Title: Classification criteria for acute posterior multifocal placoid pigment epitheliopathy

Suggested running title: Acute posterior multifocal placoid pigment epitheliopathy

Authors: The Standardization of Uveitis Nomenclature (SUN) Working Group[1]

Writing committee: Douglas A. Jabs, MD, MBA[2,3]; Antoine P. Brezin, MD[4]; Andrew D. Dick, MBBS, MD, FRCP, FRCS, FRCOphth[5-7]; Ralph D. Levinson, MD[8]; Lyndell L. Lim, MD[9]; Peter McCluskey, MD[10]; Neal Oden, PhD[11]; Alan G. Palestine, MD[12]; Jennifer E. Thorne, MD, PhD[2,3]; Brett E. Trusko, PhD, MBA[13]; Albert Vitale, MD[14]; Susan E. Wittenberg, MD[15]

Affiliations: [1]Members of the SUN Working Group are listed online at ajo.com. From [2]the Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, and [3]the Wilmer Eye Institute, the Department of Ophthalmology, the Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Department of Ophthalmology, University of Paris V – Hôpital Cochin, Paris, France; [5]the Academic Unit of Ophthalmology, Bristol Medical School, University of Bristol, Bristol, UK; [6]the National Institute for Health Research Biomedical research Centre at Moorfields Eye Hospital, London, UK; [7]University College London Institute of Ophthalmology, London UK; [8]the UCLA Stein Eye Institute and the Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [9]Center for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia; [10]the Save Sight Institute, Department of Ophthalmology, University of Sydney School of Medicine, Sydney, NSW, Australia; [11]the Emmes Corporation, Rockville, MD, USA; [12]the Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Co, USA; [13]the Department of Medicine, Texas A&M University, College Station, TX, USA; [14]the Department of Ophthalmology, the University of Utah School of Medicine, Salt Lake City, UT, USA; [15]Houston Eye Associates, Houston, TX, USA.

Corresponding author: Douglas A. Jabs, MD, MBA, Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, MD, 20215 USA. **Phone:** 410-955-1254. **Email:** djabs@jhmi.edu.

Grant support: Supported by grant R01 EY026593 from the National Eye Institute, the National Institutes of Health, Bethesda, MD, USA; the David Brown Fund, New York, NY, USA; the Jillian M. And Lawrence A. Neubauer Foundation, New York, NY, USA; and the New York Eye and Ear Foundation, New York, NY, USA.

Conflict of Interest: Douglas A. Jabs: none; Antoine P. Brezin: none; Andrew D. Dick: none; Ralph Levinson: none; Lyndell L. Lim: none; Neal Oden: none; Alan G. Palestine: none; Jennifer E. Thorne: Dr. Thorne engaged in a portion of this research as a consultant and was compensated for the consulting service; Brett E. Trusko: none; Albert Vitale: none; Susan E. Wittenberg: none.

Word count: abstract 215; précis 61; text 1588; tables 2; figures 2.

ABSTRACT

Purpose: To determine classification criteria for acute posterior multifocal placoid pigment epitheliopathy (APMPPE).

Design: Machine learning of cases with APMPPE and 8 other posterior uveitides.

Methods: Cases of posterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on diagnosis, using formal consensus techniques. Cases were split into a learning set and a validation set. Machine learning using multinomial logistic regression was used on the learning set to determine a parsimonious set of criteria that minimized the misclassification rate among the infectious posterior/panuveitides. The resulting criteria were evaluated on the validation set.

Results: One thousand sixty-eight cases of posterior uveitides, including 82 cases of APMPPE, were evaluated by machine learning. Key criteria for APMPPE included: 1) choroidal lesions with a plaque-like or placoid appearance and 2) characteristic imaging on fluorescein angiography (lesions "block early and stain late diffusely"). Overall accuracy for posterior uveitides was 92.7% (95% confidence interval [CI] 90.8, 94.2) in the learning set and 98.0% (95% CI 94.3, 99.3) in the validation set. The misclassification rates for APMPPE were 5% in the learning set and 0% in the validation set.

Conclusions: The criteria for APMPPE had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research.

PRECIS

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for acute posterior multifocal placoid pigment epitheliopathy were developed. Key criteria included choroidal lesions with a plaque-like or "placoid" appearance and a characteristic fluorescein angiogram (lesions "block early and stain late diffusely"). The resulting classification criteria had a low misclassification rate.

In 1968 Gass described the disease he named Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE).[1] The characteristic lesions were thought to be at the level of the retinal pigment epithelium and choroid, were plaque-like in appearance, and had a characteristic fluorescein angiogram appearance of early blockage and diffuse late staining. Early descriptions emphasized the self-limited nature of the disease with spontaneous remissions within 6 weeks and the good visual prognosis with most patients achieving 20/25 or better acuity, despite the poor presenting acuity.[2-5] Subsequently patients with recurrent disease and poorer visual outcomes have been reported.[6]

The disease typically affects young adults, both men and women, and has an estimated incidence of 0.15 per 100,000 population per year.[7] The etiology is unknown. Case series often emphasize a history of an antecedent viral "flu-like" illness in one-third of cases to suggest an autoimmune or autoinflammatory response to an infection.[1-5] However, these series all suffer from recall bias and the lack of a control group, making the interpretation speculative. Most cases are an isolated eye disease, but cases of APMPPE have been described in the context of systemic inflammatory diseases, particularly those with vascular involvement.[5,8,9] The most frequently reported associated systemic disease is cerebral vasculitis.[8,9] These associations raise the question of whether APMPPE is a specific disease or a phenotype of choroidal vascular and retinal pigment epithelial damage. A third possibility is that the eye-limited disease is a specific disease, whose appearance can be mimicked by systemic diseases which cause a "choriocapillaritis". The pathogenesis has been debated with some suggesting a primary inflammation of the retinal pigment epithelium and others a primary inflammation of the choroid, perhaps the choriocapillaris, with secondary retinal pigment epithelial damage. Multimodal imaging, including indocyanine green angiography, fundus autofluorescence, optical coherence tomography (OCT), and OCT angiography, has suggested that the inflammation of the choroid is primary as the choroidal lesions are more extensive than the retinal pigment epithelial damage noted on fluorescein angiography and fundus autofluorescence.[5,10-14]

As noted above, fluorescein angiography demonstrates early blockage and uniform diffuse late staining of the lesions.[1-5] Fundus autofluorescence demonstrates hypo-autofluorescent lesions acutely with hyper-autofluorescent lesions in later stages of the disease.[5,11] Indocyanine green angiography demonstrates hypofluorescent lesions, interpreted as choroidal hypoperfusion, corresponding to the lesions seen on fluorescein angiogram.[5,10] However, indocyanine green angiographic lesions may be more extensive than those seen on fluorescein angiography. On OCT imaging there is disruption of photoreceptors acutely with outer retinal hyper-reflectivity and sometimes subretinal fluid. Nevertheless, macular edema is uncommon. On OCT angiography there are flow voids at the level of the choriocapillaris, again suggesting that the pathogenesis is ischemic damage, perhaps as a result of choroidal small vessel vasculitis or occlusion.[12-14]

Untreated, APMPPE typically spontaneously remits and has a good visual prognosis.[15] A review of 15 case series[7] totaling 295 involved eyes suggested that approximately one-third of eyes presented with visual acuity 20/40 or better, one-third between 20/40 and 20/200, and one-third 20/200 or worse. At last follow-up, approximately three-fourths of eyes had a visual acuity 20/40 or better, 20% between 20/40 and 20/200, and 5% 20/200 or worse. There was no evident difference in the visual outcome between eyes treated with medical therapy (~70% 20/40 or better) and those not treated (85% 20/40 or better), but these studies likely suffered from a treatment by indication bias.[7] Nevertheless, there was little evidence for the benefit of medical (anti-inflammatory) therapy. Foveal involvement was associated with worse visual outcomes (39% 20/25 or better vs 88% 20/25 or better without foveal involvement).[7]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was APMPPE.[16-21]

Methods

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[18-21]

Case collection and case selection. De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[20,21] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database.[20,21] Because the goal was to develop classification criteria,[20] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (i.e. were "selected").[20,21]

Machine learning. The final database then was randomly separated into a learning set (~85% of the cases) and a validation set (~15% of the cases) for each disease as described in the accompanying article.[20] Machine learning was used on the learning set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the learning set and the validation set, the misclassification rate was calculated for each disease. For APMPPE the diseases against which it was evaluated were: birdshot chorioretinitis (BSCR), multifocal choroiditis with panuveitis (MFCPU), multiple evanescent white dot syndrome (MEWDS), punctate inner choroiditis (PIC), serpiginous choroiditis, sarcoidosis-associated posterior uveitis, syphilitic posterior uveitis, and tubercular (TB) posterior uveitis.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

Results

One hundred forty-nine cases of APMPPE were collected and 82 (52%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of APMPPE were compared to cases of posterior uveitides, including 122 cases of serpiginous choroiditis, 207 cases of BSCR, 51 cases of

MEWDS, 138 cases of MFCPU, 144 cases of PIC, 12 cases of sarcoid posterior uveitis, 35 cases of syphilitic posterior uveitis, and 277 cases of tubercular posterior/panuveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[21] The characteristics of cases with APMPPE are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. Key features of the criteria included the plaque-like or "placoid" appearance of the lesions (Figure 1) and the characteristic fluorescein angiogram (Figure 2). The overall accuracies for posterior uveitides were 92.7% (95% confidence interval [CI] 90.8, 94.2) in the learning set and 98.0% (95% CI 94.3, 99.3) in the validation set. The misclassification rate for APMPPE in the learning set was 5%, and in the validation set 0%. The diseases with which APMPPE was confused in the learning set were MEWDS and tubercular uveitis.

Discussion

The classification criteria developed by the SUN Working Group for APMPPE have a low misclassification rate, indicating good discriminatory performance against other posterior uveitides. The appearance is dissimilar to BSCR, MFCPU, and PIC, and the angiogram different than that in serpiginous choroiditis and MEWDS. Key exclusions include placoid syphilitic uveitis and sarcoidosis.

Ampiginous choroiditis and relentless placoid choroiditis (which may be the same disease) are rare diseases that have lesions which are similar to APMPPE in clinical appearance, but often have fluorescein angiograms more similar to serpiginous choroiditis (i.e. "block early, stain late at the borders).[23,24] The course is more similar to serpiginous choroiditis than to APMPPE, in that the disease is recurrent or chronic, and it appears to need immunosuppression as its treatment. Hence, despite the clinical appearance, ampiginous/relentless placoid choroiditis is distinct from APMPPE and may be a variant of serpiginous choroiditis or a distinct disease related to serpiginous choroiditis. Our database had

too few cases of relentless placoid choroiditis for formal analysis, but the reported descriptions appear distinct from APMPPE.

The issue of systemic disease findings (e.g. cerebral vasculitis) in some cases of APMPPE raises the question of whether these findings are a complication of APMPPE or these are diseases in which ocular involvement mimics APMPPE. Our data on systemic diseases were not adequate to address the issue at this time. Hence, we recommend that all cases of APMPPE be subclassified as "eye-limited" with only ocular involvement or with systemic features (e.g. cerebral vasculitis). Antecedent viral or other "flu-like" illnesses should not be included in the group with systemic features.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of serpiginous choroiditis should not be made in their presence. In prospective studies many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. In these studies the presence of an exclusionary criterion excludes APMPPE, but the absence of such testing does not always exclude the diagnosis of APMPPE if the criteria for the diagnosis are met.

Classification criteria are used to diagnose individual diseases for research purposes.[22] Classification criteria differ from clinical diagnostic criteria, in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity.[22] The machine learning process employed did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between two uveitis experts on diagnosis is moderate at best,[20] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such there may be cases which clinicians would diagnose as serpiginous choroiditis, which would not meet the criteria outlined in Table 2.

In conclusion, the criteria for APMPPE outlined in Table 2 appear to perform sufficiently well for use as classification criteria in clinical research.[21]

REFERENCES

1. Gass JD. Acute posterior multifocal placoid pigment epitheliopathy. Arch Ophthalmol 1968;80:177-85.
2. Ryan SJ, Maumenee AE. Acute posterior multifocal placoid pigment epitheliopathy. Am J Ophthalmol 1972;74:1066-74.
3. Vianna R, van Egmond J, Priem H, Kestelyn P. Natural history and visual outcome in patients with APMPPE. Bull Soc Belg Ophthalmol 1993;248:73-6.
4. Roberts TV, Mitchell P. Acute posterior multofocal placoid pigment epitheliopathy. Austral NZ J Ophthalmol 1997;25:277-81.
5. Steiner S, Goldstein DA. Imaging in the diagnosis and management of APMPPE. Int Ophthalmol Clin 2012;52:211-9.
6. Fiore T, Iaccheri B, Androudi S, et al. Acute posterior multifocal placoid pigment epitheliopathy. Outcome and visual prognosis. Retina 2009;29:994-1001.
7. Abu-Yaghi NE, Hartono SP, Hodge DO, Pulido JS, Bakri SJ. White dot syndromes: a 20-year study of incidence, clinical features, and outcomes. Ocular Immunol Inflamm 2011;19:426-30.
8. Thomas BC, Jacobi C, Korporal M, Becker MD, Wildemann B, Mackensen F. Ocular outcome and frequency of neurological manifestations in patients with acute posterior pigment epitheliopathy (APMPPE). J Ophthalmic Inflamm Infect 2012;2:125-31.
9. Alghatani H, Alkhotani A, Shirah B. Neurological manifestations of acute posterior multifocal placoid pigment epitheliopathy. J Clin Neurol 2016;12:460-7.
10. Mrejen S, Sarraf D, Chexal S, Wald K, Freund KB. Choroidal involvement in acute posterior multifocal placoid pigment epitheliopathy. Ophthalmic Surg Lasers Imaging Retina 2016;47:20-6.
11. Malamos P, Masaoutis P, Georgalas I, et al. The role of fundus autofluorescence imaging in the study of the course of posterior uveitis disorders. Biomed Res Int 2015 2015:247469. doi:1155/2015/247469.
12. Klufas MA, Phasukkijwatana N, Iafe NA, et al. Optical coherence tomography angiography reveals choriocapillaris flow reduction in placoid chorioretinitis. Ophthalmol Retina 2017;1:77-91.
13. Furino C, Shalchi Z, Grassi MO, et al. OCT angiography in acute posterior multifocal placoid pigment epitheliopathy. Ophthalmic Surg Lasers Imaging Retina 2018;50:428-36.

14. Burke TR, Chu CJ, Salvatore S, et al. Application of OCT-angiography to characterise the evolution of chorioretinal lesions in acute posterior multifocal placoid pigment epitheliopathy. Eye 2017;31:1399-408.
15. Xerri O, Salah S, Monnet D, Brezin AP. Untreated acute posterior multifocal placoid pigment epitheliopathy (APMPPE): a case series. BMC Ophthalmology 2018;18:76.
16. Jabs DA, Rosenbaum JT, Nussenblatt RB, the Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Report of the first international workshop. Am J Ophthalmol 2005;140:509-16.
17. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. Am J Ophthalmol 2013;156:228-36.
18. Trusko B, Thorne J, Jabs D, et al. Standardization of Uveitis Nomenclature Working Group. The SUN Project. Development of a clinical evidence base utilizing informatics tools and techniques. Methods Inf Med 2013;52::259-65.
19. Okada AA, Jabs DA. The SUN Project. The future is here. Arch Ophthalmol 2013;131:787-9.
20. Jabs DA, Dick A, Doucette JT, Gupta A, Lightman S, McCluskey P, Okada AA, Palestine AG, Rosenbaum JT, Saleem SM, Thorne J, Trusko, B for the Standardization of Uveitis Nomenclature Working Group. Interobserver agreement among uveitis experts on uveitic diagnoses: the Standard of Uveitis Nomenclature Experience. Am J Ophthalmol 2018; 186:19-24.
21. The Standardization of Uveitis Nomenclature (SUN) Working Group. Development of classification criteria for the uveitides. Am J Ophthalmol 2020;volume:pp.
22. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria. Arthritis Care Res 2015;67:891-7.
23. Nussenblatt RB, Whitcup SM, Palesting AG. Uveitis: Fundamentals and Practice. (2nd ed) St. Louis, Mosby, 1996, pp 368-72.
24. Jones BE, Jampol LM, Yannuzzi LA, et al. Relentless placoid chorioretinitis: a new entity or an unusual variant of serpiginous chorioretinitis? Am J Ophthalmol 2000;118:931-8.

255 **Table 1. Characteristics of Cases with Acute Posterior Multifocal Placoid Pigment**

256 **Epitheliopathy**

Characteristic	Result
Number cases	82
Demographics	
Age, median, years (25th 75th percentile)	25 (21, 30)
Gender (%)	
Men	61
Women	39
Race/ethnicity (%)	
White, non-Hispanic	77
Black, non-Hispanic	4
Hispanic	1
Asian, Pacific Islander	2
Other	9
Missing	7
Uveitis History	
Uveitis course (%)	
Acute, monophasic	83
Acute, recurrent	6
Chronic	5
Indeterminate	6
Laterality (%)	
Unilateral	9
Unilateral, alternating	0
Bilateral	91
Ophthalmic examination	
Keratic precipitates (%)	
None	94
Fine	5
Round	1
Stellate	0
Mutton Fat	0
Other	0
Anterior chamber cells (%)	
Grade 0	78
½+	6
1+	9
2+	5
3+	2
4+	0
Anterior chamber flare (%)	
Grade 0	94
1+	3
2+	2
3+	1
4+	0

Iris (%)	
Normal	100
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25^{th}, 75^{th} percentile)	14 (12,16)
Proportion patients with IOP>24 mm Hg either eye (%)	0
Vitreous cells (%)	
Grade 0	72
½+	22
1+	5
2+	1
3+	0
4+	0
Vitreous haze (%)	
Grade 0	99
½+	1
1+	0
2+	0
3+	0
4+	0
Chorioretinitis characteristics	
Lesion number (%)	
Unifocal (1 lesion)	7
Paucifocal (2-4)	26
Multifocal (≥5)	67
Lesion shape & character (%)	
Ameboid or serpentine	0
Oval or round	1
Placoid	97
Punched-out atrophic	0
Punctate	0
Missing	1
Lesion location (%)	
Posterior pole involved	96
Mid-periphery and periphery only	4
Typical lesion size (%)	
<125 µm	0
125-250 µm	4
250-500 µm	37
>500 µm	55
Missing	4
Other features (%)	
Retinal vascular sheathing	1
Retinal vascular leakage	6
Choroidal neovascularization	0

257

Table 2. Classification Criteria for Acute Posterior Multifocal Placoid Pigment

Epitheliopathy

Criteria
Paucifocal or multifocal choroidal lesions on clinical examination with 1. Plaque-like or “placoid” appearance to the lesions AND 2. Characteristic fluorescein angiogram in the acute phase of the disease (lesions block early and stain late diffusely
Exclusions 1. Positive serologic test for syphilis using a treponemal test 2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)

FIGURE LEGENDS

Figure 1. Fundus photograph of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the placoid chorioretinal lesions.

Figure 2. Fluorescein angiogram of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the features of early fluorescein blockage (a.) and diffuse late staining of the lesion (b.).

Figure 1.

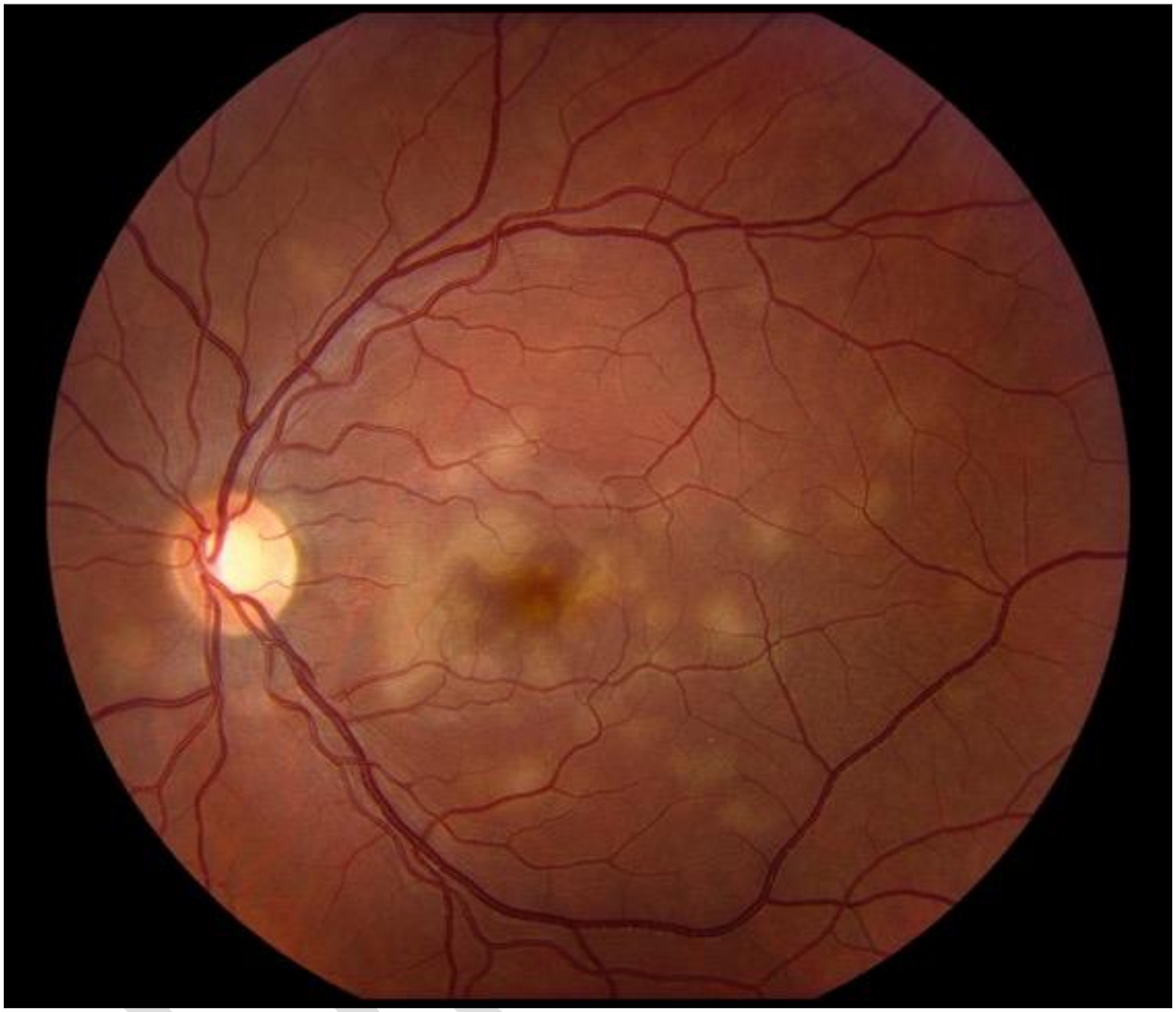


Figure 2a.

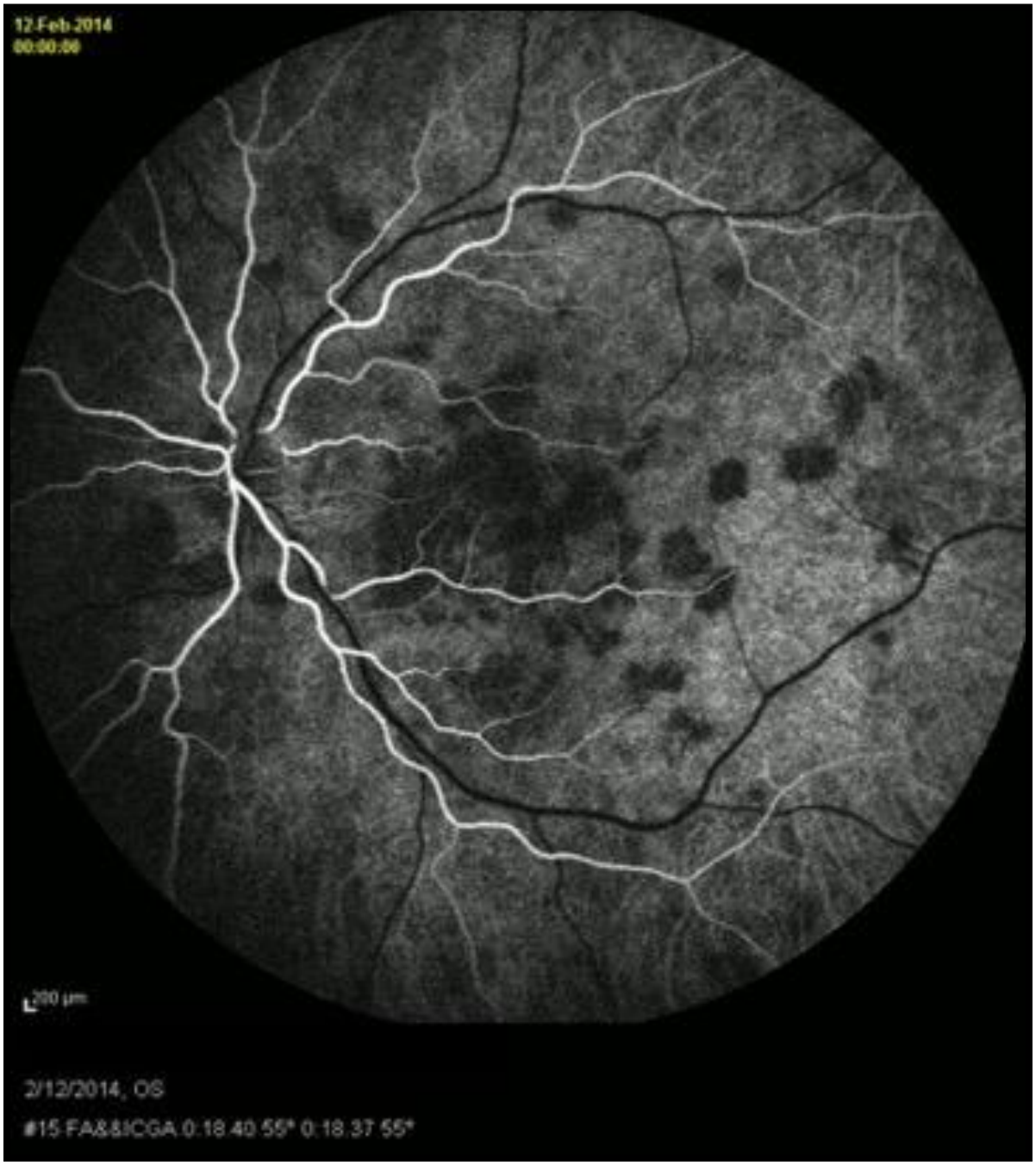
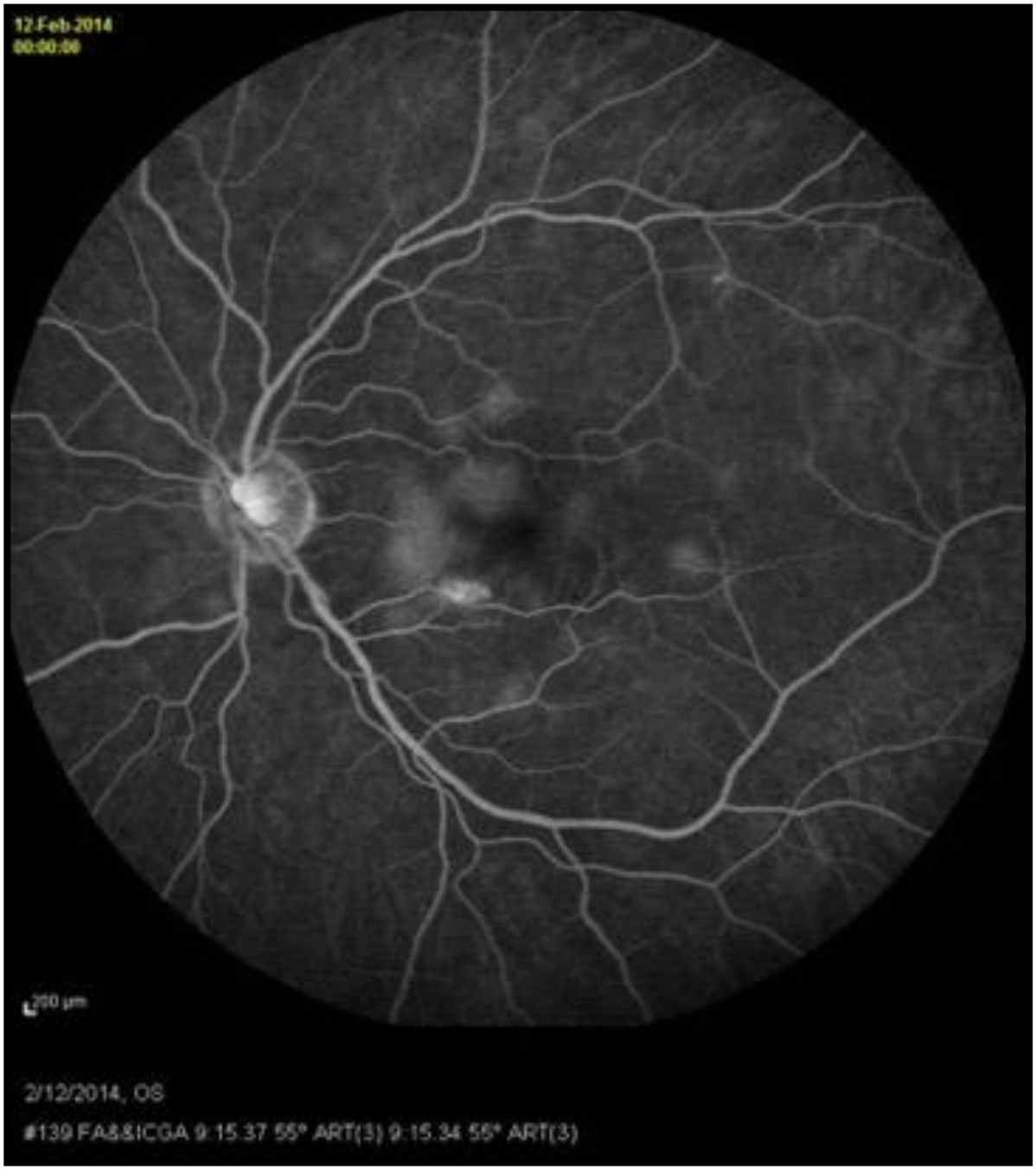

12-Feb-2014
00:00:00
200 µm
2/12/2014, OS
#15 FA&&ICGA 0:18 40 55" 0:18 37 55"

Figure 2b.


12-Feb-2014
00:00:00
200 µm
2/12/2014, OS
#139 FA&ICGA 9:15:37 55° ART(3) 9:15:34 55° ART(3)