3
Indocyanine Green Angiography: General Aspects and Interpretation

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More than three decades ago, indocyanine green angiography (ICGA) was introduced into ophthalmology. The relatively poor fluorescence efficiency of the indocyanine green (ICG) molecule and its limited ability to produce high-resolution images on infrared film initially restricted its angiographic application; however, ICG has subsequently been found to have several advantages over sodium fluorescein, especially in imaging choroidal vasculature. The emergence of high-resolution infrared digital imaging systems, specifically designed for ICGA and a growing awareness of choroidal vascular lesions has led to a resurgence of interest in ICGA.[1] The applications of ICGA continue to grow in number; the full extent of its capabilities is not yet known.

History

Initially used in the photographic industry, ICG was introduced into medicine in 1957. Its first application in medicine was in measuring cardiac output. In 1969, the first attempts at using ICGA were performed by Kogure and Choromokos[2] studying cerebral circulation in a dog. In 1971, Hochheimer[3] modified the system for ICGA by changing the color film that had been used previously to black-and-white infrared film. In 1972, Flower and Hochheimer[4] performed the first intravenous ICGA to image the human choroid. In the following years, Flower [5] and coworkers began a series of studies on primates and human to evaluate the potential utility of ICGA in the investigation of the normal and pathologic eye. They refined the procedure with recommendations for the concentration of the dye and method of injection. Flower also modified the transmission and emission filters to improve the resolution of the choroidal vessels. Flower et al. eventually found that infrared film lacked the sensitivity to adequately capture low-intensity ICG fluorescence, which limited the clinical utility of ICGA.

The resolution of ICGA was improved in the mid-1980s by Hayashi and coworkers,[6] who developed improved filter combinations with sufficient sensitivity for near-infrared wavelength. They were instrumental in the transition from film to videotape by introducing videoangiography. Although the sensitivity of the video camera system was a vast improvement, its inability to study individual images and the potential light toxicity using a 300-watt halogen bulb restricted the duration and quality of the technique.

In 1989, Destro and Puliafito [7] performed ICGA with a system very similar to that described by Hayashi. Imaging was improved by better filter combinations, but images were still stored and later analyzed using videotape recording. In the same year, the use of scanning laser ophthalmoscope for ICG videoangiography was introduced by Scheider and Schroedel. [8] In 1992, the use of a 1024 × 1024 line digital imaging system was introduced to produce high-resolution ICGA.[1] Images were digitized, displayed on a high-resolution monitor, and stored on an optical disc, but the system lacked flash synchronization with the video camera. Finally, Yannuzzi and coworkers [9] described a 1024-line resolution system that was synthesized with the appropriate flash synchronization and image storage capability, permitting high-resolution, long-duration ICGA.

Chemical Properties

Indocyanine green is a sterile, water-soluble tricarbocyanine dye with the empirical formula C43H47N2NaO6S2 and molecular weight of 775 daltons. Chemically it is an anhydro-3,3,3′,3′-tetramethyl-1-1′-di-(4-sulfobutyl)-4,5,4′,5-dibenzo-indotricyanine hydroxide sodium salt with both lipophilic and hydrophilic characteristics.

Indocyanine green is the product of a complex, synthetic process. Sodium iodine is incorporated to create an ICG lyophilisate that can be dissolved in water. Once dissolved, ICG tends to precipitate at high concentration or when mixed in physiologic saline. It is supplied with a solvent consisting of sterile water at pH 5.5 to 6.5. The aqueous ICG dye solution can decay at a rate of approximately 10% in 10 hours and should be used within this time. The final product contains no more than 5% sodium iodine.

Optical Properties

Indocyanine green absorbs light in the near-infrared range of 790 to 805 nm. The emission spectrum ranges from 770 to 880 nm, peaking at 835 nm. Both absorption and emission spectra are shifted toward shorter wavelength when ICG is in an aqueous solution while the overall intensity of the fluorescence is diminished. Fluorescein angiography (FA) does not provide detailed information about the choroidal circulation. The physical characteristics of ICG allow for visualization of the dye through overlying melanin and xanthophyll. Retinal pigment epithelium (RPE) and choroid absorb 59% to 75% of blue-green light (500 nm) used in FA, but only 21% to 38% of near-infrared light (800 nm) used in ICGA. The activity of ICG in the near-infrared light also allows visualization through serosanguineous fluid, shallow hemorrhage, pigment, and lipid exudates (Fig. 3.1). Enhanced imaging of conditions such as choroidal neovascularization (CNV) and pigment epithelial detachment (PED) is the result (Fig. 3.2).

Pharmacokinetics

In vivo, ICG is 98% protein bound. It has both lipophilic and hydrophilic properties. Although it was previously thought to bind primarily to serum albumin, 80% of ICG molecules actually bind to globulins, such as A1-lipoprotein. Therefore, less dye escapes from the fenestrated choroidal vasculature, allowing enhanced imaging of choroidal vessels and choroidal lesions. This is in sharp contrast to fluorescein, which is

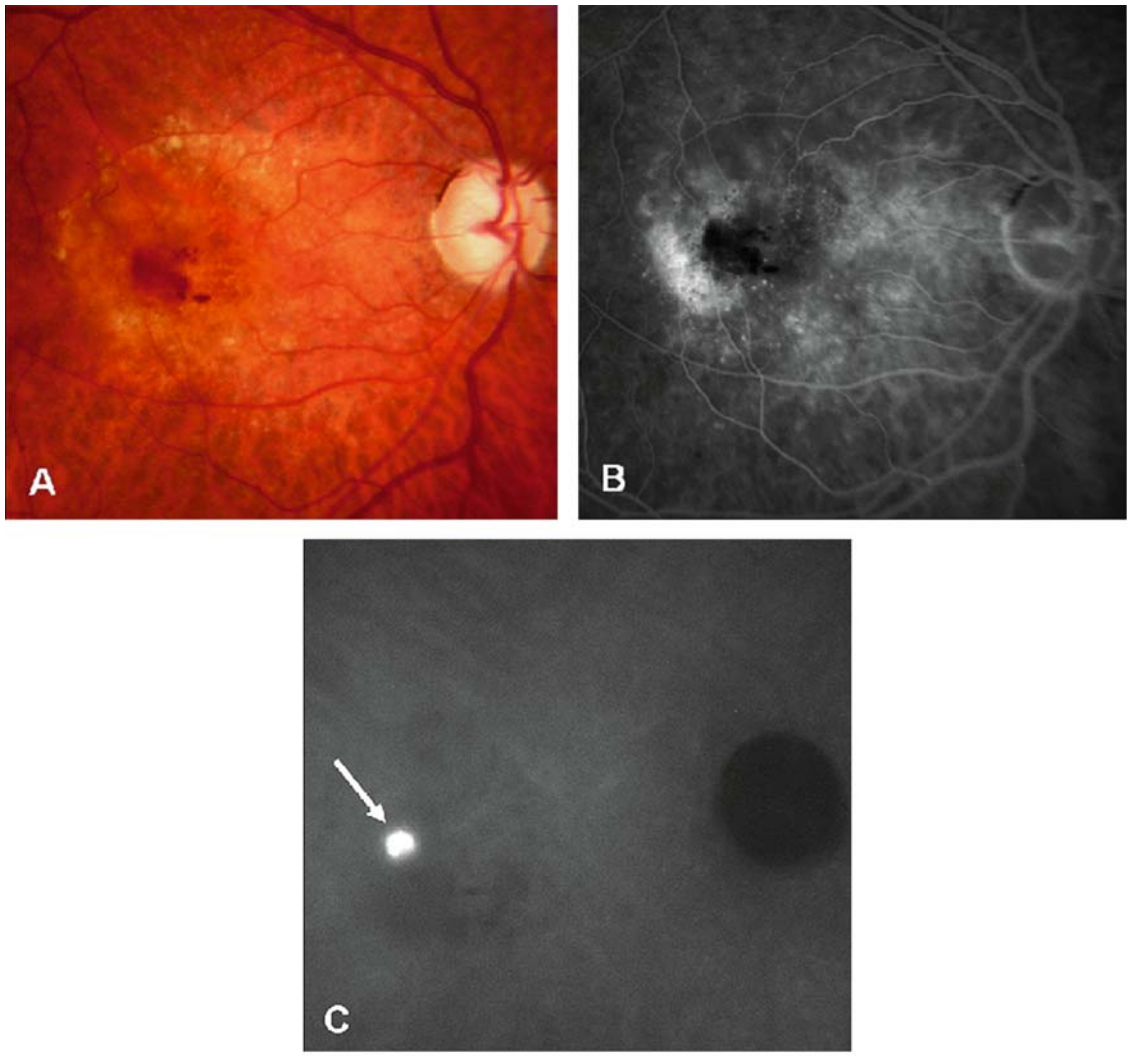

Fig. 3.1.(A) Clinical photograph demonstrates subretinal and intraretinal hemorrhages as well as detachment of the retinal pigment epithelium and the neurosensory retina in a patient with neovascular age-related macular degeneration. (B) Late-phase fluorescein angiogram reveals blocked fluorescence from the hemorrhages and indistinct leakage. (C) A late-phase indocyanine green (ICG) angiogram demonstrates a well-defined hyperfluorescence or so-called focal hot spot (arrow), representing a retinal angiomatous proliferation. This lesion is well visualized through the area of hemorrhage because of good penetration of the infrared light used in ICG angiography.

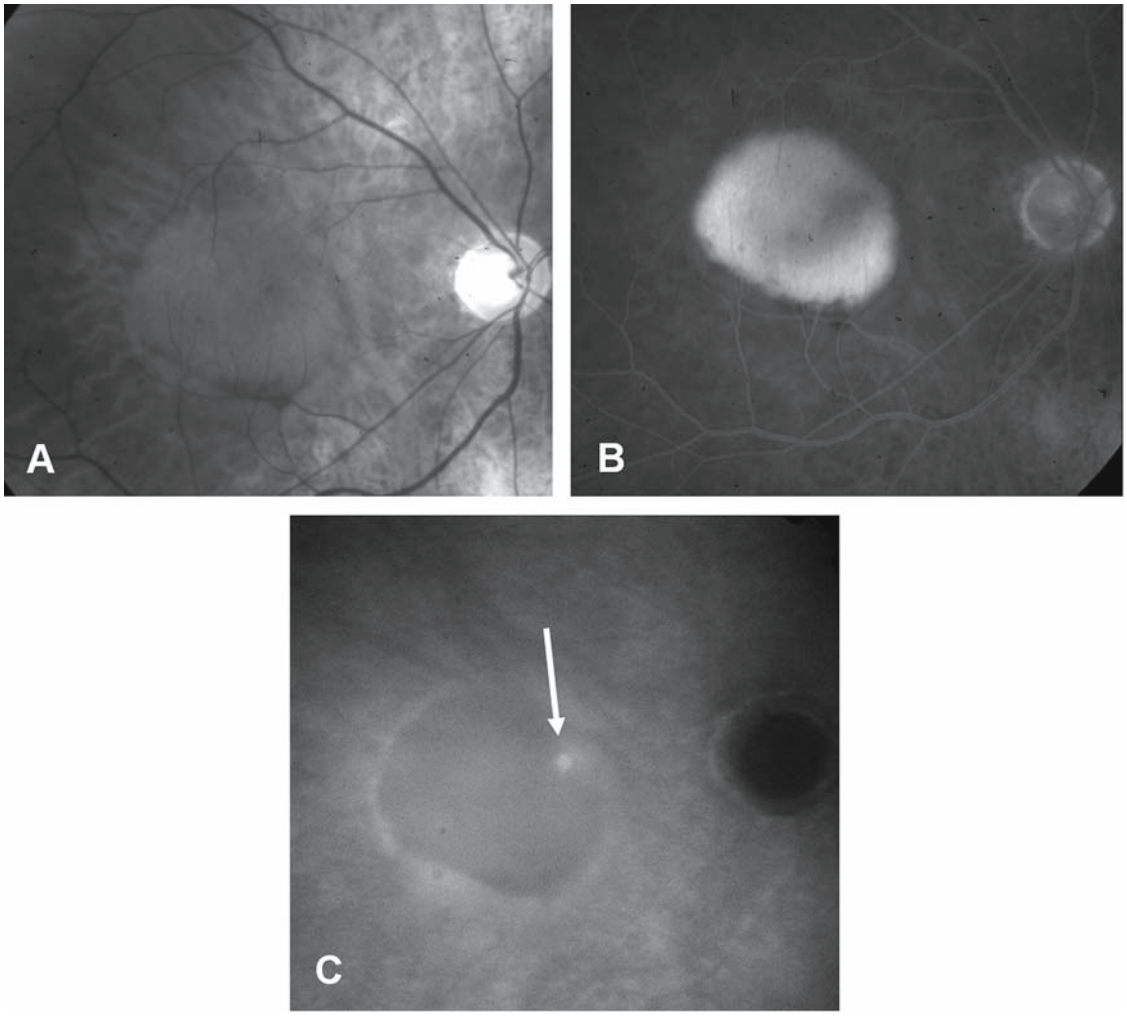

FIG. 3.2.(A) The red-free photograph of a patient with neovascular age-related macular degeneration shows a large pigment epithelial detachment (PED) in the central macula. (B) Late-phase fluorescein angiogram demonstrates hyperfluorescence of the serous PED. No focal area of choroidal neovascularization can be identified. (C) Late-phase indocyanine green (ICG) angiogram reveals a focal spot of hyperfluorescence (arrow), representing an area of localized choroidal neovascularization. The ICG molecule, which is 98% protein bound, does not leak from the neovascular membrane, and the PED remains relatively hypofluorescent throughout the study.

a relatively small molecule that remains mostly unbound from protein and extravasates rapidly from the choriocapillaris and fluoresces in the extravascular space, thus preventing delineation of choroidal anatomy.

It was thought that the protein-binding capacity of ICG limited the travel within the choroidal vessel walls. However, it has been demonstrated that ICG dye diffuses through the choroidal stroma during angiography, accumulating within the retinal pigment epithelium cells. It diffuses slowly, staining the choroid within 12 minutes after injection.

The ICG dye is excreted by the liver. It is taken up by hepatic parenchymal cells and secreted into the bile without metabolic alteration or entering enterohepatic circulation. In healthy individuals, the rate of ICG disappearance from the vascular compartment is 18% to 24% per minute with a half-life of 2 to 4 minutes; after 20 minutes, no more than 4% of the initial concentration of the dye should remain in the serum. As a result of strong binding to plasma proteins, ICG is not detected in kidney, lungs, and cerebrospinal fluid, nor does it cross the placenta.

Toxicity

Indocyanine green is a relatively safe dye; adverse reactions are rare, and less common than with sodium fluorescein. Mild reactions such as nausea, vomiting, and pruritus occur in 0.15% of patients. There have been isolated reports of vasovagal-type reactions, hypotensive shock, and anaphylactic shock. The dose of ICG does not appear to correlate with the

presence or severity of adverse reactions. Unlike sodium fluorescein, where extravasation of dye may lead to local tissue reaction and even necrosis of the overlying skin, ICG extravasation is well tolerated and resolves without complications.

Sterile ICG contains small amounts of iodine and therefore should be used with caution in patients with iodine allergy. It should also be avoided in uremic patients and in those with liver disease where delayed ICG clearance has been described. Indocyanine green has not been shown to be harmful to pregnant women or their fetus; however, it is classified as pregnancy category C due to lack of adequate studies. Therefore, there still exists reason for concern.

Injection Technique

Indocyanine green should be dissolved in aqueous solvent supplied by the manufacturer and be used within 10 hours after preparation. The standard dosage is 25 mg of ICG dissolved in 5 mL of solvent. In patients with poorly dilated pupils or heavily pigmented fundus, the dose of ICG may be increased to 50 mg. For wide-angle angiography, the dosage is increased to 75 mg. Rapid intravenous injection is essential, and the injection may be immediately followed by a 5-mL saline flush.

Digital Imaging System

An excitation filter placed over the light source allows only the passage of near-infrared light. This light is absorbed by the ICG molecules in the eye, which in turn emit slightly lower energy light. A barrier filter is used to capture only this light emitted from ICG into the camera by blocking wavelengths shorter than 825 nm.

Image acquisition can by produced by standard fundus camera, video camera, or scanning laser ophthalmoscope. The coupling of digital imaging system with an ICG camera enables production of high-resolution (1024-line) images necessary for ICGA.

Digital imaging systems contain electronic still and video cameras with special antireflective coatings as well as appropriate excitatory and barrier filters. A video camera is attached to the camera viewfinder and it is connected to a video monitor. The photographer selects the image and activates a trigger that sends the image to the video adapter. The charge-coupled device (CCD) camera captures the images and transmits these digitized (1024 × 1024-line resolution) images to a video board within a computer-processing unit. Flash synchronization allows high-resolution image capture, and images are displayed on a high-resolution video monitor.

Photographic Technique

For the purpose of obtaining an ICG study, the imaging protocol typically begins with color, red-free, and green-free fundus photographs. Indocyanine green angiography can be performed before or after FA. Images are initially taken 8 to 10 seconds after injection of the dye. This permits image capture in the early phase of choroidal filling. If the photographer waits until the dye is first noted on the alignment and focus monitor, the early phase of the study is often missed by the time the image capture is achieved. Images are obtained in a rapid, sequential manner at approximately 1-second intervals until retinal and choroidal circulations are at maximum brightness. The quality of the image exposure is continuously displayed on a high-resolution monitor, and modifications made to the image by adjusting the flash illumination control or gain setting. Initially, the gain must be set high in order to provide good illumination of the early choroidal filling phase, but reduction must be made immediately to compensate for the rapid influx of dye during the early retinal and larger choroidal filling phase.

After the images are obtained at the point of maximal brightness, they are further captured at 1-minute intervals until 5 minutes into the study. Thereafter, images are obtained at 3- to 5-minute intervals for a total duration of 30 to 50 minutes. Typically, ICG images are captured until all of the dye has exited to the retinal circulation and the optic nerve appears dark in contrast to the generalized gray background of the choroidal region. During the course of the study, the gradual decrease in the concentration of ICG dye in the retinal and choroidal circulation requires a corresponding increase in the intensity of the flash illumination.

When the angiogram is complete, the photographer reviews the images. Poorly focused, poorly aligned, or redundant information is deleted. Permanent storage is accomplished by downloading to a DVD, CD-ROM, or local server. The stored, unenhanced images can then be manipulated with the available software for enhanced analysis. Images can be "warped", a technique in which tracing of an image from the ICG study is overlaid onto the clinical or red-free photograph or fluorescein angiographic image to permit accurate localization of pathology.

New Techniques

Recent advances in the technology associated with ICGA include wide-angle,[10] digital subtraction,[11] and high-speed angiography. [8]

Wide-angle ICGA is achieved with the use of a wide-angle contact lens. Because the lens produces an image lying about 1 cm in front of the lens, the fundus camera is set on "A" or " + " in order to focus on the image plane of the contact lens. This system allows instantaneous imaging of a large fundus area up to 160 degrees of field (Fig. 3.3).[10]

Digital subtraction ICGA uses software to eliminate static fluorescence in sequentially acquired images and demonstrates the progression of the dye front within the choroidal circulation (Fig. 3.4). Pseudocolor imaging of the choroid allows differentiation and identification of choroidal arteries and veins. This technique allows imaging of occult choroidal neovascularization with greater detail and in a shorter period of time than with conventional ICGA.[11]

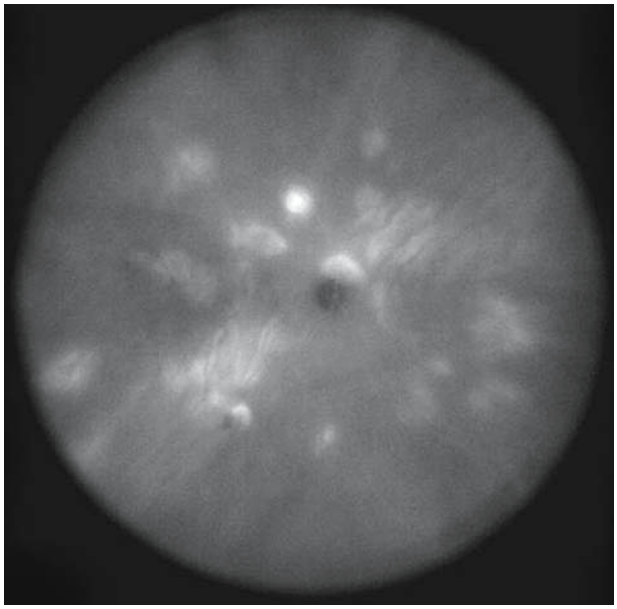

FIG. 3.3. The wide-angle indocyanine green (ICG) angiogram of a patient with central serous chorioretinopathy (CSCR) illustrates multifocal zones of choroidal hyperpermeability, which represent areas of presumed "occult" PED extending far beyond the posterior pole.

A fundamental problem for any kind of fundus imaging is reflection from interfaces of the ocular media. To obtain high-quality fundus images, these reflections must be eliminated. This is achieved by confocal scanning laser ophthalmoscopy, which separates the illuminating and the imaging beam in the eye, and can be used for high-speed ICGA. The scanning laser ophthalmoscope (SLO) can acquire FA images using an argon laser (488 nm), ICG images using an infrared diode laser (795 nm), simultaneous FA and ICGA, autofluorescence images, normal fundus reflectance images with green light (514 nm), and images of the nerve fiber layer with infrared light (830 nm). Barrier filters at 500 and 810 nm are added to provide a greater efficiency of fluorescent light detection. Single images can be acquired, as well as image sequences with a frame rate up to 30 images per second. Images are digitized in real time with a resolution of 256 × 256 or 512 × 512 pixels. The scanning laser system is able to record the filling phase with great temporal resolution but with a slight loss of spatial resolution.

Recently, three-dimensional confocal angiography has been reported.[12] This system allows for the potential to achieve reliable quantitative and qualitative analysis of defects, exudation, and proliferative vascular lesion.

Interpretation of Indocyanine Green Angiography

Age-Related Macular Degeneration

Definitions

The terminology used to describe the angiographic manifestations of age-related macular degeneration (AMD) corresponds, with certain exceptions described below, to definitions previously reported by the Macular Photocoagulation Study Group (MPS).[13] Most relevant to the interpretation of ICGA in AMD are the definitions of serous PED, vascularized PED (V-PED), classic CNV, and occult CNV.

Serous Pigment Epithelial Detachment

Serous PED is an ovoid or circular detachment of the retinal pigment epithelium (RPE). Indocyanine green angiography reveals a variable, minimal blockage of normal choroidal vessels, more evident in the midphase of the angiogram. In comparison to FA a serous PED is dark (hypofluorescent) on the ICG study. This difference is caused by the fact that the ICG molecules are larger and almost completely bound to plasma proteins, and are prevented from free passage of the ICG dye throughout the fenestrated choriocapillaris in the sub-RPE space.

Choroidal Neovascularization

Choroidal neovascularization (CNV) is defined as a choroidal capillary proliferation through a break in the outer aspect of Bruch's membrane under the RPE and the neurosensory retina. Choroidal neovascularization is divided into classic and occult based on the FA appearance.

Classic Choroidal Neovascularization. Classic CNV represents an area of bright hyperfluorescence that is usually not delineated as well as in an FA study.

Occult Choroidal Neovascularization. Occult CNV is characterized as either fibrovascular PED consisting of irregular elevation of the RPE, or late leakage of undetermined source. There are two main types of occult CNV that are recognized by the ICGA.

Without Serous Pigment Epithelial Detachment. The first type of occult CNV is caused by sub-RPE CNV that is not associated with a PED. The ICG angiogram reveals early vascular hyperfluorescence and late staining of the abnormal vessels. The image with distinct margins is considered to be a well-defined CNV on the ICGA.

With Serous Pigment Epithelial Detachment. The second type of occult CNV is associated with a serous PED of at least one disc diameter in size. Combined CNV and serous PED are called a vascularized PED (V-PED). This lesion is the result of sub-RPE neovascularization associated with a serous detachment of the RPE. Indocyanine green angiography reveals early vascular hyperfluorescence and late staining of the CNV. Indocyanine green is more helpful than FA in differentiating between a serous PED and a V-PED. It also permits better identification of the vascularized and serous component of V-PEDs. The serous component of a PED is hypofluorescent and the vascularized component is hyperfluorescent.

Occult CNV is also subdivided into two further types, one with a solitary area of well-defined focal neovascularization (hot spot) and the other with a larger, delineated area of neovascularization (plaque).

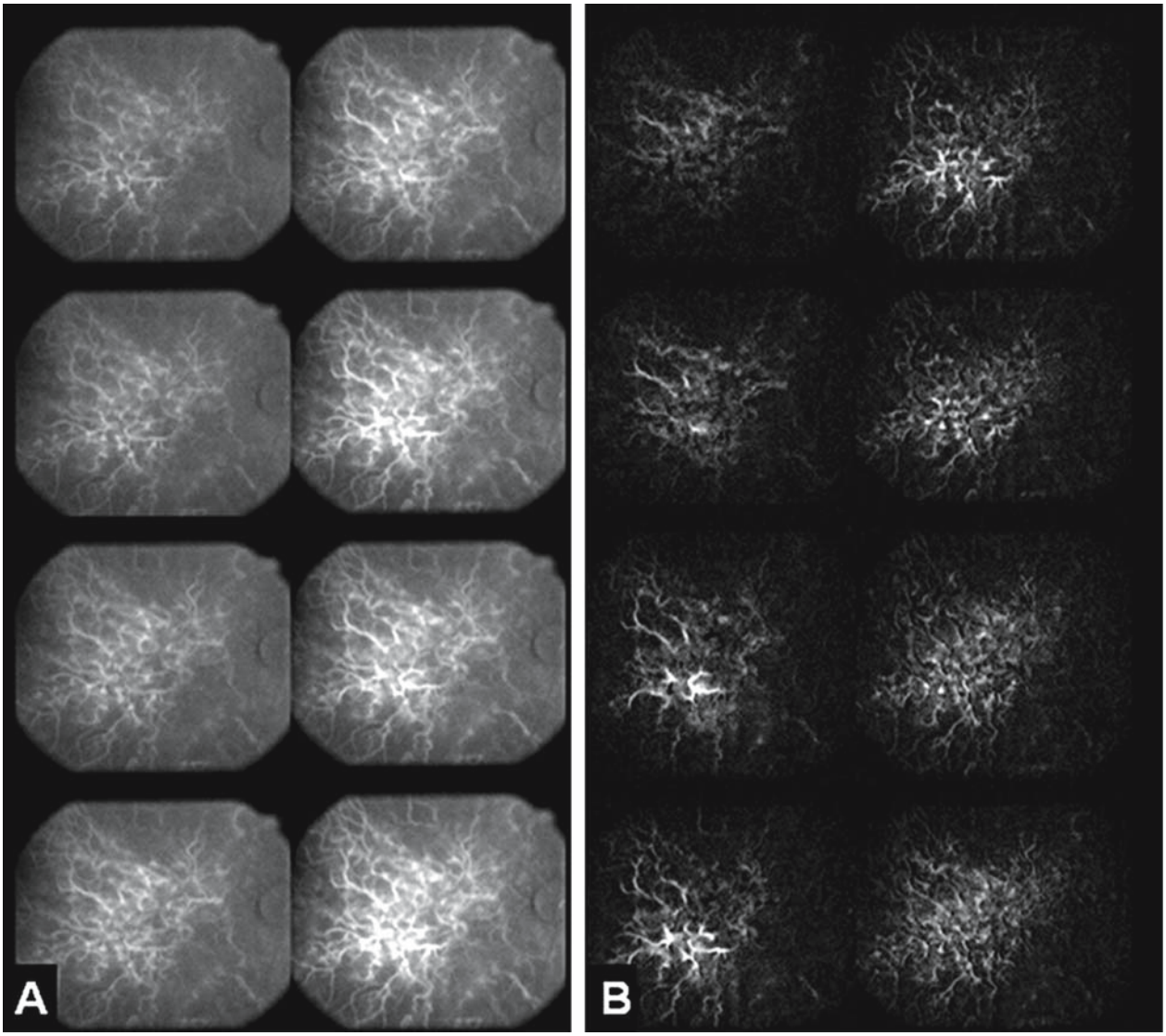

FIG. 3.4. Sequential subtraction of ICG angiogram images from the eye of a normal young male, acquired at 30 images per second (IPS) using fundus camera optics. (A) The two columns of images (read from top to bottom) are the original angiogram. (B) The two columns are the resultant subtracted images; the first image resulted from subtracting the first angiographic image from the second, the second image resulted from subtracting the second angiographic image from the third, etc. (Courtesy of Robert Flower).

Hot Spot (Focal Choroidal Neovascularization). Focal CNV or a "hot spot" is an area of occult CNV that is well delineated and no more than one disc diameter in size on ICGA. In addition, a hot spot represents an area of actively proliferating and more highly permeable areas of neovascularization (active occult CNV). Retinal angiomatous proliferation (RAP), focal occult CNV (Fig. 3.5), and polypoidal-type CNV may represent subgroups of hot spots.

Plaque. A plaque is an area of occult CNV larger than one disc diameter in size. A plaque is often formed by late-staining vessels that are more likely to be quiescent areas of neovascularization that are not associated with appreciable leakage (inactive occult CNV). Plaques of occult CNV seem to grow slowly in dimension with time. Both well-defined and ill-defined plaques are recognized on ICG study. A well-defined plaque has distinct borders throughout the study, allowing the assessment of the full extent of the lesion (Fig. 3.6). An ill-defined plaque has indistinct margins or may be the one in which any part of the neovascularization is blocked by the blood.

Imaging of Choroidal Neovascularization. Patz and associates[14] were the first to study CNV in AMD through ICGA. They could resolve only two of 25 CNVs with their early model. Bischoff and Flower [15] studied 100 ICG angiograms of patients with AMD. They found "delayed and/or irregular choroidal filling" in some patients. The significance of this finding is unclear, however, because these authors did not include an age-matched control group. Tortuous choroidal vessels and marked dilation of macular choroidal arteries, often with loop formation, were also observed.

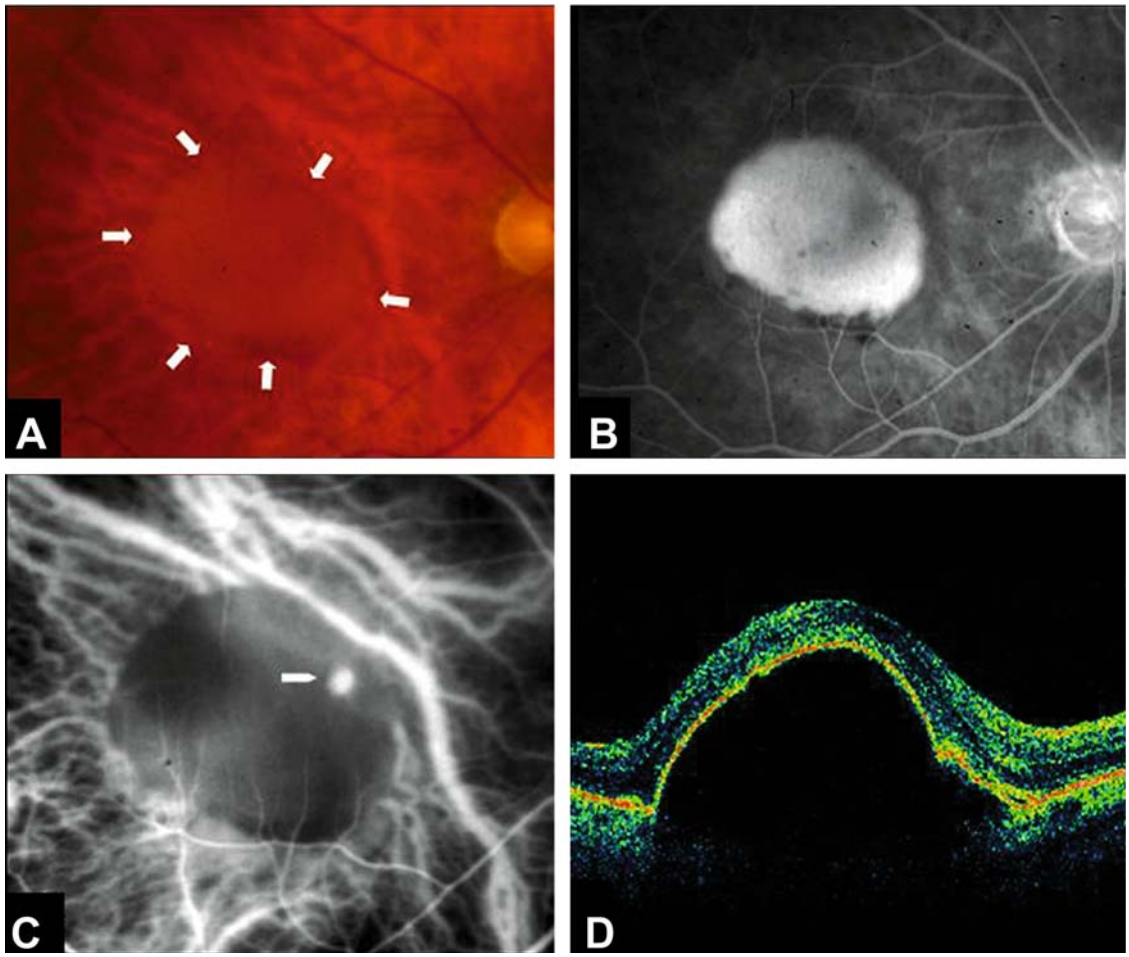

FIG. 3.5. (A) Clinical photograph showing a large PED (white arrows) in a patient with focal occult choroidal neovascularization (CNV). (B) Late-phase fluorescein angiogram illustrating late staining of the PED. (C) Midphase indocyanine green (ICG) angiogram showing a focal area of abnormal hyperfluorescence (hot spot). (D) The optical coherence tomography (OCT) scan confirms a large PED.

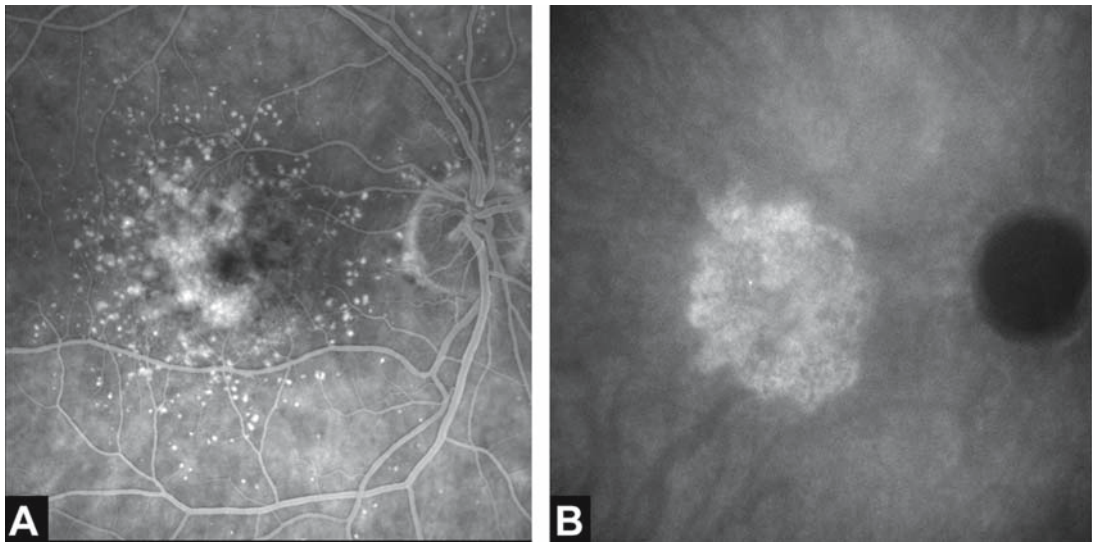

FIG. 3.6. (A) Fluorescein angiography reveals occult choroidal neovascularization. (B) Late-phase ICG angiogram shows a well-defined plaque.

Hayashi and associates[6] found that ICG videoangiography was useful in the detection of CNV. Indocyanine green angiography was able to confirm the FA appearance of CNV in patients with well-defined CNV. It revealed a well-defined neovascularization in 27 eyes with occult CNV by FA. In a subgroup of patients with poorly defined occult CNV, the ICG angiogram, but not the FA, imaged a well-defined CNV in nine of 12 (75%) cases. Indocyanine green videoangiography of the other three eyes revealed suspicious areas of neovascularization. These investigators were also the first to show that leakage of ICG from CNV was slow compared to the rapid leakage seen with sodium fluorescein. While the results of these investigators concerning ICG angiographic imaging of occult CNV were promising, the 512-line video monitor and analog tape of their ICG system limited the spatial resolution they could obtain.

Destro and Puliafito[7] reported that ICG videoangiography was particularly useful in studying occult CNV with overlying hemorrhage and recurrent CNV. It has been demonstrated that ICGA is useful in imaging occult CNV and that this technique might allow photocoagulation of otherwise untreatable lesions. Yannuzzi and associates[9] have shown that ICGA is extremely useful in converting occult CNV into a well-defined pattern of CNV. In their study, 39% of 129 patients with occult CNV were converted to a well-defined CNV based on the information added by ICGA. These authors reported that ICGA was especially useful in identifying occult CNV in patients with serous PED or with recurrent CNV.

Guyer and coauthors[16] reported their results on the ICGA study of 1000 consecutive eyes with occult CNV diagnosed by FA. They recognized focal spots in 29%, plaques in 61% (27% well-defined plaques and 34% poorly defined plaques), and combination lesions in 8% (3% marginal spots, 4% overlying spots and 1% remote spots). A follow-up study of patients with newly diagnosed unilateral occult CNV secondary to AMD showed that the patients tended to develop the same morphologic type of CNV in the fellow eye.

The above studies demonstrate that ICGA is an important adjunctive study to FA in the detection of CNV. While FA may image well-defined CNV better than ICGA in some cases, ICG videoangiography can enable treatment of about 30% of occult CNV lesions by the detection of well-defined CNV eligible for ICG-guided laser treatment. Thus, the best imaging strategy to detect the CNV is to perform both FA and ICGA.

Polypoidal Choroidal Vasculopathy

Polypoidal choroidal vasculopathy (PCV) is a primary abnormality of the choroidal circulation characterized by an inner choroidal vascular network of vessels ending in an aneurysmal bulge or outward projection, visible clinically as a reddish-orange, spheroid, polyp-like structure. The disorder is associated with multiple, recurrent, serosanguineous detachments of the RPE and neurosensory retina secondary to leakage and bleeding from the peculiar choroidal vascular abnormality. Indocyanine green angiography has been used to detect and characterize the PCV abnormality with enhanced sensitivity and specificity (Fig. 3.7). The early phase of ICGA shows a distinct network of vessels within the choroid. In patients with juxtapapillary involvement, the vascular channels extend in a radial, arching pattern and are interconnected with the smaller spanning branches that become more evident and more numerous at the edge of the PCV lesion. Larger choroidal vessels of the PCV network begin to fill before retinal vessels. The area within and surrounding the network is relatively hypofluorescent as compared to the uninvolved choroid (Fig. 3.8). The vessels of the network appear to fill at a slower rate than retinal vessels. Shortly after the network can be identified on the ICG angiogram, small hyperfluorescent “polyps” become visible within the choroid. These polypoidal structures

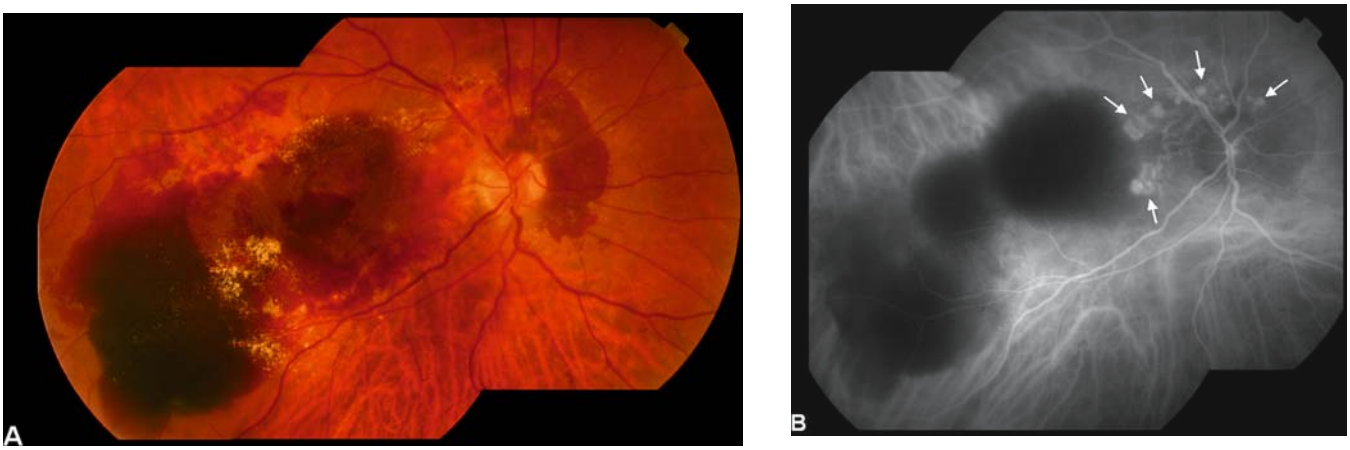

Fig. 3.7. Sudden deterioration of vision in the right eye of a 66-year-old Caucasian man. (A) Color composite photograph shows large subretinal and intraretinal hemorrhages at the posterior pole and surrounding the optic nerve. There are areas with dense lipid exudation. (B) Midphase ICG angiogram illustrates a large hyperfluorescent area. In the peripapillary area, there is a net of subretinal inner choroidal vessels that terminate in polypoidal lesions (white arrows).

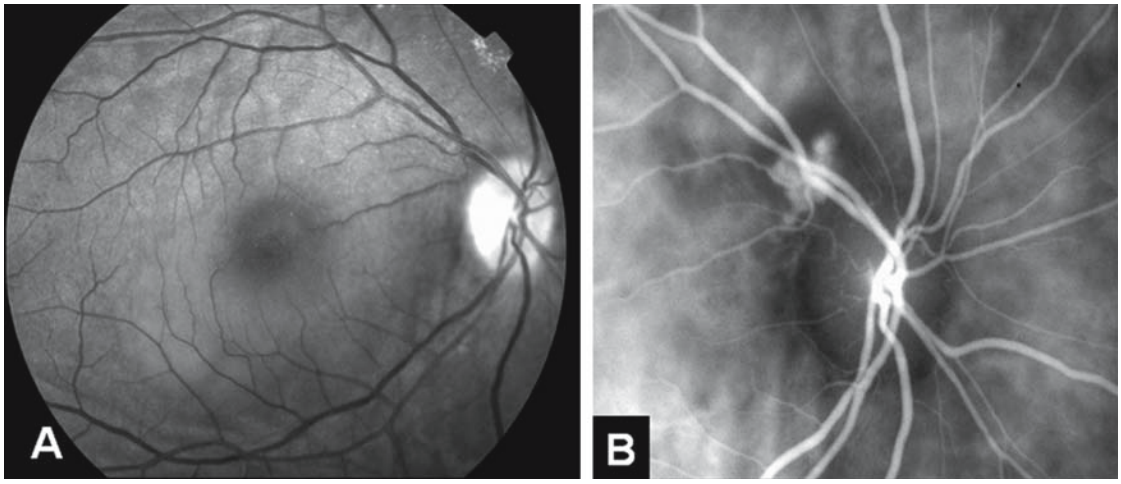

Fig. 3.8. (A) Red-free photograph of a 62-year-old woman's eye illustrating a neurosensory retinal detachment in the central macula. (B) An ICG angiogram reveals the presence of a polypoidal choroidal vascular abnormality in the superior temporal juxtapapillary region.

correspond to the reddish, orange choroidal excrescence seen clinically. They appear to leak slowly as the surrounding hypofluorescent area becomes increasingly hyperfluorescent. In the later phase of the angiogram there is uniform disappearance of dye ("washout") from the bulging polypoidal lesions. The late characteristic ICG staining of occult CNV is not seen in the PCV. Polypoidal lesions may be localized in the macular area without any peripapillary component, and it may be formed by a network of small branching vessels ending in polypoidal dilation difficult to image without ICGA.

Indocyanine green angiography has led to early discovery of polyps in the peripapillary, macular, and extramacular areas. With the identification of these choroidal polyps, new therapeutic possibilities are being explored, including the use of thermal laser treatment as well as photodynamic therapy.

Retinal Angiomatous Proliferation

Retinal angiomatous proliferation (RAP) is a distinct subgroup of neovascular AMD. Angiomatous proliferation within the retina is the first manifestation of the neovascularized process. Dilated retinal vessels, pre-, intra-, and subretinal hemorrhages, and exudates evolve surrounding the angiomatous proliferation as the process extends into the deep retina and subretinal space. One or more dilated compensatory retinal vessels perfuse and drain the neovascularization, sometimes forming a retinal –retinal anastomosis. Fluorescein angiography in these patients usually reveals indistinct staining simulating occult-CNV. Indocyanine green angiography is useful to make an accurate diagnosis in most cases. It reveals a focal area of intense hyperfluorescence corresponding to the neovascularization (hot spot) and some late extension of the leakage within the retina from the intraretinal neovascularization (Fig. 3.9). As the intraretinal neovascularization progresses toward the subretinal space and the RPE, the CNV becomes part of the neovascular complex. At this stage there is often clinical and angiographic evidence of a V-PED. Indocyanine green angiography is better for imaging the presence of a V-PED because the serous component of the PED remains dark during the study and the vascular component appears as a hot spot (Fig. 3.10). At this stage, ICGA may sometimes be able to image a direct communication between the retinal and the choroidal component of the neovascularization to form a retinal–choroidal anastomosis (RCA).

Indocyanine Green–Guided Laser Treatment of Choroidal Neovascularization in Age-Related Macular Degeneration

Patients potentially eligible for thermal laser photocoagulation therapy guided by ICGA are those with clinical and fluorescein angiographic evidence of occult CNV. Of the two types of occult CNV that can be identified by ICG study, hot spots and plaques, we recommend direct laser photocoagulation of only the hot spots. In fact, the hot spots represent areas of actively leaking neovascularization that can be obliterated by laser photocoagulation in an attempt to eliminate the associated serosanguineous complications, and to stabilize or improve the vision. On the other hand, the plaques seem to represent a thin layer of neovascularization that is not actively leaking and that may not require laser photocoagulation. This approach has practical considerations. In the case of a lesion combining a hot spot and a plaque and in which the hot spot is at the margin of the plaque (it may extend under the fovea), laser photocoagulation can be applied to the extrafoveal hot spot to spare the foveal area. But we have had poor success with the direct laser treatment of hot spots overlying plaques and confluent treatment of the entire plaque.

Two subtypes of hot spots are RCA and polypoidal-type CNV. When RCA is present, the success of laser

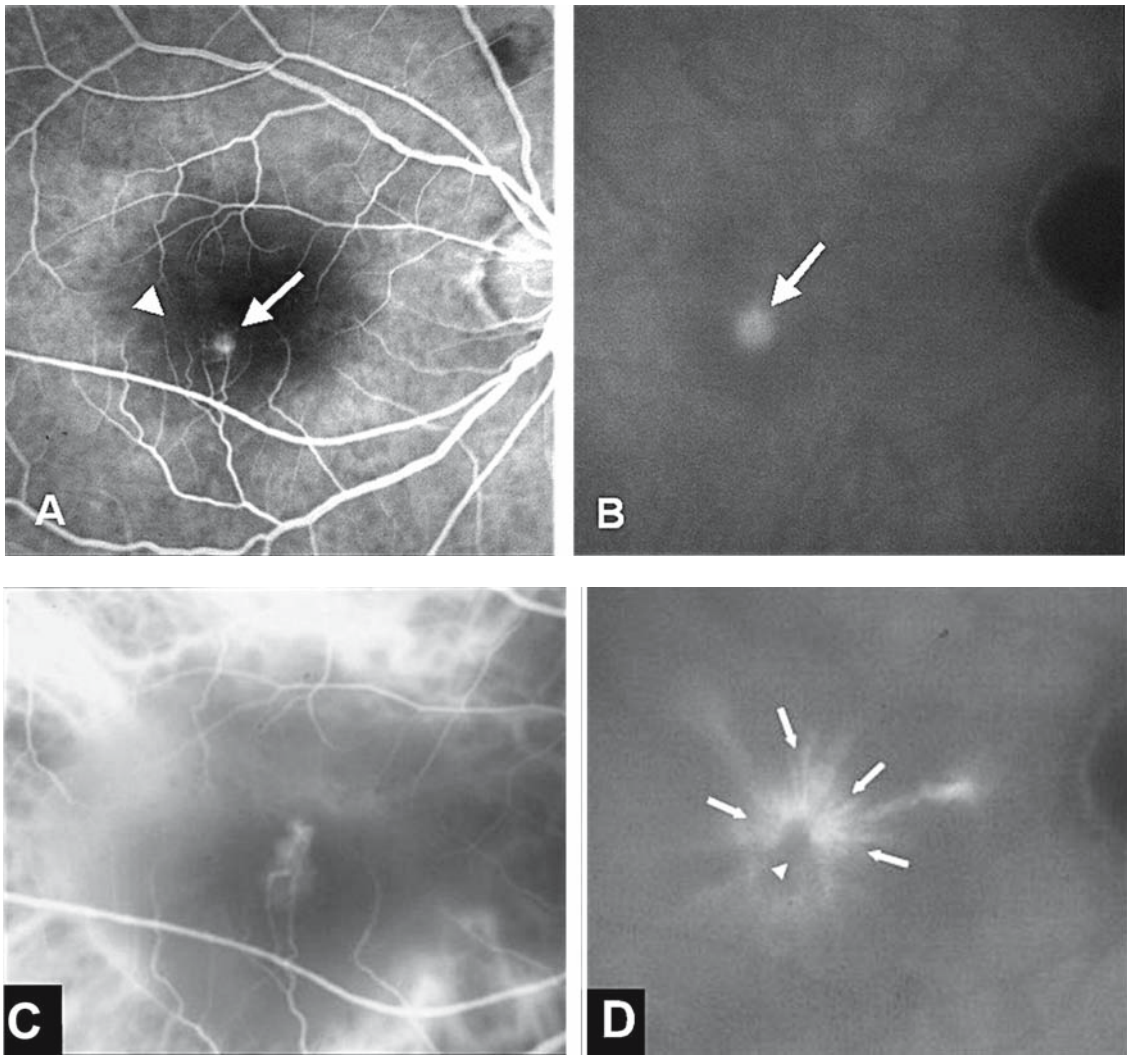

FIG. 3.9. (A) Fluorescein angiogram of a 73-year-old patient's eye reveals retinal angiomatous proliferation (RAP) stage I (arrow). Note the telangiectasia surrounding this area (arrowhead). (B) An ICG angiogram showing a focal area of intense hyperfluorescence (arrow) or so-called hot spot. (C) The ICG angiogram 1 year later illustrates a retinal–retinal anastomosis and subretinal neovascularization. (D) The late-phase ICG angiogram shows intraretinal leakage (arrows) surrounding the fading angiomatous proliferation (arrowhead).

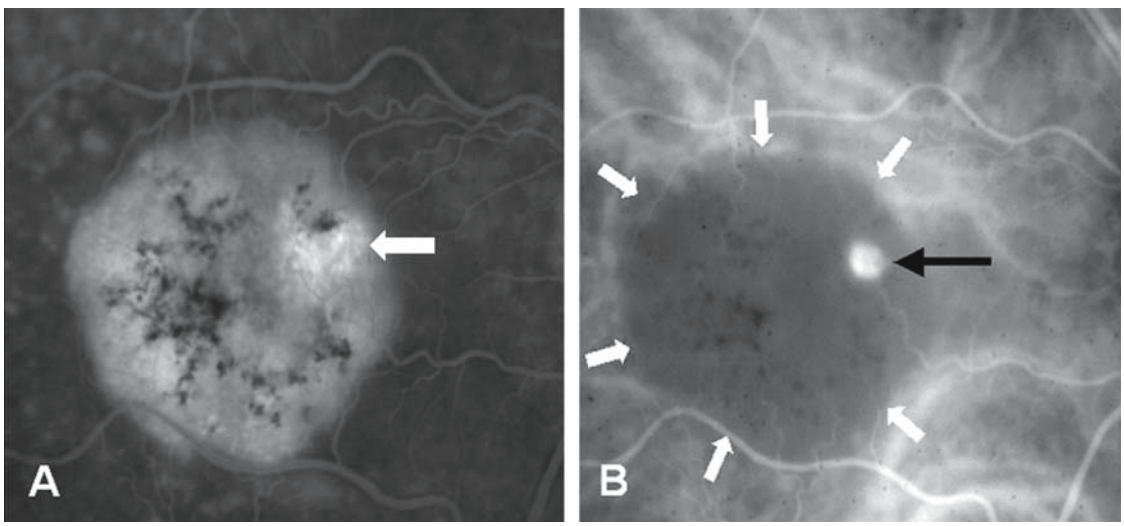

FIG. 3.10. (A) The fluorescein angiogram of a patient with RAP stage II reveals late staining of a PED. There is an increase in the intensity of fluorescence in the area of the RAP lesion (arrow). (B) The ICG angiogram shows hypofluorescence in the area of the PED (white arrows) and a "hot spot" corresponding to the RAP (black arrow).

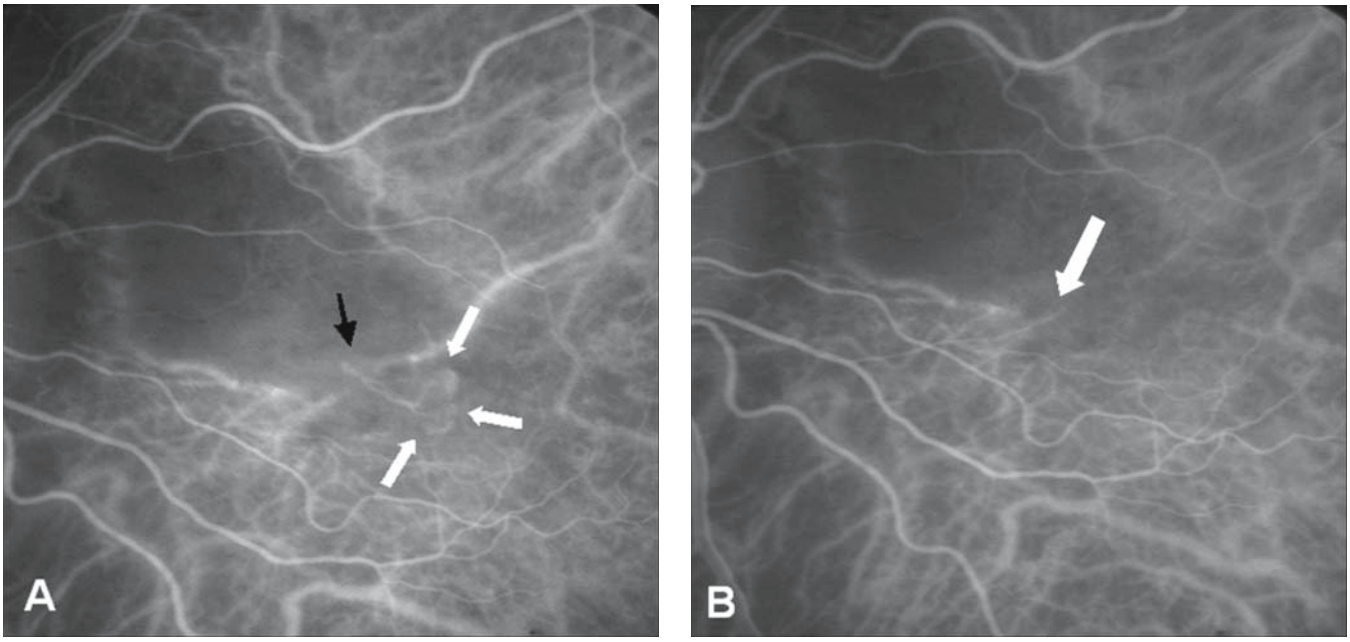

FIG. 3.11. (A) High-speed angiography of a patient with choroidal neovascularization (white arrows) demonstrates clearly the perfusing and draining feeder vessels (black arrow). (B) After focal thermal laser treatment of the feeder vessels, an ICG angiogram reveals closure of these vessels (arrow).

photocoagulation is negatively influenced by the presence of an associated serous PED.

Slakter and coauthors[17] performed ICG-guided laser photocoagulation in 79 eyes with occult CNV. Occult CNV was successfully eliminated in a majority of the cases. Visual acuity was stabilized or improved in 66% of eyes with occult CNV associated with neurosensory retinal elevations, and in 43% of eyes with occult CNV associated with PED. They demonstrated that in some cases ICGA imaging can successfully guide laser photocoagulation of occult CNV.

The high recurrence rate after laser photocoagulation of occult CNV, particularly when a V-PED is present, may be explained by the peculiar anatomy of the CNV in such cases.

Freund et al.[18] reported that approximately only 13% of patients with CNV secondary to AMD have a classic or well-defined extrafoveal choroidal neovascularization by FA that is eligible for laser treatment. With a recurrence rate of approximately 50% following fluorescein angiographic-guided laser photocoagulation for classic CNV, only approximately 6.5% of patients benefit from treatment. The remaining 87% of patients have occult CNV by fluorescein imaging. About 30% of these eyes have a potentially treatable focal spot by ICGA. Therefore, about one fourth of all eyes with exudative maculopathy may be treated by ICG-guided laser photocoagulation. With a success rate of 35%, this means that an additional 9% of patients can be successfully treated using ICG-guided laser photocoagulation. However, there are still 84.5% of patients who continue to be untreatable or are unsuccessfully treated by thermal laser photocoagulation of CNV.

Staurenghi et al.[19] considered a series of 15 patients with subfoveal CNV in whom feeder vessels (FVs) could be clearly detected by means of dynamic ICGA but not necessarily by FA (Fig. 3.11). Based on the indications of their pilot study, the authors studied a second series of 16 patients with FVs smaller than 85 μm. The FV was treated using the argon green laser, and ICGA was performed immediately after treatment. If an FV remained patent, it was immediately re-treated and the follow-up schedule was started again. The follow-up time ranged from 23 to 34 months for the pilot study, and from 4 to 12 months for the second series. In the pilot study, CNV was obliterated after the first treatment in only one patient; five patients needed more than one treatment and obliteration failed in nine patients (40% success rate). The success rate in the second series of 16 patients was higher (75%). The authors concluded that dynamic ICGA may detect smaller FVs. It enables controlling the laser effect and initiating immediate re-treatment in the case of incomplete FV closure and should be considered mandatory for this type of treatment. Clinical trials to evaluate the role of ICG-guided feeder vessel therapy are ongoing.

Central Serous Chorioretinopathy

The application of ICGA to the study of central serous chorioretinopathy (CSCR) has expanded our knowledge of the disease. The common findings in patients with CSCR are multifocal areas of hyperfluorescence in the early and middle phases of the study, which tend to fade in the late phases (Fig. 3.12). Typically, these areas of hyperfluorescence are

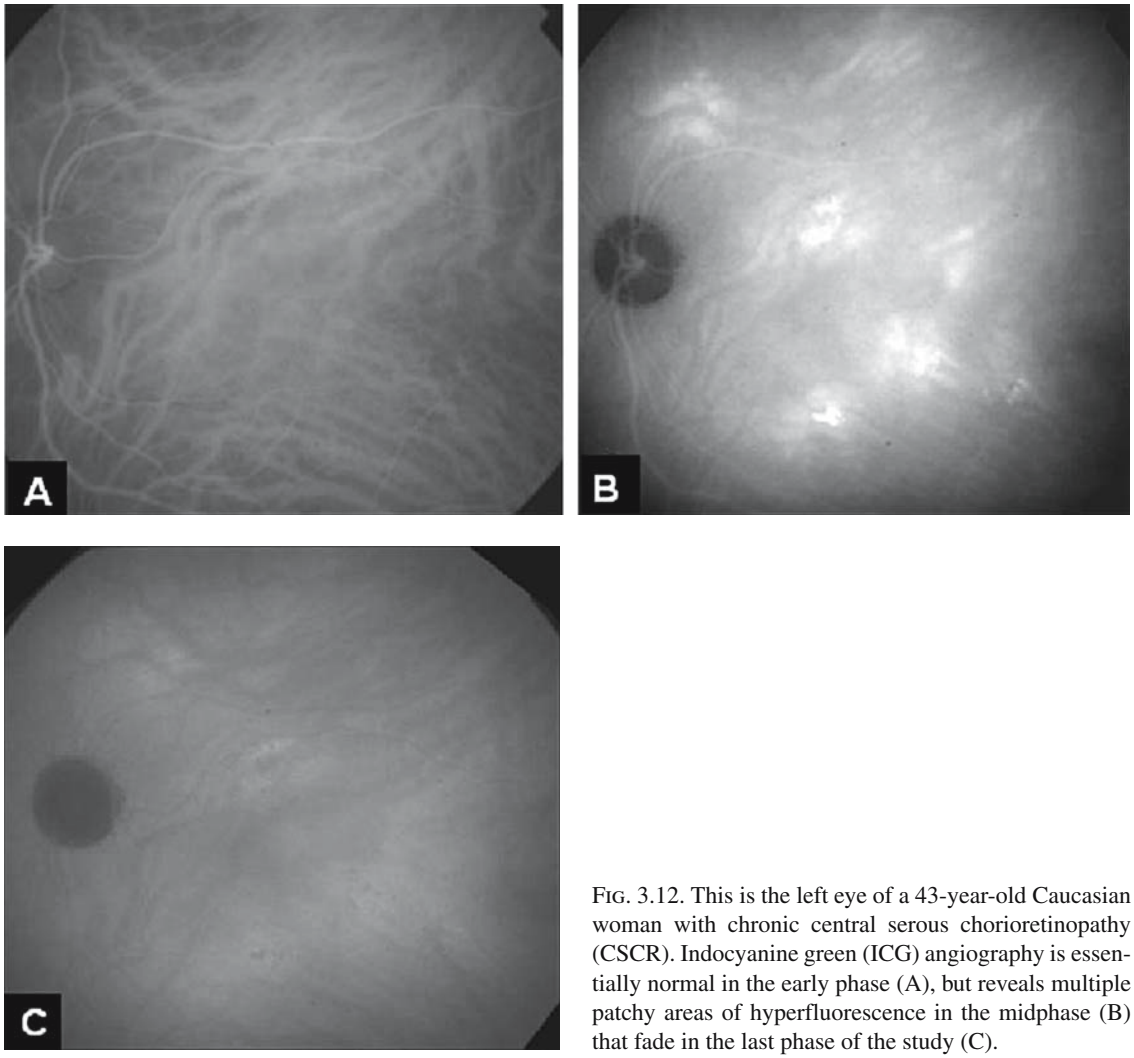

FIG. 3.12. This is the left eye of a 43-year-old Caucasian woman with chronic central serous chorioretinopathy (CSCR). Indocyanine green (ICG) angiography is essentially normal in the early phase (A), but reveals multiple patchy areas of hyperfluorescence in the midphase (B) that fade in the last phase of the study (C).

found not only in corresponding areas of leakage as seen on FA, but also with areas of the fundus that appear clinically and angiographically normal, as well as in the normal fellow eyes. The areas of early hyperfluorescence are believed to represent diffuse choroidal hyperpermeability.

Intraocular Tumors

Indocyanine green angiography is an important tool in the diagnostic and evaluation of intraocular tumors (see Chapter 8). Pigmented choroidal melanomas block ICG fluorescence because the near-infrared light is absorbed by melanin. The choroidal and tumor vasculature cannot be visualized through dense tumor pigmentation. Indocyanine green angiography can distinguish pigmented choroidal melanomas from non-pigmented tumors, such as hemangiomas and osteomas. In our experience, ICGA cannot distinguish melanomas from other pigmented lesions such as nevi or metastatic cutaneous melanoma. When a pigmented choroidal melanoma thickens or otherwise develops prominent intrinsic vasculature, ICGA shows an increase in fluorescence in the late phase.

Marked progressive hyperfluorescence is observed during ICGA of choroidal hemangiomas due to the vascularity of the lesion. A speckled pattern with stellate borders is observed. In early stages of the ICG study, a network of small-caliber vessels is seen. These vessels completely obscure the choroidal pattern. The technique is also useful in evaluating vascular lesions with overlying hemorrhage. Indocyanine green, unlike FA, may enable visualization of the tumor through an overlying hemorrhage.

Choroidal metastatic lesions show different pattern on ICGA depending on vascularity, pigmentation, and primary location of the lesion. In the early study phase, choroidal metastasis shows diffuse, homogeneous hypofluorescence. The normal perfusing choroidal pattern can often been visualized underneath. Breast metastasis shows moderate blockage on ICG videoangiography, while metastatic thyroid carcinoma and metastatic bronchial carcinoid tumors show hyperfluorescence.

Metastatic skin melanoma shows marked blockage on ICG videoangiography and thus appears indistinguishable from primary choroidal melanoma.

The early ICG phase in choroidal osteomas reveals characteristic small vessels that often leak too quickly to be detected by FA. Variable hypofluorescence is observed in the bony areas. These lesions may show midphase to late-phase ICG hyperfluorescence.

Varices of the vortex veins occasionally can be confused with choroidal tumors. Although the diagnosis usually can be made clinically, ICGA in these cases shows marked dilation of the vortex veins.

Chorioretinal Inflammatory Diseases

Serpiginous choroidopathy is a rare, progressive condition that appears to affect primarily the inner choroidal and RPE layers with secondary retinal involvement, beginning at the optic nerve and advancing centrifugally. The ICG videoangiography typically shows two patterns according also to the stage of the disease. In the acute phase, ICGA is characterized by generalized hypofluorescence through all phases of the study. In the subacute stage of the disease, mid- and large-sized choroidal vessels are visualized within the lesions. Persistent delay or nonperfusion of the choriocapillaris and smaller choroidal vessels is noted, giving the area a generalized hypofluorescent appearance but with less distinct margins and a more heterogeneous appearance (Fig. 3.13). This pattern is more typically seen after resolution of acute inflammatory changes and associated edema. In the late phase of the study, lesions present with sharp, well-demarcated borders. This is due to a combination of choroidal perfusion abnormalities as demonstrated on SLO and blockage by inflammatory exudative material, or edema of the RPE and outer retina. In the healed stages, deeper choroidal vessels become better visualized due to the associated development of RPE and choriocapillaris atrophy.

Acute multifocal placoid pigment epitheliopathy (AMPPE) is a syndrome of young adults characterized by the development of multifocal, yellow-white, flat, placoid lesions of the RPE in the posterior pole and midperipheral fundus. The lesions are hypofluorescent by ICGA in both the early and late phase of the study (Fig. 3.14). The ICG choroidal hypofluorescence in AMPPE may be due to a partial choroidal vascular occlusion secondary to occlusive vasculitis. The ICG study of healed lesions also demonstrates early hypofluorescence and more clearly delineates late choroidal hypofluorescence.

Multiple evanescent white dot syndrome (MEWDS) typically presents with unilateral acute loss of vision in healthy young women. It is a clinical condition of unknown cause, but it is thought to affect primarily the RPE-photoreceptor complex. With ICG, a pattern of hypofluorescent spots throughout the posterior pole and peripheral retina is seen (Fig. 3.15). These hypofluorescent spots appear approximately 10 minutes after dye injection in the mid-ICG phase and persist throughout the remainder of the study. These spots appear larger than the white dots seen clinically, varying in diameter from less

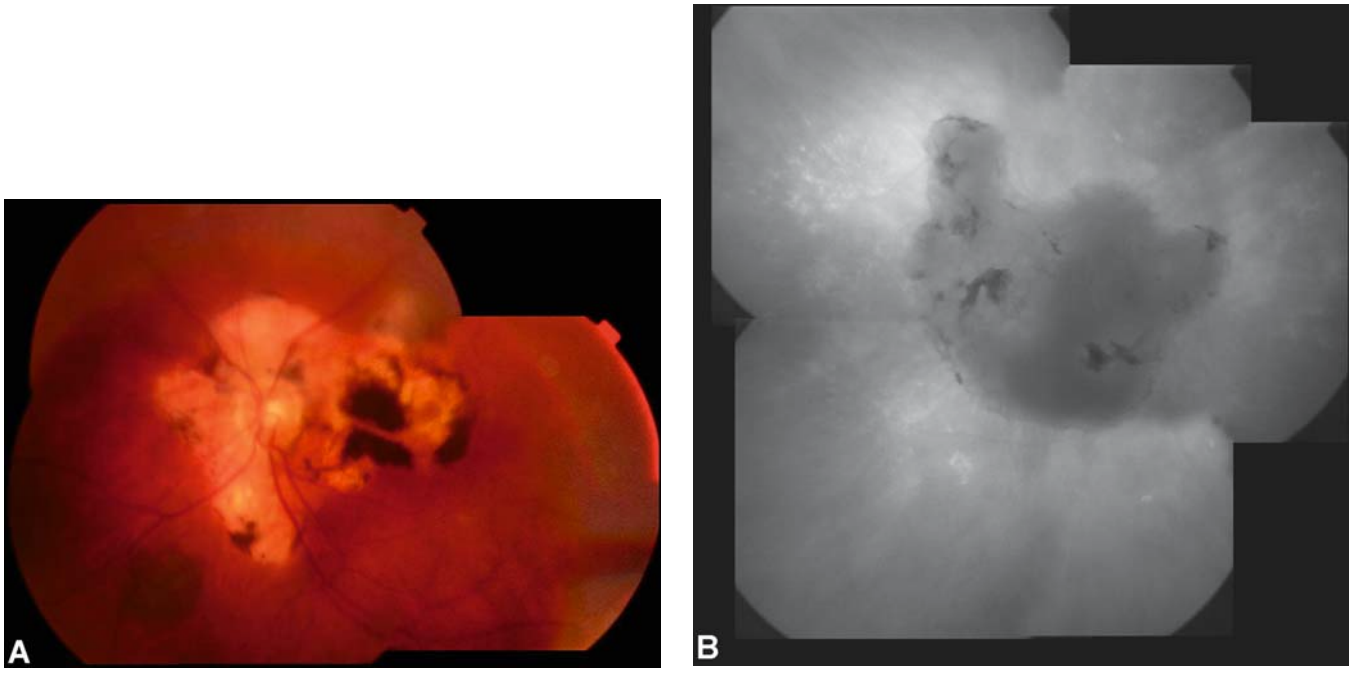

FIG. 3.13. (A) This is composite color photograph of an eye of a patient with serpiginous choroidopathy. (B) The composite of the indocyanine green (ICG) angiogram reveals a large area of hypofluorescence typical for the acute phase of the disease. The dark pigmented areas represent healed regions.

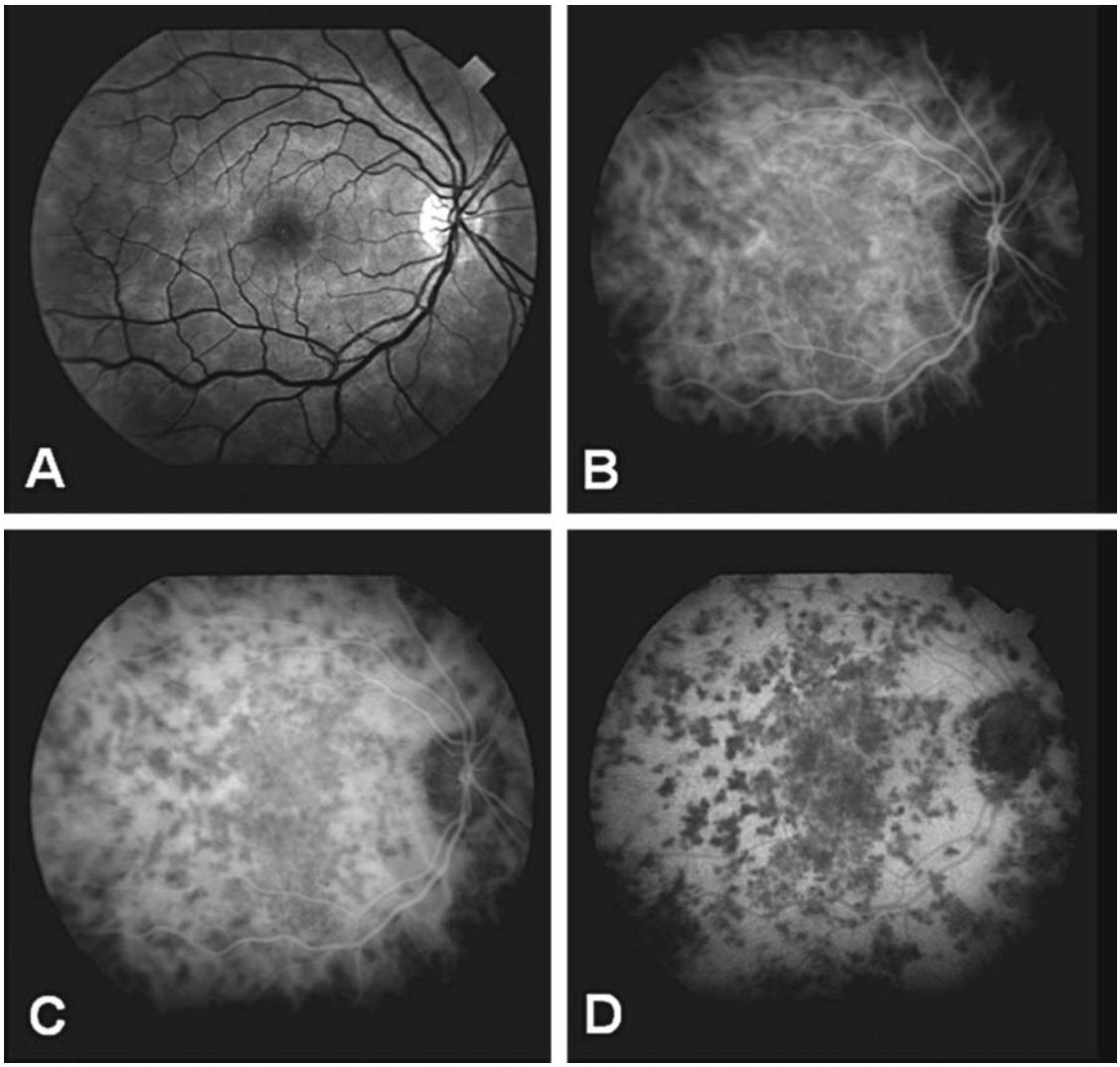

FIG. 3.14. (A) Red-free photograph of an eye of a patient with acute multifocal placoid pigment epitheliopathy (AMPPE), which shows multiple white, flat, placoid lesions. The lesions are hypofluorescent by ICGA in the early (B), middle (C), and late (D) phases of the study.

than 50 μm to about 500 μm. Many more lesions can easily be identified with ICGA than with fundus examination or fluorescence angiography. A ring of hypofluorescence surrounding the optic disc is seen in some cases. In these patients a blind spot enlargement on visual field examination is always present. During the convalescent phase, the return of visual function and normalization of the clinical examination does not correlate completely with resolution of the hypofluorescent spots seen on ICGA. These findings suggest that MEWDS may result in persistent abnormalities in choroidal circulation even after clinical symptoms disappear.

Bird-shot retinochoroidopathy is an uncommon, but potentially serious inflammatory disorder that involves both the choroid and retina. No relation to any systemic disease has been observed, while a strong association with the human leukocyte antigen (HLA) A29 class I suggests a genetic predisposition. Indocyanine green angiography reveals multiple hypofluorescent lesions resembling "holes" in the fluorescence of the choriocapillaris (Fig. 3.16). These lesions correspond to the clinical creamy lesions. The distribution of the patches follows the larger choroidal vessels. Howe et al.[20] found that ICGA detects bird-shot lesions more rapidly than FA and may be of benefit in assessing disease activity.

Multifocal choroiditis (MFC) is an idiopathic choroidal inflammatory disorder with varied presentation and clinical course. Clinical features include "punched out" chorioretinal spots, peripapillary atrophy, peripheral chorioretinal curvilinear lesions, and neovascularized macular degeneration or disciform scar. The MFC lesions block fluorescence on ICGA (Fig. 3.17). Hyperfluorescent foci that do not correlate with lesions seen clinically or by FA can also be observed. These hyperfluorescent areas may represent subclinical foci of choroiditis. Slakter et al.[21] reported on ICGA findings in a series of 14 patients with MFC. Four-

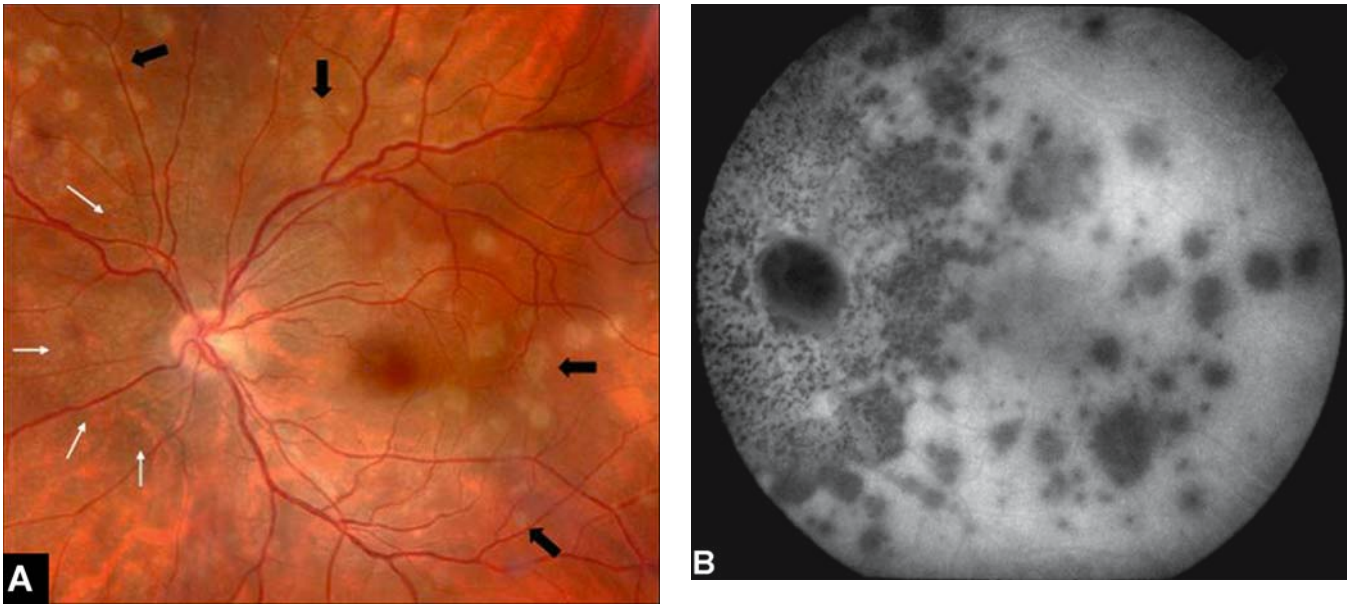

FIG. 3.15. This is an eye of a 29-year-old woman with unilateral visual disturbance caused by multiple evanescent white dot syndrome (MEWDS). (A) The clinical photograph shows multiple round, white to yellow-white spots (black arrows) distributed over the posterior fundus. In the peripapillary region, there are multiple small yellow dots (white arrows). (B) The midphase ICG reveals multiple large and small hypofluorescent spots in the posterior pole. Note the ring of hypofluorescence surrounding the optic disc.

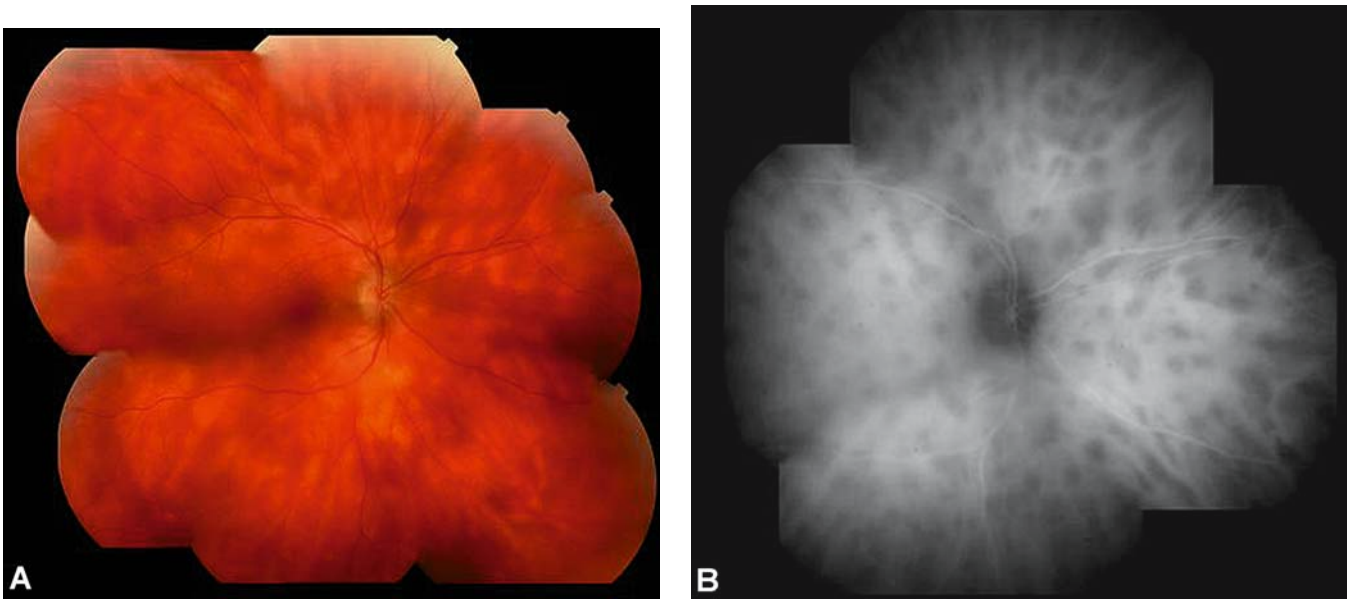

FIG. 3.16. This is an eye of a 46-year-old Caucasian woman with newly diagnosed birdshot retinochoroidopathy. (A) Clinical photograph composite reveals multiple creamy round lesions. (B) Midphase ICG illustrates multiple hypofluorescent lesions resembling "holes" in the fluorescence of the choriocapillaris.

teen (50%) of the 28 eyes were found to have large hypofluorescent spots in the posterior pole that did not correspond to clinically or fluorescein angiographically detectable lesions. In seven eyes exhibiting enlargement of the blind spot on visual field testing, ICGA showed confluent hypofluorescence surrounding the optic nerve. The ICG angiogram was useful in evaluating the natural course in two patients with MFC, as well as in evaluating the response to oral prednisolone treatment in four others. The ICGA performed in these patients showed changes correlating with the

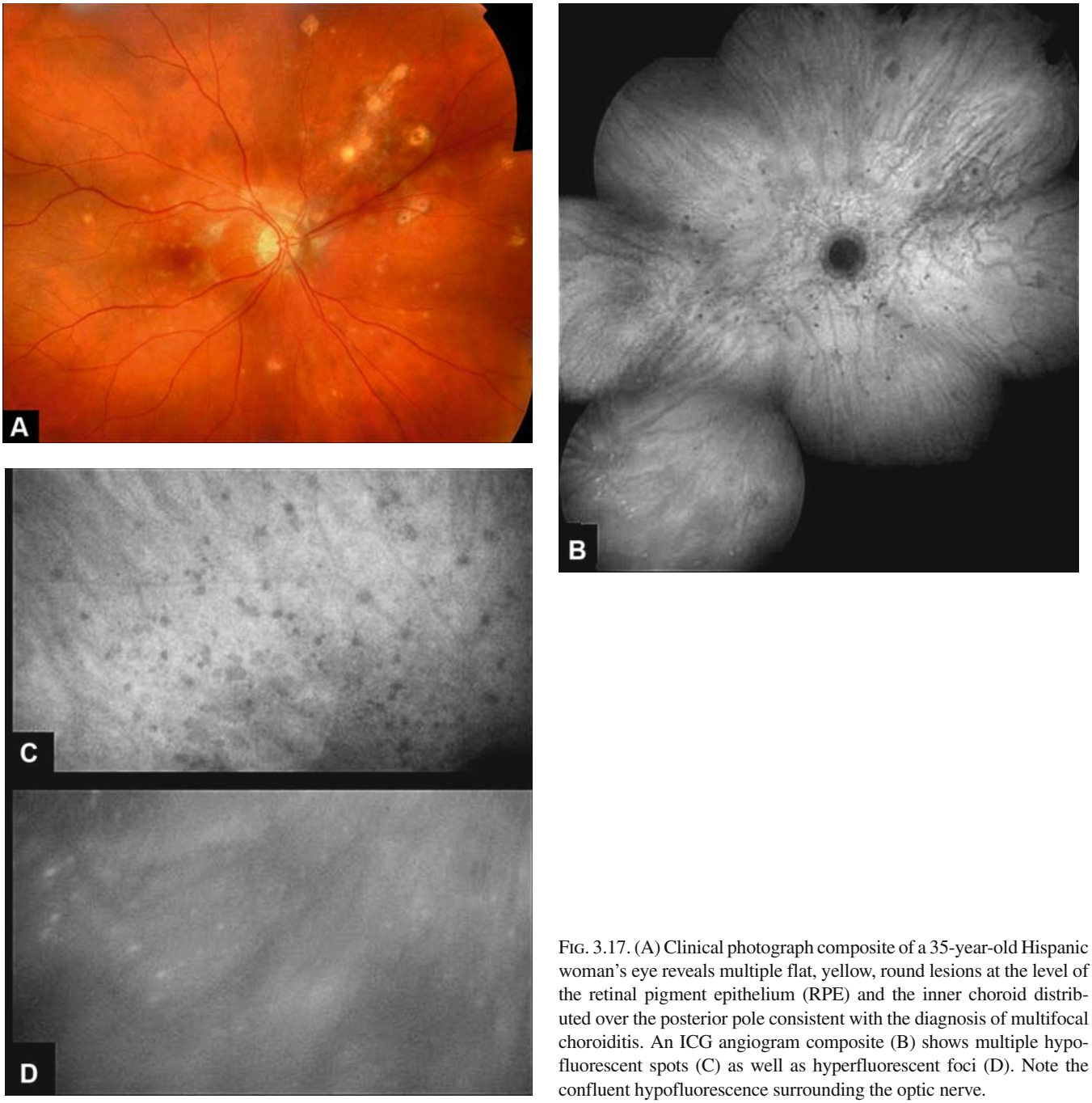

FIG. 3.17. (A) Clinical photograph composite of a 35-year-old Hispanic woman's eye reveals multiple flat, yellow, round lesions at the level of the retinal pigment epithelium (RPE) and the inner choroid distributed over the posterior pole consistent with the diagnosis of multifocal choroiditis. An ICG angiogram composite (B) shows multiple hypofluorescent spots (C) as well as hyperfluorescent foci (D). Note the confluent hypofluorescence surrounding the optic nerve.

clinical course. After administration of oral prednisolone, the patients were noted to have decreased symptoms and less vitreitis on clinical examination. Indocyanine green angiography showed a reduction in the size and number of the hypofluorescent spots in three patients, with complete resolution of these angiographic lesions in the fourth patient. Indocyanine green angiography was also helpful to differentiate MFC from presumed ocular histoplasmosis syndrome, which has similar clinical appearance. Patients with MFC clearly have hypofluorescent spots in the posterior pole during periods of relative activity, whereas patients with presumed ocular histoplasmosis syndrome may exhibit focal areas of hyperfluorescence.

Conclusion

Indocyanine green angiography is a highly specialized technique for imaging choroidal vasculature. It has several advantages over FA including lower toxicity, high protein

binding affinity, and infrared fluorescence for better penetration through pigment, serosanguineous fluid, and blood. The clinical applications of ICGA continue to expand as more experience is gained with current imaging techniques. Further advances in ICGA are likely to result from the newer high-speed imaging systems.

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