PERSISTENT PLACOID MACULOPATHY: A NEW CLINICAL ENTITY

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ABSTRACT

Purpose: To describe a previously unreported clinical entity superficially resembling macular serpiginous choroiditis but with a distinct presentation and clinical course.

Methods: A retrospective review of the medical records of five patients, aged 50 to 68 years, exhibiting this entity seen at five different centers from 1999 to 2006.

Results: The lesions in the patients in this study are in some respects similar to those of acute macular serpiginous choroiditis. The patients had well-delineated whitish plaque-like lesions involving the macula and sparing the peripapillary areas of both eyes. In contrast to serpiginous choroiditis, visual acuity remained good despite early involvement of the fovea until complications related to choroidal neovascularization (CNV) or pigmentary mottling developed. The angiographic characteristics and the clinical course were also atypical. Fluorescein angiography revealed well-defined early hypofluorescent areas, which partially filled-in in the late phase. Indocyanine green angiography showed the hypofluorescence to be persistent. Unlike serpiginous choroiditis, the white macular lesions faded over a period of months to years, but the characteristic angiographic findings often persisted longer. CNV developed in nine of 10 eyes with subsequent conversion to disciform macular scars in seven of 10 eyes. Unlike serpiginous choroiditis, none of the eyes showed chorioretinal scar formation unless related to CNV.

Conclusion: Persistent placoid maculopathy has features resembling macular serpiginous choroiditis but differs in its clinical course and effect on visual acuity. It appears to be a new entity. The majority of eyes develop CNV, which results in loss of central vision.

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INTRODUCTION

Serpiginous choroiditis is a chronic relapsing, usually bilateral inflammation of the retinal pigment epithelium (RPE) and choriocapillaris with secondary involvement of the retina.[1-8] Typically, patients initially complain of unilateral decreased vision, metamorphopsia, or scotoma, as the inflammation is usually active in one eye at a time. Eyes may present with peripapillary or macular lesions.[6,8] Approximately 80% of cases reported are of the peripapillary geographical type, and approximately 6% are of the macular type with no peripapillary involvement.[6,9]

The location of the lesions in serpiginous choroiditis is critical in determining visual outcome. As such, macular serpiginous choroiditis often results in profound visual loss and has a poor visual prognosis on account of early foveal involvement with chorioretinal scarring and choroidal neovascular complications.[8,10,11] In most cases, active inflammation resolves in 6 to 8 weeks with scarring and only partial recovery of vision.[6] Recurrence of inflammation in new areas is almost universal. Choroidal neovascularization (CNV) occurs in up to 25% of cases of serpiginous choroiditis and may be seen at the time of active choroiditis or between episodes.[12]

In this study, five patients with a macular disorder superficially resembling macular serpiginous choroiditis, but with a distinct clinical appearance and course, are described. These lesions show early involvement of the macula with minimally affected visual acuity until the development of neovascular complications. The authors believe this to be a previously undescribed clinical entity.

METHODS

Institutional review board approval and authorization to waive informed consent were obtained prior to reviewing each patient record. The five patients described in this study were examined and followed from February 1999 to January 2006 (Table 1). They were noted to have clinical features that challenge conventional diagnoses. Clinical follow-up ranged from 13 to 76 months (mean, 33 months). This study is a retrospective review of the medical and photographic records of this cohort.

CASE REPORTS

Case 1

A 56-year-old white man with a history of liver transplant secondary to idiopathic cirrhosis and amblyopia in the right eye complained of decreased vision in the left eye in November 2004. The patient had a history of cardiac disease, for which he had cardiac stent placement in 1994. Best-corrected visual acuity was 20/70 in the right eye (OD) and 20/60 in the left eye (OS). No anterior chamber

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TABLE 1. CLINICAL FEATURES OF PERSISTENT PLACOID MACULOPATHY

CASE NO./SEX/AGE	RACE	EYE	TOTAL FOLLOW-UP (MO)	INITIAL VA	DURATION OF FOLLOW-UP BEFORE CNV (MO)	ADDITIONAL CLINICAL FEATURES/ COMPLICATIONS	WORST VA	FINAL VA	DATE DARK CHOROID FIRST NOTED ON ANGIOGRAPHY	DATE DARK CHOROID LAST SEEN ON ANGIOGRAPHY
1/M/56	W	R -amb	13	20/70	CNV at presentation	CNV, disciform macular scar	20/400	20/400	11/2004	12/2005
		L	13	20/60	CNV at presentation	CNV, disciform macular scar	20/150	20/150	11/2004	12/2005
2/M/68	W	R	76	20/20	3	CNV, disciform macular scar	20/400	20/200	2/1999	2/2001
		L	76	CF	CNV at presentation	CNV, disciform macular scar	CF	20/400	2/1999	10/1999
3/F/50	W	R	26	20/25	26	Dormant CNV	20/40	20/30+	11/2003	1/2006
		L	26	20/25	26	Occult CNV	20/60	20/25	11/2003	1/2006
4/M/59	W	R	16	20/40	No CNV	RPE mottling	20/400	20/400	8/2001	12/2002
		L	16	20/50	CNV at presentation	CNV, disciform macular scar	CF	CF	8/2001	12/2002
5/M/53	W	R	34	20/25	< 12	CNV, disciform macular scar	20/400	20/80	5/2002	9/2003
		L	34	20/20	< 12	CNV, disciform macular scar	CF	20/400	5/2003	9/2003

Amb = amblyopia; CF = count fingers; CNV = choroidal neovascularization; RPE = retinal pigment epithelium; VA = visual acuity; W = white.

or vitreous inflammation was detected. Fundus examination showed white plaque-like lesions, in a jigsaw pattern, in the macula of both eyes (Figure 1). In the left eye, there was subretinal heme inferonasal and superotemporal to the center of the macula. Hypofluorescent plaques corresponding to the fundus lesions were noted early on fluorescein angiography (FA). In the right eye, a punctate area of hyperfluorescence that leaked on late frames was noted temporal to the macula. In the left eye, there were four areas of classic choroidal CNV. In the late views, multiple punctate spots of hyperfluorescence were noted in both eyes with resolution of the large hypofluorescent regions. Indocyanine green (ICG) angiography revealed hypofluorescent macular lesions corresponding to the white lesions seen clinically and focal spots of hyperfluorescence in late frames consistent with the CNV seen on FA. Large choroidal vessels were seen in the affected area on ICG angiography in both eyes. The patient was treated with laser photocoagulation to the CNV in the left eye.

Four weeks later, in December 2004, the patient's best-corrected visual acuity decreased to 20/70 OD and 20/150 OS. He was treated with laser photocoagulation of the CNV in the right eye. In addition, he was given a sub-Tenon injection of triamcinolone acetonide in the left eye. In April 2005, best-corrected visual acuity was 20/200 OD and 20/100 OS. The white macular lesions were fainter in both eyes (Figure 2). Multiple areas of subretinal heme were noted in the right macula with hyperfluorescence on FA, consistent with CNV, OD. A smaller area of hypofluorescence nasal to the disc was also noted on FA, OD. In the left eye, a subfoveal chorioretinal scar, approximately 4 disc diameters in area, developed with CNV on the superior border. The patient was subsequently treated with several applications of laser photocoagulation in both eyes as well as sub-Tenon injection of triamcinolone acetonide in the left eye followed by oral prednisone therapy (Figure 3). In December 2005, best-corrected visual acuity was 20/400 OD and 20/150 OS. The faint whitish lesions were still minimally apparent in both eyes. Large disciform scars occupied most of the macula in each eye. The area of the white lesions not involved by scarring remained hypofluorescent on FA, OU.

Case 2

A 68-year-old white man complained of gradual decrease in vision in his left eye in January 1999. The patient had a history of colon carcinoma, thrombocytopenia, and type 2 diabetes mellitus. Best-corrected visual acuity was 20/20 OD and finger counting OS. No anterior chamber or vitreous inflammation was detected. Fundus examination in each eye showed a central geographic zone of slight whitening at the level of the RPE involving the center of the macula with few smaller similar lesions superior and nasal to the discs (Figure 4). In the left eye, the lesion was fainter with minimal pigmentary changes, and subretinal heme was noted in the center of the macula. Fluorescein angiography showed early hypofluorescence corresponding to the white lesions, which partially filled-in in the late phases. There was slight late staining. ICG angiography showed hypofluorescence of the lesions, which persisted in the late phases with patent fluorescence of the large choroidal vessels throughout. The FA and ICG angiography of the left eye also showed areas of choroidal neovascularization.

The patient was treated with oral prednisone and focal laser photocoagulation to areas of extrafoveal CNV in the left eye. Four months later, in May 1999, his visual acuity was 20/20 OD and 20/400 OS. There was some decrease in the amount of whitening but no change in the size of the macular lesions. In addition, a new subretinal hemorrhage consistent with a CNV was identified in the right macula. One year after the initial presentation, despite the development of multiple bilateral neovascular lesions, a faint remnant of the initial whitish plaque-like lesion was present in both maculas. Over the course of the following few years, significant central chorioretinal scarring developed in each macula as a result of the complications associated with CNV. Final visual acuity noted in May 2005 was 20/200 OD and 20/400 OS.

Case 3

A 50-year-old white woman presented in November 2003 with complaints of decreased vision and photopsia OU. Her past medical history included hypertension, hyperthyroidism, and myocardial infarction. Three months earlier, the patient had a normal ophthalmic examination. At the time of her visual complaints, best-corrected visual acuity was 20/25 in each eye. Fundus examination revealed well-delineated jigsaw-patterned whitish plaque-like macular lesions involving the foveae and not contiguous with the optic discs (Figure 5, A through D). Early FA and ICG angiography showed hypofluorescent plaques. Late views of FA revealed partial resolution of the hypofluorescent regions, whereas on ICG angiography the choroidal hypofluorescence was persistent throughout the study, which lasted approximately 30 minutes. Large choroidal vessels were visualized within the hypofluorescent region on ICG. One week following initial presentation, best-corrected visual acuity dropped to 20/40+2 OD and 20/60 OS. No change in the fundus appearance was noted, and oral prednisone therapy was started. In late January 2004, best-corrected visual acuity was 20/25 OD and 20/30 OS. Ocular coherence tomography (OCT) showed blunting of the foveal reflex, OD. A small central defect was noted on Humphrey visual field (HVF) perimetry of the right eye, which did not correlate with the lesion size. An electroretinogram was normal. In March 2004, there was no change in her clinical status except for an improvement in the previously noted central scotoma of the right eye on HVF.

The patient returned in April 2005, complaining of increasing photopsia and metamorphopsia. Best-corrected visual acuity was 20/25 OD and 20/50 OS. She was treated with sub-Tenon injection of triamcinolone acetonide in the left eye. One month later, her best-corrected visual acuity was 20/30 OD and 20/25 OS. There was some resolution of the whitening at the level of the RPE in the macular lesions OU, but a small area of subretinal hemorrhage developed in the right macula (Figure 5, E through H). The FA remained hypofluorescent in the macula with punctate areas of hyperfluorescence and gradual resolution of the hypofluorescence in the late phases in both eyes. Repeat ICG showed persistent hypofluorescence in the right eye throughout the angiogram and partial

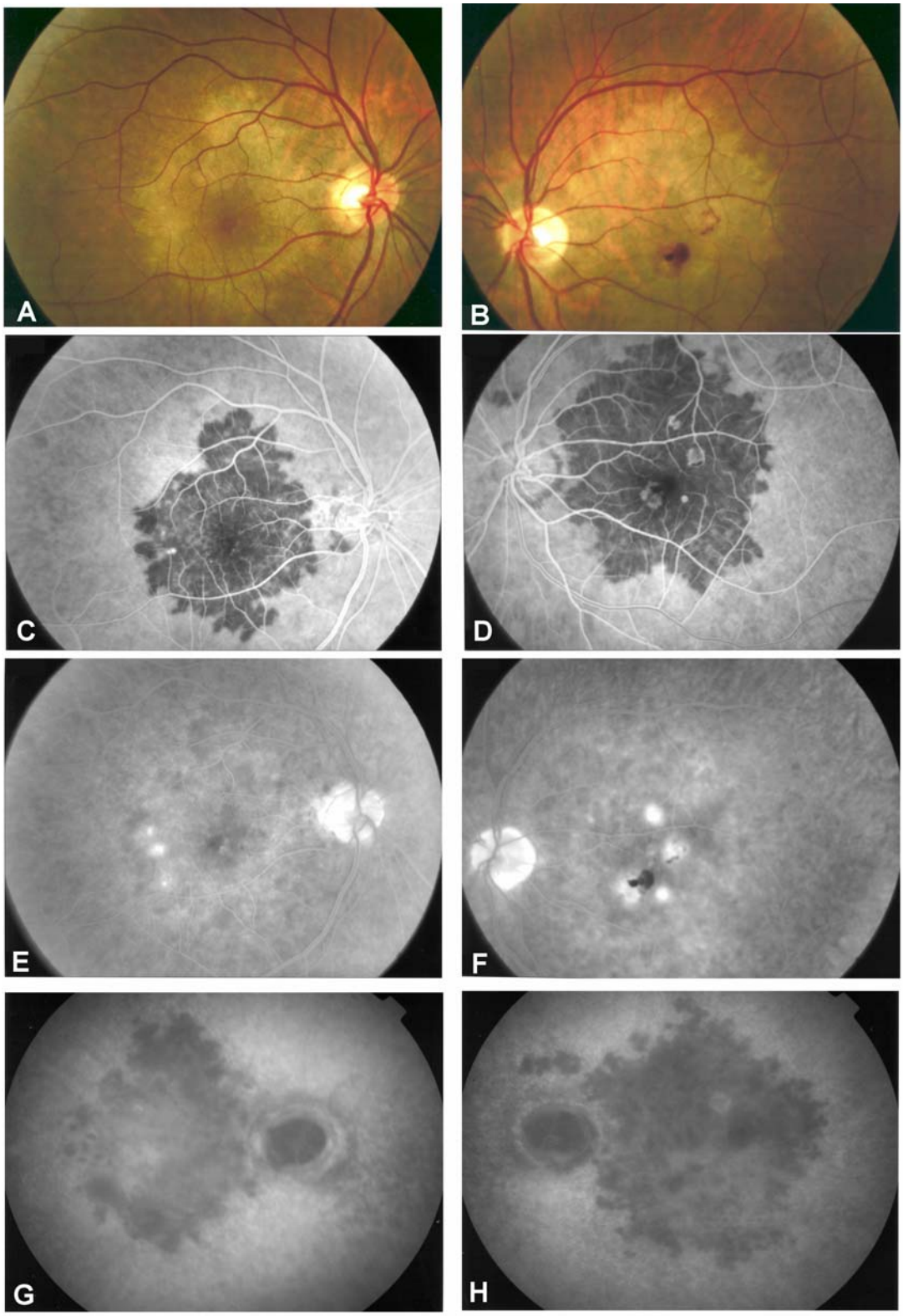

FIGURE 1

Case 1. Color fundus photographs of a patient with persistent placoid maculopathy showing whitish plaque-like lesions in the maculas OU (11/2004). A and B, Subretinal heme is present in the center of the macula OS. C and D, Early-phase fluorescein angiography (FA) showing hypofluorescent plaques and punctate areas of hyperfluorescence OU. E and F, Late-phase FA with multiple punctate spots of hyperfluorescence OU with resolution of the hypofluorescent regions OU. Early hyperfluorescent spots were associated with leakage and indicate choroidal neovascularization. G and H, Persistent hypofluorescence on indocyanine green angiography.

resolution in the late phase after approximately 20 minutes in the left eye. There was no definite evidence of CNV in either eye on FA or ICG angiography. The OCT was normal.

In January 2006, the patient's best-corrected visual acuity was 20/30+2 OD and 20/25 OS. The whitening in both macular lesions was minimally apparent. The FA remained hypofluorescent early on with punctate areas of hyperfluorescence and partial filling-in in the late phase as previously noted. However, in the area of the subretinal hemorrhage noted 5 months previously in the right macula, there was a prominent hyperfluorescent spot. This was not associated with significant leakage in the late phase of the study and may represent an area of CNV. An area of hyperfluorescence noted in the left eye superior to the fovea was associated with leakage representing occult CNV. The patient was treated with sub-Tenon injection of triamcinolone acetonide in the right eye.

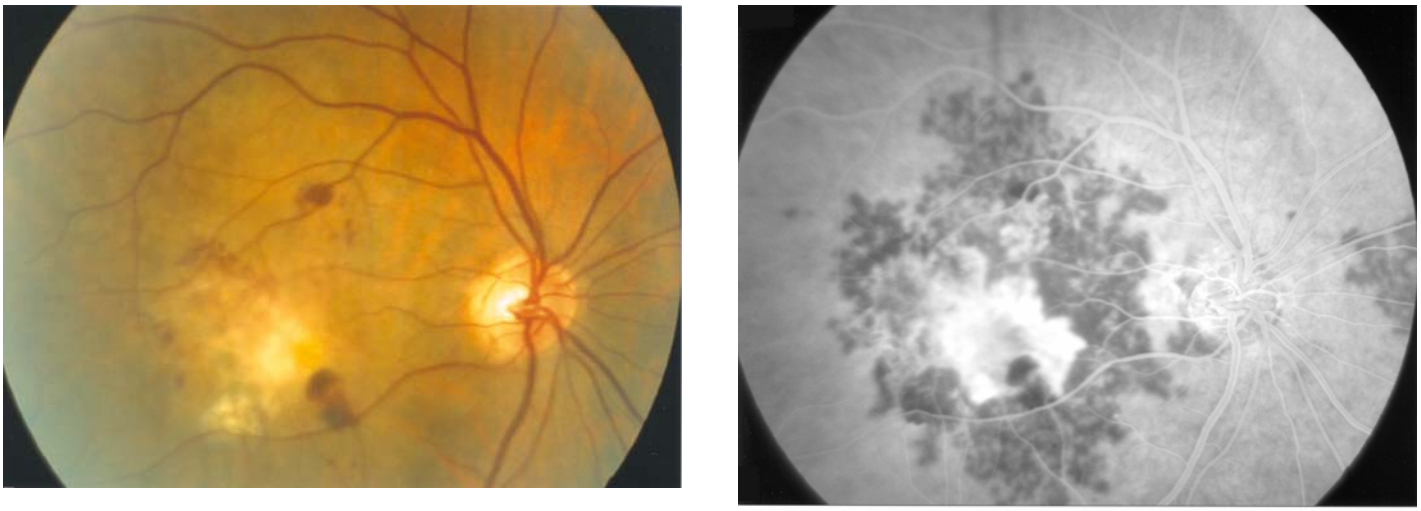

FIGURE 2

Case 1. Color fundus photographs taken 5 months after presentation (4/2005). Left, Persistent placoid macular lesions are complicated by central macular thickening and multiple areas of subretinal heme consistent with choroidal neovascularization (CNV), OD. Right, Early-phase fluorescein angiography showing areas of hyperfluorescence corresponding to leakage from CNV within the hypofluorescent plaque, OD.

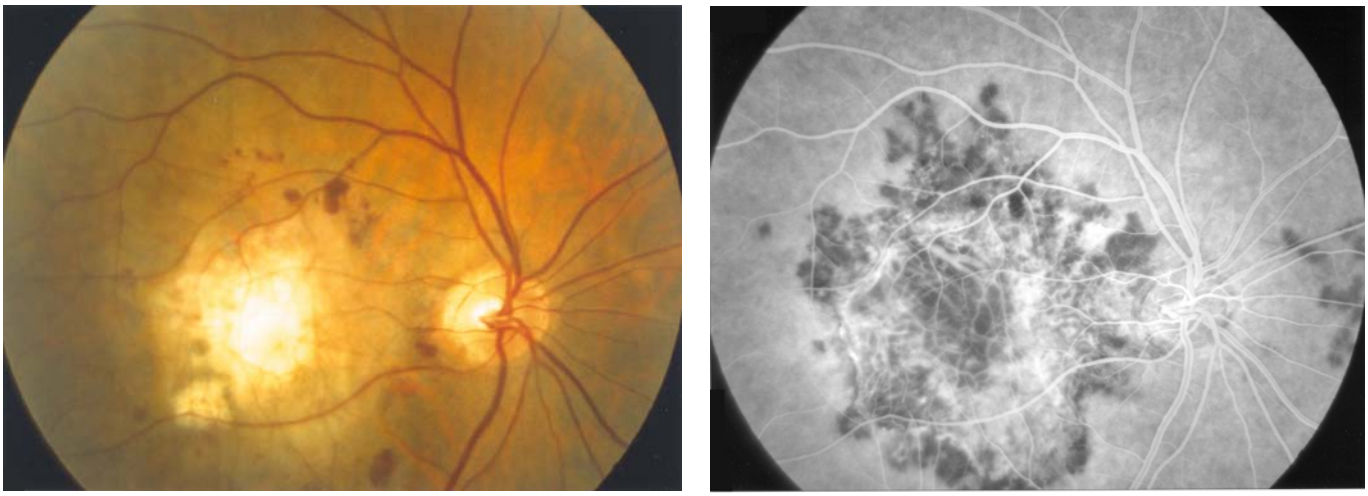

FIGURE 3

Case 1. Color fundus photographs of right eye taken 9 months after presentation (8/2005). Left, disciform scar associated with choroidal neovascularization in the center of the placoid lesion. The hypopigmented macular lesion appears more faint. Right, hypofluorescence on fluorescein angiography accentuates the area involved by the persistent placoid lesion, which becomes less obvious clinically over time.

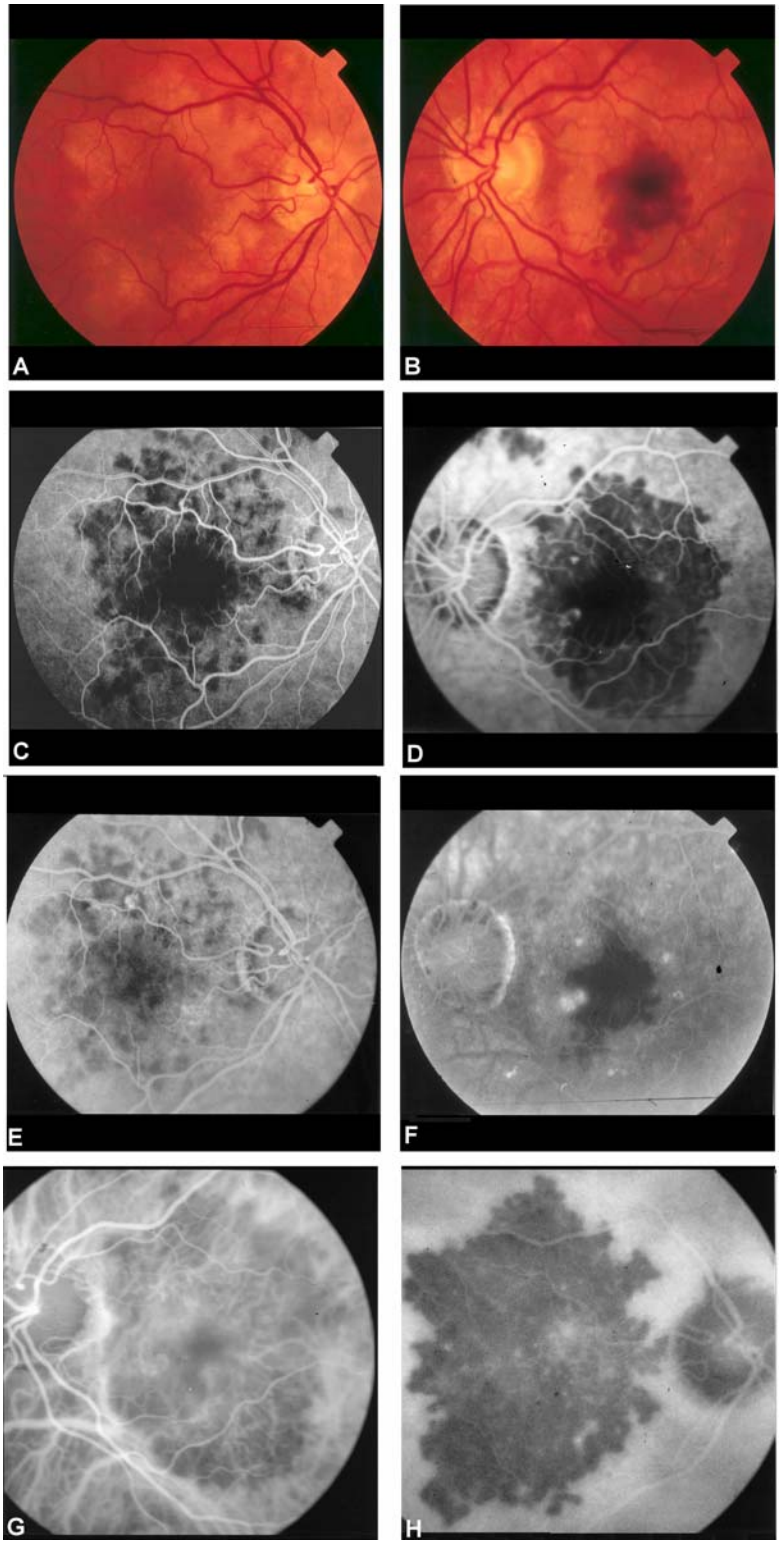

FIGURE 4

Case 2. Color fundus photographs of a patient with bilateral symmetric whitish macular lesions consistent with persistent placoid maculopathy (2/1999) (A and B). Subretinal heme secondary to choroidal neovascularization was noted OS upon initial presentation and accounted for the decrease in visual acuity in that eye. Visual acuity was 20/20 in the right eye. Early-phase fluorescein angiography of right (C) and left (D) eyes showing hypofluorescence, which partially fills-in in the late phase (E and F). G and H, The hypofluorescence on indocyanine green is persistent.

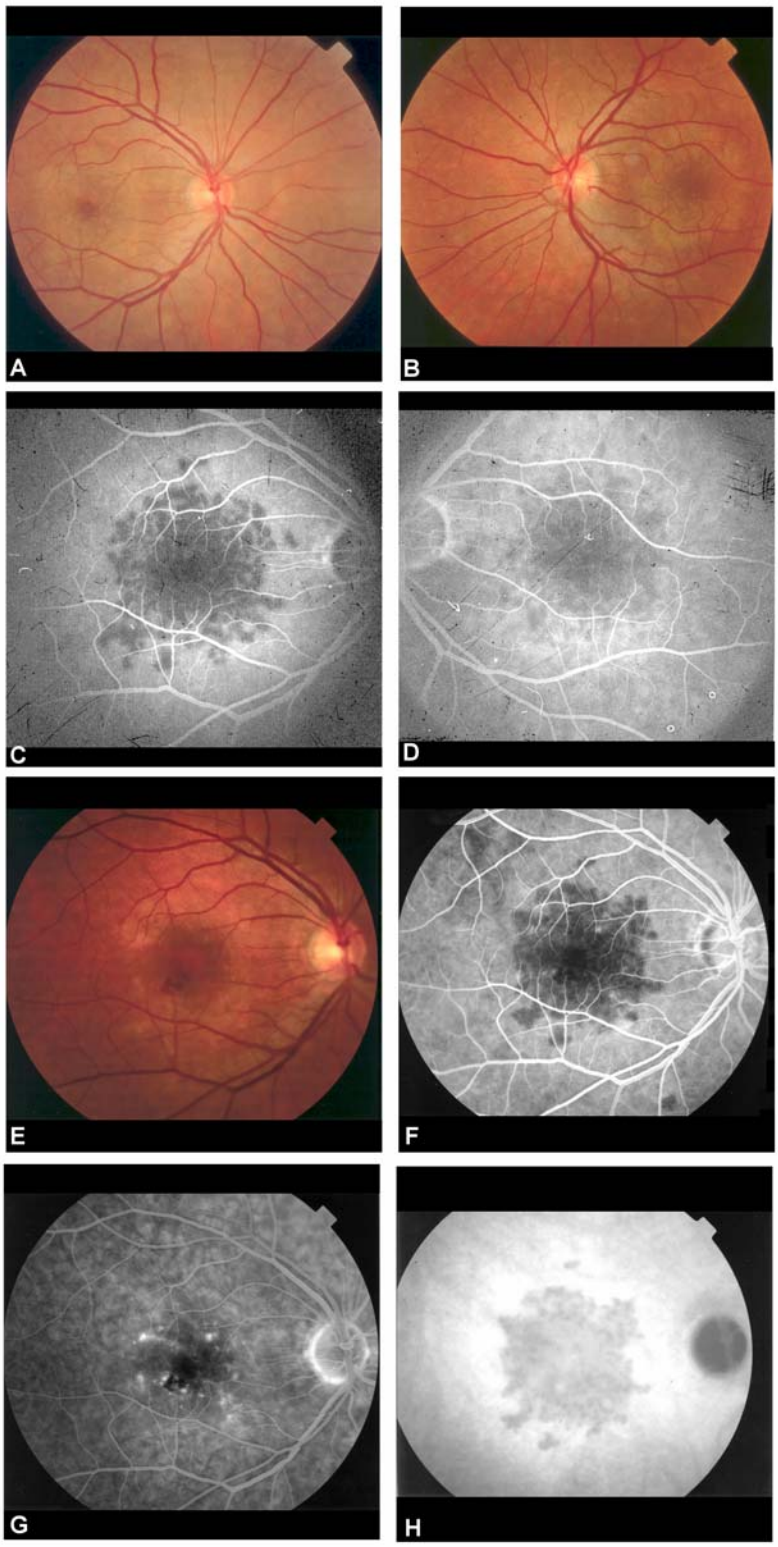

FIGURE 5

Case 3. Bilateral persistent placoid lesions involving the maculas (12/2003) (A and B). C and D, fluorescein angiography shows hypofluorescence early on with partial filling-in in the late phase. E, The persistent placoid lesion appears more faint 17 months after initial presentation (5/2005). A small area of subretinal hemorrhage is present in the right macula, OD. F and G, Initial hypofluorescence followed by punctate areas of hyperfluorescence and partial resolution in the late phase. H, Indocyanine green shows persistent hypofluorescence.

Case 4

A 59-year-old white man presented in August 2001 with complaints of decreased visual acuity and color vision OU. His past medical history included a transient ischemic attack of the brain in 1993 and cutaneous pemphigus in the past, with no signs of reactivation for more than 10 years. Five months earlier, he had a normal eye examination with best-corrected visual acuity of 20/20 OU. At the time of presentation, best-corrected visual acuity was 20/40 OD and 20/50 OS. There was no anterior chamber or vitreous inflammation. Fundus examination revealed whitish plaque-like lesions involving the macula OU. In addition, RPE mottling and hypopigmented spots were present in the center of the right macula. In the center of the lesion in the left macula, subretinal heme was noted. On FA, the main lesions were hypofluorescent, and these areas partially filled-in in the late phase. In addition, a juxtafoveal classic choroidal neovascular net was seen in the left eye. The patient was treated with photodynamic therapy in the left eye over the course of the following 2 months. During that time, the white macular lesions increased significantly in size OU. In October 2001, best-corrected visual acuity in the right eye decreased to 20/200 without any evidence of CNV on angiography. ICG angiography showed hypofluorescence of the lesions, which persisted in the late phases OU. He was treated with two sub-Tenon injections of triamcinolone acetonide in the right eye during the following few months. Significant RPE mottling in the right macula eventually resulted in best-corrected visual acuity of 20/400 in the right eye by December 2002. Best-corrected visual acuity in the left eye was finger counting secondary to complications from CNV. The placoid lesions appeared more faint 16 months after initial presentation. Similar hypofluorescent angiographic characteristics were present on FA and ICG angiography. This patient passed away in 2004 as a result of complications related to a cerebrovascular accident.

Case 5

A 53-year-old white man with diabetes without diabetic retinopathy complained of decreased vision in his right eye in May 2002. Visual acuity was 20/25 OD and 20/20 OS. There was no anterior chamber or vitreous inflammation. A whitish macular lesion involving the fovea was noted in the right eye. The macula on the left was normal on clinical examination. On FA, the lesion in the right eye was initially hypofluorescent with partial resolution noted in late frames. The FA of the left eye showed focal hypofluorescent spots superior to the macula, which also resolved in the late frames. HVF perimetry showed a small central depression in the right eye and was normal in the left eye. No treatment was given.

The patient was lost to follow-up until a year later, in May 2003, when he presented with complaints of significantly decreased vision OU and a central scotoma in the right eye. Best-corrected visual acuity was 20/400 OD and 20/100 OS. There was a well-demarcated whitish lesion in each macula as well as associated subretinal heme and fluid. The whitish lesion in the right macula appeared slightly faded compared with the previous examination. On FA, there was a focal spot of increasing hyperfluorescence in the macula within the region of hypofluorescence consistent with CNV in each eye. The patient was subsequently treated with photodynamic therapy OU. In June 2003, he continued to have leakage on FA and was treated with intravitreal triamcinolone acetonide in the right eye. ICG at that time revealed hypofluorescent macular lesions OU and a focal spot of increasing hyperfluorescence in the left fovea consistent with CNV. Over the course of the next year, the complications associated with CNV resulted in disciform macular scarring OU. Still, the macular areas initially involved by the disease but not affected by the neovascular complications remained faintly white on clinical examination and hypofluorescent on FA and ICG. Final visual acuity was 20/80 OD and 20/400 OS.

RESULTS

Table 1 summarizes the demographic data of the patients, four men and one woman, aged 50 to 68 years. There were no consistent systemic medical problems. All patients had bilateral symmetric macular involvement consisting of a whitish plaque-like lesion at the level of the RPE centered around the fovea and not contiguous with the optic disc. Over the course of follow-up, there was gradual fading of the whitish lesions in all patients. The size of the lesions was noted to increase in only one patient (case 4). One patient had smaller lesions nasal and superior to the discs at the time of initial presentation, and another patient developed a small nasal lesion in one eye over the course of follow-up. There were no recurrences.

Best-corrected visual acuity was 20/40 or better at onset in each eye, with the exception of the three eyes that presented with foveal CNV (case 1 OS, case 2 OS, and case 4 OS) and one eye that was amblyopic (case 1 OD). Visual acuity remained good in all eyes unless complications developed. The largest decrease in visual acuity in eyes with no CNV was a decrease of 4 Snellen lines to 20/60. Treatment with corticosteroids was associated with final best-corrected visual acuity of 20/25 in that eye. RPE mottling and pigment clumping were noted in only one eye (case 4 OD). In all other eyes, there was virtually no increase in pigmentation, atrophy, or scar formation during the follow-up period unless CNV developed. Significant RPE damage in that one eye resulted in a final best-corrected visual acuity of 20/400. Of the eight eyes with marked decrease in final visual acuity, only one eye had nonneovascular macular changes. The remaining seven eyes developed CNV and subsequent disciform scar formation. In addition, new-onset CNV has recently been noted in both eyes of case 3, and this patient is being closely followed. As such, nine of 10 eyes have shown evidence of CNV with the time to onset varying between 0 and 26 months.

Fluorescein angiography demonstrated early hypofluorescence followed by partial filling-in in the late phases of the angiogram. There was not marked leakage or staining. ICG angiography revealed persistent hypofluorescence throughout the angiogram. The large choroidal vessels in the affected areas were uniformly seen on ICG. In case 3, there was evidence of partial resolution of the late-phase hypofluorescence on ICG in the left eye noted after 18 months of follow-up. This was not previously seen in this patient or at any point in the other patients without CNV complications. Over the course of follow-up, the affected areas remained hypofluorescent on angiography despite fading of the whitish plaques and less obvious appearance of lesions on clinical examination.

None of the patients developed anterior chamber inflammation or any evidence of vitritis. A mildly blunted foveal reflex noted on OCT was observed in an eye that also showed a small central scotoma on HVF perimetry (case 3 OD). These findings resolved over time with an improvement in visual acuity associated with oral prednisone therapy. One patient had an electroretinogram, which was normal.

DISCUSSION

This report characterizes an entity superficially similar to macular serpiginous choroiditis, but with substantial differences in clinical appearance and course (Table 2). Serpiginous choroiditis is a progressive disease with multiple recurrences accompanied by chorioretinal atrophy, fibrous metaplasia of the RPE, and the development of CNV.[12] Foveal involvement in macular serpiginous choroiditis results in profound visual loss during the initial inflammatory phase and usually does not significantly improve as the disease progresses to chorioretinal scarring. The five patients described here were white and middle-aged and had bilateral disease. The well-circumscribed whitish plaque-like lesions were centered around the foveas, had a jigsaw pattern, and spared the peripapillary region, similar to acute lesions earlier described in cases of macular serpiginous choroiditis.[10] Visual acuity, however, was normal or mildly abnormal despite having almost the entire macula involved with a white lesion for months to years, until complications related to CNV or RPE mottling developed. RPE mottling resulting in significant loss of vision occurred in only one eye (case 4 OD). Neovascularization was more common in these patients (nine of 10) than in patients with serpiginous choroiditis (25%).[12] Three patients presented with CNV already present in at least one eye (cases 1, 2, and 4), as has occasionally been seen in cases of serpiginous choroiditis.[13]

TABLE 2. PERSISTENT PLACOID MACULOPATHY COMPARED TO MACULAR SERPIGINOUS CHOROIDITIS

VARIABLE	PERSISTENT PLACOID MACULOPATHY	MACULAR SERPIGINOUS CHOROIDITIS[4,6-8,10,12,21]
Lesion characteristics	Long-standing geographic central whitish plaques involving the fovea	Variable sizes and shapes, heal to scars and atrophy in weeks
Visual acuity	Normal to mildly affected (20/20 to 20/60) with good prognosis for recovery unless complicated by CNV	Rapid decrease in central vision to finger counting with poor prognosis for recovery
Gender	Only 5 patients	Male = female
Laterality	Bilateral, symmetric (5 of 5 patients)	Eventually all bilateral, usually asymmetric
Fluorescein angiography characteristics	Early hypofluorescence followed by partial filling-in in the late phase	Early hypofluorescence of the central portion of the lesion surrounded by progressive hyperfluorescence at the margins with eventual late staining
ICG characteristics	Persistent hypofluorescence throughout the angiogram	Early hypofluorescence with some resolution in the late phase; no staining of lesion borders
Complications	CNV in 9 of 10 eyes with 7 resulting in disciform macular scars so far. RPE mottling in 1 of 10 eyes.	CNV and disciform macular scars in up to 25%; RPE mottling and subretinal scar formation common. RPE detachments, vein and artery occlusions described
Clinical course	Persistent lesions with mild decrease in VA unless complicated by CNV or RPE damage	Multiple discrete recurrences usually adjacent to old lesions, variably spaced over many years

CNV = choroidal neovascularization; ICG = indocyanine green; RPE = retinal pigment epithelium; VA = visual acuity.

In addition to serpiginous choroiditis, differential diagnosis in these patients includes relentless placoid chorioretinitis (RPC),[14] acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and syphilitic posterior placoid chorioretinitis.[15] Patients with RPC demonstrate a prolonged clinical course, similar to the patients in this study, but have multiple lesions with prolonged activity, lesion growth, and the appearance of multiple new lesions.[14] In APMPPE, cream-colored lesions in the posterior pole result in mild decrease in visual acuity, as seen in this study. Similarly, atrophy and subretinal scarring are uncommon in APMPPE.[12,16-19] CNV, however, while common in the patients in this study, only rarely occurs in APMPPE. In acute syphilitic posterior placoid chorioretinitis, large placoid lesions with faded centers appear at the level of the RPE in the macula and juxtapapillary areas. Although these lesions also show initial hypofluorescence on FA, they are followed by diffuse late staining. They can also be distinguished by their clinical behavior and early onset of symptoms, including redness, pain, and blurred vision.[15]

Although the etiology remains unknown, various causes for serpiginous choroiditis have been suggested. The presence of uveitis, vitritis, and retinal vasculitis, as observed in some cases, supports an inflammatory etiology.[2,3,20,21] Laatikainen and Erkkila[22] suggested an immune-mediated vasculitis inducing choriocapillaris occlusion in this disorder. In general, no known systemic disease has been found to be associated with serpiginous choroiditis.[2,4,6-8,20-22] In the five patients described in this study, there was no vasculitis or prodromal illness.

Serpiginous choroiditis and APMPPE share some angiographic characteristics with the patients in this study. Early hypofluorescence on FA has been demonstrated in all affected patients. However, in serpiginous choroiditis and APMPPE, as the FA proceeds, the borders of the lesions become hyperfluorescent, representing leakage from the surrounding choriocapillaris.[6-8,16] Also, areas of active inflammation eventually stain. In the patients in this study, on the other hand, in the late stages of FA, gradual filling-in of the hypofluorescence with no or slight staining and no hyperfluorescence of the lesion borders was observed.

The hypofluorescence observed on FA and ICG angiography in serpiginous choroiditis and APMPPE has generally been attributed to either impaired choroidal vasculature and nonperfusion of the choriocapillaris, or blockage of choroidal fluorescence by swollen RPE cells and inflammatory lesions.[2,6,7,10,23,24] Extensive choroidal nonperfusion would be expected to cause marked visual loss from significant RPE and outer retinal ischemia, leading to photoreceptor dysfunction and then atrophy. In our patients, however, only mild initial decrease in visual acuity was observed. Furthermore, OCT showed a normal layer of RPE with no evidence of any pathologic changes of the RPE. Combination of the two theories of hypoperfusion and masking, as well as other mechanisms yet undiscovered, may be responsible for the hypofluorescence observed on angiography in serpiginous choroiditis, APMPPE, RPC, and our patients.

The differences of the later-phase angiographic findings in our patients between FA and ICG are not clear. Howe and associates[23] proposed that gradual resolution of the hypofluorescence in the late phase on FA in APMPPE may result from damage to RPE cell membranes and uptake of free sodium fluorescein. This, however, may not occur in the late phase on ICG because ICG is protein-bound.

Corticosteroids were used to treat four of five patients at some point with subsequent improvement in visual acuity. However, CNV and disciform scarring eventually resulted in permanent loss of vision in seven eyes. The role of corticosteroids in the treatment of this disorder requires further investigation.

In summary, five patients with an unusual unique clinical presentation and cours are described. Bilateral symmetric white lesions were seen in the macula and showed gradual fading over several months to years during follow-up. Interestingly, there was only mild decrease in visual acuity despite foveal involvement. The lesions were hypofluorescent on FA and ICG angiography. The characteristic hypofluorescence partially resolved in the late phase on FA but remained unchanged on ICG angiography. CNV resulted in loss of central vision in the vast majority of eyes. In all but one eye, no marked increase in pigmentation or chorioretinal atrophy was observed. None of the cases showed new lesions or subretinal scar formation unless related to CNV. These features suggest that this disease is a distinct new clinical entity.

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PEER DISCUSSION

DR TRAVIS A. MEREDITH: Dr. Golchet and her colleagues describe an entity they call persistent placoid maculopathy and propose that it represents a new chorioretinal disease. To identify a new disease is a difficult task particularly when it involves separating the new entity from a relatively rare condition. Such is the case here, since the most closely associated diagnosis is serpiginous choroidopathy.

Some features which can be used to separate a new condition from an established entity include demographics of the affected patients, symptoms and physical findings, the results of testing such as fluorescein angiography, treatment and treatment response, and ultimate prognosis. The most vexing issue is whether one is lumping or splitting when features of rare entities are compared. Confounding the issue is the potential bias of ascertainment due to the type of patients the authors see. Several authors on this paper are internationally known diagnosticians with a broad referral base. Thus they may be observing unique cases as a matter of referral and could be observing unusual traits of a rare but established entity. A further consideration is whether separating the new disease from a previous entity is actually clinically useful.

Serpiginous retinopathy was described by Gass[1] as an acute and chronic recurrent multifocal inflammatory disease. It affects young and middle-age patients and presents as an acute process with a gray white discoloration of the retinal pigment epithelium. Symptomatic patients usually present with macular involvement typically extending from a peripapillary lesion. The lesions have sharp borders and a jigsaw like, geographic configuration. Permanent dense scotomas develop in the areas of involvement and the lesions progress over weeks to months toward the periphery.

There are a number of contrasts between the description of persistent placoid maculopathy and serpiginous choroidopathy. The age of the placoid patients is somewhat older as the youngest of them was 50 years old. The placoid lesions are confined to the macula, although this is also been described in a small minority of serpiginous patients. Serpiginous patients present with early significant visual loss while placoid patients may have only an initial modest decline. On fluorescein angiography hypo-fluorescent areas fill in slowly in placoid patients while serpiginous patients develop a late marginal stain. Major differences are the visual outcome and the cause of visual loss. Serpiginous and placoid patients both develop macular pigmentary changes, but this is only associated with significant visual decline in the serpiginous patients. Initially placoid patients have good vision, but a large number of them develop choroidal neovascularization, unlike serpiginous patients who do not usually develop this complication. This latter finding may have therapeutic implications. While the treatments tried heretofore have not been successful in preserving central vision very often in the patients presented, combining control of inflammatory disease and suppression of vascular endothelial growth factor may have possible therapeutic benefit in these patients.

Taken as a whole it appears that this description does in fact meet the criteria of to be considered a new entity. The authors are to be congratulated for the careful and thorough description of persistent placoid maculopathy.

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DR DENNIS M. ROBERTSON: The second case that Dr. Golchet demonstrated is very reminiscent of what we have published about placoid lesions that are sometimes seen as sarcoidosis. You indicated that there were no consistent systemic diseases seen with this condition, but I wonder if sarcoid might have been one of them? The response to the steroids also suggests that that also might be true. Again this is one of those considerations that you must consider when you see lesions that look serpiginous since they can look very similar.

DR ALAN H. FRIEDMAN: Your case looks like some form of pigment epitheliopathy especially with the blocking of the fluorescence on fluorescein angiography. Why didn't you do an optical coherence tomography as is so commonly done these days? To me the clinical picture you presented does not look like geographic choroiditis. The haze at the advancing edge of lesions in geographic choroiditis and the fluorescein angiogram are very characteristic but unlike the persistent placoid maculopathy that you presented here.

DR MARK W. JOHNSON: As a result of the systemic workups that you performed, do you believe this is primarily ischemic or primarily inflammatory process?

DR JOSE S. PULIDO: There are at least two cases when there were non-macular lesions as well as macular lesions. I would like to know more about these non-macular lesions. How many had other lesions, besides the ones that could be seen by fluoroscein, that were non-macular?

DR PAUL E. TORNAMBE: I wonder why you did not compare this to AAMPE, for this appears to be a sort of aggressive form of AAMPE, rather than serpiginous. I had a patient who had a fundus picture similar to this, which I called AAMPE, who had temporal arteritis a few weeks earlier. It looks like this eye might have a posterior ciliary artery problem which affects the choroidal lobules. Was there any association with any systemic disease?

DR FREDERICK L. FERRIS: It seems that you have presented a disease that has the highest risk of sub-retinal neovascularization that I have ever seen, both across patients and even within eyes. Can you speculate as to what puts these eyes at such extraordinary risk, as this may help us understand why some people develop the neovasculization and others do not.

DR PAMELA R. GOLCHET: Dr Meredith mentioned lumping versus separating; we believe that persistent placoid maculopathy (PPM) and serpiginous choroiditis are very different and distinct entities, rather than PPM representing rare characteristics of an already established disease. I would like to mention that Dr. Gass evaluated case number two and he believed that this was not a case of macular serpiginous choroiditis.

With regard to therapeutic interventions, four of the five patients were treated with oral prednisone during the course of their follow-up and it seemed that almost all of them actually improved in visual acuity. However, some patients were not given steroids and they improved as well. Once they developed CNV, two patients were treated with laser photocoagulation, three patients were treated with photodynamic therapy, four patients were treated with Kenalog, of those three were subtenons and one was intravitreal. One patient had submacular surgery to remove the CNV membrane, and also pneumatic subretinal heme displacement. In the end they all had disciform scars. Oral prednisone seemed to help in the short run but not in the long run since these patients all ended up having the same results.

In this age of anti-VEGF therapy, we may have other options. We only have one patient to whom we can offer that therapy. Of the nine who developed CNV, there are only two eyes in one patient that may be eligible. This patient has just recently been diagnosed with CNV and does not have a disciform scar yet.

In regards to sarcoid, let me mention that our five patients were seen at five different clinical institutions and the medical history provided was sometimes limited to a statement such as "systemic workup" or "lab workup was negative." I personally contacted most of the primary ophthalmologists but sometimes the data were limited. As far as I know, the labs that were most often checked were FTA to rule out syphilis and PPD to rule out TB. I do think sarcoid was ruled out in at least some of them. Also, I would like to add that when you have an inflammatory disease or an infectious process, it does not typically look like the disease I have described. In those instances, one tends to get more vitritis and our patients did not have any. Also, the lesions tend to be more curvilinear or convex, as opposed to jigsaw-patterned as I have described in this disorder.[1-5]

There is one patient who did have an OCT and it was normal except that the foveal depression was a little bit blunted. The RPE was completely normal without any thickening and there was no evidence of sub-retinal or sub-RPE scar formation. In that particular patient, the OCT was repeated a few weeks later and the foveal depression appeared normal.

Is this an ischemic or inflammatory process? There are two possibilities. One is that the primary lesion is at the level of the choroidal vasculature and that the dark areas on FA are from non-perfusion or hypoperfusion of the choriocapillaris. The second theory is that the primary disease is in the RPE and the hypofluorescence results from masking of the underlying choroidal fluorescence.[1,2,6-9] The OCT was a little bit helpful in showing that the RPE was in fact normal and not edematous which could have caused masking of the fluorescence from the choriocapillaris. On the other hand, if the underlying disorder is hypoperfusion or non-perfusion of the choriocapillaris, you would expect to see more RPE changes and potentially photoreceptor atrophy. We have patients who have been followed for close to two years and they still have 20/25 vision. Therefore it is hard to believe that there is significant macular choroidal non-perfusion or ischemia.

Two patients had non-macular lesions. In one, the lesions were present at the time of initial presentation. In addition to the large

placoid lesion in the macula in that patient, there was one lesion superior to the disk and one nasal to the disk which did not change over time. In the other patient, there was a nasal lesion that developed during follow-up but then did not change further over time. The fluorescence pattern was the same as that of the central placoid lesions: hypofluorescence gradually filling-in in the late phase of the angiogram.

The pattern we describe does not look like APMPPE. In APMPPE, the patients are typically younger, have a viral prodrome, an d the lesions resolve within a number of weeks, often with some residual pigmentary changes.[10-14] Also, during the active phase, visual acuity is often mildly to moderately affected which later improves as the lesions resolve. Persistent placoid maculopathy on the other hand is persistent as the name implies; the lesions may last a couple of years without any change in appearance, visual acuity is minimally affected, and the fluorescence pattern is also different. In APMPPE, you do see an initial hypofluorescence but it does not have this pattern of gradually filling in over time. Instead, the hypofluorescence is followed by staining which is not seen in this entity.

With regard to the temporal arteritis query, in the literature there are suggestions of an immune-mediated vasculitis inducing choriocapillaris occlusion in some patients with serpiginous choroiditis.[15] This is supported by clinical evidence of phlebitis and lymphocytic infiltrates in the choroid and around vessel walls as seen on a histopathologic report of a patient with serpiginous choroiditis.[4,16] The etiology of persistent placoid maculopathy is really not clear and the fluorescence pattern noted in our patients could potentially be due to a vascular process. Certainly we know that the macular vasculature of the choriocapillaris is designed in a mosaic of lobules, and it is possible that the pre-capillary arterioles might be affected and this might explain the jigsaw patterned lesions observed in all eyes. Similarly, an inflammatory process rather than an immunologic one may lead to vascular occlusion. In both cases, however, there is often staining of such vessels on FA.

Why is there such high rate of choroidal neovascular membranes? Given we don't know the etiology of this disorder, it's difficult to speculate on the reasons for the high rate of complications. As such, I cannot answer that question.

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