Published in final edited form as:

Semin Arthritis Rheum. 2013 October ; 43(2): 204–208. doi:10.1016/j.semarthrit.2012.12.025.

Acute retinal artery occlusion in systemic sclerosis: A rare manifestation of systemic sclerosis fibroproliferative vasculopathy

Joanna Busquets, MD^a, Young Lee, MD^a, Leo Santamarina, MD^b, Jay L. Federman, MD^c, Ari Abel, MD^d, Francesco Del Galdo, MD, PhD^{a,f}, Ralph C. Eagle Jr, MD^e, Sergio A. Jimenez, MD^{a,*}

^aJefferson Institute of Molecular Medicine and The Scleroderma Center, Thomas Jefferson University, 233 S. 10th St, Room 509 BLSB, Philadelphia, PA 19107-5541

^bKeystone Eye Associates, Philadelphia, PA

^cRetina Service, Wills Eye Institute, Philadelphia, PA

^dAbel Center for Oculofacial Plastic Surgery, Newark, DE

^eDepartment of Pathology, Wills Eye Institute, Philadelphia, PA

^fLeeds Institute of Molecular Medicine, Leeds University, Leeds, UK

Abstract

Objectives: To describe three patients with systemic sclerosis (SSc) who developed acute unilateral blindness in the absence of any common etiologic factor for blindness. In one patient, the affected eye required enucleation and was examined histopathologically.

Methods: Following identification of the first patient with retinal artery occlusion at the Scleroderma Center of Thomas Jefferson University, every patient evaluated at the Center from May 2001 to December 2010 was prospectively assessed for the development of acute unilateral blindness. Two additional cases were identified. Here, we describe the clinical features, laboratory and ancillary examinations of the three patients with SSc who developed acute unilateral blindness and present the histopathological examination of one eye enucleated from one of the patients.

Results: Clinical and angiographic studies were consistent with acute retinal artery occlusion. The histopathological studies showed severe retinal ischemic atrophy and concentric narrowing and fibrosis of small retinal vessels.

Conclusions: These findings suggest that acute retinal artery occlusion in these patients is a manifestation of the fibroproliferative vasculopathy characteristic of SSc.

Keywords

Systemic sclerosis; Scleroderma; Acute retinal artery occlusion; Fibroproliferative vasculopathy; Endothelial cell

*Corresponding author: sergio.jimenez@jefferson.edu (S.A. Jimenez).

Introduction

Systemic sclerosis (SSc) is a systemic connective tissue disorder characterized by severe and often progressive cutaneous and visceral fibrosis [1–4]. One of the critical abnormalities in SSc is a diffuse fibroproliferative vasculopathy most commonly involving the microvasculature system [5–11]. Although patients with SSc can present a variety of ophthalmologic abnormalities [12–16], retinal artery occlusion is an unusual complication that has been described in only a few reports [17–20]. Here, we describe the clinical manifestations of three cases of acute blindness caused by retinal artery occlusion in patients with SSc and describe the histopathological features of an enucleated eye from one of these patients.

Methods

Identification of reported cases

Following identification of the first patient with retinal artery occlusion at the Scleroderma Center of Thomas Jefferson University, every patient evaluated at the Center from May 2001 to December 2010 was prospectively assessed by one of the authors (S.A.J.) by questioning of any symptoms indicative of the development of acute unilateral blindness and by evaluation of clinical records from ophthalmologic evaluations. Two additional SSc patients with unilateral blindness were identified. To provide an estimate of the prevalence of this rare complication the number of new patients evaluated for SSc at the Center and the number of follow-up visits during the 10-year period-span (2001–2010) in which the three patients identified were tabulated from the IDX system appointment records.

Literature search

A systematic review of the literature was performed on PubMed using “systemic sclerosis” and each of the following terms: “blindness”, “retinal artery occlusion”, “retinal vein occlusion”, “ocular manifestations” and “ocular”. The search revealed 0, 0, 1, 2, and 32 results, respectively. A second and more focused search was performed using “scleroderma” and “central retinal artery occlusion,” which resulted in six publications; however, only two of these were related to SSc. The relevant publications have been discussed and have been cited in the Reference list.

Results

Case reports

Case report 1: A 46-year-old Caucasian woman with rapidly progressive diffuse SSc first developed symptoms in June 2006 with Raynaud phenomenon, bilateral carpal tunnel syndrome, and gastroesophageal reflux, followed shortly by progressive cutaneous induration and tightening. Serologic studies were negative, including antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anti-Smith (anti-SM), anti-Scleroderma 70 (anti-Scl-70), anti-centromere, anti-ribonucleoprotein C (anti-RNP), and anti-Sjögren syndrome antigen A and B (anti-SSA/SSB). Pulmonary function tests, echocardiogram and chest computerized tomography scan were normal. A skin biopsy from the forearm

confirmed the diagnosis of systemic sclerosis. She began treatment with D-penicillamine in September 2007. About 15 months later, D-penicillamine was discontinued owing to the development of nephrotic range proteinuria, and treatment with mycophenolate mofetil was initiated in April 2008. Over the ensuing 2 years, there was marked skin softening and regrowth of hair follicles in most of her previously involved skin with only residual skin tightening and induration in her hands, fingers, and a small patch on her right thigh. In December 2009, the patient complained of a sudden, painless loss of vision in the lower half of her left visual field. She denied any prior visual symptoms, headaches, temporal artery or scalp tenderness, dysarthria, paresthesias, weakness in her extremities, or problems with her gait. There was no familial history of premature atherosclerosis and clinical examination did not show any abnormalities in the cardiac exam or findings suggestive of atherosclerotic vascular lesions. On examination of her visual fields, the patient exhibited an inferior altitudinal defect in her left eye. Her visual acuity was 20/20 in the right eye and 20/20 in the left eye. Intraocular pressures were within normal limits bilaterally. Dilated fundus exam showed normal findings in the right eye. However, exam of the left eye revealed superior segmental optic disc swelling and absence of spontaneous venous pulsations. These findings were consistent with severe ischemic optic neuropathy of the left eye. Extensive evaluation was performed to investigate the cause of the acute visual loss. Repeated serologic studies showed borderline ANA at a 1:40 titer with speckled pattern. Rheumatoid factor, anti-SM, anti-histidyl-tRNA synthetase (anti-Jo-1), anticardiolipin antibodies, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), perinuclear antineutrophil cytoplasmic antibodies (P-ANCA), and lupus-type anticoagulant were all negative. Serum complement levels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were normal. Additional testing showed an absence of a mutation in factor V Leiden. Magnetic resonance imaging of the brain and orbits were unremarkable with no evidence of a brain infarction or a demyelinating process. Three weeks later, follow-up examination confirmed persistence of the visual defect in the left eye.

Case report 2: A 76-year-old Hispanic woman with rapidly progressive diffuse systemic sclerosis presented with a typical scleroderma renal crisis in July 2000, resulting in renal insufficiency requiring hemodialysis. The onset of disease was in 1999 when the patient developed Raynaud phenomenon associated with solid food dysphagia and severe heartburn. She was treated with D-penicillamine and showed marked improvement in skin sclerotic changes. The patient underwent hemodialysis three times weekly for 4 years before undergoing bilateral renal transplantation in January 2004. In September 2006, the renal transplants were rejected despite treatment with mycophenolate mofetil (500 mg twice a day) and sirolimus (2 mg/day). The patient resumed hemodialysis and was maintained only on low-dose prednisone (5 mg/day).

Serologic studies for autoantibodies showed a positive fluorescent ANA at 1:1280 titer with a diffuse pattern. Rheumatoid factor, anti-centromere, anti-histone, anti-SM, anti-RNP, anti-ssDNA and anti-dsDNA antibodies were negative. Complement C4 and anticardiolipin IgG antibodies were within the normal range.

In January 2008, the patient suffered a precipitous episode of painless loss of vision in her right eye. Computerized axial tomography of the brain was normal. The ESR (Westergren)

was unchanged from previous exams, at 59 mm/h. Her visual acuity was finger counting in the right eye and 20/40 in the left eye. Ophthalmoscopic examination of the posterior segment of the right eye showed marked narrowing of the arterioles with retinal whitening and a cherry-red spot (Fig. 1A). No disc edema or hyperemia was observed, and the peripheral retina was flat in both eyes. Optical coherence tomography disclosed no macular thickening in either eye. Intravenous fluorescein angiography revealed a marked delay in the arteriole-venous transit time in the right eye with a large delay in the venous filling time. The retinal circulation in the left eye was normal. The veins did not appear dilated in either eye (Fig. 1B–D). This constellation of findings was consistent with the diagnosis of central retinal artery occlusion.

Owing to the mild elevation of the erythrocyte sedimentation rate in the setting of retinal artery occlusion, it was deemed important to exclude a diagnosis of temporal arteritis although there was no clinical evidence to suggest this diagnosis given the presence of normal temporal artery pulses and the absence of headaches or scalp or temporal artery tenderness. A right temporal artery biopsy was performed. Histopathologic examination of multiple serial sections revealed no evidence of active or healed giant cell arteritis (Fig. 2). However, there was a significant degree of subintimal fibrosis and fibrosis of the surrounding adventitia. In March 2008, a follow-up ophthalmologic exam revealed no hemorrhage, iris neovascularization, or cholesterol emboli in either eye. The right eye showed persistent retinal whitening of the edges of the fovea. Her visual acuity was hand motions in the right eye and 20/40 in the left eye.

Case report 3: An 80-year-old Caucasian woman was diagnosed with limited cutaneous SSc with esophageal involvement and minimal fibrosis in both lung bases in 1995. She developed the first symptoms of Raynaud phenomenon and gastroesophageal reflux in 1994. Serologic studies revealed a positive ANA at a 1:320 titer with a centromere pattern. Anti-mitochondrial (1:80), anticardiolipin IgG (low titer), and anti-centromere (1:640) antibodies were present, whereas anti-dsDNA, anti-Scl-70, anti-SM and anti-RNP antibodies, C-ANCA, P-ANCA, and lupus-type anticoagulant were all negative. Complement levels (C3 and C4), serum protein electrophoresis, and cryoglobulins were within the normal range.

In January 1997, ophthalmologic examination disclosed slightly increased intraocular pressures with normal appearing optic nerves and open anterior chamber angles. A posterior vitreous detachment was present in the left eye. Mild ocular hypertension and a right subcapsular cataract were noted in May 1997. No retinopathy was evident ophthalmoscopically. Magnetic resonance angiography of the extracranial carotid and vertebral arteries, performed in May 2000, demonstrated an area of focal stenosis at the origin of the left external carotid artery and tortuosity of the vertebral arteries. An area of infarction in the right occipital pole of the brain involving both gray and white matter was visualized.

In May 2001, she developed abrupt painless vision loss in her left eye. Ophthalmologic exam showed marked compromise of the inflow and outflow circulation. There was no clinical evidence to suggest either polymyalgia rheumatic or temporal arteritis. She was treated with an intravitreal corticosteroid injection, which allowed the massive intraretinal

swelling to decrease. However, her vision remained at finger counting level in the left eye. Panretinal peripheral photocoagulation was recommended to prevent discomfort and neovascularization and secondary glaucoma, but owing to severe persistent pain the left eye was enucleated.

Histopathology of the enucleated eye revealed severe inner ischemic retinal atrophy characterized by marked atrophy of all layers supplied by the central retinal artery (Fig. 3A and B). The parenchyma of the retina appeared completely avascular and thrombosed vessels were seen in the nerve fiber layer. Numerous small arterioles with fibroproliferative narrowing of their lumen were also observed (Fig. 3C and D). A small focus of vitreoretinal neovascularization was seen on the inner surface of the atrophic retina posteriorly adjoining an area where the internal limiting membrane was sinuously folded by an epiretinal membrane of glial cells. In addition, the juxtapapillary sclera was fibrotic and markedly increased in thickness.

Literature search

In order to identify previous descriptions of this unusual complication in the medical literature we performed a systematic search on PubMed using “systemic sclerosis” and each of the following terms: “blindness”, “retinal artery occlusion”, “retinal vein occlusion”, “ocular manifestations” and “ocular”. The results revealed 0, 0, 1, 2, and 32 results, respectively. Using “scleroderma” and “central retinal artery occlusion” resulted in six publications. However, only two of these were related to SSc. This search indicated that although numerous ophthalmic lesions occur in association with SSc, the most common being eyelid tightness, diminished tear secretion, keratoconjunctivitis sicca, lid telangiectasias, and shallow conjunctival fornices [12–16], the occurrence of retinal artery occlusion is extremely rare [17–20].

Discussion

We describe here three patients evaluated at the Scleroderma Center of Thomas Jefferson University who developed the abrupt onset of painless unilateral loss of vision caused by unilateral retinal artery occlusion in the absence of other common etiologic factors. These three cases were seen at the Center within a 10-year time span during which 366 new SSc patients were evaluated and a total of 4,115 SSc follow-up visits were recorded. Although retinal vascular occlusion has been described in association with several rheumatologic diseases in which vasculitis is a prominent feature, such as temporal arteritis [21,22], the occurrence of this vascular manifestation in SSc is extremely rare. Indeed, a literature search indicated that although patients with SSc are known to present a variety of ocular abnormalities [12–16], only a few published case reports have referred to retinal artery occlusion in patients with SSc, and only one study described the pathological changes of the retinal vessels in SSc and demonstrated hyalinization and occlusion with focal points of both acellularity and endothelial proliferation in the vessel walls [17].

The most common presentation of retinal artery occlusion is acute, persistent, painless loss of vision with cloudy retinal swelling and a cherry-red spot on funduscopy exam. In contrast, central retinal vein occlusions present with variable visual loss and the funduscopy

exam typically shows numerous retinal hemorrhages, dilated and tortuous retinal veins, numerous cotton-wool spots, and the presence of macular, and optic disc edema [24].

A study of the retinal vasculature of a cohort of nonhypertensive patients with SSc, using photographs of the ocular fundi demonstrated hard exudates, vascular tortuosity and macular degeneration. Other fundal abnormalities have been described in SSc including retinal edema, intraretinal hemorrhages, and cotton-wool spots which are generally regarded to be secondary to SSc renal crisis or to chronic hypertensive disease [23]. An intravenous fluorescein angiographic study revealed choroidal perfusion abnormalities that did not affect visual acuity or visual fields in 5 out of 10 SSc patients [14].

In SSc, endothelial cell dysfunction causes a severe and usually progressive diffuse proliferative vasculopathy, most commonly involving the microvasculature system [5–11]. Thus, although the mechanisms responsible for central retinal artery occlusion in SSc are not known it is most likely that SSc vasculopathy plays a central role in the involvement of retinal vessels. The vasculopathy in SSc is characterized by intimal proliferation, concentric subendothelial deposition of collagen and mucinous material, and narrowing and thrombosis of the vessel lumen [5–11]. Progression of the vascular and fibrotic changes and a decrease in the inflammatory component lead to end-stage fibrosis of affected organs [1–4]. It has been suggested that in SSc activated T cells secrete cytokines and growth factors such as transforming growth factor beta (TGF- β) which cause endothelial cell injury and induce the expression of MHC class I and II antigens and adhesion ligand intercellular adhesion molecule-1. These locally secreted cytokines cause chemoattraction of fibroblasts into the vessel wall which are induced to transdifferentiate into myofibroblasts by the effects of TGF- β . The resultant increased production and deposition of collagen and other extracellular matrix proteins in the vessel wall and the increased proliferation of subendothelial and medial layer mesenchymal cells lead to further endothelial injury, fibrosis and a reduction or obliteration of the lumen of small arteries and arterioles [1–4].

We recognize that it is not possible to conclusively establish the causality of SSc in the development of retinal artery occlusion in the cases described here. However, the absence of other etiologic factors such as systemic vasculitis, antiphospholipid antibody syndrome, cocaine use, or previous therapy with phosphodiesterase 5 inhibitors coupled with the observation of histopathologic alterations typical of a fibroproliferative vasculopathy in the small retinal arteries of the enucleated eye of one of the patients suggest that the retinal arteries can also be affected by the fibroproliferative vasculopathy which is characteristic of SSc. The description of this case series indicates that end-organ disease due to retinal vessel fibroproliferative vasculopathy may, although uncommonly, cause a catastrophic acute loss of vision and blindness in SSc patients.

Acknowledgments

The expert assistance of Melissa Bateman in the preparation of the manuscript is gratefully acknowledged.

Supported in part by NIH/NIAMSRO1 AR019616 to S.A.J. and by the Noel T. and Sara L. Simmonds Endowment for Ophthalmic Pathology, Wills Eye Institute to R.C.E.

References

- [1]. Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. *Annu Rev Pathol* 2011;6:509–37. [PubMed: 21090968]
- [2]. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med* 2009; 360:1989–2003. [PubMed: 19420368]
- [3]. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest* 2007;117:557–67. [PubMed: 17332883]
- [4]. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004;140:37–50. [PubMed: 14706971]
- [5]. Rabquer BJ, Koch AE. Angiogenesis and vasculopathy in systemic sclerosis: evolving concepts. *Curr Rheumatol Rep* 2012;14:56–63. [PubMed: 22083296]
- [6]. Trojanowska M. Cellular and molecular aspects of vascular dysfunction in systemic sclerosis. *Nat Rev Rheumatol* 2010;6:453–60. [PubMed: 20585340]
- [7]. Müller-Ladner U, Distler O, Ibba-Manneschi L, Neumann E, Gay S. Mechanisms of vascular damage in systemic sclerosis. *Autoimmunity* 2009; 42:587–95. [PubMed: 19863377]
- [8]. Flavahan NA, Flavahan S, Mitra S, Chotani MA. The vasculopathy of Raynaud's phenomenon and scleroderma. *Rheum Dis Clin North Am* 2003;29:275–91 [vi]. [PubMed: 12841295]
- [9]. Kahaleh B. Vascular disease in scleroderma: mechanisms of vascular injury. *Rheum Dis Clin North Am* 2008;34:57–71 vi. [PubMed: 18329532]
- [10]. Hummers LK. Microvascular damage in systemic sclerosis: detection and monitoring with biomarkers. *Curr Rheumatol Rep* 2006;8:131–7. [PubMed: 16569372]
- [11]. Wigley FM. Vascular disease in scleroderma. *Clin Rev Allergy Immunol* 2009;36:150–75. [PubMed: 19067252]
- [12]. West RH, Barnett AJ. Ocular involvement in scleroderma. *Br J Ophthalmol* 1979;63:845–7. [PubMed: 526467]
- [13]. Horan EC. Ophthalmic manifestations of progressive systemic sclerosis. *Br J Ophthalmol* 1969;53:388–92. [PubMed: 5794954]
- [14]. Grennan DM, Forrester J. Involvement of the eye in SLE and scleroderma. *Ann Rheum Dis* 1977;36:152–6. [PubMed: 856066]
- [15]. Gomes BA, Santhiago MR, Magalhães P, Kara-Junio N, Azevedo MN, Moraes HV. Ocular findings in patients with systemic sclerosis. *Clinics (Sao Paulo)* 2011;66(3):379–85. [PubMed: 21552659]
- [16]. Ashton N, Coomes EN, Garner A, Oliver DO. Retinopathy due to progressive systemic sclerosis. *J Pathol Bacteriol* 1968;96(2):259–68. [PubMed: 4880692]
- [17]. Saari KM, Rudenberg HA, Laitinen O. Bilateral central retinal vein occlusion in a patient with scleroderma. *Ophthalmologica* 1981;182:7–12. [PubMed: 7267001]
- [18]. Konuk O, Özdek S, Onal B, Tiftikcioglu Y, Gürelik G, Hasanreisoglu B. Ocular ischemic syndrome presenting as central retinal artery occlusion in scleroderma. *Retina* 2006;26:102–4. [PubMed: 16395147]
- [19]. Littlejohn GO, Urowitz MB, Pavlin CJ. Central retinal vein occlusion and scleroderma: implications for sclerodermatous vascular disease. *Ann Rheum Dis* 1981;40:96–9. [PubMed: 7469533]
- [20]. Minasian M, Stanford M, Graham E, Denton CP, Black C. Bilateral ischaemic retinal vasculopathy in scleroderma. *Br J Ophthalmol* 2005;89:1064–5. [PubMed: 16024867]
- [21]. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. *Am J Ophthalmol* 1998;125:509–20. [PubMed: 9559737]
- [22]. Connolly BP, Krishnan A, Shah GK, Whelan J, Brown GC, Eagle RC Jr, et al. Characteristics of patients presenting with central retinal artery occlusion with and without giant cell arteritis. *Can J Ophthalmol* 2000;35: 379–84. [PubMed: 11192446]
- [23]. Ushiyama O, Ushiyama K, Yamada T, Koarada S, Tada Y, Suzuki N, et al. Retinal findings in systemic sclerosis: a comparison with nailfold capillaroscopic patterns. *Ann Rheum Dis* 2003;62:204–7. [PubMed: 12594103]

- [24]. Hayreh SS. So-called “central retinal vein occlusion”—pathogenesis, terminology, clinical features. *Ophthalmologica* 1976;172:1–13. [PubMed: 1250571]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1. Funduscopy findings in patient 2. (A) Color fundus image of the right eye demonstrating retinal whitening and a cherry-red spot. (B–D) Fluorescein angiography of the right fundus demonstrating a significant delay in the arteriovenous transit time. (For interpretation of the references to colour in this figure legend, the reader referred to the web version of this article.)

Fig. 2. Histopathology of the right temporal artery in patient 2. Hematoxylin–eosin staining of the temporal artery biopsy shows a muscular artery with a wide and patent lumen. There is no evidence of active or healed giant cell arteritis. Moderately severe subintimal fibrosis is present, and there is also fibrosis of the surrounding adventitia. Hematoxylin–eosin, $\times 25$.

Fig. 3.

Histopathology of enucleated eye in patient 3. (A) Thickened and fibrotic juxtapapillary sclera which was several times the normal thickness. There is severe atrophy of the inner retinal layers. Hematoxylin–eosin $\times 10$. (B) All retinal layers supplied by the central retinal artery are atrophic, including most of the inner nuclear layer (severe inner ischemic retinal atrophy). A small focus of vitreoretinal neovascularization is present on the inner surface of the atrophic retina. The internal limiting membrane is sinuously folded by an epiretinal membrane of glial cells. Hematoxylin–eosin $\times 100$. (C, D) Several small arterioles in the retina and choroid showing fibrotic thickening and narrowing of the lumen. Hematoxylin–eosin $\times 200$.