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Quantitative Analysis of Ellipsoid Zone in Acute Posterior Multifocal Placoid Pigment Epitheliopathy

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Abstract

Purpose: Quantitative end points for uveitis are needed. Here we quantify the rate of ellipsoid zone (EZ) recovery on optical coherence tomography (OCT) and correlate it with visual acuity (VA) improvement in patients with acute posterior multifocal placoid pigmented epitheliopathy (APMPPE). We use automated and manually graded EZ area analysis to assess EZ recovery in APMPPE. **Methods:** We performed a retrospective review of 9 APMPPE cases (18 eyes) that had characteristic clinical examination and fluorescein angiography findings, outer retinal disruption on spectral-domain OCT, and treatment with systemic steroids after an unambiguous laboratory workup. The EZ was delineated using custom software to perform automated analysis and manual grading by 2 independent physicians. Quantitation of EZ changes was performed in ImageJ (National Institutes of Health). EZ maps were compared with equivalent findings from EZ en face OCT segmentation. **Results:** The 9 cases in our study were followed for an average of 198 days. Symptomatic improvement occurred in all eyes. VA recovery occurred in 83% of eyes and depended on presenting foveal involvement. Positive slopes of EZ area over time demonstrated recovery. EZ recovery profiles determined by manual and automated software demonstrated high Pearson correlation coefficients (0.78-0.94). Slab en face EZ analysis demonstrated moderate agreement. **Conclusions:** EZ recovery correlates with symptomatic and VA recovery. Automated EZ analysis shows strong agreement with manually graded EZ analysis in APMPPE. EZ recovery in patients with APMPPE provides a biomarker for recovery and may be applied to other diseases affecting the outer retina.

Keywords

automated analysis, ellipsoid zone, manual grading, optical coherence tomography, uveitis

Introduction

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE), first described by Gass in 1968,[1] is an inflammatory condition that affects the retinal pigment epithelium (RPE) and the photoreceptor layer.[2] Typically, patients report photopsias, metamorphopsia, and decreased visual acuity (VA), while the examination reveals white creamy lesions in the outer macula. The initial insult is an inflammatory process originating in the choroidal vasculature,[3] the RPE,[1] or the choriocapillaris.[4] Imaging modalities have expanded the methods for identifying and characterizing APMPPE. Fundus autofluorescence demonstrates significant alternations in the RPE,[5] indocyanine green angiography shows hypofluorescence in the area of lesions,[6] spectral-domain optical coherence tomography (SD-OCT) demonstrates disruption of the outer retina and ellipsoid zone (EZ),[7] and more recently optical coherence tomography (OCT) angiography has shown loss at the level of the choriocapillaris.[8] SD-OCT provides clinically valuable information because it demonstrates the loss and recovery of the EZ that is correlated to VA.[9]

APMPPE is typically self-limited and patients generally have a good prognosis,[10] but almost one-quarter of patients may have permanent vision changes.[11] Although immunosuppressive therapy with systemic steroids is usually reserved for the subset of patients with APPMPE presenting with neurological complications,[12] others argue for the use of systemic steroids in all patients.[13-15] To identify those patients who may

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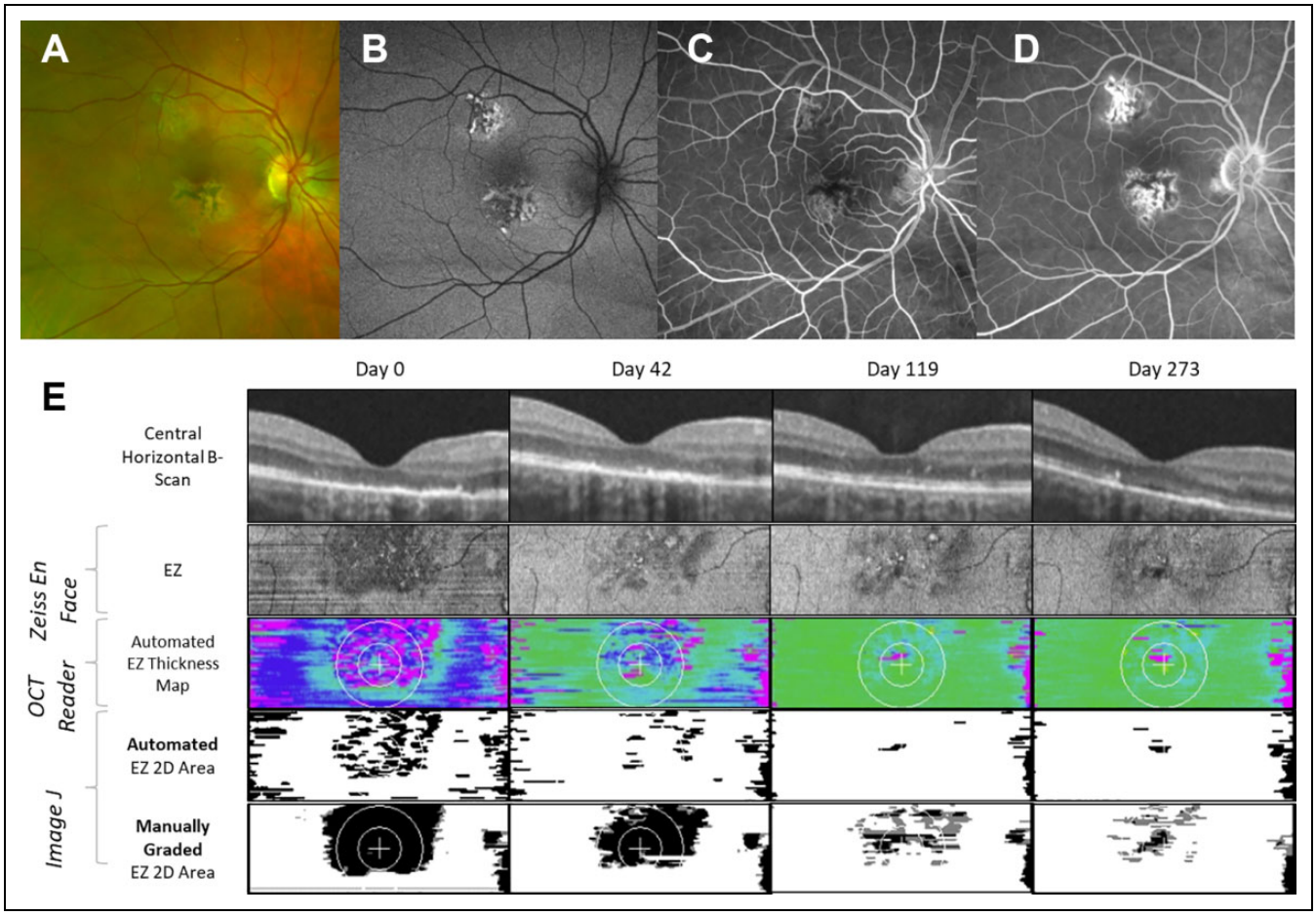

Figure 1. Patient with symmetrical findings, pigment on presentation, and progressive ellipsoid zone (EZ) recovery over 273 days. (A) Color fundus photograph demonstrating pigment and placoid lesions. (B) Fundus autofluorescence demonstrating hyperautofluorescence and hypoautofluorescence in areas of placoid lesion. Fluorescein angiogram (C) early and (D) late frames. (E) Comparison of outer retinal anatomy over time. Serial B-scans along with en face outer nuclear layer, EZ, and choroid highlight outer retinal disruption. EZ thickness maps generated by optical coherence tomography (OCT) reader by automated or manual grading are converted to binary EZ area maps (dark represents EZ loss) using ImageJ. *Manually graded* EZ area shows absent EZ in black, disagreement between graders in gray, and normal EZ in white. 2D indicates 2-dimensional.

benefit from therapy, a durable quantitative clinical end point is needed.

OCT has established its clinical utility for quantitative evaluation of age-related macular degeneration, retinal vein occlusion, diabetic macular edema, and glaucoma.[16] In posterior uveitis and white dot syndromes, OCT has been used to qualitatively monitor patients. More recently, quantitative evaluation of the external limiting membrane and photoreceptors in patients with APMPPE[17] reveals recovery of outer retinal volume as a means for tracking disease activity. Because the EZ presence on OCT correlates with VA,[9] we sought to apply quantitative EZ analysis as an additional treatment end point and introduce an automated software approach to EZ analysis. The EZ software grading package differs from existing slab en face techniques in that grading involves actively delineating the presence or absence of EZ, whereas slab en face analysis indiscriminately provides a reflectance pattern in a slab of defined thickness and depth (Supplementary Figure 1).

Methods

Patients

Nine patients with APMPPE who were referred to Cole Eye Institute from 2014 to 2016 were identified and retrospectively reviewed for this study. Patients were included if they presented with characteristic findings on clinical examination and fluorescein angiography, outer retinal disruption on SD-OCT (Figure 1), and unambiguous laboratory workup results for other potential causes including tuberculosis (Quantiferon Gold; Qiagen), syphilis (rapid plasmin reagin with fluorescent treponemal antibody screen), and sarcoidosis (angiotensin-converting enzyme). Data were collected on age, sex, race, and presenting symptoms. Ophthalmic

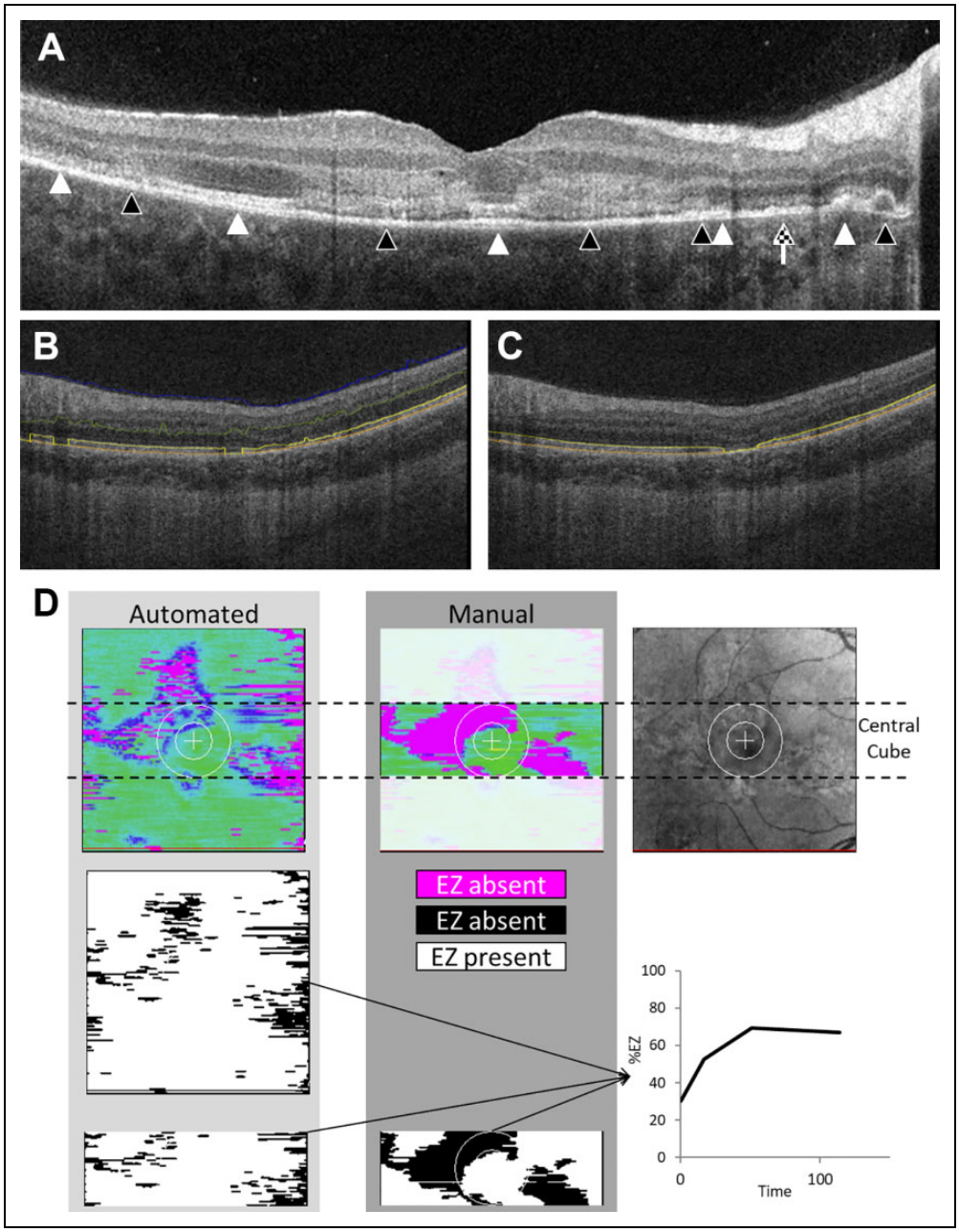

Figure 2. Methods for ellipsoid zone (EZ) analysis and quantitation. (A) Example of B-scan image demonstrating normal outer retinal anatomy (white arrowheads), abnormal anatomy (black arrowhead), and anatomy grading that may depend on the grader's interpretation (checkered arrow). (B) Example of B-scan image with automated EZ detection (yellow line). (C) Example of manually graded EZ (yellow line). (D) Diagram of methods for EZ quantitation using manual and automated EZ analysis. Automated analysis and manual grading techniques provide an analysis in which pink regions represent areas of abnormal anatomy. Binarization of the data is performed by converting pink (abnormal) to black and converting all other areas to white (normal anatomy). Automated grading was performed both for the central macula cube and the full macula cube, whereas manual grading was performed for the central macula only. The percentage of normal EZ was plotted as a function of time to indicate recovery toward normal anatomy (where 100% means a normal macula EZ surface area).

findings at the time of presentation and at each follow-up visit were recorded, including best-corrected VA and results from slit-lamp and dilated fundus examinations. Color fundus and fluorescein angiography photographs were obtained with an Optos system (Optos Panoramic 200MA; Optos PLC). B-scan SD-OCT 128-line raster cube scans were performed on first presentation and at each visit during the recovery phase using Cirrus HD-OCT 5000 (Carl Zeiss Meditec).

EZ Grading

EZ grading and analysis methods are outlined in Figure 2 and described here. For manual grading in this work, a normal EZ

was defined as the presence of both a hyperreflective EZ band overlying the RPE band[18] and a hyporeflective outer nuclear layer (ONL) (Figure 2A, white arrowheads). Abnormal EZ was defined as a hyperreflective ONL, absence of a hyperreflective EZ, or both (Figure 2A, black arrowheads). Whereas normal EZ area technically includes the interdigitation zone, the quantitative metrics obtained were for normal surface area rather than volume. Further, the interdigitation zone was not as readily detected on the Zeiss Cirrus devices used at the time of the present study as on other devices.

Manual grading was performed for the central 42-raster B-scans by each grader for a total of 66 scans (1 scan per follow-up visit) and 2772 B-scan images per grader. OCT Viewer, a previously described multilayer and pathological feature extraction platform software developed at Cleveland Clinic Foundation, was used to perform automated and manual EZ analysis. Manual analysis was performed by 2 independent graders (A.W.B. and W.A.). EZ maps were generated for manual graders (Figure 2C) and automated grading (Figure 2B). Graders were blinded to automated grading, which was performed after manual grading.

EZ thickness maps showed the segment thickness between the apical RPE and the inner edge between the EZ band and the ONL, when present. Thickness maps were converted to binary images in ImageJ version 1.50i (National Institutes of Health; available at https://imagej.nih.gov/ij/; accessed December 21, 2016) by converting pixels of zero EZ thickness to a value of 0 (black areas in Figure 2D), and areas of greater-than-zero EZ thickness to a value of 1 (white areas in Figure 2D). The percentage of total scan area with healthy EZ was quantified using the cell count function in ImageJ, which also produces cell area measurements.

One patient demonstrated macular pathology not involving the fovea, but in the superior third of the macula. The total area of macula graded was constant for all patients. Manual analysis was performed for the central third of the macular cube scan, whereas the one patient with eccentric pathology was graded for the involved lower third of the macula. Automated grading was performed using OCT Reader and quantified using the same methods in ImageJ for the full 125-raster cube scan and for the central third of the cube scan. EZ area was plotted and regression line analysis for percentage of EZ area over time was performed using Microsoft Excel 2010.

Interobserver EZ Grading Variability. The differences in EZ area was calculated between the two graders for each scan. This difference was averaged and plotted for each patient visit and plotted against the mean difference and limits of agreement (1.96 $\pm$ SD). The differences in EZ area was calculated between average manual reading and the automated reading. This difference was averaged and plotted for each patient visit and plotted against the mean difference and limits of agreement (1.96 $\pm$ SD) (Figure 4).

En Face OCT Analysis. We created a custom ONL segmentation slab by transposing the RPE segmentation line with a window thickness of 23 μm to rest at the border of the ONL and outer plexiform layer. This enabled detection of abnormal hyperreflectance in the ONL when loss of underlying EZ resulted in "sagging" of the outer plexiform layer into the ONL layer and, therefore, an area of abnormality in the en face image. Two independent graders were used to compare en face images of the intrinsic EZ window and the custom ONL window with patterns of EZ pathology in averaged manually graded EZ images. Methods for slab en face analysis using Carl Zeiss Meditec Cirrus HD-OCT Review Software (HDRSN70-7365, version 9.5.1.13585) and its comparison with graded EZ analysis are described in the supplementary materials.

Table 1. Demographic Data for Patients Diagnosed With Acute Posterior Multifocal Placoid Pigmented Epitheliopathy.

Characteristic	No.	%
Sex		
Male	2	22
Female	7	78
Age, y		
$\leq$ 20	1	11
20-30	5	56
$\geq$ 30	3	33
Race/Ethnicity		
White		
Other		
Visual acuity		
> 20/20-20/40	12	67
20/50-20/150	4	22
$\leq$ 20/200	2	11
Presenting symptoms		
Decreased vision	9	100
Viral prodrome	5	56
Photopsias	5	56
Headache	4	44
Floaters	3	33
Auras	2	22
Follow-up, mo		
2-6	5	56
6-12	3	33
> 12	1	11

Statistical Methods. Intergrader agreement was assessed by Pearson correlation coefficient and Bland-Altman analysis using Microsoft Excel.

Results

Demographic Data

Demographic data for patients on presentation are summarized in Table 1. Nine patients (18 eyes) presented with APMPPE with a mean age of 33 years (range, 15-69 years). Twelve eyes had a presenting best-corrected VA greater than 20/40 and 2 eyes had a VA of less than or equal to 20/200. The most common symptom on presentation was decreased vision (100%), followed by viral prodrome (56%), photopsias

Table 2. Clinical Course and Treatment Response for Patients Diagnosed and Treated for Acute Posterior Multifocal Placoid Pigmented Epitheliopathy.

Characteristic	No.	%
Treatment choice		
Oral prednisone	7	78
Oral prednisone + IVT	2	22
Duration oral steroid with taper, mo		
2	3	33
3	6	67
Days until pigmentation		
Pigmented at presentation	7	43
1-30[a]	5	31
> 30[a]	4	25
Weeks until VA improvement[b]		
0-2	2	22
2-6	2	22
≥ 7	3	33
Weeks until symptom improvement		
0-2	4	22
4-6	4	44
10+	1	11
Final VA		
20/20	10	56
20/25-20/40	7	39
20/50 or worse	1	6
Follow-up period, mo		
2-6	5	56
6-12	3	33
> 12	1	11

Abbreviations: IVT, intravitreal; VA, visual acuity.
[a]Photography was not performed at every visit, and pigmentation may have occurred sooner.
[b]Two patients presented with a VA of 20/20.

(56%), headache (44%), floaters, (33%), and auras (22%). No patients presented with other focal neurological symptoms. Patients were followed for an average of 7 months (range, 2-13 months). All patients had negative results from syphilis, sarcoid, and tuberculosis screenings, and they had a complete blood count and complete metabolic panel performed.

Clinical course and treatment response for all patients are summarized in Table 2. All patients were treated with a 2-month (33%) or 3-month (67%) course of oral steroid (1 mg/kg) with a slow taper. Seven patients had macular pigmentation on presentation, 5 eyes developed pigmentation in the first 30 days, and 4 eyes developed pigmentation after 30 days. Patient 2 required 2 injections of intravitreal triamcinolone and a dexamethasone implant for symptomatic changes in vision with the desire to remain off systemic steroids. Patient 9 required 3 injections of intravitreal triamcinolone until disease was stabilized for the same reason as patient 2, with symptomatic complaints as the marker.

At the end of the follow-up period, 56% of eyes recovered to 20/20, and 39% were 20/25 to 20/40. One eye (patient 9, left eye) had the worst final VA at 20/50, which started at 20/70 and had pigmentation on presentation. Patients with pigmentation on presentation were identified and their VA was plotted independently (Figure 3). Patients both with and without central macula pigmentation on presentation demonstrated improvement in VA when their central macula was involved.

Graded EZ Analysis

EZ was quantified by manual graders and automated software grading for each time point during follow-up. Possible areas with differences in grader interpretation arose in B-scans in which the perceived degree of hyperreflectivity of the EZ differed (Figure 2A, checkered arrow). Areas of grader disagreement are evident in the figures, which show manually graded EZ as an average of the 2 graders, with black areas representing grader agreement for EZ absence, gray areas representing areas of grader disagreement, and white areas representing areas of agreed EZ presence (Figure 1E, bottom row).

Manually graded EZ recovery is plotted for patients without and with pigmentation on presentation in Figure 3 (C and D). Positive slope indicates that over time, the total area of normal EZ in the graded area increases. The trend of recovery with positive slopes was seen for all eyes without pigmentation on presentation in manually graded patients; however, only 4 of 7 eyes with pigmentation on presentation demonstrated a positive slope for EZ recovery. The 3 eyes that had negative or flat slopes of EZ recovery were in the 2 patients older than 55 years. Rates of EZ recovery (% per day) were plotted as a function of age and subcategorized according to percentage of normal EZ area at time of presentation (Supplementary Figure 2A).

Interobserver agreement between 2 manual graders for each eye in each patient visit are plotted in Figure 4A, demonstrating a Pearson correlation coefficient equal to 0.9594 and a P value <.001. Seven of 66 scans (10.6%) represented graded values that fell outside 2 SDs when comparing the 2 manual graders.

Automated software–graded EZ recovery was plotted for all eyes and evaluated the central cube (Figure 3E) or the full cube area (Figure 3F). When comparing results from just the central cube EZ analysis with the full cube EZ analysis, we found a Pearson correlation coefficient equal to 0.8424 and a P value <.001.

Interobserver agreement between the EZ maps of the average of the 2 manual graders and the automated EZ reader for each eye at each patient visit demonstrated a Pearson correlation coefficient equal to 0.7817and a P value <.001, and it was subjected to Bland-Altman analysis (Figure 4B). Twenty-two of 66 scans (33%) represented graded values that were outside 2 SDs when comparing the average manual graded EZ and automated EZ delineation.

The trend of recovery was compared between manual and automated grading by 2 methods. First, the slopes of regression lines for corresponding manually graded EZ plots and both automated central cube and automated full cube were compared and found to be the same sign (positive slope or negative slope) for 100% of eyes. Second, a direct comparison between 2 independent graders of ImageJ binary images for corresponding manual

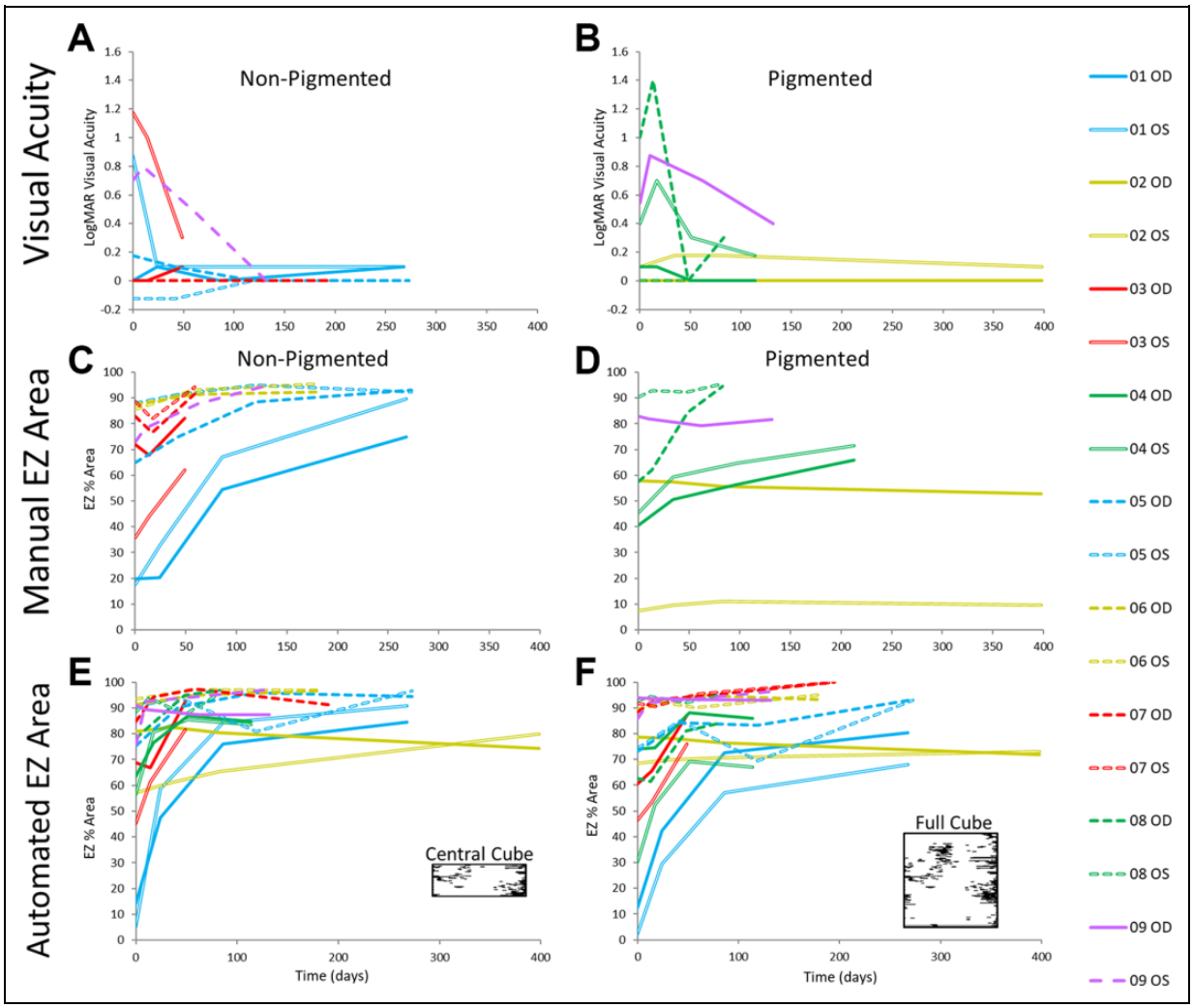

Figure 3. Visual acuity recovery plotted for patients (A) without pigmentation on presentation and (B) patients with pigmentation on presentation. Manually graded ellipsoid zone (EZ) recovery for the central cube and plotted for (C) patients without pigmentation on presentation and (D) patients with pigmentation on presentation. Automated software–graded EZ recovery both for (E) the central third of the horizontal raster and (F) the entire cube area. Inset in each plot demonstrates (E) the central cube and (F) full cube areas quantified. LogMAR indicates logarithm of the minimum angle of resolution.

and automated EZ grading was performed as described in Methods. Agreement of manual vs automated grading for the pattern of EZ loss for each visit agreed only 65% of the time. However, agreement for the trend of EZ recovery was 94%. Additionally, VA, visual symptoms, or both improved in all patients except those with persistent EZ defects.

Zeiss En Face Analysis

En face images of abnormal patterns of the ONL and EZ were compared with the pattern of pathology in manually graded EZ scans. Two independent graders compared pattern features and the trend for recovery (returning to normal appearance) between en face and graded EZ images. The pattern of abnormality agreement between en face segmentation and manually graded EZ was 78% and 63% for ONL and EZ, respectively. Trend of recovery demonstrated correlation in 72% eyes for ONL and 77% eyes for EZ.

Discussion of 3 Clinical Scenarios

Our patient population included several classic presentations and 2 cases of older patients that are worth highlighting.

Case 1 (Supplementary Figure 3) is a classic presentation of APMPPE in a patient in her mid-20s who presented acutely with bilateral vision changes and VA of 20/20 in her right eye and 20/150 in her left eye. Neither fundus was pigmented on presentation. After steroid therapy her vision recovered to a final VA of 20/25 in both eyes at 268 days. Comparison of en face ONL and EZ with manually graded EZ demonstrated poor agreement for pattern of pathology. Comparison of manual and automated EZ analysis demonstrated poor agreement of pattern of pathology for most visits, but the trend of recovery was the same.

Case 9 (Figure 5) is a patient in her 50s who presented with a history of untreated vision loss without visual recovery 1 year

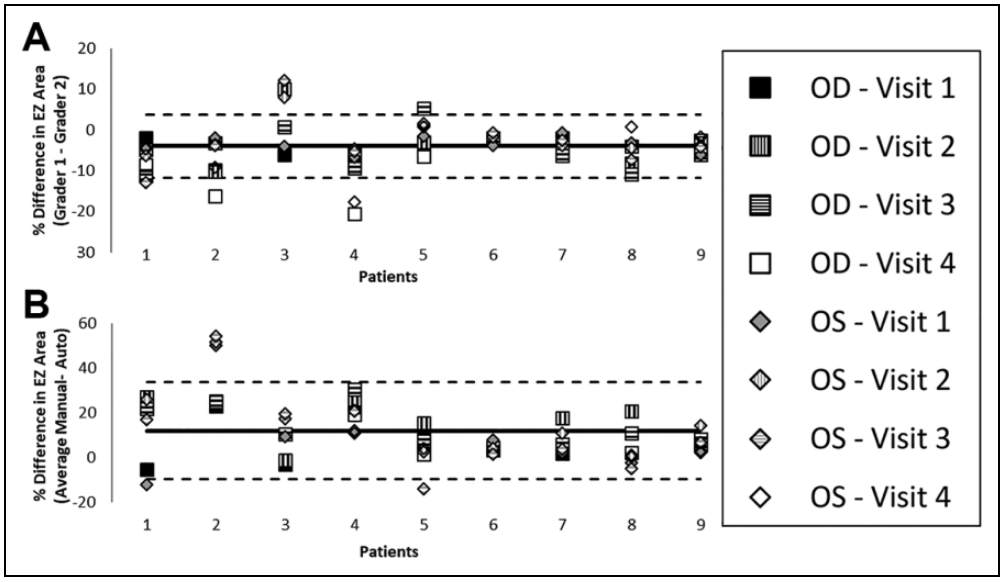

Figure 4. Bland-Altman comparison of ellipsoid zone (EZ) percentage area measurements for interobserver variability. (A) Manual grader 1 vs grader 2. (B) Manual grader average vs automated grader. OS indicates left eye; OD, right eye.

prior in her right eye. She presented acutely with new symptoms in her left eye and vision of 20/70 in her right eye and 20/100 in her left eye. On initiation of steroid therapy, she demonstrated stable EZ loss with pigmentation in the right eye but prompt symptomatic visual and anatomic EZ recovery within 10 days. Her final VA of 20/50 in her right eye represents a change in fixation pattern, as can be seen by the change in location of her en face and EZ patterns in Figure 5. Her left eye recovered to 20/20 with little residual EZ abnormality at 132 days post presentation. Comparison of en face ONL and EZ with manually graded EZ demonstrated strong agreement for pattern of pathology at each visit and trend of recovery. Comparison between manual and automated EZ analysis demonstrated a strong agreement of the pattern of pathology at each visit and trend of recovery.

Case 2 (Supplementary Figure 4) is a patient in her 60s with 2 months of vision changes in both eyes who presented with vision of 20/25 in her right eye and 20/20 in her left eye. Fundus pigmentation was bilateral. She was treated with systemic steroids with symptomatic recovery, stable VA, and no significant change in her EZ. Comparison of en face ONL, en face EZ, and automated EZ grading did not demonstrate strong agreement with manually graded EZ at each visit.

Conclusions

We sought to evaluate conventional en face OCT analysis and a novel software package for EZ analysis to develop a clinical end point for outer retinal diseases like APMPPE. Our patient population was comparable to most reports describing APMPPE in predominantly younger people with a few older outliers[17,19]; however, we had a higher proportion of women compared with prior series, in which the ratio was equal or with a slight male predominance.[11,17,19] Although this study cohort was treated with steroids, we did not seek to establish a treatment paradigm.

Long-term visual outcome as described in a pooled retrospective review of the literature in which patients were or were not given medical therapy showed that, of patients presenting with 20/40 vision or worse, 42% improved to better than 20/40.[11] Scarinci et al recently evaluated photoreceptor volumetric changes in 10 eyes of 5 patients and found that, of patients presenting with 20/40 vision or worse, 20% improved to better than 20/40.[17] In our cohort, of the 6 of 18 eyes that presented with 20/40 or worse vision and on systemic steroids, 50% improved to better than 20/40. Additionally, we noted that patients experienced visual recovery, even when fundus pigmentation existed at presentation, while on systemic corticosteroids (Figure 3B).

In this paper we sought to quantify the extent of EZ recovery over time to identify a quantitative outcome measure for this disease.

Manual EZ Analysis Demonstrates Patterns of EZ Recovery

Two independent graders manually delimited the EZ in the central OCT cube of 17 eyes and a peripheral OCT cube of 1 eye. Grading was limited to one-third of the cube, which represents the central functional vision. The EZ area was quantified and average EZ maps were generated (gray represents areas of grader disagreement, for example, in the bottom row of Figure 1E). Quantitation of EZ percentage (Figure 3, C and D) showed that patients with and without pigmentation on presentation experienced EZ improvement over time. Patients with persistent EZ defects noted persistent symptoms despite improvement from baseline symptoms. Three eyes with flat EZ recovery (09 OD, 02 OD, and 02 OS) occurred in the 2

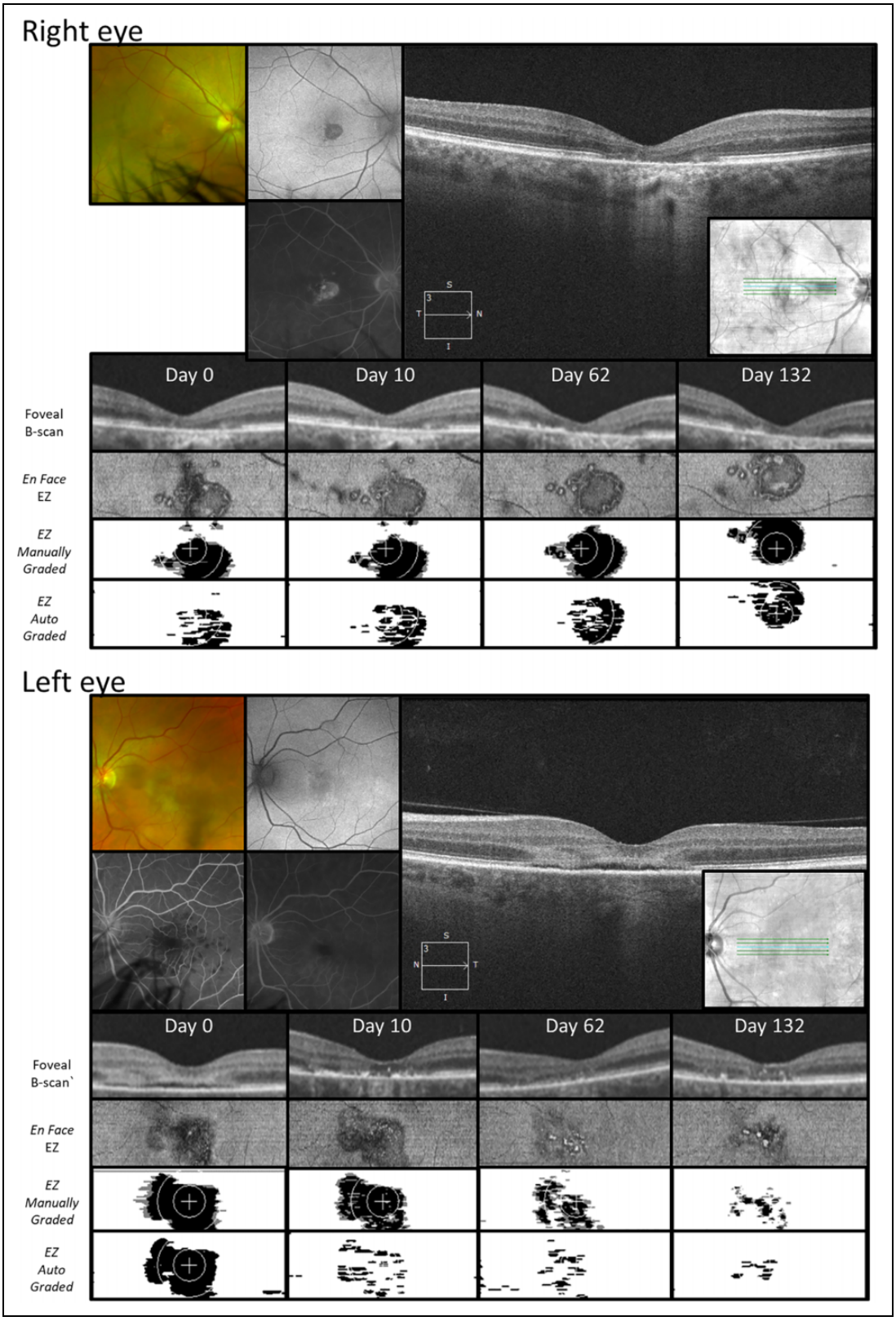

Figure 5. Patient 9's right eye with untreated episode 1 year before presentation. Left eye with second episode of identical symptoms, treated day 0 with steroid and followed for response. EZ indicates ellipsoid zone.

patients who were older than 55 years and presented with pigmentation of the posterior pole. Quantitative EZ evaluation provides a means for monitoring anatomical recovery and possibly stratifying prognoses.

Manual grading, although precise, is not practical in a clinical care environment. Automated segmentation of OCT volumes in other diseases[20] can share value for outer retinal inflammatory diseases also. We used a custom automated segmentation software (OCT Reader) to grade the central and the full OCT cube. Correlation of manually graded EZ was high for automated EZ grading of both the central cube ($r = 0.83$) and the full cube ($r = 0.85$). Therefore, automated software, although not as precise as manual graders at determining EZ area, may soon be ready for evaluating recovery in inflammatory outer retinopathies.

Finally, we sought to compare patterns of disease in graded EZs with patterns of disease revealed by en face slab segmentation of the EZ and ONL. En face slab segmentation demonstrated moderate agreement with manually graded images for pattern of disease. However, recovery trends (pattern normalization) were more reliable with automated analysis (94%) than en face slab segmentation (72%-77%).

The main limitations of our study include a retrospective design and relatively small patient sample size for this rare condition. However, more than 2000 B-scan images were evaluated and compared by manual and automated methods. Our methods validate the use of automated software for outer retinal analysis. This comprehensive analysis of 9 patients showed a trend for younger eyes and eyes with larger areas of pathology to recover more quickly than older eyes or eyes with smaller areas of pathology (Figure 3E). Comparative analysis of our cohort and the cohort in Scarinci et al (Supplementary Figure 2, A and B) demonstrates a possible trend of greater outer retinal recovery in younger patients.[17] Although all patients in our cohort were treated with oral steroids, only 1 patient in the Scarinci and colleagues cohort was treated with systemic steroids, and it was this patient who had the greatest outer retinal recovery (black triangle in Supplementary Figure 2C).

Summary

Manual and automated EZ analysis provides an end point for inflammatory conditions affecting the outer retina. Automated and manual analyses both demonstrate trends that correlate. En face slab segmentation of ONL and EZ often but not always demonstrates recovery patterns that agree with manual EZ analysis. Unique cases of recurrent APMPPE may suggest a role for steroids; however, larger cohorts of patients treated medically or by observation are necessary to draw conclusions. Therapeutic response and natural history of diseases affecting the outer retina can benefit from EZ analysis as an adjunct clinical end point.

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Ethical Approval

This study was approved by the Cleveland Clinic Institutional Review Board, complied with HIPAA (the Health Insurance Portability and Accountability Act of 1996), and followed the tenets of the Declaration of Helsinki.

Statement of Informed Consent

Informed consent was not sought for the present study because of its retrospective nature, lack of patient identifiers, and minimal risk to patient safety or privacy.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.K.S. and J.P.E. have patents related to the OCT Viewer software but no direct conflicts related to the software.

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Supplemental Material

Supplemental material for this article is available online.

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