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Ellipsoid Zone Loss as a Retinal Complication after Chimeric Antigen Receptor T-Cell Therapy

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Introduction

Chimeric antigen receptor T-cell (CAR-T cell) therapy is a form of personalized immunotherapy in which a patient's own T-lymphocytes are collected and genetically engineered in an *ex vivo* setting to express synthetic chimeric antigen receptors (CARs).[1] These receptors enable the T-cells to recognize and kill cancer cells expressing specific antigens, independent of major histocompatibility complex (MHC) restrictions. The modified cells are subsequently expanded and infused back into the patient.[1] Since its approval by the FDA in 2017, CAR-T cell therapy has led to significant advances in the treatment outcomes of hematologic malignancies, particularly in B-cell lymphoblastic leukemia and large B-cell lymphomas.[1,2]

FDA-approved CAR T-cell products are now standard of care for select relapsed/refractory cases.[1,3] However, although uncommon, CAR-T cell therapy has been shown to cause ocular complications.[2] The most frequently reported ocular adverse events include mydriasis and visual disturbances characterized by blurred vision, photopsias, floaters, and transient visual obscurations.[2] Our report describes the first documented case of a unique retinal response in a CAR-T cell therapy patient: transient ellipsoid zone (EZ) disruption with subsequent spontaneous recovery. This pattern has not been previously reported in the context of CAR-T cell therapy.

Case Report

A 57-year-old male presented with a 2-month history of gradual decrease in vision and delayed dark adaptation. His past medical history is notable for B-cell lymphoma, for which he had undergone extensive prior chemotherapy. He completed R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and

prednisone) 9 months prior, followed by GDP therapy (gemcitabine, dexamethasone, and cisplatin) 5 months prior. Two months before the initial ophthalmology evaluation, the patient presented with anemia, thrombocytopenia, and rapidly worsening dyspnea and mental status changes requiring treatment escalation by his oncologist. He underwent conditioning chemotherapy with cyclophosphamide and fludarabine, polatuzumab (a CD79b-directed antibody-drug conjugate), and CD19-targeted CAR-T cell therapy. The onset of his visual symptoms occurred shortly after the initiation of CAR-T cell therapy, though the precise day could not be recalled by the patient. The patient later developed encephalitis, a well-recognized complication of CAR-T cell therapy, from which he recovered.

Upon examination (2 months post-CAR-T cell therapy), uncorrected visual acuity was 20/40 in the right eye and 20/50−2 in the left eye. No cells were observed in the anterior chamber or vitreous humour. A dilated fundus examination did not reveal any abnormalities, and fluorescein angiography was within normal limits. However, optical coherence tomography (OCT) demonstrated bilateral attenuation of the EZ. The 2 most recent PET scans were clear and confirmed that the patient was cancer-free. A plan of watchful waiting was adopted, with a follow-up appointment scheduled in 1 month.

At the follow-up visit, uncorrected visual acuity was 20/40+1 in the right eye and 20/40−1 in the left eye. OCT demonstrated some improvement in the EZ. Once again, a plan for watchful waiting with follow-up visit in 4 months was arranged.

At the third visit, uncorrected visual acuity slightly improved, now 20/40+2 in the right eye and 20/30+2 in the left eye and the OCT demonstrated full restoration of the EZ band in both eyes. The patient also reported total symptomatic improvement in both eyes since receiving the CAR-T cell therapy.

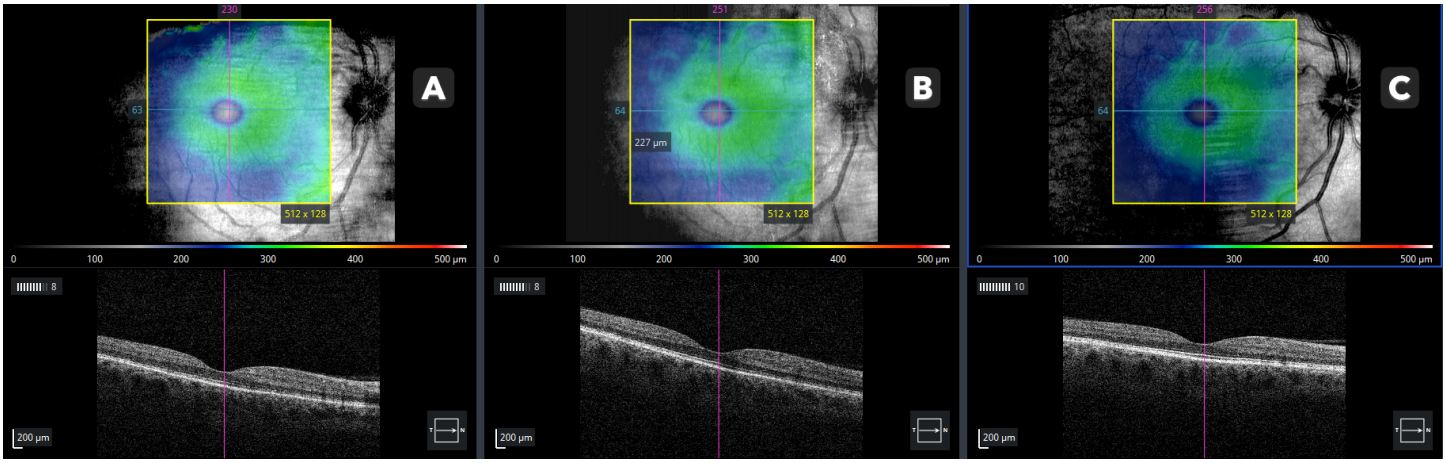

Figure 1. A. OCT scans of the right eye upon initial presentation, B. 1 month follow-up and C. 5 months follow-up. Note the progressive improvement and ultimate reconstitution of the ellipsoid zone band over time.

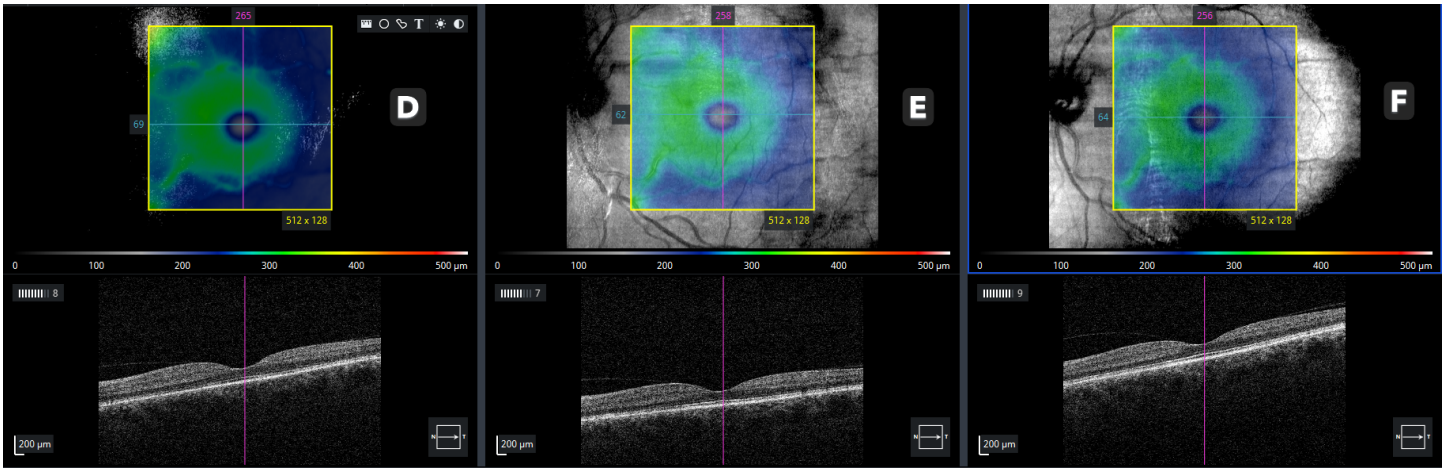

Figure 2. D. OCT scans of the left eye upon initial presentation, E. 1 month follow-up and F. 5 months follow-up. Note the progressive improvement and ultimate reconstitution of the ellipsoid zone band over time.

Discussion

The ellipsoid zone is a distinct hyperreflective band on OCT located within the photoreceptor layer of the retina.[4] Loss or disruption of the EZ is a sensitive marker of photoreceptor damage and is generally associated with reduced visual function, including decreased visual acuity and retinal sensitivity.[4] Irreversible and reversible EZ disruption has been documented in multiple retinal pathologies.[5-9] Pathologies where EZ disruption is irreversible include retinitis pigmentosa, macular telangiectasia, and hydroxychloroquine toxicity.[5-7] Reversible EZ disruption is observed in diseases like acute syphilitic posterior placoid chorioretinitis (ASPPC) and in vitreomacular traction following intravitreal ocriplasmin injection.[8,9] In our case, we describe a previously unreported phenomenon of EZ loss followed by spontaneous recovery on OCT in a patient who underwent CAR-T cell therapy.

Although primary vitreoretinal or uveal lymphoma can cause EZ disruption, several factors argue against the underlying lymphoma as the cause in this case. The patient had no prior history of ocular involvement, and the initial examination revealed none of the characteristic signs. Furthermore, the EZ loss developed after CAR-T initiation and demonstrated spontaneous recovery, both atypical for progressive, irreversible lymphoma-induced damage.

Since the preconditioning regimen has been used extensively, but without any previously reported incidents of EZ loss, we hypothesized that the transient EZ loss was temporally associated with CAR-T cell therapy.[10,11] The EZ loss and subsequent spontaneous recovery could be the direct consequence of the CAR-T cell therapy itself or an indirect consequence of CAR-T infusion. Frey et al. documented that the most common ocular side effect in patients receiving CAR-T cell therapy is mydriasis, which contributes to decreased visual acuity.[2] The authors hypothesized that the mydriasis experienced by CAR-T cell therapy is linked to neurotoxicity, specifically immune effector cell-associated neurotoxicity syndrome (ICANS), which disrupts the autonomic pathways controlling pupillary function.[2] While this leads to decreased visual acuity, retinal sequelae must also be considered a potential cause of such vision loss. As OCT findings were not reported in these cases, it remains unclear whether the acuity loss was retinal in origin.

Our finding of transient EZ loss in a CAR-T cell therapy patient closely mirrors the characteristics of ASPPC.[8,12,13] Pichi et al. noted that EZ disruption was present in all eyes affected by ASPPC within 9 days of

presentation. Following neurosyphilis therapy, 93.3% of cases exhibited improved visual acuity alongside the restoration of normal outer retinal architecture, including the EZ.[8] While EZ disruption typically resolves following syphilis treatment, spontaneous recovery without treatment has also been observed.[12,13]

The transient EZ loss observed in our patient receiving CAR-T cell therapy shares similarities with a known complication of intravitreal ocriplasmin. As reported by Reiss et al. in their 2015 case series study, 80% of patients who received intravitreal ocriplasmin experienced transient vision loss, and 50% showed reversible EZ interruption on OCT.[9] The interruption of the EZ was found to peak 2 weeks after receiving ocriplasmin.[9] Larger studies similarly reported that ocriplasmin may induce a transient reduction in EZ volume and integrity that typically resolves within 1 to 3 months.[14,15]

Based on the novel findings in our case, OCT assessment in patients with decreased visual acuity who has received CAR-T cell therapy may detect EZ loss.

Conclusion

We report the first documented case of transient EZ loss with subsequent spontaneous recovery in a patient following CAR-T cell therapy. This novel finding expands the spectrum of potential ophthalmic complications associated with CAR-T cell therapy, a novel cancer treatment. The observed phenomenon shares a remarkable resemblance to the reversible EZ disruption seen in conditions like ASPPC and following ocriplasmin injection, suggesting a shared, yet unidentified, pathway for temporary photoreceptor insult.

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Statement of Ethics

The patient gave oral and written consent to publish the data. The report does not include personal information that could identify the patient directly or indirectly. All medical interventions have been carried out according to the latest protocols of therapy. Reporting and writing are all in compliance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this topic.

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