Research article

Quantitative analysis of ultra-widefield fluorescein angiography in uveitis associated with sarcoidosis

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Keywords:
- Angiographic analysis
- Quantitative
- Ultra-widefield fluorescein angiography
- Uveitis
- Ocular sarcoidosis

ABSTRACT

Purpose: To quantitatively assess the angiographic features of uveitis associated with sarcoidosis on ultra-widefield fluorescein angiography (UWFA) and determine their correlations with clinical features.

Design: A retrospective cohort study.

Methods: Sixty-four eyes (64 patients) with sarcoidosis uveitis were included. On UWFA, presence of vasculitis, macular leakage, and optic disk leakage were assessed and features including peripheral ischemic area, vascular leakage area, and punched out lesions were quantitatively analyzed using FIJI (ImageJ2) and correlated with clinical features.

Results: The mean peripheral ischemic area and leakage area were 0.0419 ± 0.113% and 0.0333 ± 0.0287% of the total retinal area, respectively. Macular and optic disk leakage were present in 18.8% and 59.4% of eyes, respectively. The average number of punched out lesions was 10.02 ± 21.95. Those changes were most abundant in the inferotemporal area. The presence of disc leakage correlated with all the other UWFA parameters (all \( r \geq 0.260 \); all \( P \leq 0.038 \)). The leakage area correlated with vitreous cells, baseline and 6-month logMAR visual acuity, steroid dose and duration, erythrocyte sedimentation rate, and C-reactive protein (\( r = 0.472, 0.288, 0.321, 0.374, 0.250, 0.251, 0.277; \) all \( P \leq 0.46 \)).

Conclusions: This study quantitatively analyzed UWFA data in sarcoidosis uveitis. Angiographic changes were most frequent in the inferotemporal area. UWFA parameters correlated with one another and clinical variables. These quantitative imaging results warrant a subjective analysis of sarcoidosis uveitis.

1. Introduction

Sarcoidosis is a multisystem disorder defined by the presence of noncaseating granulomas and is clinically characterized by hilar lymph node enlargement, an increase in serum levels of angiotensin-converting enzyme (ACE), polyclonal B-cell activation, and cutaneous anergy [1]. The most commonly affected organs are the lungs, skin, and eyes. Ocular involvement occurs in 33%–50% of patients with systemic sarcoidosis, and 50%–60% of them will have chronic uveitis [2, 3, 4, 5].

Previous angiographic studies of ocular sarcoidosis revealed specific posterior segment findings. Posterior lesions such as peripheral retinal thickening, vitritis, chorioretinitis, and choroidal and optic nerve granulomas have been demonstrated using fluorescein or indocyanine green angiography [6, 7]. Ultra-widefield fluorescein angiography (UWFA), which enables 150-degree or 200-degree photographic and angiographic views in one shot, has greatly improved clinicians’ ability to detect vascular abnormalities in the total retinal area [8, 9].

Not only is it useful in detecting retinal vascular diseases, but UWFA also well identifies peripheral lesions of uveitis that are difficult to detect during a clinical exam or with a conventional fundus camera in eyes with uveitis [10, 11, 12, 13, 14]. The lesions can also be analyzed quantitatively. In uveitis patients, quantitative analysis of angiographic features including peripheral vasculitis, vascular leakage, ischemia, microaneurysms were introduced by several previous studies [11, 15, 16].

Angiographic studies on uveitis associated with sarcoidosis revealed characteristic features but there is a limited number of objective study using UWFA. Our aim in this study was to analyze quantitative UWFA characteristics in eyes with uveitis associated with sarcoidosis. We automatized this quantification to reduce subjectivity in measurements and increase repeatability. The measurements were performed at each

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https://doi.org/10.1016/j.heliyon.2022.e11218

Received 12 August 2022; Received in revised form 7 October 2022; Accepted 19 October 2022

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quadrant. Additionally, associations between the angiographic characteristics and clinical findings were assessed.

2. Methods

This retrospective case series study was conducted in the Department of Ophthalmology of Bucheon St. Mary’s Hospital, Catholic University of Korea. This study was approved by the institutional review board of the Catholic University of Korea and conducted according to the Declaration of Helsinki (KC20RASI0058). The need for written informed consent was waived because of the study’s retrospective design.

2.1. Patients

The medical records of consecutive treatment-naïve posterior or panuveitis patients who were diagnosed with sarcoidosis with a lung biopsy were included. The angiographic parameters were quantitatively measured using ultra-widefield fluorescein angiography. The angiographic lesions (focal vasculitis, macular edema, and optic disc leakage) were assessed for each quadrant. To measure the leakage area, ‘Subtract Background’ was performed to remove background fluorescence, and retinal vessels were identified using the ‘Tubeness’ app and removed from the image. Leakage areas were selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app and measured as pixels. Peripheral ischemic areas were measured as dark areas and selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app. Punched out lesions were counted using the ‘Analyze Particle’ app after binarization using the ‘Phansalkar’ auto local threshold method.

Figure 1. Quantitative measurements of angiographic parameters on ultra-widefield fluorescein angiography of eyes with sarcoidosis uveitis. (A) Angiographic lesions (focal vasculitis, macular edema, and optic disc leakage) were assessed for each quadrant. (B) To measure the leakage area, ‘Subtract Background’ was performed to remove background fluorescence, and retinal vessels were identified using the ‘Tubeness’ app and removed from the image. Leakage areas were selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app and measured as pixels. (C) Peripheral ischemic areas were measured as dark areas and selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app. (D) Punched out lesions were counted using the ‘Analyze Particle’ app after binarization using the ‘Phansalkar’ auto local threshold method.
between August 2016 and September 2021 were reviewed. The diagnosis of sarcoidosis was established by pulmonologists based on a compatible history of uveitis and a positive biopsy; positive broncho-alveolar lavage; bilateral hilar lymphadenopathy; or 2 of the following 3 laboratory abnormalities: elevated lysozyme level, elevated level of angiotensin-converting enzyme, and increased polycional activation [17].

Each patient underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), slit-lamp examination with anterior chamber (AC) and vitreous cell counts, and dilated fundus examination. Clinical assessments followed criteria from the standardization of uveitis nomenclature (SUN) by the SUN Working Group [18]. In patients with bilateral disease, the eye with the most severe symptoms was chosen for this study. The following clinical information was collected: age, sex, presence of diabetes or hypertension, serum level of ACE, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and steroid treatment dose and duration.

### 2.2. Image analysis

Mydriatic UWFA (Optos California P2000Tx iCG; Optos, Dunfermline, United Kingdom) was performed using a standard image view of 200° in a single capture. Angiographic lesions, including presence of focal vasculitis, macular edema, and optic disc leakage, were assessed for each quadrant using the whole series of UWFAs (Figure 1A). The best UWFA image between 40 s and 3 min after dye injection was obtained for a quantitative analysis. Presence of focal vasculitis was confirmed when perivascular sheathing or cuffing, vascular leakage and/or occlusion was observed, macular edema and optic disc leakage was confirmed with dye leakage in macular and optic disc area, respectively.

FIJI software (U.S. National Institutes of Health, Bethesda, MD, USA; available at http://fiji.sc) was used for the analyses. All UWFA images were saved as JPEG files, sized to 1024 × 800 pixels, and subjected to contrast adjustment. Quantitative detection of the ischemic and leakage areas was automated using the method described by Ehlers et al. with some modifications [15]. To measure the leakage area, ‘Subtract Background’ was performed to remove background fluorescence instead of ‘flattening’ two early and late images, as Ehlers et al. did. Furthermore, retinal vessels were identified using the ‘Tubeless’ app and removed from the image. Leakage areas were selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app and measured as pixels (Figure 1B). Peripheric ischemic areas were measured as dark areas and selected by adjusting the ‘Brightness’ window on the ‘Threshold Color’ app in the original image (Figure 1C). Punched out lesions were counted using the ‘Analyze Particle’ app (size 30–500 pixels and circularity 0.3–1.0) after binarization using the ‘Phansalkar’ auto local threshold method (radius 30) (Figure 1D). All parameters were measured for each quadrant with the optic disc as a reference point (Figure 1B and 1C).

### 2.3. Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 23.0.1; SPSS Inc., Chicago, IL, USA). The Snellen BCVA was converted to logMAR (logarithm of minimal angle resolution) for the statistical analysis. Continuous variables are described as means ± standard deviations. Repeated-measurement analysis of variance (RM-ANOVA) and paired t-test were used to compare differences among and between quadrants. Pearson's correlation analysis were used to determine the coefficients of correlation between UWFA and clinical parameters after confirmation of a normal distribution. A P-value < 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Demographics and clinical characteristics of the patients

In total, 64 eyes of 64 patients were analyzed. The mean age was 57.31 ± 15.01 years, and 19 (30%) patients were male. The mean anterior chamber and vitreous cell counts were 0.4 ± 0.69 and 1.33 ± 0.94, respectively. The clinical characteristics of the study patients including the mean values for ACE, ESR, and CRP are summarized in Table 1.

### 3.2. Quantitative analysis of UWFA

In the total UWFA area, the mean peripheral ischemic area and leakage area were 0.0419 ± 0.1136 and 0.0333 ± 0.0287, respectively. Macular and optic disc leakage was present in 18.8 % and 59.4 % of eyes, respectively. The mean number of punched out lesions in the total UWFA area was 10.02 ± 21.95.

The results from the quantitative analysis of UWFA on the study eyes are summarized in Table 2. In the RM-ANOVA by quadrant, the infero-temporal area had the largest areas of ischemia and leakage and the largest number of punched out lesions (P = 0.001, < 0.001 and 0.001, respectively; Figure 2). The presence of peripheral focal vasculitis was also most frequent in the infero-temporal area (P < 0.001 by RM-ANOVA).

### 3.3. Correlations among UWFA parameters and between the UWFA and clinical parameters

The presence of optic disc leakage correlated positively with all the other UWFA parameters (all P ≤ 0.038). The leakage area correlated with macular leakage (r = 0.605, P < 0.001). Correlations among the UWFA parameters are summarized in Table 3.

We found positive correlations between the leakage area and vitreous cells, BCVA at baseline and 6 months, initial dose and duration of steroid, ESR, and CRP (all P ≤ 0.046), and peripheral ischemia correlated with vitreous cells (P = 0.036). The presence of macular leakage correlated positively with vitreous cells, BCVA at baseline and 6 months, initial steroid dose, and CRP (P < 0.001, = 0.001, < 0.001, = 0.033, and = 0.040, respectively), and optic disc leakage correlated with vitreous and AC cells and with BCVA at baseline and 6 months (P < 0.001, = 0.046, = 0.002, and = 0.001, respectively). The number of punched out lesions correlated positively with vitreous cell, BCVA at 6 months, the duration of steroid use, and ACE (P = 0.003, = 0.008, = 0.004, and = 0.018, respectively.). The correlations between the UWFA parameters and clinical parameters are summarized in Table 4.

### 4. Discussion

Visualization of the peripheral retinal area was made possible by the introduction of ultra-widefield imaging and has demonstrated the

| Table 1. Baseline clinical characteristics of patients with sarcoidosis uveitis. |
|------------------|-------------|
| **Variables**    | **Values**  |
| Age (years, mean ± SD (range)) | 57.31 ± 15.01 (25–85) |
| Sex (male n, (%)) | 19 (30) |
| Laterality (right eye n, (%)) | 32 (50) |
| Diabetes (presence, (%)) | 14 (22) |
| Diabetes duration (years, mean ± SD (range)) | 2.91 ± 8.14 (0–40) |
| Hypertension (presence, (%)) | 19 (29) |
| Hypertension duration (years, mean ± SD (range)) | 3.26 ± 7.34 (0–35) |
| Anterior chamber cells (+s, mean ± SD (range)) | 0.4 ± 0.69 (0–3) |
| Vitreous cells, (+s, mean ± SD (range)) | 1.33 ± 0.94 (0–3) |
| Angiotensin converting enzyme (u/l, mean ± SD (range)) | 73.91 ± 35.75 (23.3–147.7) |
| Erythrocyte sedimentation rate (mm/hr, mean ± SD (range)) | 16.11 ± 12.89 (2–47) |
| C-reactive protein (mg/L, mean ± SD (range)) | 0.47 ± 0.55 (0.041–4.6) |
| SD: standard deviation. |


importance of peripheral lesions in numerous diseases, including uveitis [12, 14]. Sarcoidosis uveitis produces characteristic changes on fluorescein angiography (FA), including peripheral vasculitis, peripheral ischemia, and punched out lesions [19]. In this study, we quantitatively assessed angiographic features on UWFA by quadrant and correlated angiographic features with clinical parameters.

It had been reported that UWFA might alter management decisions compared with standard-of-care imaging and clinical examinations of patient with uveitis [20]. UWFA helps to identify and document the entire extent of retinal capillary non-perfusion and peripheral neovascularization, and it can detect disease activity in intermediate uveitis, including sarcoidosis cases, that might be missed on conventional FA [12]. However, only a few studies have considered UWFA in sarcoidosis uveitis. Recently, Tanaka et al. compared a uveitis scoring system between standard FA and UWFA in sarcoidosis uveitis [21]. The peripheral capillary leakage scores from the UWFA in their study were particularly high.

In this study, we analyzed the peripheral ischemia and leakage areas using automated quantification. Quantitative analysis of UWFA data from uveitis patients was introduced in several previous studies [11, 15, 16]. Karampelas et al. [11] quantitatively analyzed peripheral vasculitis, vascular leakage, and ischemia in uveitis using UWFA. Ehlers et al. automated the quantification of leakage and microaneurysms in UWFA data and demonstrated a strong intra-study correlation [15, 16]. In this study, we simplified the Ehlers et al. automatization scheme and used our modified method to measure the peripheral ischemic area, leakage area, and punched out lesions.

Previously, Thomas et al. [14] demonstrated a possible association between the presence of peripheral leakage and cystoid macular edema and treatment augmentation in uveitis. Krampel et al. also showed that the peripheral leakage area was associated with increased macular thickness and that macular ischemia and increased macular thickness were independently associated with visual acuity [11]. We not only confirmed that finding in sarcoidosis uveitis, but also added information about the relationship between the leakage area and clinical parameters for inflammation.

The leakage area was associated with inflammatory status and visual acuity, as demonstrated by its correlation with vitreous cells, BCVA, ESR, and CRP, as well as with macular and optic disc leakage. Elevated ESR and CRP levels in sarcoidosis patients are often associated with systemic disease such as sarcoidosis-associated arthritis and erythema nodosum [22]. A larger leakage area was associated with high ESR and CRP; therefore, more attention to systemic evaluation might be required in those patients. Also, a higher initial dose and longer duration of steroid treatment might be needed due to the higher incidence of systemic disease when the eyes show a larger leakage area.

Peripheral punched out lesions in the retina are characteristic of peripheral multifocal chorioretinitis, an ocular disorder already linked to sarcoidosis in older female patients [23]. In a clinicopathological study, those lesions were shown by biopsy to be chorioretinal noncaseating granulomas centered on the choriocapillaris and invading the Bruch membrane and outer retina [24]. Those lesions did not respond well to

| Variables                         | Values                  |
|-----------------------------------|-------------------------|
| Peripheral ischemia, ST (%)       | 0.003963 ± 0.016142     |
| Peripheral ischemia, IT (%)       | 0.027297 ± 0.07575      |
| Peripheral ischemia, IN (%)       | 0.008914 ± 0.04293      |
| Peripheral ischemia, SN (%)       | 0.001706 ± 0.010757     |
| Peripheral focal vasculitis, ST (presence, mean ± SD) | 0.64 ± 0.48 |
| Peripheral focal vasculitis, IT (presence, mean ± SD) | 0.81 ± 0.39 |
| Peripheral focal vasculitis, IN (presence, mean ± SD) | 0.39 ± 0.49 |
| Peripheral focal vasculitis, SN (presence, mean ± SD) | 0.28 ± 0.45 |
| Leakage area, ST (%, mean ± SD)   | 0.009517 ± 0.009636     |
| Leakage area, IT (%, mean ± SD)   | 0.013665 ± 0.014865     |
| Leakage area, IN (%, mean ± SD)   | 0.006429 ± 0.011102     |
| Leakage area, SN (%, mean ± SD)   | 0.003704 ± 0.008211     |
| Macular leakage (presence, mean ± SD) | 0.1875 ± 0.393398 |
| Disc leakage (presence, mean ± SD) | 0.59375 ± 0.495015 |
| Punched out lesion, ST (n, mean ± SD) | 0.63 ± 2.37 |
| Punched out lesion, IT (n, mean ± SD) | 10.73 ± 31.37 |
| Punched out lesion, IN (n, mean ± SD) | 3.37 ± 10.29 |
| Punched out lesion, SN (n, mean ± SD) | 1.16 ± 4.95 |

SD: standard deviation; ST: superotemporal; IT: inferotemporal; IN: inferonasal; SN: superonasal.
treatment, as demonstrated by the longer duration of steroid use in this study.

When we divided our findings by quadrant, the angiographic lesions were most frequent in the inferotemporal quadrant. That could be explained by gravity, which might create a preferential downward displacement of noncaseating granuloma in sarcoidosis [25], or it might just reflect the fact that the inferotemporal area is the largest visible area on UWFA. Another explanation could be a lower rate of clearance of inflammatory cells at the inferior quadrant. Because the retina and choroid are considered to be alymphatic tissues, the drainage of inflammatory cells could occur through blood vessels. Venous blood at the inferior vortex should flow upward against gravity into the inferior or temporal area, and the UWFA parameters correlated with one another and the clinical variables. This quantitative imaging analysis is thus of clinical significance, and a subjective analysis of sarcoidosis uveitis is warranted.

### Table 3. Correlations among ultra-widefield fluorescein angiography variables in sarcoidosis uveitis.

| Variables                  | Leakage area | Leaking area | Macular leakage | Disc leakage | Punched out lesion |
|----------------------------|--------------|--------------|-----------------|--------------|-------------------|
| Correlation coefficient    | .199         | 1.00         | .605**          | .420**       | .232              |
| P-value                    | .115         | .000         | .001            | .065         |                   |
| Peripheral ischemia        | 1.00         | .199         | −.055           | .260*        | .072              |
| Correlation coefficient    | .115         | .665         | .038            | .017         |                   |
| P-value                    | .665         | .000         | .001            | .135         |                   |
| Macular leakage            | −.055        | .605**       | 1.000           | .397**       | .189              |
| Correlation coefficient    | .605         | .000         | .001            | .299*        |                   |
| P-value                    | .605         | .000         | .001            | .179         |                   |
| Disc leakage               | .260*        | .420**       | .397**          | 1.000        | .299*              |
| Correlation coefficient    | .260         | .038         | .001            | .017         |                   |
| P-value                    | .260         | .038         | .001            | .179         |                   |
| Punched out lesion         | .072         | .232         | .189            | .299*        | 1.000              |
| Correlation coefficient    | .072         | .232         | .189            | .299*        |                   |
| P-value                    | .072         | .232         | .189            | .299*        |                   |

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

### Table 4. Correlations between ultra-widefield fluorescein angiography variables and clinical variables in sarcoidosis uveitis.

| Variables                  | Vitreous cells | AC cells | BCVA, baseline | BCVA, 6 m | PO steroid, initial dose | PO steroid, duration | ACE | ESR | CRP |
|----------------------------|----------------|----------|----------------|-----------|-------------------------|----------------------|-----|-----|-----|
| Leakage area               | .472**         | −.028    | .288**         | .321**    | .374**                  | .250*                | .007| .251*| .277*|
| P-value                    | .000           | .826     | .021           | .010      | .002                    | .046                 | .954| .045| .027|
| Peripheral ischemia        | .262*          | .012     | .225           | .096      | .121                    | .048                 | .038| .088| .026|
| P-value                    | .036           | .928     | .074           | .449      | .341                    | .705                 | .764| .487| .838|
| Macular leakage            | .473**         | −.236    | .417**         | .574**    | .266*                   | .188                 | −.130| .124| .258*|
| P-value                    | .000           | .061     | .001           | .000      | .033                    | .137                 | .307| .328| .040|
| Disc leakage               | .426**         | −.251*   | .377**         | .404**    | .081                    | .044                 | −.031| −.005| .129|
| P-value                    | .000           | .046     | .002           | .001      | .525                    | .729                 | .811| .966| .310|
| Punched out lesion         | .361**         | −.046    | .122           | .329**    | −.079                   | .357**               | −.296| −.218| −.219|
| P-value                    | .003           | .718     | .337           | .008      | .532                    | .004                 | .018| .083| .082|

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

In conclusion, angiographic parameters measured automatically on UWFA results in sarcoidosis uveitis were most frequent in the inferotemporal area, and the UWFA parameters correlated with one another and the clinical variables. This quantitative imaging analysis is thus of clinical significance, and a subjective analysis of sarcoidosis uveitis is warranted.

** Declarations **

** Author contribution statement **

Hyun Suh and Anna Lee: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ho Ra: Contributed reagents, materials, analysis tools or data.

Jun Hyuck Lee: Analyzed and interpreted the data.

Jiwon Baek: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

** Funding statement **

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No. NRF001663041G0003101) and Catholic Medical Center Research Foundation made in the program year 2022.

** Data availability statement **

Data will be made available on request.
**Declaration of interest’s statement**

The authors declare no conflict of interest.

**Additional information**

No additional information is available for this paper.

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