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Unilateral foveomacular retinitis resembling solar retinopathy among young soldiers in Korean army and associated multimodal imaging findings

**Running title: "Imaging findings in foveomacular retinitis"** *Chang Ki Yoon*<sup>1,2</sup>, *Kyu Hyung Park*<sup>1</sup>, *Se Joon Woo*<sup>1</sup>

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### Abstract

AIM: To describe the clinical features and multimodal images of unilateral foveomacular retinitis in young Korean soldiers.

**METHODS:** Ten patients having foveomacular retinitis were included. Fluorescein angiography, fundus autofluorescence (FAF), infrared reflectance (IR), and spectral-domain optical coherence tomography (SD-OCT) were analyzed.

**RESULTS:** All patients were young males experienced insidious visual decline without exposure to bright light. Initial and final vision ranged from hand movement to 20/20 (median 20/80) and 20/2000 to 20/20 (median 20/200), respectively. Vision decreased in 6 patients while improved in two. Typical macular abnormality was yellow granular spots. SD-OCT showed ellipsoid (EZ) or interdigitation zone (IZ) disruption of fovea. The degree of EZ/IZ damage correlated with vision. Lesions were clearly visualized through IR and matched with SD-OCT findings.

**CONCLUSION:** This is the first case series of foveomacular retinitis diagnosed with multimodal imaging. Foveomacular retinitis is a vision threatening disease. SD-OCT is the most important diagnostic modality.

**KEYWORDS:** Foveomacular retinitis, Korean, multimodal, imaging, solar retinopathy, soldiers, unilateral

### **INTRODUCTION**

Foveomacular retinitis is a term used to describe an eye disease characterized by central vision loss from a foveal retinitis which subsequently develops into a foveal cyst or hole. It was first reported in naval personnel and has been mostly reported and studied in the military field<sup>[1]</sup>. As the fundus appearance of foveomacular retinitis is similar to that of solar retinopathy, it was often regarded as synonymous to solar retinopathy. However, it mostly appears in patients who deny history of exposure to bright light. Besides it has been reported that foveomacular retinitis shows different clinical course and distinct morphologic features from solar retinopathy. Therefore, the pathogenesis of foveomacular retinitis remains poorly understood, not like solar retinopathy.

We recently evaluated 10 patients having foveomacular retinitis from among young Korean soldiers who were referred from the military hospital of South Korea. The patients complained of unilateral visual decline with distinct macular abnormality. Herein, we present the detailed clinical course, including multimodal imaging features, of 10 patients with foveomacular retinitis.

### SUBJECTS AND METHODS

All patients were enlisted personnel who visited the Armed Forces Capital Hospital (AFCH) of South Korea between November 2010 and June 2014, and were referred to the Retina Clinic at the Seoul National University Bundang Hospital (SNUBH). All patients underwent a thorough ophthalmologic examination including fundus color photography, fluorescein angiography (FA), and spectral-domain optical coherence tomography (SD-OCT). Visual field test, electroretinography, and multifocal electroretinography were performed in selected cases. The Cirrus SD-OCT (Carl Zeiss Meditech Inc., Dublin, California, USA) was used to obtain the SD-OCT images. Additionally, Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and Infrared reflectance (IR) (820 nm) imaging were performed on 7 patients (Cases 1, 3, 4, 5, 7, 9, and 10). Blue-light fundus autofluorescence (488 nm) images were obtained for four patients (Case 1, 4, 7, and 10) using Heidelberg retinal angiography (HRA, Heidelberg Engineering, Heidelberg, Germany). Central foveal thickness was measured using the caliper tool provided in the Cirrus SD-OCT

software. The best corrected visual acuity (BCVA) was measured with a standard Korean Landolt visual acuity chart, and the decimal visual acuity was converted to the logarithm of the minimal angle resolution (logMAR) units for statistical analyses. All study conduct adhered to the tenets of the Declaration of Helsinki (Edinburgh, 2000) and the study protocol was approved by the Institutional Review Board of the Seoul National University Bundang Hospital.

#### RESULTS

All ten patients were male and ranged from 19 to 22 years in age (mean,  $20.0\pm1.0$  years). All patients presented with unilateral central visual disturbances such as central scotoma, blurred vision, or metamorphopsia. Every patient denied the history of bright light exposure such as sun-gazing, laser injury, sunbathing or arc welding and significant trauma. None of the patients could recollect any coexisting viral infection or family history of retinal disease and were taking any medication concurrently. Only one patient (Case 3) was participating in regular military training at the time of onset. Others recollected no hard, outdoor physical drill around the time of onset of symptoms. All patients had been assigned to ground duties. The clinical features of a representative case (Case 7) are presented in Figure 1 and the clinical characteristics of all patients and involved eyes are summarized in Table 1.



**Figure 1 Results of ophthalmologic examination of a representative case (Case 7) who presented with a visual acuity of 20/200** (A) Color fundus photography showing a small foveal yellow granular spot with surrounding pigment mottling. (B) Fluorescein angiography showing a mild transmission defect. (Arrow) (C and D) SD-OCT showing external limiting membrane (ELM) depression (white arrow), EZ defect and fragmentation (white arrowhead), and IZ defect (black arrowhead). Note that (C) is a horizontal scan and (D) is a vertical scan. (E) IR image (820 nm) showing a granular pattern of hyperreflectivity at the central fovea (arrow) and an enlarged foveal hyporeflective signal (arrowhead). Note that this alteration is more prominent than in the fundus photograph. (F) Blue peak reflectance showing hyper-reflective lesion at fovea (white arrow). (G) Blue-light autofluorescence image is unremarkable. (H) Multifocal electroretinography displaying decreased amplitudes at central retinal areas.

Visual acuity at presentation varied between hand movement and 20/20 (median 20/200, average 20/160). The average visual acuity at final follow-up was 20/350. (Average follow-up period: 10.1 months) Visual acuity decreased in 6 patients and improved in two patients finally. (from 20/32 to 20/25 in one case and hand movement to 20/1000 in

another). The mean (standard deviation[SD]) central foveal thickness was 191.3 (8.7) µm in the diseased eyes and 211.6  $\mu$ m (10.0) in the contralateral healthy eyes (P = 0.005, Wilcoxon signed rank test). On fundus photography, retinal lesions were usually located in the central macula area: one or more small yellow granular spots with unclear margins were visible in the foveal region. Large confluent granular yellow lesioin with surrounding geographic depigmentation were seen only in Case 10. Fluorescein angiography up(FA) of mid arteriovenouse phase showed hyperfluorescence from retinal pigment epithelium (RPE) atrophy in Cases 2, 5, and 7 (Figures 1 and 2). Unlike these, confluent hypofluorescence with surrounding hyperfluorescence was observed in case 10 (Figure 3). In other 6 Journal of Ophthalmol patients, abnormal findings were not detected on FA.



Figure 2 A, C and E: Fluorescein angiogram, fundus photograph, and SD-OCT of Case 2, A speckled pattern of transmission defects on FA and corresponding pigment mottling on fundus photography are observed. The lesion corresponds to the decreased EZ and RPE reflectivity on OCT. B, D and F: Case 5. A ring-shaped transmission defect and corresponding pigment mottling are observed. The lesion also coincides with EZ and RPE defect on OCT



**Figure 3 Images of Case 10** (A) Fundus photography at first visit shows yellow hypopigmented geographic lesion at macula. (B) IR images and (C) OCT at first visit. Green line indicates the OCT scan location. Hyperreflective lesion is well visualized and the margin of the lesion is delineated sharply with hyporefective line in FAF. On OCT, thinning in the outer nuclear layer and disruption of photoreceptor layers are observed. A hyperreflective band continuous with external limiting membrane is detected. (D) Fundus fluorescent angiography one month after first visit, showing tissue defect (E) Fundus autofluorescence image and (F) fundus photography at 2 months shows central dark pigmentation and RPE atrophy. (H) OCT at 2 months shows outer retinal disruption, hyperreflective dots, and cysts in the fovea. (G) Fundus photography after one year shows central dark pigmentation and surrounding circular chorioretinal atrophy. (I) OCT shows progression of outer retinal layer thinning. Focal choroidal excavation and choroidal thinning have developed and the choroidal lesion corresponds to the round atrophic lesion seen in fundus photography.

The SD-OCT images showed varying degrees of photoreceptor disruption in all cases. The cases were categorized into two groups based on the severity of photoreceptor disruption. The mild group showed photoreceptor layer blurring with a relatively preserved ellipsoid zone (EZ) (Group 1; Cases 1, 2, 3, and 4; Figure 4) and the severe group had discrete photoreceptor layer defect involving EZ (Group 2; Cases 5, 6, 7, 8, 9, and 10; Figure 5). Case 5 showed a unique, hyperreflective, central columnar structure, which disappeared after 8 months. In Group 1, the EZ was relatively preserved and visual acuity was better than in Group 2 (20/30 vs 20/500 respectively, P = 0.011 Wilcoxon rank sum test). LogMAR visual acuity correlated with the photoreceptor defect size in the EZ and interdigitation zone (IZ). (EZ vs LogMAR,  $R^2 = 0.612$ , P = 0.008; IZ vs LogMAR,  $R^2 = 0.834$ , P < 0.001, Spearman correlation) (Figure 6). The visual acuity improved in Cases 3 and 10, was maintained in Case 2 of group 1 and declined in all other cases. However, during follow-up, outer retinal contour disruption recovered and EZ defect size decreased in Cases 1, 3, 5, 6, and 7. In Case 10, thickened outer plexiform layer and a hyperreflective band continuous with the external limiting membrane were observed; focal choroidal excavation gradually developed during 3 years of follow-up. (Figure 3)



**Figure 4 SD-OCT images of cases that presented with photoreceptor layer blurring with relatively preserved ellipsoid zone (EZ)** (**Group 1**). Case 1 (A and B), Case 2 (C and D), Case 3 (E and F), and Case 4 (G and H). Despite EZ blurring, EZ band is dimly visible in all cases. B, D and F are follow up images of A, C and E images. Follow up images of B, D, and F were taken at 3, 12, and 3 months, respectively. White arrowheads indicate EZ defect area and black arrowheads indicate IZ defect. EZ and IZ blurring and defects show improvement in the follow-up images. (B, D, and F) The black arrows indicate abnormal hyperreflectivity at the photoreceptor layer. This hyperreflectivity decreased during the follow-up (F). (G and H) G and H are the initial OCT images (horizontal and vertical scans) of Case 4 because consecutive photo was not obtained. Central hyperreflective columnar structure is observed with surrounding hyporeflective area (black arrow).



**Figure 5 SD OCT images of cases that presented with discrete photoreceptor layer defects involving EZ (Group 2)** Case 5 (A and B), case 6 (C and D), case 7 (E and F), case 8 (G), case 9 (H), and case 10 (I and J). (A, C, D, E, G, H and I) The baseline images show severe outer retinal defects and surrounding hyporeflective areas with discontinuation of EZ. (B, D, F and J) The follow-up images of Cases 5, 6, 7, and 10 taken after 8, 5, 16 and 12 months, respectively. White arrowheads indicate EZ defects and black arrowheads indicate IZ defects. The photoreceptor disruption recovered either partly or completely, except in Case 10. (A) Black arrows in image A indicate hyperreflective columnar structure in the photoreceptor layer. (I) Outer plexiform layer is thickened but its margin is indistinct. Hyperreflective band continuous with external limiting membrane is visible between white arrowheads. (J) Outer nuclear layer and outer plexiform layer are invisible; instead hyperreflective material is detected at foveola. Choroidal curvature has become steeper after a year.



Figure 6 Scatter plot showing correlation between size of ellipsoid zone (EZ) defect and LogMAR visual acuity (A) and between interdigitation zone (IZ) defect size and LogMAR visual acuity (B). Visual acuity significantly correlated with size of EZ and IZ defect. Note that outliers, located at the right upper corner in A and B, indicate Case 10.

IR image revealed irregularly increased reflectance signal at the fovea with surrounding low reflective ring in six out of seven (85%) patients. (Figures 3 and 7) In all cases, IR images could better delineate the lesion than conventional fundus photography. However, no abnormal finding on fundus IR was observed in the healthy contralateral fellow eyes. Fundus autofluorescence (FAF) images revealed no remarkable findings in all patients, except Case 10 (Figure 1)

in which irregular hypofluorescent spots were observed (Figure 3).



Figure 7 Infrared reflectance (IR) images (820 nm) of Case 1 (A and B), Case 3 (C and D), Case 4 (E and F), Case 5 (G and H), Case 7 (I and J), and Case 9 (K and L) Increased reflectivity with surrounding hyporeflective ring is observed in all cases except Case 4. Corresponding OCT images are shown under the respective IR images. A, D, E, G, I, and K are images of the involved eyes.

	Table 1. Clinical	characteristics	of patients	with foved	omacular retinitis.
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Case No	Age (y)	Lat	BCVA (Initial)	S.E.	BCVA (Final)	FU (mo)	onset	symptom	CFT-d	CFT-h	FA	IR	FAF	mfERG	ERG, color vision, HVF	OCT	Group
1	22	R	20/50	0	20/250	4	10 days	central scotoma	178	193	unremarkable	abnormal	NL	unremar kable	NA	EZ blurring	1
2	20	L	20/20	0	20/20	16	unknown	central scotoma	188	221	transmission defect	NA	NA	NA	NA	EZ blurring	1
3	19	L	20/32	-1	20/25	6	3 weeks	central scotoma	200	220	NA	abnormal	NA	NA	NA	EZ blurring	1
4	21	R	20/40	-4.25	NA	NA	2 weeks	central scotoma	197	210	unremarkable	unremark able	Nl	NA	NA	EZ blurring	1
5	21	R	20/200	-1.75	20/320	9	2 months	central scotoma	201	223	transmission defect	abnormal	NA	unremar kable	normal color vision, normal visual field	hole like defect in EZ	2
6	20	L	20/200	-3.5	20/1000	5	3 weeks	metamorphopsia	195	215	unremarkable	NA	NA	NA	NA	hole like defect in EZ	2
7	19	R	20/200	-7	20/2000	17	6 weeks	central scotoma	201	209	transmission defect	abnormal	Nl	reduced central amplitud	nonspecific scotoma	hole like defect in EZ	2

8 9	20 19	R R	20/200 20/400	1.25 -1.5	20/2000 20/500	1 3	unknown 3 months	blurred vision blurred vision	178 182	202 223	unremarkable NA	NA abnormal	NA NA	NA unremar kable	NA normal standard ERG	EZ fragment ation hole like defect in EZ	2 2
10	19	R	НМ	-10	20/1000	40	1 week	central scotoma	193	200	blocked fluorescence, staining of the edge	abnormal	mild hypo fluor escen ce	reduced central amplitud e	central scotoma	EZ defect, focal choroida l excavati	2

Lat: laterality of the involved eye, BCVA: best corrected visual acuity, S.E.: refractive error by spherical equivalent, FU (mo): follow up duration (months), CFT: central subfoveal thickness, FA: fluorescein angiogram, IR: infrared reflectance image, FAF: fundus autofluorescence photo, mfERG: multifocal electroretinography, HVF: Humphrey visual field test, NA: test was not performed, EZ: inner segment ellipsoid zone, IZ: interdigitation zone, SD-OCT group - 1 : mild, 2: severe photoreceptor disruption, HM; hand movement.

#### DISCUSSION

This is the first case series of foveomacular retinitis in young male soldiers, that presents multimodal imaging data, including high resolution SD-OCT. Typical yellow granular spots in the fovea were observed on fundus photography. Photoreceptor disruption involving IZ and/or EZ was observed on SD-OCT and visual loss correlated with OCT features. Fundus IR imaging was also useful to detect the foveal lesions, while FAF was not. Although photoreceptor disruption on SD-OCT improved either partially or completely, visual acuity did not recover in most cases.

A red, sharply demarcated, foveal or juxtafoveal spot located at the level of the outer retina is suggestive of solar retinopathy.<sup>[2]</sup> In our cases, yellow spots and pigment mottling were consistently observed. This ophthalmoscopic appearance and the OCT findings resemble chronic solar retinopathy despite the absence of direct sun gazing or sunbathing history. Several studies have reported presumed solar retinopathy in patients who denied direct sun gazing. Rai et al.<sup>[3]</sup> reported that only 51% of patients could recollect a history of sun-gazing. Following their suggestion, absence of a history of sun viewing may not be sufficient to exclude solar retinopathy. Generally, soldiers are more likely to be exposed to the sun than civilians of the same age in industrialized nations. However, our patients were not assigned to hard training unit performing a lot of outdoor work. All the patients included in this series repeatedly denied sun gazing or bright light exposure. Further, additional case was not reported in the same military units. Our patients also denied using laser beam or welding are which can produce lesions similar to solar retinopathy. <sup>[4]</sup> Thus, light-associated toxicity was probably not the relevant etiological factor in our study.

Up to now, there have been two case reports of OCT findings in foveomacular retinitis. Topouzis et al.<sup>[5]</sup> described the localized loss of the RPE and photoreceptor layers at fovea. Badhani et al.<sup>[6]</sup> reported 10-year-old boy with a full-thickness, rectangular, hyperreflective lesion which was replaced by a sharp defect in the outer retina over the course of five years. Regarding solar retinopathy, several studies have described OCT findings. Entire retinal hyperreflectivity can appear for several days, which corresponds to yellow retinal lesions in acute stage of solar retinopathy.<sup>[7,10,13]</sup> Other reports of chronic cases revealed hyporeflective spaces in the outer retina, especially the photoreceptor layer, while sparing the RPE layer. These OCT findings are similar to those observed in chronic solar retinopathy. These are also consistent with the OCT features in the two cases of foveomacular retinitis. <sup>[5, 6]</sup> The hyporeflective photoreceptor defect and EZ contour disruption recovered in all cases except Cases 2 and 10 (Cases 4, 8, and 9 had no follow-up OCT). We divided the hyporeflective pattern into two groups and this classification correlated well with the degree of visual impairment.

Interestingly, a hyperreflective columnar structure was observed on OCT in Case 5 (Figure 5). Which is a similar finding in acute solar retinopathy. This hyperreflective lesion is also detected in a recently reported case of foveomacular retinitis.<sup>[6]</sup> Longitudinal observation revealed that the hyperreflective band was detected at 1 month and resolved after 3 months. It seems that this lesion may be an early OCT finding in both solar retinopathy and foveomacular retinitis.

We observed focal choroidal excavation (FCE) in Case 10. This case had a severe form of foveomacular retinitis with poor visual outcome. FCE has been reported in several retinal diseases including central serous chorioretinopathy, multiple evanescent white dot syndrome, multifocal choroiditis, punctate inner choroidopathy etc. <sup>[14-16]</sup> Although the exact mechanism of FCE has not been clearly elucidated, our case indicates that localized choroidal damage and atrophic thinning may play a role. To the best of our knowledge, this is the first case showing FCE development in

case of foveomacular retinitis.

IR images in our cases revealed more visible alteration than conventional color fundus images and the abnormality was observed only in the affected eyes. Charbel et al. <sup>[17]</sup> have reported similar IR findings in solar retinopathy. They also reported increased foveal reflectance/fluorescence with blue reflectance (488 nm) and blue-light autofluorescence (488 nm) and the foveal abnormality was also found in the healthy fellow eyes. However, in the present study, the fellow eyes showed no abnormality on any imaging examinations. Ahn et al. <sup>[18]</sup> also showed a macular abnormality on IR images in occult macular dystrophy that could not be detected on fundus photography. Taken together, IR imaging is useful for detecting subtle foveal abnormalities in foveomacular retinitis that might be difficult to detect on color fundus photography.

Solar retinopathy usually occurs bilaterally. <sup>[20]</sup> Sometimes, patients with eccentric fixation or uniocular occlusion can show unilateral involvement. Foveomacular retinitis has been known to involve both eyes at variable rates from 30% to 100%. <sup>[1, 20]</sup> Marlor et al. <sup>[21]</sup> reported sequential involvement of both eyes in some patients. In contrast, our cases presented exclusively with unilateral lesions and there was no sequential involvement of the other eye. None of the patients in our series evinced eccentric fixation or large angle strabismus. Therefore, absence of bright light exposure history andunilateral involvement in orthotropic patients supports a diagnosis of foveomacular retinitis rather than light exposure associated retinopathy.

Retinal diseases reported in young soldiers are mostly associated with trauma, hard exercise, flight, etc.<sup>[22-24]</sup> In our cases however, traumatic maculopathy, whiplash maculopathy, and toxic maculopathy can be excluded as all patients denied relevent histories. Another possible differential diagnosis is unilateral acute idiopathic maculopathy (UAIM), a rare disorder presenting with transient visual loss in a young patient secondary to exudative macular detachment and infiltrates, preceded by a viral infection.<sup>[25]</sup> Although unilateral involvement in young healthy adults matches the clinical profile of our patients. , viral prodrome and complete recovery of vision in UAIM differ. Recent reports on UAIM have described similar photoreceptor EZ loss on SD-OCT.<sup>[26, 27]</sup> However, RPE hyperreflectivity on SD-OCT and macula hypofluorescence on FA also reported in UAIM were not observed in any of our cases. Acute retinal pigment epitheliitis (ARPE) affects healthy young adults with the symptom of painless blurring or vision loss and should also be ruled out. <sup>[28, 29]</sup> The SD-OCT findings in ARPE include inner RPE involvement, disruption of IS, a dome-shape hyperreflective lesion at the outer retina, and external limiting membrane displacement. The condition is usually unilateral and shows visual improvement within 3 months. However, in our cases, the RPE layer was spared and no substantial visual recovery occurred despite noticeable resolution of photoreceptor lesions on OCT. Foveomacular retinitis has been reported to show variable degrees of visual decline. <sup>[1, 21]</sup> Marlor et al.<sup>[21]</sup> reported that

Foveomacular retinitis has been reported to show variable degrees of visual decline. <sup>[1, 21]</sup> Marlor et al.<sup>[21]</sup> reported that 32% (89 out of 274) had 20/200 or worse vision and only 5% (14 out of 274) had 20/40 or better vision at the time of discharge. Among patients with poor vision at presentation ( $\leq 20/200$ ), 46% (15 out of 70) showed visual improvement while 67% (6 out of 9) of those with good visual acuity ( $\geq 20/40$ ) showed visual decline during 5 years of follow-up. In our cases, 8 of 10 patients (80%) had reached lower than 20/200 vision and only two patients showed visual recovery. Compared to foveomacular retinitis, the visual outcome is reported to be better in cases of solar retinopathy. Abdellah et al.<sup>[30]</sup> reported that 9 (90%) of 10 eyes had a final visual acuity of 20/25 or more. Rai et al.<sup>[31]</sup> reported that visual acuity was 6/12 or better in more than 80% of patients and did not deteriorate in 319 patients. Recent reports have also shown mild to moderate visual loss ranged from 20/25 to 20/200 in solar retinopathy.

In conclusion, foveomacular retinitis can cause serious visual impairment in young male soldiers. Although the etiology and risk factors have not yet been established, it is an important disease to be suspected in cases of sudden or insidious unilateral visual loss in young soldiers. SD-OCT and fundus IR imaging are required for proper diagnosis. Further research to elucidate the etiology is needed to prevent vision loss from this little-known disease.

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This is the first case series of foveomacular retinitis reported in military soldiers and diagnosed with multimodal imaging. Foveomacular retinitis is a rare and irreversible vision threatening disease without a definite etiology. SD-OCT is the most important diagnostic modality and provides information on visual prognosis.

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Conflicts of Interest: Yoon CK, None; Park KH, None; Woo SJ, None. REFERENCES

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