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Case Report

Human Amniotic Membrane Graft in the Management of Peripheral Hypertrophic Subepithelial Corneal Degeneration: A Case Report

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Keywords
Peripheral hypertrophic subepithelial corneal degeneration · Human amniotic membrane · Corneal surgery

Abstract
Introduction: In this report, we describe the case of peripheral hypertrophic subepithelial corneal degeneration (PHSCD), managed with surgical excision and a human amniotic membrane (hAM) graft. ***Case Presentation:*** A 45-year-old female Caucasian patient presented with decreased vision, itching, and burning in both eyes, and a presence of pseudopterygium in the right eye, causing visual decline. Routine ocular exams and anterior segment OCT led to the diagnosis of PHSCD, after a careful differential diagnosis with other similar clinical occurrences. Subsequently, the patient was successfully managed with surgical intervention and an amniotic membrane graft placement. ***Conclusion:*** PHSCD is a rare disease, which in advanced cases can be successfully managed with hAM graft. No recurrence of the lesions was observed at 1-year follow-up in our patient.

Introduction

Peripheral hypertrophic subepithelial corneal degeneration (PHSCD) was first described in 2003 by Maust and Raber [1] in 6 patients. It is a rare, usually bilateral and symmetrical, idiopathic disorder, occurring predominantly in otherwise healthy, middle-aged white women [1, 2].

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PHSCD lesions consist of peripheral, circumferential, elevated areas of corneal opacification of various size and location around the cornea, with frequent anomalous limbal vasculature and keratoconjunctival proliferation, and the variable presence of associated pseudopterygium [1–4]. The characteristic superficial fibrotic lesions are located between the corneal epithelium and the Bowman's layer, potentially causing astigmatism or high-order aberrations.

Patients may experience no symptoms, or present with ocular surface discomfort, visual decline or both. The pathogenetic mechanisms underlying PHSCD development and progression have not been completely defined.

It should be noted that the absence of ocular or systemic disease suggests that PHSCD is a primary condition. Gore and colleagues [2] also hypothesized a genetic component of the disease, reacting to unknown environmental factors.

Diagnosis of PHSCD is based on demographic, clinical and imaging features, including slit lamp (SL) examination, corneal topography/tomography, anterior segment-optical coherence tomography (AS-OCT), and OCT angiography [5, 6]. PHSCD should be carefully differentiated from several similar entities, mainly including Salzmann's nodular degeneration (SND) [7], pterygium [8], and pseudopterygium [9] but also more rare entities, such as Terrien's marginal degeneration [10], carcinoma in situ [11], and limbal stem cell deficiency [12].

Treatment modalities for PHSCD include observation, conservative management with lubricants, superficial keratectomy with or without mitomycin C (MMC), regular phototherapeutic keratectomy (PTK), PTK-assisted anterior keratectomy with fibrous peeling, and fibrous peeling and amniotic membrane transplantation [2, 13–15]. Here, we aim to report the efficacy and safety of human amniotic membrane (hAM) graft in the management of an advanced case of PHSCD. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541162).

Case Report

A 45-year-old Caucasian woman came to our clinic (Eye Unit, Humanitas San Pio X, Milan, Italy) in 2022 with a history of itching and burning in both eyes and increasingly blurred vision in her right eye. At this point, it was noted that she had a previous diagnosis of pseudopterygium in 2006, which was managed symptomatically, including topical steroids, until the current presentation. No surgeries were done from 2006 until 2022, as the patient's visual axis was not involved, and the patient did not have any other accompanying visual signs or symptoms apart from the pseudopterygium.

The patient was otherwise healthy, and only reported a positive family history for glaucoma. At her first visit, her best-corrected visual acuity (BCVA) was 0.70 LogMAR with +2.00/−3.50 × 170 in her right eye, and 0.10 LogMAR with 0.25/−2.00 × 020 in her left eye.

Anterior segment examination was remarkable for the presence of superficial corneal vascularization, confluent subepithelial perilimbal fibrosis associated with corneal thickening in both eyes, with involvement of the central cornea and for the presence of a pseudopterygium in the right eye (shown in Fig. 1). No signs of limbal deficit on fluorescein staining were noted. Intraocular pressure, measured with Goldmann Tonometer, was 17 mm Hg in both eyes. Dilated fundoscopic examination was not remarkable for any pathological sign.

MS-39 technology (Costruzione Strumenti Oftalmici, CSO, Florence, Italy) was employed to perform keratoscopy, corneal topo-tomography, and AS-OCT. Keratoscopic images were irregular in both eyes, with involvement of the optic zone in the right eye.

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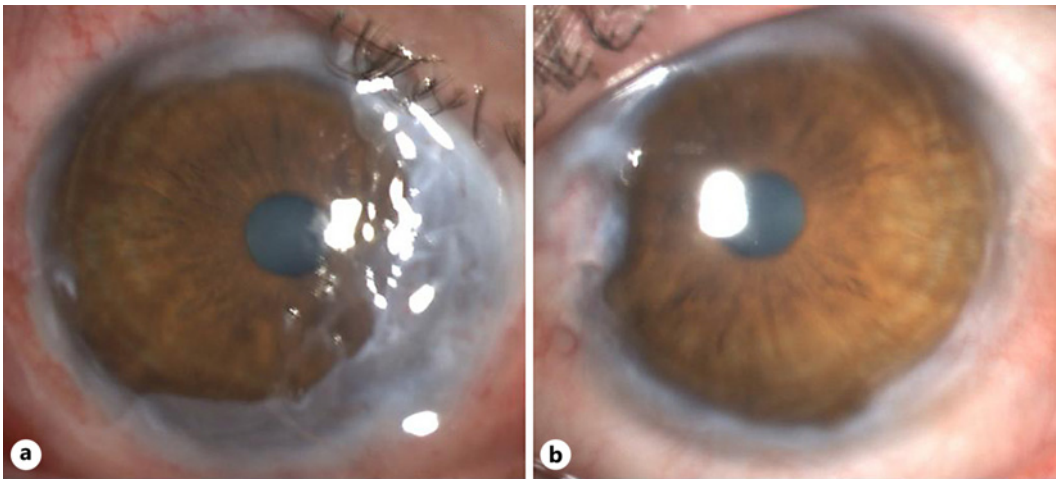

Fig. 1. a, **b** SL examination showing the presence of superficial corneal vascularization, confluent subepithelial perilimbal fibrosis associated with corneal thickening in both eyes, with involvement of central cornea and for the presence of a pseudopterygium in the right eye (**a**).

Corneal topo-tomography showed significant irregular astigmatism in both eyes (9.72 diopters in the right eye and 2.68 diopters in the left eye), a central pachymetry of 608 microns and 603 microns in the right eye and left eye, respectively, and a maximum corneal thickness of 767 microns and 759 microns in the right eye and left eye, respectively. AS-OCT confirmed the presence of circumferential subepithelial perilimbal fibrotic lesions in both eyes and of the pseudopterygium in the right eye (shown in Fig. 2).

We excluded all other causes of bilateral, peripheral, circumferential corneal opacification, including SND, Terrien's marginal degeneration, carcinoma in situ, and limbal stem cell deficiency. Therefore, the patient was diagnosed with bilateral PHSCD and surgery for her right eye was planned because of significant symptoms and visual axis impairment.

Scheduled surgery included the following three procedures: superficial keratectomy, pseudopterygium excision, and hAM transplantation. Local anesthesia with retrobulbar injection and subconjunctival lidocaine injection was employed.

The surgeon (Dr. P.R.) performed a peritomy, thus exposing the sclera, with conjunctival opening 4 mm from the limbus. Finally, hAM was placed on 210° (nasal, inferior, and temporal) to facilitate corneal healing. While placing the amniotic membrane, the basement membrane was placed facing upwards to reduce inflammation and for integration of the cornea. Subsequently, fibrin glue was used to secure the periphery of the membrane. At the end of the surgery, the eye was covered with an eye shield to protect it from external irritants.

The hAM was cultured and provided by Banca degli Occhi di Monza, Italy. After the surgery, the patient was put on doxycycline 40 mg/day (for 2 months), Prednisone 25 mg/day (for 7 days) and chloramphenicol + dexamethasone eye drops twice a day for 1 month. Doxycycline was mainly used for its anti-inflammatory purpose in this case, in order to reduce MMP-9 (Matrix metalloproteinase-9) formation.

At 1-month follow-up visit, the patient's ocular surface discomfort improved, and her BCVA improved to 0.0 LogMAR with +0.25/−2.00 × 0.20 in her right eye. SL examination showed a significant improvement of the lesions, MS-39 technology of the right eye illustrated the sparing of the central Keratoscopic rings, a reduction of astigmatism to 2.51 diopters, and a significant improvement of the subepithelial lesions on AS-OCT (shown in Fig. 3).

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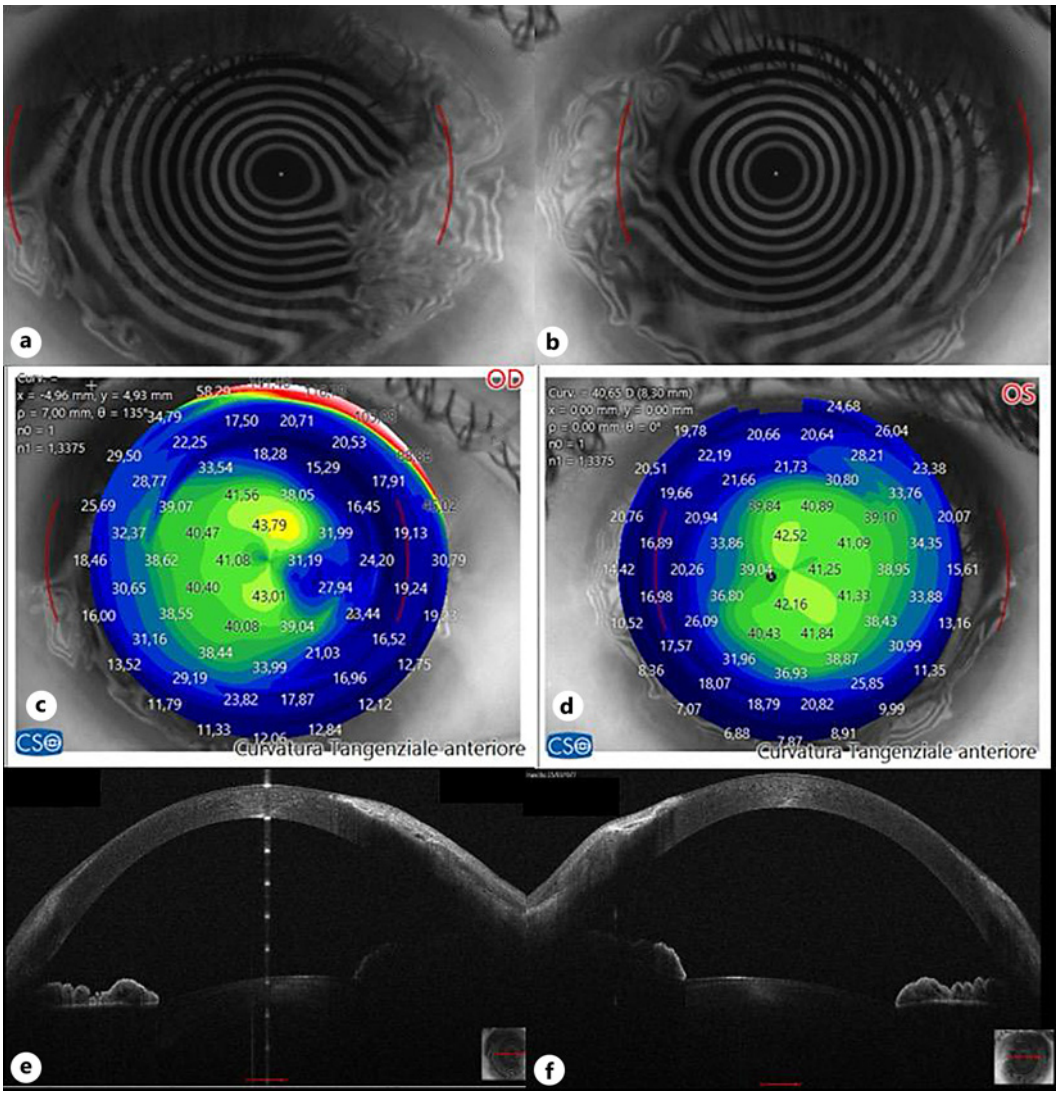

Fig. 2. a, **b** Irregular Keratoscopic images in both eyes, with involvement of the optical zone in the right eye (**a**). **c**, **d** Corneal topography shows significant irregular astigmatism in both eyes. **e**, **f** AS-OCT shows the presence of circumferential subepithelial perilimbal fibrotic lesions in both eyes and of the pseudopterygium in the right eye.

At her latest follow-up 1 year after surgery (17 years after the initial presentation), her BCVA was 0.0 LogMAR in the right eye and 0.10 in her left eye. No recurrence of subepithelial fibrosis or pseudopterygium was observed in her right eye. No progression of the PHSCD lesions was detected in her left eye. She continues to use tear supplements as required.

Results/Discussion

PHSCD is a rare and recently described disease, which could be misdiagnosed with other several disorders, mainly SND and pterygium. Typical characteristics of PHSCD include peripheral, circumferential, subepithelial lesions, commonly accompanied by limbal vascularization, keratoconjunctival proliferation, and pseudopterygium.

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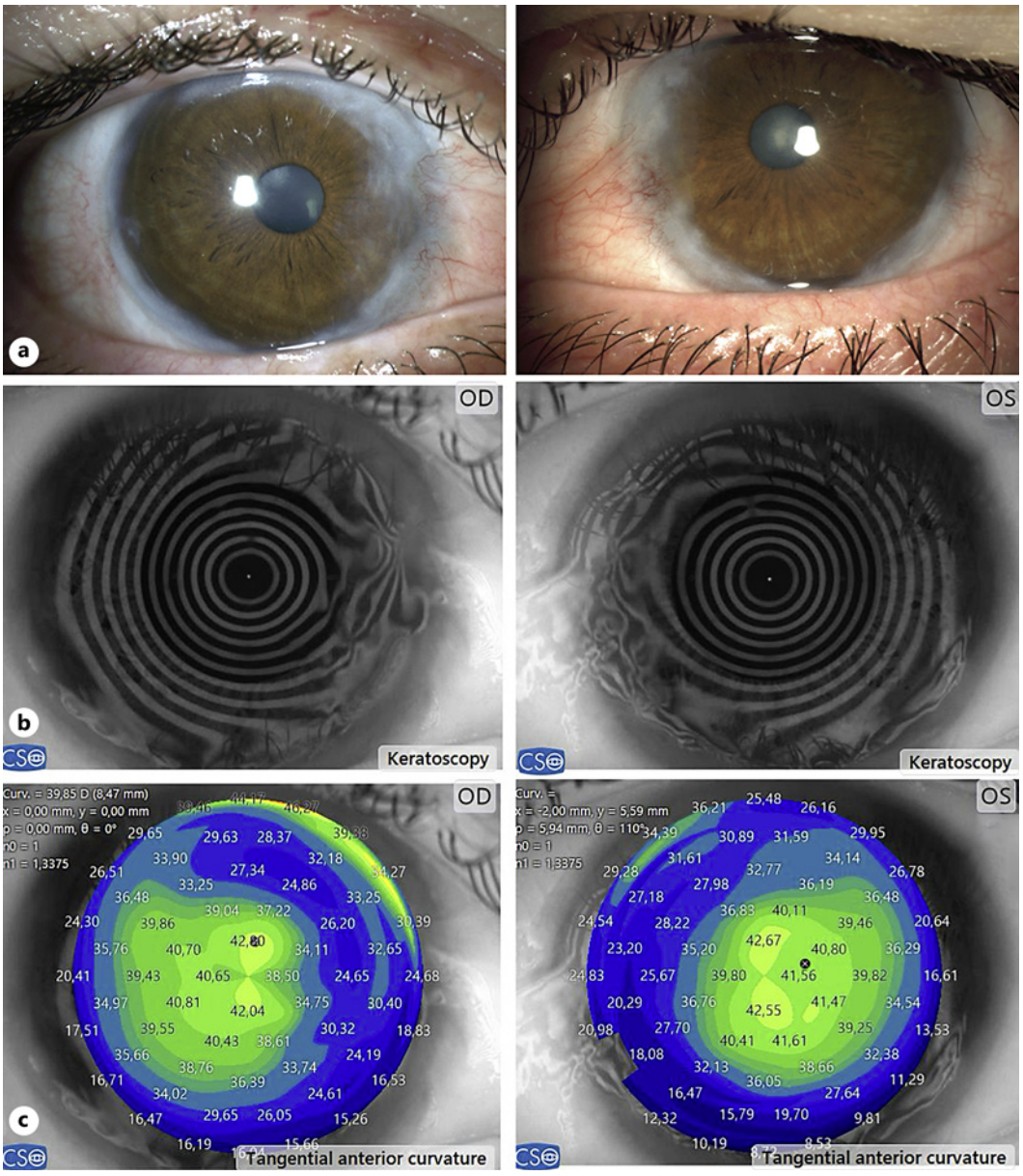

Fig. 3. One-month follow-up visit. **a** SL examination shows central transparent cornea. **b** Regularization of Keratoscopic image. **c** Improvement of astigmatism.

PHSCD is quite similar to SND in appearance and pathophysiological basis and hence a careful differentiation between the two was done in our patient. A majority of the patients with PHSCD are often clinically asymptomatic in the beginning stages of the disease. The initial sign of our patient was also a simple pseudopterygium, diagnosed in 2006, without any accompanying symptoms until 2022. This was the reason why PHSCD was not considered as an initial diagnosis and it was managed symptomatically as a pseudopterygium. PHSCD became more evident as a diagnosis when the visual acuity was seen to be decreased in 2022, and AS-OCT findings aided in a clear differentiation between a simple pseudopterygium and PHSCD. SND was also an unlikely diagnosis as the lesions seen in this patient did not fit the classic SND presentation.

As previously mentioned, PHSCD may be managed with different therapeutic approaches, based on disease severity. Observation and topical therapy with lubricants were found to be

sufficient to manage the slowly progressive nature of the disease in about half of the cases in a series by Gore et al. [2], whereas surgical and PTK-related approaches are considered necessary in cases of significant ocular discomfort, progressive astigmatism, visual axis involvement of suspected neoplastic lesions [2, 13, 14]. The surgical treatment involves careful excision of the pseudopterygium around the limbus. It is important to pay attention not to damage the underlying tissue while excising the overlying pseudopterygium as there is a great risk of damage to the stem cell reservoir of the limbus. The excision was followed by an amniotic membrane graft.

In the case of our patient, alternative treatments such as MMC were not considered as its use has been deemed dangerous for limbal stem cells. Thus, amniotic membrane graft was used due to its multiple beneficial effects on corneal re-epithelization and healing, as mentioned in literature [16–21] for a better outcome.

In addition, the use of hAM transplantation for PHSCD has been previously reported [6, 14, 15]. Amniotic membrane grafts have also been used in other ocular surface pathologies, and it is important to carefully consider the use of MMC, amniotic membrane or other adjuvant therapies. Amniotic membrane has shown to offer support for re-epithelization after corneal surgery, functioning as a basement membrane substitute, offering anti-inflammatory and anti-scarring effects, in addition to minimization of post-operative pain, and reduction of ocular surface inflammation.

Therefore, hAM graft is emerging as a valid therapy in ophthalmology, not only for ocular surface surgery, but also for glaucoma and vitreoretinal procedures, frequently in challenging situations [16, 22]. Regarding pathogenetic mechanisms of PHSCD, although histologic analysis of primary excisions of PHSCD lesions showed similarities to SND and pterygium in the absence of inflammation, the presence of silent ocular surface inflammatory and/or immune-mediated mechanisms cannot be totally excluded due to the presence of accompanying anomalous limbal vascularization [6, 23, 24].

Lastly, the more common presence of HLA-B*44 allele and AH 8.1 haplotype in PHSCD patients has been proposed as a genetic factor promoting the disruption/alteration of the limbal barrier, leading to corneal peripheral fibrosis [6, 13]. Considering all the above mentioned properties of hAM and the pathogenesis of PHSCD, we believe that the use of this tissue in our advanced case had a strong rationale, not only in surgical terms, but also in preventing disease recurrence.

Conclusion

In conclusion, hAM graft can represent a safe and effective treatment strategy for advanced cases of PHSCD. No recurrence of the lesions was observed at 1-year follow-up after surgery. Larger randomized controlled studies with longer follow-up are needed to confirm our results. This case is a unique contribution to the existing literature as the technique and clinical and topo-tomographic outcomes using hAM have been described in detail.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and methodology: P.R. and A.F.; resources: S.W. and B.B.; data curation: P.R.; writing – original draft preparation: P.R. and A.F.; writing – review and editing: P.R., S.W., and A.F. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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