

Chapter 2

Indocyanine Green Angiography in Uveitis

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Introduction

Indocyanine green angiography (ICGA) became available in the early 1990s and has since greatly increased our understanding of chorioretinal uveitic diseases [1]. The properties of indocyanine green (ICG) confer superiority to fluorescein dye for imaging of choroidal circulation. These properties include (1) the high molecular weight of ICG (775 Da) and its highly protein bound status (98%), which together limit the rate of leakage through the fenestrated choriocapillaris and thus facilitate longer retention in the choroidal vasculature, and (2) the longer wavelength transmission peak (835 nm) enabling better RPE penetration [1, 2].

The early and intermediate phases of ICG permit visualization of both the retinal and choriocapillaris vasculature. Given the slow leakage of ICG from the choriocapillaris, the late phases are characterized by a background hypercyanescence and highlight stromal pathology [3].

ICGA has allowed for the direct investigation of the disease processes underlying the various forms of choroid involving uveitic diseases. Despite this, the correlation of pathophysiology with ICG signs is still not fully understood. A theory linking choroidal pathophysiology and corresponding ICGA findings has been proposed by Herbert. He classified diseases into primary inflammatory choriocapillaropathies (PICCPs) and stromal choroiditis. It has been hypothesized that hypocyanescent areas are due to decreased perfusion of the choriocapillaris. In contrast, in stromal choroiditis, he attributed hypocyanescent lesions to space-occupying granulomas [3]. However, further research, including with

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newer imaging modalities such as OCT angiography, will help to better assess these theories and further elucidate the underlying pathophysiology of these diseases.

Clinical Utility of ICG

ICG and fluorescein angiography (FA) are complementary imaging techniques allowing for assessment of both the choroidal and retinal circulations. Often, in posterior uveitis, ICGA signs exceed those visible on either fundoscopy or FA. Thus, not only does ICGA have diagnostic value through assisting in the localization of choroidal pathology, but the modality is also helpful in evaluating the full extent of choroidal disease. The latter is especially useful in early or mild presentations of disease [3]. ICGA is also emerging as a useful modality to evaluate the response to immunomodulatory therapy (IMT) and to further guide treatment [4]. Lastly, ICGA has a role in the visualization of choroidal neovascularization (CNV), which can occur as a complication of posterior uveitis [3, 5] (Fig. 2.1).

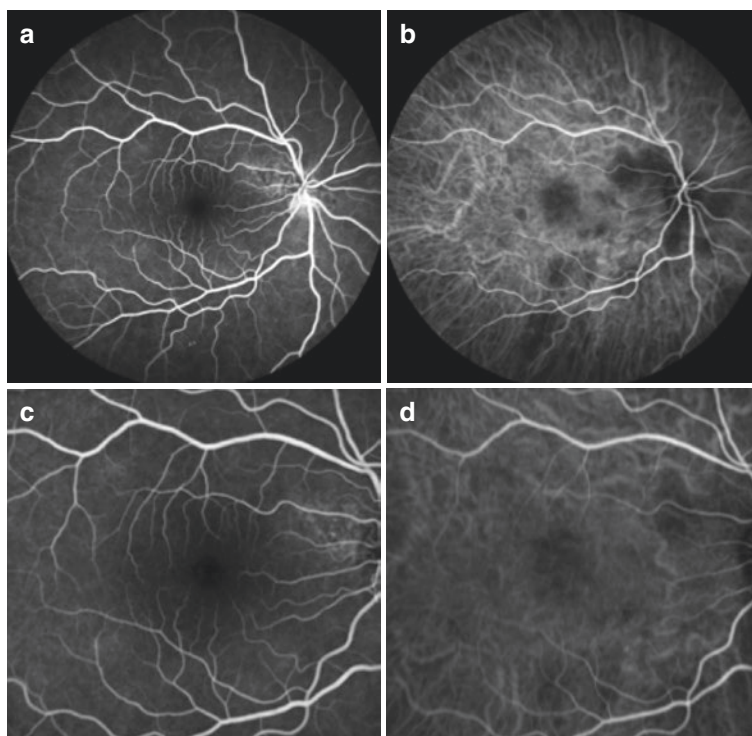


Fig. 2.1 Sarcoidosis granuloma. A patient with a several month history of blurred vision and confirmed sarcoidosis by lymph node biopsy. Prior to beginning treatment, no lesions could be seen on FA (a) whereas peripapillary and macular presumed granulomas were obvious on ICGA (b). After a year of immunosuppressive therapy with mycophenolate mofetil and prednisone, lesions could still not be seen on FA (c) while smaller granulomas on ICGA (d) indicated partial resolution

Vogt-Koyanagi-Harada Disease, Sympathetic Ophthalmia, and Sarcoidosis-Associated Choroiditis

Vogt-Koyanagi-Harada disease (VKH) is a chronic systemic autoimmune disease characterized by bilateral, granulomatous panuveitis, as well as skin, auditory, and neurological involvement [6]. Multiple signs associated with VKH on ICGA have been described; however, the most commonly reported sign is small hypocyane-scent spots [7]. These hypocyane-scent areas have been attributed to choroidal granu-lomas, are apparent on early to intermediate frames, and often persist to late frames, depending on the thickness of the granuloma [3, 7]. In more advanced cases of VKH, the extent of chorioretinal atrophy can be visualized on ICGA as hypocyane-scent areas, typically present throughout the study [7, 8]. Other characteristic ICGA signs that have been noted in VKH include early hypercyanescent stromal vessels, intermediate to late peripapillary hypercyanescence, and late diffuse hypercyanescence [7]. ICGA has also been shown to be useful in assessing the response to therapy and in detecting subclinical posterior disease in anterior uveitis flares [9].

Sympathetic ophthalmia (SO) also presents with a bilateral granulomatous panuveitis and occurs following traumatic injury or surgery to the inciting eye. Inflammation in both the inciting eye and sympathizing eye ensues [10]. The posterior segment findings are similar to VKH, although SO has his-torically been described as sparing the choriocapillaris. Similarly to VKH, early to intermediate hypocyane-scent spots, with variable persistence, are seen [11].

Choroidal granulomas resulting in hypocyane-scent spots are also seen in sarcoid choroiditis but are more irregularly distributed [3, 12] (Figs. 2.2 and 2.3).

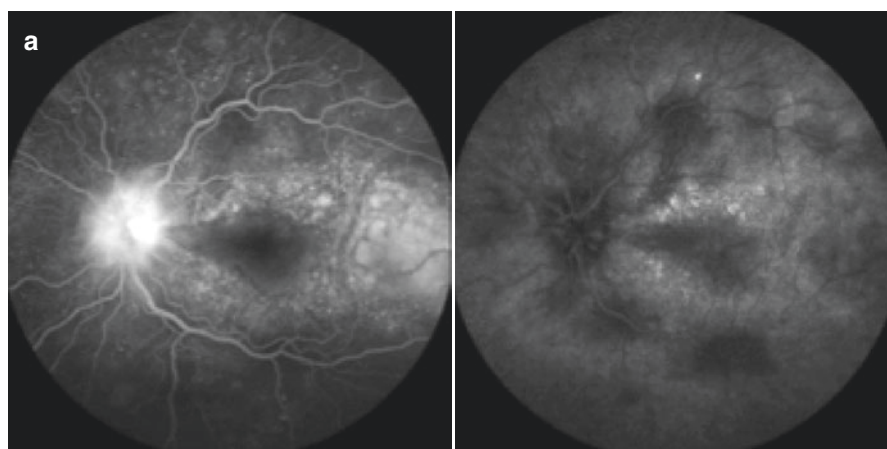


Fig. 2.2 Vogt-Koyanagi-Harada disease. (a) Early phase FA (*left*) and ICGA (*right*) of a patient with VKH. FA shows areas of pinpoint hyperfluorescence. ICGA demonstrates patches of hypocyane-scent. (b) In a second patient with VKH, ICGA (*right*) reveals multiple hypocyane-scent lesions with a central confluent area. In contrast, minimal changes are seen on FA (*left*). (c) Characteristic bilateral hypocyane-scent spots, typical of VKH on late phase ICGA

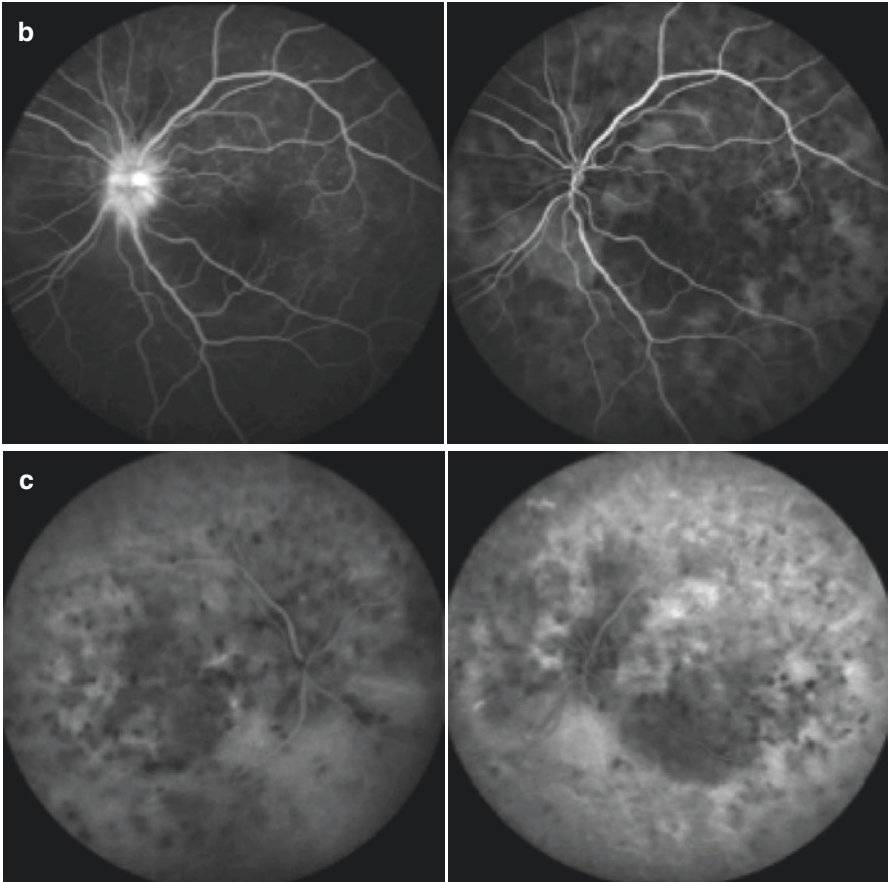


Fig. 2.2 (continued)

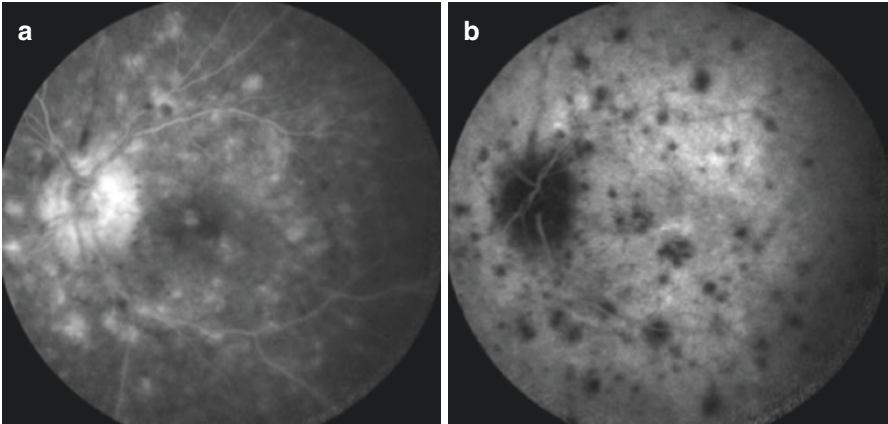


Fig. 2.3 Sympathetic ophthalmia. Hypofluorescent spots of varying sizes are seen throughout the posterior pole on ICGA (**b**) and are more numerous than corresponding hyperfluorescent areas seen on FA (**a**)

Birdshot Chorioretinopathy

Birdshot chorioretinopathy (BCR) is characterized by the presence of bilateral ovoid hypopigmented lesions, low-grade anterior chamber and vitreous inflammation, retinal vasculitis, and HLA-A29 positivity [13]. Ovoid or circular hypocyanescent lesions, especially nasal and inferior to the optic disc, are seen on early to intermediate frames, and frequently appear more prominent on late frames [14]. The hypocyanescent lesions have been postulated to be due to non-penetration of the ICG dye at the site of inflammatory choroidal infiltrates [3].

Given that ICG lesions exceed the lesions visible on fundus exam or color fundus photos, ICGA has an important role in the diagnosis of this disease, especially in early presentations of BCR, when the characteristic ovoid lesions may be absent or minimal on examination and FA findings may also be mild [3, 14]. More recently, ICGA is emerging as a useful modality in monitoring the response to immunomodulatory therapy, since a decrease in the number of ICGA lesions with treatment has been reported [4] (Fig. 2.4).

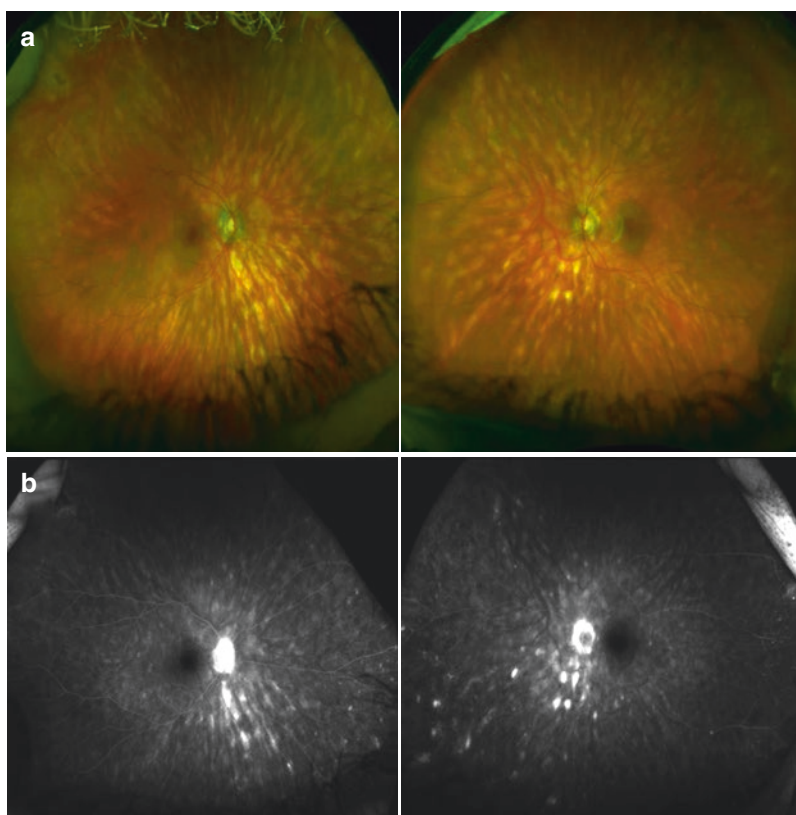


Fig. 2.4 Birdshot chorioretinopathy. Color fundus photos showing characteristic, widespread bilateral, hypopigmented ovoid lesions (a). Optos FA late frames showing bilateral hyperfluorescent lesions consistent with staining. (b). Wide-field (102°) late ICGA frames showing densely distributed hypocyanescent birdshot lesions (c)

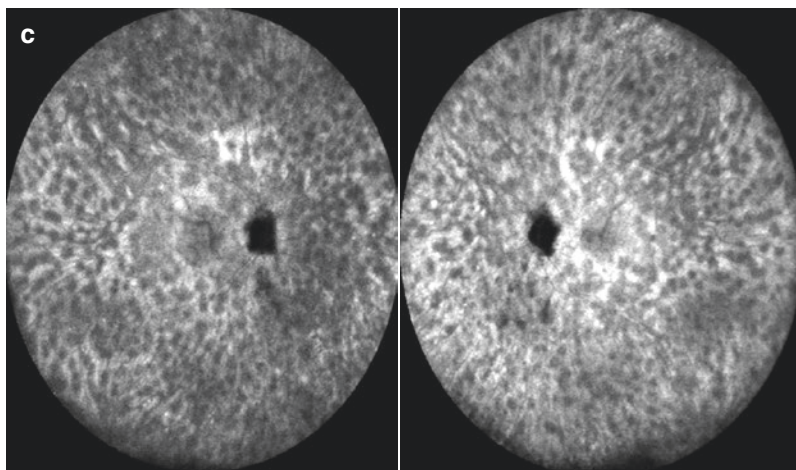


Fig. 2.4 (continued)

Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Although acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was originally proposed by Gass to be a disorder of the pigment epithelium [15], APMPPE is now believed to primarily affect the choriocapillaris with secondary retinal epithelium and outer retinal changes [16]. During acute disease, ICGA shows confluent areas of hypocyancescence, evident on all phases, but especially prominent on late frames. These hypocyancscent areas are thought to correspond to hypoperfusion of the choriocapillaris and are typically more numerous than and extend beyond the placoid lesions observed on funduscopy. Some of these hypocyancscent lesions resolve completely following recovery, while others decrease in size but persist consistent with atrophy [3, 17, 18] (Fig. 2.5).

Multiple Evanescent White Dot Syndrome

Multiple evanescent white dot syndrome (MEWDS) is considered to be a self-limiting disease of the outer retina. The fundus examination findings of MEWDS can include posterior vitreous cell, disc hyperemia or edema, small multifocal white lesions involving the posterior pole and mid-periphery, and foveal granularity [19, 20].

The white MEWDS lesions have been classified by size and location into “spots” (larger than 200 μm , localizing to the RPE/photoreceptor junction) and “dots” (smaller than 100 μm , localizing to the outer nuclear layer) [21]. This classification

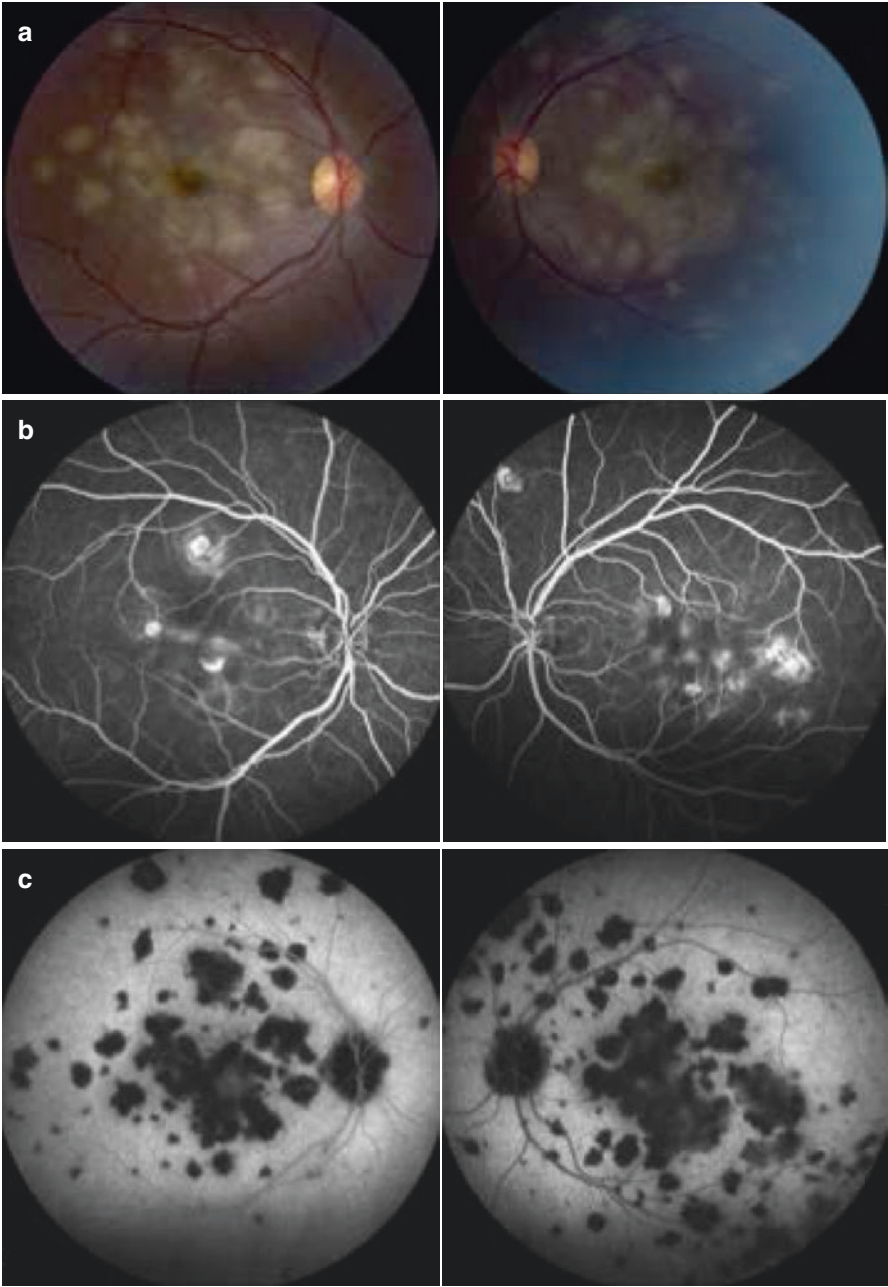


Fig. 2.5 APMPE. 13-year-old presented with complaints of gray spots OS and over the next 3 days experienced a significant decrease in visual acuity OU. Posterior pole fundus photographs demonstrate extensive yellow placoid lesions (**a**). FA typically reveals early phase hypofluorescent areas and late staining (shown in **b**). ICGA showed confluent areas of hypocyancescence, which correspond to, but extend beyond the lesions apparent on photography (**c**)

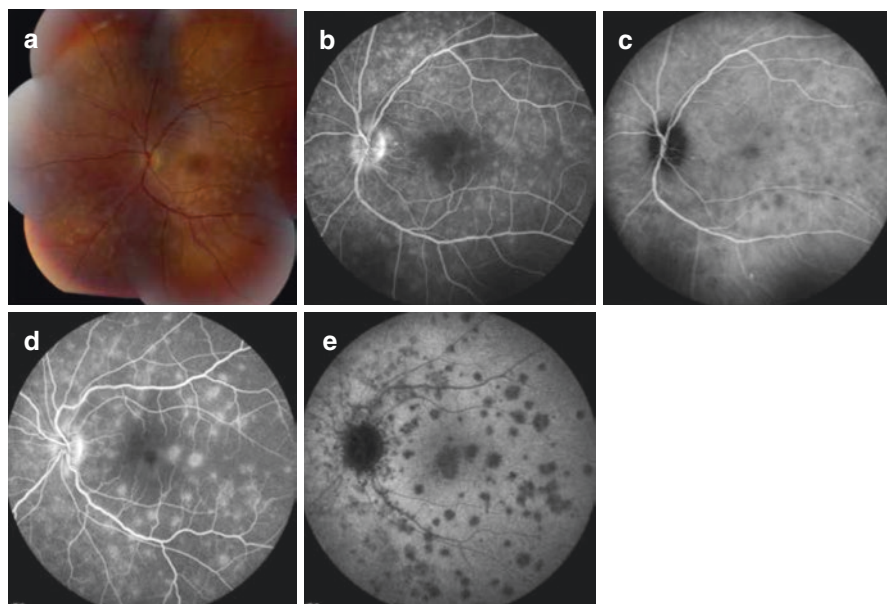


Fig. 2.6 MEWDS. In the first case, white spots are seen in the posterior pole and mid-periphery (a). Hyperfluorescent spots in a “wreath-like” pattern are apparent on FA (b) with corresponding hypocyanescent spots on late phase ICGA (c). In the second case, more numerous hypocyanescent spots are seen on late phase ICGA (e), especially in the peripapillary area, compared to the hyperfluorescent spots on FA (d)

has also been used to apply to FA and ICGA signs [20–22]. On ICGA, hypocyanescent dots have been described on early to mid phase ICGA, which correspond to hyperfluorescent dots on FA [20, 22]. In contrast, hypocyanescent spots observed on mid to late frames correspond to hyperfluorescent spots on FA [20, 22]. In more severe cases, confluent areas of hypocyanescence can be present [3]. Additionally, peripapillary hypocyanescence has also been described in MEWDS. It is now thought that the hypocyanescent areas on ICGA may not be stemming from hypoperfusion of the choriocapillaris [3]. Indeed, this has been corroborated by recent reports showing an absence of choriocapillaris flow voids on OCTA in MEWDS [22]. The cause of the hypocyanescent areas on ICGA remains unclear, although it has been proposed that the hypocyanescent spots may be caused by focal RPE dysfunction [23].

The MEWDS lesions on ICGA are typically more numerous than those apparent on fundus examination or FA. Thus, ICGA, in combination with FAF, is especially useful in mild cases of MEWDS, when only minimal findings are apparent on funduscopy [3]. In accordance with the transient nature of this disease, ICGA findings usually resolve within 4–6 weeks, in tandem with exam findings and signs on other imaging modalities [3] (Fig. 2.6).

Multifocal Choroiditis and Punctate Inner Choroidopathy

MFC is characterized by variably sized posterior pole and mid-peripheral chorioretinal lesions, as well as the presence of vitreous cell, and often anterior chamber inflammation [24]. In contrast, PIC typically presents without vitreous inflammation, and with smaller-sized lesions (100–300 μm), restricted to the posterior pole [25]. Both entities are associated with choroidal neovascularization [26].

On ICGA, hypocyanescent lesions are seen in both MFC and PIC across early to late phases. Both active lesions and lesions that have scarred down appear hypocyanescent. In MFC, a predominance of lesions in the peripapillary region is frequently observed. The areas of hypocyanescence representative of active lesions are thought to either correspond to choriocapillaris hypoperfusion or due to the presence of inflammatory cell aggregates. Similarly to other white dot syndromes, the lesions apparent on ICGA are typically more numerous than those apparent on either fundus examination or other imaging modalities, including FA [25, 27]. Thus, ICGA is invaluable in assessing the full extent of chorioretinal lesions and choriocapillaris ischemia, as well in the diagnosis of an early flare. Additionally, ICGA complements FA in the detection of CNV in these diseases [3] (Fig. 2.7).

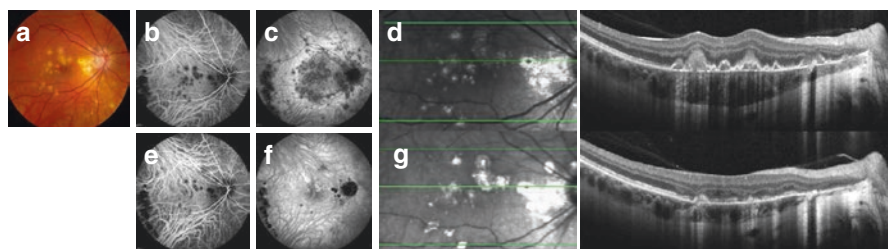


Fig. 2.7 PIC. 27-year-old female with a history of PIC, presenting at the start of a new flare OD. Color fundus photo of the right posterior pole showing cream-colored juxtafoveal active chorioretinal lesions (a). Note the contrast with the more atrophic, inactive appearing nasal peripapillary lesions. Corresponding early phase (b) and late phase (c) ICGA of the right posterior pole, showing multiple juxtafoveal hypocyanescent lesions, especially apparent on late phase. There is also late, mild diffuse macular hypocyanescence, consistent with widespread ischemia. 4-month follow-up early (e) and late phase (f) ICGA showing resolution of the majority of hypocyanescent lesions and diffuse macular hypocyanescence. The atrophic nasal peripapillary and temporal hypocyanescent lesions are still present. Corresponding horizontal OCT line scan through active PIC lesions at the start of the flare (d) and at 4-month follow-up (g). (d) Shows hyper-reflective conical RPE elevations with some nodules breaking through the RPE, associated outer retinal thickening and loss of the ellipsoid layer. At 4 months (g), these RPE and outer retinal nodular elevations have largely resolved with some ellipsoid reconstitution

Serpiginous Choroiditis

Serpiginous choroiditis (SC) is characterized by a serpentine pattern of outer retinal and RPE involving choroiditis, extending outward from the disc. The disease is usually bilateral, and the disease course, although variable, is usually characterized by episodes of recurrences [28]. A classification of SC lesions and their associated ICGA findings has been proposed where the initial subclinical or choroidal stage shows hypocyantescent areas detectable on ICGA, attributed to choriocapillaris hypoperfusion. No corresponding signs of activity on FA are observed, which may be due to the inflammation being restricted to the choroid in subclinical or early SC lesions [29]. Active lesions are commonly found to appear hypocyantescent on early to late ICGA [29, 30]. The areas of hypocyantescence correspond to but exceed the areas of hyperfluorescence on FA [29, 31]. Active lesions typically evolve into chorioretinal atrophy, which also appear early and late hypocyantescent [3, 28]. The borders of the atrophic areas are typically more defined compared to those of the active lesions [28] (Fig. 2.8).

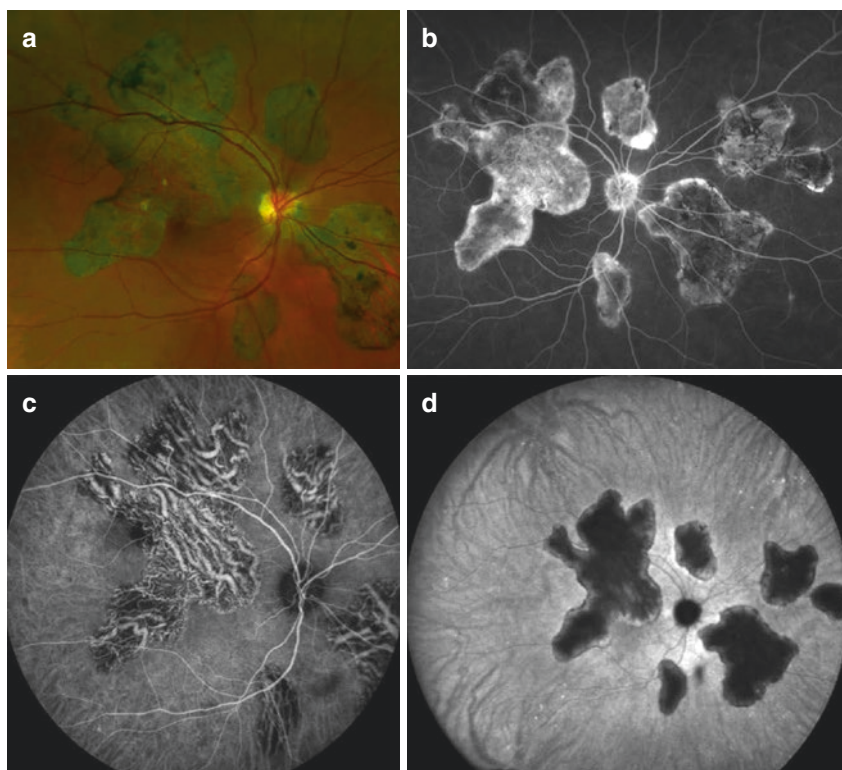


Fig. 2.8 Serpiginous choroiditis. 58-year-old female with chronic atrophic serpiginous lesions of the right eye. Color fundus photo (a) showing the characteristic lesions in the typical serpentine pattern. Late phase FA (b) revealing staining of the atrophic lesions. Early (c) and late (d) phase ICGA showing well-demarcated corresponding areas of hypocyantescence. Note the partial preservation of the choriocapillaris evident on the early phase.

Summary

- ICGA is an effective tool to visualize the choroidal circulation due to both its peak fluorescence in the infrared spectrum, allowing superior penetration, and to highly protein bound nature that leads to lower rate of leakage from the fenestrated choriocapillaris.
- Hypocyanescent lesions are the most frequent finding on ICGA in the choroid involving uveitides and are thought to be representative of either choriocapillaris hypoperfusion or choroidal granulomas.
- ICGA findings in the white dot syndromes usually exceed in number and extent the findings apparent on funduscopy or FA. The modality is thus especially useful in the diagnosis of early or mild presentations of disease
- In addition to having a valuable role in diagnosis, since ICGA signs often improve or resolve with treatment, ICGA is also useful in assessing the response to therapy or evaluating the extent of residual chorioretinal atrophy.

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