



Central retinal vein occlusion – A patient with systemic sclerosis

Okluzija centralne vene retine kod bolesnice sa sistemskom sklerozom

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Abstract

Introduction. Scleroderma (systemic sclerosis) is a severe chronic connective tissue disease, which results in involvement of numerous internal organs. Changes in the eye are the consequences of organ-specific manifestations of scleroderma or adverse effects of immunosuppressive treatment applied. **Case report.** We reported a 42-year-old woman with systemic sclerosis and acute deterioration of vision in the left eye, with visual acuity 0.9. After thorough clinical examination, including fluorescein angiography and optical coherence tomography, the diagnosis of nonischemic central retinal vein occlusion was made. Further biochemical, rheumatological and immunological investigation, apart from inactive systemic sclerosis, showed normal findings. Therefore, the cause of central retinal vein occlusion could only be attributed to the microvascular changes in systemic sclerosis. After three months, visual acuity deteriorated to 0.6 due to the development of cystoid macular edema. The patient received intravitreal injection of bevacizumab and after a single dose visual acuity improved to 0.9. After a 6-month follow-up, macular edema resolved and visual acuity stabilized. **Conclusion.** According to our knowledge and current data from the literature, central retinal vein occlusion is a rare vision threatening manifestation of scleroderma. There are only few published case reports on central vein occlusion in scleroderma patients. Examination of the ocular fundus is recommended for evaluation of vascular disease in patients with systemic sclerosis.

Key words:

scleroderma, systemic; retinal vein occlusion; diagnosis; angiogenesis inhibitors; treatment outcome.

Apstrakt

Uvod. Skleroderma (sistemska skleroza) je ozbiljna hronična bolest vezivnog tkiva, koja zahvata brojne unutrašnje organe. Promene u oku mogu da budu posledica organ-specifičnih manifestacija skleroderme ili se mogu javiti usled neželjenih efekata imunosupresivne terapije koja se koristi u lečenju. **Prikaz bolesnika.** U radu je prikazana 42-godišnja bolesnica sa dijagnozom sistemske skleroze i naglim pogoršanjem vida na levo oku (sa vidnom oštrinom 0,9). Nakon detaljnog kliničkog pregleda, uključujući fluoresceinsku angiografiju i optičku koherentnu tomografiju, postavljena je dijagnoza neishemične forme okluzije centralne vene retine. Dalja biohemijska, reumatološka i imunološka ispitivanja, osim inaktivne sistemske skleroze, pokazala su normalan nalaz. Stoga je utvrđeno da je jedini uzrok venske okluzije predstavljaju mikrovaskularne promene u sklopu sistemske skleroze. Nakon tri meseca, vidna oština levog oka se pogoršala na 0,6 usled razvoja cistoidnog makularnog edema. Bolesnica je primila intravitrealnu injekciju bevacizumaba i nakon samo jedne doze vidna oština se popravila na 0,9. Nakon šest meseci praćenja, makularni edem se povukao, a vidna oština je ostala nepromenjena. **Zaključak.** Prema našim saznanjima i uvidom u literaturu, okluzija centralne vene retine je retka manifestacija skleroderme, koja može da ugrozi funkciju vida. Postoji svega nekoliko objavljenih radova u kojima je prikazana centralna venska okluzija kod ovih bolesnika. Kod bolesnika sa sistemskom sklerozom preporučuje se pregled zadnjeg segmenta oka radi procene mogućih vaskularnih promena.

Ključne reči:

sklerodermija, sistemska; okluzija retinalne vene; dijagnoza; angiogeneza, inhibitori; lečenje, ishod.

Introduction

Systemic sclerosis (scleroderma – SSc) is an autoimmune disorder with fibrovascular manifestations that may affect many organ systems¹. It is an unusual but not rare disease², characterized by immune system disorders and altered

structure and function of blood vessels³. Clinical forms of SSc can range from limited skin involvement (limited cutaneous systemic sclerosis) to forms with diffuse skin sclerosis and severe and often progressive internal organ involvement (diffuse cutaneous systemic sclerosis)⁴. Criteria for the diagnosis of SSc established by the American College of

Rheumatology include major and minor criteria. Major criteria consist of anterior scleroderma (thickening of the skin) affecting the arms, face, and/ or neck, while minor criteria include digital pitting scars or the loss of the volar pads of the finger tips, pulmonary fibrosis and sclerodactyly (sclerosis affecting the fingers or toes). SSc is diagnosed when a patient has one major or two minor criteria⁵. Treatment of SSc comprises the use of drugs that affect collagen formation such as D-penicilamin, colchicine and interferon gamma⁶.

Scleroderma patients often report eye problems, although there are few reports available concerning ophthalmological manifestations in systemic sclerosis⁷. Because of the rare nature of the disease, most papers had single case reports or small case series⁸. Ocular symptoms may occur at any stage of the disease. Their course may be clinically latent or very intensive, and they may involve numerous ocular structures⁷. Although patients with SSc are known to have variety of vascular abnormalities, retinal vascular changes are not well understood. Only a few published case reports have referred to occlusion of retinal arteries or veins in SSc^{2, 8-10}. The aim of this paper was to review the variety of ocular manifestations in patients with systemic sclerosis. We also reported a case of central retinal vein occlusion (CRVO) as a rare manifestation of scleroderma.

Case report

A 42-year-old woman presented with acute, painless vision loss in the left eye of 10 days duration. In her medical history

was noted systemic sclerosis that was treated for 22 years in the rheumatology and dermatology clinic. The patient underwent complete ophthalmological examination at baseline including medical history; visual acuity assessment (measured by Snellen chart); applanation tonometry; slit lamp examination; indirect ophthalmoscopy with 90D lens; optical coherence tomography (OCT); fundus photography and fluorescein angiography (FA); immunological and biochemical investigation.

General examination revealed terminal ulceration and flexion deformity of the digits (Figure 1). The skin on her face and upper limbs was taut, thickened and hidebound with scattered telangiectatic changes. The nose was pinched and the mouth slightly smaller than normal and puckered. History was negative for any other medical problems such as pulmonary, cardiac or renal diseases. The admission best corrected visual acuity (BCVA) was 1.0 and 0.9 in the right and left eye, respectively; intraocular pressure was within the range. Both pupils were normal with no relative afferent pupillary defect. Slit-lamp examination revealed reduced tear meniscus. Schirmer's test showed diminished tear secretion after 5 minutes, right 5 mm and left 8 mm. Fundus examination of the right eye showed no abnormalities, while in the left eye central retinal vein occlusion (CRVO) was noted (Figure 2). Fluorescein angiography of the right eye had normal findings for her age, while in the left eye delayed filling of choroidal lobules, enhanced perivascular leakage and macular edema were present (Figures 3, 4). Optical coherence tomography of the left eye showed cystoid macular edema with the central macular thickness of 377 μm (Figure 5).



Fig. 1 – The fingers were fixed in a flexion deformity and terminal ulcers were present on both hands.



Fig. 2 – Fundus photography of the left eye showed central retinal vein occlusion.

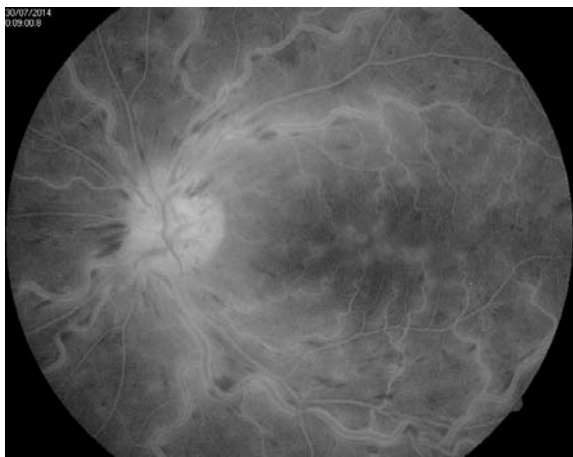


Fig. 3 – Fluorescein angiography of the left eye showing enhanced perivascular leakage, macular edema and capillary closure.

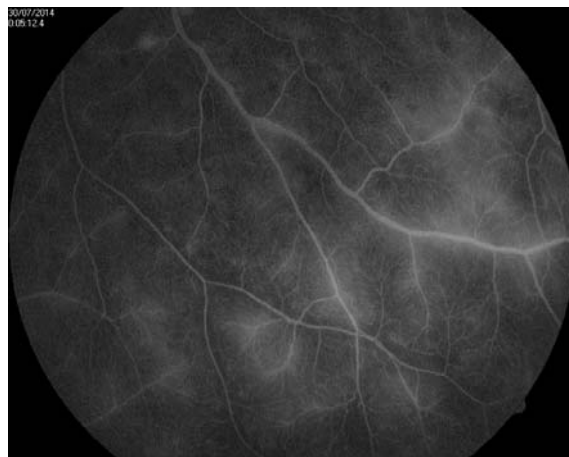


Fig. 4 – Fluorescein angiography of the left eye in the late venous phase shows inflammatory reaction within the peripheral venous vessel with increasing dye leakage.

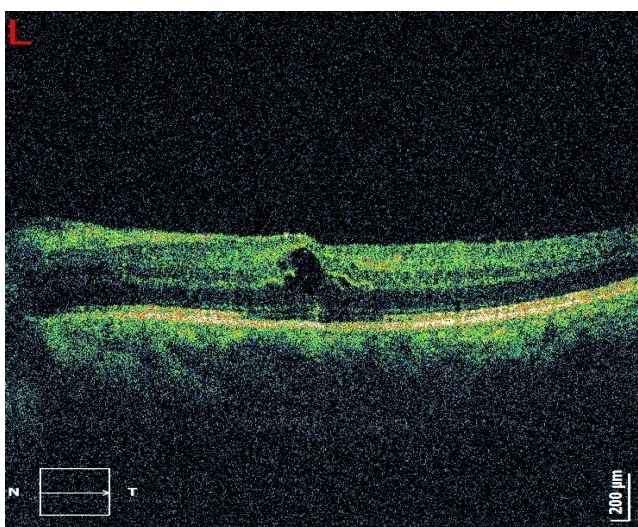


Fig. 5 – Spectral Domain (SD) optical coherence tomography of the left eye showing macular edema.

All investigations at presentation such as complete blood count (white blood cells $7.7 \times 10^9/L$; neutrophils 64.2%; lymphocytes 25.8%; monocytes 8.4%; eosinophiles 1.5%; basophiles 0.1%; erythrocytes 5.0×10^{12} ; platelets $265 \times 10^9/L$); parameters of inflammation (erythrocyte sedimentation rate 10 mm/h; fibrinogen 3.61 g/L; C-reactive protein 0.2 mg/L); parameters of hemostasis (prothrombin time 12 s; partial thromboplastin time 28 s); blood glucose level (5.2 mmol/L); parameters of renal function (urea 4.7 mmol/L; creatinine 62 mmol/L; uric acid 289 mmol/L); parameters of liver function (AST 16 U/L; ALT 12 U/L; total bilirubin 9.5 mmol/L); total serum proteins (70 g/L) and protein fractions (albumin 53.6%, α_1 3.4%, α_2 13.2%, β_1 9.0%, β_2 5.9, γ 14.9%); serum lipids (cholesterol 4.8 mmol/L; triglycerides 1.3 mmol/L) and homocystein (14.75 $\mu\text{mol/L}$) were within normal limits. Immunofixation of serum proteins did not reveal M component. Serum autoantibody profile was obtained and only titer of anti-nuclear antibodies (ANA Hep-2, IIF) were positive (in $> 1:640$ dilution), while other autoantibodies including anticardiolipin antibodies, anti- β_2 glycoprotein antibodies, antineutrophil antibodies (IIF) and ANCA were nega-

tive. Lupus anticoagulant was absent (activated partial thromboplastin time –APTT 27.9 s; LA1 40.80 s). Hematologist was consulted and genetic analyses including polymerase chain reaction (PCR) for mutations of clotting factor II (prothrombin G20210A), factor V (Leiden G1691A) and methylene tetrahydrofolate reductase (MTHFR C677T) genes were performed showing no genetic predisposition for hypercoagulability state. Also, other potential causes of CRVO, such as arterial hypertension, diabetes and glaucoma were assessed and excluded. After workup, patient underwent rheumatological treatment that included D-penicillamine (Metalcaptase[®]), calcium channel blockers (nicardipin 50 mg) and vitamin D drops.

Based on the ophthalmological findings, the diagnosis of nonischemic CRVO in the left eye was established. Three months after the onset of CRVO, best corrected visual acuity of the left eye decreased to 0.6 due to the development of macular edema. The patient received intravitreal injection of bevacizumab and after a single dose, the central retinal thickness (CRT) decreased to 229 μm and BCVA of the left eye improved to 0.9. The patient was followed up for 6 months

and although partial capillary nonperfusion on the periphery of the retina was noted (Figure 6), no other complications including retinal neovascularization, occurred.

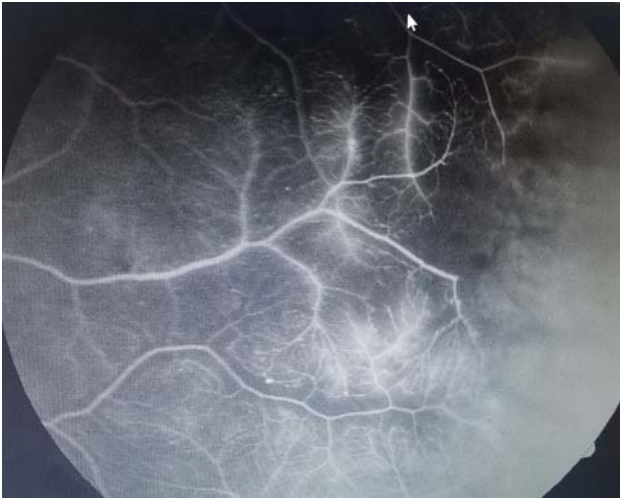


Fig. 6 – After a 3-month follow-up fluorescein angiography of the left eye showed areas of partial capillary nonperfusion on the periphery of the retina, with no neovascularization.

Discussion

Systemic sclerosis is an immunological connective tissue disease, which results in involvement of numerous internal organ systems⁷. The most characteristic feature of scleroderma is the increased collagen content in the skin and visceral organs, while the second feature is vascular disease, including Raynaud's phenomenon and diffuse microvasculopathy¹¹. Our patient fulfilled diagnostic criteria for SSc provided by The American College of Rheumatology⁵, as she had thickening and tightening of the skin of her face and arms, sclerodactyly, facial telangiectasia and digital pitting scars.

The ocular manifestations of scleroderma have not been sufficiently previously reported in the literature. Ocular changes can be one of the manifestations of scleroderma or adverse effects of immunosuppressive treatment applied⁷. Changes in the eye which are specifically related to scleroderma are: telangiectasia and dermal sclerosis of the eyelids, a tear defect of varying severity, injection and slugging of the blood column in conjunctival vessels and possibly punctate defects of the iris pigment epithelium⁸. Involvement of the posterior segment is frequently subclinical and visual loss as a direct result of the disease is not very often¹². The retinal and choroidal microvascular changes are important because systemic sclerosis is practically a disease of small arteries². Reported changes seen in the retina in patients with SSc are intraretinal hemorrhages, cotton wool spots and optic disc edema, which are most often related to malignant hypertension¹³. Ushiyama et al.¹⁴ found that the main retinal changes in patients with SSc are hard exudates and tortuous vessels, most of whom were not hypertensive. They also reported that patients with SSc had a higher incidence of retinal changes associated with vascular damage than controls ($p = 0.01$)¹⁴. Fluorescein angiography from previous studies demon-

strated abnormalitis of perfusion, which affected the chorio capillaris and small choroidal arterioles¹⁵. In addition, Milenkovic et al.¹⁶ presented a case of localized scleroderma with well demarcated areas of choroidal sclerosis and retinal capillary nonperfusion. These observations suggest that vascular alterations in scleroderma, does occur, although uncommonly¹⁵.

Besides SSc, the presented patient had no related systemic diseases that could cause CRVO and this manifestation of scleroderma was reported only few times in the literature^{9, 10, 14, 17}. The cases reported by Saari et al.⁹ and Gomes et al.¹⁰ suffered from other systemic diseases such as secondary polycythemia, cardiovascular insufficiency and pulmonary fibrosis which could contribute to the pathogenesis of CRVO and therefore, scleroderma could not be considered as the direct cause of CRVO. On the other hand, Malik and Al Habash¹⁷ excluded diabetes, hypertension, blood dyscrasias, clotting disorders and sickle cell disease as the causes of CRVO.

No signs of retinal neovascularization were noted in the presented case during the follow-up period, although partial capillary nonperfusion on the periphery of the retina was present. Waszczykowska et al.⁷ in their study of 27 patients with SSc found no case of retinal neovascularization, even with significantly advanced ischemic retinopathy, which could be contributed to the impairment of angiogenesis that is typical in the course of scleroderma⁷. However, Minasian et al.¹² first reported a case of bilateral ischemic retinopathy with neovascularization of the disc with beneficial response to laser photocoagulation¹². To date, only two cases of proliferative retinopathy in SSc patients with concomitant autoimmune diseases, including dermatomyositis and polymyositis, have been reported in the literature¹⁸.

Previous reports warrant further investigations to evaluate the involvement of small choroidal and retinal arterial system in systemic sclerosis, since small vessels are involved in other organs¹⁶.

Conclusion

Ocular symptoms are relatively common manifestation of systemic sclerosis. However, they can greatly vary from discomfort due to dry eye symptoms to complete blindness and should be systemically looked for during ophthalmological exam. In the presented case, ocular symptoms were caused by nonischemic central retinal vein occlusion. Thorough work-up and timely treatment was needed in order to prevent more serious irreversible changes in the organ of vision, such as retinal neovascularization and neovascular glaucoma. An ophthalmologist should look for the presence of even subtle retinal vascular abnormalities in patients with systemic sclerosis since the presence of those can aid in proper monitoring of the disease progression and indicate the need for more aggressive systemic treatment.

Declaration of interest

The authors declare no conflict of interest.

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