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Case Report

A Case of a Central Retinal Artery Occlusion in a Patient with Rheumatoid Arthritis

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A 50-year-old woman, who had been treated for rheumatoid arthritis (RA) over a 10-year period, suddenly presented with monocular vision loss while the RA had a stable course over many years. She was diagnosed with central retinal artery occlusion (CRAO) based on ophthalmologic examinations including optical coherence tomography and fluorescein angiography. There was no evidence of atherosclerosis, infection, and malignancy that can cause CRAO. Considering the association between CRAO and other rheumatic diseases, such as systemic vasculitis and systemic lupus erythematous in previous reports, it was presumed that her RA might have contributed to the development of CRAO. Although cases of CRAO in patients with RA are extremely rare, these findings suggest that physicians need to be aware of the possibility of CRAO in patients with RA who experience decreased visual acuity. **(J Rheum Dis 2016;23:326-331)**

Key Words. Retinal artery occlusion, Rheumatoid arthritis

INTRODUCTION

Central retinal artery occlusion (CRAO) is a rare condition that causes acute, painless, monocular vision loss and results in significant functional morbidity. A CRAO is associated with cardiovascular disease and has several risk factors in common with atherosclerotic disease (e.g., stroke and heart disease) [1,2]. Patients with systemic inflammatory disorders (e.g., giant cell arteritis, Wegener's granulomatosis, Churg-Strauss vasculitis, polyarteritis nodosa, systemic lupus erythematosus [SLE], and Behçet's disease) are at an increased risk for developing a CRAO [3]. In these diseases, an excessive inflammatory burden may contribute to vascular occlusion development and appropriate immunosuppressive therapy is required. However, the association between CRAO and rheumatoid arthritis (RA) has not been well established. Here, we report a case of CRAO in a patient with established RA.

CASE REPORT

A 50-year-old woman presented to our emergency department with acute, painless vision loss in her left eye. When she was getting ready for work that morning, she was unable to distinguish objects with her left eye. Ten years earlier, she had been treated for livedo reticularis at a dermatology department and was referred to our rheumatology clinic because of polyarthralgia and bilateral swelling in the second to fourth metacarpophalangeal, knee, and right third metatarsophalangeal joints. The swelling had persisted for 2 months and was accompanied by morning stiffness that lasted longer than 1 hour. At the time of referral, the rheumatoid factor (RF) level was 196.2 IU/mL, anti-cyclic citrullinated peptide antibody level was 98.5 U/mL, antinuclear antibodies

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were negative, erythrocyte sedimentation rate (ESR) was 120 mm/h, and C-reactive protein (CRP) level was 4.56 mg/dL. The resulting disease activity score with 28-joint assessment (DAS28)-CRP was 5.69. Radiography revealed erosions in the right third metatarsophalangeal joint.

The patient was diagnosed with RA, according to the 1987 American College of Rheumatology criteria, and treated using disease-modifying antirheumatic drugs. She was initially prescribed hydroxychloroquine and sulfasalazine because no ocular abnormalities were found at a baseline ophthalmologic examination. Hydroxychloroquine was changed to methotrexate one month later and the patient discontinued hydroxychloroquine at that time (Figure 1). At this time, the patient complained of numbness in her left fourth and fifth fingers. Electromyography was performed and revealed a left ulnar neuropathy, which her physician suspected was caused by vasculitic occlusion. Treatment with high-dose glucocorticoids improved the neuropathy. Fortunately, the patient had a stable course of RA over many years and deflazacort had been tapered from 9 to 3 mg per day. The patient did experience intermittent swelling of the right wrist joint during that time.

When the patient presented to the emergency department, visual acuity in the left eye was counting fingers and an ophthalmologic examination revealed a relative afferent pupillary defect. Fundoscopic examination was unremarkable in the right eye, but revealed cherry-red spots in the left eye that were caused by a retinal infarction and arteriole cattle trucking (Figure 2). We did not observe

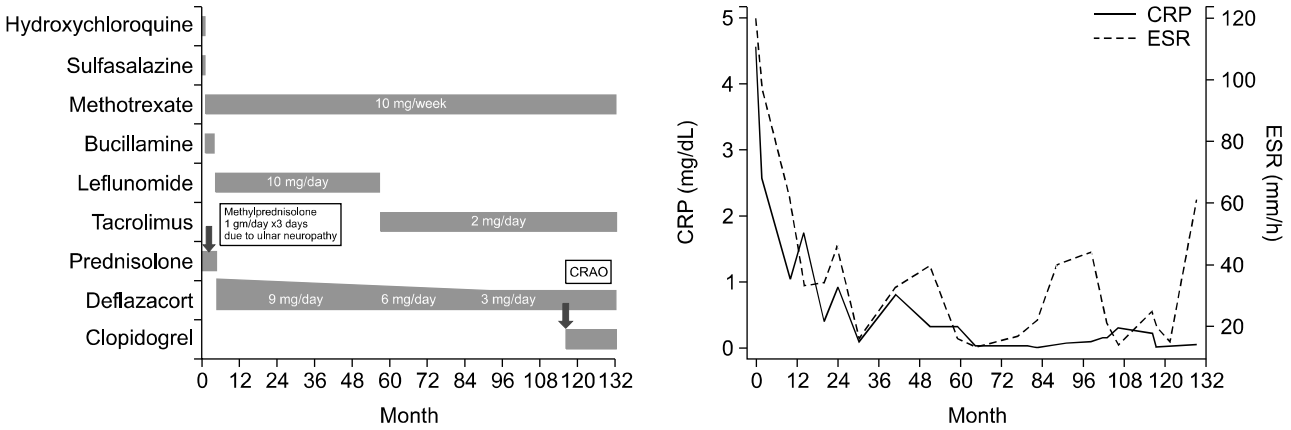

Figure 1. Clinical course of the patient during her 10-year follow-up period. CRAO: central retinal artery occlusion, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

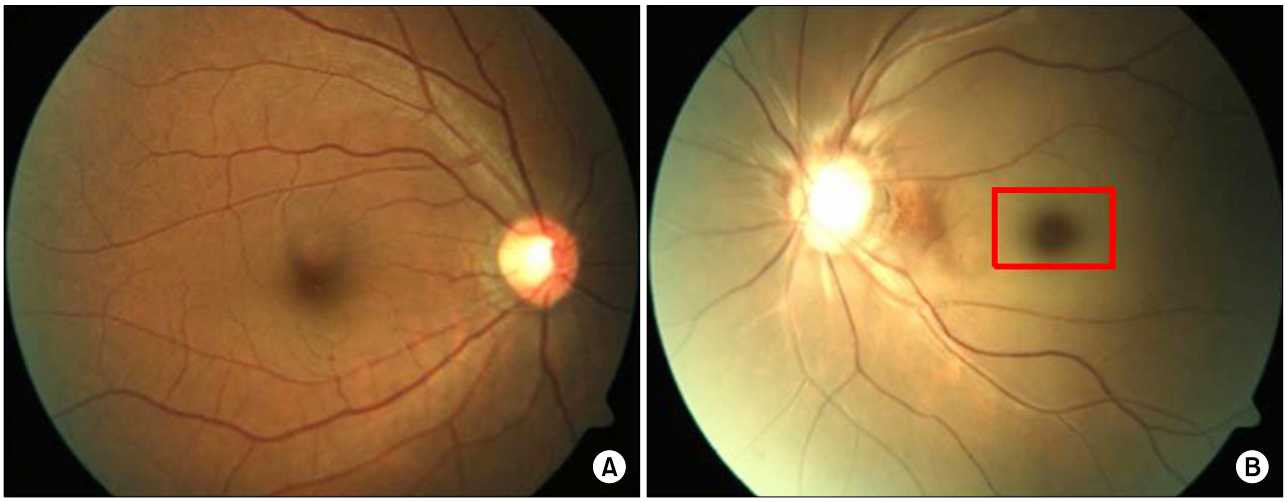

Figure 2. Fundoscopic findings. (A) A photograph of the right eye's fundus reveals no specific findings. (B) A photograph of the left eye's fundus reveals acute central retinal artery occlusion with cherry-red spots that were caused by a retinal infarction and arteriole cattle trucking. No definite emboli were observed.

any definite emboli. Optical coherence tomography revealed inner retinal layer thickening caused by retinal edema in the left eye (Figure 3). Fluorescein angiography revealed a markedly delayed arterial filling in the early phase and a prolonged arteriovenous transit time with no venous flow in the middle phase (Figure 4). Therefore,

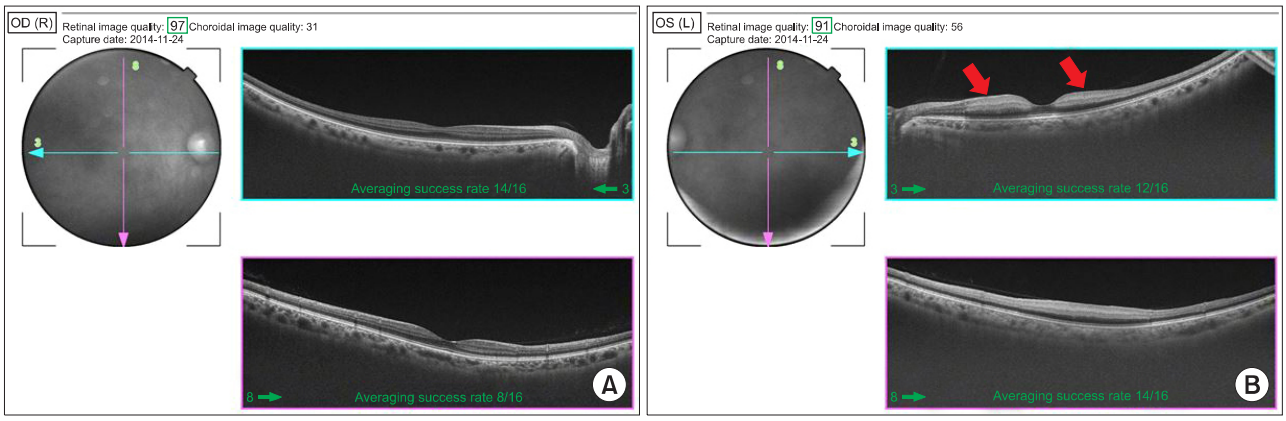

Figure 3. Optical coherence tomography (OCT) shows cross-section images of retina. (A) OCT of the right eye shows normal appearance. (B) OCT of the left eye shows the inner retina layer (nerve fiber layer) infarct presented as thickening and whitening (red arrows).

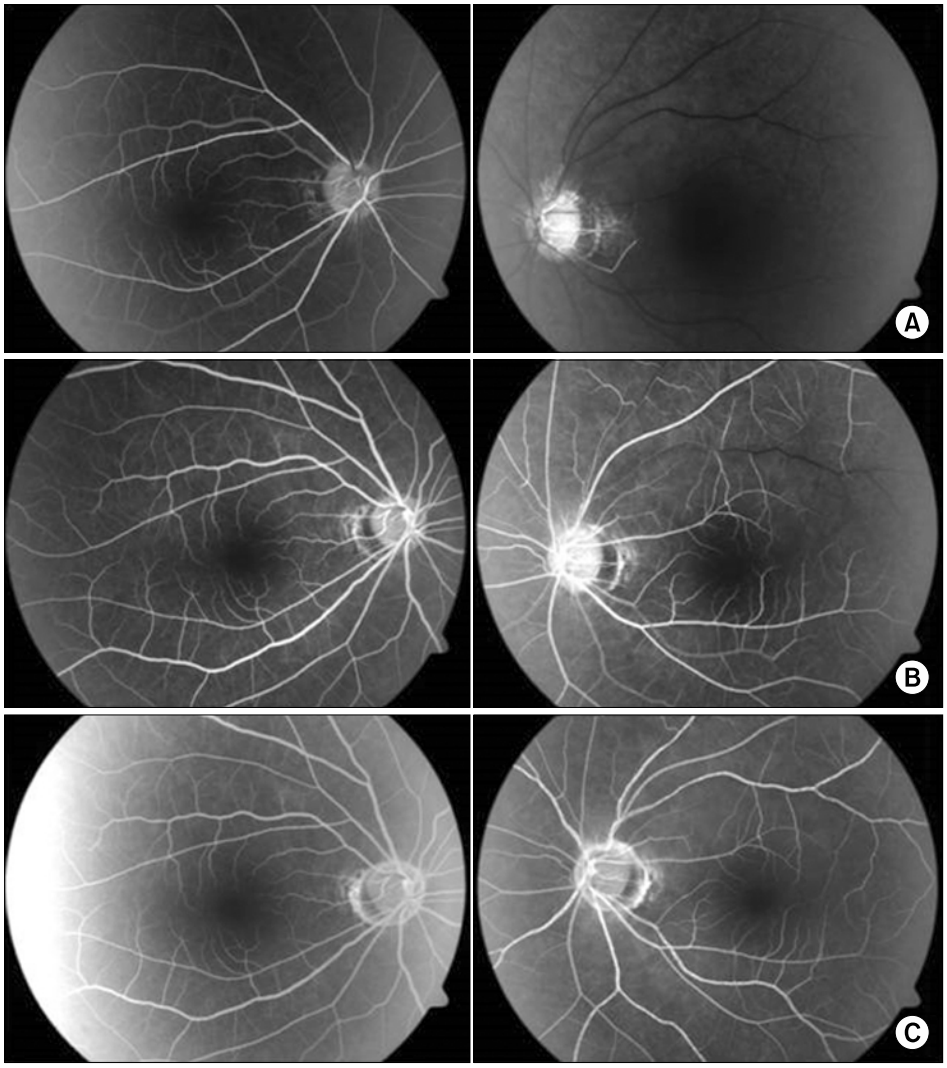

Figure 4. Fluorescein angiography at the onset of the central retinal artery occlusion. (A) Arterial filling in the left eye was markedly delayed in the early phase. (B) The arteriovenous transit time was prolonged with no venous flow in the middle phase. (C) Fluorescein pooling is visible in the late phase.

the patient was diagnosed with a CRAO in the left eye.

The patient did not have fever, headache, temporal artery tenderness, or hip and shoulder girdle stiffness/pain, which was suggestive of giant cell arteritis. The patient did not complain of Raynaud's phenomenon and did not have hypertension or dyslipidemia, both of which are potential causes of CRAO. The patient never smoked, was not taking oral contraceptives, and never had facial cosmetic surgery, a known cause of CRAO. An electrocardiogram revealed a normal sinus rhythm and an echocardiograph showed normal left ventricular function with no evidence of heart valve disease. Carotid Doppler ultrasonography revealed no significant carotid atherosclerosis or plaque and brain magnetic resonance imaging and angiography were normal. Peripheral angiography was not performed.

Blood lipid profile tests measured a low-density lipoprotein level of 74 mg/dL, a high-density lipoprotein level of 78 mg/dL, and a triglyceride level of 62 mg/dL. Laboratory findings to examine the possibility of a hypercoagulable state showed a prothrombin time of 11.7 s (normal, 10.0~12.5 s), an activated partial thromboplastin time of 25.0 s (normal, 27~42 s), a D-dimer level of 0.5 μg/mL (normal, 0~0.5 μg/mL), a fibrinogen level of 346.5 mg/dL (normal, 170~380 mg/dL), a protein C antigen level of 111% (normal, 72%~160%), a protein C activity of 99.4% (normal, 73%~142%), a protein S antigen level of 89% (normal, 60%~150%), a free protein S level of 84.9% (normal, 50%~150%), a protein S activity of 65% (normal, 65%~140%), a negative result for factor V Leiden, and a homocysteine level of 7.9 μmol/L (normal, 5~15 μmol/L). Antinuclear antibody results remained negative and antineutrophil cytoplasmic antibody, lupus anticoagulant, and anticardiolipin antibody immunoglobulin G and M were all negative. Complement C3 was 93.5 mg/dL (normal, 90~180 mg/dL) and complement C4 was 15.9 mg/dL (normal, 10~40 mg/dL). The patient had a DAS28-CRP of 2.55, determined by the presence of swelling and tenderness in her right wrist, an ESR of 25 mm/h, and a CRP level of 0.24 mg/dL. Computed tomography of the chest and abdomen was performed to rule out other CRAO etiologies, including infection or malignancy, but there were no remarkable findings.

The patient was treated for the CRAO with ocular massage, anterior chamber paracentesis, intravenous mannitol, and an oral antiplatelet agent. After 2 months, visual acuity in the left had slightly improved and no retinal opacification had occurred, although retinal atrophy persisted. After 10 months, visual acuity was 20/1,000, which was still in the counting fingers range. The patient has been followed closely for her RA at our rheumatology clinic. She still has swelling and tenderness in her right wrist, but no RA flare. At the patient's last visit, CRP level was 0.03 mg/dL and DAS28-CRP was 2.15.

DISCUSSION

Rheumatoid arthritis is a systemic inflammatory disease that is occasionally associated with extra-articular complications, including ocular manifestations. The most common ocular complication is secondary Sjögren's syndrome, although other ophthalmological conditions (e.g., episcleritis, scleritis, and peripheral ulcerative keratitis) are known to be associated with systemic inflammation in patients with RA [4]. Optic neuritis, anterior optic neuropathy, and retinal vasculitis associated with RA are rarely reported [5]. A CRAO, the ocular equivalent of a cerebral stroke [6], results in acute, painless monocular vision loss. It is considered to be an ophthalmic emergency because it is associated with significant functional morbidity. In Korea, the incidence rate of CRAO was 1.80 per 100,000 person-years, with this rate exponentially increasing with age [7]. Embolism is the most common cause of CRAO and is generally caused by the formation of atherosclerotic plaques [6]. Other etiologies of CRAO include systemic vasculitis, SLE, and Behçet's disease, all autoimmune rheumatic diseases [3]. The relationship between CRAO and RA has not been extensively investigated because of its rarity.

Intensive investigation revealed no evidence of infection, malignancy, or autoimmune diseases (e.g., SLE or antiphospholipid antibody syndrome), all of which are potential causes of CRAO. Therefore, we cautiously hypothesize that RA led to CRAO development. First, RA is a systemic inflammatory rheumatic disease with extra-articular manifestations and, though rare (<1% of patients), rheumatoid vasculitis can accompany long-standing disease. The signs of rheumatoid vasculitis vary and can include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and lower extremity ulceration. Given that our patient had ulnar neuropathy and livedo reticularis, both recognized clinical manifestations of vasculitis, rheumatoid vasculitis may have also affected the central retinal artery and subsequently resulted in CRAO. Second, RA is associated with cardiovascular diseases

and rheumatic inflammation can contribute to atherosclerotic changes. Significant atherosclerosis was not detected via imaging studies in this patient and RA was stable during the follow-up period. However, it is possible that long-term subclinical inflammation might have led to undetected atherosclerotic changes in the microvasculature, including the ophthalmic artery, which branches off of the internal carotid artery. Because epidemiologic data and CRAO case reports in patients with RA are lacking, the pathogenetic association between CRAO and RA could not be thoroughly examined. However, we speculate that rheumatoid vasculitis and subclinical atherosclerosis associated with long-standing inflammation may have independently or synergistically contributed to CRAO development in our patient. Further research is needed to investigate pathophysiologic processes of CRAO in patients with RA.

Our literature review identified two case reports of retinal arterial occlusion in patients with RA (Table 1) [8,9]. Matsuo [8] presented a case of branch retinal artery occlusion in both eyes. Although the female patient did not have arthralgia, the finger joints in both hands were deformed. This patient had an ESR of 23 mm/h, a CRP level of 0.2 mg/dL, and an RF of 25.2 IU/mL. The author suggested that elevated ESR and RF levels indicated persistent RA activity, which led to CRAO development. Our patient had similar ESR and CRP levels, but a much higher RF level of 196.2 IU/mL. Kachmaryk et al. [9] reported the second case, in which a patient with RA developed a cilioretinal artery occlusion with the sickle cell trait. The patient also had mild hypergammaglobulinemia secondary to RA and an elevated RF level. The authors hypothesized that increased serum viscosity led to vascular stasis, which resulted in further vascular sludging and cilioretinal artery occlusion. We did not check immunoglobulin levels in our patient because her albumin/globulin ratio was normal and she did not have the sickle cell trait. Together, hyperinflammatory status associated with RA and hypergammaglobulinemia resulting from autoantibody production could result in occlusion of the retinal vasculature.

No cases of CRAO in an RA patient have been previously reported in South Korea, but 3 cases of CRAO in patients with other rheumatic diseases have been published. Kim et al. [10] reported a case of CRAO that occurred during methylprednisolone pulse therapy treatment for polyarteritis nodosa. Once CRAO was diagnosed, cyclophosphamide pulse therapy was added. The remaining cases occurred in SLE patients. Hwang and Kang [11] reported on a combined central retinal vein and artery occlusion in a patient with SLE. Their clinical observations led them to believe that CRAO was of a thrombotic, and not of a vasculitic, origin [11]. Song et al. [12] reported that retinal vaso-occlusion was an earlier manifestation of SLE without anticardiolipin antibodies. Evidence from a few other case reports suggested an association between some drugs and CRAO development, including oral contraceptives [13]. However, an association between glucocorticoids and CRAO development has not yet been reported.

Further evidence supporting an association between RA disease activity and retinal vasculitis was presented in a report that suggested that suppressing RA-related inflammation improves vascular health [14]. Another report showed that orbital blood flow velocity in RA patients is lower than in healthy controls, which suggests that systemic inflammation may also affect the ocular vessels [15]. Given the increased risk of cerebrovascular disease in RA patients and the influence of systemic inflammation on blood vessels, CRAO likely has clinical relationship with RA rather than simply being an incidental finding in our patient. In the current case, CRAO develop-

Table 1. Cases of central retinal artery occlusion in rheumatoid arthritis

Author [Reference]	Age (yr) /sex	Cause of CRAO	Treatment	Nationality	Year of publication
Matsuo [8]	67/F	Vascular inflammation, rheumatoid vasculitis	Hyperbaric oxygen, intravenous prostaglandin E1, urokinase	Japan	2001
Kachmaryk et al. [9]	49/F	Sickle cell trait, hypergammaglobulinemia	Not mentioned	USA	1995
Park et al. (present study)	50/F	Not clearly defined, may be inflammatory	Conservative, oral antiplatelet agent	Korea	2016

CRAO: central retinal artery occlusion, F: female.

ment may reflect long-term subclinical systemic inflammation. However, more research is needed to verify the association between CRAO and RA.

Conventional treatments for CRAO include vasodilators, ocular massage, anterior chamber paracentesis, intravenous mannitol, tissue plasminogen activator, and surgery [2]. Intravenous glucocorticoids can also be used when a CRAO was caused by systemic inflammatory disease. Because our patient showed no direct evidence of high grade active inflammation and RA had been stable, systemic immunosuppressive agents (e.g., high-dose glucocorticoids) were not administered and, with the input of an ophthalmologist, the patient was conservatively managed. However, close follow-up was needed in this patient to monitor for CRAO deterioration, RA disease activity, and new rheumatoid vasculitis signs.

SUMMARY

In conclusion, this is the first case of CRAO reported in a Korean patient with RA. Clinical findings in this patient support an association between CRAO and RA, similar to CRAO associations with other systemic inflammatory rheumatic diseases (e.g., SLE and systemic vasculitis). Thus, clinicians need to consider the possibility of CRAO in patients with RA who complain of decreased visual acuity.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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