Multifocal Choroiditis and Panuveitis

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Introduction

Multifocal choroiditis and panuveitis (MCP) is an idiopathic chorioretinal inflammatory disease accompanied by prominent vitritis and anterior segment uveitis. The acute inner chorioretinal lesions subsequently evolve into pigmented scars and may lead to the development of choroidal neovascularization (CNV). In late 1973, two patients with bilateral anterior uveitis associated with a chorioretinopathy that resembled ocular histoplasmosis syndrome were reported for the first time (Nozik and Dorsch 1973). Additionally, 28 patients with anterior uveitis, vitritis, and multiple lesions at the retinal pigment epithelium (RPE) level were described (Dreyer and Gass 1984), and they coined the term MCP. Subsequently, several investigators documented clinical features of diffuse subretinal fibrosis (Doran and Hamilton 1982), multiple evanescent white dot syndrome (Jampol et al. 1984), and punctate inner choroidopathy (PIC) (Watzke et al. 1984), each of which are distinctly different clinical entities. Additionally, a characteristic inner choroidal lesion that subsequently evolves into RPE pigmentation, fibrosis, and development of CNV in the absence of anterior or vitreous inflammation was described by Morgan et al. as multifocal choroiditis (MFC) (Morgan and Schatz 1986). These diseases were previously classified as the same disease entity because of their similar clinical characteristics (Jampol et al. 1984). Later, these disorders were classified as different entities in 79 patients having enlarged blind spots with other clinical, angiographic, and electroretinographic evidence (Reddy et al. 1996).

Epidemiology

MCP occurs more frequently in women and predominantly in young and otherwise healthy people. The median age of onset is the mid-30s (Dreyer and Gass 1984; Morgan and Schatz 1986; Reddy et al. 1996). A moderate degree of myopia was present in all but one patient with MCP (Morgan and Schatz 1986). There has been no reported ethnic or genetic predisposition related to this disease. The geographic distribution of MCP is different from that of presumed ocular histoplasmosis syndrome (POHS) (Dreyer and Gass 1984), which is endemic for histoplasmosis, and MCP shows a relatively low percentage of positive responses to the histoplasmin skin test (Dreyer and Gass 1984).

Etiopathogenesis

The etiology and pathogenesis are not well known. Patients with MCP have no associated systemic disease or familial history. The hypothesis suggested that white spot syndromes occur in individuals with common non-disease-specific autoimmune susceptibility factors (Jampol and Becker 2003). Subsequently, the same group reported a high prevalence of systemic autoimmunity not only in patients with MCP but also in their relatives (Pearlman et al. 2009).

Some investigators have suggested a viral etiology. Herpes simplex type 1 was cultured in the chorioretinal specimens of a patient suspected of having bilateral MCP (Grutzmacher et al. 1983). Moreover, intraocular antibodies against varicella zoster were detected in two cases and herpes simplex virus in one case among seven patients with MCP (Frau et al. 1990). The relationship between MCP and chronic infection with the Epstein–Barr virus was also suggested by detecting viral capsid antigen IgM or antibodies to Epstein–Barr early antigens in 10 patients with MCP (Tiedeman 1987). However, the reappraisal research (Spaide et al. 1991a) failed to support this association. Histopathologic examination of MCP lesions has revealed non-granulomatous perivascular choroidal infiltrates of mixed lymphocytes, consisting mainly of B lymphocytes, in association with early CNV (Dunlop et al. 1998; Nolle and Eckardt 1993; Shimada et al. 2008). These findings were not significantly different from the findings of PIC.

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Clinical Features

Although asymmetric, MCP occurs frequently in both eyes. Bilaterality has been reported to be as low as 45% (Morgan and Schatz 1986) and as high as 79% (Reddy et al. 1996). Patients with MCP usually present with blurred or decreased central vision with scotoma. Floaters and photopsia are less common. The mean initial vision on examination of 68 eyes with MCP was 20/50 (Reddy et al. 1996), varying from 20/40 to light perception. Mild-to-moderate anterior uveitis was observed in 52% (Dreyer and Gass 1984) of patients with MCP, with the signs including anterior chamber cells and flare, non-granulomatous keratic precipitates, and posterior synechiae. Vitreous inflammation was more common, observed in 100% of eyes by the same study group (Reddy et al. 1996). In the absence of anterior uveitis and/or vitritis, it may be classified as idiopathic MFC (Fung et al. 2014), and MFC is often regarded as a spectrum of disease that is indistinguishable from PIC (Essex et al. 2013). MCP eyes have a very similar pattern of multiple choroiditis that suggests POHS (Raven et al. 2017). In the acute phase of MCP, multiple round to oval, yellow-gray lesions at the RPE levels, measuring about 50–350 μm, are scattered throughout the posterior pole and mid-periphery (Joondeph and Tessler 1990; Quillen et al. 2004) (Fig. 4.1). Occasionally, the lesions may be clustered, or they may be linearly arranged, parallel to the ora serrata, similar to the clinical findings shown in POHS (Spaide et al. 1991b) (Fig. 4.2). Exudation may develop over the areas of active lesion during the active phase. The active lesions change to round and atrophic scars, appearing as punched-out lesions with various degrees of hyperpigmentation, and the scars can enlarge in size (Raven et al. 2017) (Fig. 4.3). Peripapillary atrophy is frequently observed in MCP eyes (Fig. 4.4). Optic disc swelling and hyperemia occur not uncommonly, with prevalence up to 34% according to prospective follow-up studies (Reddy et al. 1996), but the development of optic neuropathy is not common, reported in only 11% of 122 examined MCP eyes (Kedhar et al. 2007).

Acute enlargement of the blind spot without disc swelling was described in observational studies on MCP (Khorram et al. 1991; Callanan and Gass 1992). The etiology of the blind spot enlargement is unknown. Some investigators explained that it was because the nasal retina is more involved through the medial posterior ciliary artery, as MCP develops hematogenously (Brown and Folk 1999; Hayreh 1975). Others suggested that preferential involvement of rod photoreceptors in MCP may induce a field defect around the blind spot (Curcio et al. 1990; Reddy et al. 1996).

Electroretinography (ERG) findings in MCP show diffuse involvement depending on the disease severity associated with chorioretinal involvement. Normal to borderline ERGs were noted in 41% of examined MCP eyes, while moderately to severely depressed ERGs were observed in 38%

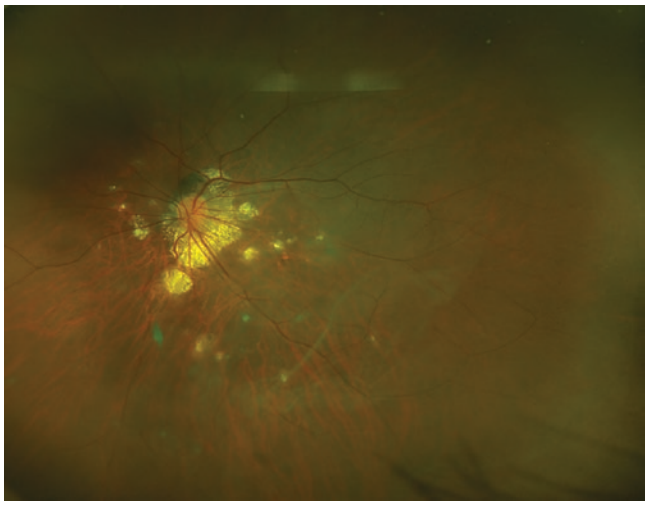

Fig. 4.1 Wide-field fundus imaging shows multiple round to oval gray-yellowish chorioretinal lesions of variable size (about 50–1000 μm) in the posterior pole and mid-periphery of the retina

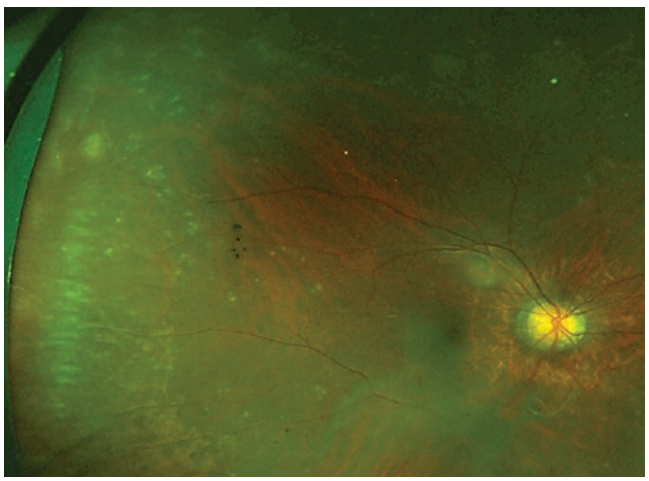

Fig. 4.2 Wide-field fundus imaging demonstrates a linear peripheral arrangement of yellow-gray spots denoting choroiditis

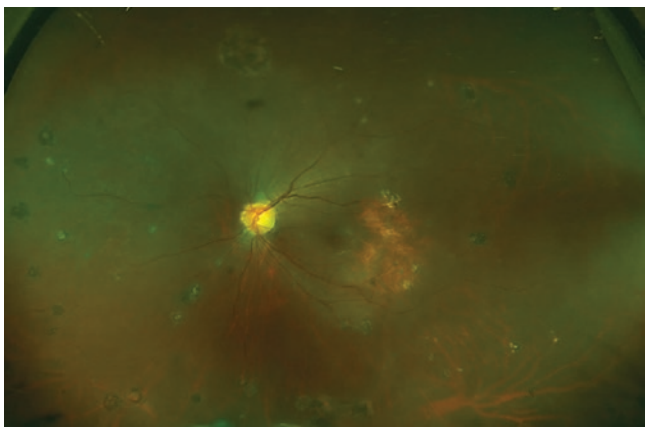

Fig. 4.3 Wide-field fundus imaging reveals multiple punched-out atrophic lesions that are indicative of choroiditis

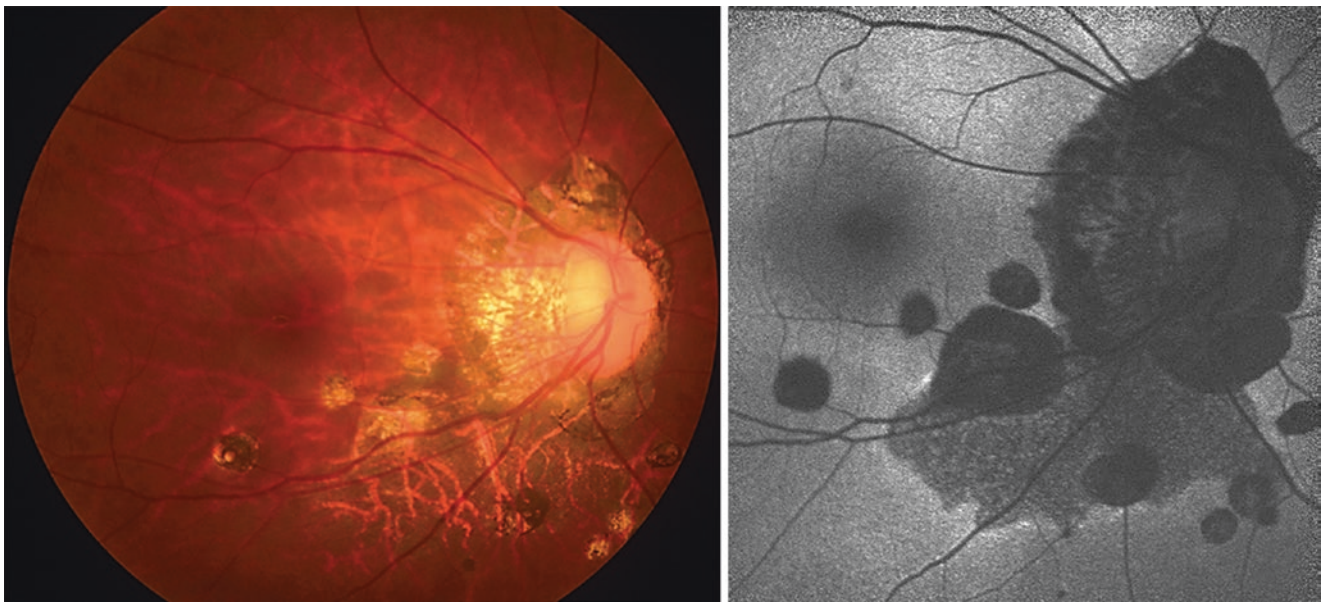

Fig. 4.4 Color fundus photography and autofluorescence imaging demonstrate extensive peripapillary atrophy

(Dreyer and Gass 1984). Abnormal ERG responses in MCP were described as rod dysfunction, prolonged cone b-wave implicit times, and poor oscillatory potentials (Reddy et al. 1996). Multifocal ERG revealed a diffuse and irreversible depression in first-order responses in MCP patients, most of which did not correspond to the scotomas on the Goldman visual field (Curcio et al. 1990).

MCP is a chronic disease that may persist for many years and typically has multiple recurrences in one or both eyes (Reddy et al. 1996; Fung et al. 2014). Reactivation of inflammation includes cellular infiltrates of the anterior chamber and vitreous, enlargement of previous lesions, and the appearance of new lesions (Reddy et al. 1996). The mean final visual acuity was 20/42 when 65 eyes with MCP were followed-up for an average of 92 months (Fung et al. 2014). The reported incidence of cystoid macular edema (CME) in MCP varies, ranging from 14% (Dreyer and Gass 1984) to more than 40% (Kedhar et al. 2007). CNV, responsible for 45% of irreversible visual loss to 20/200 or worse (Thorne et al. 2006), has been reported in 32–46% of patients with MCP (Dreyer and Gass 1984; Reddy et al. 1996; Fung et al. 2014). Epiretinal membrane (ERM), with a reported incidence of about 5% in eyes with MCP (Kedhar et al. 2007), accounted for 28% of vision loss to less than 20/50 in one study (Thorne et al. 2006).

Diagnosis

The diagnosis of MCP is usually a clinical one based on the characteristic fundus findings, and ancillary tests only help establish the diagnosis of MCP.

Fluorescein Angiography

In the acute phase, the active lesions of MCP may appear hypofluorescent on the fluorescein angiogram (FA) with staining and leakage in the late phase. The punched-out atrophic scars in the healed phase show early hyperfluorescence with fading out in the late phase as window defects (Fig. 4.5). If CNV is present, characteristic early hyperfluorescence with late leakage appears in the peripapillary or macular areas.

Indocyanine Green Angiography

Indocyanine green (ICG) angiography provides additional information not detected by fundus examination and FA alone, which helps to understand the pathophysiology of MCP, to differentiate from other inflammatory chorioretinopathies and to identify the progression and recovery of MCP. Multiple hypofluorescent spots of variable size can be found on the posterior pole on ICG angiography that are not apparent on FA or clinical examination (Slakter et al. 1997) (Fig. 4.6). These hypofluorescent lesions on ICG angiography generally represent acute or subacute disease. They are not constant, resolving spontaneously as the acute process subsides or with anti-inflammatory therapy. Visual field defects and corresponding areas of hypofluorescence on the ICG study were found in the same study group (Slakter et al. 1997). In seven eyes showing enlarged blind spots on visual field testing, ICG angiography showed confluent hypofluorescence surrounding the optic nerve (Slakter et al. 1997). The authors described that the hypofluorescent lesions in

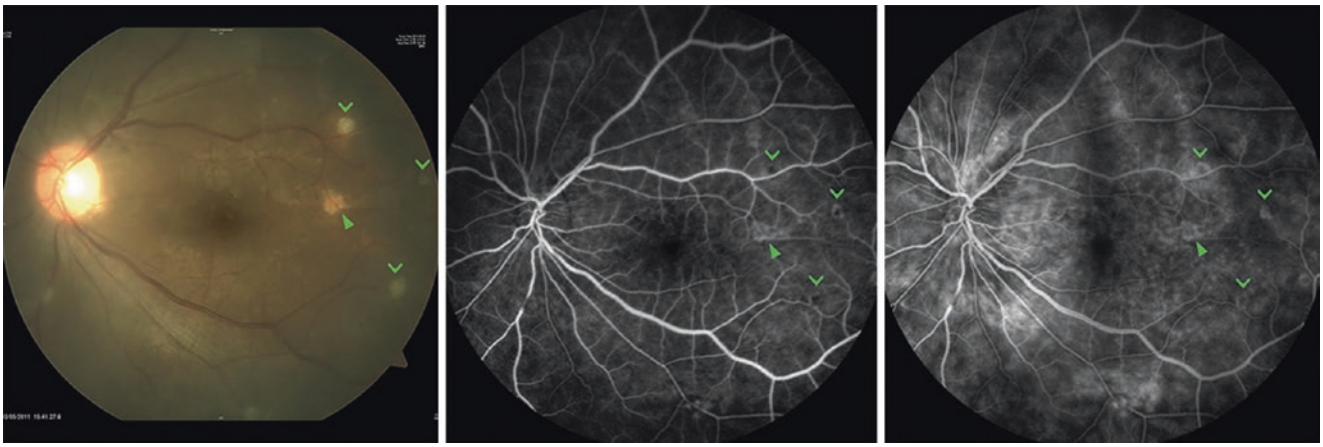

Fig. 4.5 Color fundus photo (left) and fluorescein angiogram of the early (middle) and late (right) phases show multifocal chorioretinal lesions in the different stages. The active lesions (three arrowheads) appear with decreased fluorescence in the early phase and fluorescence staining in the late phase. Early hyperfluorescence with fading out in the late phase is observed in the atrophic lesion (filled triangle)

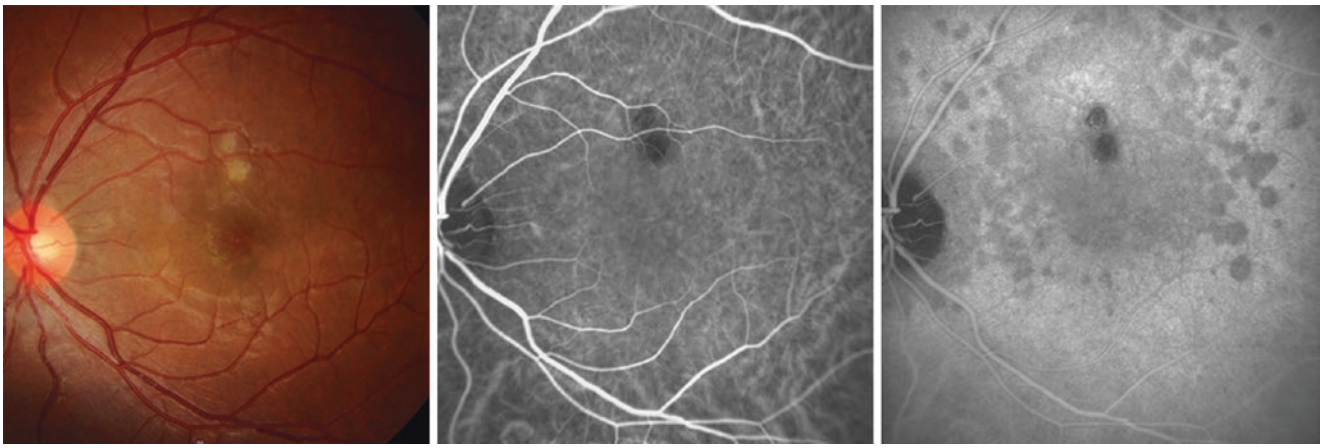

Fig. 4.6 Early phase indocyanine green angiogram (middle) demonstrates focal hypofluorescent spots which are also visible in the color fundus photograph (left). Late phase indocyanine green study (right) shows a large number of hypofluorescent spots of variable size throughout the posterior pole. These lesions are not apparent on the fundus photo

MCP may be the result of focal collections of inflammatory cells or debris at the level of the choriocapillaris producing "blocked fluorescence" or in the middle layer of the choroid causing a "space occupying effect." Underlying perfusion abnormalities of the choroid and choriocapillaris have been suggested as another potential pathophysiology of the hypofluorescent lesions seen on ICG angiography.

Fundus Autofluorescence

Two major types of hypoautofluorescence have been identified. Chorioretinal hypoautofluorescent spots greater than 125 μm were usually observed corresponding to the area of a punched-out scar visible by color fundus photography (Haen and Spaide 2008) (Fig. 4.7). Autofluorescence imaging also demonstrates hypoautofluorescent lesions measuring less than 125 μm that were typically not visible by color fundus photography (Haen and Spaide 2008) (Fig. 4.8). Subsequently, in another study of 16 MCP eyes, 12 eyes predominantly presented with punctate hypoautofluorescent spots corresponding to multiple areas of chorioretinal atrophy (Yeh et al. 2010). Macular hyperautofluorescence may be observed in the area of active chorioretinitis (Fig. 4.8), which also correlated with complete resolution with immunosuppressive therapy.

Optical Coherence Tomography

Optical coherence tomography (OCT) is useful not only in the evaluation of chorioretinal lesions in the macula but also in the detection of CME and CNV lesions. Thinning of the retina with disruption of the photoreceptor inner and outer segment junction was described mainly in the macular lesions and in the peripapillary atrophic scars of MCP by

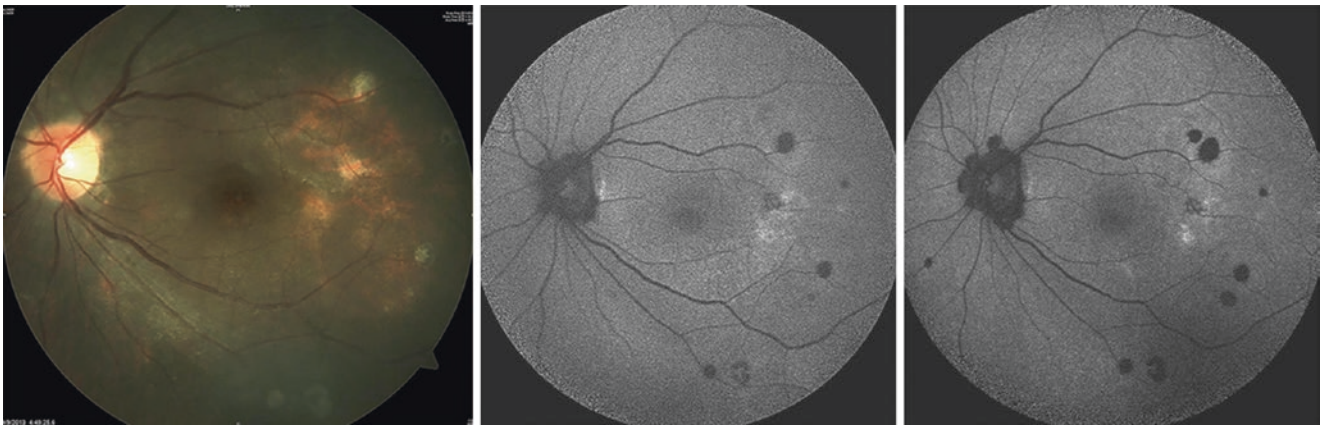

Fig. 4.7 Autofluorescence imaging (middle) at the initial visit shows multiple small hypoautofluorescent lesions in the posterior pole that correspond to the subretinal yellowish to creamy lesions on the color fundus photograph (left). Over the course of 3 years, enlargement of the size and increase in the number of hypoautofluorescent spots can be seen (right)

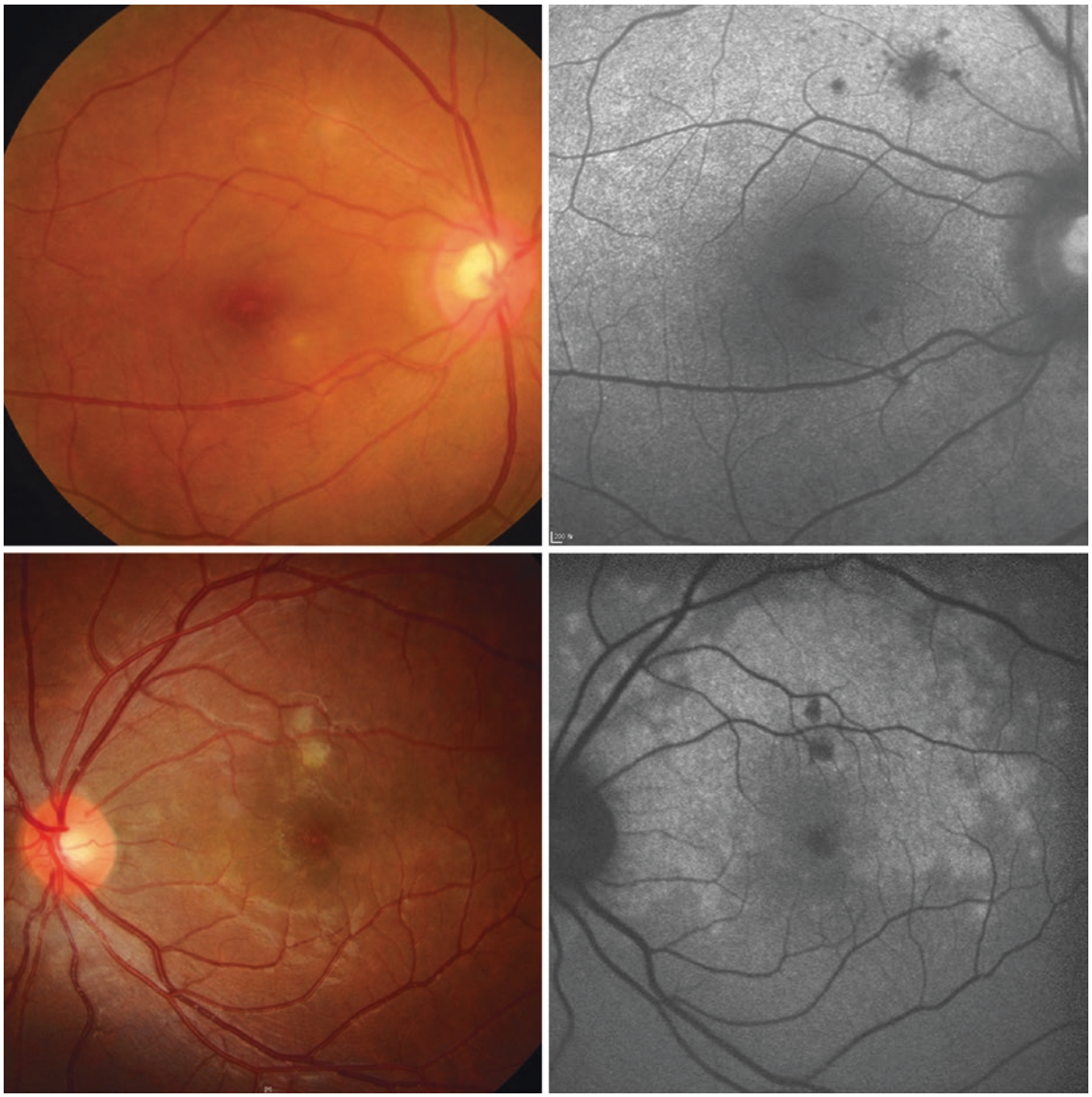

Fig. 4.8 Autofluorescence photography (upper right) demonstrates multiple tiny hypoautofluorescent spots which are not well visualized in color fundus photography (upper left). Autofluorescence photography (lower right) shows macular hyperautofluorescence, indicative of active chorioretinitis in the posterior pole that is also not revealed on color fundus photography (lower left)

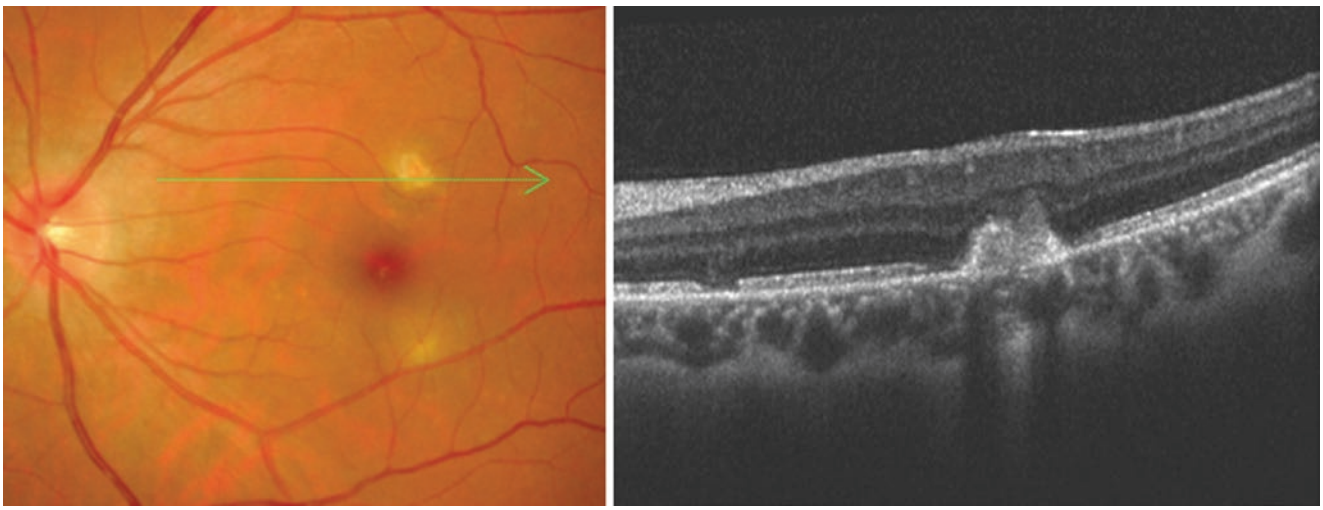

Fig. 4.9 Spectral-domain optical coherence tomography shows drusen-like subretinal accumulation of hyperreflective inflammatory lesion during the acute stage with disruption of the outer nuclear layer and the photoreceptor inner and outer segment junction

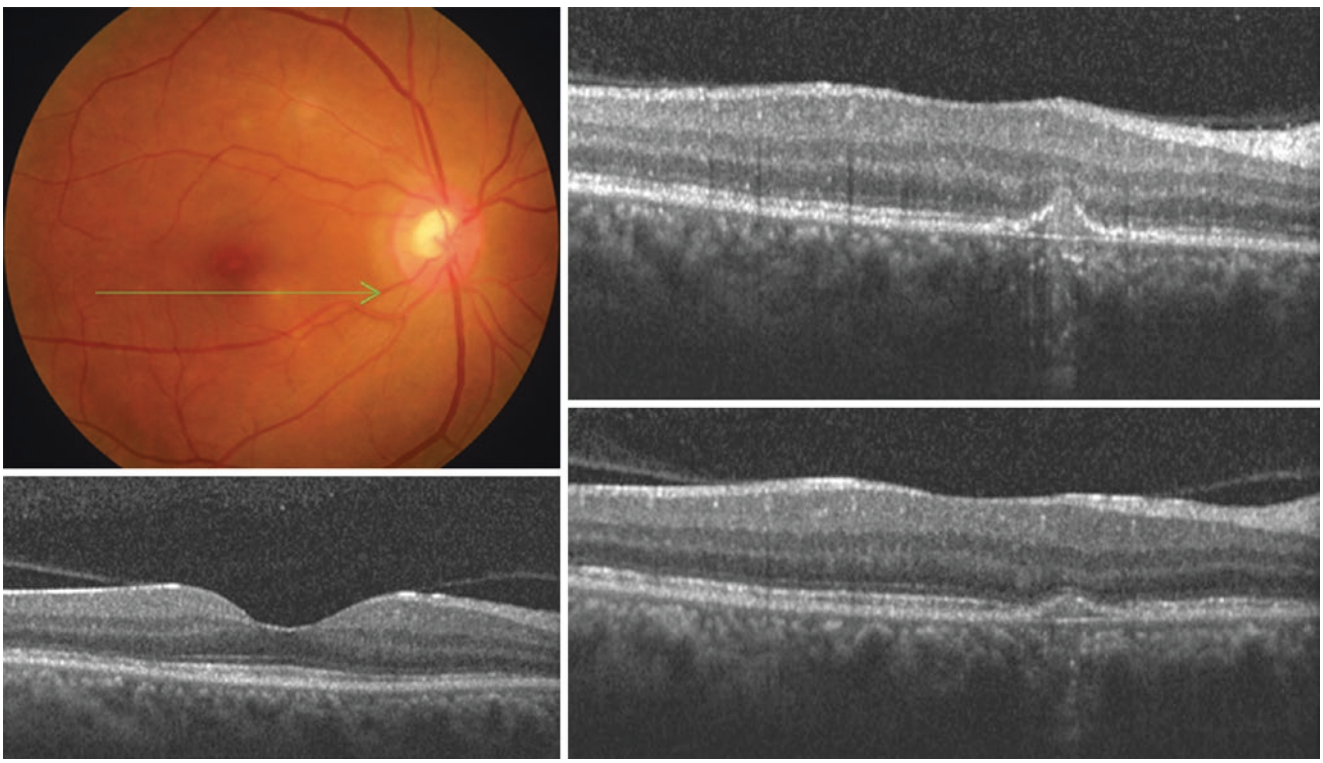

Fig. 4.10 On spectral-domain optical coherence tomography (OCT), the acute lesion initially appears as a "volcano eruption"-like subretinal infiltration (upper row), with remarkable resolution after oral steroid therapy (lower right). OCT image through the fovea also reveals the presence of inflammatory cells in the posterior vitreous (lower left)

several authors (Spaide et al. 2008; Yasuno et al. 2009). Drusen-like accumulation at the sub-RPE layer and inflammatory cells in the posterior vitreous can also be found in the acute lesions of MCP (Vance et al. 2011) (Fig. 4.9). The sub-RPE lesion may sometimes have a vertically elevated "volcano eruption-like" appearance on OCT, which can decrease in size in response to anti-inflammatory therapy (Fig. 4.10). OCT also allows visualization of inflammatory cells in the posterior vitreous. The choroidal pathologies were visualized by the development of high-penetration OCT. Localized thinning of the choroid, occlusion of the choroidal vessels, and localized hyper-reflectivity were noted in MCP lesions, accounting for hyper-pigmentation of the choroid (Yasuno et al. 2009) (Fig. 4.11). It can be difficult to distinguish the

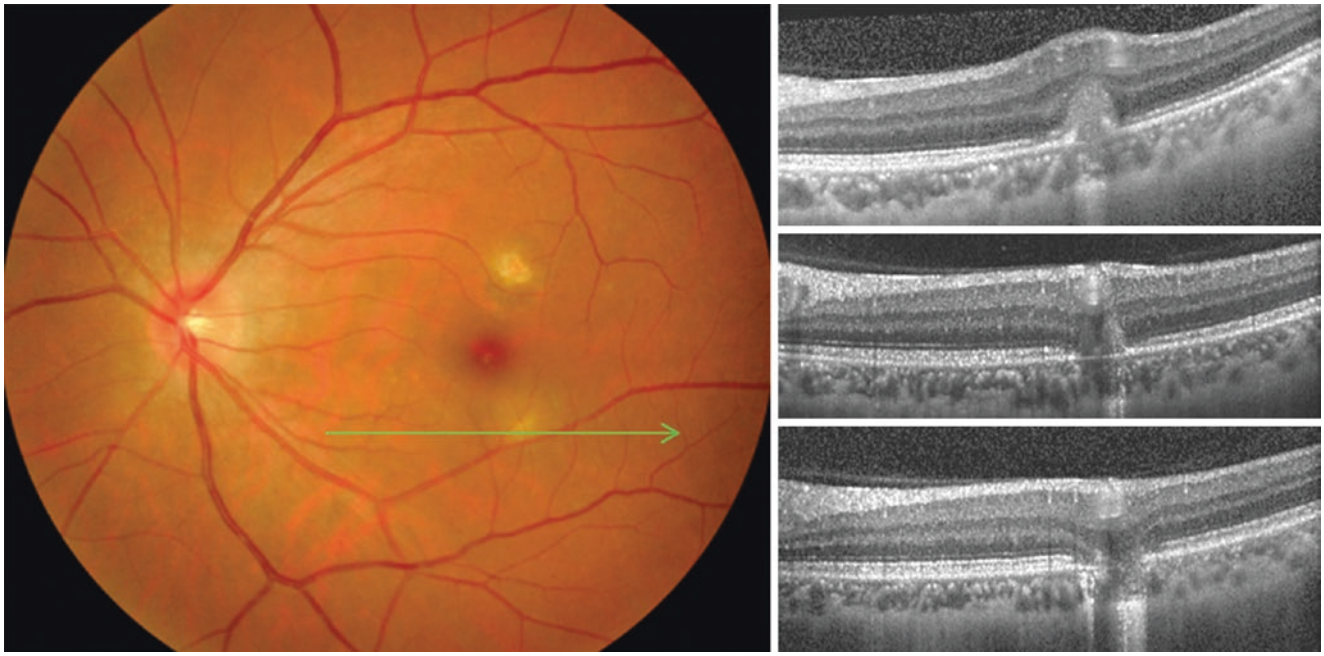

Fig. 4.11 Sequential spectral-domain optical coherence tomography of 1-year interval shows the chronic changes of a lesion. With the resolution of subretinal inflammatory material accumulation, the disruption of the outer retinal layer progresses (top and middle, right), and afterwards, localized atrophic changes to the choroid with an increase in hyper-reflectivity is observed (bottom, right)

acute lesions of chorioretinitis from inflammatory CNV based on clinical examination and FA. However, CNV demonstrates characteristic OCT features, such as a sub-RPE component infiltrating the outer retinal layer and associated fluid exudation, not so commonly seen with inflammatory lesions (Amer et al. 2015)

Optical Coherence Tomography Angiography

In addition to OCT, optical coherence tomography angiography (OCT-A) is a promising tool in detecting inflammatory CNV and in differentiating it from inflammatory lesions of MCP. OCT-A flow signatures consistent with neovascularization can be identified mixed in subretinal and sub-RPE layers (Zahid et al. 2017) (Fig. 4.12). Lesions with no definitive signs of FA leakage were frequently found to have neovascularization using OCT-A. OCT-A showed an increase in the hyporeflective ring around the CNV and in the hyper-reflectivity of the CNV vessels themselves after anti-vascular endothelial growth factor (VEGF) therapy (Levison et al. 2017).

Management

Steroids and Immunomodulatory Therapy

The use of systemic or periocular corticosteroids can be effective in controlling intraocular inflammation in patients with MCP. An improvement of visual acuity in MCP eyes had been reported previously (Dreyer and Gass 1984; Morgan and Schatz 1986), and it was more significant in those associated with CME (Cantrill and Folk 1986; Nussenblatt et al. 1996). However, there have been serial reports that the therapeutic effect of corticosteroids in MCP is temporary and limited in the acute phase (Nolle et al. 1998). In those studies, most patients with MCP eventually had visual deterioration due to CNV development during corticosteroid therapy (Cantrill and Folk 1986; Brown et al. 1996).

Since MCP is chronic and recurrent in nature, long-term immunomodulatory therapy may be a more effective alternative treatment modality in MCP. The immunomodulatory agents for MCP include immunosuppressive agents such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, chlorambucil, tacrolimus, leflunomide, mycophenolate mofetil, infliximab, adalimumab, and etanercept. A retrospective case series report of 19 patients with MCP revealed that immunomodulatory therapy effectively controlled inflammation and preserved vision without any significant drug-related complications (Michel et al. 2002). In a retrospective cohort study of 122 MCP eyes, immunomodulatory therapy significantly reduced the risk of developing posterior pole complications such as CME, ERM, and CNV by 83% (Thorne et al. 2006). In a paper outlining immunosuppressive treatment guidelines for ocular inflammatory disease suggested by 12 uveitis specialists, MCP was cited as an entity that frequently requires immunomodulatory therapy at some point in its disease course (Jabs et al. 2000).

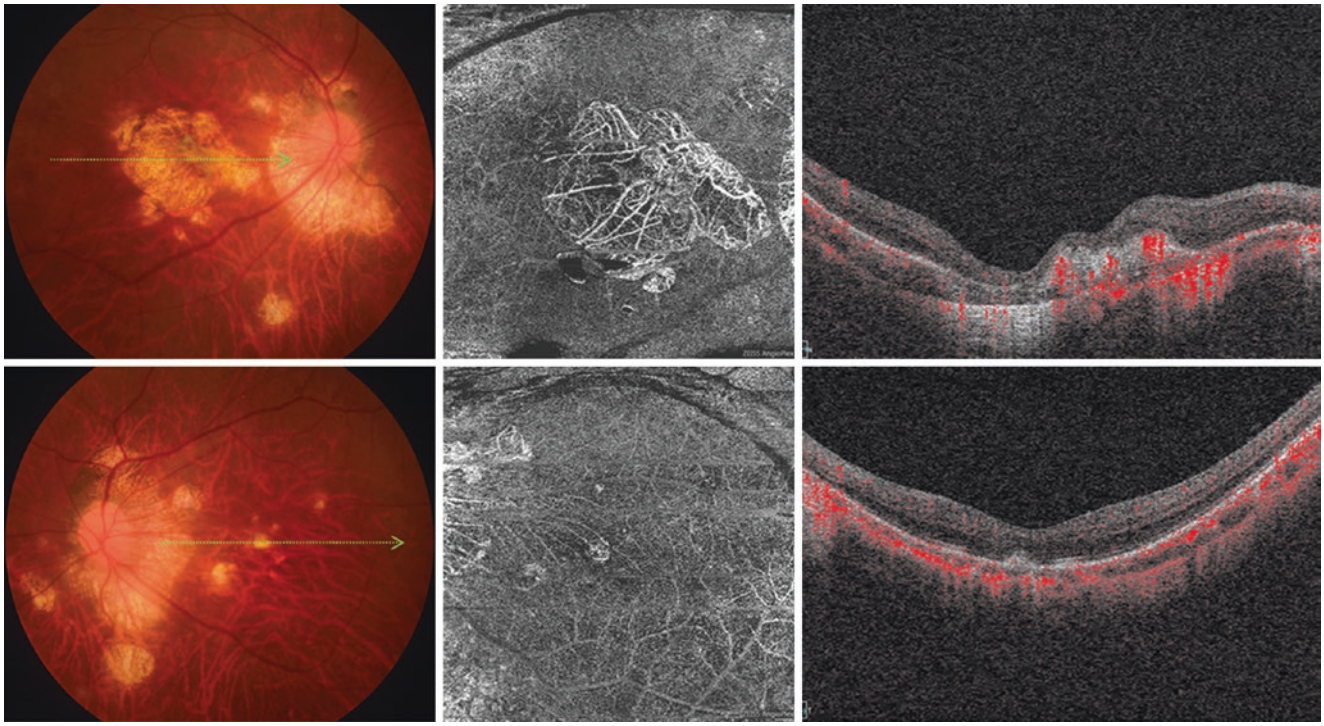

Fig. 4.12 Color fundus photograph demonstrates a large patchy chorioretinal atrophy at macula with subretinal grayish membrane involving the fovea and peripapillary atrophy (upper left). Optical coherence tomography angiography (OCT-A) through this lesion reveals the presence of choroidal neovascularization (CNV) with an area of active vascular flow in the subretinal hyperreflective material (upper right). In an eye with active multifocal choroiditis and panuveitis without CNV (lower left), no blood flow signal was detected on the OCT-A image of the active inflammatory chorioretinal lesion (lower right)

Treatment of Choroidal Neovascularization

Choroidal neovascularization is the most common posterior pole complication of MCP (Dreyer and Gass 1984; Morgan and Schatz 1986; Brown et al. 1996), accounting for the major cause of vision impairment, up to 45% of vision loss to worse than 20/200 (Thorne et al. 2006). The treatment modalities in the management of CNV due to MCP are very similar to the methods used for exudative age-related macular disease treatment. Several investigators reported that sustained visual improvement was achieved by intravitreal injections of anti-VEGF agents in CNV associated with MCP (Fine et al. 2009; Chang et al. 2008). In those retrospective studies, the mean number of intravitreal injections was 1.6 and 3.4 per year. Photodynamic therapy has also proven effective in preserving visual acuity in CNV due to MCP (Parodi et al. 2004; Brown et al. 2009).

The efficacy and safety of laser photocoagulation for the treatment of CNV secondary to MCP have not been extensively studied. In four cases, extrafoveal and juxtafoveal CNVs arising due to MCP were significantly regressed with sparing of central vision (Brown et al. 1996), but subfoveal CNV lesions should not be treated with laser. Intravitreal methotrexate for the treatment of CNV in MCP was reported in one case report as being effective for preserving vision and preventing flare for over 20 months of treatment (Mateo-Montoya et al. 2013).

Submacular surgery for CNV associated with MCP was widely studied before the development of antiangiogenic drugs; however, because of the high incidence of adverse events in the perioperative period and the lack of significant visual benefit to the patients, its role was extremely limited in the treatment of CNV complicating MCP (Hawkins et al. 2004; Giansanti et al. 2009).

Pars Plana Vitrectomy

There has been no randomized controlled study on the efficacy of pars plana vitrectomy in the treatment of general or MCP-related uveitis. In a case series of nine patients having medically refractory MCP, pars plana vitrectomy did not result in any meaningful therapeutic effect (Nolle and Eckardt 1993).

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