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Case report

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ASYMPTOMATIC UVEITIS AS PRIMARY MANIFESTATION OF SARCOIDOSIS

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Key words: granulomatous uveitis, indocyanine green angiography, sarcoidosis

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5 **Abstract**

6 **Aim:** To emphasize that ocular involvement in sarcoidosis may be the initial manifestation
7 of the disease and can be completely asymptomatic.

8 **Presentation of case:** A 36 year-old female was referred to uvea service with detection of
9 keratic precipitates and anterior chamber cells during routine eye examination. She did
10 not show any symptoms of uveitis. A slit lamp examination revealed bilateral medium-
11 sized, round, centrally located granulomatous keratic precipitates on corneal endothelium
12 and +1 cell reaction in anterior chamber. Dilated fundus examination showed bilateral
13 vitreous cells and small vitreous opacities in the right eye. Serum levels of angiotensin-
14 converting enzyme were increased. Her chest X-ray study was significant for bilateral hilar
15 adenopathy, and transbronchial needle aspiration biopsy confirmed the diagnosis of
16 sarcoidosis. Patient responded well to systemic steroid therapy with complete
17 disappearance of the signs.

18 **Discussion:** Ocular involvement in sarcoidosis may occur as the disease process, it also
19 can be the first clinical manifestation of the disease. Although the incidence of pulmonary
20 involvement is nearly one and half times higher than ocular involvement, the most
21 frequent initial symptom of sarcoidosis is eyesight disorder. The reason for that is late
22 emergence of symptoms caused by lung involvement such so symptoms related to ocular
23 involvement generates the major complaints at the first application.

24 **Conclusion:** Early diagnosis of sarcoidosis is important for avoiding ocular complications
25 as well as prevention of other system involvements. Ophthalmologists have a critical role
26 in the diagnosis and follow-up of the disorder because of increasing incidence of the
27 ocular involvement.

28 **Introduction:**

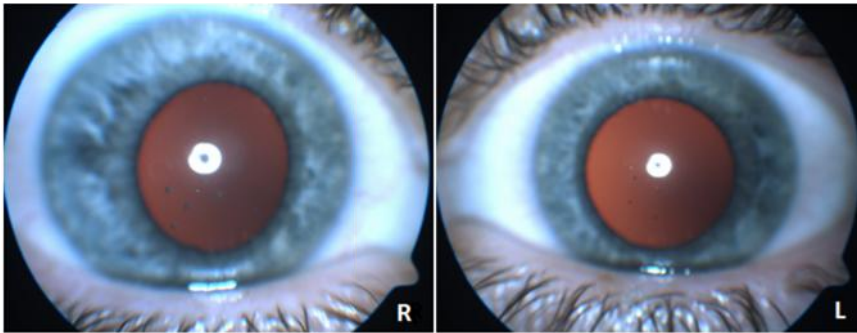
29 Sarcoidosis is a systemic disease with unknown etiology and characterized by non-
30 caseous granulomas [1]. It mainly affects individuals between the ages of 20-50 and
31 slightly more common in women [2]. The disease process is caused by accumulation of T
32 lymphocytes and mononuclear macrophages forming epithelioid granulomas in target
33 tissues [1]. Most common site of involvement is lung and includes 90 % of the cases [2].
34 Ocular involvement was reported to be seen in 30 - 60 % of the patients [3]. Sarcoidosis
35 may also affect lymph nodes, skin, joints, central nervous system and heart [3].

36 Ocular involvement usually includes anterior or posterior uveitis, also can include lacrimal
37 gland, conjunctiva and optic nerve [4]. The incidence of the ocular involvement is
38 increasing according to recent studies [5, 6] and early detection of ocular findings is
39 gaining importance to prevent disease progression. The aim of this report is to emphasize
40 that ocular involvement in sarcoidosis may be initial manifestation of the disease and can
41 be asymptomatic.

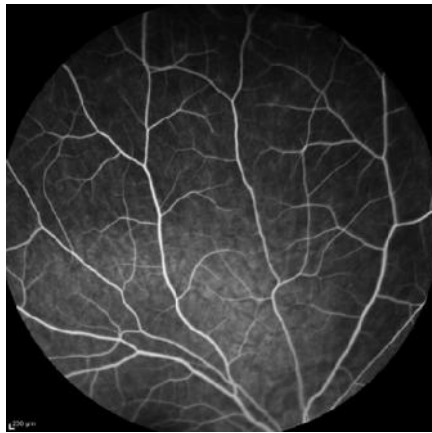
42 **Presentation of case:**

43 A 36-year-old female was referred to our uvea service due to detection of keratic
44 precipitates and anterior chamber cells during routine eye examination. She did not show
45 any symptoms of uveitis. Best corrected visual acuity in both eyes was 20/20. A slit lamp
46 examination revealed bilateral medium-sized, round, centrally located granulomatous
47 keratic precipitates on corneal endothelium (Figure 1) and +1 cell reaction in anterior
48 chamber. Dilated fundus examination showed bilateral vitreous cells and vitreous
49 opacities below the right eye. In the fluorescein angiography, there was fluorescein
50 leakage from peripheral vessels in the right eye (Figure 2).

51 **Figure 1:** Bilateral medium-sized, round, centrally located granulomatous keratic
52 precipitates. R, right eye; L, left eye



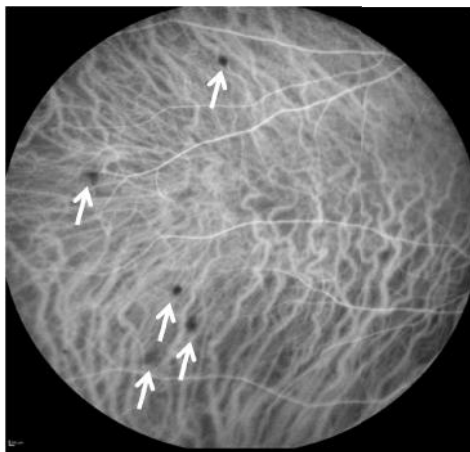
53
54 **Figure 2:** Fluorescein leakage from peripheral vessels of the right eye on early phase of
55 fluorescein angiography



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57 Indocyanine green angiography showed infrequent hypofluorescent small round spots in
58 the right posterior pole (Figure 3). The results of laboratory examinations for syphilis and
59 tuberculosis were negative, including venereal disease research laboratory (VDRL) test,
60 rapid plasma regain (RPR) test and Quantiferon test. Serum level of angiotensin-
61 converting enzyme (ACE) was raised to 67 U/L (8 - 52 U/L). Serum calcium level was
62 normal. A posteroanterior chest x-ray showed bilateral hilar lymphadenopathy (Figure 4).
63 With the pre-diagnosis of asymptomatic uveitis associated with sarcoidosis, pulmonary
64 disease consultation was requested. Pulmonary disease department performed

65 endobronchial ultrasound-guided transbronchial needle aspiration biopsy and diagnosis
66 of sarcoidosis was confirmed by detection of non-caseous granulomatous lymphadenitis.
67 Patient was completely asymptomatic in terms of pulmonary involvement and
68 pulmonary function tests were totally normal. Therefore treatment was not needed for
69 pulmonary disease. 30 mg prednisolone (Deltacortril 5 mg tablets ®) treatment was
70 initiated due to ocular involvement and tapered 5 mg per week. After six weeks, anterior
71 chamber inflammation, keratic precipitates and vitreous opacities were completely
72 disappeared. Indocyanine green angiography was repeated and it showed initially
73 hypofluorescent small round spots turned to isofluorescent spots three months later
74 (Figure 5).

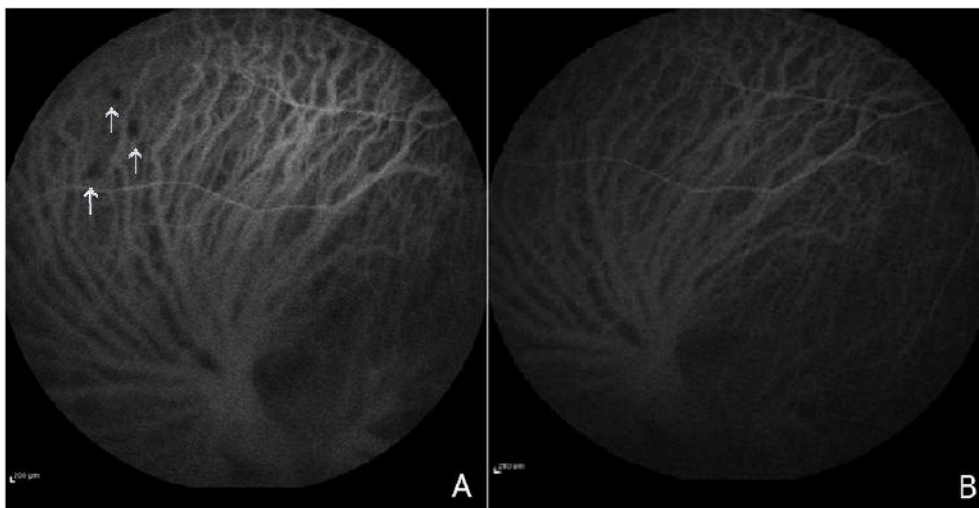
75 **Figure 3:** Hypofluorescent small round spots (arrows) on the right posterior pole on
76 indocyanine green angiography



81 **Figure 4:** Posteroanterior chest x-ray showing bilateral hilar lymphadenopathy



82
83 **Figure 5:** Hypofluorescent small spots (arrows) on the inferior mid-periphery of right eye
84 on indocyanine green angiography **(A)**, three months later hypofluorescent spots became
85 isofluorescent **(B)**



87 **Discussion:**

88 Ocular involvement in sarcoidosis may occur as the disease process, but it also can
89 precede the non-ocular manifestation of the disease[7]. Hunter *et al.* reported that the
90 first signs of sarcoidosis was ocular granulomatous lesions in % 2 of the patients [8].
91 However, an epidemiological study in Japan showed that the most frequent symptom was
92 eyesight disorder (28.8 %) [6]. The same study also reported that incidence of pulmonary
93 and ocular involvements were 86.0 % and 54.8 %, respectively, and eye involvement was
94 the most common extrapulmonary manifestation of sarcoidosis [9]. Although the
95 incidence of pulmonary involvement is nearly one and half times higher than ocular
96 involvement, the most frequent initial symptom of sarcoidosis is eyesight disorder. The
97 reason for this situation is late emergence of symptoms caused by lung involvement such
98 as dyspnea, so symptoms related to ocular involvement generates the major complaints
99 at the first application. Heiligenhaus *et al.*, studied 1800 sarcoidosis patients and indicated
100 that ocular disease was commonly the first manifestation of sarcoidosis (21.2%) [5].

101 Ocular involvement of sarcoidosis includes intraocular inflammation, adnexal and
102 orbital lesions[10]. Heiligenhaus *et al.* reported that the most frequent form of eye
103 involvement was anterior uveitis with a rate of 76.4%, followed by intermediate uveitis ,
104 17.3% [5]. Anterior uveitis may either presents as acute iridocyclitis or chronic
105 granulomatous uveitis [3]. Large 'mutton fat' type keratic precipitates are most
106 characteristic findings of chronic uveitis. Iris and trabecular meshwork nodules and tent-
107 shaped peripheral anterior synechiae could also be seen. Chronic involvement may also
108 lead to band keratopathy, glaucoma and cataract formation [11]. In our case, chronic
109 granulomatous uveitis was the first manifestation of sarcoidosis proved by biopsy later.

We would like to emphasize the importance of our case as being completely asymptomatic until it was incidentally detected.

Considering the intermediate uveitis, snowballs and string of pearls vitreous opacities are suggestive of granulomatous process but differentiation from idiopathic pars planitis and uveitis related to multiple sclerosis is required [12]. Posterior uveitis involves multiple chororetinal lesions, periphlebitis, granulomas of retina and optic nerve. Periphlebitis is associated with perivenous cuffing, sheathing and exudates referred as 'candle wax drippings' [3]. The present case did not show abnormality on dilated fundus examination and fluorescein angiography showed dye leakage from peripheral vessels which was nonspecific for differential diagnosis. However, indocyanine green angiography revealed infrequent hypofluorescent small round spots in the right posterior pole and midperiphery resembling the type 1 hypofluorescent lesions on early phase that Wolfensberger and Herbort had defined [13]. These spots were invisible on dilated fundus examination and fluorescein angiography. After six weeks, these lesions became isofluorescent as Wolfensberger and Herbort had reported in the late phase of sarcoidosis [13]. Therefore, indocyanine green angiography have a critical role for diagnosis and follow-up especially when the posterior segment involvement could not be detected on routine ophthalmoscopy and fluorescein angiography.

Conclusion:

In conclusion, ocular involvement in sarcoidosis may occur as the first clinical manifestation. Early diagnosis of the disease is important for avoiding ocular complications as well as prevention of other system involvements. For this reason, ophthalmologists have a critical role in the diagnosis and follow-up of the sarcoidosis.

References:

1. Newman LS, Rose CS, Maier LA (1997) Sarcoidosis. *N Engl J Med* 336: 1224-1234 DOI 10.1056/NEJM199704243361706
2. Dempsey OJ, Paterson EW, Kerr KM, Denison AR (2009) Sarcoidosis. *BMJ* 339: b3206 DOI 10.1136/bmj.b3206
- bmj.b3206 [pii]
3. Herborn CP, Rao NA, Mochizuki M (2009) International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm* 17: 160-169 DOI 10.1080/09273940902818861
- 912965083 [pii]
4. Umur KA, Tayfun B, Oguzhan O (2012) Different ophthalmologic manifestations of sarcoidosis. *Curr Opin Ophthalmol* 23: 477-484 DOI 10.1097/ICU.0b013e328358c7a6
5. Heiligenhaus A, Wefelmeyer D, Wefelmeyer E, Rosel M, Schrenk M (2011) The eye as a common site for the early clinical manifestation of sarcoidosis. *Ophthalmic Res* 46: 9-12 DOI 10.1159/000321947
- 000321947 [pii]
6. Sungur G, Hazirolan D, Bilgin G (2013) Pattern of Ocular Findings in Patients with Biopsy-proven Sarcoidosis in Turkey. *Ocul Immunol Inflamm* 21: 455-461 DOI 10.3109/09273948.2013.775311
7. Kaye GB, Salmon JF, Isaacs S (1993) Risk factors for uveitis in sarcoidosis. *S Afr Med J* 83: 342-344
8. Hunter DG FC (1994) Ocular manifestations of sarcoidosis. Saunders, Philadelphia
9. Morimoto T, Azuma A, Abe S, Usuki J, Kudoh S, Sugisaki K, Oritsu M, Nukiwa T (2008) Epidemiology of sarcoidosis in Japan. *Eur Respir J* 31: 372-379 DOI 09031936.00075307 [pii]
- 10.1183/09031936.00075307
10. Bradley D, Baughman RP, Raymond L, Kaufman AH (2002) Ocular manifestations of sarcoidosis. *Semin Respir Crit Care Med* 23: 543-548 DOI 10.1055/s-2002-36518
11. Baughman RP, Lower EE, Kaufman AH (2010) Ocular sarcoidosis. *Semin Respir Crit Care Med* 31: 452-462 DOI 10.1055/s-0030-1262213
12. Rothova A (2000) Ocular involvement in sarcoidosis. *Br J Ophthalmol* 84: 110-116
13. Wolfensberger TJ, Herborn CP (1999) Indocyanine green angiographic features in ocular sarcoidosis. *Ophthalmology* 106: 285-289 DOI S0161-6420(99)90067-2 [pii]
- 10.1016/S0161-6420(99)90067-2

Figure Legends:

Figure 1: Bilateral medium-sized, round, centrally located granulomatous keratic precipitates. R, right eye; L, left eye

Figure 2: Fluorescein leakage from peripheral vessels of the right eye on early phase of fluorescein angiography

Figure 3: Hypofluorescent small round spots on the right posterior pole on indocyanine green angiography

Figure 4: Posteroanterior chest x-ray showing bilateral hilar lymphadenopathy

Figure 5: Hypofluorescent small spots (arrows) on the inferior mid-periphery of right eye on indocyanine green angiography **(A)**, three months later hypofluorescent spots became isofluorescent **(B)**