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Idiopathic Acute Exudative Polymorphous Vitelliform Maculopathy

Clinical Spectrum and Multimodal Imaging Characteristics

Irene Barbazetto, MD,[1,2] Kunal K. Dansingani, MA, FRCOphth,[1,2] Rosa Dolz-Marco, MD, PhD,[1,2] Alfonso Giovannini, MD,[3] F.C. Piccolino, MD,[4] Anita Agarwal, MD,[5] Luiz H. Lima, MD,[6] Raul N. Vianna, MD, PhD,[7,8] Lawrence A. Yannuzzi, MD[1,2]

Purpose: To describe clinical findings in patients with acute exudative polymorphous vitelliform maculopathy (AEPVM).

Design: Retrospective, observational, multicenter case series review.

Participants: Consecutive patients diagnosed with idiopathic AEPVM.

Methods: Review of clinical charts, multimodal imaging, electrophysiologic findings, and genetic findings in previously unpublished patients and review of the literature.

Main Outcome Measures: Clinical features of idiopathic AEPVM and differential diagnosis.

Results: Eighteen patients (age range, 21–74 years) with typical features of AEPVM, including initial localized, serous detachments followed by the development of characteristic yellow-white deposits in the vitelliform space. Over time, this hyperautofluorescent material gravitated within the larger lesions, resulting in typical curvilinear deposits characteristic of later stages. Symptoms and clinical findings lasted from weeks to several years. Some patients showed previously undescribed features such as fluorescein-negative intraretinal cystic changes, choroidal neovascularization, serous retinal elevations mimicking retinal folds, increased choroidal thickness, lack of rapid visual recovery, and recurrence years after complete resolution of initial manifestations.

Conclusions: Acute exudative polymorphous vitelliform maculopathy can present with a more variable natural course than previously described. Paraneoplastic retinopathy and autosomal recessive bestrophinopathy closely resemble AEPVM, necessitating medical and hereditary evaluation to exclude these clinical possibilities. This series of patients with AEPVM expands the clinical spectrum of the disorder, including demographics, clinical manifestations, imaging features, natural course, and visual prognosis. *Ophthalmology 2018;125:75-88 © 2017 by the American Academy of Ophthalmology*

The first description of vitelliform changes in the macula has been attributed to Adams,[1] who published in 1883 a case report describing "peculiar macular changes." In 1905, Friedrich Best[2] described for the first time a similar condition segregating in a family and affecting 8 members. However, the term *vitelliform* (Latin *vitellum*, meaning egg yolk) was not introduced until the early 1950s by Zanen and Rausin[3] in their publication "Kyste vitelliforme congénital de la macula." Over the years, it has become apparent that vitelliform lesions are not exclusive to Best disease, but rather that a variety of other conditions can present with similar shallow, yellowish-appearing photoreceptor detachments in the posterior pole. These include familial disorders, dystrophies, vitreoretinal traction, retinal pigment epithelium (RPE)–choroid degenerations, and paraneoplastic syndromes (Table 1).

Acute exudative polymorphous vitelliform maculopathy (AEPVM) is a rare condition first described in 2 patients by Gass et al[4] in 1988. Only 15 additional idiopathic cases have been reported in the literature to date, but other cases associated with different tumors have been reported. The disorder is characterized by acute vision loss associated with multiple, yellow-white, morphologically variable lesions at the level of the RPE and serous macular detachments. In contrast to the macular detachments, numerous small bleb-like lesions, scattered along the arcades and encompassing the macula, may develop in a honeycomb pattern.[4] During the course of the disease, patients typically develop polymorphous subretinal yellowish deposits in the form of a meniscus simulating the appearance of vitelliform macular dystrophy. Patients experience gradual visual recovery over months to years, but electrophysiologic abnormalities may persist.[5] The findings on fluorescein angiography (FA), indocyanine green angiography (ICGA), OCT, and recently fundus autofluorescence (FAF) have been described in several case reports and small case series.[4–13] Although the clinical features of AEPVM are well described, there is little

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Table 1. Spectrum of Conditions Featuring Vitelliform Detachments

Best disease
Multifocal vitelliform dystrophy
Sjögren-Larsson syndrome
Pattern dystrophies/systemic diseases associated with pattern dystrophies
Adult-onset pigment epithelial dystrophy (pattern dystrophy group 1)
Kjellin syndrome
Myotonic dystrophy
McArdle's syndrome
Cuticular drusen
Reticular pseudodrusen
Drusenoid pigment epithelium detachment
Acute exudative polymorphous vitelliform maculopathy
Pseudoxanthoma elasticum
Vitreomacular traction syndrome
Macular telangiectasia type 2
Central serous choroidopathy
Paraneoplastic syndromes
Mitogen-activated protein kinase inhibitor toxicity

information available regarding its pathogenesis, natural course, or response to treatment. Although the disorder shows similarities with vitelliform macular dystrophy, no patient with AEPVM has been reported in a vitelliform pedigree or has shown positive results for mutations in *BEST1* or *peripherin/RDS*.

The purpose of this study was to examine the clinical presentation and course of AEPVM in 18 new patients and to compare these findings with those in previously reported cases. The aim of this meta-analysis was to gain a better understanding of the clinical heterogeneity of the disease and to help differentiate it from other phenotypes with single or multiple vitelliform lesions in the macula as well as masquerading disorders.

Methods

The study was conducted with approval of the Institutional Review Board of Columbia University (identifier, IRB-AAAD8689). Diagnosis of AEPVM was confirmed based on clinical and available imaging information. Clinical diagnostic criteria included the presence of bilateral and symmetric serous retinal detachments with evolving vitelliform material or the presence of bleb-like lesions along vascular arcades, as well as an absence of known genetic mutations or a family history and absence of known malignancy.

The literature was reviewed by way of a PubMed search using search terms including *acute exudative polymorphous vitelliform maculopathy*, *vitelliform maculopathy*, *best-like maculopathy*, and *pseudovitelliform maculopathy*. Paraneoplastic cases were excluded, and only idiopathic cases were included in the final analysis.

Eighteen previously unpublished patients with the diagnosis of AEPVM were included in this review from different settings: Vitreous Retina Macula Consultants of New York (New York, New York), the University of Ancona (Ancona, Italy), the University of Genova (Genova, Italy), and Vanderbilt Eye Institute (Nashville, Tennessee). Patients were selected from a group of 31 patients with multiple vitelliform detachments reminiscent of AEPVM at presentation. Ten patients were excluded from the study after additional workup: 6 patients had a known history of cancer or were diagnosed with a malignancy during workup and were excluded on the basis of possible paraneoplastic cause; 3 patients, all younger than 21 years, were found on genetic testing to have autosomal recessive bestrophinopathy; and 1 patient was excluded for showing positive results for a mutation in *BEST1*.

Patients underwent a complete ophthalmic examination, including determination of best-corrected visual acuity; slit-lamp and fundus assessment; color photography, and time-domain or spectral-domain OCT (Stratus or Cirrus OCT [Carl Zeiss Meditec, Inc., Dublin, CA] or Spectralis HRA-OCT [Heidelberg Engineering, Dossenheim, Germany]). In selected patients, FA, ICGA (TRC 50IX fundus camera; Topcon Medical Systems, Tokyo, Japan), and

Table 2. Summary of Acute Exudative Polymorphous Vitelliform Maculopathy Patients in

Patient No.	Age (yrs)	Gender	Race	Family History	Viral Prodrome	Headaches	Visual Symptoms	Visual Acuity		Curvilinear Deposits	Cysts on OCT	Serous Macular Detachment	Honeycomb
								Right Eye	*Left Eye*				
1	52	F	White	N	N	N	Y	20/40	20/40	Y	N	Y	N
2	35	F	White	N	N	N	Y	20/25	20/25	Y	N	N	N
3	34	F	White	N	N	N	Y	20/40	20/20	Y	N	N	N
4	36	M	White	N	Y	Y	Y	20/25	20/25	Y	N	Y	
5	54	F	White	N	N	N	Y	20/25	20/20	Y	N	Y	N
6	35	F	White	N	Y	Y	Y	20/20	20/40	Y	N	N	N
7	34	M	White	N	N	Y	Y	20/25	20/25	Y	Y	Y	N
8	26	M	White	N	N	N	Y	20/80	20/80	N	Y	Y	Y
9	29	M	Hispanic	N	N	N	Y	20/30	20/30	Y	Y	Normal	
10	32	M	White	N	N	N	Y	20/30	20/30	Y	Y	NA	
11	35	M	White	NA	NA	NA	Y	20/40	20/40	Y	Y		
12	74	F	Black	N	N	N	Y	20/50	20/100	Y	Y	Y	
13	36	M	White	N	N	N	N	20/20	20/20	N	N	Y	Y
14	21	M	White	N	Y	N	Y	20/20	20/20	Y	N	Y	N
15	72	F	White	N	NA	NA	Y	20/60	20/70				
16	42	M	White	N	N	Y	Y	20/40	20/30	Y	NA	NA	N
17	38	F	Native American	N	N	N	Y	20/60	20/80	Y	N	Y	N
18	32	M	White	N	Y	N	Y	20/70	20/50	Y	Y	Y	N

F = female: M = male; N = no; NA = not applicable; Y = yes.

electrophysiologic testing were also performed. Fundus autofluorescence imaging was carried out, where available, using either a modified fundus camera (Topcon USA, Paramus, NJ) with an excitation filter centered at 580 nm (bandwidth, 500−610 nm) and a barrier filter centered at 695 nm (bandwidth, 675−715 nm), as previously described, or the HRA II Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany).[14] Genetic screening for variants in the *BEST1* and *peripherin/RDS* genes was performed by direct sequencing in 4 patients.

Results

Demographics and Medical History

Images and clinical information of 18 patients (10 men and 8 women) diagnosed with AEPVM at a mean age of 39.9 years (range, 21−74 years) were reviewed for this retrospective, noncomparative case series. Fifteen patients were white, 1 was Hispanic, 1 was black, and 1 was Cherokee Indian. None of the patients included had a known family history of Best disease, pattern dystrophy, adult-onset macular dystrophy, or other forms of early-onset macular degeneration. Imaging available included color photography, FA, FAF, and OCT scans in the macular area in all cases; ICGA was available in 11 cases.

Most of the study participants were healthy with no previous medical history. Pre-existing conditions included celiac disease (1 patient); asthma (1 patient); HIV (2 patients); intra-atrial defect (1 patient); hepatitis C, anemia, osteoporosis, and rheumatoid arthritis (1 patient); and gender reassignment surgery with hormone replacement therapy (1 patient).

Clinical Findings

All patients in this series reported central visual symptoms at presentation. Although viral prodrome, headaches, or both were described in 7 of the 15 cases in the literature, these symptoms were reported by only 9 of the 18 patients in our study (for 2 of our patients, this information was unavailable because of our retrospective design). Three of the patients in this study were diagnosed in tertiary referral centers long after the onset of symptoms, and certain details of presenting or preceding symptoms may not have been elicited by the evaluating specialist (Table 2).

Based on 2 patients who allowed us to study the earliest changes in AEPVM, it is apparent that the first exudative manifestations in fact are serous in appearance. Ophthalmoscopy revealed the same sequence of events in each patient, beginning with the formation of multiple bilateral, well-defined serous retinal detachments, which vary in size. These lesions were elevated, bleb-like, and multiple (at least 5 per eye), with foveal involvement (Fig 1).

In addition to these serous retinal detachments, numerous small bleb-like lesions developed in a honeycomb distribution along the vascular arcades a few months after initial symptoms (Fig 2). This pattern, although part of the initial description by Gass et al[4] and Chan et al,[10] seems to be less common than initially described: this lesion type was observed in only 4 of our patients during the entirety of the follow-up.

Over time, yellow-white ("polymorphous") material is seen to accumulate within the serous detachments, giving a serous-yellowish appearance. The serous component in the detachments is the first to resolve during the recovery phase, leaving only the yellowish subretinal deposits. These deposits then persist for months to years. The time required for complete resolution of the yellow polymorphous material varies considerably depending on how much has accumulated. Patients who demonstrate predominantly serous detachments may recover fully in just a few months, whereas patients with large amounts of yellow-white material in the vitelliform space show the legacy of the disease for several years, even after improvement of clinical symptoms, visual acuity, and electrophysiologic findings. In some patients, hardened or solidified yellow exudates persist in a multifocal distribution throughout the posterior pole. They may be reabsorbed over many years but can leave residual changes in the RPE (Fig 3).

the Literature and in the Acute Exudative Polymorphous Vitelliform Maculopathy Study

Electro-oculography Results	Electroretinography Results	Genetics	Duration (mos)	Follow-up (mos)	Resolution of Detachment	Other Findings	Choroidal Neovascularization	Final Visual Acuity		Recurrence
								Right Eye	*Left Eye*	
Abnormal	NA	Normal	24	24	Y	Y	N	20/20	20/20	N
NA	NA	Normal	NA	NA	NA	NA	N	NA	NA	N
NA	NA	Normal	30	30	NA	N	Y	20/30	20/20	N
Normal	NA	NA	3 mos for detachment	3	Y		N	20/20	20/20	Y
NA	NA	NA	2 mos for detachment	5	Y		N	20/20	20/20	N
Normal	NA	NA	NA	6	NA	N	N	20/20	20/20	N
Abnormal	NA	NA	7 wks	1	N	N	N	20/20	20/20	N
NA	NA	NA		1 wk	N	N	N	20/40	20/40	N
NA	NA	NA			NA			NA	NA	
NA	NA	NA			NA	N		NA	NA	
									NA	
Normal	Normal	NA	10	10	Y		N	20/25	20/40	N
NA	NA	NA	15	15	Y	N	N	20/20	20/20	N
NA	NA	NA	3	8	Y	N	N	20/20	20/20	N
									NA	
NA	NA	NA	5 wks	1	N	N	N		NA	
NA	NA	NA	15	15	Y	N	N	20/100	20/100	N
Normal	Normal	Pending						NA	NA	

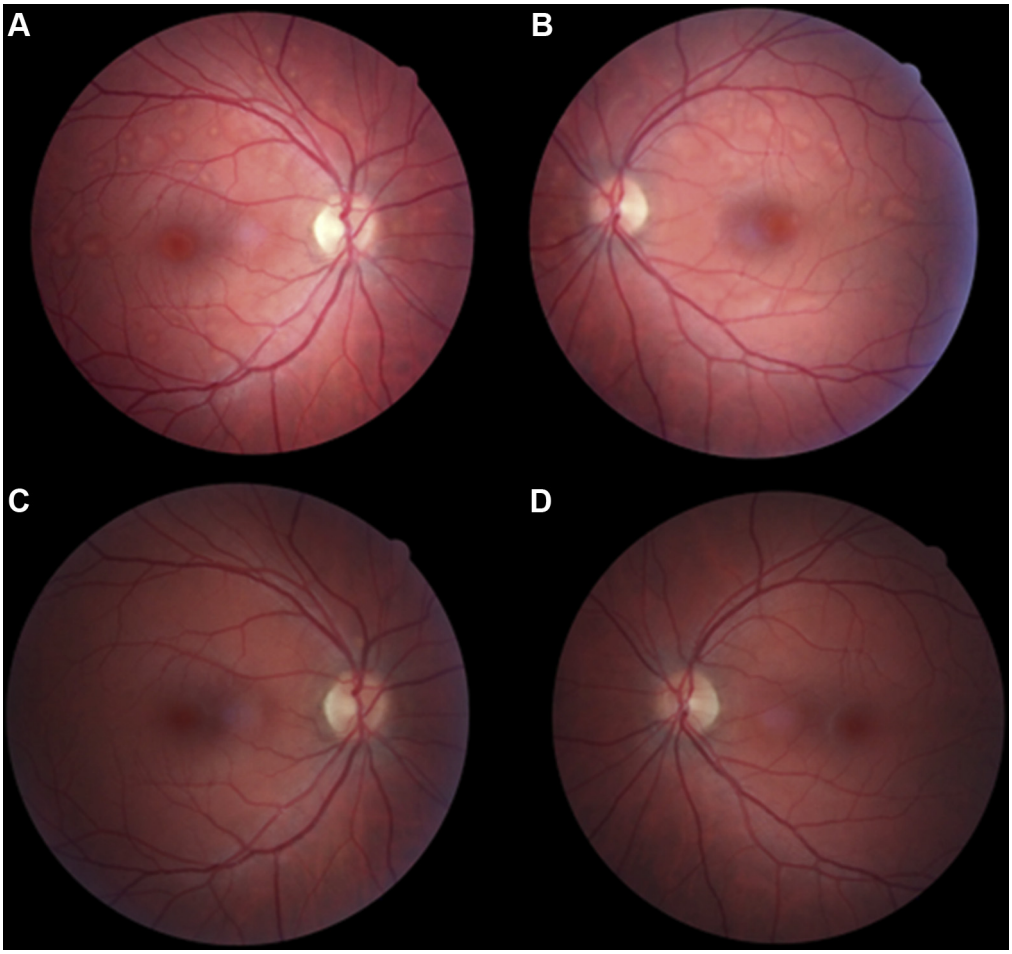

Figure 1. Color fundus photographs showing discreet multifocal yellowish subretinal material (**A**, **B**), that progressively fade away over the following months (**C**, **D**).

Acute exudative polymorphous vitelliform maculopathy is a bilateral and, in most cases, a rather symmetric disease at onset. However, asymmetry can be observed during the later stages, after the subretinal fluid has disappeared and the subretinal deposits start to reabsorb. Posterior vitreous cells, sometimes seen clinically or by spectral-domain OCT in inflammatory disease, were not seen in any of the patients with AEPVM in our series.

Genetic Evaluation

Four of the 18 patients were screened for variants in *BEST1* and 3 patients for mutations in *peripherin/RDS* by direct sequencing of the entire open reading frames and exon–intron boundaries of the 2 genes (R. Allikmets, Columbia University). No disease-associated variants were found in these patients. Three patients, initially evaluated as part of the study but subsequently excluded, were diagnosed with autosomal recessive bestrophinopathy after genetic testing revealed biallelic mutations in *BEST1*.[15] Interestingly, all 3 patients were children or teenagers, emphasizing the need for genetic testing in this age group.

Natural Course

In our retrospective series, follow-up examinations were available for 12 of the 18 patients. Follow-up time varied greatly, from 1 week to 30 months (mean, 11.1 months). The time from first presentation to reabsorption of the dome-shaped subfoveal serous detachments was between 2 and 5 months. Complete resolution of fluid was observed in 7 of 10 patients with dome-shaped subfoveal detachment. Resolution of curvilinear yellowish deposits could take significantly longer—even years—and complete resolution was not observed in most patients (12 of 15). These persistent deposits potentially could be attributed to lack of significant follow-up in most patients in our series. However, significant reduction in the amount and distribution of subretinal material was observed in almost all patients with time.

Visual acuity at the time of diagnosis ranged from 20/20 to 20/100 (mean, 20/40) and improved to or remained stable at 20/20 to 20/100 (mean, 20/30) during follow-up, with the exception of 1 patient. This patient demonstrated a visual acuity of 20/60 in the right eye and 20/80 in the left eye at presentation, and visual acuity deteriorated over the ensuing 15 months to 20/100 in both eyes despite improvement in retinal findings and resolution of submacular fluid. Contributing factors such as corneal or lens changes were not identified. Electrophysiologic testing was not available for this patient. Two additional patients with visual acuity of approximately 20/100 did not show significant improvement over at least 3 years; however, they did not deteriorate further.

Imaging

Fluorescein Angiography. Fluorescein angiography typically is far less impressive than the clinical presentation. The amorphous

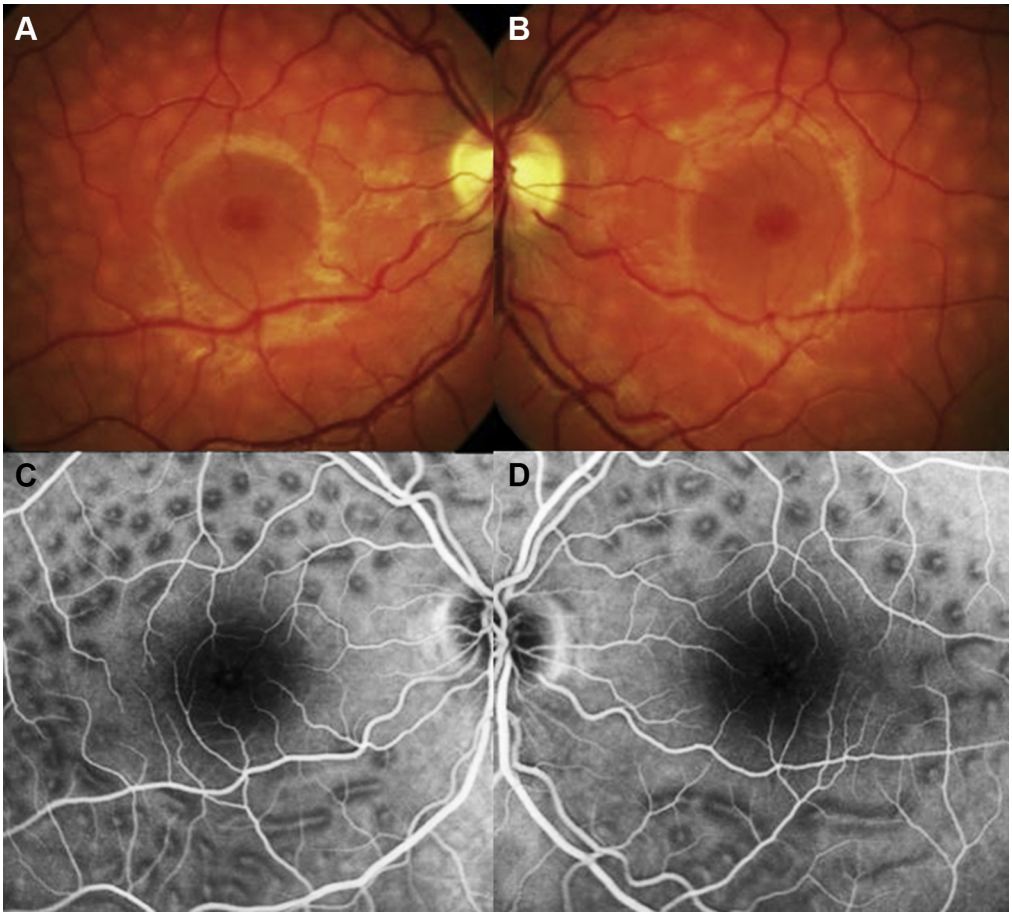

Figure 2. Color fundus photographs showing bilateral symmetric multifocal yellowish subretinal material (**A**, **B**). Fluorescein angiogram demonstrate hypofluorescence of the vitelliform lesions (blockage) with central hyperfluorescence (**C**, **D**).

material is either isofluorescent or, in larger accumulations, hypofluorescent, whereas the serous detachments may show faintly increased fluorescence, if any. The optic nerve and retinal vasculature appear normal, without signs of inflammation or increased permeability. Interestingly, the cystic changes seen on spectral-domain OCT do not show up on FA, similar to the fluorescein-negative cystoid macular degeneration seen in hereditary retinal diseases and niacin maculopathy (Fig 4).

Indocyanine Green Angiography. As with FA, ICGA may fail to detect fundus changes in the earliest stages of AEPVM or may demonstrate them only weakly. However, in patients with honeycomb-pattern deposits, late-phase ICGA shows multiple small hyperfluorescent blebs that correlate with, and sometimes exceed in number, the lesions seen clinically along the arcades. Although in early disease hyperfluorescence correlates with serous fluid, the converse is observed during later stages as serous fluid and vitelliform deposits resolve sequentially. In late disease, the polymorphous subretinal material itself appears as hyperfluorescent plaques on mid- and late-phase ICGA images (Fig 5).

Fundus Autofluorescence. The serous fluid during the earliest stages of AEPVM is not autofluorescent. As soon as the subretinal yellow-white material starts to accumulate, FAF imaging shows the characteristic bright increased autofluorescence of the polymorphous deposits. This material frequently precipitates and gravitates within the vitelliform space to form menisci or curvilinear deposits along the inferior margins of the serous detachments (Fig 6). In the so-called pseudohypopyon stage, small punctate or stippled hyperautofluorescent dots have been observed lining the outer retina in the detached areas as well as areas of polymorphous deposits (Fig 7). Later, paralleling the resolution of the deposits, the intense hyperautofluorescence subsides and FAF imaging normalizes. In general, the degree of autofluorescence corresponds to the quantity of yellow material, which has a masking effect on choroidal fluorescence in the angiogram. The fluorescein angiogram and autofluorescence map therefore constitute inverse images in this disorder.

OCT. On spectral-domain OCT, the serous retinal detachments of AEPVM are large and dome shaped when situated in the central macula, or multiple and smaller when located along the vascular arcades. In the latter, OCT shows small pockets of subretinal fluid simulating an undulating waveform, corresponding with the clinical honeycomb appearance.

Inner retinal cystic changes were observed in a subset of patients (9 of 18). These cystic changes usually are present during the earlier stages of the disease in the presence of subretinal fluid. In 1 patient, seen 3 days after onset of symptoms, de novo cystic changes developed within the first month after serous detachment of the macula. Although most patients have a few small intraretinal cysts overlying the dome-shaped macular detachment, 2 patients demonstrated multiple, densely packed intraretinal cysts overlying honeycomb lesions at presentation (Fig 8).

Regardless of the location of the serous detachments, OCT reveals a remarkably thick layer of amorphous material accumulating on the

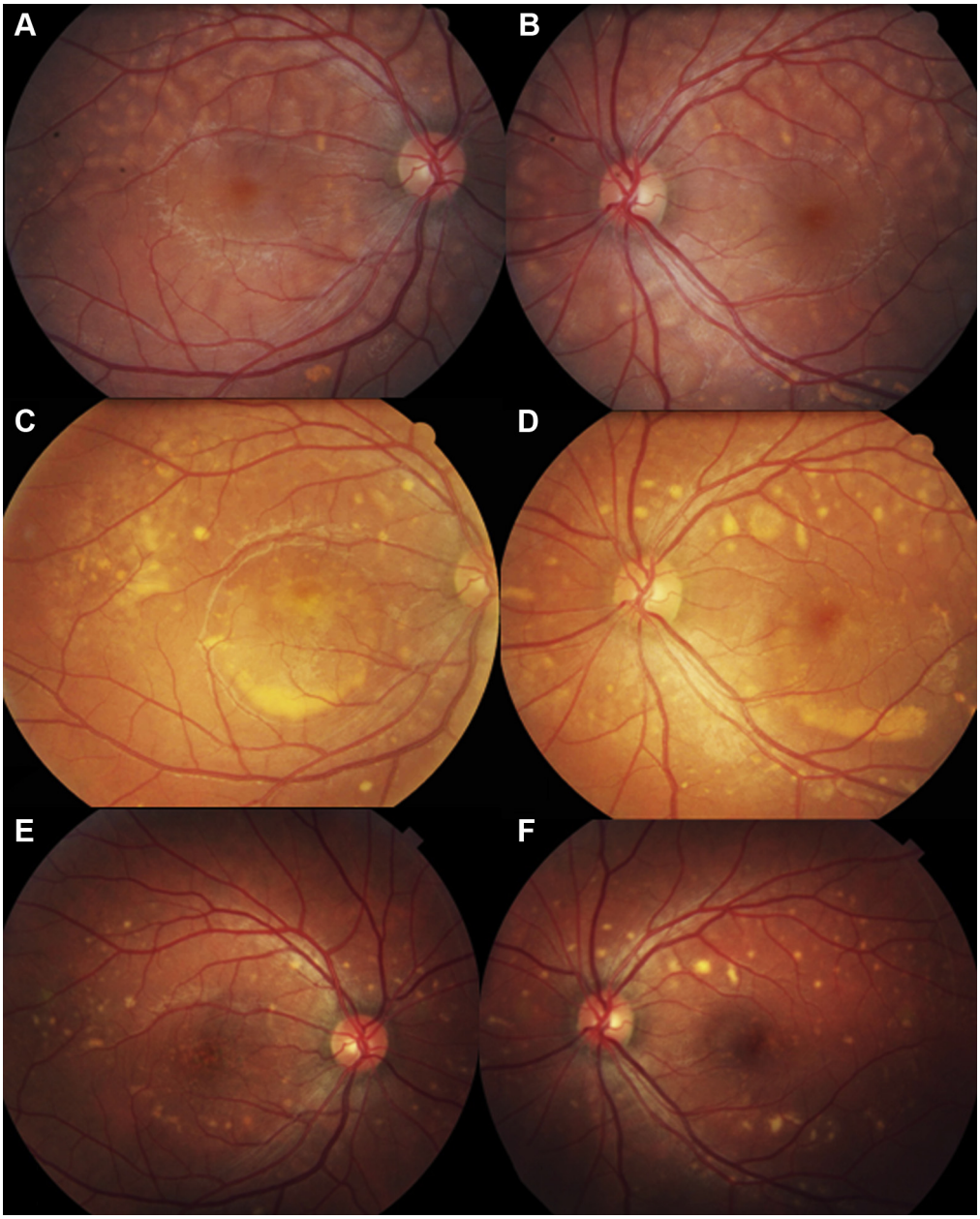

Figure 3. Color fundus photographs showing multifocal yellowish subretinal material with a "honeycomb pattern" (**A**, **B**). Progressively the macular region develops a large vitelliform detachment with a "pseudo-hypopyon" appearance (**C**, **D**). During the follow-up, the reabsorption of the vitelliform material lead to pigmentary changes within the macular region (**E**, **F**).

outer retinal surface. Over time, the material seems to be shed off the outer retinal surface and to gravitate toward the inferior aspect of the detachment. This material seems to correspond with the yellowish subretinal deposits seen clinically, which seem to have precipitated within the resolving serous detachments. The gravitation of this polymorphous yellowish material is one of the most intriguing features of AEPVM, although in smaller foci, the reabsorption of subretinal fluid may precede any significant migration. The later stages of the disease are characterized by the resolution of subretinal fluid with reapposition of retina and RPE, leaving some remaining accumulation of material in a retinal detachment extending from the RPE to the ellipsoid and, less commonly, beyond to the external limiting membrane. Finally, after months to years, the patients show resolution of the deposits and preservation or realignment of the ellipsoid, which may explain the restoration of good central visual function in most patients.

As stated before, the accumulation of "amorphous" material is not limited to the exposed outer retinal surface roofing serous detachments. Marked ellipsoid thickening can be observed in areas neighboring serous elevations in the acute, early phase of the disease (Fig 9). Further studies will have to determine whether these thickened layers are solely the result of reabsorption of subretinal fluid or whether the accumulation of this material represents cellular dysfunction preceding the separation of retinal layers.

Choroidal thickness measurement on spectral-domain OCT using enhanced depth imaging was performed in a single patient. In this case, choroidal thickness was increased during the initial phase

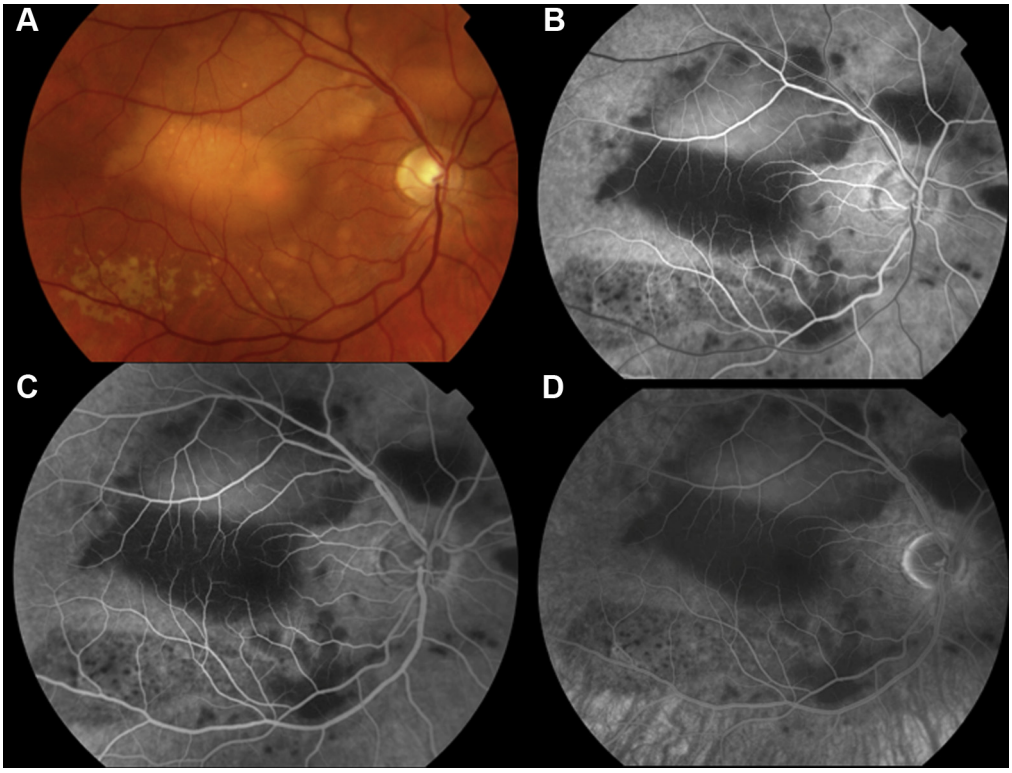

Figure 4. Color fundus photographs showing multifocal yellowish subretinal material (**A**). Early frame (**B**) and late frames (**C**, **D**) of fluorescein angiogram of the right eye are showing marked hypofluorescence (blockage) from the subretinal material.

of the disease, exceeding 300 μm beneath the subfoveal and neighboring retinal detachments.

Near-Infrared, Infrared, and Red-Free Imaging. Near-infrared reflectance imaging (820 nm) frequently is acquired before ICGA or in conjunction with OCT using spectral-domain devices. The near-infrared image of serous detachments in AEPVM is characterized by an isofluorescent center surrounded by a hypofluorescent ring delineating the elevation caused by the subretinal fluid seen on OCT. This allows for easy detection of very small lesions missed by indirect ophthalmoscopy or other imaging methods. Precipitated polymorphous material may exhibit slightly increased fluorescence but does not contrast nearly as well as seen on FAF imaging. In fact, there is only poor correlation when comparing pathologic findings on FAF with infrared imaging. Similar observations are made using red-free imaging, where serous detachments show a center of slightly increased intensity, but mostly isointensity, surrounded by decreased intensity, which gives these elevations an appearance of plasticity. There is a close correlation between lesions detected with near-infrared and red-free imaging. However, shallow subfoveal lesions, which do not differ from other small serous detachments on near-infrared imaging, may appear completely dark and centered, but still encircled, on red-free imaging. Unfortunately, we were not able to confirm these findings in different sizes and stages of detachments because of the small number of patients, who underwent imaging with all methods at the same visit.

Electrophysiologic Examinations. Electro-oculography (EOG) images were recorded in 9 patients and showed abnormalities in 4 patients, 2 of whom (50%) showed complete recovery at follow-up examination. Electroretinography (ERG) was performed and the resulting imaging showed normal results in 2 patients. One patient was reported to have slightly abnormal findings on multifocal ERG (mfERG).

Additional Observations

As in Best disease, secondary choroidal neovascularization (CNV) can complicate the course of AEPVM. In our series, a 34-year-old patient demonstrated CNV 2 years after the onset of symptoms and polymorphous retinal findings. After a single treatment with intravitreal triamcinolone acetate, the CNV regressed completely. However, persistent yellow subretinal deposits could still be observed 30 months after injection. Another previously unreported feature of AEPVM is recurrence. A 36-year-old man in this study had a second episode 2 years after complete resolution of previous clinical findings, consistent with AEPVM (Fig 9).

Discussion

The aim of this report was to increase the appreciation and recognition of idiopathic AEPVM, a rare condition previously reported in only 15 patients. We were able to identify and study 18 additional patients with AEPVM. Although the review of these patients did not allow us to identify causative mechanisms, it has helped us to understand better the sequence of events leading to the characteristic clinical pictures and to broaden our understanding of potential complications as well as the differential diagnosis. Different features identified in our series include recurrent disease after complete remission, secondary CNV at the border of long-standing deposits, fluorescein-negative cystic changes during the more acute stages of the disease, increased choroidal thickness, prolonged persistence of subretinal

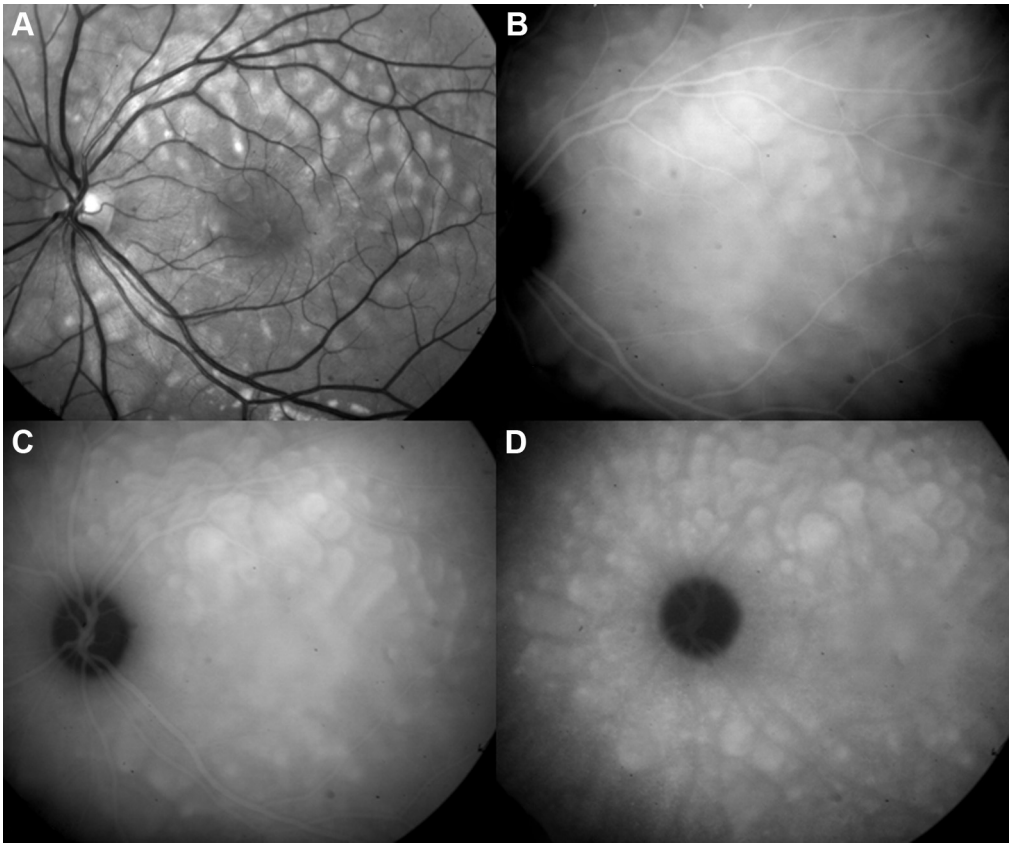

Figure 5. Red free fundus photograph (**A**) showing multiple deposits with a "honeycomb pattern." Late phase indocyanine green angiography images show multiple small hyperfluorescent blebs that exceed in number the lesions seen clinically (**B**–**D**).

deposits (possibly for years), early onset of the disease, and failure to recover vision despite clinical improvement.

Even with several new and emerging imaging methods on the horizon, FAF imaging remains one of the key diagnostic tests for AEPVM. The intensity of autofluorescence is thought to parallel the amount and distribution of lipofuscin.[7] Hyperautofluorescence in our patients supports the concept that lipofuscin accumulates in AEPVM. In the past, autofluorescence in the ocular fundus had been attributed solely to lipofuscin in the RPE. However, it has been suggested more recently that the autofluorescent material in vitelliform maculopathy and central serous retinopathy is derived from indigestible components of phagocytized photoreceptor outer segments and that autofluorescent material may accumulate on the outer retina before phagocytosis by the RPE.[14,16,17] This material, which is thought to comprise aggregates of shed photoreceptor outer segments containing various precursors to bisretinoid N-retinylidene-N-retinylethanolamine (A2E) and lipofuscin, may accumulate in part because of the lack of apposition of the retina to the RPE.[14] It is quite possible that a similar mechanism exists in AEPVM. Although the serous detachment of the acute phase is only mildly autofluorescent, we find increasing autofluorescence paralleling the accumulation of gravitating yellow material. It is not completely understood whether the increase in autofluorescence is indeed an increase in lipofuscin or its precursors or whether it is simply a result of concentrating the weak hyperautofluorescent material in a smaller area.

In vitelliform macular dystrophy, lipofuscin typically masks the choroidal circulation during FA. In AEPVM, there is variable masking of the choroid by the subretinal material. It is striking that several patients showed very little masking on FA during the acute stages of the disease. This finding eventually changed as the pseudohypopyon in the subretinal space matured 1 year later. Fundus autofluorescence imaging of the same patient showed an increase in hyperautofluorescence over time as well. Clearly, these observations support the notion that the chemical composition in the subretinal space early in the course of the disease differs from that in later stages. It is conceivable that initially there is a transudate, resulting from the impaired RPE function (or compromised RPE–retina apposition), that subsequently becomes enriched with lipofuscin and A2E precursors from photoreceptor outer segment shedding. Some authors have hypothesized that initial inflammation leads to an increase of permeability of the choriocapillaris with secondary RPE dysfunction and transient accumulation of lipofuscin.[7]

Genetic analysis of the *BEST1* and *peripherin/RDS* genes by direct sequencing did not reveal any disease-associated mutations in 4 of our patients, excluding known mutations in these 2 genes from being causal in these patients. Boon

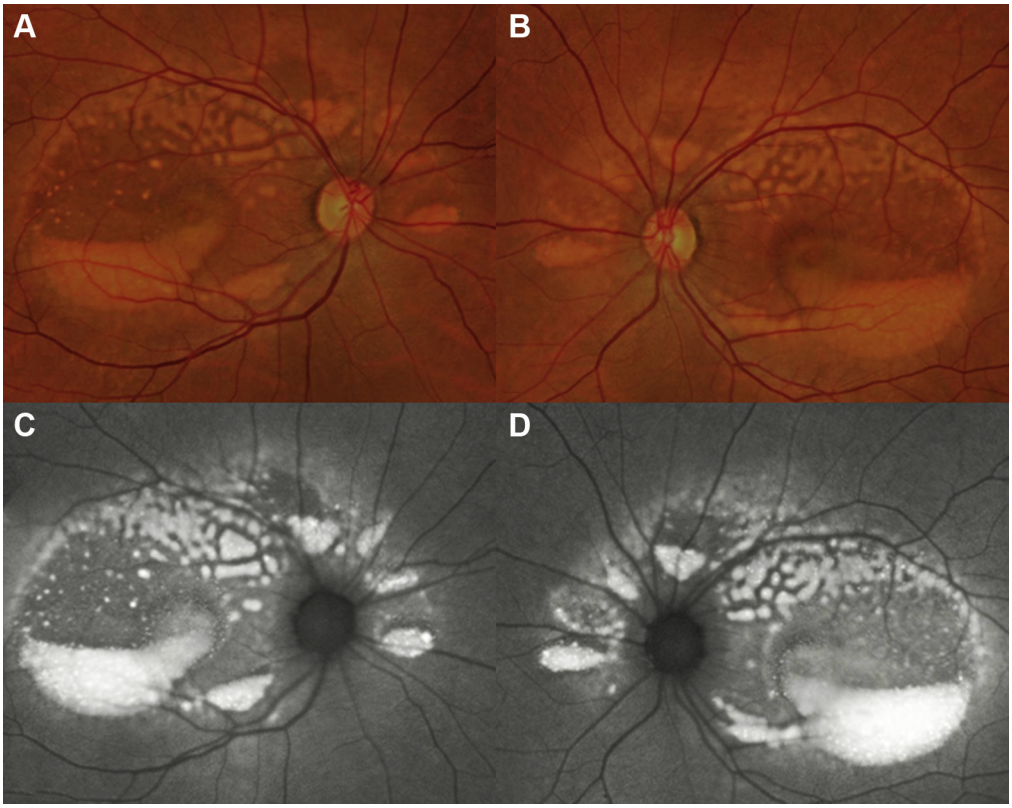

Figure 6. Color fundus photographs showing multifocal yellowish subretinal material with a large central vitelliform detachment on the "pseudo-hypopyon" stage (**A**, **B**). Fundus autofluorescence highlights the vitelliform lesions with the characteristic bright hyperautofluorescence (**C**, **D**).

et al[18] reported a series of patients with multifocal vitelliform dystrophy. A subset of their patients demonstrated typical features of Best disease, including abnormal EOG findings and an autosomal dominant inheritance pattern, but did not carry a disease-causing mutation in the *VMD2* gene. In the same report, they described an opposite, well-known observation of nonpenetrance, where individuals heterozygous for *VMD2* mutations in families with Best disease did not show any clinical signs of the disease nor any EOG abnormalities. Based on their findings, Boon et al[18] postulated that in addition to the underlying genetic mutation, environmental factors also may influence the development of (multifocal) vitelliform lesions in patients with mutations in *VDM2*. The same may be true in AEPVM, whereby affected individuals may possess an unidentified genetic predisposition for expressing a multifocal Best-like phenotype, potentially triggered by an infectious or inflammatory stimulus.

Given the overlap of clinical features of AEPVM with multifocal Best disease—of which CNV is a recognized but infrequent complication—it is not surprising that one of our patients demonstrated CNV (patient 2). The efficacy of a single intravitreal injection of triamcinolone acetonide in this patient is reminiscent of patients with CNV secondary to ocular inflammatory or infectious diseases such as idiopathic multifocal choroiditis or presumed ocular histoplasmosis syndrome.[19–21]

The degree to which systemic corticosteroids generally facilitate visual recovery in AEVPM is unclear, because most of the patients reported in the literature recovered without medical intervention. A recent report evaluated the inefficacy of intravitreal steroid implant.[13] Spontaneous reduction of autofluorescence with resolution of subretinal deposits previously was described by Vaclavik et al[7] as part of the natural course of AEPVM. However, in their patients, the regression pattern was rather symmetrical. Interestingly, patient 1 in our series showed reduction of hyperautofluorescence in the treated eye after 1 dose of intravitreal triamcinolone acetonide, whereas the fellow eye showed a continuous increase of autofluorescence during the same period. Therefore, it is possible that the more rapid regression of findings in the treated eye of our patient with respect to the fellow eye is attributable to the treatment.

Because all reported patients diagnosed with AEPVM (including most of ours) eventually recovered normal or near-normal vision, it was believed previously that this disease does not result in significant damage to the RPE. However, our case series suggests that this condition can be recurrent or more chronic with long-term vision loss. This is supported further by the fact that EOG abnormalities, if present, fail to improve completely in a subset of patients, despite recovery of vision.[7] In a recent report describing persistent changes of the mfERG in a patient with AEVPM, the vision of the patient improved over time, but the mfERG showed only partial recovery.[5] This could be the result of a clinicohistopathologic overlap

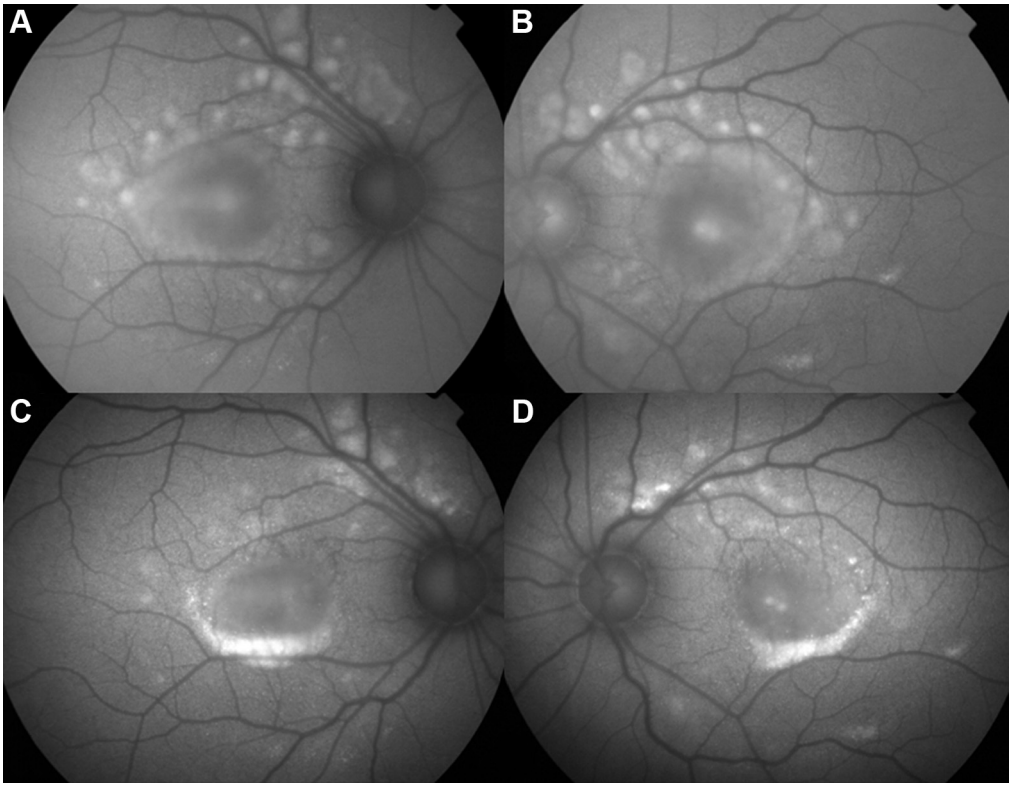

Figure 7. Fundus autofluorescence imaging showing hyperautofluorescence of the subretinal material (**A**, **B**). Seven months later, fundus autofluorescence imaging (**C**, **D**) revealed an increase in autofluorescence on the macular area with decrease of the autofluorescence in the lesions around the macular area.

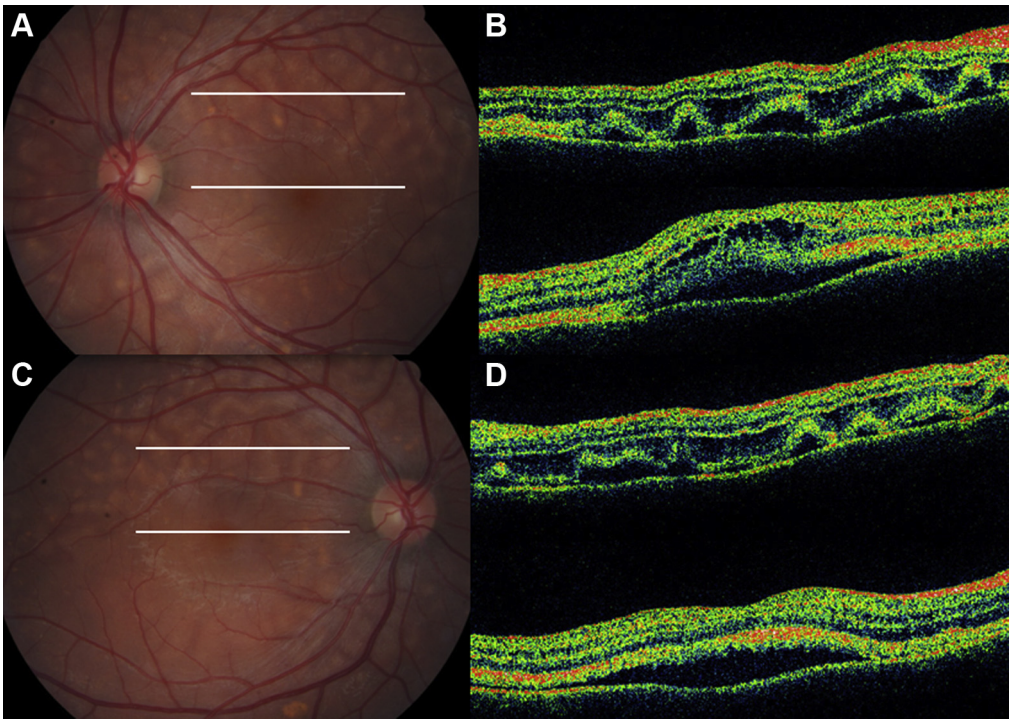

Figure 8. Fundus images during the first episode of acute exudative polymorphous vitelliform maculopathy (**A**, **C**). The OCT scans (**B**, **D**) at the corresponding areas in panels **A** and **C** demonstrate multiple areas of lobulated serous retinal detachment with bilateral foveal involvement.

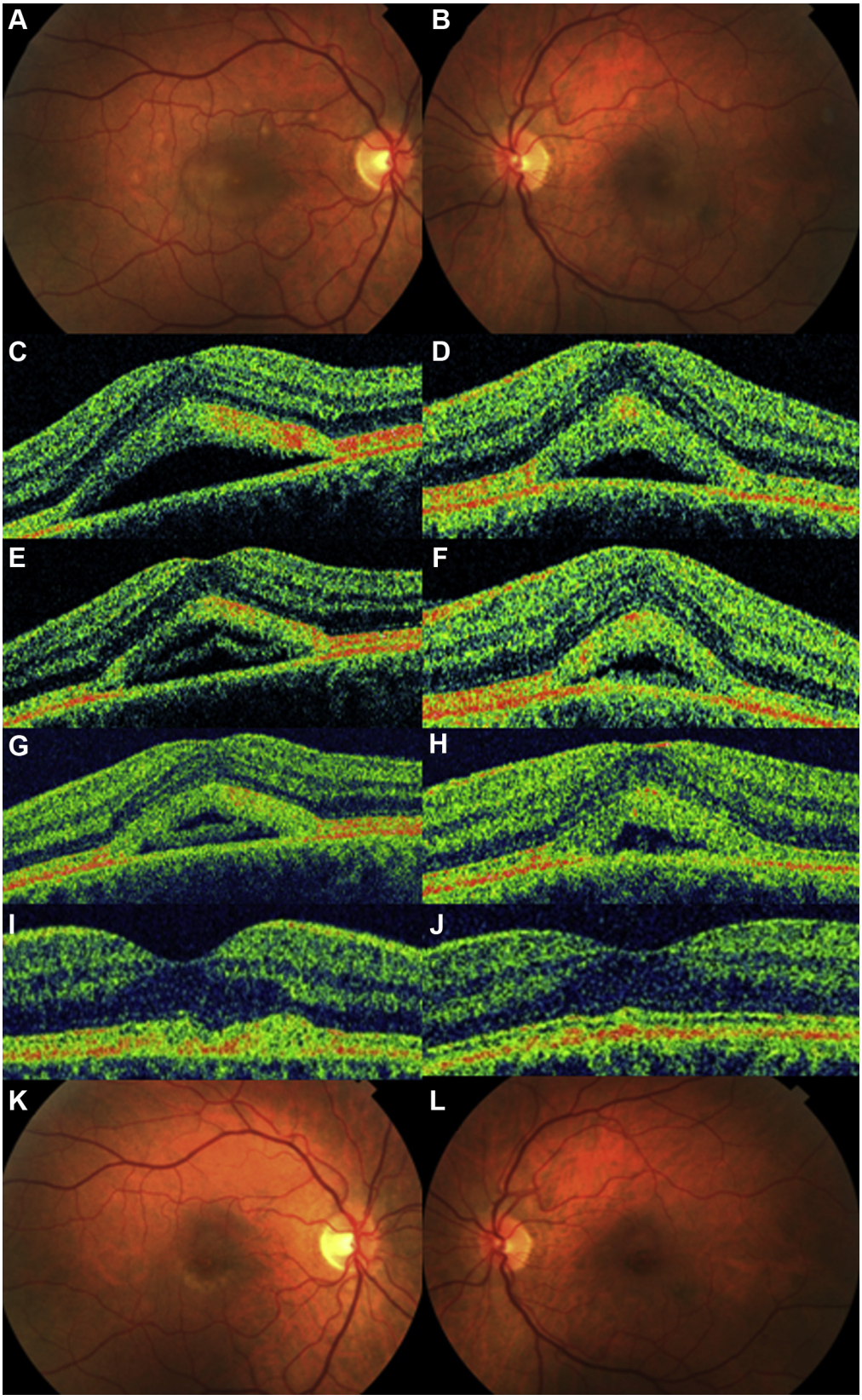

Figure 9. Fundus images during the first episode of acute exudative polymorphous vitelliform maculopathy at baseline (**A**, **B**) and after the spontaneous resolution leaving only mild pigmentary changes in the perifoveal region at 11 months (**K**, **L**). The tomographic scans show serous retinal detachment at baseline (**C**, **D**), that progressively resolved at 1-month follow-up (**E**, **F**), 3-month follow-up (**G**, **H**), and led to mild pigmentary changes at 11-month follow-up seen as hyperreflective clumps of the retinal pigment epithelium bands and minimal small irregularities in the ellipsoid band (**I**, **J**).

Table 3. Comparative Characterization of Acute Exudative Polymorphous Vitelliform Maculopathy, Autosomal Recessive Best Disease, and Paraneoplastic Polymorphous Retinopathy

	Idiopathic Acute Exudative Polymorphous Vitelliform Maculopathy	Autosomal Recessive Best Disease[13]	Paraneoplastic Polymorphous Retinopathy
Symptoms	Central visual symptoms	Reduced VA	
First onset of symptoms	Incomplete data (we did not record every case at baseline)	Typically first or second decade; 1 patient sought treatment at age 45 years	
Associations	None known	Hyperopia±subacute angle closure[24]	
Family history	Negative	Recessive segregation, possible consanguinity	Negative
Lesions	Two distinct lesion types: serous RDs with evolving vitelliform material and bleb-like lesions along vascular arcades	Bilateral subretinal yellowish deposits from posterior pole to equator	Oval or circular retinal elevations without yellow material
Autofluorescence	Increases within serous lesions, then decreases as vitelliform material is absorbed	Intensely hyperautofluorescent lesions as vitelliform material accumulates	
OCT	Subretinal fluid, cystoid maculopathy (no leakage on FA)	Frequent cystoid maculopathy (nonleaky on FA)	
Fluorescein angiography	Serous lesions mask choroidal fluorescence; no leakage associated with cystoid macular degeneration	No leakage associated with cystoid macular degeneration	
Electrophysiologic findings	Abnormal EOG results in 50% of patients	Abnormal EOG results	
Genetic testing results	No known genetic associations or mutations	*BEST1*	
Clinical course			
Laterality	Bilateral with symmetric lesion appearance and progression; regression may be asymmetric	Bilateral	Polymorphous findings may be unilateral and may occur in fellow eye
Inflammatory or cellular infiltrate	No	No	Infiltrating lesions (e.g., lymphoma) may release vitreous cells
Complications	Choroidal neovascularization	Choroidal neovascularization	

EOG = electro-oculography; FA = fluorescein angiography; RD = retinal detachment; VA = visual acuity.

between Best disease and AEVPM. Mullins et al[22] published the histologic features of a patient with a known *VMD2* mutation who sought treatment for late-onset vitelliform lesions and flecks. They described central areas of severe photoreceptor degeneration with eosinophilic material in the space normally occupied by the outer nuclear layer and inner photoreceptor segments. The authors also found widespread loss of photoreceptor cells with preserved underlying RPE in areas outside the vitelliform lesion. A similar process potentially could explain the persistent mfERG findings in the reported AEVPM patients.[5] Based on clinical findings in our cases series, patients seem to segregate into 2 groups: those who show resolution of clinical signs and symptoms within a few months and those who have visible retinal changes for years. The latter are less likely to experience a swift visual recovery and may even demonstrate decreased vision years after the onset of initial symptoms. Autosomal recessive bestrophinopathy is a recently described condition in patients carrying biallelic *BEST1* mutations. Clinically, this disorder is characterized by reduced visual acuity, intensely autofluorescent subretinal deposits, as well as cystic and even exudative retinal changes.[23,24] Most of the patients reported in the literature had significantly reduced light rise on the EOG images.[23–25] The ERG findings vary: although children and young adults may demonstrate normal patterns and full-field ERG scans,[24] these tests are usually reported to show abnormal results in older patients.

In addition to the need to differentiate AEPVM from autosomal dominant Best disease, there is another important masquerading disorder that warrants clinical investigation in these patients. Paraneoplastic disease—originally melanocytic in nature, but over recent years including various other forms of cancer—may have a clinical presentation in the fundus that is indistinguishable from AEPVM. Koreen et al[26] described a patient with paraneoplastic findings resembling AEPVM in a patient with metastatic melanoma. They were able to detect anti-RPE (peroxiredoxin 3) antibodies in the acute phase, but not during remission. The authors postulated that cross-reactive antibodies generated in response to an infectious or neoplastic process could explain the overlapping phenotypes observed in AEPVM and paraneoplastic syndromes. More importantly, the disappearance of these antibodies, and thereby their potential effect on RPE or retinal vasculature, during later stages of the disease may explain the transient nature of the clinical findings.

Accordingly, the need to differentiate AEPVM from paraneoplastic disease and autosomal recessive bestrophinopathy remains a significant challenge to the clinician. Common and distinguishing characteristics are summarized in Table 3. Clinical overlap is significant between these diseases, and current standard imaging is unable to

distinguish between these entities. The course of AEPVM mostly is benign, but resolution of detachments and deposits with recovery of visual function can be observed in both idiopathic and paraneoplastic cases.[10,26] A known history of cancer, especially of melanoma, helps in identifying paraneoplastic cases, in which the polymorphous findings in fact may be unilateral. In the absence of an established diagnosis, all patients should undergo a thorough clinical examination to rule out an occult malignancy.

The main limitation of the present study is the lack of direct comparison with those patients with paraneoplastic AEPVM and autosomal recessive bestrophinopathy. Table 3 includes a comparison of idiopathic and paraneoplastic AEPVM; however, in most cases, no differences may be found clinically. Thus, a systemic workup is mandatory to rule out malignancies, even months after the onset of the vitelliform retinopathy.[27] Also, all patients with an early onset (<20 years) of polymorphous fundus changes and abnormal electrophysiologic test results should be considered for genetic screening.

In summary, AEPVM is a rare disease of unknown origin that has been characterized by its clinical appearance, sequence of disease stages, and good visual prognosis in most patients. However, although distinctively different from Best disease, AEPVM can be recurrent or chronic with rather asymmetric manifestations and also may be complicated by CNV. This is consistent with the notion that diseases (phenotypes) characterized by, among other features, multifocal vitelliform lesions have multiple genetic origins but overlapping clinical spectra. When making the diagnosis of AEPVM, one should rule out carefully other underlying masquerading diseases and specifically paraneoplastic syndromes.

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Footnotes and Financial Disclosures

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[1] Vitreous Retina Macula Consultants of New York, New York, New York.
[2] The LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear and Throat Hospital, New York, New York.
[3] Department of Ophthalmology, University of Ancona, Ancona, Italy.
[4] Biostatistics Section, Department of Health Sciences, University of Genova, Genova, Italy.
[5] Vanderbilt Eye Institute, Nashville, Tennessee.
[6] Federal University of São Paulo, São Paulo, Brazil.
[7] Department of Ophthalmology, Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil.
[8] Department of Ophthalmology, Universidade Federal Fluminense, Niterói, Brazil.

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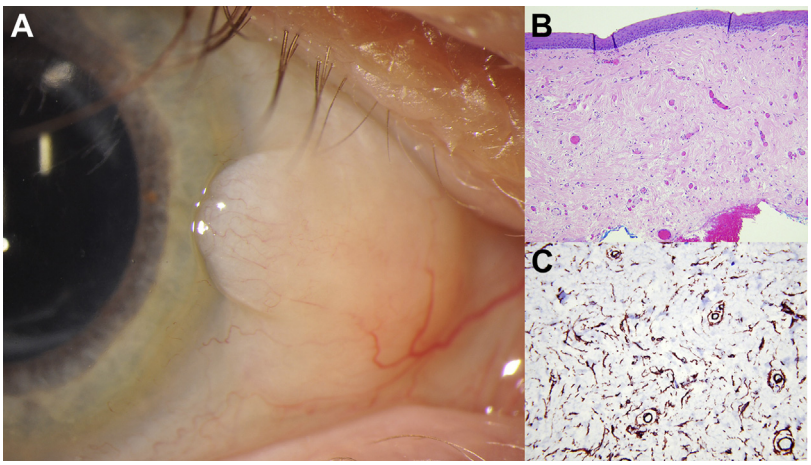
Abbreviations and Acronyms:
A2E = bisretinoid *N*-retinylidene-*N*-retinylethanolamine; **AEPVM** = acute exudative polymorphous vitelliform maculopathy; **CNV** = choroidal neovascularization; **EOG** = electro-oculography; **ERG** = electroretinography; **FA** = fluorescein angiography; **FAF** = fundus autofluorescence; **ICGA** = indocyanine green angiography; **mfERG** = multifocal electroretinography; **RPE** = retinal pigment epithelium.

Correspondence:
Rosa Dolz-Marco, MD, PhD, Vitreous Retina Macula Consultants of New York, 460 Park Avenue, Fifth Floor, New York, NY 10022. E-mail: rosadolzmarco@gmail.com.

Pictures & Perspectives



Conjunctival Stromal Tumor

A 66-year-old woman developed a 4×8-mm slow-growing, buff-colored mass of her left conjunctiva over 5 years. The lesion was firm, fixed to underlying tissue, and straddled the limbus eccentrically (Fig 1**A**). Biopsy showed the substantia propria replaced with a paucicellular tumor, consisting of delicate spindle cells separated by bundles of collagen and scattered blood vessels (Fig 1**B**). The spindle cells expressed CD34 (Fig 1**C**) and vimentin. The diagnosis of conjunctival stromal tumor describes a CD34-positive benign mesenchymal tumor with matrix varying from purely myxoid to purely collagenous. Differential diagnosis is broad ranging from fibroxanthomatous lesions to scar. (Magnified version of Fig 1**A**–**C** is available online at www.aaojournal.org).

Erin L. Greenberg, MD[1]
Edgar M. Espana, MD[1]
Curtis E. Margo, MD, MPH[1,2]

[1]Department of Ophthalmology, Morsani College of Medicine, University of South Florida, Tampa, Florida; [2]Department of Pathology and Cell Biology, Morsani College of Medicine, University of South Florida, Tampa, Florida