Paracentral acute middle maculopathy after uneventful ocular surgery with local anaesthetic blocks Carolina Bernal-Morales, MD,¹ Daniel Velazquez-Villoria, MD PhD,² Juan Manuel Cubero-Parra, MD,³ Pearse A. Keane, MD FRCOphth,⁴ Dawn A. Sim, MD FRCOphth, ⁴ Alfredo Adán, MD PhD, ^{1,5} Adnan Tufail, MD FRCOphth, ⁵ Javier Zarranz-Ventura, MD PhD^{1,4,5} ¹Clinic Institute of Ophthalmology (ICOF), Hospital Clinic, Barcelona, Spain ²Vitreo-Retinal Unit, Hospital Povisa, Vigo, Spain ³Hospital La Arruzafa, Cordoba, Spain ⁴NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom ⁵Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona. Spain **Corresponding author:** Carolina Bernal-Morales, MD Clinic Institute of Ophthalmology (ICOF), Hospital Clínic, Barcelona C/ Sabino Arana 1 Barcelona Email: carolbernalmo@gmail.com Running title: Paracentral middle maculopathy after local anaesthesia.

Abstract 34 **Objective:** To describe the role of local anaesthetic blocks as a potential cause of 35 paracentral acute middle maculopathy (PAMM) after uneventful ocular surgery. 36 Methods: Retrospective, observational, international, multicentre case series. Nine 37 cases of PAMM with associated visual loss following uneventful ocular surgery with 38 local anaesthetic blocks were observed in a 9-year period (2011-2020). 39 40 Demographic, ocular and systemic data, anaesthetic data and surgical details were collected. Visual acuity (VA), fundus photography, fluorescein angiography, optical 41 coherence tomography (OCT) and optical coherence tomography angiography 42 (OCTA) images were reviewed. 43 44 Results: All nine cases were associated with decreased VA at 24h postoperative check (ranging from hand movement to 20/200). A hyperreflective band within the 45 middle retinal layers was observed in the structural OCT in the acute phase. 46 evolving to thinning and atrophy of the inner retinal layers in sequential follow-up 47 48 scans performed. Fluorescein angiography showed delayed perfusion in early arterial phase with normal perfusion in late venous phases. OCTA showed 49 50 decreased perfusion in the deep capillary plexus. Visual recovery was variable between cases during follow-up (ranging from count fingers to 20/20). 51 **Conclusions:** A combination of a vasoconstrictive effect of the anaesthetic agent, 52 an intraocular pressure spike and a mechanical effect of the volume of anaesthetic 53 injected may result in decreased retinal artery perfusion and be evidenced as 54 PAMM in OCT scans. PAMM may present as a potential complication of local 55 anaesthetic blocks in cases of unexpected visual loss after uneventful ocular 56 surgery. 57

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Keywords:

Anaesthetic block; Paracentral Acute Middle Maculopathy; peribulbar; retrobulbar; sub-Tenon; optical coherence tomography.

Introduction

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Paracentral acute middle maculopathy (PAMM) is an optical coherence 65 tomography (OCT) finding defined as a band-like hyperreflective lesion mostly 66 confined to the inner nuclear layer (INL) owing to ischaemia or infarction of the 67 intermediate and deep retinal capillary plexus. 1-3 Several retinal diseases have 68 been associated with this finding, including retinal vascular occlusive disorders 69 70 such as branch or central retinal arterial occlusions (RAO), cilioretinal artery 71 occlusion, central retinal vein occlusion (RVO), and systemic diseases such as diabetic retinopathy, hypertensive retinopathy, Purtscher retinopathy or sickle cell 72 retinopathy.^{4,5} PAMM may be seen as as an isolated finding or associated with 73 other OCT features, including hyperreflectivity of the superficial retinal layers 74 75 (retinal nerve fiber layer -RNFL-, ganglion cell layer -GCL- and Inner plexiform layer -IPL-) in RAO or diffuse thickening and macular edema in RVO. 76 Local anaesthetics (sub-Tenon, peribulbar and retrobulbar) have been employed in 77 ocular procedures for decades, and although these techniques are widely used. 78 they are not free of complications. Well-known risks include intraorbital 79 haemorrhage, local toxicity and, in worst case-scenarios, ocular perforation. The 80 presence of impaired blood flow in the optic nerve head and therefore the retina 81 has also been reported. Small case series and case reports describing retinal 82 artery occlusions following cataract or pterygium surgery under local anaesthesia 83 have been reported, using retrobulbar, peribulbar or sub-Tenon's techniques.^{6–12} 84 Whereas in some clinical presentations these features are obvious, sometimes the 85 fundus phenotype is more subtle and alterations can easily be overlooked in 86 fundoscopy, and in certain cases, even in OCT images. 87 With this aim, we hereby describe the clinical phenotypes of a series of cases of 88 PAMM and unexpected postoperative visual loss after uneventful ocular surgery 89 with local anaesthetic blocks. The detailed ocular and systemic clinical 90 characteristics of these cases are described as an attempt to share this data with 91 the ophthalmic community, in order to identify future potential relationships 92 between these preoperative features and PAMM which could help predict this 93 94 postoperative complication.

Methods

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Nine cases of PAMM following local anaesthetic blocks were observed in four 97 medical centres, three in Spain (Hospital Clínic of Barcelona, Hospital la Arruzafa 98 of Córdoba and Hospital Povisa of Vigo) and one in the United Kingdom 99 (Moorfields Eye Hospital, London). Data collection was systematically performed 100 retrospectively from clinical records produced during routine clinical care. 101 Demographics and systemic data, including cardiovascular data and medications 102 103 used were collected from all study centres. Ocular data included axial length and refraction. Details of the anaesthetic procedures included type of local anaesthesia. 104 (sub-Tenon's, peribulbar or retrobulbar), dose and volume of anaesthesia 105 administered, and surgical details were collected from surgical logbooks. Visual 106 107 acuity (VA), fundus photography, fluorescein angiography (FA), OCT, Spectral Domain OCT (SD-OCT) and optical coherence tomography angiography (OCTA) 108 109 images, when possible, were reviewed. When appropriate, electrodiagnostic tests (EDDs) were performed at physician discretion. This study was approved by the 110 institutional review board at Hospital Clínic (Comité Ético de Investigación Médica, 111 CEIM) and was conducted in accordance with the Declaration of Helsinki. 112

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Results

Baseline Characteristics

116 Nine cases developed PAMM (seven men, two women, age range 40 to 83 years) with associated severe vision loss immediately after uneventful ocular surgery in a 117 nine-year period (2011-2020). Indications for surgery were cataract (66.6%, 6/9) or 118 pterygium surgery (33.3%, 3/9), performed under local anaesthesia of different 119 120 types (peribulbar 66.6%, 6/9; retrobulbar, 22.2%, 2/9; Sub-Tenon's, 11.1%, 1/9). No optic nerve injury or globe perforation was derived from retrobulbar or 121 peribulbar blocks in any of these cases. Five patients presented typical findings of 122 CRAO (55.5%, 5/9), but in the rest of cases, ischemic damage to the retina was 123 subtle in fundoscopy and diagnosis was made by structural OCT examination 124 (44.4%, 4/9). In all cases, macular OCT images obtained 24-hours after surgery 125 revealed a hyperreflective band at the level of the inner retinal layers (from inner 126 nuclear layer -INL- to outer plexiform layer -OPL-) sparing the outer retina. 127

consistent with the diagnosis of PAMM. Optic nerve head OCT images were also 128 obtained and showed no additional findings. Sequential SD-OCT (Cirrus HD-OCT, 129 Carl Zeiss Meditec Inc, Dublin, CA, USA) images captured during follow-up 130 showed progressive thinning of the inner retinal layers. In two cases, VA improved 131 after presentation (22.2%, 2/9), whereas in 7 out of 9 cases vision alteration was 132 permanent (77.7%, 7/9). The details of each individual case are described below. 133 Demographics and clinical characteristics of cases included in the series are 134 135 summarized in Table 1. Case 1 136 A 40-year-old man underwent uneventful pterygium surgery in his right eye (OD) 137 under sub-Tenon's block (2% lidocaine). No significant past medical history (PMH) 138 139 was described. Twenty-four hours after the procedure, the patient complained of a central scotoma and VA was 20/200. Fundoscopy revealed a subtle perifoveal 140 yellowish halo with thinning of the retinal vessels in the macular region (Fig. 1). FA 141 showed a delayed arterial filling in the macular bundle, with normal perfusion in the 142 late phase. SD-OCT images (Spectralis, Heidelberg Engineering, Heidelberg, 143 Germany) revealed a hyperreflective band at the level of INL, consistent with the 144 diagnosis of PAMM. EDDs tests showed OD marked macular dysfunction without 145 generalized retinal dysfunction. Conservative management was indicated, and six 146 weeks after the procedure OD VA improved to 20/32, with persistence of the 147 hyperreflective band, thinning of the inner retinal layers and moderate macular 148 atrophy in the SD-OCT scan. 149 Case 2 150 An 82-year-old man with an OD preoperative VA of 20/50 underwent an uneventful 151 152 phacoemulsification surgery under retrobulbar block (4mL of a mixture of bupivacaine 0.75%, lidocaine 5% and hyaluronidase 150 IU). Significant PMH 153 included hypertension and atrial fibrillation on anticoagulant treatment. In the 24-154 hour postoperative check, he complained of central scotoma and VA was 20/200. 155 Funduscopy showed a cherry red spot with whitening of the perifoveal region 156 consistent with the diagnosis of CRAO. OCT scans revealed a hyperreflective band 157 in the inner retinal layers. After 6 months of follow-up, VA was light perception (LP) 158 and OCT scans confirmed a progressive retinal and optic nerve atrophy. 159

100	Case 3
161	An 80-year-old woman with an OD preoperative VA of 20/50 underwent an
162	uneventful phacoemulsification surgery under peribulbar block in her OD (6mL of a
163	mixture of lidocaine 1%, bupivacaine 0.5% and hyaluronidase 150 IU). Significant
164	PMH included diabetes mellitus, HTA, hypercholesterolemia, hypothyroidism, a
165	history of coronary bypass and peripheral vascular disease, on treatment with
166	antiplatelet drugs which were discontinued 3 days prior to the surgery. The day
167	after the surgery she presented with a VA of hand movement (HM). Fundoscopy
168	revealed a cherry red spot with whitening of the perifoveal region (Fig. 2),
169	compatible with diagnosis of CRAO. A hyperreflective band in INL was present in
170	the SD-OCT scan, consistent with the finding of PAMM. FA performed after 48h
171	confirmed delayed perfusion of the macular region. Sequential follow-up SD-OCT
172	scans showed progressive thinning of middle retinal layers and macular atrophy.
173	Final VA in the OD was count fingers (CF).
174	Case 4
175	A 49-year-old man with preoperative VA of 20/20 in both eyes underwent an
176	uneventful OD pterygium surgery under retrobulbar block (2.5mL of a mixture of
177	lidocaine 2% and bupivacaine 0.75%). No significant PMH was described. On day
178	1 he complained of decreased vision, VA was 20/200 and fundoscopy revealed
179	whitening of the perifoveal region. SD-OCT images revealed an OD hyperreflective
180	band in INL consistent with the diagnosis of PAMM. FA reported no ischaemia nor
181	oedema. Carotid doppler ultrasonography and blood tests for prothrombotic factors
182	were performed, resulting all within normal limits. Sequential follow-up SD-OCT
183	scans showed progressive atrophy in INL and final VA was 20/200.
184	Case 5
185	An 83-year-old man with OD preoperative VA of 20/200 underwent an uneventful
186	phacoemulsification surgery under peribulbar block (4mL of a mixture of
187	bupivacaine 0.75% and lidocaine 2%). Significant PMH included hypertension,
188	myocardial infarction and hypercholesterolemia. At the moment of the surgery, he
189	was on antiplatelet, anticoagulant and on tamsulosin treatment. On the first
190	postoperative review 24h after the surgery VA was HM. Fundoscopy revealed a
191	cherry red spot with whitening of the perifoveal region. A diagnosis of CRAO was

made and SD-OCT revealed a hyperreflective band in INL consistent with PAMM. 192 FA showed delayed arterial filling in the macular bundle in early phases with 193 normal perfusion in late phases. Sequential follow-up SD-OCT scans showed 194 progressive inner nuclear retinal atrophy layers and macular atrophy. Final VA was 195 CF with residual permanent central scotoma. 196 Case 6 197 A 55-year-old male underwent an uneventful OD refractive phacoemulsification 198 199 surgery under peribulbar block (4mL of a mixture of bupivacaine 0.75% and lidocaine 2%). No significant PMH was described and preoperative VA was 20/20. 200 201 On the first postoperative review 24h after the surgery the patient complained of central scotoma and VA was 20/50. Fundoscopy was apparently normal so an SD-202 203 OCT scan was performed revealing a hyperreflective band in the INL. Sequential follow-up SD-OCT showed persistence of the hyperreflective band, thinning of 204 205 middle retinal layers and moderate macular atrophy. OCTA performed 1 month after surgery showed decreased small vessel branching of the deep capillary 206 207 plexus in the OD compared to the fellow eye. After six weeks of follow-up, VA was 20/20 but complained of mild decreased vision. 208 Case 7 209 An 83-year-old woman with an OD preoperative VA of 20/100 underwent an 210 211 uneventful phacoemulsification surgery under peribulbar block (6mL of a mixture of bupivacaine 0.75%, mepivacaine 2% and hyaluronidase 150 IU). Significant PMH 212 included hypertension, acute myocardial infarction, chronic kidney failure, chronic 213 myelocytic leukaemia, essential tremor and previous thyroidectomy and colostomy. 214 At the moment of surgery, she was on antiplatelet treatment and bisoprolol. On the 215 216 24-hour postoperative review, OD VA was 20/200 and fundoscopy revealed a subtle whitish perifoveal halo in the papillomacular bundle, with spared perfusion of 217 the cilioretinal artery. OCT-A (SS-OCTA, Atlantis DRI, Topcon Corp, Japan) was 218 performed revealing a markedly decreased small vessel branching of the deep 219 capillary plexus in the OD compared to the normal left eye (OS) (Fig. 3). A 220 hyperreflective band in the OD INL was observed in structural OCT scans. Five 221 months after surgery, OD VA was 20/100 with a residual paracentral scotoma. 222

A 53-year-old male underwent an uneventful OD pterygium surgery under 224 peribulbar block (4mL of a mixture of bupivacaine 0.75% + lidocaine 5% + 225 hyaluronidase 150 IU). Preoperative OD VA was 20/20 with no remarkable PMH. 226 The day after the surgery he complained of central scotoma and VA was reduced 227 to 20/200. Fundoscopy revealed a cherry red spot in the OD. SD-OCT revealed a 228 hyperreflective band in the INL consistent with the diagnosis of PAMM. Final VA 229 was 20/200 with a residual permanent central scotoma. Sequential OCT scans 230 231 showed progressive retinal atrophy over 3 months follow-up visits. Case 9 232 A 68-year-old woman with an OS preoperative VA of 20/50 underwent an 233 uneventful phacoemulsification surgery under peribulbar block (5mL of 234 235 mepivacaine 2%). Significant PMH included hypertension, diabetes mellitus, hypercholesterolemia and arrhythmia (pacemaker carrier). At the moment of the 236 237 surgery, she was on antiplatelet treatment with acetylsalicylic acid (100mg OD PO), atorvastatin, insulin and amiodarone. On the first postoperative review 24h after the 238 239 surgery, OS VA was HM and the patient complained of no vision. Fundoscopy revealed a cherry red spot and OCT showed a hyperreflective band in the middle 240 retinal layers. Moderate improvements in OS VA were observed during follow-up, 241 resulting in a final VA of 20/200, a permanent central scotoma and macular atrophy 242 243 on OCT scans. 244 **Discussion** 245 Unexpected postoperative severe visual loss after uneventful ocular surgery 246 represents a rare but important concern for both the patient and the treating 247 248 ophthalmologist. Postoperative retinal arterial occlusions after local anaesthesia may present with a broad spectrum of clinical patterns, from typical findings to very 249 subtle alterations only apparent by structural OCT. This paper highlights the 250 possible relationship between local anaesthetic blocks as a potential trigger for 251 impaired foveal perfusion, resulting in a PAMM presentation pattern in structural 252 OCT scans. A detailed description of preoperative clinical characteristics is 253 presented to the ophthalmic community, as an attempt to identify predictive 254 features in future studies to avoid this complication.

Different types of local anaesthesia (sub-Tenon's, peribulbar or retrobulbar) are 256 routinely used to carry out ocular surgeries, albeit with some potential side 257 effects.¹³ From the local complications perspective, traditional needle blocks such 258 as retrobulbar and peribulbar provide good analgesia and akinesia but can cause 259 serious sight threatening complications including globe or optic nerve perforation.¹⁴ 260 Sub-Tenon's block appears as a safer anaesthetic technique for ocular 261 procedures, providing good analgesia and akinesia without the risks derived from 262 sharp needle use. 15 From the systemic complications perspective, peribulbar and 263 retrobulbar blocks can cause major complications in cases of inadvertent injection 264 265 through the optic nerve sheath such as brainstem anaesthesia, unconsciousness, severe cardiorespiratory collapse and even death. 14,16 Cardiovascular events have 266 also been associated to sub-Tenon's block in some reports. 15 267 Retinal artery occlusions related to peribulbar and Sub-Tenon's blocks have been 268 described in several publications.^{7–12} Since the initial description of PAMM as a 269 manifestation of retinal capillary ischaemia.² multiple series have associated this 270 271 entity with several retinal vascular and systemic disorders.⁴ The lack of adequate perfusion in the deep capillary plexus (DCP) seems to be the main cause of 272 PAMM, as assessed by OCTA findings. 3,17,18 The deep capillary system is 273 composed of an intermediate capillary plexus (ICP) and a deep capillary plexus 274 (DCP). Anatomically, it is conceivable that the INL may receive its blood supply 275 predominantly from the proximal ICP, whereas the OPL may receive its blood 276 supply predominantly from the DCP.³ The oxygen demand of the macula, 277 especially at the level of the OPL and photoreceptor inner segments, is higher than 278 any other region of the retina.¹⁹ Furthermore, oxygen diffusion from the choroid to 279 280 the retina is inherently limited by retinal thickness, which becomes greater parafoveally.³ Taken together, the middle layers of the retina (INL and OPL) in the 281 parafoveal region have a high-perfusion demand whose supply is limited by 282 anatomical configuration, making these structures most vulnerable to ischaemia.³ 283 Recent reports have been directed to study the pathophysiology of retinal vascular 284 occlusive disease.³ Although retinal arterial occlusion can cause total inner retinal 285 ischaemia involving all three plexuses, isolated PAMM lesions may appear as a 286 result of preferential ICP and DCP ischaemia. In clinical practice, this means that 287

the transient occlusion of a large retinal arteriole with rapid restoration of normal 288 flow could induce ischaemia in the deep stratus of the middle retina, while sparing 289 the retinal nerve fibre and ganglion cell layers presenting as isolated PAMM. We 290 believe that this theory may help to explain the subtle clinical pictures presented by 291 four of our patients, with minimal clinical findings of arterial hypoperfusion on direct 292 funduscopy examinations. 293 294 After a systematic literature review on potential causative mechanisms for CRAO 295 or transient retinal artery occlusion (TRAO) after routine intraocular procedures, we suggest three hypotheses for this PAMM phenomenon observed in this series and 296 other preliminary reports. 9,10,12 First, a vasoconstrictive effect of the anaesthetic 297 agent on the central retinal artery, second, an intraocular pressure spike resulting 298 299 in decreased retinal artery perfusion and, third, a mechanical effect of the volume of anaesthetic injected in the orbit compressing the optic nerve and the central 300 301 retinal artery (a sort of transient acute orbital compartment syndrome-like process). Several publications addressing the effect of local anaesthesia on ocular 302 303 haemodynamic have confirmed a decreased ocular blood flow during the procedure, even without vasoconstrictors.^{20–22} These flow reductions were still 304 present 5 minutes after peribulbar anaesthesia, when intraocular pressure returned 305 to baseline values, supporting the theory of drug-induced vasoconstriction after 306 peribulbar anaesthesia.²² This vasoconstriction may relate to the anaesthetic drugs 307 308 themselves, as bupivacaine or lidocaine have been reported to cause temporary reduction in the blood flow of the central retinal artery.²² In our series, 8/9 cases 309 received at least one of these two anaesthetic drugs, with a single case receiving 310 only mepivacaine. None of the anaesthetic block mixtures included adrenalin or 311 similar vasoconstrictive agents, commonly used in other local procedures 312 elsewhere in the body. With regards to the possibility of an inadvertent 313 intraoperative IOP spike, although it cannot be excluded, all surgeries were 314 performed at normal infusion parameters in the phacoemulsification procedures, no 315 particular findings were reported in pterygium surgical notes by any of the surgeons 316 and IOP was normal at the 24h postoperative check in all nine cases. Finally, local 317 anaesthetic blocks imply injecting a certain volume of fluid into a non-expansible 318 compartment, and consequently, an increase of pressure in the orbit. Therefore, 319

the injection of anaesthetics into the connective tissue surrounding the optic nerve might cause a temporary compression of the central retinal artery, resulting in a transient hypoperfusion to the retinal vasculature. In our series, the anaesthetic volume injected was similar in all cases (ranging from 2.5 to 6 mL), as was the axial length of study eyes (ranging from 23.02 to 23.76 mm). We believe that all these three situations may not have been exclusive, and a combination of them may have played a role in our patients resulting in retinal ischaemia presenting as PAMM. We should bear in mind that PAMM is an OCT abnormality that may herald the presence of an underlying systemic condition, as it has been associated to several retinal vascular occlusive disorders.^{3,4} It is possible that patients with underlying cardiovascular pathologies could be more susceptible to transient compression or spasm on the retinal arterial circulation. Five of the patients included in our series had previously diagnosed cardiovascular diseases, but the rest had no previous relevant medical history which may indicate that these disorders might be a predisposing factor, but not a necessary condition for developing PAMM. As in other surgical complication report studies, our series has limitations, as the relatively small number of cases and the retrospective design. Unfortunately, most of the cases were observed prior to the advent of OCTA. OCTA is the only image modality that can address the loss and extension of capillary perfusion specifically in the deep capillary plexus, the main stratus affected in this condition. Given its non-invasive nature, we would recommend performing OCTA imaging in all patients with unexplained visual loss in the early postoperative period after cataract surgery. In conclusion, PAMM may appear secondary to local anaesthetic blocks in a broad spectrum of retinal hypoperfusion presentations, associating unexpected postoperative vision loss after uneventful ocular surgery. Increasing the awareness of this complication would lead physicians to perform OCT investigations in such cases, as no robust data are present in the literature about the incidence or prevalence of this OCT finding at the present time, and this condition may be underreported due to the absence of fundoscopic findings in the more subtle

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cases. Until potential risk factors for this complication are identified, an empiric 352 alternative would be to recommend topical or intracameral anaesthesia when 353 possible in patients with known underlying vasculopathy. Future studies with larger 354 study populations will provide new insights to identify such predictive features and 355 inform us for better counselling in patient-doctor discussions. 356 357 **Acknowledgments / Disclosure** 358 359 Funding / Support Javier Zarranz-Ventura is a grant recipient of the Spanish Retina & Vitreous 360 Society (Sociedad Española de Retina y Vítreo). This work was partly supported by 361 the National Institute for Health Research Biomedical Research Centre based at 362 Moorfields Eye Hospital National Health Service Foundation Trust and University 363 College London Institute of Ophthalmology. The views expressed are those of the 364 authors (Pearse A. Keane, Dawn A. Sim, Adnan Tufail) and not necessarily those 365 of the National Health Service, the National Institutes for Health Research or the 366 Department of Health. 367 Financial disclosures 368 Carolina Bernal-Morales, none; Daniel Velazguez-Villoria, none; Juan Manuel 369 Cubero-Parra has been in advisory boards, has given lectures and has received 370 371 travel grants from Alcon, Allergan, Bausch & Lomb, Bayer, DORC and Novartis and has been a lecturer for Novartis and Bausch & Lomb; Pearse A. Keane acts as 372 a consultant for Novartis, Roche, Apellis, and DeepMind, he has received speaker 373 fees from Allergan, Bayer, Topcon, and Heidelberg Engineering and has stocks in 374 Big Picture Eye Health.; Dawn A. Sim no disclosures; Alfredo Adan has been in 375 376 advisory boards for Abbvie and Novartis; Adnan Tufail has been in advisory boards and has given lectures for Allergan, Alimera Science, Bayer, Novartis and Roche, 377 and has received grants from Medisoft Ltd, Notal Vision and Novartis; Javier 378 Zarranz-Ventura has been in advisory boards, is a consultant, lecturer and has 379 received travel grants from Alcon, Alimera Science, Allergan, Bausch & Lomb, 380 Bayer, Brill Pharma, DORC, Novartis and Roche, is a grant holder from Allergan 381 and Novartis, and has been a lecturer for Topcon and Zeiss. 382

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Figure Legends:

Fig. 1. Case 1. Paracentral Acute Middle Maculopathy (PAMM) is seen in the OD of a 40-year-old man 24 hours after uneventful pterygium surgery with sub-Tenon's block of lignocaine 2%, presenting with central scotoma and decreased visual acuity (3/60). Colour fundus photographs of both eyes. In the OD, a subtle perifoveal yellowish halo with a very subtle thinning of the retinal vessels is seen in the macular region, whereas OS fundoscopy is unremarkable (a,b). Fundus fluorescein angiography revealed a delayed arterial filling in the macular bundle of the OD in the early arterial phase (c), with normal perfusion in the late phase (d). Spectral Domain Optical Coherence Tomography (SD-OCT) shows normal reflectivity of inner retinal layers in the OS (e). A hyperreflective band in the inner retinal layers is observed in the OD, consistent with the diagnosis of PAMM (f). Six weeks after the surgery, SD-OCT reveals thinning of the inner retinal layers, with persistence of the hyperreflective band and moderate macular atrophy in the SD-OCT retinal scan (g).

Fig. 2. Case 3. Paracentral Acute Middle Maculopathy (PAMM) associated to Central Retinal Artery Occlusion (CRAO) in the OD of an 80-year-old woman with pre-existing cardiovascular disease after uneventful phacoemulsification. Colour fundus photographs of the OD (a) and the OS (b) of the patient 24 hours after the surgery in the OD. The presence of a cherry red spot with whitening of the perifoveal region and a perfused optic disc is seen in the OD (a). Spectral domain optical coherence tomography (SD-OCT) 24 hours post-surgery (c,d). A hyperreflective band is seen in the inner retinal layers of the OD (c), in contrast with the normal reflectivity observed in the OS (d). Sequential follow up SD-OCT scans were performed in the next 2-8 weeks (e: 2 weeks, g: 4 weeks, f: 6 weeks, h: 8 weeks), which showed progressive thinning of the inner retinal layers and macular atrophy 2 months after the surgery.

Fig. 3. Case 7. Paracentral Acute Middle Maculopathy (PAMM) in the OD of an 83-year-old woman 24 hours after routine phacoemulsification under peribulbar anaesthesia. Colour fundus photographs of the OD 24 hours after the surgery (a). A subtle whitish perifoveal halo is seen in the OD papillomacular bundle, with spared perfusion of the cilioretinal artery. Swept source optical coherence tomography angiography (SS-OCTA, Atlantis DRI, Topcon Corp, Japan) of the deep capillary plexus of the right eye (b) and the left eye (c) 24 hours post-surgery, with the corresponding segmentation slabs inferiorly. Note a marked decrease in the small vessel branching of the PAMM-affected right eye compared to the unaffected left eye. Swept source optical coherence tomography (SS-OCT, Atlantis DRI, Topcon Corp, Japan) of the OD revealing a hyperreflective band in the inner retinal layers (d) in contrast with the normal reflectivity observed in the OS (e).