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PUNCTATE INNER CHOROIDOPATHY–LIKE REACTIONS IN UNRELATED RETINAL DISEASES

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Purpose: To report a cohort of patients with a punctate inner choroidopathy (PIC)-like reaction in concurrent, unrelated, chorioretinal disorders.

Methods: This was a retrospective observational study of patients seen at two referral centers with lesions consistent with PIC on multimodal imaging; patients with lesions resembling idiopathic multifocal choroiditis were also included. Active PIC-like lesions appeared as focal hyperreflective lesions splitting the retinal pigment epithelium/Bruch membrane (RPE/BrM) complex on optical coherence tomography. Chronic PIC-like lesions included subretinal fibrosis, multifocal punched-out chorioretinal atrophy, and curvilinear streaks. Patients' demographics, additional imaging features, and treatment responses were collected and summarized.

Results: Twenty-two eyes of 16 patients with a PIC-like reaction were included (75% females; median age 40 years). Underlying diagnoses included hereditary retinal conditions (10 patients, 63%) and acquired etiologies, all characterized by the RPE/BrM or outer retinal disruption. Fifteen eyes (68%) had active PIC-like lesions; seven eyes (32%) had chronic PIC-like lesions. Active PIC-like lesions regressed with time and responded to systemic steroids. Subretinal fibrosis (3 eyes, 20%), macular atrophy (3 eyes, 20%), and concomitant subretinal fibrosis and macular atrophy (5 eyes, 33%) developed on follow-up. Recurrences occurred in five eyes (23%).

Conclusion: RPE/BrM or outer retina disruption may trigger a PIC-like reaction in susceptible patients, presumably because of the loss of immune privilege. A PIC-like reaction may influence the clinical progression and the visual prognosis of the primary chorioretinal disease.

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Advances in multimodal imaging (MMI) have contributed to a detailed characterization of idiopathic inflammatory chorioretinopathies known as white dot syndromes (WDS). The integration of data obtained by fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), fundus autofluorescence (FAF), and optical coherence tomography (OCT), together with the implementation of ultra-widefield (UWF) fundus photography, has allowed an increasingly precise distinction between multiple evanescent white dot syndrome (MEWDS)[1] and punctate inner choroidopathy (PIC).[2,3]

Although MEWDS and PIC may share the same demographics and occur concurrently in the same eye,[3,4] the two entities have a different clinical course and response to treatment.[3] On the one hand, MEWDS is an acute condition, often unilateral, which resolves without treatment and has no permanent functional or anatomical legacy.[5] On the other hand, PIC is usually bilateral, may have a relentless course, and may cause progressive chorioretinal atrophy and scarring if not adequately treated.[6,7]

A clinical syndrome of outer retinal disruption resembling primary MEWDS has recently been described in eyes with traumatic, iatrogenic, or degenerative diseases.[4,8–11] Secondary MEWDS or MEWDS-like reaction has the same benign clinical course as primary MEWDS and does not seem to modify the visual prognosis of the underlying disease.[9,12] The acronym EpiMEWDS for epiphenomenon MEWDS has also been proposed, suggesting that MEWDS may be a secondary phenomenon that occurs alongside or in

parallel to a primary retinal condition.[12] Parallelly, PIC is clinically associated with pathologic myopia (PM).[7,13] As PIC lesions tend to cluster around sites of pre-existent retinal pigment epithelium/Bruch membrane (RPE/BrM) complex damage (e.g., lacquer cracks) in eyes with PM, a causative relationship between local inflammation and mechanical insults to RPE/BrM has been postulated.[7,13]

In this study, we collected a series of patients with features of PIC on MMI in the setting of apparently unrelated posterior segment diseases, assuming that the PIC lesions were not incidental but related to the underlying condition. Therefore, we collectively referred to them as secondary PIC or PIC-like reactions. We excluded cases with PM because we intended to show other diseases in which structural damage to the outer retina/BrM/inner choroid preceded and presumably induced the inflammatory lesions.

As PIC-like reactions may cause additional retinal damage than expected by the underlying condition, this study may help properly recognize secondary PIC and provides provisional recommendations on therapeutic management.

Material and Methods

This was a retrospective observational study of patients seen at two tertiary referral centers, the Department of Ophthalmology of the San Raffaele Scientific Institute in Milan, Italy, and the Vitreous Retina Macula Consultants of New York, NY. The study complied with the Health Insurance Portability and Accountability Act of 1996 and followed the Declaration of Helsinki tenets for research involving human subjects; the procedures were approved by the local ethics committee at the two institutions. The patients gave their written consent to be engaged in noninterventional clinical research.

Patients with concurrent chorioretinal diseases were included if they had active lesions on OCT consistent with PIC, identified as the presence of focal moderately reflective lesions splitting the RPE/BrM complex.[2,3] Adjunctive OCT features included hump-shaped nodules with homogeneous moderate reflectivity centered at the photoreceptor layer,[14] RPE/BrM discontinuities with posterior choroidal hypertransmission, ellipsoid/interdigitation zone (EZ/IZ) disruption, downward deflection of the BrM, and underlying choroidal thickening with loss of the normal vascular architecture.[15] Given the clinical overlap between PIC and idiopathic multifocal choroiditis (iMFC),[16] patients with typical iMFC scars (e.g., subretinal fibrosis, multifocal punched-out chorioretinal atrophy, or curvilinear streaks or Schlaegel lines[17,18]) were also included.

Patients were excluded if they had a known history of ocular histoplasmosis or systemic diseases causing signs of PIC/iMFC (e.g., tuberculosis or sarcoidosis). We also excluded patients with more than 6 diopters of myopia, as PIC is often associated with PM,[7] and those with incomplete clinical data on electronic medical health record (EHR) review.

Demographic and clinical data of each potentially eligible patient were retrieved from the EHR charts. In patients with hereditary dystrophies, genetic testing was reviewed when available; in the remaining ones, the diagnosis was made based on the family history, the accompanying systemic signs, retinal electrophysiology, and MMI features.

Each patient underwent a complete ophthalmic evaluation, including measurement of best-corrected visual acuity (BCVA) on decimal or Snellen charts, slit-lamp examination, and ophthalmoscopic examination. Multimodal imaging included fundus photography (TRC-50IX; Topcon America, Paramus, NJ; California, Optos Inc, Marlborough, MA; Eidon, Centervue, Padova, Italy), blue- or green-wavelength FAF (Spectralis; Heidelberg Engineering, Heidelberg, Germany; California, Optos Inc, Marlborough, MA), FFA, ICGA, spectral-domain OCT (SD-OCT) (Spectralis+HRA; Heidelberg Engineering), and OCT angiography (PLEX Elite 9000 SS-OCT, Carl Zeiss Meditec, Inc, Dublin, CA; DRI OCT Triton, Topcon Corporation, Japan). The choroid was qualitatively assessed on OCT scans acquired with an enhanced-depth imaging strategy.

As the study was multicenter and retrospective, patients' follow-up schedule, MMI protocol, and treatment approaches were not set in advance but performed at the discretion of each physician. All the EHR and MMI data available were reviewed by the first three authors (M.V.C., A.M., and P.R.). Questionable cases were adjudicated by the two senior physicians (M.B.P. and K.B.F.). Quantitative data are

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summarized as their median and interquartile range (IQR) and categorical data as their absolute and relative prevalence.

Results

Twenty-two eyes of 16 patients with a PIC-like reaction and concomitant chorioretinal diseases were included (12 females, 75%). Demographic and clinical features are listed in Table 1. One patient (a 52-year-old woman) with a history of retinal detachment 8 years before undergoing scleral buckling was excluded because of PM (refraction −8 diopters). The median age was 40 years (IQR 25–51), the median refraction was −1.12 diopters (IQR −2.15 to 0), and the median follow-up was 50 months (IQR 12–104).

Ten patients (63%) had inherited retinal disease: pseudoxanthoma elasticum (PXE) (5 patients), rod-cone dystrophy (3 patients), Stargardt disease (1 patient), and autosomal recessive (AR) bestrophinopathy (1 patient, genetic details reported elsewhere[19]). One patient with PXE had pattern dystrophy–like features with subfoveal acquired vitelliform lesions and was reported elsewhere as a case report.[20]

Acquired etiologies included idiopathic angioid streaks (1 patient), neovascular age-related macular degeneration (1 patient), ocular trauma with RPE/BrM rupture (1 patient), acute toxoplasmic chorioretinitis (1 patient), chronic retinal detachment (1 patient), and laser retinopexy for rhegmatogenous retinal detachment (1 patient).

In 15 eyes (68%), a PIC-like reaction was detected at the first visit. The remaining seven eyes (47%) developed a PIC-like reaction on follow-up after a median of 38 months (IQR 32.5–38.5). Ten cases (63%) had unilateral findings. Eight eyes (36%) had pre-existent or concurrent macular neovascularization (MNV); in one eye, MNV occurred 8 months after detecting a PIC-like reaction.

No patient had prodromal symptoms, such as flu-like symptoms or headache, or potentially inciting events, such as vaccinations or viral infections, at the time of PIC-like reactions. On clinical and MMI examination, none showed anterior chamber cells and flare, vitritis, or vasculitis.

Active Punctate Inner Choroidopathy–like Reaction

Fifteen eyes (68%) of 13 patients had active PIC-like lesions on MMI; all these patients were symptomatic and complained of recent visual worsening.

Fundus photography showed deep yellow multifocal lesions at the posterior pole (n = 6 eyes, 40%) (Figure 1). As per the inclusion criteria, all eyes (n = 15 eyes, 100%) had mid- to hyperreflective lesions splitting the RPE/BrM complex and associated with disruption of the EZ/IZ and discontinuities of the underlying RPE/BrM complex with posterior choroidal hypertransmission (Figures 1 and 2). Irruption of the focal lesions in the outer nuclear layer and a downward deflection of the BrM were seen in 13 eyes (87%). In 3 eyes (20%), there were hump-shaped nodules with homogeneous moderate reflectivity overlying focal defects in the RPE/BrM complex (Figures 3–5).

Focal PIC-like lesions colocalized with areas of focal choroidal thickening, loss of inner choroidal architecture, and hyperreflective foci in all the eyes (15 eyes, 100%) (Figures 1–3 and Supplementary Figure 1, http://links.lww.com/IAE/B797). In the two patients with vitelliform lesions (AR bestrophinopathy and PXE with pattern dystrophy–like features), a PIC-like reaction occurred after the reabsorption of the vitelliform material (Figures 3 and 4).

Eleven of the 15 eyes (73%) showed MMI features consistent with MEWDS-like reaction, including transient EZ/IZ disruption on OCT that colocalized with hyperautofluorescent spots on FAF, early-phase and late-phase hyperfluorescent spots on FFA, and late-phase hypofluorescent spots on ICGA (Figure 2 and Figure 5).

Chronic Punctate Inner Choroidopathy–like Reaction

Seven eyes (32%) of five patients had chronic PIC-like lesions on MMI. Two eyes were the fellow eyes of the patient with active lesions (Patient 1 with PXE and pattern dystrophy–like features and Patient 7 with AR bestrophinopathy); in the remaining eyes, the findings were incidental. Two of these seven eyes (29%) had concurrent inactive MNV.

Chronic PIC-like lesions included multifocal punched-out chorioretinal atrophy in the mid and far periphery (7 eyes, 100%), peripheral curvilinear streaks (7 eyes, 100%), and peripapillary or macular subretinal fibrosis (2 eyes, 29%) (Figure 4, Figure 6, and Supplementary Figure 2, http://links.lww.com/IAE/B798). These lesions were clinically indistinguishable from those resulting from resolved active PIC-like lesions.

Treatment and Clinical Course

Among the 13 patients with active PIC-like reaction, 7 (54%) were treated with oral steroids. Seven patients received intravitreal injections of anti–vascular endothelial growth factor agents because of a concurrent MNV. One patient (Patient 1) was observed because of low residual visual acuity.

Table 1. Demographic and Clinical Characteristics of Patients With Punctate Inner Choroidopathy (PIC)-like Lesions and Unrelated Retinal Diseases

Patient	Gender	Age (Years)	Disease	Eye	Presence of MNV	Laterality	Spherical Equivalent (Diopters)	Follow-up (months)	Baseline Visual Acuity (Snellen)	Final Visual Acuity (Snellen)	Prodromes or Eliciting Events	Time From Diagnosis to First PIC-like Features (months)
Active PIC/iMFC-like lesions												
1	F	62	PXE with pattern dystrophy–like features	LE	Yes	Bilateral	0	120	20/100	20/200	None	0
2	M	43	PXE	RE	Yes	Bilateral	−5, 2	72	20/50	20/60	None	0
				LE	Yes		−5, 2	72	20/50	20/80	None	0
3	M	49	PXE	RE	Yes (8 months later)	Unilateral	−1, 25	12	20/70	20/100	None	0
4	M	58	PXE	RE	No	Unilateral	1, 5	12	20/20	20/20	None	0
5	F	56	PXE	LE	No	Unilateral	−2	168	20/40	20/25	None	0
6	F	48	Idiopathic AS	RE	Yes	Bilateral	−2	120	20/100	20/200	None	0
				LE	Yes		−2	120	20/100	20/200	None	0
7	F	10	AR bestrophinopathy	RE	Yes	Bilateral	1, 7	110	20/100	20/100	None	31
8	F	22	Rod-cone dystrophy	RE	No	Unilateral	0	12	CF	CF	None	0
9	F	88	nAMD	LE	Yes	Unilateral	0	52	20/200	20/50	None	39
10	F	24	Ocular trauma with RPE/BrM rupture	LE	No	Unilateral	0	2	20/70	20/20	None	1
11	M	40	Chronic retinal detachment	LE	No	Unilateral	−2	60	20/200	20/25	None	48
12	F	53	Rhegmatogenous retinal detachment	RE	No	Unilateral	−1	10	20/25	20/20	None	36
13	F	27	Acute toxoplasmic chorioretinitis	LE	No	Unilateral	0	84	20/25	20/20	None	1
Chronic PIC/iMFC-like lesions												
1	F	62	PXE with pattern dystrophy–like features	RE	Yes	Bilateral	−2, 2	24	20/60	CF	None	60
7	F	10	AR bestrophinopathy	LE	Yes	Bilateral	2, 5	110	CF	CF	None	0

Table 1. (*Continued*)

Patient	Gender	Age (Years)	Disease	Eye	Presence of MNV	Laterality	Spherical Equivalent (Diopters)	Follow-up (months)	Baseline Visual Acuity (Snellen)	Final Visual Acuity (Snellen)	Prodromes or Eliciting Events	Time From Diagnosis to First PIC-like Features (months)
14	F	25	Stargardt disease	RE	No	Unilateral	−3, 5	0	20/100	N/A	None	0
15	F	34	Rod-cone dystrophy	RE	No	Bilateral	1, 35	48	20/30	20/40	None	0
				LE	No		0	48	20/100	20/25	None	0
16	F	18	Rod-cone dystrophy	RE	No	Bilateral	−4, 25	0	20/20	N/A	None	0
				LE	No		−4, 75	0	20/20	N/A	None	0

On follow-up, OCT showed regression of the hyperreflective lesions splitting the RPE/BrM complex, with a legacy of focal ELM and EZ/IZ disruption, sagging of the outer plexiform layer/outer nuclear layer, and focal discontinuities of the RPE/BrM complex (Figures 2 and 3). Underlying focal choroidal thickening also regressed; in two eyes (13%), loss of the underlying choroidal tissue beneath the compromised RPE/BrM complex resulted in focal choroidal excavation (Supplementary Figure 1, http://links.lww.com/IAE/B797). MEWDS-like reaction regressed in all the eyes with no legacy.

Complications of PIC-like reaction included subretinal fibrosis in three eyes (20%), macular atrophy in three eyes (20%), and both subretinal fibrosis and macular atrophy in five eyes (33%) (Figure 3–5).

A PIC-like reaction recurred in five patients (38%), with features overlapping those of the first episode. At each recurrence, the patient noted a subjective worsening in visual acuity, and the BCVA scored worse than previously reported. The BCVA at the last available visit was similar to baseline (0.5 logMAR [IQR 0.1–0.9; 20/63 Snellen equivalent] at baseline vs. 0.45 logMAR [IQR 0.04–1; 20/60 Snellen equivalent] at the last visit), but it irreversibly worsened to 20/200 or worse in three eyes because of macular atrophy or subretinal fibrosis.

Discussion

In this article, we used literature-based OCT criteria to collect patients with imaging features consistent with active PIC[2,3,6,14,21] in the setting of various unrelated chorioretinal diseases. We also included eyes with chronic chorioretinal lesions possibly consistent with previous PIC-like episodes. We collectively referred to this presentation as a PIC-like reaction. Active PIC-like reaction was detected concurrently to the primary diseases or, more rarely, on follow-up and was associated with visual function decline. Active PIC-like reaction responded to systemic steroid treatment; recurrences were documented in one-third of the patients. Half of the eyes developed typical PIC complications, including macular atrophy, subretinal fibrosis, and MNV.

Primary white dot syndromes (WDS) are believed to be an autoimmune response against retinal antigens in the presence of predisposing factors and precipitating events. Both genetic susceptibility[13,16,22] and environmental stimuli, including infections, vaccinations, and stress,[15,23] are implicated. A novel hypothesis has been advanced, according to which *secondary* WDS are triggered by damage to the choriocapillaris, the

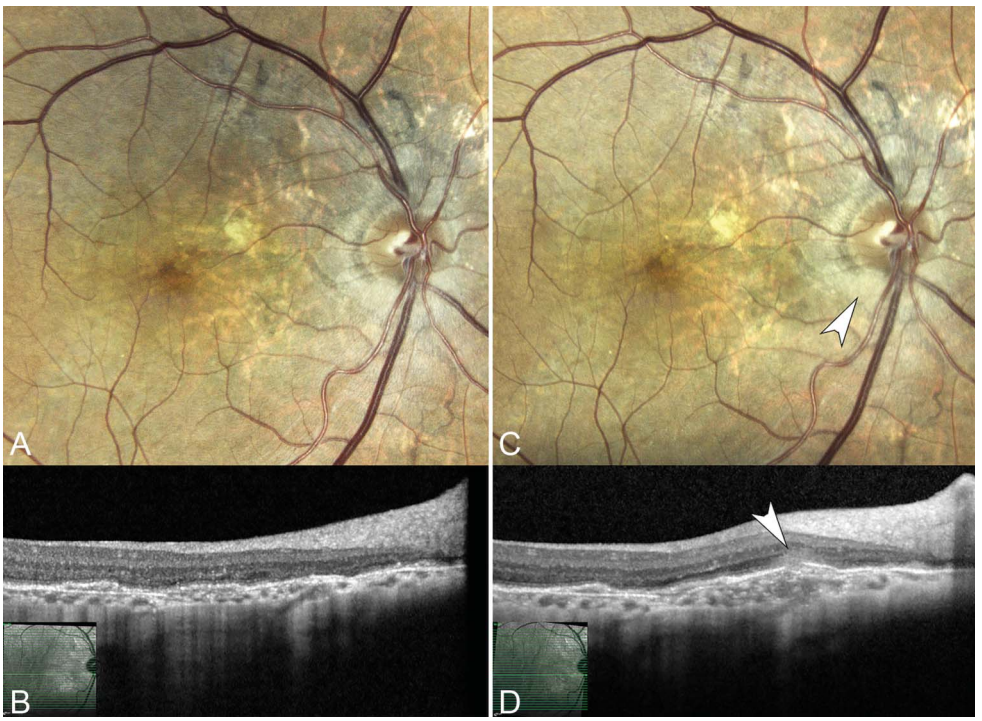

Fig. 1. PIC-like reaction in pseudoxanthoma elasticum and angioid streaks (Patient 4). **A.** Confocal color fundus photography of the right eye acquired 2 months before the PIC-like reaction development shows angioid streaks and macular neovascularization superior to the optic disc with pigmentary changes. **B.** Spectral-domain optical coherence tomography (SD-OCT) B-scan at that time shows a thin choroid and focal area of retinal pigment epithelium/Bruch membrane (RPE/BrM) disruption associated with angioid streaks. **C.** Confocal color fundus photography at the occurrence of PIC-like reaction. There is a whitish lesion at the inferior margin of the optic disc (white arrowhead). **D.** SD-OCT B-scan at that time shows mid-reflective material splitting the RPE/BrM (white arrowhead), an area of RPE discontinuity, focal choroidal thickening, posterior choroidal hypertransmission, and loss of the normal choroidal architecture.

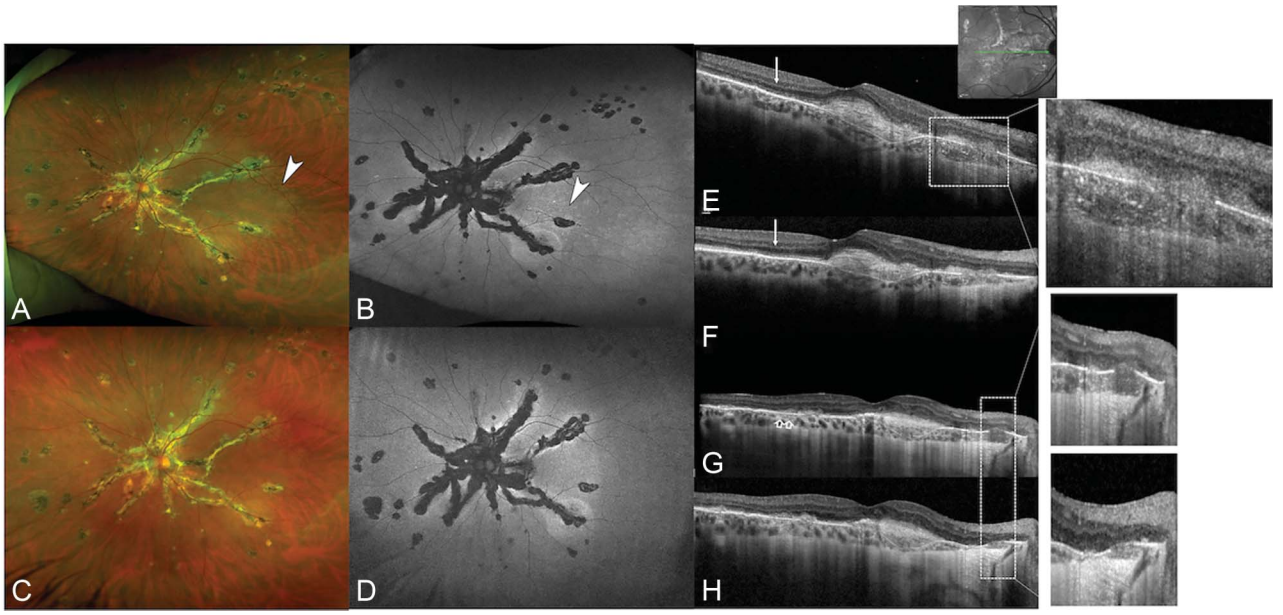

Fig. 2. PIC-like reaction in pseudoxanthoma elasticum and angioid streaks with bilateral subretinal fibrosis and MEWDS-like reaction (Patient 2). **A.** Fundus pseudocolor image of the left eye shows diffuse subretinal fibrosis, multifocal punched-out chorioretinal atrophy, and tiny deep yellow retinal spots (arrowhead) in the near/mid-peripheral temporal retina. **B.** FAF of the same eye shows radial and multifocal hypo-FAF, corresponding to fibrosis and punched-out chorioretinal atrophy, respectively, and faint hyper-FAF spots (arrowhead) in the near/mid-peripheral temporal retina corresponding to the yellow spots on color fundus. **C**–**D.** Fundus pseudocolor image and FAF acquired after 2 months show the regression of the retinal spots and the hyper-FAF lesions. **E.** Spectral-domain optical coherence tomography (SD-OCT) B-scan of the fellow eye shows a large hyperreflective subfoveal lesion, deflecting the Bruch membrane (BrM). Nasally to the fovea, there is an area with moderately reflective material in the sub-BrM and the subretinal space, colocalizing with a BrM defect, focal choroidal thickening, and posterior choroidal hypertransmission (panel). Temporally to the fovea, there is diffuse attenuation of the ellipsoid zone/interdigitation zone (EZ/IZ) (arrow). **F.** SD-OCT B-scan acquired with a follow-up mode shows partial reabsorption of the moderately reflective material nasally to the fovea, with relative thinning of the choroid and reappearance of its normal vascular pattern. There is also a reconstitution of the EZ/IZ temporally to the fovea (arrow). **G.** SD-OCT B-scan acquired 3 years later showing a recurrence of choroidal thickening nasally. Temporally to the fovea, multiple areas with moderately reflective material emerging from RPE/BrM defects, with exquisite inner choroidal involvement, were detected (empty arrows). **H.** SD-OCT B-scan at 2-month follow-up showing the regression of the choroidal thickening but persistence of the hyperreflective material.

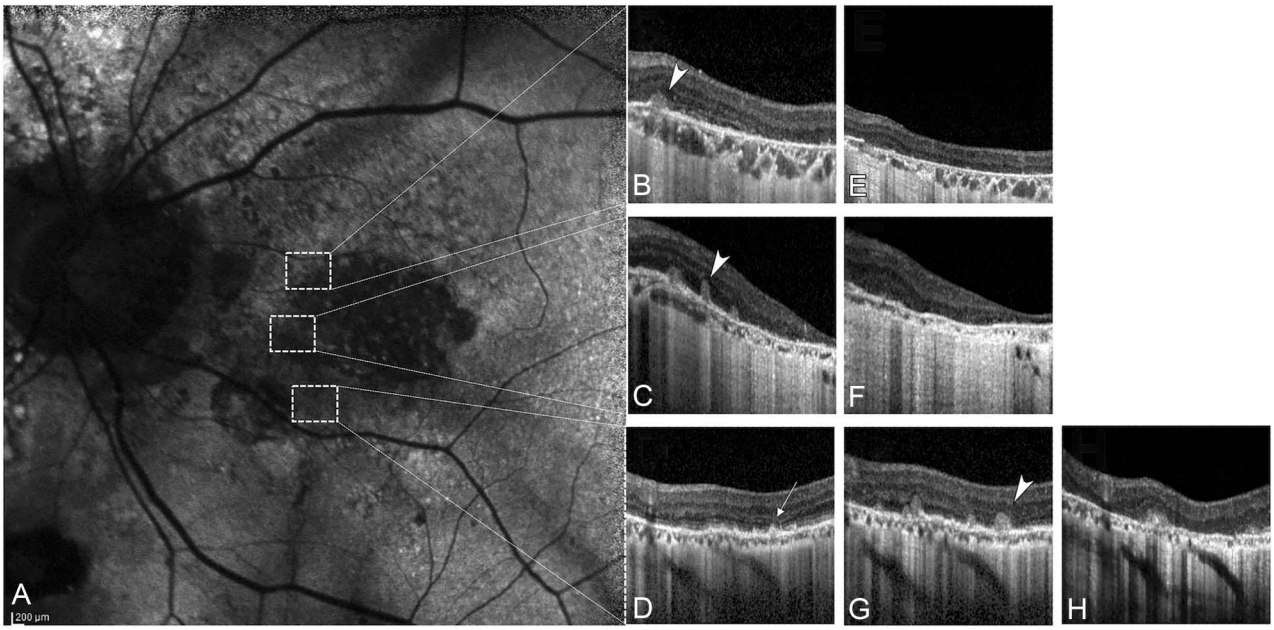

Fig. 3. PIC-like reaction in pseudoxanthoma elasticum with angioid streaks and pattern dystrophy–like features (Case 1). **A.** FAF of the left eye shows hypo-FAF angioid streaks, diffuse hyper/hypo-FAF changes in the peripapillary area, and a large circular area of hypo-FAF in the macula, consistent with retinal pigment epithelium (RPE) atrophy. **B** and **C.** SD-OCT B-scans show extensive RPE atrophy with retinal thinning. There are multiple hump-shaped nodules with homogeneous moderate reflectivity in the photoreceptor layers overlying focal defects in the RPE/BrM complex (arrowheads). There is choroidal thickening with choroidal material with the same reflectivity of the nodule in the part of the inner choroid. **D.** SD-OCT B-scans show multiple focal elevations of the RPE (arrow) with a hyperreflective content and interruption of the overlying ellipsoid/interdigitation zone (EZ/IZ). E, F, G and H. Follow-up SD-OCT B-scans show the evolution of the active PIC-like lesions. The hump-shaped nodules disappeared, leaving extensive RPE atrophy and focal BrM defects. There is diffuse choroidal thinning with shrinkage of the luminal components.

BrM, and the RPE after unveiling antigens usually hidden to the immune system.[9,12] White dot syndromes with PIC-like features have been well described in eyes with PM.[7] Our cases are examples of WDS with PIC-like features in eyes with extensive outer retinal disruption because of inherited or acquired conditions other than PM. We suggest that PIC-like reactions may develop in these eyes with pre-existent outer retinal disruption resulting in loss of the immune privilege. The presence of MNV, characterized by leaky, incompetent vessels, may also trigger or sustain outer retinal inflammation.[8]

Although there is general consent that MEWDS and MEWDS-like reactions primarily involve the photoreceptors,[1] there is no definitive evidence whether inflammation in PIC and PIC-like reactions starts in the outer retina,[14] the RPE/BrM complex,[2,3] or the inner choroid.[15,24] What defines the predominant clinical manifestations is currently unknown. It could be either the target of the autoimmune insult (i.e., the photoreceptors, the RPE/BrM complex, or the inner choroid) or the type of antigen that initiates the inflammatory response. Similarly, the genetic and environmental background predisposing to secondary WDS is undetermined. It is known, for instance, that patients with inherited retinal dystrophies are at increased risk of intraocular inflammation.[25] Further research is warranted related to this topic.

As described in MEWDS-like reactions, PIC-like reactions did not fit the typical demographics of primary PIC. One-quarter of our sample was unusually young (10 years) or unusually old (88 years) than the reported age range for PIC,[6,7] and 13 eyes were emmetropes or slightly myopic (>-3D). Ten cases were unilateral and involved the eye with the primary retinal disease. None of the patients reported a trigger event, such as a history of viral illness or vaccination. These features reinforce the hypothesis that the PIC-like reaction was not incidental but related to the underlying condition.

Notably, most patients with acute PIC-like reactions had a concurrent MEWDS-like reaction. PIC frequently presents with transient outer retinal disruption, suggesting that the two clinical syndromes have a common predisposing background and might be manifestations of the same activation of the immune system. Nonetheless, the natural history and the therapeutic response between the two clinical syndromes may differ considerably.[3] In our retrospective data collection, we could identify at least three patients with PIC-like lesions preceding MEWDS-like reaction (Figure 2, 4, and 5). This temporal sequence may

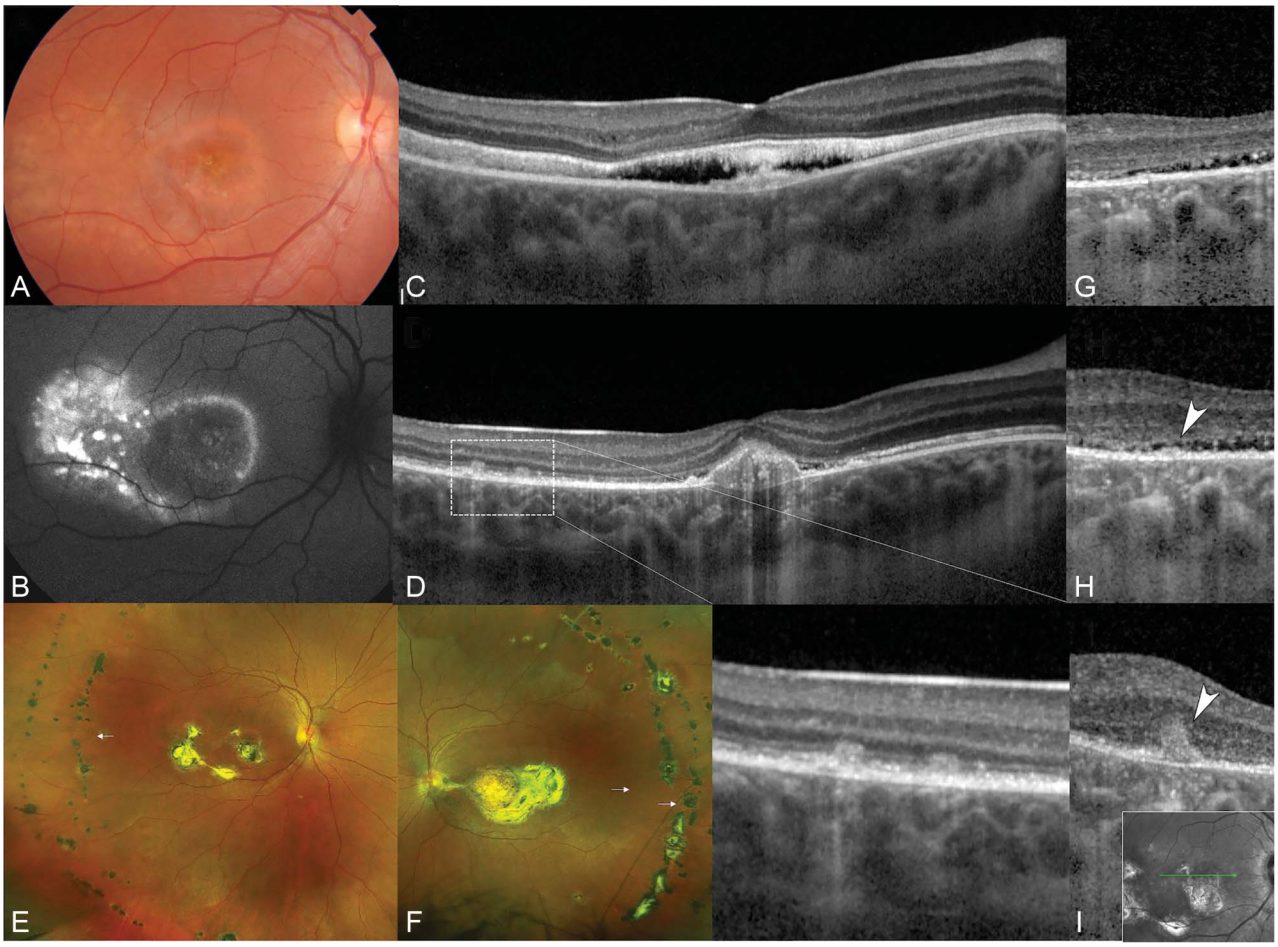

Fig. 4. PIC-like reaction in a patient with autosomal recessive bestrophinopathy (Patient 7). **A.** Fundus photography of the right eye at the first visit shows areas of depigmentation in the macula and yellow deep retinal lesions temporally to the macula. **B.** FAF shows multifocal hyper-FAF consistent with vitelliform lesions. **C.** SD-OCT B-scan shows a shallow neurosensory detachment with photoreceptor elongation and flat RPE detachment under the fovea. **D.** SD-OCT B-scan acquired 2 years later shows the disappearance of the neurosensory detachment and a hyperreflective solid lesion under the fovea corresponding to subretinal fibrosis. Temporally to the fovea, there are hump-shaped nodules with homogeneous moderate reflectivity centered at the photoreceptor layers with choroidal hypertransmission (panel). **E–F.** Pseudocolor fundus photography acquired 5 years later shows bilateral extensive subretinal fibrosis at the posterior pole and areas of punched-out chorioretinal atrophy arranged in multiple curvilinear streaks (Schlaegel lines). **G–I.** SD-OCT B-scan at the last three visits showed a recurrence of a hump-shaped nodule with homogeneous moderate reflectivity (arrowheads) centered at the photoreceptor layers superiorly to the fovea with changes in the inner choroidal optical texture.

support the hypothesis that inflammatory RPE/BrM disruption occurring in PIC-like reactions is a prerequisite for triggering a MEWDS-like reaction. Moreover, the delay in MEWDS-like reaction occurrence may suggest different cellular and molecular mechanisms of inflammation than those occurring in PIC.[3]

Punctate inner choroidopathy–like reactions in apparently unrelated retinal disorders have been only rarely described before.[26] Hady et al[7] have recently reported on the prevalence and characteristics of PIC in eyes with PM and found the inflammatory lesions were often present at the end or along the course of lacquer cracks. Therefore, the authors postulated RPE/BrM complex damage as a possible inflammatory trigger. Fung et al[11] reported a focal area of moderately reflective material emanating from the choroid into the subretinal space through an RPE/BrM complex defect in a case of trauma and choroidal rupture. Bryan et al[4] described a case of Best disease with multiple atrophic pigmented scars resembling punched-out chorioretinal lesions in the inferior periphery. One author from our group reported on punched-out chorioretinal lesions and progressive subretinal fibrosis in a young female patient with fundus flavimaculatus.[27] Finally, Tamaki et al[28] described punched-out chorioretinal lesions and peripheral curvilinear streaks in a 57-year-old woman with generalized rod-cone dystrophy. Besides the aforementioned case reports, a clinical syndrome reminiscent of PIC-like reaction and called "acute retinopathy" was described by Gliem et al[29] in patients with PXE and angioid streaks.

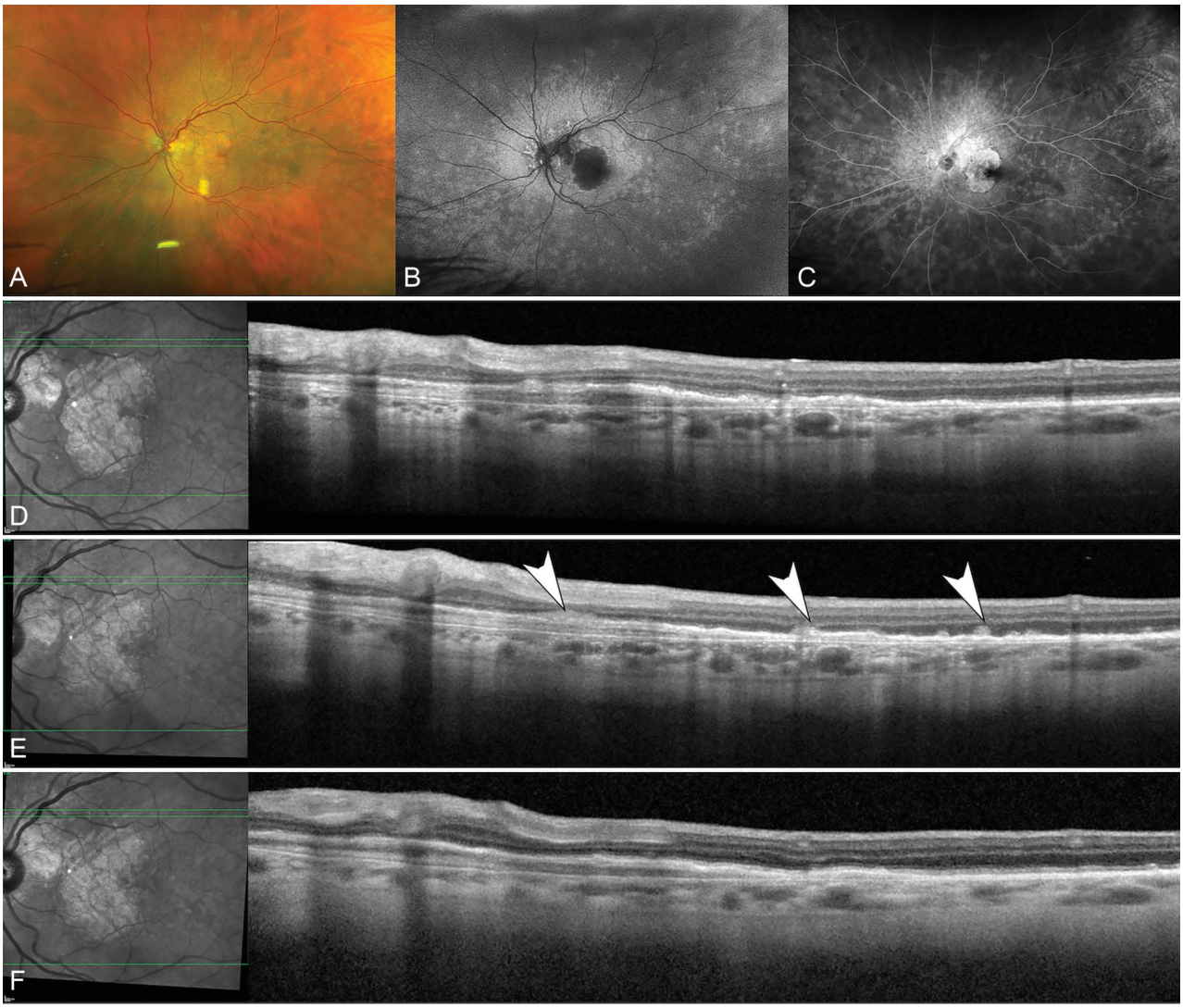

Fig. 5. PIC-like reaction and MEWDS-like reaction in neovascular age-related macular degeneration (Patient 9). **A.** Pseudocolor fundus photography of the left eye shows macular neovascularization and atrophy. There is a yellowish zonal area at the posterior pole with scattered yellow spots in the mid-periphery. **B.** Blue-light FAF shows a zonal hyper-FAF at the posterior pole with mid-peripheral hyper-FAF spots. **C.** Late-phase fluorescein angiography shows a confluent hyperfluorescence at the posterior pole and scattered mid-peripheral hyperfluorescent spots consistent with a MEWDS-like reaction. **D.** SD-OCT B-scan through the superior macula acquired 2 months before the PIC-like reaction occurrence shows a broad pigment epithelial detachment consistent with MNV. The ellipsoid and interdigitation zones (EZ/IZ) can be traced on the temporal side of the B-scan. **E.** SD-OCT B-scan during the PIC-like reaction and MEWDS-like reaction shows multifocal, mid-reflective lesions arising from the MNV and the retinal pigment epithelium discontinuities (white arrowheads). The EZ/IZ is disrupted in the temporal side of the B-scan and colocates with the MEWDS-like reaction. **F.** SD-OCT B-scan acquired 1 month after the PIC-like reaction occurrence shows a regression of the PIC-like lesions and recovery of the EZ/IZ in the temporal side of the B-scan. The patient was treated with oral steroids (0.5 mg/kg/day).

Resolution of active PIC-like reactions was characterized by anatomical sequels, such as outer retina and RPE/BrM complex disruption. Further complications included recurrence, macular atrophy, and subretinal fibrosis. Although our data are retrospective and we have only a short follow-up of some patients, eyes with a PIC-like reaction appeared to have a more aggressive clinical course compared with those with a MEWDS-like reaction alone. Therefore, we suggest that PIC-like reactions should not be observed but specifically managed. Under the assumption of an autoimmune process, steroid therapy may be considered to be added to the treatment of the primary disease or the concurrent complications, such as MNV. Nevertheless, our study did not provide enough data to support therapeutic recommendations, and additional clinical observations are needed.

Among the possible limitations of this study, we acknowledge the retrospective data collection. Although we sorted the EHR for causes of secondary choroiditis, we cannot exclude the presence of underlying undiagnosed diseases, such as tuberculosis or sarcoidosis.

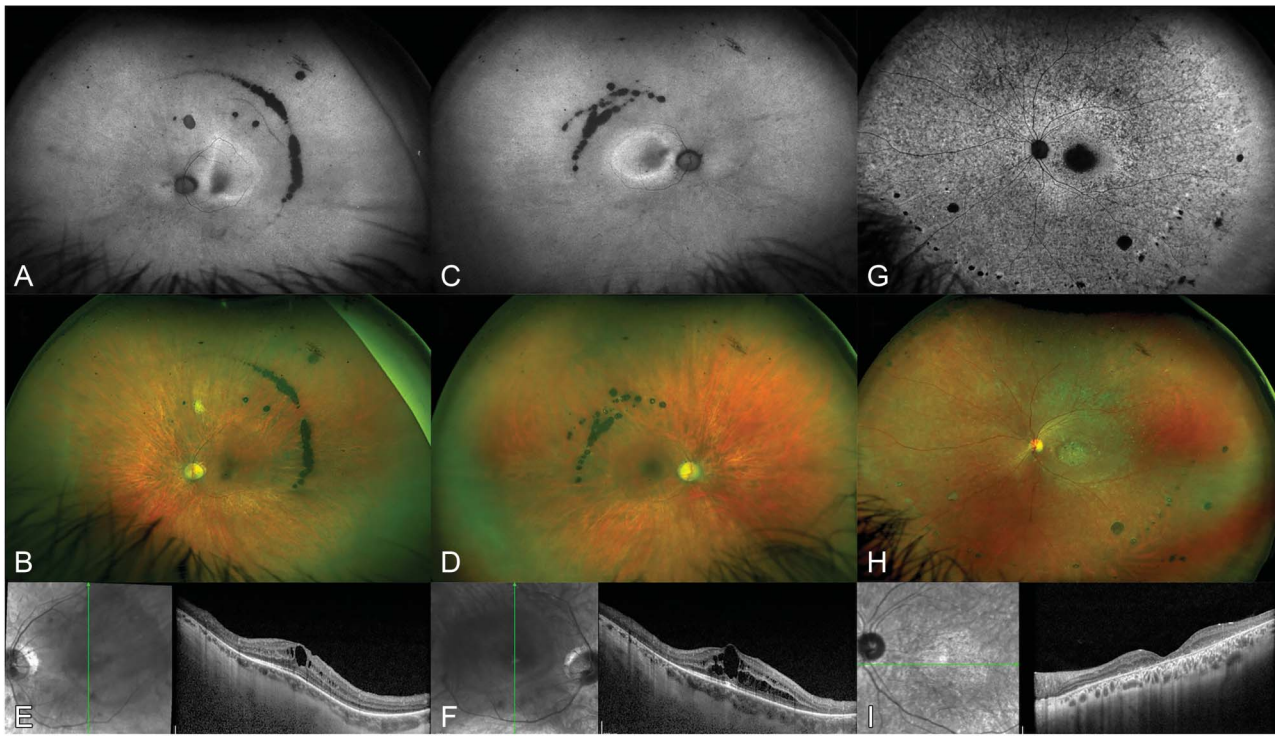

Fig. 6. Chronic PIC-like reaction in eyes with hereditary dystrophies. **A–D.** Pseudocolor fundus photography and FAF of a patient with genetically confirmed retinitis pigmentosa (Patient 15, heterozygous for BBS1 and RP1L1 mutations). Color fundus and autofluorescence show punched-out chorioretinal atrophy arranged in multiple curvilinear streaks (Schlaegel lines) bilaterally. **E and F.** SD-OCT B-scan shows the absence of the ellipsoid and interdigitation zone (EZ/IZ) extrafoveally and macular edema. **G and H.** Pseudocolor fundus photography and FAF of a patient with Stargardt disease (Patient 14). FAF shows extensive hyper-FAF and hypo-FAF changes and punched-out chorioretinal atrophy arranged in a curvilinear streak (Schlaegel lines). **I.** SD-OCT shows a diffuse absence of the EZ/IZ and the external limiting membrane.

Given the rarity of the clinical picture, we also included eyes with chorioretinal scars suggestive of chronic PIC-like reactions. Nonetheless, the pathogenesis of some lesions, such as peripheral curvilinear lesions, is debated and encompasses noninflammatory mechanisms.[20,28] Excluding eyes with PM, we could have missed other potential clinical associations. Finally, the lack of a standardized treatment and follow-up schedule prevented us from reaching definitive guidelines on the appropriate management of PIC-like reactions in the setting of underlying chorioretinal diseases.

In conclusion, a PIC-like reaction may occur in patients with apparently unrelated chorioretinal diseases, suggesting that disruption of the outer retina–RPE/BrM complex–inner choroid may trigger an inflammatory syndrome resembling PIC in susceptible patients. Our study expands the spectrum of reactive, inflammatory lesions presumably promoted by loss of the outer retinal immune privilege in pre-existent chorioretinal diseases. Although they may present together in some patients, active PIC-like reactions should be distinguished from pure MEWDS-like reactions because the clinical course was characterized by further functional and anatomical sequels. Although immunosuppression with steroids may be beneficial for active PIC-like reactions, we cannot conclude on the chronic PIC-like reactions management. Further studies are needed to elucidate the predisposing factors and the treatment response of secondary white dot syndromes.

Key words: punctate inner choroidopathy, idiopathic multifocal choroiditis, multiple evanescent white dot syndrome, white dot syndromes, multimodal imaging, ocular inflammatory disease.

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