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Chapter

Multimodal Imaging of White Dot Syndromes

Cristian de los Santos, Lidia Cocho and José María Herreras

Abstract

White dot syndromes are an uncommon group of posterior uveitis affecting the outer retina, retinal pigment epithelium, choriocapillaris, and/or choroidal stroma. Multimodal imaging, including fundus fluorescein angiography, indocyanine green angiography, autofluorescence, and optical coherence tomography angiography, has improved our understanding regarding their pathophysiology, helping us to rename or even regroup some of these disorders as one disease in opposition to the historical description. It also provides useful information to evaluate disease activity and monitor response to treatment. This chapter will review the different findings on multimodal imaging of these heterogenous disorders and classify them according to their primary anatomic involvement.

Keywords: white dot syndromes, noninfectious choroiditis, Choriocapillaritis, multimodal imaging, autofluorescence, optical coherence tomography angiography (OCT-A), fundus fluorescein angiography (FFA), Indocyanine green angiography (ICGA)

1. Introduction

White dot syndromes are an uncommon group of posterior uveitis affecting the outer retina, retinal pigment epithelium (RPE), choriocapillaris, and/or choroidal stroma. However, the clinical finding of white spots itself is variably present, the pathophysiology, as supported by multimodal imaging, may differ between them and the clinical course is different. For this reason, the term "noninfectious choroiditis" has been suggested to be more appropriate [1–4].

These noninfectious choroiditis are the result of autoimmune infiltration of the choroidal stroma (primary stromal choroiditis) such as birdshot retinochoroiditis (BRC) or immune-mediated choriocapillaris non-perfusion (primary choriocapillaritis) [3] which includes conditions self-resolving as multiple evanescent white dot syndrome (MEWDS) or sight threatening as acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis (MFC)/punctate inner choroidopathy (PIC), and serpiginous choroiditis (SC).

Multimodal imaging includes several imaging modalities, such as fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), fundus autofluorescence (FAF), and optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A), that play a key role, in determining the primary level of tissue involvement, evaluate disease activity, and monitor response to

treatment. The aim of this chapter is to describe the different findings on multimodal imaging of these heterogenous disorders.

2. Primary stromal choroiditis with additional independent retinitis: birdshot retinochoroiditis (BRC)

It is also known as vitiliginous chorioretinitis [5], and it is a bilateral, asymmetric, and progressive disease without known systemic involvement first described in 1980 by Ryan and Maumenee [6] that predominates in Caucasian women past the fourth decade of life and presents a strong association with HLA-A29 (90–95%) [7]. Because of this strong association, the disease should be better called HLA-A29 BRC [3]. Early symptoms include floaters, decreased vision, and photopsias, and later, it can present with nyctalopia, decreased color vision, and diminished contrast sensitivity. All these complaints may be related to vitritis, macular or optic disk edema and/or outer retina atrophy, or other complications. Multimodal imaging shows a dual and independent retinal and choroidal inflammation in BRC.

Fundus photography is useful in documenting retinal vasculitis of large veins, papillitis, and the classic depigmented ovoid spots that are more prominent inferonasal to the optic disk (**Figure 1**) and radiate to the equator. These choroidal spots typically indicate stromal scars and may never appear if the disease is treated early [3].

FAF exhibits hypoautofluorescent spots if RPE atrophy occurs more numerous than clinically and sometimes is not uniformly correspondent with the birdshot choroidal lesions suggesting a dual independent RPE damage by inner retina and choroid. A placoid macular hypoautofluorescence which correlates with poor visual outcome may also be seen [8].
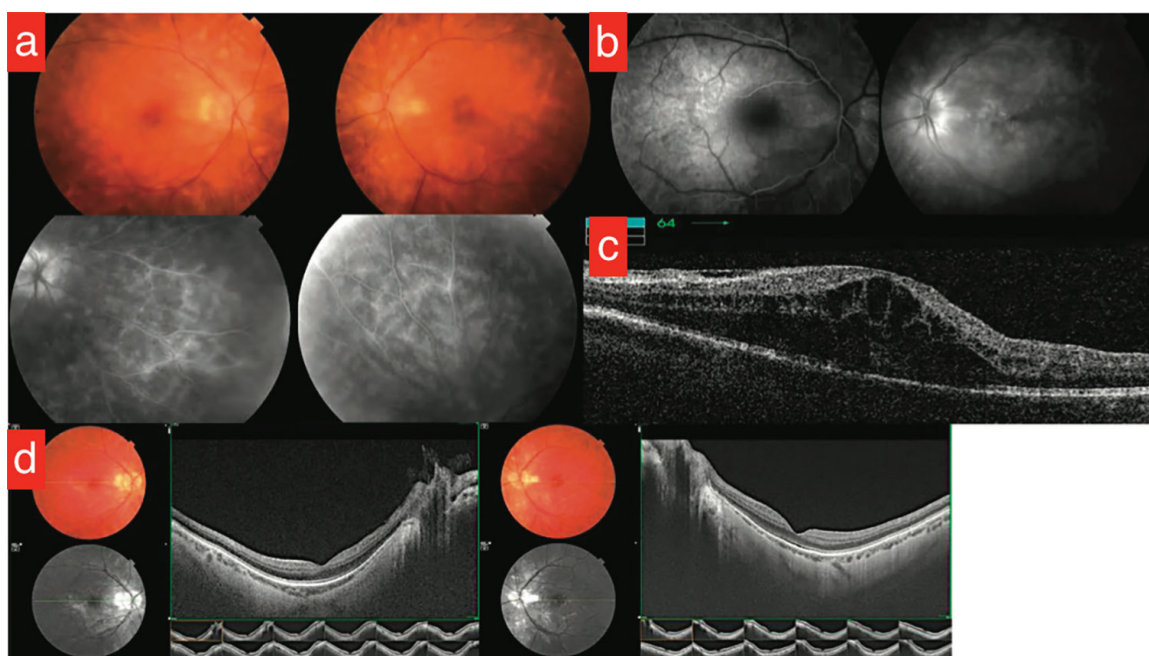

Figure 1.
This patient presents mild vitritis, birdshot choroidal depigmented spots. (a) FAF shows optic nerve leakage and phlebitis in both eyes. Petaloid macular leakage is seen in late phase in the left eye. There is also "quenching" of the dye in the right eye. (b) Optical coherence tomography (OCT) in the left eye demonstrates ERM and CME. (c) In advanced stage, there is choroidal thinning in both eyes on OCT. (d) ERM: Epiretinal membrane; CME: Cystoid macular edema.

FFA shows optic nerve hyperfluorescence, vascular leakage (predominantly phlebitis), and macular leakage (**Figure 1**) [9]. Moreover, circulation times are called to be "delayed" in the venous circulation but in fact is a pseudo-delay or "quenching" of the dye due to diffuse capillary leakage of fluorescein into the surrounding tissue so that there is not enough dye to normally mark the veins (**Figure 1**) [10]. Active choroidal inflammatory lesions are not generally visible until they affect the overlying RPE appearing hypofluorescent in early phases with subtle late staining [11].

ICGA shows more numerous choroidal lesions and even before than clinical examination or FFA. They are seen as multiple hypofluorescent round spots in the early and mid-phases becoming isofluorescent in the late angiographic phase if active, probably, partial thickness granulomas, indicating non-penetration of the dye only at the site of inflammatory choroidal infiltrates. If the lesions remain hypofluorescent in late phase, it may be due to full thickness lesions or that the lesions have become atrophic [12, 13]. Also, there may be seen fuzzy vessels in active disease showing choroidal vasculitis during the intermediate and late phases [11–13].

OCT may show cystoid macular edema (CME), secondary epiretinal membrane (ERM) (**Figure 1**), loss of ellipsoid zone (EZ) with RPE degeneration beneath the areas of photoreceptor involvement, as well as other complications, such as macular atrophy, optic atrophy, and rarely, choroidal neovascularization (CNV). Enhanced-depth OCT imaging may be useful to evaluate choroidal thickening early in the disease and thinning in advanced disease (**Figure 1**).

En-face OCT-A has identified areas of flow void in the Haller layer corresponding to those hypofluorescent spots on ICGA with initial sparing of the choriocapillaris, thereby supporting the primary involvement of choroidal stroma in the disease with secondary involvement of choriocapillaris and the RPE [14]. It also demonstrates retinal capillary density reduction at the deep retinal capillary plexus level, which may indicate that ischemia, in addition to inflammation, may play a role in the development of retinal neovascularization (NV), retinal thinning, and reduction of visual function [15]. Other changes in both the superficial and deep capillary plexus that may explain the common finding of CME in BRC have been documented such as capillary dilatations and loops, telangiectatic vessels, increased intercapillary space, and decreased capillary density without a change in the size of the foveal avascular zone (FAZ) [16–18], and alternatively, it has been found a larger area of FAZ [19].

3. Primary choriocapillaritis

3.1 Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)/acute multifocal ischemic choriocapillaritis (AMIC)

APMPPE is an idiopathic, commonly bilateral although asymmetric, disorder affecting young healthy adults who complain of having visual loss, photopsias, and paracentral scotomas of acute onset. However, there have been some unilateral cases or delayed involvement of the second eye by several weeks [20].

The disease origin was first attributed to the RPE by Gass in 1968 [21]; hence the name, however, Deutman and coworkers [22], in the same period, hypothesized that it is a disease primarily affecting the choriocapillaris; therefore, they suggested the name acute multifocal ischemic choroidopathy (AMIC). This last term seems to be more proper as multimodal imaging has demonstrated [9].

Fundus photography shows multifocal, yellowish creamy, or pale discolored placoid chorioretinal lesions [23], located posterior to the equator (generally at the posterior pole) (**Figure 2**) that tend to progressively fade over the weeks, although new lesions may appear more peripherally later without extending beyond the equator, resulting in hyperpigmentation (clumping of pigment) and chorioretinal atrophy with potential damage to visual function.

FFA shows hypofluorescent lesions in early phases due to choriocapillaris non-perfusion, becoming hyperfluorescent by exudation and pooling in late frames due to increased permeability of retinal vascular plexuses induced by the massive ischemia in choriocapillaris and therefore in the overlying outer retina (**Figure 2**), which correspond to the yellow discolored plaques seen on fundus examination [3]. Inactive lesions appear hyperfluorescent due to window defects derived from RPE atrophy and blocked fluorescence from pigment clumping [24].

ICGA exhibits geographic hypofluorescent spots across all phases due to choriocapillaris non-perfusion. Acute lesions are more numerous or extensive than those seen clinically or on FFA [23] suggesting a primary choroid involvement. Inactive lesions tend to become smaller, probably due to the absence of swollen outer retina and RPE secondary to choroidal ischemia, and thus, less blockage [24]. When healed, hypofluorescence can also completely resolve except for a few areas of persistent hypofluorescence due to chorioretinal atrophy.

FAF shows hypoautofluorescence in acute lesions due to the blocking effect of overlying retinal edema [25] and hyperautofluorescence in areas where loss of photoreceptor outer segments has occurred causing increased exposure of RPE lipofuscin (**Figure 2**). Healed lesions develop increased central hyperpigmentation appearing hyperautofluorescent and a surrounding depigmentation zone that shows hypoautofluorescence due to RPE dysfunction/damage/atrophy in areas with severe vascular drop out that do not always correlate with the fundus lesions and/or FFA, and are fewer in number, implicating a primary choroidal alteration. These patterns in advanced lesions suggest centripetal contraction of the placoid lesions with atrophy and depigmentation of surrounding RPE cells [13].
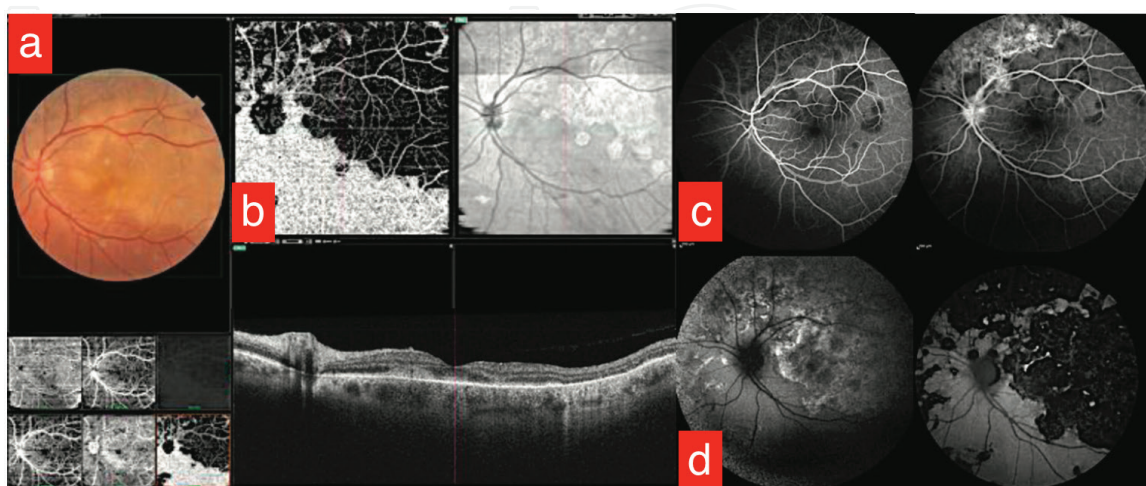

Figure 2.
Patient presents a yellowish confluent placoid chorioretinal lesion. (a) On optical coherence tomography (OCT), there is loss of outer retina and EZ with a hyperreflectivity lesion nasal to the fovea. Optical coherence tomography angiography (OCT-A) demonstrates flow deficit at the level of choriocapillaris. (b) Later, FFA was made showing early hypofluorescence and late hyperfluorescence. (c) FAF shows mixed areas with hypo/ hyperautofluorescence at the initial visit and hypoautofluorescence in follow-up. (d) EZ: Ellipsoid zone.

On OCT, there may be hyperreflectivity probably due to ischemic edema or presence of inflammatory cell infiltrates (**Figure 2**) [24, 26, 27] with subsequent disruption or loss of the outer retina and EZ, and sometimes subretinal fluid. As the lesions resolve, RPE disruption or atrophy may also occur. OCT-A demonstrates that this changes correlate with greater areas of hypoperfusion at the level of choriocapillaris being detected also on FFA and ICGA [9].

All these findings thus support the theory that APMPPE/AMIC is a disorder primarily caused by ischemic events occurring in the choriocapillaris and secondarily affecting the outer retina and RPE.

3.2 Serpiginous choroiditis (SC)

SC is a bilateral, although asymmetric, progressive, and recurrent ocular disorder, representing the most severe form of primary choriocapillaritis, probably because the vaso-occlusive involvement occurs in the larger arterioles producing a more widespread choriocapillaris non-perfusion with secondary involvement of the outer retina and RPE, and leading to an extensive and irreversible chorioretinal scarring if not treated promptly, in contrast to MEWDS, which involves the more distal end-choriocapillary vessels, causing less ischemia and consequently less damage that frequently is reversible [4]. Patients report decreased vision, metamorphopsias, scotomas, and photopsias.

Fundus photography shows gray-white-yellow choroidal active lesions [28] which start from the peripapillary region and spread centrifugally in a serpiginous pattern, hence the name. Rarely, macular may present without peripapillary involvement. Over time, these lesions become pigmented chorioretinal scars and recurrences can occur at the border of these atrophic lesions, weeks to years after prior episodes of inflammation (**Figure 3**).

FFA reveals active lesions with early diffuse hypofluorescence probably by blockage of the underlying choroidal fluorescence by swollen outer retina and RPE cells and/or impaired perfusion of choriocapillaris [24, 29] with late hyperfluorescence at the borders [28] by leakage of surrounding intact choriocapillaris [29]. Gradually,
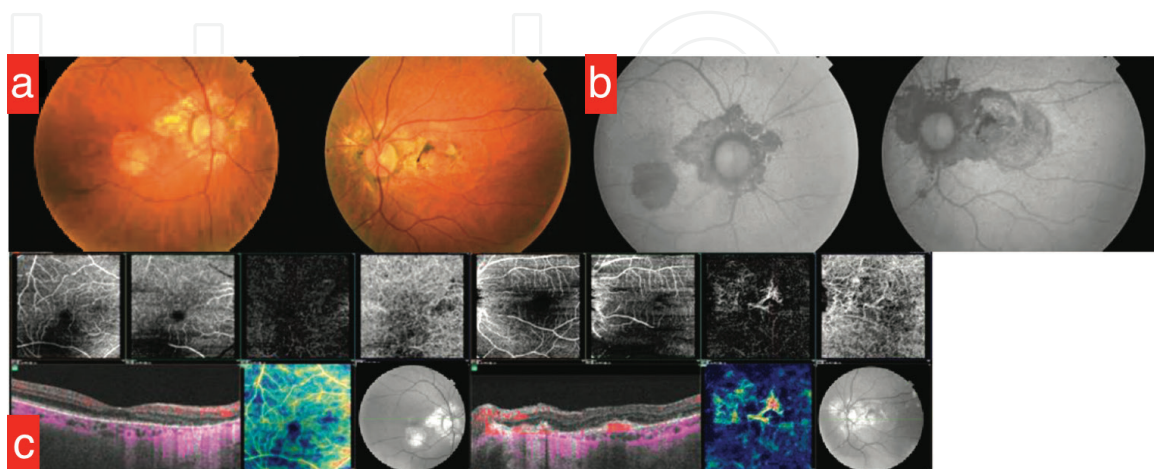

Figure 3.
This patient presents a peripapillary chorioretinal scar affecting also the macula. (a) On FAF, lesions appear hypoautofluorescent. (b) OCT shows outer retina/RPE loss and choroidal thinning in the atrophic areas. In the left eye, there is also a subretinal hyperreflective lesion suggestive of CNV which is better defined by optical coherence tomography angiography (OCT-A) in the outer retina and choriocapillaris and with flow signals in the B-scan. OCT-A also shows flow deficit in choriocapillaris in both eyes. (c) RPE: Retinal pigment epithelium; CNV: Choroidal neovascularization.

there is profuse leakage of the dye from larger choroidal vessels which is observed as hyperfluorescence of the lesion [30]. Early hyperfluorescence with late leakage may represent CNV, usually at the edge of lesions. Older atrophic lesions appear early hypofluorescent by the choriocapillaris atrophy and in late phases hyperfluorescent by diffuse staining of the chorioretinal scar [29]. Some areas show hypofluorescence by blockage (masking effect) from pigment clumping [3].

On ICGA, lesions appear hypofluorescent throughout all phases and are more extensive than FFA or clinically, as it represents both atrophic and active choriocapillaris non-perfusion which explains the pathophysiology. In addition, there may be a diffuse perilesional hyperfluorescent halo that indicates progression of disease [3].

OCT-A demonstrates areas of flow deficit at the level of the choriocapillaris which correlate the hypofluorescence on ICGA, what confirms the choriocapillaris non-perfusion as a primary alteration. Also, it is helpful in detecting CNV and monitoring treatment (**Figure 3**).

OCT shows outer retinal/RPE loss and choroidal thinning in the center of atrophic lesions (**Figure 3**), and at the border there is hyperreflectivity and thickening of the outer retina corresponding with ICGA halo around atrophic lesion and disruption of the EZ representing active lesions.

On FAF, active lesions appear with central hypoautofluorescence, when choriocapillaris and RPE are lost, surrounded by a hyperautofluorescent halo as choriocapillaris and RPE are still present but there is loss of photoreceptor outer segments (**Figure 3**).

3.3 Relentless placoid chorioretinitis (RPC)/ampiginous choroiditis (AC)

Ampiginous choroiditis is an uncommon variant that overlap features of both APMPPE/AMIC and SC [9]. It is characterized by chronic and recurrent clinical course as SC unlike APMPPE/AMIC. Fundus photography shows an atypical distribution of lesions in the mid-periphery and posterior pole in contrast to APMPPE/AMIC or SC which are usually limited to the posterior pole (**Figure 4**) and are smaller than SC and APMPPE/AMIC, approximately 1/2 disk area and more numerous than APMPPE/AMIC (50 or more). There is often active disease in both eyes simultaneously with white placoid lesions present throughout the fundus [31] in contrast to serpiginous chorioretinitis in which usually only one eye is active at a time [24].

Angiographic changes are comparable to SC [9, 23], but active lesions may start distant from previous lesions, but in SC they usually start at margin of an atrophic scar [31]. FAF shows a marked hypoautofluorescence in areas of chorioretinal atrophy (**Figure 4**) [24] and OCT-A detects flow reduction at the level of the choriocapillaris which is also the pathophysiology of both SC and APMPPE/AMIC [32].

3.4 Idiopathic multifocal choroiditis (MFC)/punctate inner choroidopathy (PIC)

MFC is a chronic and recurrent bilateral inflammatory disease that predominantly affects healthy myopic White women in their third to fifth decade of life with no known associated systemic or ocular diseases [9, 33]. It was first called multifocal uveitis and panuveitis [34], although the panuveitis finding in most cases is absent or rarely seen with minimal vitreous or anterior inflammation. Therefore, a group of experts merged different sub-entities that have been described separately in the past, such as PIC, pseudo-POHS (presumed ocular histoplasmosis syndrome) in
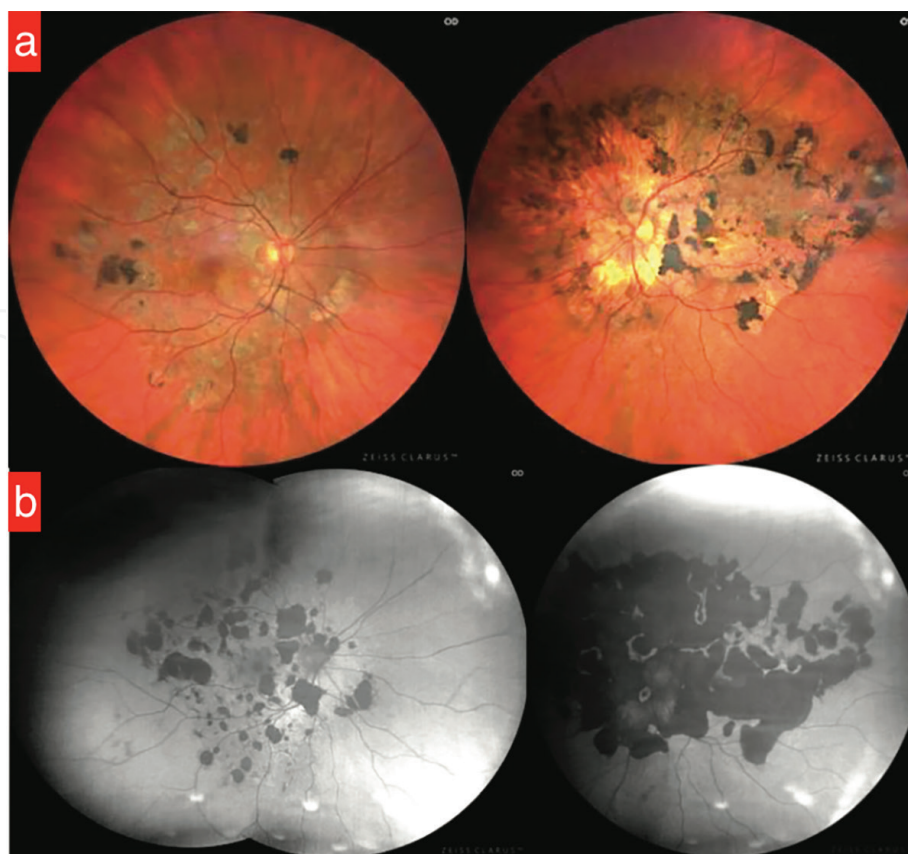
Figure 4.
This patient has an initial presentation as APMPPE/AMIC in the right eye and as SC in the left eye, but then the lesions were extending and affecting both the posterior pole and the mid-periphery leaving chorioretinal atrophy (a) seen as hypoautofluorescence on fundus autofluorescence (FAF). (b) APMPPE/AMIC: Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)/acute multifocal ischemic choriocapillaritis; SC: Serpiginous choroiditis.

Figure 5.
Atrophic chorioretinal lesions. (a) Optical coherence tomography (OCT) shows sub-RPE hyperreflective lesions with overlying outer retina disruption and thinning of choroid. There is also disruption of RPE/Bruch complex with hyperreflectivity beneath. (b) RPE: Retinal pigment epithelium.

non-endemic areas, progressive subretinal fibrosis, and others, with the single term of idiopathic multifocal choroiditis, regarding them as the same disease [35]. Symptoms include photopsias, blurred vision, and scotomas.
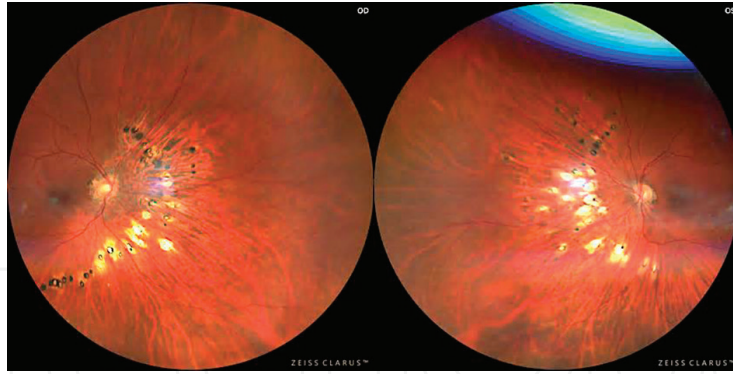
Figure 6.
Schlaegel lines.

Fundus photography shows numerous randomly distributed yellow-white chorio-retinal lesions that leave atrophic scars with variable degree of pigmentation in the posterior pole around the disk and/or the mid-periphery (**Figure 5**) that may cluster forming curvilinear chorioretinal streaks (Schlaegel lines) (**Figure 6**) [33]. In as much as one third of cases, there may be seen CNV due to repeated ischemic attacks, which is more frequent than in other primary choriocapillaritis.

FFA identifies recurrences or acute lesions, even in the absence of clinical scars, as early hypofluorescence [9, 36], although early hyperfluorescence can also occur [37–39], and late hyperfluorescence by retinal and subretinal leakage and/or staining due to severe hypoperfusion of the choriocapillaris causing ischemia of outer retina as for APMPPE/AMIC [3, 40]. Early hyperfluorescence with late leakage may represent CNV. Atrophic scars show early hyperfluorescence due to atrophy of the RPE and outer retina (window defect) [9] and areas of hypofluorescence by blockage (masking effect) from pigment deposition (**Figure 7**) [40].

ICGA demonstrates hypofluorescence in new lesions reflecting choriocapillaris hypo or non-perfusion, sometimes in the absence of clinical signs or changes on FFA and helps in detecting progression or regression following inflammation suppressive treatment. Old scarred chorioretinal lesions appear hypofluorescent in all phases [40].
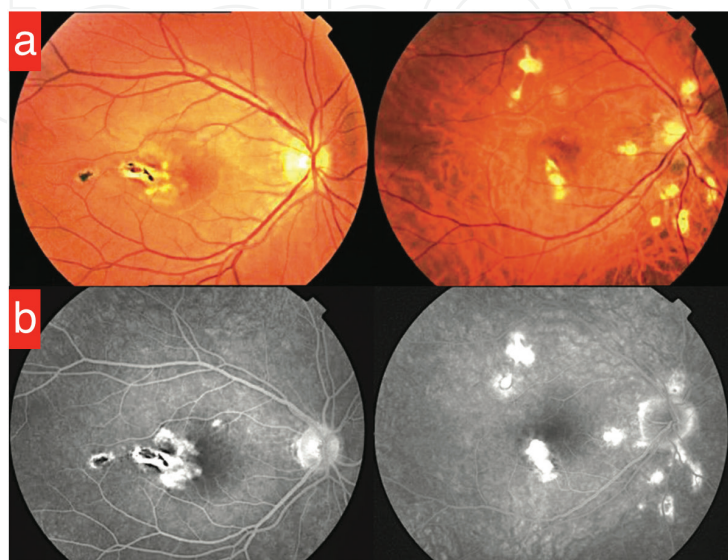

Figure 7.
Atrophic chorioretinal lesions (a) with mixed hype/hypoautofluorescence on fundus autofluorescence (FAF) (b).

OCT-A identifies reduced flow in the choriocapillaris co-localizing with FFA and ICGA findings but less extensive, and it is also useful to identify CNV [9, 40, 41]. OCT shows drusen-like sub-RPE material corresponding to fibrosis with overlying outer retinal disruption and choroidal hyperreflectivity beneath them (**Figure 5**). Chorioretinal atrophic areas can also be seen [9, 40].

FAF shows hyperautofluorescence (exposure of RPE lipofuscin due to loss of outer segments of photoreceptors) and hypoautofluorescence by blockage in cicatricial areas [9, 40].

3.5 Multiple evanescent white dot syndrome

MEWDS is an idiopathic and unilateral inflammatory disorder first described by Lee Jampol et al. in 1984 [42] with a predilection for women in their second to fourth decade of life [27]. As the name indicates, it is self-limited, resolving within 8–10 weeks without sequelae and no need for treatment [43].

Flu-like symptoms may precede ocular manifestations in about half of cases, and there is also association with influenza and other vaccinations [3, 44]. Patients refer sudden visual loss, photopsias, dyscromatopsia, and scotomas.

Fundus photography depicts yellowish-white deep chorioretinal lesions, commonly located at the posterior pole and extending to mid-periphery (**Figure 8**). Foveal granularity is seen, and mild intraocular inflammation can be present in the form of vitritis and/or optic disk edema.

FAF shows hyperautofluorescence produced by exposure of RPE due to loss of outer segments photoreceptors/ellipsoid zone and co-localize with ICGA findings (**Figure 8**). A particular finding of MEWDs is the presence of foveal granularity seen as irregular hyperautofluorescence in near-infrared FAF that remains a little longer than other imaging modalities or clinically [45].

ICGA shows early- to mid-phase hypofluorescence [44] better seen in the late phase due to lesions in the ellipsoid zone causing thickening of RPE resulting in abnormal indocyanine green uptake by the RPE [9] or by choriocapillaris non-perfusion of end-capillary portions [3] which can explain both the self-limited

Figure 8.
Yellowish-white chorioretinal lesions that later resolved. (a) On acute lesions, FFA shows early hyperfluorescence than persists in late phases and a mild hot disk (b).

damage and the reversibility of the disease in contrast to other primary choriocapillaritis [4, 26].

OCT shows loss of EZ zone which corresponds to FAF and ICGA lesions, and accumulation of hyperreflective material over RPE that may extend anteriorly through the interdigitation zone, EZ, and outer nuclear layer (ONL) [27, 45].

OCTA does not typically detect areas of flow deficit in the choriocapillaris [41, 46] unless severe damage has occurred showing discrete areas of dropout [47, 48]. Nevertheless, OCTA is probably unable to show end-capillary circulation in contrast to larger vessels such as in APMPPE/AMIC, MFC, and SC [26] and needs sufficient flow to identify the presence or absence of vessels, in contrast to ICGA [3, 49].

FFA shows early faint hyperfluorescence (**Figure 8**) that persists in late phases in wreath-like configuration [44] probably due to lesions involving the EZ/RPE or by outer retinal ischemia that in comparison to APMPPE/AMIC is less pronounced because smaller vessels are affected [3, 26]. Less frequently, optic disk hyperfluorescence and focal retinal vascular stain can be seen [44, 50, 51].

Therefore, there is an ongoing debate about pathophysiology of this disorder whether it is a primary phtoreceptoritis [46] or a primary choriochapillaritis leading to secondary ischemic damage at the outer retina and RPE [49], and more studies are needed.

4. Secondary choriocapillaritis: acute zonal occult outer retinopathy (AZOOR)

AZOOR is a primary disease of the outer retina (photoreceptoritis) with a secondary choriocapillaris involvement. It was first described by JD Gass in 1992 [52] and affects young- to middle-aged patients (13–63 years), predominantly myopic women which present an acute onset of scotomas and photopsias in one or both eyes, sometimes associated with mild vitritis. Furthermore, there may be recurrences in one-third of cases [53].

Fundus photography is normal at presentation, but later can present zonal or multizonal retinochoroidal atrophy, often seen as peripapillary depigmentation, occasionally with a demarcation line if there is active disease expansion or pigment clumping, retinal arteriolar attenuation, and focal perivenous sheathing in later stages (**Figure 9**).

FAF shows a trizonal distribution (**Figure 9**) of normal autofluorescence outside the lesion (zone 1), speckled hyperautofluorescence in the rim of the expanding lesion (zone 2) which correspond to loss of photoreceptor outer segments and increased exposure of RPE lipofuscin and/or the result of accumulated lipofuscin in RPE cells due to metabolic overactivity as a response of photoreceptor outer segment turnover [54, 55], and a central area of hypoautofluorescence within the lesion (zone 3) that indicates RPE and choriocapillaris atrophy [56].

OCT also demonstrates a trizonal pattern corresponding to FAF characterized by normal retina outside the lesion (zone 1), subretinal hyperreflective deposits and loss or irregularity of EZ (zone 2) in the rim of the lesion, and EZ, RPE and choriocapillaris atrophy (zone 3) inside the lesion (**Figure 9**), although thinning can also extend to the inner retina [56].

OCT-A detects markedly reduced flow in choriocapillaris in areas of retinochoroidal atrophy [57]. Active lesions may present an increase in the deep flow density which may be the source of mediators of inflammation, in contrast to inactive phase where it is decreased, but further studies are needed [55]. En-face OCTA demonstrates hyperreflective dot structures at the level of ellipsoid zone that might represent degenerating photoreceptor segments (**Figure 9**) [58].

Figure 9.
This patient present a retinochoroidal atrophic lesion inferotemporal to the disk in right eye and two lesions in the left eye located in peripapillary area and another nasal to the optic disk. (a) Fundus autofluorescence (FAF) shows hypoautofluorescence inside the lesions and a rim with faint hyperautofluorescence. (b) Optical coherence tomography (OCT) shows outer retina/EZ atrophy and choroidal thinning, (c) and en-face optical coherence tomography angiography (OCT-A) at the level of EZ shows hyperreflective dots (more evident in the left eye) in a hyporreflective background. (d) EZ: Ellipsoid zone.

ICGA also shows a trizonal pattern of preserved fluorescence (zone 1) indicating choriocapillaris integrity, a late hyperfluorescence with minimal leakage in subacute areas demarcating the lesion (zone 2), and an inner area of hypofluorescence due to retinochoroidal atrophy [56].

FFA depicts faint late hyperfluorescence indicating loss of photopigment of outer segments, except in those areas with retinochoroidal atrophy that are early and late hyperfluorescent due to window effect. Retinal arteriolar narrowing in the areas of involvement may be seen. Retinal vessel staining and leakage may be present [24].

5. Conclusion

In summary, combining multiple imaging modalities, including OCT, FFA, ICGA, FAF, and OCT-A, may help us in classifying better this heterogenous group of diseases according to their pathophysiological process and therefore differentiate between one another, detect ocular complications, and monitor response to treatment.

Conflict of interest

The authors declare no conflict of interest.

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