to the lack of monthly dosing arms and small sample sizes [125, 135, 142, 145, 148–150, 154, 156, 159]. Some studies seemed designed to use as few doses of intravitreal anti-VEGF agents as possible with some bordering on therapeutic nihilism [160, 161]. In an ordinary informed consent, patients are told of the extraordinarily low risk of complication from intravitreal injections of anti-VEGF agents. There does not seem to be a compelling reason to having the limitation of anti-VEGF injections as being a worthwhile goal when there is a lack of knowledge about the visual acuity response to frequent periodic dosing given the findings in CNV secondary to AMD.

As reviewed by Cohen in 2009 [141], reports of intravitreal anti-VEGF agents have yielded similar results: there appears to be a significant improvement in visual acuity with an excellent safety profile. Since then several larger salient studies have been published. Parodi and coworkers [162] performed a comparative trial, randomly allocating 54 patients with juxtafoveal CNV to PDT, intravitreal bevacizumab, or laser photocoagulation. The sample sizes were small, but there appeared to be a treatment benefit favoring bevacizumab. Over the 2-year follow-up, the eyes receiving PDT had a significant decrease in acuity from 0.52 logMAR (which is 20/66) to 0.72 logMAR (20/105). The vision in the laser-treated group remained stable. The intravitreal bevacizumab group had a significant improvement from 0.6 logMAR (20/80) to 0.42 logMAR (20/52). A number of patient series have been reported with fairly consistent results, although wide variations in treatment approach used in studies make derivation of summary data impossible. In general the treated eyes had at least stabilization of visual acuity. In a prospective series reported by Calvo-Gonzalez and coauthors of 67 patients treated for CNV secondary to myopia with 3 loading doses of ranibizumab followed by an as needed phase, the mean change in visual acuity was 12 letters at the end of a mean 15.9-month follow-up [154]. Baseline visual acuity was positively correlated with final acuity as was a nonsubfoveal lesion location. In a prospective study of 32 eyes of 30 patients by Gharbiya and coworkers [158], the visual acuity improved by a mean of 15 letters at 3 years of follow-up in a study based on bevacizumab; patients were first treated with a loading dose of 3 injections at monthly intervals followed by an as needed phase. Eyes with juxtafoveal had a better outcome as compared with subfoveal CNV, and the visual acuity at last follow-up was positively correlated with baseline acuity and negatively correlated with age.

Vadala and coworkers studied 40 eyes of 39 patients in a prospective study of ranibizumab given in an as needed strategy [150]. The median follow-up was 13.3 months, during which the mean acuity improved by 19.5 letters. Previous PDT did not seem to influence the results. Yoon and coauthors reported a retrospective study of 142 eyes of 128 consecutive patients in which the treatment used was PDT, intravitreal injection of an anti-VEGF agent, or the combination of both [163]. The anti-VEGF group showed a significant improvement in acuity as compared with either the PDT or combination therapy groups with the mean visual acuity increasing from a baseline of 0.57 logMAR (20/74 approximate Snellen equivalent) to 0.33 (20/43).

15.10 Recommended Treatment of Eyes with Myopic Choroidal Neovascularization

The first step in management of myopic CNV is to be absolutely sure the patient does not have MCP. Eyes with MCP have CNV as a frequent complication, and most eyes with MCP are myopic. It is common to see patients with MCP being considered to have myopic CNV as a consequence. Treating the CNV alone without treating the underlying inflammatory condition puts patients at risk for vision loss in both eyes because of scarring or atrophy. If the eye is thought to have myopic CNV that is active, the treatment with the highest probability of visual gain appears to be injection of an anti-VEGF agent. Choice of bevacizumab versus ranibizumab appears to involve regulatory and funding issues and not efficacy of one drug over another. Patients are given a dose of medication at baseline (Figs. 15.4 and 15.5). A regimen of using one injection as compared with three initial doses has been evaluated in small studies, none of which had more than 40 eyes [153, 164, 165]. One study

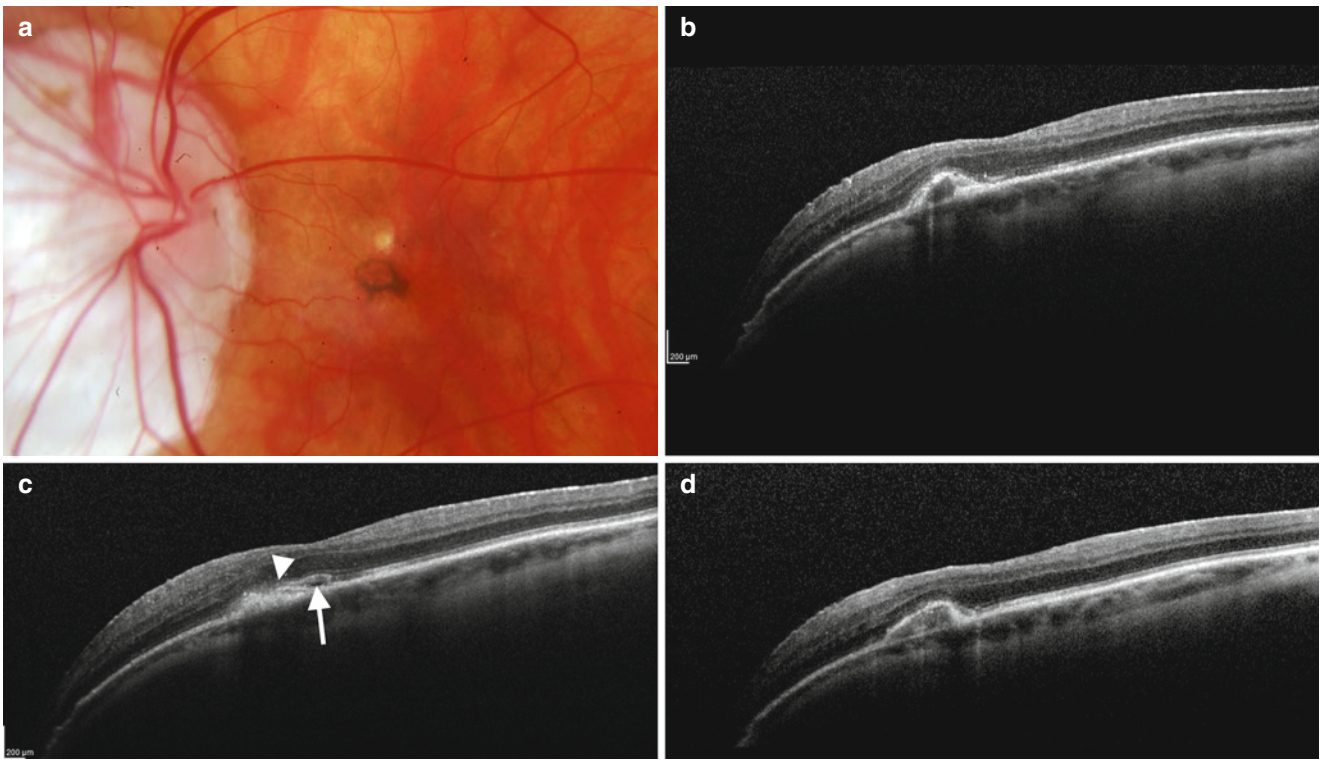

Fig. 15.4 Anti-VEGF treatment effect. (**a**) Two months after treatment the lesion shown in Fig. 15.2 with ranibizumab, the lesion developed a ring of hyperpigmentation. (**b**) The optical coherence tomography image shows a smaller lesion with a well-defined outer surface interface with the overlying retina. (**c**) Several months later the patient developed signs of recurrent disease activity. The lesion had a change in internal reflectivity, the boundary between the lesion and the retina was blurred (*arrowhead*), and there was a small amount of subretinal fluid (*arrow*). (**d**) Following treatment the lesion regained signs of inactivity with decreased internal reflectivity, a sharp boundary between the lesion and retina, and no subretinal fluid. Over the following 2 years of follow-up, the patient needed repeat injections on a periodic basis, but the appearance of the lesion and his visual acuity, 20/25, remained stable

concluded there was no difference, one study concluded three loading doses were better, and the third study was equivocal. However in AMD monthly dosing has produced the best results. The 2-year results of the CATT showed that even after 1 year of monthly dosing, switching to an as needed approach was associated with a slight decrease in vision. Given the small sample sizes of the myopic CNV studies, it is probably better to conclude that there is not any biologically plausible reason to suspect acuity would be better after one loading dose as compared with three, but three doses would suppress exudation more effectively than one dose.

The key unresolved problem with treatment of myopic CNV is treatment frequency. Myopic CNV has a natural tendency to achieve a metastable state in which the exudation appears to decrease and the vision in some cases may temporarily improve. So any dose of an anti-VEGF agent likely promotes a situation in which there appears to be decreased or absent exudation. This raises the difficulty of knowing when to give the next dose. In CNV secondary to AMD the best course is to give frequent periodic injections; as needed dosing does not appear to be quite as good. Treatment of CNV needs to be balanced against other needs of the patient, and there is a possibility monthly dosing is not possible, even in AMD. For myopic CNV we do not know what the outcome is with monthly dosing, and we don't know how much different the outcome would be with the various as needed strategies that have been proposed.

As needed strategies are based on a particular abnormality being detected, for fluorescein leakage would be a threshold indicator, while for OCT the indications may be intra- or subretinal accumulation of fluid. The problem is that these tests are not particularly sensitive in high myopes. As way of example untreated active cases may not show much leakage during fluorescein angiography or sub- or intraretinal fluid by OCT examination. In a true as needed regimen, these eyes would not merit treatment, even at baseline. This scenario illustrates the difficulty of using one or more tests in isolation as a guide to as needed treatment of high myopes with CNV. As a consequence some retinal physicians treat myopes based on objective tests such as fluorescein angiography or OCT but also according to the subjective

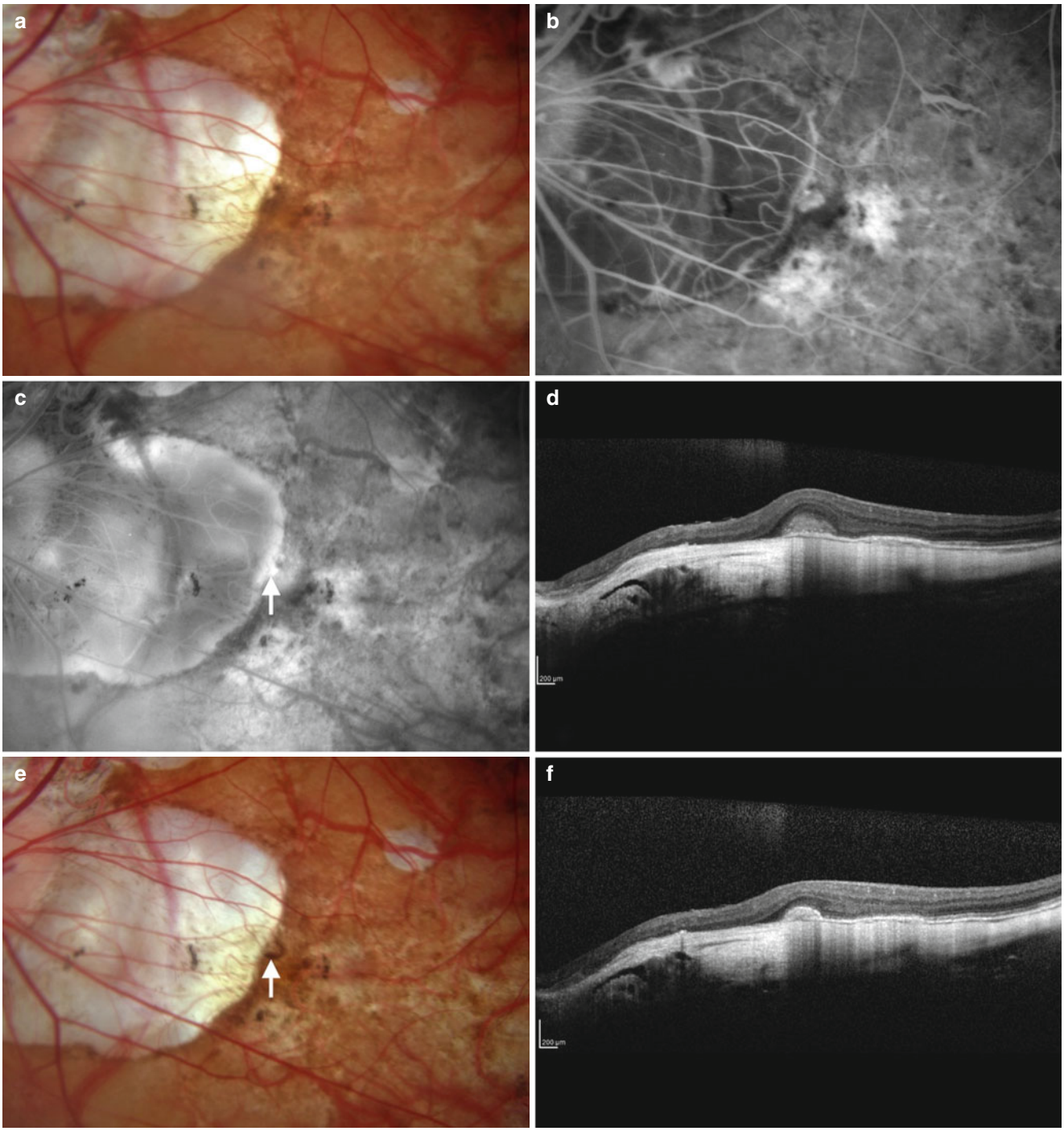

Fig. 15.5 This patient thought there may have been distortion in her vision, but was not quite certain. (**a**) The color fundus photograph shows a large area of peripapillary atrophy, but little in the way of an explanation of a cause of the symptoms. (**b**) The early phase fluorescein angiogram shows multiple transmission defects. (**c**) Later in the angiographic sequence, there is an increase in the fluorescence of one spot (*arrow*). (**d**) In one section of the optical coherence tomographic examination, there was an elevation of reflective material under the retina, in the region corresponding to the increased brightness in the angiogram. (**e**) Two months after presentation, and following 2 intravitreal injections of an agent directed against vascular endothelial growth factor, a rim of pigment around the neovascularization could be seen (*arrow*). (**f**) The optical coherence tomographic section shows a smaller lesion with a sharp boundary between the lesion and the outer retina. Note the lack of any intra- or subretinal fluid in either (d) or (f). This case illustrates the use of an anti-VEGF injection not only as a therapeutic agent but also a potential diagnostic one as well

complaints of the patient. It is common to have patients complain about vision changes before any testing modality shows an abnormality and also for these same patients to return stating their vision improved after the injection. Since there is an absence of a good randomized trial, constant vigilance with aggressive treatment when indicated is probably the best approach.

There are numerous potential signs of recurrent disease. Patients may have a sudden decrease in acuity not explainable by the expansion of atrophy, which is generally slow. Patients have complaints of increased distortion, but measurements obtained with an Amsler grid are not quantifiable and therefore difficult to compare from one examination to the next. Recurrent activity of the lesion can produce the ophthalmoscopic signs of blurring of the margin of the CNV, visible hemorrhage, and rarely lipid. Fluorescein angiography can show modest amounts of increased leakage and faint increases in the size of staining. There are numerous potential indications using OCT imaging. When a treated lesion shows cessation of activity, the lesion becomes more compact, the internal reflectivity is often less than the surface, the boundary between the lesion and retina is sharp, and there is no associated intra- or subretinal fluid. When the lesion becomes active, any of these parameters may change. The lesion becomes larger, the reflectivity in the lesion can increase, the boundary between the lesion and retina becomes less distinct, and there can be subretinal fluid and less commonly intraretinal fluid.

Patients starting with good acuity, small lesions, or non-subfoveal location have better acuity over time, but none of these attributes are selectable by either the patient or physician. There have been studies using a combination of an anti-VEGF agent with photodynamic therapy, but much like in AMD, evidence is lacking showing any improvement in visual acuity performance as compared with the use of anti-VEGF agents alone [163, 166]. Patients with MCP are generally treated with a short course of corticosteroids, and long-term immunosuppression is commonly started simultaneously. Any concurrent CNV is treated with anti-VEGF agents. These eyes may have a rapid loss of visual acuity secondary to inflammatory disease exacerbation, to activity of the CNV, or to both. Evidence of inflammatory activity includes seeing an increase in cells in the vitreous, infiltration in the subretinal space, sub-RPE accumulation s of material, fluid within or under the retina, and areas where the outer retinal architecture, particularly the ellipsoid band, shows widespread disruption. These changes are generally rapidly responsive to corticosteroids. Signs of active CNV include an increase in intra- or subretinal blood, thickening or expansion of the CNV lesion, or hemorrhage. Treatment of the CNV is done with anti-VEGF agents, although some patients may show some response to corticosteroids.

15.11 Retinal Pigment Epithelial Loss and Atrophy

High myopes have a number of anatomic disturbances prior to the development of CNV: they have RPE disturbances, lacquer cracks, and usually very thin choroids. There may be concurrent focal areas of chorioretinal atrophy. With no treatment, the CNV follows a stereotypical life cycle in which the vessels proliferate and cause exudation and bleeding, and then in many cases there is enveloping of the neovascularization with proliferating pigment cells. The CNV complex shrinks and there can be a centripetal retraction of the lesion from the surrounding RPE monolayer, causing a halo of absent RPE around the CNV. This absent RPE is not really atrophy, in that the word atrophy implies a withering of the normally present cells.

Laser photocoagulation uses thermal energy to destroy the newly growing vessels, but there is significant collateral damage to the underlying RPE and choroid (Fig. 15.6). This induces a region of cell loss that is commonly called atrophy even though the RPE and choriocapillaris were actively killed by the treatment. Atrophy implies the cells shrank or became less active, while laser photocoagulation increases the temperature of the cells to the point where they are destroyed. The choriocapillaris is a confluent layer of vascular channels with the spaces between vessels nearly vanishing in the posterior pole because of the packing density of the vessels. The blood flow is functionally lobular, but regionally blood from any one section has the potential to flow to adjacent areas based on instantaneous pressure differences. The area destroyed by laser photocoagulation cannot participate in this shared flow across the choriocapillaris network, so one would expect the regional flow immediately around the laser photocoagulation to be somewhat less than in comparable people without CNV or laser photocoagulation. Under the choroid are layers of larger vessels, Haller's and Sattler's layers that feed into the choriocapillaris in the superjacent or adjacent choriocapillaris. Laser destruction of these layers also affects regional choriocapillaris flow. High myopes have thinning of the choroid that often progresses to areas of complete absence of the choroid and overlying RPE. Since there is an absence of pigmented tissue (only a thin remnant of retina remains), the sclera is directly visible, so consequently these lesions appear as ovoid or round areas that are white. Decreases in regional blood supply could be expected to advance the process and may explain why the "atrophic" area of tissue absence related to laser photocoagulation increases with size over time.

PDT also causes collateral damage to the choroid. Early on in the investigation of treatment of CNV secondary to AMD, indocyanine green angiography showed patients treated with PDT could develop choroidal hypoperfusion abnormalities. The first paper looking at the choroidal thickness of myopes as measured by enhanced depth

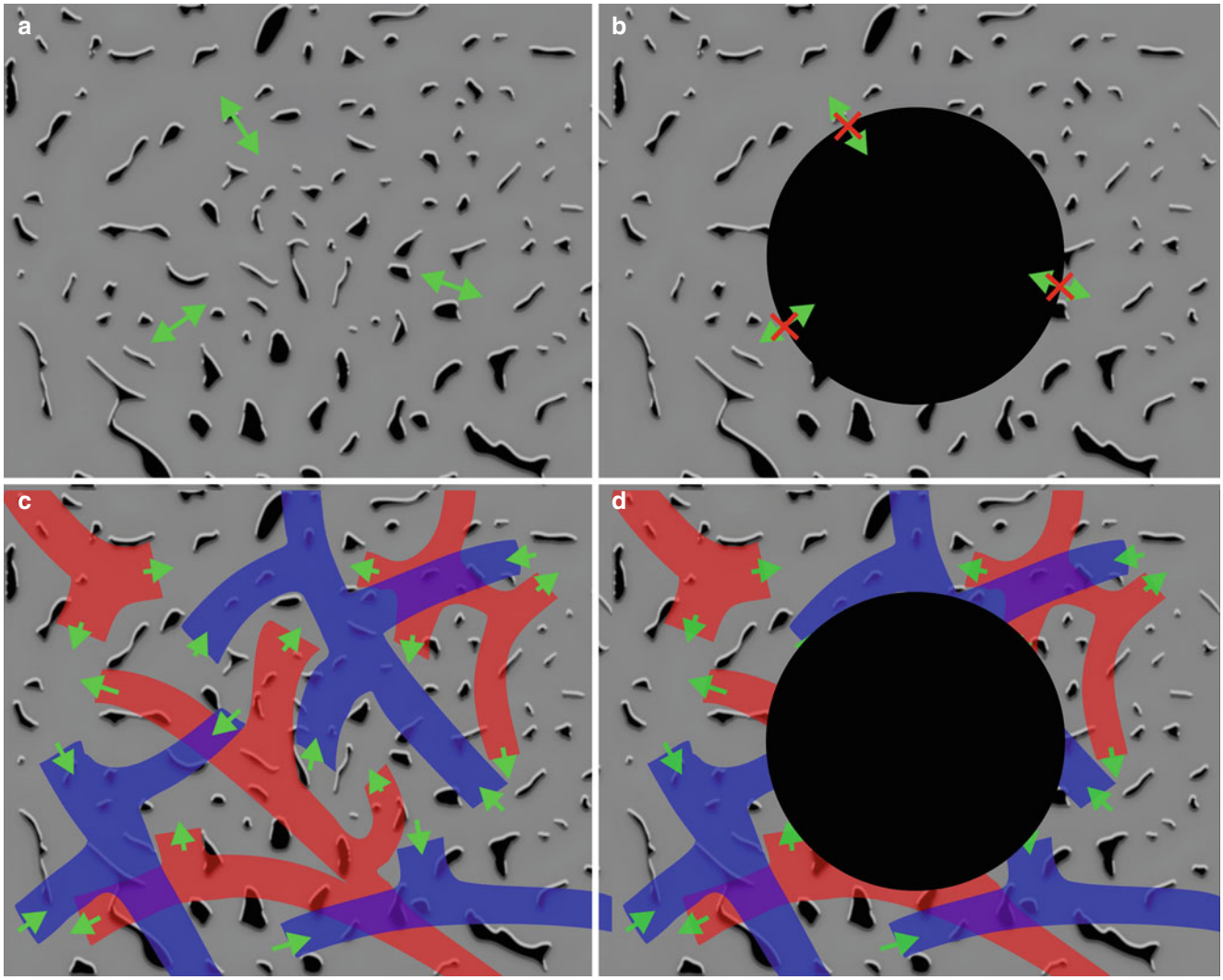

Fig. 15.6 Hypothesis of atrophy generation posttreatment for myopic choroidal neovascularization. (**a**) The choriocapillaris is a densely packed interconnected set of specialized capillaries. There are no anatomical lobules per se, but local flow is a function of regional pressure differences as illustrated by the green arrows. (**b**) Laser photocoagulation has the potential to destroy the choriocapillaris. Clearly the area treated will be harmed, but the regional flow coming from this area will also be absent. (**c**) Under the choriocapillaris are larger vessels of Haller's and Sattler's layers drawn in a stylized way with green arrows showing the flow in the respective arterioles (*red*) or venules (*blue*). Laser photocoagulation (**d**) has the propensity of altering this flow as well, thus affecting local choriocapillaris areas by more than one mechanism. The choroid in highly myopic eyes is thin and with each passing year gets thinner. By affecting the flow in the choroid, localized laser could hasten this process. The same argument could be made for the effects of photodynamic therapy

imaging OCT noted that patients who had a history of PDT for CNV had thinner subfoveal choroidal thicknesses [9]. It is conceivable that PDT damages an already infirm choroidal vascular system, which may encourage or hasten the atrophic, degenerative processes seen in high myopia. Eyes with high myopia are on a path to develop increasing manifestations of atrophy over time, and the occurrence of CNV, along with any trauma its attendant treatment may induce may well hasten this fated process.

Some eyes treated with anti-VEGF agents may also develop atrophy or loss of the RPE, and if it occurs, it is usually located around the outer border. Some of these eyes show further outward expansion of the outer border of the area of absent RPE, and the inner, formerly hyperpigmented, central region can gradually become increasingly hypopigmented. It is possible that pharmacologically induced scarring and shrinkage of the CNV lesion could lead to circumferential rips of the RPE. Some eyes develop areas of atrophy, but not necessarily where the CNV is located. Figure 15.7 shows an eye that developed an area of CNV was treated with an anti-VEGF agent and a year later developed another region of CNV. This second lesion was treated with an anti-VEGF agent as well. After 3 years of follow-up the patient had areas of profound atrophy, but not

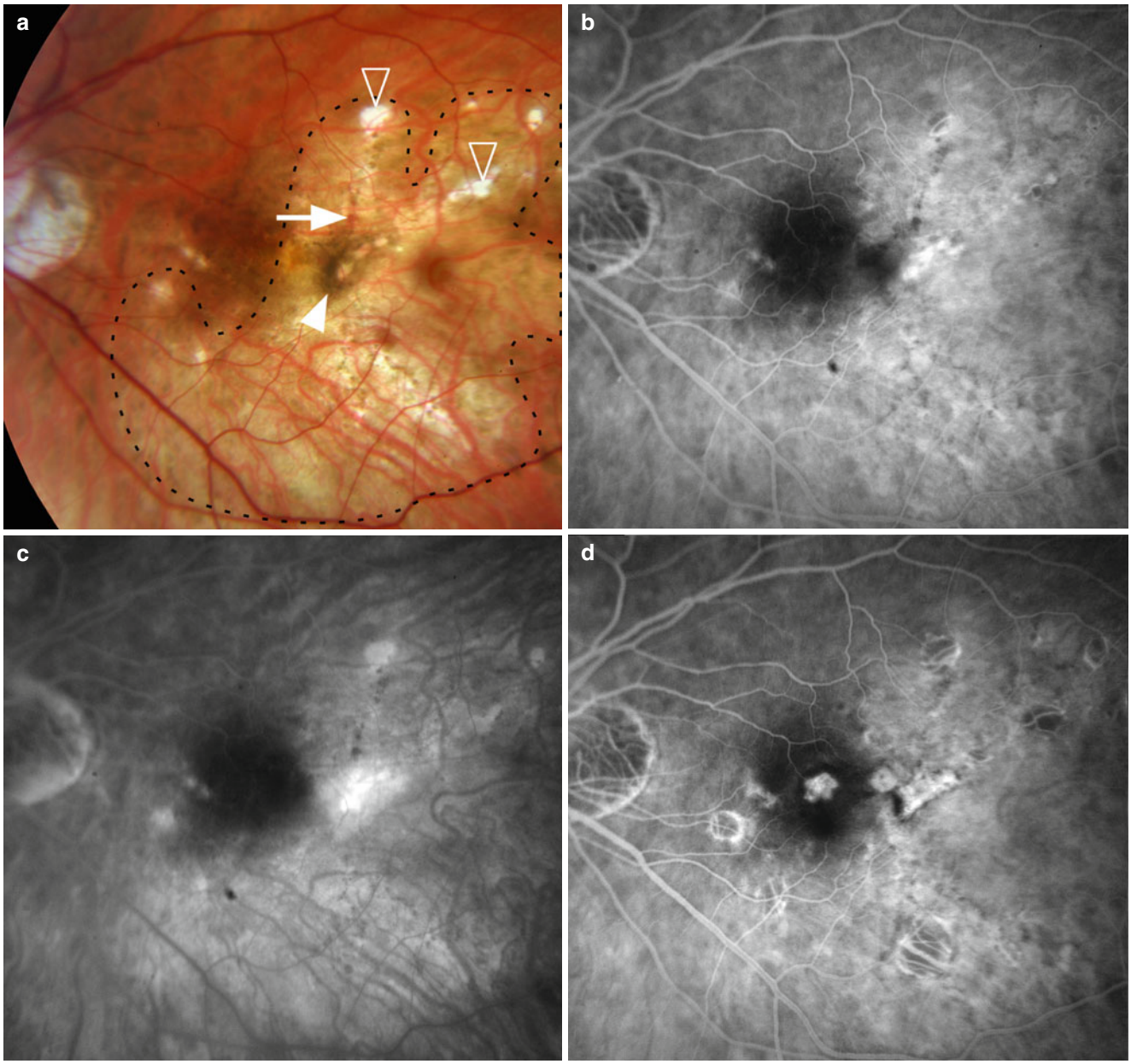

Fig. 15.7 (**a**) This 61-year-old high myope presented with a dot of hemorrhage in the temporal macula (*arrow*) and an area of increased pigmentation (*arrowhead*) straddling a lacquer crack. There was an area of choroidal thinning (contained in the *dashed line*) with small regions of more profound tissue loss (*open arrowheads*). (**b**) Early and late (**c**) fluorescein angiogram shows expanding hyperfluorescence caused by leakage from an area of choroidal neovascularization. (**d**) The patient was treated with injections of an agent directed against vascular endothelial growth factor and the neovascularization became quiescent. Nearly a year later the patient presented with new symptoms caused by a second area of neovascularization located under the fovea. This showed leakage in the later phases of the angiogram (**e**). The patient was treated with additional injections. (**f**) Three years later the patient showed multiple regions of profound atrophy, located within the area of choroidal thinning identified in (a). Note that the areas of neovascularization themselves did not show atrophy

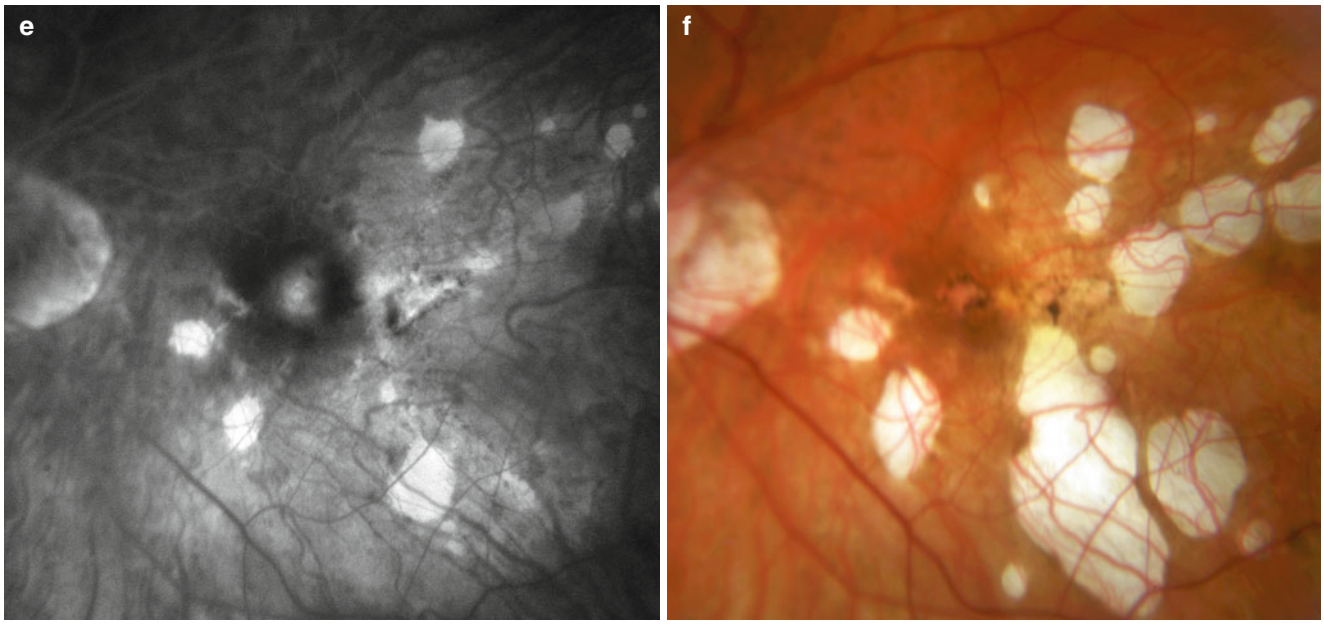

Fig. 15.7 (continued)

exactly where the CNV was located. The patient presented with choroidal atrophy, which progressed to chorioretinal atrophy over time.

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