NOn-Pachychoroid PEripapillary Schisis (NOPPES) of the retina: a new phenotype and its differential diagnosis

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NOn-Pachychoroid PEripapillary Schisis (NOPPES) of the Retina: A New Phenotype and its Differential Diagnosis

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Purpose: The presence of peripapillary intraretinal fluid (IRF) has a broad differential diagnosis, including several types of neovascular and pachychoroid-related diseases. However, the clinician may encounter cases without signs of neovascular or pachychoroid disease, or any other previously described diagnosis. For these patients, we propose the term NOn-Pachychoroid PEripapillary Schisis (NOPPES) of the retina, and we discuss the differential diagnosis.

Design: A retrospective chart study set in a tertiary referral center for retinal diseases in Amsterdam, the Netherlands.

Methods: Using multimodal imaging, cases suspected of peripapillary pachychoroid syndrome were reviewed. Cases without signs of neovascular or pachychoroid disease were included in this study. These cases were discussed in a group of senior retinal specialists to establish a diagnosis, and if there was no evidence for any previously described diagnostic entity, these cases were categorized as NOPPES.

Results: Four cases of NOPPES were identified, 3 female patients and 1 male patient, aged between 58 and 75 years. Two patients were myopic, and 1 patient had a mild hyperopia. Three out of 4 cases showed unilateral peripapillary IRF, and 1 case had bilateral IRF. No improvement was seen after intravitreal bevacizumab or aflibercept, nepafenac eye drops, oral acetazolamide, vitrectomy with internal limiting membrane peeling, or surgery for carotid stenosis. One case showed a reduction in IRF after starting prednisolone eye drops.

Conclusions: We describe NOPPES, a new form of peripapillary schisis-like IRF. NOPPES seems relatively therapy-resistant. More research is needed to delineate the clinical spectrum of NOPPES and its pathogenesis and treatment.

Key Words: indocyanine green angiography, intraretinal fluid, pachychoroid disease, peripapillary pachychoroid syndrome, retinoschisis

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INTRODUCTION

Subretinal fluid (SRF) in combination with intraretinal fluid (IRF) can be present in a broad spectrum of (chorio)retinal diseases, including neovascular age-related macular degeneration (AMD), advanced diabetic retinopathy, central serous chorioretinopathy (CSC), venous occlusions, and many others.[1] Remarkably, almost all causes of SRF or IRF will cause similar visual symptoms, including blurred vision, metamorphopsia, micropsia, or macropsia, and loss of depth perception. It is important to establish the correct diagnosis, as the prognosis and treatment for the aforementioned diseases differ markedly.[1] When IRF or SRF is situated outside the fovea or even outside the macula, visual symptoms may not always be evident to the patient, as their central visual field can remain unaffected. However, the progression of such diseases may lead to the extension of fluid to the macula or to peripheral scotomas.

One of the causes of peripapillary SRF and IRF is peripapillary pachychoroid syndrome (PPS). This disease was first reported by Phasukkijwatana et al.[2] PPS has been described as part of the pachychoroid disease spectrum, as it shares some clinical signs with other diseases in this group, such as CSC, and may, therefore, share a common pathophysiology.[2–4] Phasukkijwatana and colleagues defined PPS as a peripapillary choroidal thickening with the presence of IRF and/or SRF in the nasal macula. Similar to CSC, PPS was shown to be associated with the male sex and a relatively short axial length. These authors also highlighted the importance of using multiple imaging modalities to establish the diagnosis of PPS.[2] Indocyanine green angiography (ICGA) can be used in PPS to assess both the presence of peripapillary dilated large choroidal veins ("pachyvessels") and peripapillary multifocal choroidal vascular hyperpermeability visible as indistinct hyperfluorescent areas on mid-phase ICGA. According to Phasukkijwatana et al,[2] one of the main characteristics that differentiated PPS from other entities in the pachychoroid disease spectrum is the fact that the nasal macular choroid was significantly thicker on optical coherence tomography (OCT) than the temporal macular choroid, in contrast to CSC.[5] However, in our experience, there seems to be considerable overlap between PPS and CSC.

Besides PPS, peripapillary SRF or IRF can be caused by a wide spectrum of diseases, such as neovascularization

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(eg, in neovascular AMD or polypoidal choroidal vasculopathy), diseases from the pachychoroid disease spectrum (eg, CSC or PPS), diabetic macular edema, or glaucoma-related retinoschisis.[1,6–9] A comprehensive differential diagnosis of peripapillary schisis-like IRF is shown in Table 1. It is important to ascertain the correct diagnosis, using multimodal imaging (MMI), as a correct diagnosis ensures the choice of a fitting treatment, when available. For example, if the fluid is caused by a disease from the pachychoroid disease spectrum, such as CSC or PPS, photodynamic therapy may be the treatment of choice.[10–16]

However, cases may be encountered where IRF and/or SRF can be seen around the optic disc, but in whom hardly any or no abnormalities on fluorescein angiography (FA) or ICGA are observed. In these cases, it may not always be easy to establish an exact diagnosis, and as a result, it may be difficult to prescribe the correct treatment. In this article, we aim to focus on those patients who show peripapillary IRF and/or SRF but display no signs of neovascular or pachychoroid disease.

METHODS

This is a retrospective chart study performed in Amsterdam University Medical Centers, a tertiary referral center for retinal diseases in Amsterdam, the Netherlands. This study adhered to the tenets of the Declaration of Helsinki and the need for further ethics committee evaluation was waived by the Medical Ethical Committee of Amsterdam University Medical Centers based on the retrospective nature of this study. Initially, 2 cases of unexplained peripapillary IRF-like fluid were identified by one of the authors (C.J.F.B.) based on MMI. Subsequently, consecutive cases that were initially suspected to have a form of PPS were reviewed for this study. Using MMI (OCT, FA, ICGA, fundus autofluorescence, and color fundus photography), the cases were examined by 2 of the authors (M.J.S. and L.J.B.P.) for signs of neovascular disease or pachychoroid disease. Neovascular disease was defined as the presence of a macular neovascularization on OCT, together with corresponding leakage on FA. Pachychoroid disease was defined as the presence of large, apparently dilated vessels of the Haller and Sattler layer of the choroid ("pachyvessels"), together with thinning of the overlying choriocapillaris, in combination with hyperfluorescent abnormalities with indistinct borders on mid-phase ICGA, indicative of choroidal hyperpermeability.[3,4] The cases without signs of neovascularization or pachychoroid were discussed with senior retina specialists (E.H.C.V.D., R.M.H.D., and C.J.F.B.) to determine what was deemed the most likely diagnosis per case based on extensive MMI. If PPS or another established cause of peripapillary schisis of the retina (eg, neovascular disease, vitreoretinal traction, diabetic edema, advanced glaucoma, optic disc pit) could not be established, the case was included in this study and described as NOn-Pachychoroid PEripapillary Schisis (NOPPES). The medical records and MMI of these cases were further analyzed and compared to delineate the clinical picture as extensively as possible. Choroidal thickness measurements were performed as described by Phasukkijwatana et al.[2] The choroidal thickness was measured using the measuring tools provided by the software of Heidelberg Engineering. It was defined as the distance between the outer boundary of Bruch's membrane and the choroidal-scleral junction, with the measurement taken perpendicular to Bruch's membrane. In addition to measuring the choroidal thickness in the locations defined by Phasukkijwatana et al, we also measured the choroidal thickness at 1500 μm nasally to the optic disc whenever possible.

TABLE 1. Differential Diagnosis of Peripapillary Schisis-like IRF

Neovascularization, for example, related to neovascular AMD
Polypoidal choroidal vasculopathy
Diabetic macular edema
CSC
PPS
Glaucoma-related peripapillary retinoschisis
Vitreoretinal traction and epiretinal membrane
Myopia-related peripapillary traction
Macular telangiectasia type 2
Optic neuropathies (eg, multiple sclerosis, neuromyelitis optica, and Leber hereditary optic neuropathy)
Inherited anomaly of the optic disc (eg, optic disc pit and morning glory optic disc anomaly)
Tumors (eg, choroidal hemangioma and melanoma)
Paraneoplastic syndromes
Drug toxicity
SNIFR
Inherited retinal diseases (eg, X-linked retinoschisis, retinitis pigmentosa, and bestrophinopathies)
NOPPES

AMD indicates age-related macular degeneration; CSC, central serous chorioretinopathy; IRF, intraretinal fluid; NOPPES, NOn-Pachychoroid PEripapillary Schisis; PPS, peripapillary pachychoroid syndrome; SNIFR, stellate nonhereditary idiopathic foveomacular retinoschisis.

RESULTS

For this case series, a total of 23 patients with peripapillary IRF and/or SRF due to previously suspected PPS were reviewed. Of these 23 patients, 7 patients were identified who did not show any signs of peripapillary neovascular or pachychoroid disease on MMI. These cases were evaluated by the senior retina specialists. Three of these cases were identified to have a clear non-PPS and non-NOPPES diagnosis: 1 case with an optic disc pit, 1 case with a morning glory anomaly resulting in maculopathy, and 1 case with long-standing glaucoma and presumed associated intraretinal cysts around the optic disc. The remaining 4 cases were included in the current study. The flowchart of patient selection is depicted in Figure 1.

Case 1

A 58-year-old man was referred to our tertiary referral center by a local ophthalmologist because of peripapillary IRF in the left eye. The patient had no history of previous ophthalmic disease and had a mild myopia of −3 diopters. General medical history included mild hypercholesterolemia. There was no recent use of medication. The patient complained of blurred vision in the left eye for several months. The best-corrected visual acuity (BCVA) in the Snellen equivalent was measured as 20/16 in the right eye and 20/40 in the left eye. Upon slit-lamp examination, no signs of in-

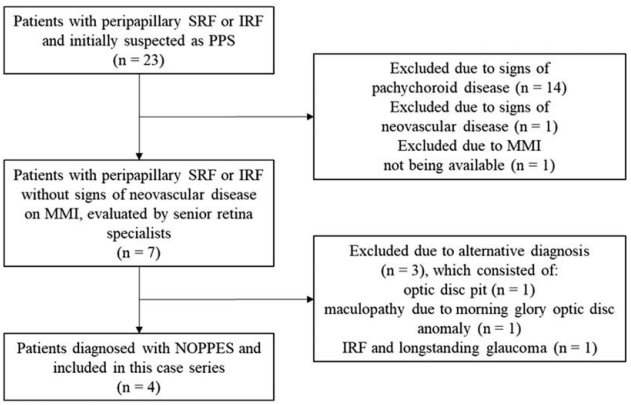

FIGURE 1. Flow diagram that depicts the patient selection for the current case series of patients with NOPPES. IRF indicates intraretinal fluid; MMI, multimodal imaging; NOPPES, NOn-Pachychoroid PEripapillary Schisis; PPS, peripapillary pachychoroid syndrome; SRF, subretinal fluid.

flammation were seen. An OCT scan revealed schisis-like IRF that extended from the nasal side of the optic disc to the nasal part of the macula, including the fovea (Fig. 2A, B). In the nasal macular area, the schisis-like IRF mainly affected the outer nuclear layer, whereas the IRF in the area nasally of the optic disc affected both the outer and inner nuclear layers. The choroid had a normal thickness, without dilated Haller layer vessels ("pachyvessels"). Choroidal thickness measurements can be reviewed in Supplemental Digital Content Table 1 (http://links.lww.com/APJO/A294). At the nasal side of the optic disc, some SRF was present. FA revealed no leakage, and the area with SRF appeared as hypofluorescent on FA. Except for the same hypofluorescent nasal area corresponding to the SRF, ICGA showed no areas of hyperfluorescence or hypofluorescence that could for example be characteristic of choroidal hyperpermeability in the pachychoroid disease spectrum. In the late-phase ICGA, a stellate pattern of hyperfluorescence and hypofluorescence could be observed in the central macula of the left eye. The right eye showed no abnormalities on MMI.

The patient was prescribed prednisolone eye drops 4 times daily, but this proved ineffective as the amount of IRF in the left eye increased under treatment. Later, based on the MMI, vitreoretinal traction was considered a potential (partial) cause of the abnormalities seen. Therefore, it was decided to perform a pars plana vitrectomy with the creation of a posterior vitreous detachment and peeling of the internal limiting membrane in the macula up to the optic disc and in the affected area nasally of the optic disc. The main aim of the procedure was to halt further deterioration of BCVA in the left eye. The surgery was performed without complications. At 4 weeks postoperatively, the patient's symptoms had not improved and the BCVA was 20/

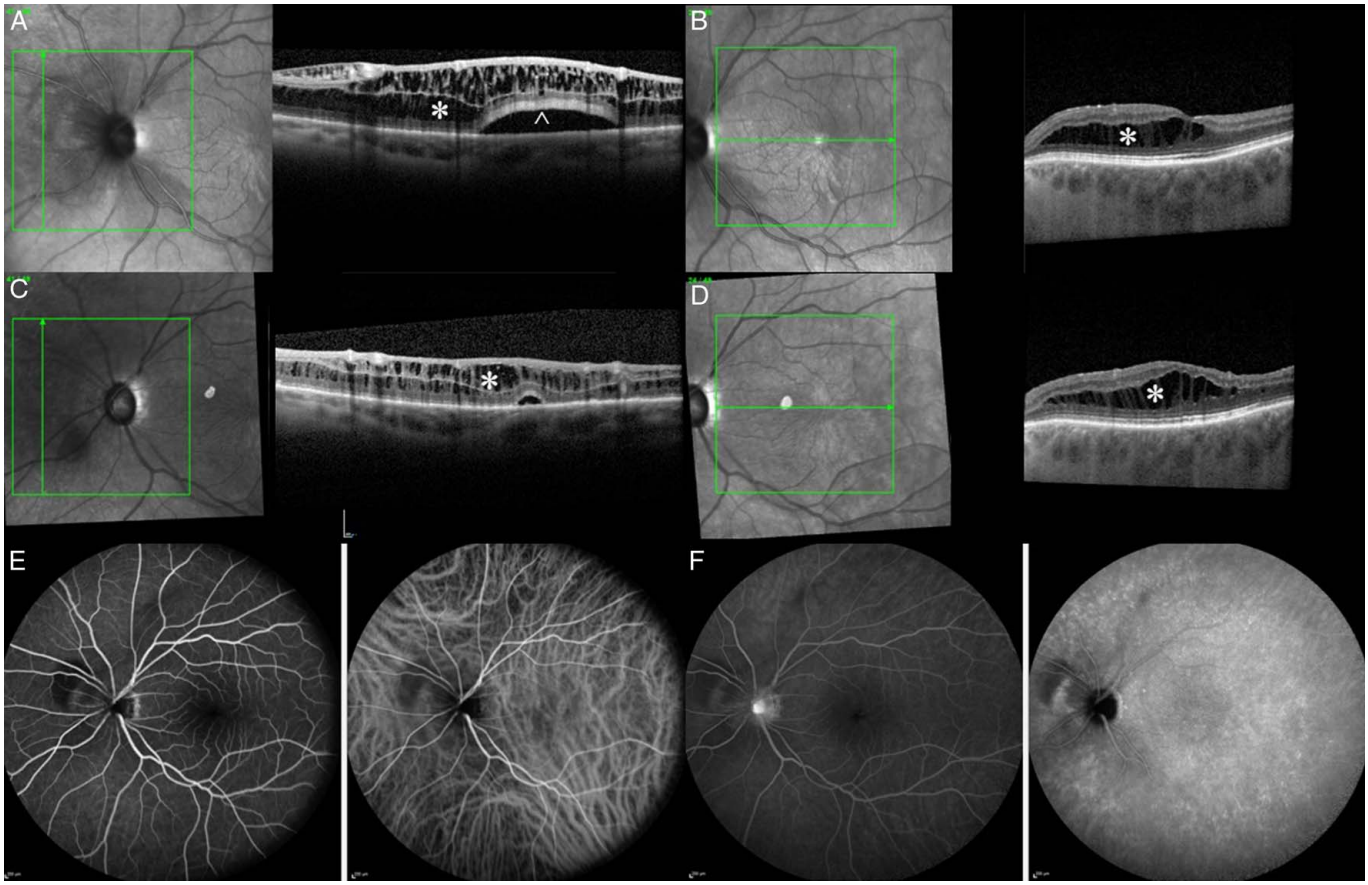

FIGURE 2. MMI of the left eye of case 1. A and B, OCT scans at the time of referral show the presence of schisis-like IRF around the optic disc and extending to the fovea. In the nasal macular area, the schisis-like IRF mostly affects the outer nuclear layer; the IRF in the area nasally of the optic disc affects both the outer and inner nuclear layers. Nasal to the optic disc there is an area with SRF. C and D, OCT scans of the left eye 1 month after PPV had been performed, showing that the amount of IRF has not decreased after PPV with peeling of the ILM. E and F, Early (E) and late-phase (F) FA and ICGA show minimal abnormalities and no signs of focal leakage, pachyvessels, or choroidal hyperpermeability around the optic disc. IRF is marked with white asterisks (*). SRF is marked with white carets (^). FA indicates fluorescein angiography; ICGA, indocyanine green angiography; ILM, internal limiting membrane; IRF, intraretinal fluid; MMI, multimodal imaging; OCT, optical coherence tomography; PPV, pars plana vitrectomy; SRF, subretinal fluid.

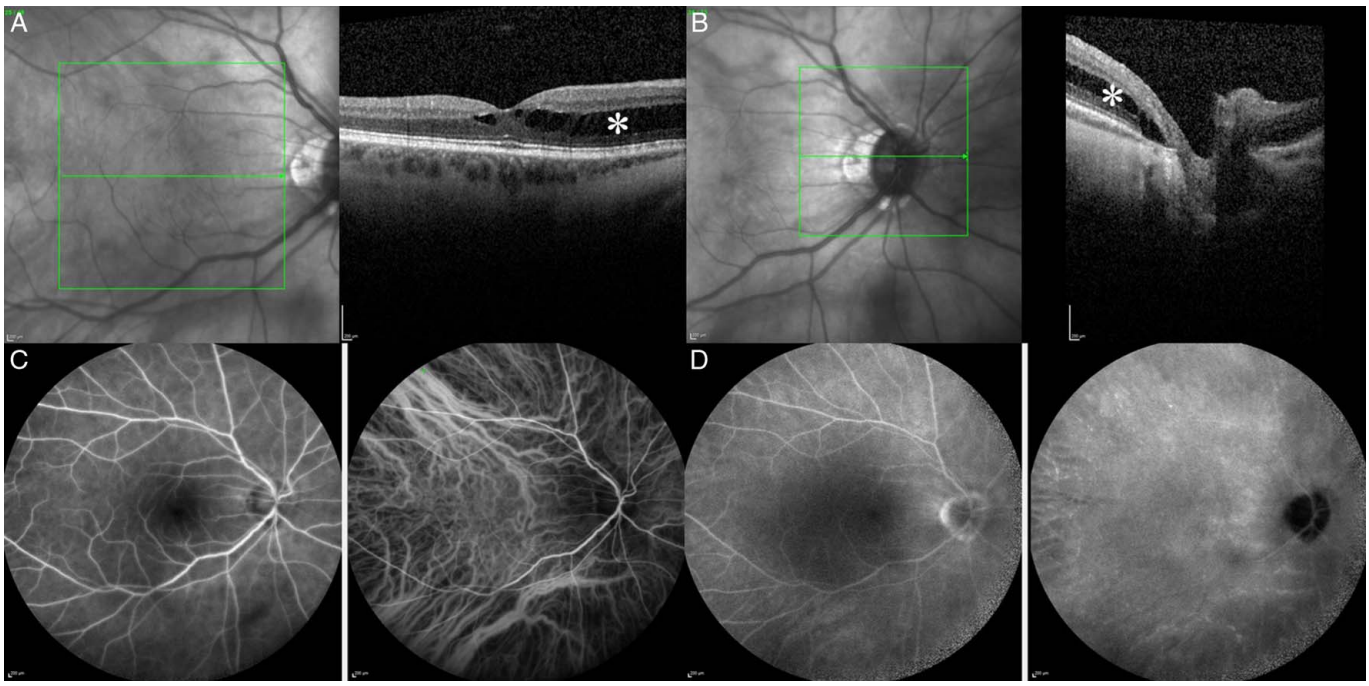

FIGURE 3. MMI of the right eye of case 2 at the time of referral. A and B, OCT scans showing schisis-like IRF that extends from close to the temporal optic disc margin to the fovea. IRF is marked with white asterisks (*). C, Early-phase FA and ICGA image that shows no evident pachyvessels around the optic disc or in the nasal macula. D, Late-phase FA and ICGA image that shows no leakage of dye and no focal choroidal hyperpermeability. FA indicates fluorescein angiography; ICGA, indocyanine green angiography; MMI, multimodal imaging; OCT, optical coherence tomography.

63 in the left eye. On OCT, a reduction of IRF and SRF was present nasally to the optic disc (Fig. 2C). However, on OCT of the macular area, the amount of IRF seemed stable (Fig. 2D), which explained why BCVA and symptoms did not improve.

Case 2

A 63-year-old woman was referred with peripapillary IRF in the right eye. She had previously undergone cataract surgery in the left eye. A mild Fuchs endothelial corneal dystrophy had been diagnosed in both eyes 10 years prior. The refractive error in the right eye was −6 diopters. The current refractive error of the left eye was −5 diopters. As the patient had undergone cataract surgery 35 years ago, information on the preoperative refractive error was missing. The patient was not using any medication at this time. At the time of referral, the patient mentioned a possible increase in blurred vision in the right eye over the past year. The BCVA was 20/40 in the right eye and 20/25 in the left eye. Fundoscopy showed mild peripapillary atrophy, but no other abnormalities. Based on an intraocular pressure of 17 mm Hg, the aspect of the optic disc, and the OCT scan of the ganglion cell layer, there was no suspicion of glaucoma. The OCT scan of the right eye showed schisis-like IRF in the outer nuclear layer, from the temporal optic disc extending to the fovea and a relatively thin choroid (Fig. 3A, B; Supplemental Digital Content Table 1, http://links.lww.com/APJO/A294). FA and ICGA showed no abnormalities. After a discussion with the patient, it was decided to treat only in case of disease progression.

Case 3

A 71-year-old man was referred for peripapillary schisis-like IRF in the left eye. This patient had a non–insulin-dependent type 2 diabetes mellitus, which was fairly well-regulated (recent HbA1c value 48.7 mmol/mol). The patient was using metformin, dapagliflozin, acetylsalicylic acid, hydrochlorothiazide, simvastatin, ezetimibe, and desloratadine. The right eye had a poor BCVA of 20/640 (Snellen equivalent) after a history of recurring herpes keratitis, perforating keratoplasty, and secondary glaucoma. The left eye had undergone cataract surgery at a different center 10 years ago, and the preoperative refractive error was unknown to us. The schisis-like IRF of the left eye was noticed on an OCT scan by the referring ophthalmologist 2 months before referral and had increased since then. BCVA was 20/16 in the left eye. Fundoscopy showed several microaneurysms and small hemorrhages in the posterior pole. There was no evidence of glaucoma. The OCT scan showed a schisis-like picture of the retina surrounding the optic disc, including the nasal macula, which did not resemble diabetic macular edema (Fig. 4A, C, E). The choroid was thin, both in the central macula and the peripapillary area (Supplemental Digital Content Table 1, http://links.lww.com/APJO/A294). FA showed several microaneurysms with leakage, but FA and ICGA did not show clear leakage in the peripapillary area (Fig. 4B, D, F). The patient commenced prednisolone eye drops 3 times daily and nepafenac once daily. However, after 4 weeks, the amount of IRF had increased. In addition, subsequent treatments with intravitreal bevacizumab, subconjunctival betamethasone, and oral acetazolamide had no effect on the schisis-like IRF. At that time, a second combined FA-ICGA of the left eye again showed signs of nonproliferative diabetic retinopathy without peripapillary leakage. However, FA showed a delayed and incomplete filling of retinal vasculature, leading to the potential diagnosis of ocular ischemic syndrome in the left eye. An ultrasound examination of the carotid arteries showed a stenosis of the left carotid artery, and the patient was referred for a carotid endarterectomy. Six months after this surgery, no change in IRF had been observed in the left eye.

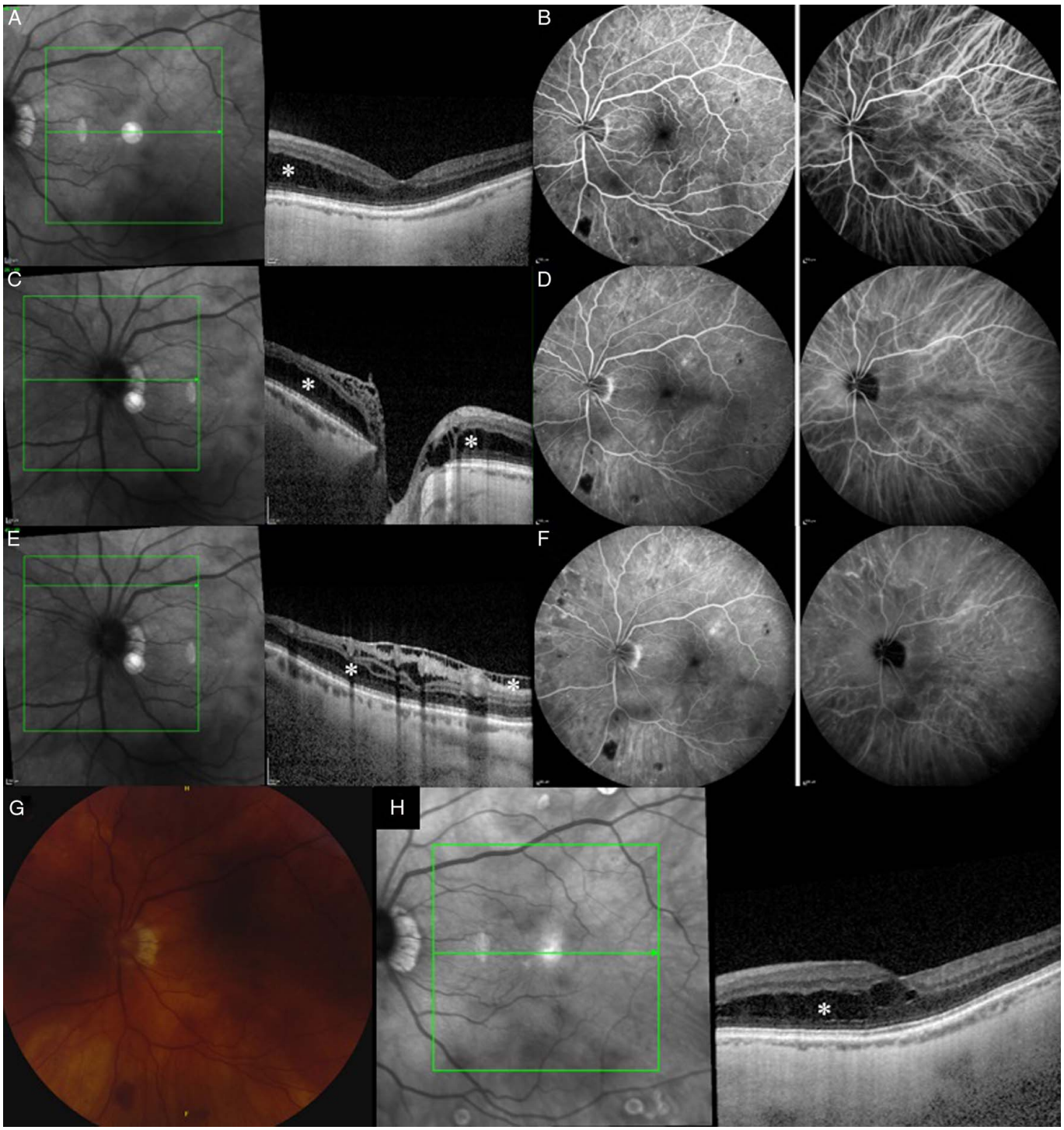

FIGURE 4. MMI of the left eye of case 3. A–G, MMI at the time of referral. A, C, and E, OCT scans showing an intraretinal schisis-like picture, with fluid (asterisks) mostly in the outer nuclear later, but also in multiple inner retinal layers of the peripapillary retina up to the nasal macula. B, D, and F, Early (B), mid (D), and late-phase (F) FA and ICGA showing no leakage around the optic disc and no evident pachyvessels or choroidal hyperpermeability. G, Color fundus photo showing peripapillary atrophy and several hemorrhages. H, OCT scan 6 months after carotid endarterectomy had been performed. The amount of IRF (asterisk) had not improved and had actually progressed towards the fovea. FA indicates fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MMI, multimodal imaging; OCT, optical coherence tomography.

Case 4

A 75-year-old man was referred with bilateral peripapillary schisis-like IRF. The patient had a history of coronary heart disease and previous coronary artery bypass graft surgery, multiple myeloma, and type 1 diabetes mellitus. He was also known to have mild nonproliferative diabetic retinopathy. Systemic medication included atorvastatin, acetylsalicylic acid, rivaroxaban, and pantoprazole. Upon presentation at our institution, a BCVA of 20/20 was measured in the right eye and 20/29 in the left eye. Both eyes had a mild hyperopia of 0.75 diopters. The intraocular pressure was 15 mm Hg in the right eye and 17 mm Hg in the left eye. Fundoscopy revealed many cuticular drusen in both eyes. OCT scans

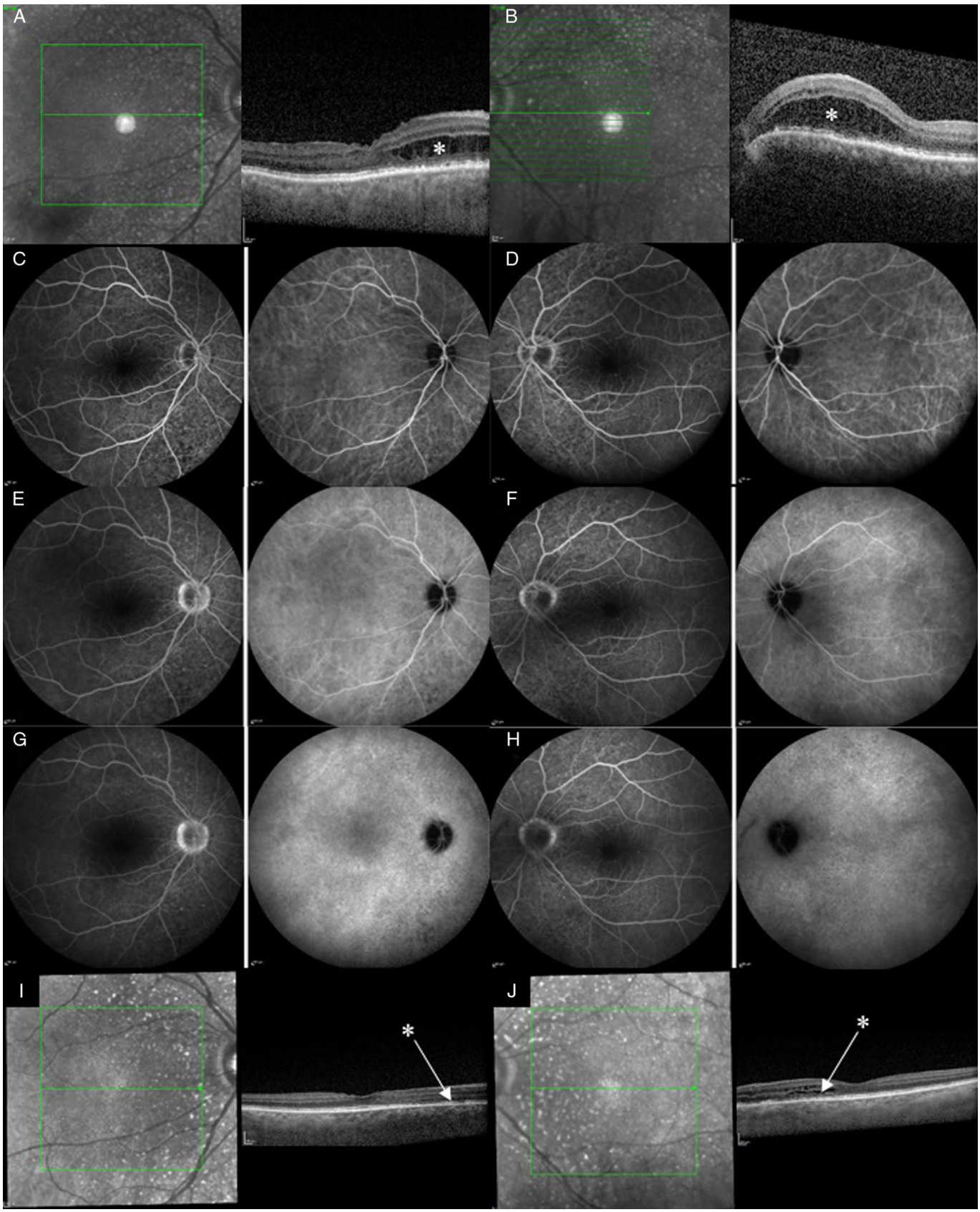

FIGURE 5. MMI of both eyes of case 4. A–H, MMI at the time of referral. A and B, OCT scan of the right (A) and left (B) eye showing IRF present between the temporal disc margin and the nasal macula, as well as cuticular drusen and reticular pseudodrusen (subretinal drusenoid deposits). C–H, Early (C and D), mid (E and F), and late-phase (G and H) FA shows diffuse speckled hyperfluorescence compatible with cuticular drusen, without signs of leakage, pachyvessels, or choroidal hyperpermeability on either FA or ICGA images. I and J, OCT scan of the right (I) and left (J) eye showing a reduction of IRF, after the patient had used prednisolone eye drops 2 to 4 times daily for 2 months. FA indicates fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MMI, multimodal imaging; OCT, optical coherence tomography.

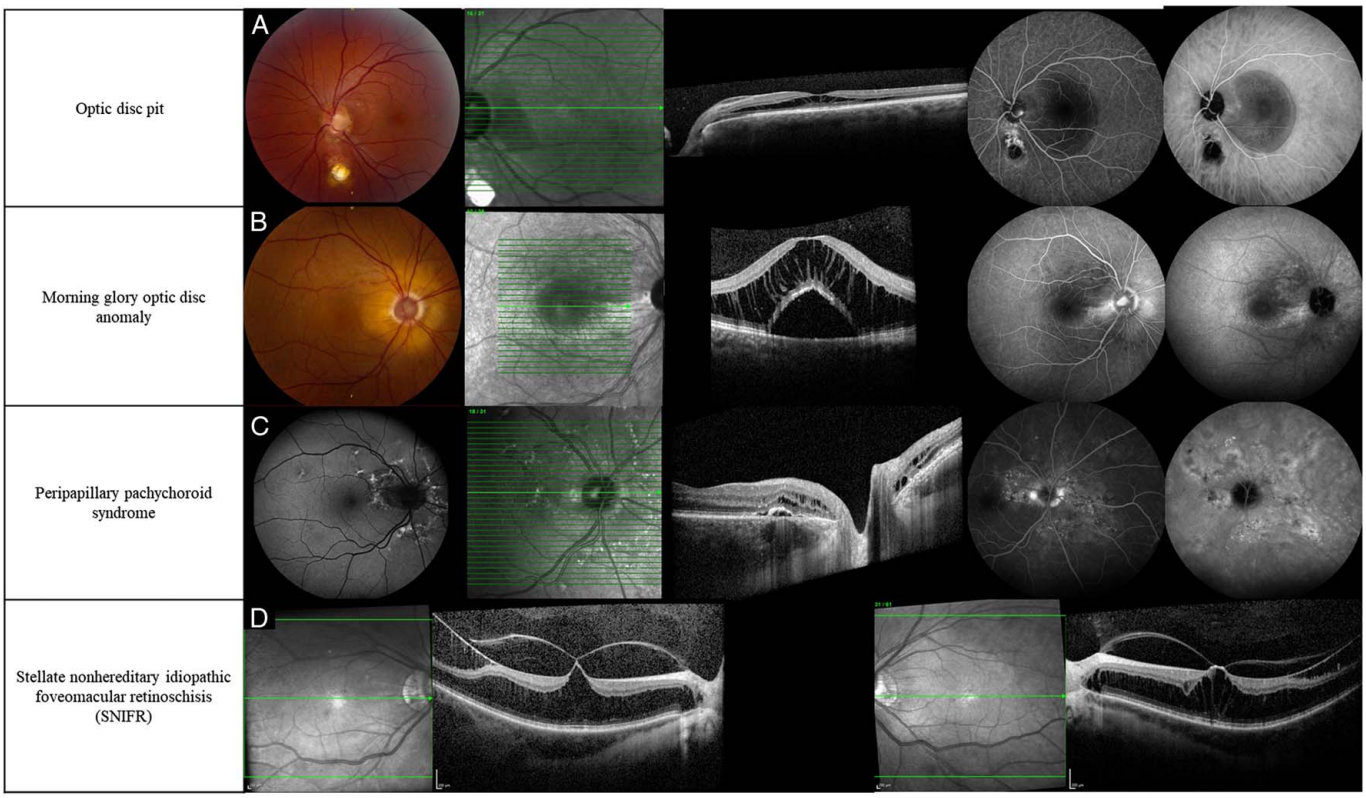

FIGURE 6. Example cases of alternative diagnoses that need to be ruled out when considering nonpachychoroid peripapillary schisis. A, MMI of a case with an optic disc pit with associated IRF, and a small inferior optic disc coloboma: color fundus photograph showing optic disc pit; OCT scan showing extensive IRF arising from the peripapillary area and extending to the fovea; FA and ICGA show minor hyperfluorescence and no clear signs of neovascularization or pachychoroid. When considering the diagnosis of NOPPES, the presence of a congenital optic disc pit should be ruled out by looking at the optic disc on fundoscopy and OCT. In the case of such an optic disc pit, a cavity with gray discoloration can be seen within the optic disc, typically at the temporal disc margin. B, MMI of an example case with a morning glory optic anomaly and associated maculopathy: color fundus photograph showing morning glory aspect of the optic disc: the optic disc appears enlarged, with blood vessels emanating individually over the optic disc rim in a radial manner; OCT scan showing extensive IRF and SRF in the central macula; FA and ICGA showing mild hyperfluorescence around the optic disc. C, MMI of an example of PPS: FAF showing hyperautofluorescent and hypoautofluorescent irregular changes around the optic disc; OCT scan showing IRF on the nasal and temporal side of the optic disc; late-phase FA showing hyperfluorescent and hypofluorescent changes around the optic disc with some possible focal leakage near the temporal edge of the optic disc, and on mid-to-late-phase ICGA patchy, focal indistinct hyperfluorescent areas that are typical of the pachychoroid disease spectrum. The presence of hyperfluorescence on FA and ICGA discerns PPS from NOPPES. D, OCT scans of a patient with bilateral SNIFR, showing extensive IRF in the central macula, with central vitreomacular traction. The abnormalities in SNIFR are typically centered around the fovea, whereas the IRF in NOPPES is centered around the optic disc. FA indicates fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MMI, multimodal imaging; NOPPES, NOn-Pachychoroid PEripapillary Schisis; OCT, optical coherence tomography; PPS, peripapillary pachychoroid syndrome; SNIFR, stellate nonhereditary idiopathic foveomacular retinoschisis; SRF, Subretinal fluid.

revealed peripapillary IRF (more in the left than in the right eye) that surrounded the optic disc and extended to the nasal macula (Fig. 5A, B). Choroidal thickness was difficult to assess on OCT in both eyes, but no evident pachyvessels were visible. Combined FA-ICGA showed cuticular drusen but no signs of either peripapillary or macular neovascularization or pachychoroid disease. Treatment with prednisolone eye drops 4 times daily resulted in a reduction of IRF (Fig. 5I, J) and could later be tapered to 2 times daily without improvement of BCVA.

DISCUSSION

In this case series, we describe NOPPES of the retina, which consists of peripapillary schisis-like IRF, in 1 case in combination with localized SRF, that was not caused by macular neovascularization, a diagnosis from the pachychoroid disease spectrum, such as PPS, or any other diagnostic entity that has been described previously. NOPPES may, therefore, be considered a differential diagnostic entity that has not been described within the broad spectrum of diseases that can cause peripapillary or nasal macular IRF, as well as SRF.[1,6]

NOPPES provides a challenge for clinicians, as alternative diagnoses should first be excluded.

The presence of peripapillary IRF has a broad differential diagnosis (Table 1), and some notable examples are depicted in Figure 6. Diseases that can cause peripapillary IRF range from neovascular diseases (eg, neovascular AMD and polypoidal choroidal vasculopathy) to diseases that are part of the pachychoroid disease spectrum [PPS (Fig. 6C), CSC], tumors (choroidal hemangioma and melanoma), advanced glaucoma, and vascular eye disease (diabetic retinopathy and retinal vein occlusions).[1,6] Furthermore, ocular developmental disorders, such as an (acquired) optic disc pit (Fig. 6A), or a morning glory optic disc anomaly (Fig. 6B) can cause a similar phenotype. Mechanical vitreoretinal causes of peripapillary schisis-like clinical pictures include, for example, peripapillary vitreoretinal traction (with or

without associated high myopia). Stellate nonhereditary idiopathic foveomacular retinoschisis is another clinical picture of unknown origin that may resemble and even partly overlap with NOPPES (Fig. 6D). Advanced glaucoma is also known as a possible cause of peripapillary retinoschisis.[7–9] This type of retinoschisis usually occurs in the retinal nerve fiber layer and may present with an outer macular hole or a defect in the lamina cribrosa visible on OCT or adaptive optics.[9] These diseases may actually encompass a range of different pathophysiological mechanisms resulting in peripapillary schisis-like IRF. To disentangle these different causes of peripapillary IRF, it is important to perform a thorough clinical assessment with meticulous fundoscopy and MMI, if needed with FA and ICGA, to establish the correct diagnosis and, subsequently, initiate the correct treatment if possible. Fundoscopy can reveal the presence of drusen and other retinal pigmentary changes, retinal hemorrhages, and optic disc anomalies. OCT scans can help further visualize the location of the IRF and possibly SRF.

In addition, the thickness of the choroid and the presence of pachyvessels can be assessed, which may point toward a disease that is part of the pachychoroid disease spectrum. However, in our experience, performing FA and especially, if available, ICGA, can be of key value as an imaging method in the differential diagnosis of diseases with schisis-like parapapillary or peripapillary IRF. This is especially true when using confocal imaging systems, which can provide a more detailed assessment in particular of the choroidal vascular architecture and abnormalities. If there is focal leakage on FA and (multi)focal indistinct mid-phase hyperfluorescence on ICGA, in combination with a thick peripapillary choroid and dilated Haller layer vessels, this suggests a pachychoroid etiology and PPS (Fig. 6C). In PPS, retinal pigment epithelial detachments may also be present. When there is a normal or thin choroid on OCT, with an absence of the aforementioned FA or ICGA abnormalities, other diagnoses such as myopic maculopathy, vitreoretinal traction, stellate nonhereditary idiopathic foveomacular retinoschisis, and NOPPES, should be considered. In the cases presented in this study, there was a variance in choroidal thickness (Supplemental Digital Content Table 1, http://links.lww.com/APJO/A294). However, it can be noted that in none of these patients, the choroidal thickness nasally to the fovea was greater than the choroidal thickness temporally to the fovea, as is the case in patients with PPS. The peripapillary schisis-like IRF in the patients with NOPPES in this study appeared remarkably resistant to treatment. One patient (case 4) showed a decrease of IRF after treatment with prednisolone eye drops, but treatment with these drops, nepafenac eye drops, oral acetazolamide, intravitreal bevacizumab or aflibercept, or even vitrectomy with internal limiting membrane peeling or surgery for carotid stenosis did not result in any improvement in cases 1 and 3.

The pathophysiology of NOPPES is unknown. NOPPES does not seem to display any signs of neovascular or pachychoroid disease, and there are no other clues that pertain to its origin. Cases 2 and 3 showed some temporal juxtapapillary chorioretinal atrophy, which may suggest a role for the breakdown of the outer blood-retina barrier as a pathogenetic contributor in the occurrence of NOPPES in these cases. The apparent lack of response to a range of treatments, at least in 2 of our described cases (cases 1 and 3), could suggest a degenerative disease mechanism. The response to prednisolone drops in case 4 could suggest a potential inflammatory component in this patient who also showed cuticular drusen without choroidal neovascularization. Future studies on NOPPES-like phenotypes may improve our understanding of this clinical manifestation, the clinical spectrum, its pathogenesis, and potential treatment options.

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