

Corneal stromal deposits in connective tissue disease, a case series

Momoko K. Ponsetto^a, Abdelrahman M. Elhousseiny^{a,b,c}, James Kwan^a, Hajirah N. Saeed^{a,b,*}

^a Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

^b Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

^c Jones Eye Institute, University of Arkansas for Medical Sciences, Little rock, AR, 72205

ARTICLE INFO

Keywords:

Connective tissue disease
Collagen vascular disease
Ehlers Danlos syndrome
Arterial tortuosity syndrome
Stromal deposits
Terrien's marginal degeneration
Ectasia
Pseudopterygium
Case report

ABSTRACT

Purpose: We report two cases of refractile, peripheral, corneal stromal deposition in two patients with arterial tortuosity syndrome (ATS) and Ehlers-Danlos syndrome (EDS), two closely related connective tissue diseases (CTDs).

Observations: **Patient 1:** A 21-year-old man with history of ATS and keratoectasia presented with bilateral peripheral corneal neovascularization with numerous whitish brown, refractile, deep stromal opacities that were circumferential along the inferotemporal cornea. After 3 years of follow-up, the corneal deposits did not progress, but the ectasia did, with significant bilateral corneal steepening and thinning for which the patient was recommended to undergo repeat corneal collagen cross linking. **Patient 2:** A 26-year-old man with presumed diagnosis of EDS presented with numerous whitish brown, refractile, deep stromal opacities that were circumferential along the temporal cornea in the right eye, and superiorly in the left eye. The left eye had a pseudopterygium involving 50% of the cornea. After 2 years of follow-up, the corneal opacities did not progress; however, the patient underwent primary excision of the pseudopterygium and subsequently had conjunctivalization of the entire cornea. The lesions in both cases resembled those seen in Terrien's marginal degeneration.

Conclusions and importance: Peripheral corneal stromal deposits have never been reported before in EDS or ATS or other connective tissue diseases. This case series may prompt further inquiry and characterization of these findings in patients with CTDs.

1. Introduction

Ehlers Danlos syndrome (EDS) and arterial tortuosity syndrome (ATS) are rare connective tissue diseases (CTDs). Until 1969, EDS and ATS were considered to be diseases on the same spectrum with the latter being defined as "EDS with multiple pulmonary artery stenoses and tortuous systemic arteries".¹ Since then, ATS has been considered distinct from EDS but the two share many phenotypic similarities, including their ophthalmic manifestations. Most notably, these manifestations include high myopia, keratoconus, and keratoglobus.^{1,2} Brittle cornea syndrome has been reported in association with EDS type VI, a rare autosomal recessive disease affecting extracellular matrix and collagen synthesis characterized by blue sclera and corneal thinning which increases the risk of corneal rupture either spontaneously or with minor trauma.^{3,4} CTDs in general may manifest with conjunctivitis, keratoconjunctivitis sicca, keratitis, uveitis, episcleritis, and scleritis.⁵ There have been reports of acute corneal stromal infiltration and edema

in systemic lupus erythematosus (SLE) patients and diffuse stromal opacification in patients with ATS, but there are no reports on peripheral corneal deposits with neovascularization, similar to that seen in Terrien's marginal degeneration (TMD).^{2,6-10} In this observational case series, we report two cases of refractile, peripheral, corneal stromal deposition in patients with ATS and EDS, two closely related CTDs.

2. Findings

2.1. Case 1

A 21-year-old man with a past medical history of EDS, later characterized as ATS, presented for management of his corneal ectasia, which first manifested at age 11 years with progressive astigmatism of the right eye. He was diagnosed with ATS after the SLC2A10 gene defect was found. His medical history was also notable for cervical spine disc prolapse and heart murmur, which were presumed to be related to the

* Corresponding author. Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243 Charles St, Boston, MA, USA.

E-mail address: Hajirah_Saeed@meei.harvard.edu (H.N. Saeed).

<https://doi.org/10.1016/j.ajoc.2022.101264>

Received 24 June 2021; Accepted 14 January 2022

Available online 26 January 2022

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underlying ATS. He had two distant cousins with the same genetic defect. Otherwise, his family history was noncontributory. There was no history of consanguinity. On initial presentation to us, he had already undergone corneal collagen crosslinking (CXL) of both eyes 1 year prior. He had no other ocular surgical history.

Uncorrected visual acuity on presentation was 20/60 in the right eye and 20/200 in the left eye. Slit lamp examination revealed mild scleralization and neovascularization of the peripheral cornea bilaterally with numerous whitish brown, refractile, deep stromal opacities that were circumferential along the inferotemporal cornea bilaterally (Fig. 1). No Vogt's striae or Fleischer's rings were noted but Munson's sign was present in both eyes. There was no anterior chamber inflammation. The rest of the anterior exam and dilated fundus exam were within normal limits.

During the 3-year follow-up period, the opacities did not progress, but his ectasia did, with significant corneal steepening and thinning bilaterally for which the patient was recommended to undergo repeat CXL (Fig. 2 A and B). At the final follow-up visit, best corrected visual acuity (BCVA) was 20/30 and 20/50 with scleral lenses in the right and left eye, respectively.

2.2. Case 2

A 26-year-old man was admitted to our hospital after developing a spontaneous pneumothorax. A chest tube was inserted, and pleurodesis was performed. He subsequently had multiple episodes of spontaneous pneumothorax. Systemic examination revealed palmar contractures of both hands, hearing loss due to cholesteoma, and facial atrophy. He had a sister and multiple aunts with a history of recurrent miscarriages, a niece with palmar hand contractures, and a cousin with autism. There was no history of consanguinity. Prior to the pneumothorax episode, this patient had inconsistent medical care and did not have any known, unifying diagnosis. Medical and genetic evaluation for a CTD was performed and the patient was referred to us for ocular evaluation.

Upon evaluation, he was found to have a BCVA of 20/20 in each eye. Slit lamp examination revealed bilateral peripheral corneal scleralization and neovascularization with numerous whitish brown, refractile, deep stromal opacities that were circumferential along the temporal cornea in the right eye, and superior cornea in the left eye. There was a temporal pseudopterygium covering 25% of the left cornea from 2 o'clock to 8 o'clock (Fig. 1). There was no anterior chamber

inflammation. The rest of his anterior exam and dilated fundus exam were within normal limits.

After two and a half years of follow-up, the corneal opacities in both eyes remained stable. The BCVA remained stable in the right eye with no significant change in astigmatism (Fig. 2C and D), however his left eye pseudopterygium progressed to involve more than 50% of the cornea resulting in hand motion vision. After discussing several options for treatment of the pseudopterygium including observation, primary excision, and combined limbal allograft with immunosuppression, primary excision was performed. Autograft from the right eye was not possible given the signs of limbal stem cell dysfunction. Reactive response after surgery resulted in conjunctivalization of the entire cornea and maintenance of hand motion vision. The patient declined any further surgery. Comprehensive genetics evaluation did not reveal a definitive diagnosis. An EDS genetics panel revealed two variants of uncertain significance in genes COL5A1 and ZNF469. Whole exome sequencing revealed two variants in the DCHS1 gene which may be associated with Van Maldergem syndrome, but a brain MRI was not consistent with this diagnosis. His working diagnosis was EDS musculocontractural type.

3. Discussion and conclusions

We report the unique ocular findings of peripheral corneal stromal deposits in the setting of limbal scleralization in CTDs, specifically EDS and ATS. These lesions resemble those in TMD, though they do not follow its typical course including initial superior corneal involvement, associated peripheral thinning, and progressive nature. TMD is a rare, slowly progressive corneal disease characterized by peripheral corneal thinning with superficial neovascularization, lipid deposition at the leading edge and intact corneal epithelium. There is often against-the-rule astigmatism.¹¹

Though there is not enough evidence that the peripheral deposits in these patients are secondary to TMD, Patient 1 had astigmatism and relative peripheral thinning, attributed to his corneal ectasia. His topographic pattern was consistent with pellucid marginal degeneration. Patient 2 had oblique astigmatism in the right eye and against-the-rule astigmatism in the left eye, both without associated thinning. He also had a characteristic pseudopterygium which has been reported previously in TMD (Fig. 1). Goldman et al. have described atypical pterygia in TMD. They may occur at the initial stages of the disease at

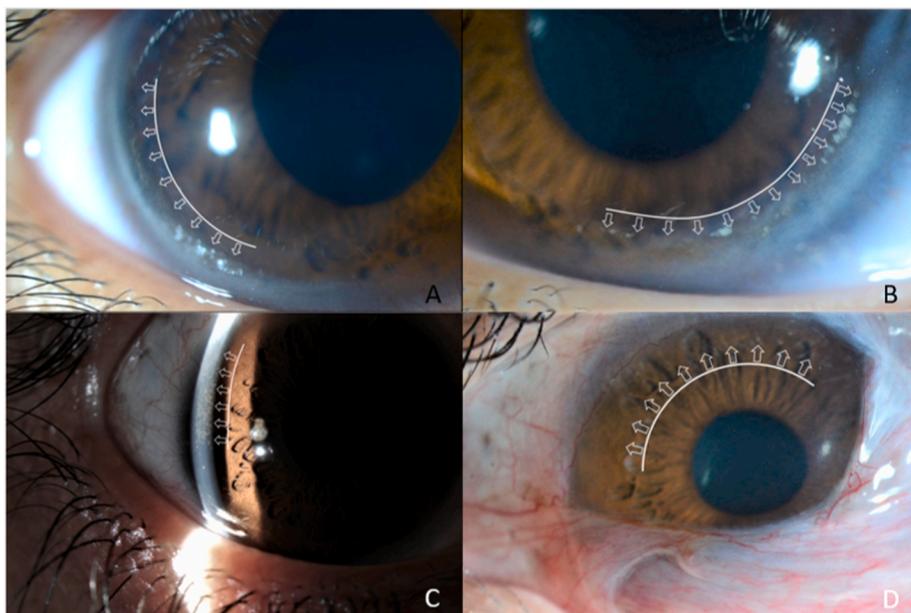


Fig. 1. Slit lamp photos of Patients 1 and 2. A and B: Slit lamp photo of the right and left eyes of Patient 1, respectively. Mid and deep stromal opacities are present in the peripheral cornea (arrows). Also note the scleralization and fine neovascularization of the peripheral cornea. C and D: Slit lamp photo of the right and left eyes of Patient 2, respectively. Mid and deep stromal opacities are present in the peripheral cornea (arrows). The left eye has a pseudopterygium covering 25% of the cornea. Also note the scleralization and fine neovascularization of the peripheral cornea.

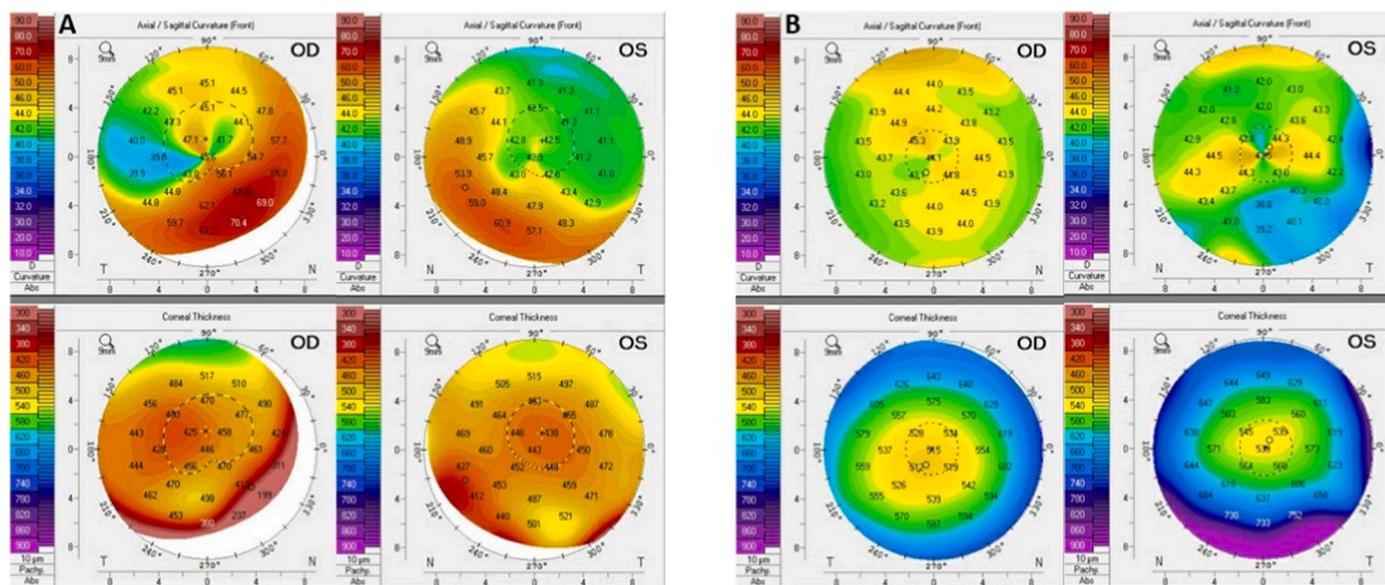


Fig. 2. Corneal topographies with a Pentacam device. A) Topography for Patient 1 showing a pellucid marginal degeneration pattern for both right (OD) and left (OS) eyes. Thinnest pachymetry is 342 and 402 for right and left eyes, respectively. B) Topography for Patient 2 showing irregular, oblique, bowtie astigmatism of the right eye and against the rule bowtie astigmatism of the left eye. Thinnest pachymetry is 511 and 536, respectively. The thickened periphery is due to the pseudopterygium.

positions other than the 3 and 9 o'clock and grow onto the cornea at an oblique axis with a broad, flat, leading edge.¹² The authors suggested that pseudopterygia in TMD may appear extremely early in the disease when the marginal furrow may still be a subtle finding. It may be that Patient 2 would have developed classic signs of TMD if given enough time. It may also be that Patient 1 had thinning from TMD that was masked by his ectasia, which is also a manifestation of CTDs. Patient 1 had progressive ectasia even after CXL, perhaps because of peripheral corneal disease that was not fully addressed with CXL. Patient 2 developed conjunctivalization of his cornea after surgery. It is likely that his underlying CTD and/or pseudopterygium resulted in reactive fibrosis.

The normal corneal stroma is composed of heterotypic type I and V collagen fibrils organized as an orthogonal lamellae.⁶ The reliance on maintenance of this collagen structure for the cornea to preserve its transparency and strength, as well as its relation to the vascular supply of the conjunctiva, could explain its vulnerability in the setting of CTDs.^{13,14} Other forms of CTDs, such as scleroderma, rheumatoid arthritis, SLE, polyarteritis nodosa, and granulomatosis with polyangiitis, which are autoimmune in nature and therefore distinct from EDS/ATS, may have inflammatory corneal manifestations like peripheral ulcerative keratitis. Obliterative microangiitis from deposition of immune complexes in the limbal vasculature, and collagenase and protease activity, may result in peripheral thinning and stromal collagen degradation.¹⁴

Involvement of deep corneal layers is rarely reported in the context of CTDs; however, a few case reports have been described in SLE patients. Adan et al. described a bilateral deep keratitis associated with iridocyclitis in a patient diagnosed with SLE.⁸ Similar findings were reported by Reeves et al. who described a patient with SLE who developed a bilateral interstitial keratitis and intermittent uveitis associated with progressively increasing deep stromal opacities one year after developing SLE. The lesions slowly progressed to become more dense, granular, and reluctant, with involvement of Descemet's membrane and deep stromal layers.⁹ Recently, Abbas et al. reported a case of bilateral interstitial keratitis in a 9-year-old girl with SLE.⁷ The lesions in our cases were not associated with PUK or other ocular surface or intraocular inflammation.

EDS/ATS are often associated with other corneal manifestations, but thus far, associations between EDS/ATS and peripheral corneal deposits

have not been reported. These lesions resemble those of Terrien's marginal degeneration, though larger observational studies are needed to corroborate this. Clinicians should observe for the atypical signs presented here in CTDs to further characterize this possible association.

Patient consent

The patient(s)/patient's legal guardian consented to publication of the case orally and in writing.

Credit Author Statement

Momo Ponsetto: Conceptualization, Methodology, Investigation, Data Curation, Writing-Original Draft, Visualization; **Abdelrahman Elhousseiny**: Data Curation, Writing – Original Draft, Writing – Review & Editing; **James Kwan**: Data Curation, Writing – Review & Editing, Project Administration; **Hajirah Saeed**: Writing – Original Draft, Writing – Review & Editing, Supervision

Funding

No funding or grant support

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: MK, AE, JK, HNS.

Acknowledgements

None.

References

1. Lees MH, Menashe VD, Sunderland CO, et al. Ehlers-Danlos syndrome associated with multiple pulmonary artery stenoses and tortuous systemic arteries. *J Pediatr*. 1969;75(6):1031–1036.
2. Hardin JS, Zarate YA, Callewaert B, et al. Ophthalmic findings in patients with arterial tortuosity syndrome and carriers: a case series. *Ophthalmic Genet*. 2018;39(1):29–34.
3. Al-Hussain H, Zeisberger SM, Huber PR, et al. Brittle cornea syndrome and its delineation from the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VI): report on 23 patients and review of the literature. *Am J Med Genet*. 2004;124a(1):28–34.
4. Eleiwa T, Raheem M, Patel NA, et al. Case series of Brittle cornea syndrome. *Case Rep Ophthalmol Med*. 2020;2020:4381273.
5. Young S. Ocular involvement in connective tissue disorders. *Curr Allergy Asthma Rep*. 2005;5(4):323–326.
6. Sivraj RR, Durrani OM, Denniston AK, et al. Ocular manifestations of systemic lupus erythematosus. *Rheumatology*. 2007;46(12):1757–1762.
7. Abbas N, Megalla M, Zhang LY, Meskin SW. Bilateral interstitial keratitis as the presenting manifestation of systemic lupus erythematosus in a child. *Can J Ophthalmol*. 2021 Jun;56(3):e77–e78.
8. Adan CB, Trevisani VF, Vasconcellos M, et al. Bilateral deep keratitis caused by systemic lupus erythematosus. *Cornea*. 2004;23(2):207–209.
9. Reeves JA. Keratopathy associated with systemic lupus erythematosus. *Arch Ophthalmol*. 1965;74:159–160.
10. Hasler S, Stürmer J, Kaufmann C. Keratoglobus and deep stromal corneal opacification in a case of arterial tortuosity syndrome. *Klin Monbl Augenheilkd*. 2011; 228(4):345–346.
11. Ding Y, Murri MS, Birdsong OC, et al. Terrien marginal degeneration. *Surv Ophthalmol*. 2019;64(2):162–174.
12. Goldman KN, Kaufman HE. Atypical pterygium: a clinical feature of terrien's marginal degeneration. *Arch Ophthalmol*. 1978;96(6):1027–1029.
13. Segev F, Héon E, Cole WG, et al. Structural abnormalities of the cornea and lid resulting from collagen V mutations. *Invest Ophthalmol Vis Sci*. 2006;47(2):565–573.
14. Sii F, Lee GA, Sanfilippo P, Stephensen DC. Pellucid marginal degeneration and scleroderma. *Clin Exp Optom*. 2004 May;87(3):180–184.