Bilateral Keratoconus in Diffuse Cutaneous Systemic Sclerosis: A Rare Presentation - Is There Any Role of Autoimmunity?

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Dear Editor,

Keratoconus (KC) has long been defined as a non-inflammatory disease of the cornea. However, recent evidence increasingly suggests the possibility of an underlying subclinical inflammation that may contribute to KC pathogenesis.[1,2] Studies have linked KC to various systemic illnesses such as allergy, atopy, collagen vascular diseases, and autoimmune diseases like ulcerative colitis, rheumatoid arthritis, and Hashimoto's thyroiditis.[1,2] Systemic sclerosis (SSc) or scleroderma is a chronic multi-system autoimmune connective tissue disorder that primarily affects the skin.[3] Ocular involvement is mostly in the form of eyelid abnormalities, dry eye, and retinal and choroidal vasculopathy.[4] In the literature, there are a few solitary reports of KC in SSc.[5,6,7] Here we present two cases of bilateral KC associated with the diffuse cutaneous type of SSc.

Case 1: A 24-year-old Asian female with a history of SSc (anti-SCL70+) diagnosed 2 years earlier presented with complaints of worsening vision in both eyes for 6 months. She was on oral corticosteroids and immunosuppressives that included oral hydroxychloroquine sulfate 200 mg once daily (IPCA Laboratories Ltd., Mumbai, India), mycophenolate mofetil 500 mg twice daily (Panacea Biotec Ltd., New Delhi, India), and nifedipine 20 mg once daily (Cipla Ltd., Mumbai, India) for the last 2 years. There was no history of parental consanguinity, family history of KC, or personal history of chronic eye rubbing, allergic eye disease, atopic disease, or any other systemic diseases. Physical examination revealed generalized skin tightening, taut eyelid skin, and puffy pale fingers suggestive of Raynaud's phenomenon (Figure 1A). The best corrected Snellen's visual acuity (BCVA) was 6/6 in both eyes. Slit-lamp examination showed an incomplete Fleischer's ring (Figures 1B and C) and corneal tomography revealed an inferior cone in both eyes (Figures 1D and E). Dry eye investigations and ocular surface staining were normal. Fundus examination was also normal. Based on the tomographic findings, a diagnosis of stage 1

and stage 2 KC of the right and the left eye respectively was made (as per the Amsler-Krumeich classification system). The patient underwent collagen cross-linking (CXL) in the left eye as per the Dresden protocol. A combination of moxifloxacin eye drops (Cipla Ltd., Mumbai, India) 4 times a day for 1 week and loteprednol etabonate (Sun Pharmaceutical Industries Ltd., Mumbai, India) starting at 4 times a day and tapering weekly over 4 weeks was administered in the immediate postoperative period. The cornea was fully epithelized within 4 days of the procedure. At 1-year follow-up, there was no progression of KC in either eye, and the patient continued to maintain a BCVA of 6/6 binocularly.

Case 2: A 32-year-old Asian female with a 14-year history of diffuse cutaneous SSc (anti-SCL70+) presented with complaints of increased discomfort of dryness for 6 months. The patient was on oral mycophenolate mofetil 500 mg twice daily (Panacea Biotec Ltd., New Delhi, India), methotrexate 5 mg once a week (IPCA Laboratories Ltd., Mumbai, India), deflazacort 6 mg once daily (Sun Pharmaceutical Industries Ltd., Mumbai, India), and pilocarpine hydrochloride 5 mg once daily (FDC Ltd., Mumbai, India) for 6 years. Ocular medications included cyclosporine 0.05% twice daily (Allergan India Pvt. Ltd., Bangalore, India) and a combination of polyethylene glycol and hydroxymethyl cellulose eye drops (Allergan India Pvt. Ltd., Bangalore, India) several times a day. She underwent CXL in both eyes for progressive KC and had secondary Sjögren syndrome dry eye (SSDE). Topical treatment continued with cyclosporine 0.05% twice daily and hydroxymethyl cellulose eye drops several times a day. No familial history of KC or personal history of chronic eye rubbing, allergic eye disease, atopic disease or any autoimmune diseases was reported. Physical examination revealed significant skin stiffness, atrophic patches, digital ulcerations, and dental abnormalities (Figure 2A and B). Her BCVA was 6/12 in the right eye and 6/18 in the left eye. Slit-lamp examination revealed incomplete Fleischer's ring, Vogt's striae, and CXL haze in both eyes (Figure 2C and D) along with moderate papillary changes in the upper tarsal conjunctiva. Dry eye evaluation revealed Schirmer values of 3 mm/5 min, a tear breakup time of 3 seconds, and diffuse corneal and conjunctival punctate staining in both eyes suggestive of SSDE. Corneal tomography revealed an inferior-temporal cone in both eyes (Figure 2E and F). Fundus examination was normal. The topographical parameters seemed stable when compared with previous images. The diagnosis of stage 4 KC and secondary SSDE associated with SSc was made. She was recommended punctal cautery for severe dryness and advised to continue her same ocular medications.

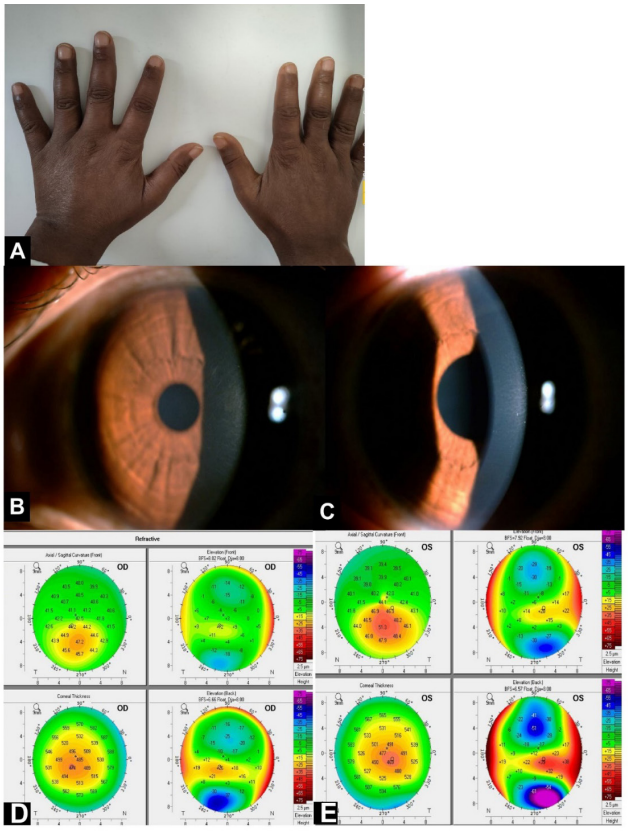

Figure 1. Dorsal view of both hands (A) showing pale fingertips suggestive of Raynaud's phenomenon, sclerodactyly, and skin atrophy. Slit-lamp photographs of the right (B) and left (C) eyes after collagen cross-linking (CXL) therapy. Note the mild post-CXL haze in the left eye. Corneal topography maps of the right (D) and left (E) eyes show an inferior cone corresponding to the thinnest pachymetry suggestive of keratoconus. Both eyes had moderate (stage 2) keratoconus (Amsler-Krumeich classification)

To date, only three cases of KC associated with SSc have been reported in the literature, all with bilateral involvement.[5,6,7] Of these, one case was successfully treated with bilateral CXL,[7] one patient had advanced KC in both eyes and was therefore recommended corneal transplantation,[5] and one was offered hard contact lenses.[6] The outcome of CXL in all five eyes (including the three eyes in this paper) with KC was satisfactory, with no complications or further progression. Case two in this paper reports the longer follow-up post CXL in KC associated with SSc.

SSc is a complex disease involving primary microangiopathy, immune dysregulation, and abnormal T lymphocyte differentiation. It involves the overexpression of extracellular matrix, uncontrolled fibroblast activation, and collagen synthesis, resulting in tissue fibrosis.[3] The sclera, uvea, and cornea are primarily composed of collagen fibers, are susceptible to connective tissue and collagen vascular diseases. The rich vascular supply may provoke immune-complex depositions that can manifest in the form of limbitis, peripheral ulcerative keratitis, and peripheral corneal thinning. There is growing consensus on the role of ocular surface and systemic inflammation in the pathogenesis of KC.[1,2,4] Higher levels of tear cytokines, including interleukin (IL)-4, IL-6, IL-8, tumor necrosis factor (TNF)-alpha, TNF-beta, and tear proteases such as matrix metalloproteinase (MMP)-1, MMP-3, and MMP-9 have been reported in KC eyes.[8,9] In a nationwide study of 2051 cases, KC was associated with various systemic immune-mediated diseases, such as Hashimoto's thyroiditis, inflammatory skin conditions, rheumatoid arthritis, ulcerative colitis, autoimmune chronic active hepatitis, and arthropathy.[2] Another study reported a

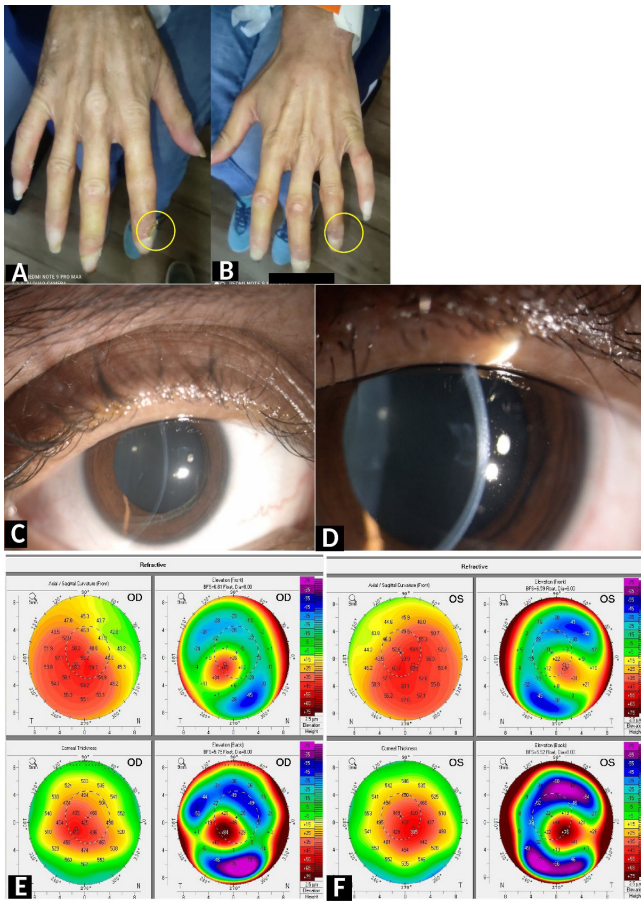

Figure 2. Dorsal views of the right (A) and left (B) hands show sclerodactyly, Raynaud's phenomenon, areas of ulcerations (yellow circles), flexion contracture, and atrophic changes affecting hand function. Slit-lamp photographs show the corneal slit section of the right (C) and left (D) eyes. Corneal topography shows an inferior-temporal cone in both eyes (E and F). Both eyes had stage 4 keratoconus (Amsler-Krumeich classification

significantly higher density of mature corneal Langerhans cells in KC eyes, indicating an immune-related inflammatory response and an active state of inflammation.[10] These findings collectively suggest that the immune system and inflammatory pathways may play a potential role in the pathogenesis of KC.

SSc is associated with upregulation of transforming growth factor-beta and ILs that induce chronic fibroblast activation, as well as increased collagen synthesis and deposition of ultrastructurally altered extracellular matrix.[3] KC, on the other hand, is associated with loss of keratocytes, breakdown of stromal crosslinks with collagen lamellae, and corresponding corneal thinning. The association of these seemingly dissimilar diseases is thus both interesting and intriguing. Chronic systemic inflammation may add synergistically to other forms of KC-related inflammation.[4] CXL effectively stabilizes KC, but its safety and efficacy in patients on immunosuppressants and with autoimmune diseases remain unclear because of potential healing complications and infection risks. Therefore, the authors recommend that systemic disease activity must be controlled before performing CXL to avoid corneal complications.

In conclusion, this report presents rare cases of bilateral KC in diffuse cutaneous SSc, challenging the non-inflammatory classification of KC and suggesting possible autoimmune contributions. Though ocular surface inflammation may not be clinically visible, subclinical inflammatory processes could be present. Further research into KC-autoimmune disease connections may reveal underlying mechanisms and guide anti-inflammatory treatments. Clinicians should monitor corneal topography in SSc patients, particularly early in the disease.

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms both for the use of the patient's images and the reporting of other clinical information in the journal.

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Declarations

Authorship Contributions

Surgical and Medical Practices: B.S., M.L., P.P., Concept: S.S., Design: S.S., M.L., P.P., Data Collection or Processing: S.S., B.S., M.L., P.P., Analysis or Interpretation: S.S., B.S., M.L., P.P., Literature Search: S.S., P.P., Writing: S.S., B.S., M.L., P.P.

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